

Federal Register

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PART II



**DEPARTMENT OF
HEALTH,
EDUCATION, AND
WELFARE**

Food and Drug Administration



LAETRILE

Commissioner's Decision on Status

**DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE**

Food and Drug Administration

[Docket No. 77N-0048]

LAETRILE

Commissioner's Decision

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Commissioner of Food and Drugs announces that he has compiled a comprehensive administrative record containing information about the drug Laetrile in general and, specifically, about two issues concerning Laetrile's "new drug" status: (1) Whether Laetrile is generally recognized by qualified experts as a safe and effective cancer drug, and (2) whether Laetrile is exempt from the premarket approval requirements for new drugs by virtue of the "grandfather" provisions of the Federal Food, Drug, and Cosmetic Act. The Commissioner concludes, after careful review of this administrative record, including oral argument presented at a public hearing, that: (1) Laetrile is not generally recognized by qualified experts as a safe and effective cancer drug, and (2) Laetrile is not exempt from the premarket approval requirements for new drugs by virtue of the "grandfather" provisions of the act. Distribution of Laetrile in interstate commerce is thus illegal and subject to regulatory activity by the Food and Drug Administration. Conclusions on other issues related to the controversy concerning Laetrile are also set out.

EFFECTIVE DATE: August 5, 1977.

ADDRESSES: The transcript of oral argument presented at the public hearing, affidavits, written testimony, and all other submissions compiled as the administrative record for this proceeding may be seen in the office of the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday. In addition, one copy of the administrative record (except two videotapes of interviews with cancer patients who had been treated with Laetrile) is available for public examination at the following Food and Drug Administration offices during regular business hours: 850 Third Ave., Brooklyn, NY 11232; 880 W. Peachtree St., Atlanta, GA 30309; 433 W. Van Buren St., Chicago, IL 60607; 1009 Cherry St., Kansas City, MO 64106; 1521 W. Pico Blvd., Los Angeles, CA 90015; 909 First Ave., Seattle, WA 98104.

FOR FURTHER INFORMATION CONTACT:

Tenny P. Neprud, Compliance Regulations Policy Staff (HFC-10), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 310-44-3480.

SUPPLEMENTARY INFORMATION: In a notice published in the FEDERAL

REGISTER of February 18, 1977 (42 FR 10066), the Commissioner announced that he was initiating a rulemaking proceeding to comply with the opinion of the Court of Appeals in *Rutherford v. United States*, 542 F.2d 1137 (10th Cir. 1976), and the order of the District Court in *Rutherford v. United States*, 424 F. Supp. 105 (W. D. Okla. 1977). In those proceedings, the Food and Drug Administration (FDA) was ordered to develop an administrative record concerning the following two issues:

1. Whether the product Laetrile (also known as vitamin B-17 and amygdalin) is a "new drug" within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) in that it is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use in the cure, mitigation, treatment, or prevention of cancer in man ("the new drug issue").

2. Whether, if Laetrile is a "new drug" within the meaning of the act, it is exempt from the premarket approval requirements of section 505 of the act (21 U.S.C. 355) in that:

(a) At any time before June 25, 1938, it was subject to the Food and Drugs Act of 1906, as amended, and at such time its labeling contained the same representations concerning the conditions of its use as its present labeling ("the 1938 grandfather issue," 21 U.S.C. 321(p)(1)); or

(b) It meets each of the following conditions: (1) On October 9, 1962, it was commercially used or sold in the United States; (2) On October 9, 1962, it was generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use in the cure, mitigation, treatment, or prevention of cancer in man; (3) On October 9, 1962, it was not covered by an effective new drug application (NDA) under section 505 of the act (21 U.S.C. 355); (4) It is currently intended solely for use under conditions prescribed, recommended, or suggested in its labeling on October 9, 1962 ("the 1962 grandfather issue," Pub. L. 87-781, section 107(c)(4)).

The February 18, 1977, notice included detailed information regarding the submission of testimony. In response to the notice, over 400 submissions totaling more than 5,500 pages were received. These submissions, representing the views of both proponents and opponents of Laetrile, came from cancer patients, consumers, experts in drug testing and cancer therapy, physicians, State governments, universities, hospitals, and interested organizations.

The District Court, in directing FDA to develop an administrative record, suggested that the agency invite the following individuals to participate in the administrative proceeding: Dr. Dean Burk, Ernst Krebs, Jr., Mike Culbert, Edward Griffin, and Mike Spencer, *Rutherford v. United States*, supra, 424 F. Supp. at 108. The three individuals whose addresses could be obtained were specifically in-

vited to give their views (R 3, 4, 5).¹ (Kenneth Coe, attorney for plaintiff Glen Rutherford, who had proposed that FDA be required to invite the five named individuals, could not provide the addresses for Griffin and Spencer and agreed that invitations to the three individuals whose addresses he could supply would suffice.) Mr. Griffin did receive notice of the proceeding and he participated (see R 404). Written submissions were received from Dr. Burk (R 302) and Mr. Griffin (Tr. Ex. 1) and from plaintiff Glen Rutherford (R 258).

The Bureau of Drugs, FDA, presented evidence probative of the new drug and grandfather status of Laetrile. For the purposes of the administrative proceeding, separation of functions requirements were observed between the Commissioner and persons advising him and the Bureau of Drugs and persons advising it (see 21 CFR 10.55).

The February 18, 1977 notice stated that oral argument would be held in Kansas City on May 2. A subsequent notice published in the FEDERAL REGISTER of March 25, 1977 (42 FR 16191) set forth the exact time and place: beginning at 9 a.m. on May 2 at the Radisson Muehlebach Hotel, Kansas City, MO. Dr. John Jennings, Associate Commissioner for Medical Affairs, presided over the oral argument. Approximately 40 persons filed written requests to make oral presentations; others took advantage of the opportunity to speak without the filing of such a request as time allowed. Every person who wished to participate in, and who was present at, the oral argument was given an opportunity to express his or her views. In all, 47 persons made presentations. The transcript of the oral argument has been made a part of the record of the administrative proceeding.

Individuals named by the District Court were again notified of the exact time and place of the argument (R 253-55, see also R 247). Oral presentations were made by Edward Griffin (Tr. at 11), Michael L. Culbert (Tr. at 35), Ernst T. Krebs, Jr. (Tr. at 228) and Dr. Dean Burk (Tr. at 401). In addition, plaintiff Glen L. Rutherford and his attorney, Kenneth Coe, Esq., spoke at oral argument (Tr. at 297, 442).

Written submissions presented at the time of oral argument were made part of the record and considered despite the fact that they were received at a date later than the one set forth in the February 18, 1977, notice. The record of this proceeding was, however, closed at the conclusion of the oral argument. Submissions received thereafter have been docketed with the FDA Hearing

¹ Submissions to the record are referred to by the number assigned to them upon filing by the Hearing Clerk. When exhibits or attachments accompany a submission, they follow the record number of that submission, e.g., "R 12, Ex. A". References to the transcript of the oral argument are cited as "Tr. at" with the applicable page number supplied. Written submissions presented to the agency at the time of oral argument are referred to as transcript exhibits, e.g., Tr. Ex. 1.

Clerk but have not been considered as part of the record. The Commissioner's opinion is based entirely upon the administrative record and does not reflect information brought to FDA's attention subsequent to the closing of that record.

No legal memoranda were solicited by the Commissioner in this proceeding. One such memorandum was submitted by the American Cancer Society and has been made a part of this docket in the Hearing Clerk's office.

In the Commissioner's opinion, the use of Laetrile in the United States has become a genuine public health problem. Increasingly, doctors dealing with cancer patients are finding that the patients are coming to legitimate therapy too late, having delayed while trying Laetrile. It seems clear that another substantial group of persons afflicted with cancer is avoiding effective therapy altogether and using Laetrile instead. The question has become one of life and death for these patients and for others who may be convinced to use Laetrile in the future. For this reason the Commissioner has considered not only the evidence in the record addressed to the specific legal issues remanded to FDA by the courts, but also the great amount of evidence submitted by both proponents and opponents of Laetrile regarding other issues of importance to the controversy over the use of the drug. Since the Commissioner's discussion of these issues is necessarily detailed, he is setting forth, for the reader's convenience, an outline of that discussion as follows:

I. LAETRILE

A. DEFINITION OF CANCER

B. COMPOSITION AND IDENTITY OF "LAETRILE"

1. Glossary.
2. What is Amygdalin?
3. What is Laetrile (with a capital L)?
4. What is laetrile (with a small l)?
5. What is Sarcocarpinase?

C. CLAIMS FOR LAETRILE

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2. Analgesic (Pain Killer).
3. Prevention of Cancer.
4. Facilitation of Other Cancer Therapy.
5. Hemoglobin Index.
6. Reduction of Odor Associated with Malignancy.
7. Sickle Cell Anemia.
8. Parasitic Diseases.
9. Regulating Intestinal Flora.
10. Hypotensive Effect.

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 - (c) The "Evidence" of Laetrile's Effectiveness.
 - (i) Case Reports.
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2. Testimony of Experts.
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B. THE 1962 GRANDFATHER CLAUSE

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 - (b) Statements by Experts.
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 - (b) Attacks on the "Establishment."
 - (c) Claimed Parallel with Scientific Pioneers.
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 - (g) Simplistic Theories of Causation and Reliance on Diet.
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 - (a) Proponents' Claims.
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I. LAETRILE

A. DEFINITION OF CANCER

Laetrile has been, over the years, recommended for use in the treatment of cancer. An understanding of the issues concerning the drug requires that the term "cancer" be defined. Cancer has been stated to include " * * * all malign-

nant neoplasms regardless of the tissue of origin including malignant lymphoma, Hodgkins disease, and leukemia" (R 173, Att., "Laws and Regulations Relating to the Diagnosis and Treatment of Cancer," State of California, Division 2, Chapter 7, Section 1705). For an almost identical definition by the American Cancer Society, Inc., see R 173, Att., "American Cancer Society, Inc., Medical Affairs Department, (State) Cancer Remedy Act." A neoplasm is a new and abnormal growth such as a tumor. Malignant neoplasms are "neoplasms that are characterized by unregulated, uncontrolled, and unrestrained growth and proliferation" (R 190 at ¶ 14; R 194 at 3; R 195 at ¶ 11). It has been said that the "distinguishing feature of cancer is its ability to invade, erode and to metastasize to more or less distant parts" (R 183, Att. 7 at 15). Metastasis, in relation to cancer, means the transfer or spread of the cancer from one site to another, usually through the blood stream or the lymphatic system. In this process, cells may travel throughout the body; when they finally lodge they begin to grow as a new cancer.

There are more than 100 different entities involved in the disease known as "cancer." These many forms of clinical cancer differ materially in terms of the factors which cause them as well as in terms of populations they affect, their prognosis, and the ease with which they may be treated (Tr. at 144; cf. R 190 at ¶ 14; R 186 at ¶ 7-9). The cause of cancer is not a question addressed in this proceeding. It should be noted, however, that the record includes indications that various cancers are associated with chronic irritation (e.g., a high frequency of cancer of the groin in textile workers whose jobs required straddling a metal shaft) (R 318 at 37), with cancer-causing chemical substances called carcinogens (e.g., a high frequency of lung cancer in chimney sweepers and coal miners probably caused by inhaling dust particles) (id.), with irradiation (id. at 38), with virus (Tr. at 223; R 318 at 38), and with hereditary effects (R 318 at 38).

Two novel theories, neither of which has gained acceptance by the scientific community, have been at various times espoused by Laetrile's proponents to explain how cancer is caused. The first of these theories is said to have been first developed by Professor John Beard of Scotland. In 1902, Professor Beard announced his "findings" that the cancer cell and the "trophoblast" cell were one and the same (R 318 at 60). Trophoblast cells are present during pregnancy and they prepare a niche in the uterine wall where the fertilized egg can nestle (R 318 at 56). According to Beard, they share several characteristics with cancer cells: Both are invasive, erosive, corrosive and can be carried through the blood stream to other parts of the body (R 318 at 57). Beard believed that trophoblast cells could be expected to develop at various places in the body from precursor cells distributed throughout the body during the embryonic stage. If the pancreas gland were functioning properly it

would, in his theory, produce enzymes which destroy these trophoblast cells. If such enzymes were not produced, cancer would occur (R 318 at 58-59).

The proponents of Laetrile have more recently taken the position that cancer is a metabolic deficiency or dietary disease (cf. R 302, Ex. H at 76-77). It is claimed that cancer is a " * * * systemic, chronic, metabolic deficiency disease" (Tr. at 348) or " * * * a chronic or metabolic disease that is not caused by some mysterious virus" (Tr. at 234). The "nutritional deficiency" theory is refuted by at least one expert (Tr. at 223).

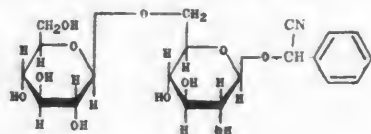
B. COMPOSITION AND IDENTITY OF "LAETRILE"

Several terms, such as "Laetrile," "laetrile(s)," "amygdalin," "nitriloside(s)," "vitamin B-17," and "Sarcarcinase" have in many instances been used interchangeably by both proponents and opponents of Laetrile. There are, however, distinctions among these terms, which must be understood in order to deal with the issues in this proceeding. The Commissioner will discuss in detail what the record indicates about the meaning of the terms "amygdalin," "Laetrile," "laetrile" and "Sarcarcinase."

1. Glossary

The following glossary provides a definition or description of the above terms and others that will be used in this opinion:

Amygdalin: A specific chemical entity having the chemical formula:



D-mandelonitrile-beta-D-glucosido-6-beta-D-glucoside (Merck Index, 9th Ed. at 81).

beta-Cyanogenic glucosides; beta-cyanophoric glucosides; beta-cyanogenetic glucosides: Terms used interchangeably in the record. In general, they are used in the record to include compounds which can break down to yield cyanide and glucose. The terms are used to refer to amygdalin, a glucoside present in kernels or seeds of practically all fruits (see, e.g., R 302, Ex. H at 75; R 173, Att., California Administrative Code, Section 10400.1 at 16; Tr. at 272). **beta-Cyanogenic glucosides** belong to the large class of chemicals known as **beta-cyanogenic glycosides**. (See definition of glucosides and glycosides below.)

beta-Glucosidase: An enzyme present in plants that participates in the metabolism of glucosides. The enzyme has been identified in apricot and peach kernels and catalyzes the breakdown of amygdalin to free two molecules of glucose and a molecule of mandelo-

nitrile. The enzyme is found only in trace amounts in animal tissues (R 173, Att., "The Vitamin Fraud in Cancer Quackery" (hereinafter "Vitamin Fraud") at 345).

beta-Glucuronidase: An enzyme present in animal tissues that participates in the metabolism of glucuronic acid derivatives (also called glucuronosides). The enzyme reportedly catalyzes the breakdown of "Laetrile" (1-mandelonitrile-beta-glucuronic acid) to free glucuronic acid and mandelonitrile.

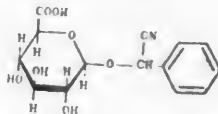
Enzymes: Chemical compounds (all of them proteins) produced by living organisms that serve as catalysts in metabolic reactions. The suffix "-ase" is given to most enzymes.

Glucoside: A term applied to any glycoside having glucose as its sugar constituent.

Glucuronide; glucuronoside: Terms used in the record to refer to chemical derivatives of glucuronic acid. As an example, Laetrile is identified as 1-mandelonitrile-beta-glucuronic acid" in the Merck Index 9th Ed., at 702 and as "laevo-mandelonitrile-beta-glucuronoside" in the book *Control for Cancer* (R 318 at 73).

Glycosides: A broad term which encompasses glucosides. Not all glycosides are glucosides (cf. *The Condensed Chemical Dictionary*, 7th Ed. at 455).

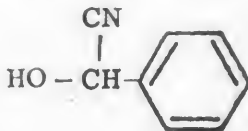
Laetrile: A specific chemical entity having the chemical formula:



1-mandelonitrile-beta-glucuronic acid (Merck Index, 9th Ed. at 702). The name "Laetrile" was purportedly assigned to this compound by Ernst T. Krebs, Jr. (R 318 at 73).

laetrile: A term used interchangeably with "Laetrile," "amygdalin," "nitriloside," and "vitamin B-17" (R 302, Ex. A; R 183, Att. 10c). The term is also used to include a number of compounds, in which case it may appear as "laetriles."

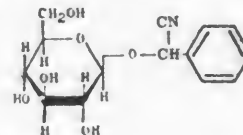
Mandelonitrile: A specific chemical entity having the chemical formula:



(Merck Index, 9th Ed. at 743).

Nitriloside: A term proposed by Ernst T. Krebs, Jr., for all cyanophorioglycosides of dietary significance (R 302, Ex. H at 75).

Prunasin: A specific chemical entity having the chemical formula:



Mandelonitrile Glucoside (Merck Index, 9th Ed. at 743).

Sarcarcinase: The name given to an enzyme preparation developed by Dr. E. T. Krebs, Sr., and described by him in a 1933 patent application as a mixture of the following enzymes—amygdalase, prunase, oxynitrilase, catalase, peroxidase, and a proteolytic enzyme. He also suggested the presence of isomaltase and a lipase and perhaps other enzymes (R 424).

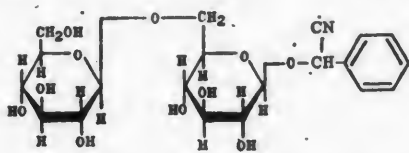
Vitamin B-17: Described as a group of compounds which include water-soluble, essentially nontoxic, sugary compounds found in over "800 plants" (R 302, Ex. H at 75) used interchangeably with "nitriloside," "Laetrile," "amygdalin," "beta-cyanogenic glucosides" and "cyanophoric glucosides" (e.g., R 302, Ex. H at 75; R 302, Ex. A).

2. What is Amygdalin?

Amygdalin was reportedly first isolated from bitter almonds by the French chemists Robiquet and Burton-Charland in 1830 (R 173, Att., "Vitamin Fraud" at 345). The name "amygdalin" was derived from the word "amygdala," Greek for almond (R 302, Ex. L at ¶ 9). Amygdalin is a chemical compound composed of two glucose molecules and one molecule of mandelonitrile. Mandelonitrile is a chemical in which cyanide is combined with benzaldehyde (cf. R 173, Att., "Vitamin Fraud" at 345). The German chemists Liebig and Wohler observed that an enzyme preparation (later called emulsin) from bitter almonds was capable of hydrolyzing amygdalin, i.e., breaking it down into the two glucose molecules, the benzaldehyde molecule and a hydrogen cyanide molecule (id.). It was later shown that this hydrolysis occurs through the action of two enzymes (*beta-D-glucosidase* and *beta-oxynitrilase*) which are present in emulsin (id.). The *beta-D-glucosidase* hydrolyzes the *beta-D-glucoside* bond and thus frees the two glucose molecules from the mandelonitrile. *beta-Oxynitrilase* is the catalyst for the breakdown of mandelonitrile into benzaldehyde and hydrogen cyanide (id.).

Amygdalin may be extracted from apricot kernels (id.), and is present in seeds of other members of the rose family (R 416 at ¶ 31A). The Commissioner concludes that amygdalin, a cyanogenic glucoside, is a chemical having the chem-

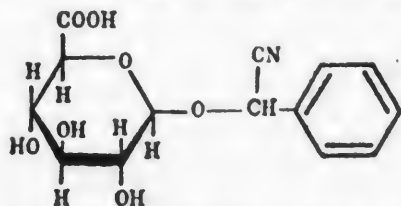
ical name D-mandelonitrile-beta-D-glucosido-6-beta-D-glucoside (Merck Index, 9th Ed. at 81, compounds 630; R 183, Att. 10b). The chemical structure of amygdalin is:



3. What is Laetril (With a Capital L)?

The term "Laetrile" has been used interchangeably with "amygdalin," "laetrile," "vitamin B-17," "nitrilosides," and "beta-cyanogenetic glucosides" (R 173, Att., Laws and Regulations Relating to the Diagnosis and Treatment of Cancer 10400.1 at 16; R 302, Ex. A; Tr. at 405, 272, 465). It appears, however, that the term "Laetrile" (with a capital L) has been used by the drug's proponents to refer to a particular substance. There are essentially two versions of what that substance is:

(a) The term has been used to refer to a specific chemical compound which was prepared in 1952 by Ernst T. Krebs, Jr., who is said to have derived the name "Laetrile" from the compound's chemical name: laevo-mandelonitrile-beta-glucuronoside (R 318 at 73; see also R 262; R 183, Att. 16 at 1 and 2). This chemical is related to, but is distinctly different from, amygdalin. It is claimed that the laevo-mandelonitrile-beta-glucuronoside was derived by Ernst T. Krebs, Jr., while working with the apricot extract his father had prepared and studied some 20 years earlier (R 318 at 70-73). The chemical structure of this material is depicted in several places (R 318 at 154, 157, 162) and is in agreement with the chemical name. The chemical structure of this version of Laetrile is:



(b) In a 1965 affidavit, however, Dr. Krebs, Sr., stated that the name "Laetrile" was devised in 1949 by his son, Ernst T. Krebs, Jr., for a form of amygdalin which Dr. Krebs, Sr., was producing at that time (R 183, Att. 13). As can be seen from the diagrams set out in this opinion, the chemical structure of amygdalin is different from that of Laetrile as described by Mr. Krebs, Jr.

In the second version of the identity of Laetrile, the source of the name is stated as follows: "Because this apricot preparation was 'laevorotatory' (left-handed) to polarized light, and because Amygdalin was chemically a 'mandelonitrile,' Krebs, Jr., united the first and the last syllables to invent a name for the

new cancericidal drug—LAETRILE" (R 183, Att. 7 at 24).

The confusion about the meaning of the term "Laetrile" is long-standing and may in part be the result of a desire on the part of promoters to continue to use drugs containing amygdalin while justifying the use of the drugs by theories associated with the Laetrile of Krebs, Jr. For example, in a February 17, 1953 letter to Dr. Ian Macdonald, the Chairman of the Cancer Commission of the California Medical Association, Ernst T. Krebs, Jr., advised that he was forwarding " * * * samples of the biosynthetically degraded amygdalin in which one dextrose was removed by prunasin and the resulting compound, in the presence of platinum black, was oxidized to the corresponding glucuronoside" (R 183, Att. 14). (Note: the compound thus obtained should have been 1-mandelonitrile-beta-glucuronoside or "Laetrile" as described by E. T. Krebs, Jr., R 318 at 73.) The Cancer Commission of the California Medical Association, in its 1953 report, stated: "Chemical analyses done independently for the Commission have identified in the product distributed as Laetrile only the presence of a natural laetrile termed amygdalin" (R 378, Att. 15 at 326).

The question of the identity of the material distributed as "Laetrile" arose again in the early 1960's when the Cancer Advisory Council of the State of California was gathering information on Laetrile in order to enforce the 1959 California law dealing with cancer quackery. In 1963 the Council reported that the California State Department of Public Health had examined different varieties of Laetrile and found that the products were markedly different in composition but did contain varying percentages of amygdalin (R 183, Att. 16, App. 7 and 8). A Canadian Medical Association report published in 1965 found that the United States and Canadian versions of the drug were different—a larger percentage of the Canadian version than of the United States version was found to be made up of amygdalin (R 189; see also R 378, Att., "Supplementary Report by the Cancer Advisory Council" at 1-2).

The record reveals a number of references by Laetrile proponents which use the terms "Laetrile" and "amygdalin" interchangeably (see, e.g., Tr. at 238 and 246, and the book Control for Cancer (R 318)). Even some labels for the drug use the terms synonymously: one identifies the product as "Laetrile (Amygdalin) 400 mg capsules" (R 183, Att. 10a; see also R 183, Att. 10d). The National Cancer Institute, in its October 1975 "Background Statement on Laetrile" notes the fact that supporters of the drug have used the names "Laetrile" and "amygdalin" interchangeably. The report then correctly identifies amygdalin as mandelonitrile-beta-gentiobioside (this chemical name for amygdalin is listed in the Merck Index, 9th Ed. at 81, compound No. 630) and states that the compound actually tested in 1957, 1960, 1969, 1973, and 1975 by the National Cancer

Institute was amygdalin (R 173, Att., "NCI Testing of Laetrile (Amygdalin)").

Yet it is not possible simply to conclude that the many references to Laetrile as a specific substance are a hoax on the part of Mr. Krebs, Jr., and that Laetrile as used is simply amygdalin. A number of reports by Dr. Manuel Navarro of the Philippines stated that the Laetrile of Ernst T. Krebs, Jr., was in use (R 318 at 155, 161), as did a report by Dr. John A. Morrone of New Jersey (R 318 at 205).

Additional confusion is added to the record by an article "Nitrilosides (Laetriles) Their Rationale and Clinical Utilization in Human Cancer (December 1962)," by Ernst T. Krebs, Jr., and Dr. N. R. Bouziane, in which the authors report on their use of "non-toxic nitrilosides (Laetrile), to which the trophoblast is susceptible, on terminal cancer cases for two years in Canada * * *" (R 318 at 187). While the article refers to "cyanophoric glucosides and cyanophoric glucuronosides" (id. at 189), the authors do not identify the "Laetrile" they had been using and about which they were reporting. The authors cite a chemical compound in their discussion (id. at 190) that is not amygdalin nor is it "Laetrile" as described and named by Ernst T. Krebs, Jr. (id. at 73).

While the prevailing confusion over the true identity of material called "Laetrile" would be a severe drawback to anyone seeking to show through testing that Laetrile was safe and effective, this lack of uniformity has been adopted by Laetrile proponents as a means of discounting data showing the drug to be ineffective and thus unsafe. An example is found in the statement by Ernst T. Krebs, Jr., that "The * * * single negative report on Laetrile, which is based upon the observations of unidentified investigators in unidentified institutions administering a purported Laetrile not obtained from the only source of the material, is to be found in California Medicine, 78:320 (1953)" (emphasis added) (R 318 at 251). It should be recalled that at least some of the material supplied to the California Cancer Commission was sent by Ernest T. Krebs, Jr., himself (R 183, Att. 14). In May of 1971, Mr. McNaughton of the pro-Laetrile McNaughton Foundation, in a meeting with FDA's Ad Hoc Committee of Oncology Experts, stated that data obtained prior to 1968 are frequently not valid because of the variability of Laetrile formulations (R 173, Att. "Report of the Ad Hoc Committee of Oncology Consultants" at 1). See also statement of Robert Bradford, President of the Committee for Freedom of Choice in Cancer Therapy, Inc.: "As an aside, an important aspect of animal tests, and indeed, of human tests has been from time to time the availability of amygdalin which did not meet the specified identification criteria, that is, for its use. Tests with defective materials, as Sloan-Kettering found out, will not be efficacious. Defective material likewise will not be effective in humans" (Bradford, Tr. at 350).

In its 1971 report to FDA, the Ad Hoc Committee of Oncology Consultants

agreed that uncertainty about the identity of the drug tested makes the test results obtained questionable. The Committee stated that because of the variability in composition of early preparations, doubt was cast on the bulk of the 1970 McNaughton Foundation Notice of Claimed Investigational Exemption for a New Drug (IND) for Laetrile, which was based almost exclusively on such early material (R 173, "Report of the Ad Hoc Committee of Oncology Consultants" at 1). The Committee further suggested that any protocol for study contain a full description of the drug (formulation, stability etc.) (id. at 4).

There is, quite simply, no one answer to the question "What is Laetrile?". In the glossary to this opinion, the chemical composition of Laetrile is considered to be that described by Ernest T. Krebs, Jr. Yet if some other substance is being used to treat cancer patients, testing of that "Laetrile" would be of no relevance.

Because different persons have used the terms "Laetrile" and "amygdalin" to mean different substances, uniformity of definition will not be possible in discussing the evidence in the record. For this reason, the Commissioner will not, in quoting or citing parts of the administrative record, attempt to define or to determine the identity of the material under discussion but will simply use the term as it appears in that portion of the record. Attempts to identify the material referred to will be made only when necessary for a rational resolution of an issue, e.g., a reference to Sarcarcinase as amygdalin or as Laetrile will not be accepted blindly.

4. What is laetrile (With a Small l)?

As noted in the glossary, the term "laetrile" (with a small l) has been used interchangeably with or synonymously for: nitriloside, Laetrile, vitamin B-17, and amygdalin (e.g., R 302, Ex. A; R. 183, Att. 10c; R 378, Att. 6). The term has, however, also been used to describe a class or group of compounds. For example, amygdalin and prunasin are described as "two common Laetriles" (R 173, Att., "Vitamin Fraud" at 345). It has been stated that: "The term LAETRILE is used to designate the laevorotatory containing glucosides in general and the corresponding glucuronoside in particular. The former are found in plants whereas the latter are synthetic" (italics in original) (R 318 at 155). (See also, R 318, at 240 ¶ 9 which defines natural laetriles as beta-cyanogenetic glucosides and glucuronosides.) The Commissioner concludes that the term "laetrile" is an imprecise term and that it does not imply a specific chemical compound. The term is, rather, a broad or generic term for a group of compounds of unknown number.

5. What is Sarcarcinase?

Dr. Ernst T. Krebs, Sr., claims to have developed a product called "Sarcarcinase" in 1926 (R. 183, Att. 13). "Sarcarcinase" is stated to be a registered trademark in the United States and 10 other countries (with registrations dating from

March 1933 to January 1934) (see R. 260; R 259). The process for preparing the product is stated to be patented in 15 countries including the United States (see R. 260). It is also reported that Sarcarcinase was used in Japan in 1934 and in Czechoslovakia in 1935 (R. 259). Other references in the same timespan refer to an "enzyme preparation" or "enzyme injection" used within the United States as well as several foreign countries (id.).

Ernst T. Krebs, Jr., stated at oral argument that as early as 1932 his father " * * * observed the use of amygdalin, or laetrile; made it available across the country and abroad under the term 'Sarcarcinase' to physicians, to researchers" (Tr. at 238). He also stated, " * * * the first amygdalin was used—1932—it was labeled as 'Sarcarcinase'" (Tr. at 246). Sarcarcinase was not, however, amygdalin nor did it contain amygdalin in any quantity. Rather, in the words of Dr. Krebs, Sr.'s 1933 patent application, Sarcarcinase was "an enzyme for treatment of malignant growths." The patent application actually describes the product as "an enzyme complex" containing "amygdalase, prunase, oxynitrilase, catalase, peroxydase and proteolytic enzyme" plus a suggestion of "isomaltase and a lipase with possibly others" (Patent application attached to R 424 and to R 259).

Amygdalin is not an enzyme. As will be discussed in more detail below, enzymes are chemicals which catalyze the breakdown of other chemicals and which are often named by attaching the ending "-ase" to the chemical which they attack. Thus, "amygdalase," stated by Dr. Krebs, Sr., to be part of his enzyme complex, may have been meant to describe an enzyme which would break down amygdalin.

It has been argued that Sarcarcinase contained some quantity of amygdalin (R 183, Att. 13, and Att. 7 at 23). An expert chemist has stated, however, that much or all of the small amounts of amygdalin in the apricot kernels used in making Sarcarcinase would be destroyed by enzyme action when the kernels are ground up and that only a small fraction of any that remained would survive the rest of the process (R 424). It should be noted that, even if there were any amygdalin in Sarcarcinase, that would not make that drug equivalent to a drug made up of amygdalin either totally or in greater proportions either in a scientific sense or in a legal sense.

There is some indication that Dr. Krebs, Sr., had abandoned Sarcarcinase even at the time when the patent applications were being obtained. One submission by a Laetrile proponent states that Dr. Krebs, Sr., " * * * resigned himself to the fact that there was no sense continuing this particular research to identify the toxic element or elements in the apricot extract he prepared (sometime after 1926) until he acquired the additional knowledge necessary to understand the mysteries that were occurring in his test tubes. He put his extract aside and returned his books"

(R 318 at 42). Krebs himself states that in 1936 he developed a new product, whose "active principle" was amygdalin of 66 percent purity (R 183, Att. 13). (The inactive ingredients of this preparation are not identified.) It is not clear whether it is Sarcarcinase or this new product about which Krebs, Sr., speaks when he states that his "apricot extract" was "so toxic that he and colleagues who were experimenting with him were reluctant to continue its use, except in dire circumstances" (R 183, Att. 7 at 23). It was apparently these toxicity problems that led Krebs, Jr., to seek to improve his father's work (id.). Since "Laetrile" was not developed until 1952 by Krebs, Jr., any statement that "Laetrile" was sold as Sarcarcinase in the 1930's is patently erroneous.

C. CLAIMS FOR LAETRILE

Laetrile (or amygdalin) has been recommended over the years primarily for use in the treatment and, more recently, "control" of cancer. The claims appear to vary in relation to the sophistication of the intended audience. Thus in the 1962 new drug application (NDA) for Laetrile submitted by Ernst T. Krebs, Jr., to FDA, the drug was claimed to be a palliative (i.e., a drug that mitigates the symptoms of a disease without curing it) to be used with other recognized therapies (R 201, Ex. B at 102). By contrast, in a pamphlet in use in 1965, apparently addressed in part to prospective patients, it is stated that "Laetrile does not palliate, it acts chemically to kill the cancer cell selectively * * *," and use of other cancer therapies concurrently is discouraged (R 201, Ex. C., # III). The following claims have been made for Laetrile (amygdalin):

1. Treatment (Cure or Mitigation) of Cancer

The pamphlet discussed above and others obtained from Dr. Krebs, Sr., by FDA investigators at the same time recommended Laetrile for treatment of cancer (see, generally, R 201, Ex. C). Dr. Krebs, Sr., in a pamphlet entitled "The Treatment of Breast Cancer with Laetrile by Iontophoresis" promotes the drug for treatment of a number of cancers (R 183, Att. 7 at 26-27 and 30).

A label for 400 mg capsules of "Laetrile (Amygdalin)" claims that the "non-toxic cyanide glucoside is used for specific treatment of cancer by physicians or under directions of a physician" (R 173, Att. 102). Amygdalin has been promoted (as an ingredient of "Bitter Food Tablets") for the cure, mitigation, and treatment of cancer in man (R 173, Att., *United States v. Spectro Foods*, Civ. No. 76-101 (D.N.J., Jan. 28, 1976) Findings 16 through 23).

As noted above, some claims are limited to palliation. (See, e.g., R 216 at 348; R 318 at 175; Tr. at 238.) Recently, Laetrile has been touted as a "control" for cancer. Proponents of Laetrile making this claim assert that no "cure" for cancer exists (see Tr. at 303). Control for Cancer is also the title of a paperback book on Laetrile (R 318). It is not entirely clear

from the record whether "control" means palliation. Laetrile therapy is said to be responsible for increased appetite and weight gain and an increased "sense of well-being" among treated cancer patients (R 318 at 158 and 165).

2. Analgesic (Pain Killer)

An information booklet for physicians about amygdalin makes the claim that the product is a nontoxic analgesic that is highly effective in relieving the pain of terminal cancer (R 183, Att. 10b). The booklet claims that the oral route is the most convenient route of administration for both patient and physician.

NOTE.—The Commissioner points out that both proponents and opponents have warned against oral use of amygdalin or Laetrile.

See R 318 at 167: " . . . it (Laetrile) should never be given by mouth because the HCl (of the stomach) is capable of hydrolyzing the Laetrile"; see also R 318 at 158. Compare R 173, Att., Interview with Robert C. Eyerly, American Cancer Society: "Taken orally, it (Amygdalin) is decomposed in the intestinal tract by *beta*-glucosidase into highly lethal hydrogen cyanide." "Orally it (Laetrile) is extremely toxic due to the release of hydrogen cyanide on contact with the hydrochloric acid of the gastric juice (R 318 at 205).

A label for "The Original Laetrile" claims that the product "relieves pain due to malignancy" (R 183, Att. 9). For another claim that Laetrile reduces cancer-connected pain, see Tr. at 44. It has also been asserted that the hydrogen cyanide and benzaldehyde liberated by hydrolysis of Laetrile are potent analgesics (R 318 at 164).

3. Prevention of Cancer

With the advent of their theory that cancer is a deficiency disease and that that deficiency can be overcome by their product, either characterized as a pro-vitamin for vitamin B-12 (R 201, Ex. C, No. IV), or as new vitamin B-17 (see R 183, Att. 10c), proponents of Laetrile have promoted it as a preventative for cancer (see the above references and R 198, Ex. 2 (transcript of the film *World Without Cancer*); cf. Tr. at 465). (See also R 173, Att., *United States v. Spectro Foods*, supra, Findings 16 through 23.) While proving that Laetrile (or amygdalin) did not prevent cancer would be extremely difficult, the record does contain evidence that at least one person taking it as a preventative did contract cancer (Tr. at 120).

4. Facilitation of Other Cancer Therapy

While, as noted above, some labeling recommends against use of other cancer therapies with Laetrile, it has been stated that " . . . if you combine toxic chemotherapy with Laetrile, you can give very high doses of toxic chemotherapy with no side effects, physical and no effects on the blood. That is, you don't get neutropenia (leukopenia?) and you don't get chromositemia (chromocytopenia?)" (Tr. at 480).

5. Hemoglobin Index

One set of labeling for "Laetrile (Amygdalin)," which appears at two points in the record, recommends the product "for raising hemoglobin index and red count * * *" (R 183, Att. 9; R 201, Ex. C, No. I).

6. Reduction of Odor Associated with Malignancy

It is also claimed that topical application of Laetrile relieves fetor (odor) resulting from the secondary infection of ulcerated carcinoma and that parenteral administration takes care of fetor associated with internal cancers. This action is ascribed to the "antiseptic" properties of HCN and benzaldehyde, which is converted by the cells to benzoic acid (R 318 at 158 and 165).

7. Sickle Cell Anemia

It is theorized that nitriloside (Laetrile) might be of value in the treatment of sickle cell anemia because of the release of cyanide and the subsequent formation of thiocyanates (R 217, article by R. G. Houston). (See also Tr. at 465.) This claim is reportedly refuted by experts in sickle cell hemoglobin (R 416 at 23).

8. Parasitic Diseases

The Houston article also references a report by Navarro and others of the clinical control of schistosomiasis (a snail-borne infection) with nitriloside (Laetrile) (R 217, Houston article at 58). The possibility of using Laetrile to treat parasitic diseases such as schistosomiasis or malaria is discussed in the book *Control for Cancer* but there are no reports of actual use in the book (R 318 at 111-12).

9. Regulating Intestinal Flora

It has also been suggested that amygdalin has some utility in regulating intestinal flora (Tr. at 476).

10. Hypotensive Effect

It has also been claimed that use of Laetrile causes a hypotensive effect (i.e., it reduces blood pressure), at least in cancer patients (R 318 at 165; cf. Tr. at 465).

In addition to these claims by Laetrile proponents (developers, distributors, and promoters), numerous comments from interested citizens contained references to or claims for its therapeutic effects as a cancer cure or as a preventative. There are also references to relief, attributed to Laetrile, from other ailments unrelated to cancer, e.g., arthritis (R 391).

D. THEORIES OF LAETRILE'S ACTION

A thorough understanding of the manner in which a compound achieves its therapeutic or beneficial effects is highly desirable. A cancer drug which had been shown to be safe and effective would not, however, be denied marketing approval simply because its action could not be explained. Experience has shown that a good theory to explain or predict the action of a chemical in the body,

does not assure success; neither does a weak theory, or even what turns out to be a totally incorrect theory, mean certain failure.

Some cancer patients may be turning to Laetrile in the mistaken belief that its use is supported by a respectable—even if not widely accepted—scientific theory. (Unproven remedies throughout the years have benefited from the use of the type of "scientific" theories associated with Laetrile (see, generally, R 413).) The Commissioner finds from the record that the theories advanced for Laetrile's supposed action are based on false or questionable assumptions. An understanding of these theories, furthermore, points up important differences between the "Laetrile" whose use is "justified" by the theories of Krebs, Jr., and the amygdalin-containing products actually being used.

Since a large part of the Laetrile theory of action deals with enzymes, the Commissioner believes that a few brief introductory comments about enzymes would be useful. Enzymes are protein molecules manufactured in the cells of the body which help the cells perform chemical reactions involving other compounds. As an example, trypsin, a common enzyme, aids in the metabolism of proteins in food by breaking these large molecules into smaller, easier-to-handle pieces. Enzymes generally are very specific in the types of chemicals they will attack. Frequently, the name of an enzyme is derived from the compounds that enzyme will break down. The ending "-ase" is often used to indicate an enzyme.

The chemical "*beta*-glucosidase" appears frequently in the Laetrile record. The name of this chemical indicates that it is an enzyme (-ase) and, furthermore, the name indicates that it attacks glucose-containing compounds (glucosides) from which it will liberate glucose molecules. As an example, *beta*-glucosidase liberates two molecules of glucose from amygdalin. If the chemical compound does not contain glucose molecules, *beta*-glucosidase will not attack it. In a similar vein, *beta*-glucuronidase will attack chemical compounds that contain glucuronic acid. (These chemical compounds are called "glucuronides" or "glucuronosides" or "glucuronic acid derivatives.")

The original theory of Ernst T. Krebs, Jr., for Laetrile's action involved two enzymes, rhodanase and *beta*-glucosidase (R 318 at 72). Krebs claimed that normal cells produced these two enzymes, while cancer cells were deficient in rhodanase. In cancerous areas, the theory continues, the *beta*-glucosidase accumulates in great quantities (R 318 at 72).

According to the theory, when Laetrile comes into contact with the cancerous areas it is hydrolyzed by the enzyme *beta*-glucosidase to liberate cyanide and benzaldehyde. In normal cells, the enzyme rhodanase converts the liberated cyanide to the less toxic thiocyanate. Cancer cells, lacking rhodanase, are said to be killed by the liberated cyanide

when it reacts with cellular components. Rhodanese from normal cells cannot protect cancer cells because, it is claimed, cancer cells produce chorionic gonadotropic hormone that effectively blocks the action of rhodanese (R 318 at 153). In later versions of the theory, the benzaldehyde is also considered to be responsible for killing the cancer cells, either alone or in concert with the cyanide. According to this theory, benzaldehyde is normally converted by a cell to benzoic acid by oxidation. Cancer cells are said to oxidize the benzaldehyde at a slower rate than normal cells, making it toxic to cancer cells and nontoxic to normal cells. (See Krebs, Jr., "The Nitrilosides (Vitamin B-17)—Their Nature, Occurrence and Metabolic Significance (Antineoplastic Vitamin B-17)" (R 183, Att. 10c at 80).)

In fact, it has been reported that only traces of *beta*-glucosidases have been found in animal tissues and even less in experimental tumors than in such organs as liver and spleen (R 173, Att., "Vitamin Fraud" at 345). Apparently for this reason, Krebs, Jr., at one time modified his theory. In the modified version it is *beta*-glucuronidase rather than *beta*-glucosidase which is abundant in cancerous areas. This change is reflected in a 1955 pamphlet co-authored by Dr. Krebs, Sr., and Dr. Arthur T. Harris, in which it is stated: "As soon as the Laetrile *beta*-glucuronidase, which bathed the cancer cell, because of its affinity for sugar split the glucoside (or sugar radical) from the Laetrile molecule" (R 183, Att. 7 at 24). (See also R 318 at 151-53.)

The change in theory is important. *beta*-Glucuronidase hydrolyzes (breaks down) *beta*-glucuronosides (or "*beta*-glucuronic acids" or "*beta*-glucuronides") but does not hydrolyze *beta*-glucosides (R 318, Att. 16 at 24). Thus, *beta*-glucuronidase will hydrolyze "Laetrile" of the formulation devised by Krebs, Jr. (i.e., laevo-mandelonitrile-*beta*-glucuronoside), but it will not hydrolyze amygdalin (D-mandelonitrile-*beta*-D-glucosido-6-*beta*-D-glucoside) or other "nitrosides" found in nature. What this means is that amygdalin, which has been sold as "Laetrile," would not be hydrolyzed by the body to liberate cyanide (R 183, Att. 16 at 41).

Recognition of this fact apparently led Krebs, Jr., to formulate his version of Laetrile in the first place. He is reported to have stated in a manuscript that "the natural laetriles have been

³In his 1933 patent application for Sarcinase, Dr. Ernst T. Krebs, Sr., discussed his own theory of cancer, apparently now abandoned by Laetrile proponents. He perceived a malignant protein ("... a so-called abnormal glucosido-protein ...") in cancer cells and explained why his enzyme extract, prepared from apricot kernels, should be effective against those cells (R 424). He believed that the enzyme would break up the abnormal gluco-protein and thus be an effective treatment against cancer (R 318 at 40-41). While it is claimed that some positive effects were observed in cancers in mice, the extract proved to be toxic and Dr. Krebs, Sr., discontinued working on the extract (id. at 42).

abandoned for the more specific synthetic laetrile tailored as specific glucuronoside substrates for the tumor *beta*-glucuronidase" (R 183, Att. 16 at 14).

The specificity of *beta*-glucuronidase for glucuronides (or glucuronosides) and its lack of activity against glucosides (such as amygdalin) is rigorously addressed in the record:

Numerous glucuronosides are hydrolyzed by *beta*-glucuronidase. * * * Methyl-alpha-D-glucuronide and alpha-and beta-methyl-D-glucosides are not split by the enzyme.

Further checking of this important point is consistent with the idea that the enzyme in question (*beta*-glucuronidase) not hydrolyze the *beta*-glucosides, which are the only Laetriles actually utilized by the Krebs' for human treatment (R 183, Att. 16 at 24).

(It should be remembered that the Cancer Commission of the California Medical Association had determined that the material labeled "Laetrile" was in fact amygdalin—a glucoside and not a glucuronoside (R 183, Att. 15 at 326).)

The conclusion seems justified that the presence of the terminal carboxyl group on position 6 appears to be the important factor in determining a specificity which is markedly different from that of *B*. Glucosidase * * * (R 183, Att. 16 at 25).

(The Commissioner points out that amygdalin has two glucose molecules but does not have a carboxyl group. Laetrile, as reportedly prepared, described, and named by Ernst T. Krebs, Jr., in the late 1940's or early 1950's (R 318 at 73) does have a carboxyl group on position 6 (the glucuronic acid portion of the molecule).)

Dr. Krebs, Sr., in his 1955 pamphlet on Laetrile appears to recognize that "animal *beta*-glucuronidase" and *beta*-glucosidase are different substances. (He characterizes the latter as a "prepared enzyme.") He does claim that the two enzymes react with Laetrile in the same manner (R 183, Att. 7 at 24).

There is some indication that Ernst Krebs, Jr., in later years abandoned his attempt to develop a Laetrile that could be broken down by *beta*-glucuronidase and began treating *beta*-glucuronidase and *beta*-glucosidase as equivalent. In a 1962 letter, Krebs, Jr., seems to refer to the former as an example of the latter: "*beta* glucosidases (e.g., *beta* glucuronidase)" (R 183, Att. 16, App. 12 at 2) and seeks, in describing an experiment with water fleas he had designed, to extrapolate results obtained with *beta*-glucosidase to results with *beta*-glucuronidase he feels is found in malignant lesions (id. at 4). (See also Krebs' 1970 article "The Nitrilosides (Vitamin B-17)—Their Nature, Occurrence and Metabolic Significance (Antineoplastic Vitamin B-17)" in which he again equates *beta*-glucosidase with *beta*-glucuronidase (R 183, Att. 10c at 82).)

Three other problems with this theory are quickly identifiable: (1) there is evidence that *beta*-glucuronidase is not particularly abundant in malignant tissues. The record shows that "... *beta*-glucuronidase is found in all tissues of the animal body and in particularly high concentrations in spleen, liver, and en-

doctrine organs, as well as in plasma and in tumors arising from estrogen-influenced tissues. Per gram of tissue, the spleen and liver have a higher concentration of *beta*-glucuronidase than do most tumors," (R 183, Att. 16 at 15 and App. 14). It is further stated, "Such a statement as '... the malignant cell ... is virtually an island surrounded by a sea of *beta*-glucuronidase' is sheer nonsense" (R 183, Att. 16 at 15 and App. 14).

(2) There is no evidence that cancer cells are deficient in the enzyme rhodanese. In reviewing the record, the Commissioner has not found any support for the bald assertion by the Krebs and other Laetrile proponents that cancer cells are deficient in the production of a hydrogen cyanide-inactivating enzyme called rhodanese. If there is any scientific support for that assertion, it is indeed strange that it has never been cited by the Krebs' or otherwise brought to the attention of the scientific community. The record shows, in fact, that: "There is no evidence of pronounced differential between the rhodanese content of comparable normal and cancerous tissue" (R 378, Att. 9 at 346).

(3) The complete breakdown of Laetrile into cyanide may require an enzyme not found in animal tissues. Hydrolysis of Laetrile by *beta*-glucuronidase (and hydrolysis of amygdalin by *beta*-glucosidase) only represents the first step in breaking down the molecules to release hydrogen cyanide and benzaldehyde (which are supposed to kill the cancer cell). The first reaction in each case would yield mandelonitrile plus (for Laetrile) glucuronic acid or (for amygdalin) glucose. Mandelonitrile must then be hydrolyzed or broken down to yield hydrogen cyanide and benzaldehyde (R 416 at ¶ 8).

Enzymes present in apricot kernels (specifically oxynitrilase) will hydrolyze mandelonitrile to cyanide and benzaldehyde, but this enzyme is not reported to exist in animal tissues (R 399 at ¶ 7B). Nor does the record show that any other enzyme capable of breaking down the mandelonitrile exists in animal tissues (or in malignant lesions). Thus, if Laetrile were injected into the blood stream and did go to the malignant lesion, even if it were broken down into mandelonitrile and gluconic acid, it might never be further broken down to yield hydrogen cyanide and the supposed action of that substance in killing the cancer cell would never take place.

At one time, Ernst T. Krebs, Jr., apparently attempted to deal with some of these problems by separating out the elements of the apricot extract his father had prepared. The fact that both *beta*-glucosidase and oxynitrilase are present in apricot pits and thus in the extract provides the potential for the whole breakdown process to occur in the apricot extract itself at the time when it is prepared. Krebs, Jr., sought to prevent this from happening (and perhaps sought to reduce toxicity) by separating amygdalin from "emulsin" by purifying the apricot extract. Emulsin contains, among

other things, *beta*-glucosidase and *beta*-oxynitrilase (R 173, Att., "Vitamin Fraud" at 345).

Ernst T. Krebs, Jr., reportedly separated amygdalin from emulsin in 1952 and " . . . advised their administration separately in order to avoid the premature trigger-off of HCN (hydrogen cyanide) from the chemical breakdown in the somatic (or normal) tissue . . ." (R 183, Att. 7 at 23). It is further stated that by injecting the cyanogenetic glucoside (amygdalin) followed 15 minutes later by the enzyme *beta*-glucosidase a "high degree of safety" as well as cancerolytic effect was obtained (id. at 23-24).

If the *beta*-glucosidase preparation preparation reached the same area of the body that the amygdalin had reached, its presence would lead to the breakdown of amygdalin to release mandelonitrile (see R 416 at ¶ 18; R 183, Att. 7 at 31). While Ernst T. Krebs, Jr., apparently recommended that the second injection be of emulsin (R 183, Att. 7 at 23), Dr. Krebs, Sr., states that his second injection would consist only of the enzyme *beta*-glucosidase (id. at 24). If the second injection did contain emulsin, the presence of the oxynitrilase in that complex might in fact lead, assuming the emulsin caught up with the amygdalin in the body, to breakdown of the mandelonitrile to release hydrogen cyanide (and benzaldehyde). However, there is little reason to believe that this release of cyanide would occur only in or near tumor cells. (In the same article in which Ernst T. Krebs, Sr., explained the process of injecting the *beta*-glucosidase, he stated his understanding that it was the *beta*-glucuronidase "which bathed the cancer cell" that acted to break down the amygdalin (id. at 25).) It should be noted that, since the time of the 1955 pamphlet, no evidence has appeared, at least in this record, that two injections, one containing *beta*-glucosidase, are being used in Laetrile therapy.

In light of the above, one must be concerned that products are being used that contain not only amygdalin but emulsin. As the Krebs themselves recognized, unless emulsin is separated from amygdalin (both of which exist in the apricot extract), there may occur the premature trigger-off of HCN (hydrogen cyanide) from the chemical breakdown in the somatic (or normal) tissue (R 183, Att. 7 at 23). It is this type of cyanide poisoning which has occurred from ingestion of Laetrile and from eating apricot kernels. (See R 378, California Morbidity, Nov. 14, 1975, No. 45.)

It is thus clear that the theory propounded by the promoters of Laetrile is based on faulty and unproven assumptions. The invention of Laetrile as described by Krebs, Jr., and his suggestion that an injection of amygdalin be followed by an injection of emulsin were two different ways to deal with the fact that enzyme *beta*-glucosidase does not exist in human tissues. What is perhaps most important about the proffered theoretical justification for Laetrile's action

is that, even if they were accepted, they would not justify the administration of amygdalin alone.

II. THE "NEW DRUG" ISSUE

The Commissioner will now address the first of the two issues remanded to the agency: Whether Laetrile is a "new drug" within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 et seq. (hereinafter the act). Based upon a careful review of the administrative record, as detailed below, the Commissioner finds that Laetrile is not generally recognized by qualified experts as a safe and effective cancer drug. Accordingly, the Commissioner concludes as a matter of law that Laetrile is a new drug and thus subject to the premarket approval requirements of the act.

The term "new drug" is defined by section 201(p) (1) of the act (21 U.S.C. 321 (p) (1)) as follows:

Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . .

Although the act defines "new drug", it does not contain a definition of "generally recognized as safe and effective."

In 1973, the Supreme Court, in a series of four cases (*Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *Ciba Corp. v. Weinberger*, 412 U.S. 640 (1973); *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973); *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655 (1973)) involving the procedures adopted and utilized by FDA to regulate new drugs pursuant to the Drug Amendments of 1962 (76 Stat. 780), established the legal principles that are applicable and controlling here. In *Hynson*, the Court discussed "general recognition" as it pertains to the effectiveness of a drug as follows:

The thrust of § 201(p) is both qualitative and quantitative. The Act, however, nowhere defines what constitutes "general recognition" among experts. . . . We agree with FDA, however, that the statutory scheme and overriding purpose of the 1962 amendments compel the conclusion that the hurdle of "general recognition" of effectiveness requires at least "substantial evidence" of effectiveness for approval of an NDA. In the absence of any evidence of adequate and well-controlled investigation supporting the efficacy of (a drug), a fortiori (that drug) would be a "new drug" subject to the provisions of the Act. 412 U.S. at 629-30.

We accordingly have concluded that a drug can be "generally recognized" by experts as effective for intended use within the meaning of the Act only when that expert consensus is founded upon "substantial evidence" as defined in § 505(d). 412 U.S. at 632.

The term "substantial evidence" is defined in the last sentence of section 505 (d), 21 U.S.C. 355(d), as:

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scien-

tific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

In *Bentex*, based upon its discussion of the term "general recognition" in *Hynson*, the Court concluded:

Whether a particular drug is a "new drug" depends in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by substantial support in scientific literature. 412 U.S. at 652.

It accordingly held that "the reach of scientific inquiry under both section 505 (d) and under section 201(p) is precisely the same" (id.).³

The requirements that a drug have not only controlled clinical investigations but also publication of the studies concerning it in the scientific literature are designed to assure that the community of qualified experts in general is aware of the data concerning the drug. Thus, one could not obtain general recognition just by doing the required studies without publishing them in the scientific literature, making them available to other scientists. (Studies submitted to scientific publications must undergo peer review before they are published. A study published in a scientific journal is thus more likely to form a basis for expert recognition than is one published by the lay press.) A practical effect of the statutory system, as the Supreme Court acknowledged in *Hynson*, supra, is that drugs will have accumulated for themselves sufficient scientific evidence to justify approval of an NDA "long before they are in a position to drop out of active regulation by ceasing to be a 'new drug'" (412 U.S. at 631).

Under the Supreme Court's authoritative interpretation of the act, therefore, general recognition of the safety and effectiveness of Laetrile depends upon two criteria: (1) Controlled clinical investigations conducted by qualified experts establishing the safety and effectiveness of the drug and published in the scientific literature, and (2) expert consensus, based upon that evidence, that the drug is safe and effective. Both requirements must be met in order for Laetrile to escape the need for premarket approval under the act; however, a finding of a failure to meet either set of requirements is sufficient to classify the drug as a new drug.

With respect to the first criterion, the safety of Laetrile must be established by adequate tests by all methods reasonably

³Section 505(d) of the act (21 U.S.C. 355 (d)) sets forth the standards applicable to obtain marketing approval of a new drug. With respect to reports of investigations which are required to be submitted concerning the safety of a drug, the act provides that such reports must include "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof".

applicable (see 21 U.S.C. 355(d); 21 CFR 314.111(a)(1)). In addition, the effectiveness of Laetrile must be established by "substantial evidence," which the statute (21 U.S.C. 355(d)) defines as evidence consisting of adequate and well-controlled clinical investigations. (Clinical investigations are studies involving human beings as test subjects.) The requirements for an adequate and well-controlled clinical investigation are set forth in 21 CFR 314.111(a)(5) (see discussion below). Both types of testing must be available to the community of experts in the evaluation of drug safety and effectiveness by means of publication in the scientific literature.

For satisfaction of the second criterion, a showing must be made of recognition among the qualified experts which is "general." It has been held that a genuine difference of opinion among experts on the question of general recognition is sufficient to show that such recognition of a drug's safety does not exist (see *United States v. An Article of Drug, Etc.*, 294 F. Supp. 1307, 1311 (N.D. Ga. 1968) aff'd 415 F. 2d 390 (5th Cir. 1969); *United States v. 354 Bulk Cartons, Etc.*, 178 F. Supp. 847, 853 (D.N.J. 1959); *Merritt Corp. v. Folsom*, 165 F. Supp. 418, 421 (D.D.C. 1958)). This interpretation of "general recognition" has been criticized as requiring "unanimous" recognition (see *United States v. 7 Cartons, More or Less, Etc.*, 293 F. Supp. 660, 662-63 (S.D. Ill. 1968) aff'd 424 F. 2d 1364 (7th Cir. 1970). For purposes of completeness, the Commissioner in his opinion will consider "general recognition" to require, as the 7 Cartons Court suggested, recognition "extensively, though not universally; most frequently, but not without exception" (id.).

A. GENERAL RECOGNITION OF EFFECTIVENESS

1. Objective Evidence of Effectiveness

The Courts thus have determined that, as a matter of law, no "general recognition" of a drug's effectiveness can exist absent adequate and well-controlled clinical investigations and substantial support in the scientific literature. There are no clinical investigations of Laetrile's effectiveness, published or otherwise, which are even arguably adequate and well-controlled. (See, e.g., R 185 at ¶ 19; R 186 at ¶ 12; R 390 at ¶ 19). For this reason, Laetrile cannot escape "new drug" status as "generally recognized" as safe and effective. It is thus a new drug without an approved new drug application whose sale or distribution, where interstate commerce is involved, is illegal.

There is, however, an apparent public lack of understanding of what the required studies consist of and why they are required. The Commissioner will thus include in this opinion a discussion of what adequate and well-controlled studies are and why they are needed. He will then discuss the deficient "evidence" of effectiveness submitted by Laetrile's proponents.

(a). *What Are the Required Studies.* "(A) adequate and well-controlled clinical investigations," as those terms are used

in the act (21 U.S.C. 355(d)) are defined in detail by regulation (21 CFR 314.111(a)(5)(ii)). These regulations, discussed with approval by the Supreme Court in *Weinberger v. Hynson, Westcott & Dunning, Inc.*, supra, 412 U.S. at 617-19, were upheld in *Upjohn v. Finch*, 422 F.2d 944 (6th Cir. 1970) and *Pharmaceutical Manufacturers Ass'n v. Richardson*, 318 F. Supp. 301 (D. Del. 1970). Simply stated, such investigations are designed to determine whether an improvement noted after administration of a drug is in response to the drug or whether it is caused by some other factor. To do this, patients as nearly identical in their disease state as possible are divided into groups and treated, insofar as possible, exactly the same in all respects except one: One group receives the test drug; the other receives a placebo (a substance that looks just like the test drug but is not a drug). Since a patient might feel better through knowledge of receiving the test drug, and since the investigator might subconsciously record better results because of the knowledge that he or she were administering the test drug, the experiment is "double-blind": Neither the patient nor the investigator knows until after the experiment which patient is getting the test drug and which the placebo. If, at the end of the investigation, the patients receiving the drug did better than those not receiving it, one can be fairly certain that it was the drug and not some other factor that caused the improvement.

(b) *The Need for Controlled Studies.* In 1962, the Congress of the United States, after extensive hearings,⁴ concluded that testimonial evidence of a drug's effectiveness—even including testimonials and illustrative "case histories" by physicians—was simply not reliable. It passed the law requiring that effectiveness be shown by "adequate and well-controlled clinical investigations" which is discussed elsewhere in this opinion.

The Supreme Court examined this issue closely in 1973 and determined that Congress' decision and FDA's enforcement of that decision were supported by the evidence elicited at the congressional hearings:

(The FDA's strict and demanding standards, barring anecdotal evidence indicating that doctors "believe" in the efficacy of a drug, are amply justified by the legislative history. The hearings underlying the 1962 Act show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous. (Emphasis added.)

Weinberger v. Hynson, Westcott & Dunning, Inc., supra, 412 U.S. at 619. It noted:

the conclusion of Congress, based upon hearings, that clinical impressions of practicing

⁴ See, e.g., Hearings on S. 1552 before the Subcommittee on Antitrust and Monopoly of the Senate Committee on the Judiciary, 87th Cong., 1st Sess., pt. 1, at 195, 282, 411-12. For a detailed discussion of the Congressional decision in 1962 to require adequate testing of drugs' effectiveness, see *Pharmaceutical Manufacturers Ass'n v. Richardson*, supra, 318 F. Supp. at 306 et seq.

physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy.

(id., 412 U.S. at 630).

Since both the Congress and the Supreme Court have spoken on this question, no further discussion by the Commissioner of the need for adequate and well-controlled studies,⁵ rather than reliance on testimonial evidence, to show a drug's effectiveness is legally necessary. However, there is a continued public belief in testimonial or anecdotal evidence, fostered even by the lawyer of one of Laetrile's supporters. (See oral argument of Kenneth Coe, in which he contends that the safety and effectiveness of Laetrile has been shown by "anecdotes of people who have been diagnosed as terminal with cancer, anecdotes of people who have been cured of cancer, anecdotes of people who are walking around today, that are here today—well" (Tr. at 453). For this reason, the Commissioner will discuss the evidence in the record illustrating the need for scientific studies to show a drug's effectiveness.

In his affidavit (R 175, Ex. A at ¶ 3), Dr. William Beaver, an expert in drug testing, notes that critics of well-controlled studies "often point out the undisputed fact that great strides have been made in therapy in the past without the benefit of this experimental device, but simply on the basis of the uncontrolled observations of astute clinicians * * *". (However), these critics often fail to mention the thousands of drugs which, on the basis of "clinical experience," were once accorded an "indispensable place" in therapy, and which are now known to be useless." Dr. Beaver states (id., at ¶ 4): "The function of the controlled clinical trial is not the 'discovery' of a new drug or therapy. Discoveries are made in the animal laboratory, by chance observation, or at the bedside by an astute clinician. The function of the formal controlled clinical trial is to separate the relative handful of discoveries which prove to be true advances in therapy from a legion of false leads and unverifiable clinical impressions, and to delineate in a scientific way the extent of and the limitations which attend the effectiveness of drugs." See also affidavit of Bryant L. Jones (R 431 at ¶ 8): "Most medical mistakes of past centuries were a direct result of beliefs that were predicated on conviction rather than evidence. Most medical advances in modern times can be traced directly to the scientists insistence on valid scientific evidence to support use of today's drugs."

Because of the insidious nature of cancer, it is all the more important that the effectiveness of a drug purported to be useful in the treatment of cancer be demonstrated by well-controlled clinical studies and not solely by testimonials or anecdotes. Cancers in humans vary greatly in their behavior, i.e., their rate

⁵ It should be noted that other types of testing are required to show a drug's safety, some of which must be completed before clinical investigations to show effectiveness can begin. (See 21 U.S.C. 355(d).)

of growth, pattern of spread, effects on the normal organs of the person, and the types of clinical symptoms or signs they produce. There is wide variability in the pattern of spread and the outcome for an individual. The effects of cancer on an individual have an element of randomness, that is, an element of chance. Physicians are therefore simply unable to predict the outcome of any cancer at any stage of development with great accuracy. Patients with terrible and widely spread cancer will occasionally have miraculous or unexpected remissions of the disease. Untrained clinical investigators who administer any remedy to a large enough group of patients with cancer will ultimately observe a miraculous outcome. This apparently miraculous outcome may well mislead the untrained investigator into belief that the remedy was responsible for the result (R 390 at ¶ 14-15).

It has been noted above that, in an adequate and well-controlled study, neither the patient nor the investigator is told that the test drug is being administered because, if they knew, they might report results based merely on high expectations. This problem of assigning improvement to a drug when the improvement was simply a result of high expectations is known as the problem of the "placebo effect." The placebo effect is particularly common in cancer patients. A study of the placebo effect among 288 cancer patients undergoing controlled trials of oral analgesics showed that 112 patients received 50 percent or greater relief from placebo (i.e., non-drug formulations (R 186 at ¶ 13)).

In his affidavit (R 185 at ¶ 20f) Dr. Daniel S. Martin states: "Humans are very susceptible, particularly when ill and desperate with hope, to the power of positive suggestion—namely, when given a 'drug' by an authority figure (e.g., a physician) with the firm statement and promise they will now begin to feel better, to have pain relief, to eat better, and to get well, these hopeful patients frequently do just what they have been told to expect." This, Dr. Martin states "is termed the placebo effect." Dr. Martin also explains that "Cancer is a chronic disease which some patients can live with for years before dying of the disease. During this slow death there are periods of 'ups' as well as 'downs,' and it is not surprising to have a Laetrile patient ascribe the 'up' to Laetrile, when it was merely coincidental timing" (id.). Similarly, Dr. Carl M. Leventhal states (R 184 at ¶ 7): "(P)sychogenic responses, popularly known as the placebo effect, are well documented and have been shown to occur from 30 to 70 percent of patients who are treated for pain."

The need for controlled testing as opposed to testimonial or anecdotal evidence of effectiveness is well-recognized by experts in the evaluation and use of drugs. As Dr. Bayard H. Morrison states: "The problem is the anecdote doesn't permit you to know what happened yesterday. It doesn't permit you to know what is really going on today and cer-

tainly it doesn't give you any insight at all in what will happen to a given patient tomorrow, next week, or next year. To really know what a drug, any treatment, does to a patient you have to be able to evaluate him in the context of a large group whose disease you can follow carefully over a considerable period of time" (Tr. at 150).

(c) *The "Evidence" of Laetrile's Effectiveness.* (1) *Case Reports.*—The proponents of Laetrile (or amygdalin) have not submitted anything to the record that could be characterized as an adequate and well-controlled clinical study of Laetrile. In the regulation which defines adequate and well-controlled clinical investigations, it is clearly stated that: "Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered," even as corroborative evidence for adequate and well-controlled studies (21 CFR 314.111(a)(5)(ii)(c)). Yet that kind of report is the only "evidence" of Laetrile's effectiveness which has been submitted.

Because of the possible public belief in this kind of report, the Commissioner will discuss those submitted to this record. In addition, evaluations, submitted to the record, of earlier "case histories" or testimonials relating to use of Laetrile will be discussed.

(a) Reports Submitted to This Record

(1) Dr. Binzel

Phillip E. Binzel, Jr., M.D., Scientific Advisor to the Committee for Freedom of Choice, and in private practice as a family physician since 1955, appeared at the hearing to make an oral presentation (Tr. at 360-364) and to submit written testimony (Tr. Ex. 13). Dr. Binzel's submission at the hearing (id.) was a report of a study he conducted on more than 200 cancer patients to whom he administered a nutritional program, including Laetrile. Dr. Binzel stated that he had excluded from his report the following patients: "1: Those who were alive but who had been under treatment for less than 4 months. 2: Those who had died within the first 3 months of treatment. These are the patients whose disease was already too far advanced for any form of treatment to be beneficial 3: Those on whom there is not sufficiently adequate follow-up information to know for certain what their present condition is" (id.).

After the above exclusions, there remained 107 patients in Dr. Binzel's study who had been treated between 4 months and 2½ years and who, according to Dr. Binzel, "are spread pretty equally throughout those time periods" (id.). He reported that 57 patients had primary carcinoma, and 50 patients had proven metastatic carcinoma at the time they started "nutritional therapy" (id.).

Dr. Binzel's exclusion from his study of patients for whom adequate followup information could not be obtained can be expected to exclude those patients who were dissatisfied with Laetrile treatment and left his care. That exclusion, together with the exclusion from con-

sideration of patients who died within 3 months of the first treatment, would be expected to bias the study in favor of effectiveness.

Dr. Binzel states that he "did not attempt to differentiate between those patients who have had surgery and/or cobalt and/or chemotherapy and those who had none of these 'conventional' treatment" (Tr. Ex. 13, "Nutrition and the Cancer Patient" at 2). This, as Dr. Binzel notes, presents a "very valid question." Without knowing whether the patients in whom he saw improvement had had other, recognized effective, treatments, his conclusions cannot be evaluated (cf. 21 CFR 314.11(a)(5)(ii)(a)(2)(iii)).

Dr. Binzel's three-page "study," which was submitted without supporting documentation, simply lacks the details necessary to permit scientific evaluation and would not, for that reason, be considered by experts in drug evaluation even as corroborative of adequate and well-controlled studies if such studies existed (21 CFR 314.11(a)(5)(ii)(c)).

(2) Dr. Richardson

Edward Griffin, at the oral argument in this proceeding, submitted page proofs of a book entitled *Laetrile Case Histories, The Richardson Cancer Clinic Experience* by John A. Richardson and Patricia Griffin (Tr. Ex. 1). Griffin stated: "Previously the opponents of Laetrile have said that there is no evidence that Laetrile works. There has been evidence of course, known to those of us who have been close to the subject. But admittedly, there has not been a great deal of medically documented evidence open to the public. And I believe that with the publication of this book at least we will be able to put an end once and for all to this claim of there not being any evidence" (Tr. at 15-16). Dr. Richardson does not claim to have conducted a research program and his case histories in no way even approximate an adequate and well-controlled clinical investigation.

Dr. Richardson's license for the practice of medicine has been revoked by the State of California (R 183 at 13) because he was found to have discouraged patients from seeking conventional therapy and to have practiced a type of treatment of cancer patients characterized as "an extreme departure from the standard practice of medicine" (R 179, Ex. B at 5). The California State Board of Medical Quality Assurance stated that these two findings established "gross negligence" on the part of Dr. Richardson (id. at 10). Dr. Richardson did not choose to appear in the administrative proceeding in which his license was ordered revoked (id. at 1-2).

A number of obvious questions are raised by Dr. Richardson's book: (1) There is no indication in this book—nor is there in the other reports in this section—of the chemical composition of the "Laetrile" which was used. Since there are variations in the composition of the drugs called by the name "Laetrile," this fact leaves the reader with no certainty

as to what substance is claimed to be effective.

(2) The technique for selecting patients for reporting is hardly scientific. The book states: "Out of (a group of approximately 4,000 cancer patients), we selected a cross-section of about 500 for our study. We were able to establish contact and a working relationship with only about 250 of these. The cases with the weakest medical histories were discarded, as were those which were overly repetitious. The remainder (62) are contained in the study; but by no means do they represent our entire files" (Tr. Ex. 1 at 118-19).

It is absolutely incredible that anyone would expect to show the effectiveness of a drug by describing 62 out of over 4,000 patients with a selection process of the type Richardson describes. The Commissioner has no means of knowing what happened to the other 3,938 or more patients. No details are given to show how the 500 patients representing a "cross-section" of the 4,000 were chosen. The failure "to establish contact and a working relationship" with half of the patients that were chosen illustrates a serious lack of followup. Logic suggests that those patients who were not benefited by Laetrile would be less likely to be willing to develop a "working relationship" with Dr. Richardson's office. Clearly patients who had died would not be available for such a relationship. The discarding of weak medical histories has never been an accepted practice in the study of any drug. What constitutes the weakness of a medical history is not explained.

(3) There is some question whether what Richardson claimed to be positive effects were in fact positive. The authors admit that one of the weaknesses of the study is the shortage of cases involving 5-year survival or longer (Tr. Ex. 1 at 120).

Indeed, the case histories section of the book (Tr. Ex. 1 at 126-276) list for each of the 13 different groupings of cancer the expected death rate for those cancers in terms of percentage survival over a set number of years, usually 5 years. Many of the patients simply had not survived long enough at the time of the book's writing to constitute successes.

For example, six cases of female breast cancer are reported (Tr. Ex. 1 at 126-137). According to Dr. Richardson, these women have received metabolic therapy, including Laetrile, for periods varying from 13 to 32 months with an average of less than 21 months. Since Dr. Richardson states (Tr. Ex. 1 at 126): "Two out of every 3 patients with cancer of the breast who do not use Laetrile but choose instead to submit to orthodox therapies will be dead within five years," the fact that he has six patients who have survived 13 to 32 months with a mean of less than 21 months does not provide any evidence of the effectiveness of Dr. Richardson's treatment.

Dr. Richardson recognizes that some of the patients whom he has selected may not have had cancer. See, e.g., Tr. Ex. 1 at 148, patient B1381 where Dr. Richardson, in discussing the chest x-rays of a

patient, states that the period of May 73 to January 77 represented: "A three-and-one-half-year remission of probable cancer of the lung." (Emphasis added). For several other patients, Dr. Richardson does not quote from the pathology report but merely reports that such a report was positive for cancer (see, e.g., patient P131B (Tr. Ex. 1 at 167)).

(4) Dr. Richardson relies in many instances upon what patients have told him about their medical histories, either orally or in writing. Some patient reports upon which he relies are hardly credible. (See, e.g., patient C106MA (Tr. Ex. 1 at 146): "The patient states the local doctors strongly recommended removal of both lungs and the permanent hospitalization of the patient, who then would be forever dependent on machines to do her breathing.")

(5) Some patient reports are so sketchy as to provide no basis for any conclusion. See, e.g., patient B144J (Tr. Ex. 1 at 202-203): There is no information regarding how the diagnosis of cancer was made. There is no indication that Dr. Richardson ever characterized the size of the tumor or whether he relied on the patient's description. There is no indication whether the patient had received any Laetrile since January 1970. There is no indication that there has been any contact with the patient since February 1976.

(6) As noted above, for each of the 13 groups of cancer which Dr. Richardson has used in his book he cites the anticipated fatality rates for patients receiving only orthodox treatment. As discussed elsewhere in this opinion, cancers are very different in their behavior, i.e., their rate of growth, their pattern of spread, their effects on the normal organs of the person and the types of clinical symptoms or signs that they produce (R 390 at ¶ 14). Experts in the testing of cancer drugs stress that the effects of cancer on a person have an element of randomness and that the ability to predict the outcome of any cancer at any stage of development varies (id.). In light of the regularity with which cancer patients' diseases vary from their expected courses, it would have been surprising if Dr. Richardson were unable to report that 62 out of 4,000 (c. 1½ percent) of patients he saw had remissions for periods of up to, but often much shorter than, 5 years.

Thus, the Richardson book is not only not the kind of adequate and well-controlled clinical investigation necessary to show the effectiveness of a drug, it is not even on its face a particularly credible recounting of medical case histories.

(3) Dr. McDonald

Lawrence Patton McDonald, M.D., a urologist, and a member of the United States House of Representatives, submitted a statement in which he reported the following observations after treating almost 200 cancer patients (R 509 at 3):

"(1) Most patients had proven cancer and had had surgery and radiation and/or chemotherapy. Most cases would

have been hopeless by routine medical standards.

"(2) Perhaps 30-35% received minimal to no benefit from the program.

"(3) Approximately 40-45% received notable benefits from the program such as improved appetite, improved interest in life, weight gain, lessening or cessation of pain. This category ultimately died but were individually pleased with their improvements.

"(4) About 20% were in the category of marked improvement. In some cases this has been miraculous with these same patients doing very well today."

Dr. McDonald provided no details whatsoever other than those quoted above. Dr. McDonald's report was not, nor does it appear to have been submitted as, an adequate and well-controlled clinical investigation.

(4) Dr. Soto

Although Dr. Mario H. Soto appeared and testified (Tr. at 478-481) on the oral argument and was given an opportunity (Tr. at 481) to submit for the record data from his treatment of cancer patients with Laetrile, no data have been received from him.

(b) Case Reports Evaluated Previously

Much of the evaluation of case reports has been done in California, where Laetrile originated and was, along with a number of other "unproven" remedies, responsible for the 1959 passage of a State law aimed at cancer quackery. In 1952, the Cancer Commission of the California Medical Association collected information on 44 patients treated with Laetrile, all of whom either had active disease or were dead of their disease, with 1 exception. In some instances, the members of the Cancer Commission had the opportunity of seeing the patients thus treated. The conclusions of the Cancer Commission were that, of those alive with disease at the time of the study, no patient had been found with objective evidence of control of cancer under treatment with Laetrile. Nine patients who died from cancer after treatment with Laetrile were autopsied. Histological studies done for the Commission by five different pathologists showed no evidence of any chemotherapeutic effect (R 378, Att. 15 at 320-326; R 183, Att. 16 at 2-19 and App. 2-3).

In June 1962, the Cancer Advisory Council of the State of California Department of Public Health examined a total of 35 case histories of cancer patients treated with Laetrile. The Council unanimously judged these cases inadequate for any critical evaluation of Laetrile. "Many of the cases had received orthodox treatment; objective evidence of benefit was absent or insufficient, most of the documentation (dealt) with subjective improvement; some contained no pathological proof of malignancy; many were 1961 cases without followup; the duration of treatment was frequently unknown because the data reported the period of hospitalization only and often discharge dates were not shown" (R 183, Att. 16 at 30-31).

Thirty-six clinical records translated into English from the French were evaluated by the Cancer Advisory Council in December 1962. The Council reached the following conclusions:

1. The records failed to indicate that the patients treated with Laetrile secured either palliation or regression of their cancerous affliction as a result of the therapy.
2. In several instances, there was absolutely no evidence presented as to the response of the patient to the therapy.
3. In other instances, objective evidence documenting the statement of benefits, was not provided.
4. In one group of 17 of these cases, sufficient followup was absent. The longest period of followup was 14 months, 12 days and 23 days of hospitalization. The next longest was 381 days and the last was 127.
5. Results which were reported as "improved" were without meaning since no criteria, subjective or objective, were provided.
6. The evidence presented lends no credence to the alleged efficacy of Laetrile and Vitamin B₁₂ in the treatment, durative or palliative, of advanced cancer (R 183), Att. 16 at 34-35).

In preparing its 1963 report, the Cancer Advisory Council also reviewed about 16 pounds of documentary material delivered by Laetrile proponents. The material contained a total of 63 case histories, 15 of which were submitted by two doctors in the United States (Dr. Ray Evers, Allusia, Ala., and Dr. John R. Morrone, Jersey City, N.J.).

The opinion [of the Cancer Advisory Council] on review of these cases is that they give no credence to the claimed curative effects of Laetrile in human cancer nor in those animal cancers where it had been investigated. The evidence of palliative response, both subjective and objective, is tenuous and poorly documented. Except in the cases in which death intervened and one or two others in which there was questionable diagnosis of cancer, no followup has been recorded, with the result that the final outcome of the cases is not recorded (R 183, Att. 16 at 35-36).

In January 1963, the McNaughton Foundation and the North End Medical Center, both in Montreal, Canada, submitted to the Cancer Advisory Council of the California State Department of Public Health a total of 14 clinical records on patients treated with Laetrile. These were not complete records but were abstracts furnished by various hospitals in Canada to the McNaughton Foundation. The Cancer Advisory Council appointed a committee of three physicians highly qualified and actively engaged in the treatment of cancer to review and evaluate these records. Each physician made an independent evaluation.

The committee reported: "These 14 records provided by the McNaughton Foundation were examined and fail to indicate that the patient treated with Laetrile secured either palliation or regression of their cancerous affliction as a consequence of the therapy. In several instances, there is absolutely no evidence presented as to the response of the patient to the therapy and in other instances objective evidence which documents claims of benefit is not provided.

It is concluded from careful review of these records that they are inadequate as reports of therapeutic use of Laetrile, and they do not indicate that therapeutic benefit resulted from treatment with Laetrile, and do not indicate that this agent is of value in the treatment, cure, or palliation of cancer. In only one instance is there a statement by the examining physician indicating that a definite beneficial effect from Laetrile *might* have occurred" (emphasis in original) (R 378, Att. 14 at 26).

In 1971-72, the FDA, together with the National Cancer Institute, investigated and evaluated 12 clinical histories submitted by Dr. Ernesto Contreras of Mexico covering his experience with Laetrile in the treatment of cancer (see R 184, Ex. 3). FDA was able to obtain documentation covering the full course of the disease in 7 of the 12 case reports. All seven patients whose records were reviewed had received treatment other than Laetrile, including surgery, chemotherapy, or radiotherapy, or more than one of these approaches, either before, after, or concurrently with Laetrile therapy (R 184, Ex. 3; R 198 at 9-10).

Most of the alleged improvements stated, in the 7 case reports which could be evaluated, to be associated with Laetrile treatment have been found to be associated with one or more of the following events in the patient's disease (see R 183, Att. 16 at 10-11):

- a. *Subjective improvement* was interpreted as being evidence of the agent's affecting the neoplasm, rather than being due to the general effect on the host, whether by metabolic or psychologic reasons.
- b. *Phases in the natural history of malignant neoplasm* not infrequently observed in patients who are receiving no treatment whatever were interpreted as being due to the therapy employed (emphasis in original). * * * (For example,) occasional patients with widespread peritoneal carcinomatosis will exhibit regression of their disease following simple exploratory procedures.
- c. Patients reported as showing regression of cancer with Laetrile were either receiving concurrent treatment by other methods, or had in their recent past been treated by some (orthodox therapy) and were exhibiting a degree of control of their disease *entirely attributable to the previous treatment* (Emphasis in original). * * *
- d. A few of the patients treated did not have proof of the presence of cancer in the form of histological diagnoses, the evidence being more or less inferential, as radiographic observation of lesions in the lung, or a surgeon's diagnosis of a lesion as cancerous on observations of gross pathology at operation, without confirmation with biopsy.
- e. Very few of the clinical records to which the Cancer Commission had access contained any sort of satisfactory evidence as to objective, accurate evaluation of the progress of the primary neoplasm or its metastases while under treatment.

(ii) *Animal Testing of Laetrile.*—As indicated elsewhere in this opinion, general recognition of Laetrile's effectiveness among experts in the evaluation of drug effectiveness could only be based upon adequate and well-controlled clinical (i.e., human) investigations. Thus, even if Laetrile had been shown to be effective in animal test systems, and the

Commissioner concludes it has not, that fact would not remove Laetrile from the category of "new drug."

Nevertheless, in the interest of providing the public with all the information available in the record concerning this drug, the Commissioner will discuss the animal tests done with amygdalin about which there is controversy. Amygdalin has been extensively tested in animal systems. From the tests done, Dr. Dean Burk, president of the Dean Burk Foundation, Inc., has selected three tests done in the United States as showing a positive effect (R 302). In each case the laboratories which ran the tests found them to be negative. Dr. Burk also cites two foreign reports, one of which was not published (id.). His contentions, and the evidence relating to each in the record, will be discussed point by point and other animal testing done with the drug will be noted.

(a) Tests Claimed to Show a Positive Effect

(1) Sloan-Kettering

Dr. Burk includes the following in his list of animal studies showing a positive effect for amygdalin:

Sloan-Kettering Cancer Center (New York), with CD₁F₁ mice bearing spontaneous mammary carcinomas: Inhibition of formation of lung metastases, inhibition of growth of primary tumors, and greater health and appearance of animal hosts, upon treatment with 1-2 gm crystalline amygdalin/kg body weight/day (Report of K. Suglura, June 13, 1973) (R 302, Ex. A at 15).

Regarding the studies conducted at Sloan-Kettering, C. Chester Stock, Ph. D., Vice President and Associate Director for Administrative and Academic Affairs, Sloan-Kettering Institute for Cancer Research, stated in his affidavit (R 195) that:

We have tested amygdalin at high doses, 1000 mg/k/day, in over a dozen transplantable tumor systems and one induced tumor system without seeing any action against the tumors. The chemotherapeutic agents effective in clinical cancer have had or would have had their activities detected in one or more of those systems.

In spite of demonstrated utility of transplanted experimental animal tumor systems, some individuals believe that use of spontaneous animal tumors is more appropriate for seeking drugs for use in man. It was considered that this would be true of the advocates of the use of Laetrile who believe it needs to be used for relatively long periods of time.

Consequently, Dr. K. Suglura in my laboratory looked for the effects of amygdalin on the growth of spontaneous mammary tumors in CD₁F₁ mice and also on metastatic spread to lungs of the hosts. Early observations of Suglura featured an apparent inhibition of the appearance of metastases in the lungs of mice given daily (except Sunday) doses of 2000 mg/k of amygdalin in his 3 initial experiments. The treated mice showed lung metastases in 20% while 80% of the controls had metastases. The mice had been injected until death or until the primary tumors were over 2.5 cm in diameter. The data from these experiments were leaked to the press unfortunately before they could be checked adequately. Subsequent experiments, in some of which Dr. Suglura participated, some conducted with Dr. Daniel Martin of the Catho-

lic Medical Center of Brooklyn and Queens and some which were independent by other investigators in our Institute, showed that the initial results were not consistently observable. In some experiments there were more metastatic mice in the treated than in the control mice. In the latest experiment in which Dr. Sugiura read the lungs of the mice without knowing what treatment they had received, there was essentially no difference found between the treated and control groups (R 195 at ¶ 10).

In his affidavit (R 185), Daniel S. Martin, M.D., states that: "My laboratory's tests with Laetrile demonstrated Laetrile to be without effect (on spontaneous tumors in experimental animals). Further, these negative tests on these animal tumors were confirmed by three other investigators at Memorial Sloan-Kettering Cancer Center in New York. One of the latter investigators (Dr. K. Sugiura) reported his initial experiments to demonstrate Laetrile to have anti-cancer activity, but his subsequent results were negative. A degree of variability in results is common in biological research, and the final opinion is based on whatever the majority of the findings are. In this instance, the totality of the data clearly and unequivocally reveals Laetrile to be without anti-cancer activity" (R 185 at ¶ 21 (c-d)).

(2) Southern Research Institute

Dr. Burk's citations continue:

Southern Research Institute (Birmingham, Alabama) for the National Cancer Institute, in a majority of 280 BDF mice bearing Lewis lung cancers, treated with up to 400 mg crystalline amygdalin per kg body weight, with respect to increased life span (Report, December 3, 1974) (R 302, Ex. A at 15).

The results of two studies conducted by Southern Research Institute for the National Cancer Institute were published in the scientific literature in 1975. One of the studies involved an experiment "in which four transplantable rodent tumors (L1210 lymphoid leukemia, P388 lymphocytic leukemia, B16 melanoma, and Walker 256 carcinosarcoma) were used to investigate the antitumor activity of amygdalin MF . . . alone and in combination with beta-glucosidase" (R 184, Ex. 3b at 939). No antitumor activity was observed in any of the four tumor systems tested with amygdalin alone or in combination with beta-glucosidase (*id.*; see also R 173, Att., Memorandum, March 12, 1973).

The second study, in which amygdalin MF (i.e., amygdalin provided by the McNaughton Foundation) was evaluated alone or in combination with beta-glucosidase against three transplantable rodent tumors (Ridgeway osteogenic sarcoma, Lewis lung carcinoma, and P388 leukemia), showed that amygdalin alone or in combination with beta-glucosidase did not demonstrate antitumor activity against any of these three tumor systems (R 184, Ex. 3C at 952-53).

At the oral argument, Bayard H. Morrison, M.D., Assistant Director at the National Cancer Institute stated that the Institute:

has sponsored—other organizations have conducted—tests of Laetrile at various dose

age levels in a variety of animal tumor systems, probably exceeding 15 or more, probably closer to 20.

This indeed really is about the most extensive that NCI and other laboratories in the aggregate have tested of essentially a non-active substance. For in all of these tests which include tumors ranging from carcinomas, sarcomas, lymphomas, any kind of tumor which parallels to a large degree the human type of tumor, the results have been essentially negative. There have been occasional, marginal evidences of activity which have not been reproducible.

So, in balance, Laetrile has failed the test of demonstrating activity in the preclinical animal tumor systems that we know now predict for activity in human cancer.

And I should add that of the 30 or 40 drugs that are now regularly available and known to have effect in certain forms of human cancer, all of these drugs have demonstrated activity, significant activity, in one or more of these animal tumor systems (Tr. at 146A-47).

The proponents of Laetrile question the statistical controls and experimental design employed in the studies conducted by Southern Research Institute (see R 302, Ex. E). They suggest the utilization of methods of statistical analysis developed for use in judging results obtained with physical, rather than biological, systems. One of the research scientists at the National Cancer Institute responsible for the studies conducted by Southern Research Institute points out that "[t]he variation in all biological systems is far greater than that involving physical phenomena" (R 438 at 1). He suggests that it is, for that reason, not possible to use the internal statistical analyses suggested by the proponents of Laetrile (*id.*).

(3) Scind Laboratories

Dr. Burk's third reference is:

Scind Laboratories, University of San Francisco, 400 rats bearing Walker 256 carcinoma (200 treated with amygdalin, 200 controls), with 80 percent increase in life span at optimum dosages (500 mg amygdalin/kg body weight) (October 10, 1968). Cf. FDA-IND application No. 6734, pp. 247-8, 00080-00093 (R 302, Ex. A at 15).

The Scind Laboratory data were submitted to FDA in support of the McNaughton Foundation's IND for amygdalin in 1970. An ad hoc committee of cancer experts evaluated these data during its review of the IND. In its report, the Committee stated: "We are particularly cognizant of the lack of adequate evidence of *in vivo* antineoplastic characteristics. The Scind Laboratory data in the initial submission of IND 6734, April 6, 1970, concerning two experiments with a Walker 256 system are considered unacceptable because of inadequate documentation of status of animals, percentage of tumor take, rate of growth, and accounting for acute deaths[,] and the other substantial lack is a statistical analysis. Scind Laboratory, in a letter dated October 18, 1968, filed with [an] October 31, 1970, amendment, states 'Laetrile, when administered without Beta glucosidase has little or no effect upon transplanted rodent tumor systems tested.' (emphasis theirs [i.e., Scind Laboratory's])" (R 184, Ex. 2 at 1).

(4) Pasteur Institute

Dr. Burk's fourth reference is:

Pasteur Institute (Paris), with human cancer strain maintained in mice treated at optimal dosage of 500 mg Amygdalin Mar-san/kg body weight/day; increased life span and delayed tumor growth up to 100 percent (Dec. 6, 1971 report by M. Metianu) (R 302, Ex. A at 15).

In a sworn affidavit (R 422), a medical officer in the Bureau of Drugs, who is trained in medicine and experienced in scientific research and who is fluent in both French and German, commented on the cited studies conducted at the Pasteur Institute in Paris and the Institute von Ardenne in Dresden (see discussion below).

The medical officer, through the American Embassy in Paris, learned that the report entitled, "Anti-Tumor Toxicity and Activity" was written on the letterhead of the Institute Pasteur and was an internal report of the Institute that has never been published in any scientific journal. In the affidavit, the medical officer states that the fact that the report "represents preliminary work only and has not been published in any scientific journal since it was prepared six years ago raises my suspicions that the preliminary results obtained could not be reproduced" (R 422 at ¶ 6).

(5) Institut von Ardenne

The fifth reference cited by Dr. Burk is:

Institut von Ardenne (Dresden, Germany), H strain mice bearing Ehrlich ascites carcinoma treated with bitter almond amygdalin ad libitum in addition to the regular chow diet: increased life span and decreased rate of cancer growth, treatment beginning 15 days before cancer inoculation (Arch. Geschwulstforsch 42, 135-7, 1973) (R 302, Ex. A at 15).

After reviewing the article published in the Arch. Geschwulstforsch, the Bureau of Drugs medical officer made the following comments:

The author's terms (in the summary section) "feeding with bitter almonds," "prolongation of survival" (due to feeding with bitter almonds), and "inhibition of tumor growth" are not adequately defined in the subsequent text or by the content of the text and thus are uninterpretable.

The description of the methodology is deficient for a number of reasons. It fails to provide information whether the mice were kept singly or caged in groups. It fails to provide information on the techniques for demonstrating whether and how much of the bitter almonds had been eaten by each experimental mouse. It fails to inform on the origin, quality, and composition of the bitter almonds with respect to the latter alleged role of "amygdaline" and HCN. Due to these failings it is not possible to draw conclusions from any differences of events between experimental and control animals—if such differences could be demonstrated at all. The author also fails to give the age of the mice and the body weight of each individual mouse of each group and at each weighing date. The use of sole mean values in this paper is potentially misleading. (The scientific evaluation of data requires implementation of variabilities of the individual measurements.)

The author makes statements on "tumor growth" which are based on implications, indirect deductions, and on arbitrary assumptions.

The term "tumor growth" is potentially misleading for the Ehrlich ascites cancer which consists of a cancer cell suspension in the peritoneal fluid. The study fails to use precise methods of measuring the number of cancer cells present in each mouse.

In my opinion, this article fails to provide any evidence that bitter almonds are effective in inhibiting the growth of tumors (R 422 at § 7).

(b) Other Tests

As noted above, the two tests done by the Southern Research Institute and the Sloan-Kettering studies now completed have demonstrated conclusively, in the view of most experts, that amygdalin, either alone or in conjunction with the enzyme *beta*-glucosidase, exhibits no antitumor effect. These results are in accord with the negative findings of three earlier animal studies commissioned by the National Cancer Institute. Those tests are summarized in the record as follows:

1957: Amygdalin was tested with three transplanted mouse tumor systems used at the time by the NCI Cancer Chemotherapy National Service Center (CCNSC) to screen compounds for anti-cancer activity. Amygdalin produced no significant inhibition or growth of the carcinoma 775 or sarcoma 180 tumors, and produced no significant increase in the lifespan of mice with leukemia L1210 tumors.

1960: Material from a different source was tested against the same three mouse tumors. The compound failed to show antitumor activity.

1969: Amygdalin was tested alone and in combination with *beta*-glucosidase against leukemia L1210 in mice. Amygdalin was inactive against the tumor, alone and in combination with the enzyme. Toxic side effects increased when the drug and enzyme were given together (R 173, Att., "NCI Testing of Laetrile (Amygdalin)"):

A study, entitled "Failure of Amygdalin to Arrest B16 Melanoma and BW5147 AKR Leukemia," Hill et al., *Cancer Research*, 36:2102-07, June 1976, appears as Exhibit 3 to R 170. The December 9, 1976 report of yet another animal test of amygdalin is Exhibit 3D to R 184. The drug was found not to be active against human breast and colon tumor xenografts in athymic mice.

The failure of Laetrile (or amygdalin) to show any effect in animal systems is important because those systems have shown an ability to predict effectiveness in humans. See the statement of Dr. James F. Holland (R 396): "No drug has been proved active in human cancer which does not show anti-cancer activity in experimental animals. Human cells are not so different from other mammalian cancer cells that an active drug does not act on at least one other mammalian system . . . Laetrile is completely inactive against animal cancers. It has been repeatedly tested in reputable laboratories against a broad spectrum of rodent neoplasms. Inasmuch as no drug has been found active against

cancer which isn't active in the screening tumors, there is no basis to consider Laetrile a candidate chemotherapeutic compound against human cancer No scientifically accepted data whatever have been presented indicating evidence of benefit from Laetrile."

See also the statement of Dr. Bayard H. Morrison, Assistant Director of the National Cancer Institute: "[O]f the 30 or 40 drugs that are (now) regularly available and known to have effect in certain forms of human cancer all of these drugs have demonstrated activity, significant activity, in one or more of these animal tumor systems." (Tr. at 147).

One comment theorized that the reason why animal tests do not show Laetrile to have any anticancer activity is because the laboratory animals are bred to have defective immune rejection systems (R 235 at 7). This theory assumes that Laetrile is hydrolyzed by an enzyme that is in greater concentration at the cancer site than at other locations in the body. The comment explains that: "If, because of a defective immune system, laboratory animals produce no hydrolyzing enzyme at the cancer, (sic) site, that fact alone would explain why Laetrile doesn't work on laboratory animals. It can't work on any organism that has a defective immune system." (See R 235 at 7-8). No evidence has been submitted to support the comment's theory.

The Commissioner concludes that the animal studies conducted to date fail to show that Laetrile (or amygdalin) has anticancer activity in laboratory animals. As has been noted previously, even if these tests showed that the drug had anticancer activity in laboratory animals, such findings would not be relevant to the question whether it is generally recognized by qualified experts as a safe and effective anticancer drug, since general recognition must be based upon testing in human beings. The lack of positive effect in test animals is of some importance, since a clear showing of success in animals might suggest the propriety of clinical testing in humans. The failure of amygdalin to produce an anticancer effect in animals is added reason for skepticism concerning the claims that it is effective in humans.

2. Testimony of Experts

(a) *Experts Opposed to Laetrile.* The evidence that experts in the evaluation of drug safety and effectiveness do not "generally" recognize Laetrile as effective for any therapeutic use is overwhelming. (It should be remembered that for recognition to be general it must be shown that most qualified experts recognize the drug's safety and effectiveness. The fact that a few persons claiming expertise believe the drug safe and effective is thus not sufficient.) The record contains statements that Laetrile is not considered as an effective cancer therapy from several organizations with members who are experts in cancer drug evaluation—e.g., the American Cancer Society, the

American Medical Association, the Committee on Neoplastic Diseases of the American Academy of Pediatrics—and from a large number of the Nation's most eminent and well-qualified experts in the area of cancer drug evaluation. It is difficult to conceive of a clearer showing of a lack of "general" recognition of a drug's effectiveness than the expression of the views of these many experts.

The Commissioner will describe the qualifications of some of these experts and either quote from or summarize the views which they have expressed. Each of the submissions referred to contains a great deal of information concerning Laetrile and the consensus of expert opinion about it, and the following excerpts are meant only to be illustrative of the views each expert expressed:

Arthur I. Holleb, M.D., Senior Vice President for Medical Affairs, American Cancer Society, Inc., submitted an affidavit (R173). His curriculum vitae lists his membership in and leadership of several professional societies, which include the James Ewing Society and the American Radium Society. He also serves on the Cancer Commissions of the American College of Surgeons and the American College of Radiology and is editor-in-chief of CA, a cancer journal published by the American Cancer Society.

Dr. Holleb stated (R 173 at 13) that he had reviewed three basic documents attached as exhibits to his affidavit and supporting documents for these basic documents and that the information contained therein was true and correct. Submitted as an attachment to Dr. Holleb's affidavit is a "Statement Concerning Laetrile" by Frank J. Rauscher, Jr., Ph. D., Former Director, National Cancer Program, National Cancer Institute. Dr. Rauscher states, "There is no evidence that Laetrile works. Over the last decade, or more, NCI has repeatedly conducted tests of Laetrile in a variety of animal tumor systems. Most have been completely negative. The others have shown only marginal levels of activity which could not be reproduced. The animal systems used are those which have detected the active properties of the scores of drugs which, unlike Laetrile, have proven to be of demonstrable value in patients with many forms of cancer. The therapeutic benefits as well as the attending side effects of these materials have been clearly and amply documented in clinical literature based on carefully conceived, meticulously conducted and monitored clinical trials. The same cannot be said for Laetrile where clinical reports are largely anecdotal and unsubstantiated. Thus, there is no laboratory or clinical evidence of the effectiveness of Laetrile" (id. at 2).

See also testimony of R. Lee Clark, M.D., President, American Cancer Society, in which he states: "The American Cancer Society views Laetrile as having no proven value in the treatment of human cancers. The Society has made a continuing review of all the literature and other information available and finds no evidence that treatment with Laetrile results in objective benefits to

patients with cancer. Since 1956, the National Cancer Institute, in conjunction with the cancer research centers of America, has reviewed over 300,000 drugs, chemicals, antibiotics, and other agents including Laetrile to evaluate them in regard to their usefulness in cancer treatment. From this research, more than forty specific agents have been found to have an effect against cancer in animal and in man. Although several trials have been made with Laetrile, it has never been proved effective in cancer in any way whatsoever" (R 307 at 1).

Frederick N. Silverman, M.D., Chairman, Committee on Neoplastic Diseases, American Academy of Pediatrics, submitted testimony (R 233 and 317) which included the following comments from his committee: "Laetrile has never been shown to exhibit any efficacy in the treatment of neoplastic disease in children. It cannot be regarded as safe if it is used in lieu of drugs currently employed either as accepted treatment or in carefully designed investigative treatment protocols."

William R. Barclay, M.D., testified (Tr. 269-281) for the American Medical Association (AMA). The AMA supports the "FDA's contention that laetrile is a new drug and is neither generally recognized by experts as safe and effective for its purported use nor should (it) be distributed in interstate commerce until such time as its safety and efficacy for the treatment of cancer have been established through controlled preclinical and clinical studies" (Tr. at 272).

Dr. Barclay discussed (Tr. at 274) a May 1965 report in the Canadian Medical Association Journal which "concluded that laetrile could not be considered as a palliative in cancer therapy on the basis of the biological rationale advanced by the manufacturer." He further states that: "the American Cancer Society has long pointed out through its continuous reviews of the scientific literature that laetrile is not a proven or generally recognized treatment for cancer. The American Medical Association likewise views laetrile as ineffective in the treatment of cancer" (Tr. at 275-276). At its 1976 Clinical Convention, the AMA adopted the following resolution pertaining to the profession's view of Laetrile: "Resolved: That the American Medical Association continue to inform the public of the danger of delay in the diagnosis and treatment of malignancies by methods not generally recognized by the medical profession as beneficial and effective; and be it *Further resolved*, That the American Medical Association inform the public that the safety and efficacy of amygdalin for the treatment or palliation of malignancies is unproven and that the use of amygdalin in such cases exploits the victims of malignancies and their families by preying upon the emotions of the hopelessly ill, in some cases for the profit of the unscrupulous." Dr. Barclay (Tr. at 276) states: "We believe that experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs are vir-

tually unanimous in their recognition of the ineffectiveness of laetrile for the treatment of cancer." The AMA testimony concludes (Tr. 280): "It is clear that laetrile is not generally recognized by experts qualified to evaluate the safety and effectiveness of drugs as safe and effective."

W. Sherwood Lawrence, M.D., a Medical Officer of the State of California Department of Health, Public Health Division, Food and Drug Section, serves as the Executive Secretary of the State of California Cancer Advisory Council. He is the custodian of the records of the Council and is knowledgeable of the work of the Council and the study that the Council has conducted (R 183 at 1). Dr. Lawrence states (R 183 at 17): "The evaluation by the Council of all the clinical data available here and in Canada has failed to establish any evidence of clinical efficacy. The proponents have never published competent well-designed controlled clinical studies demonstrating the slightest efficacy of Laetrile in the cure, amelioration or control of cancer. Laetrile (amygdalin) is not generally recognized by qualified experts as either safe or effective in cancer therapy."

Jonathan E. Rhoads, M.D., is National Chairman of the National Cancer Advisory Board, a surgeon, former President of the American Cancer Society and a member of a number of organizations focusing on research, including the American Association for Cancer Research and the American Institute on Nutrition. He made a presentation at the oral argument (Tr. at 109-115), on behalf of himself, as a citizen, and the American Cancer Society. Dr. Rhoads stated (Tr. at 114): "The position of the American Cancer Society is that Laetrile can be toxic in some doses and some modes of administration. But that more importantly, it is unsafe because its effectiveness has not been demonstrated scientifically so that reliance on it may lead patients to forego better treatment. Laetrile certainly has not been proven effective as a cancer treatment or cure and is not generally recognized by qualified experts as safe and effective for cancer."

Jesse L. Steinfeld, M.D., is Dean of the School of Medicine, Medical College of Virginia, Richmond, Va.; he was formerly Deputy Director of the National Cancer Institute; United States Surgeon General; Deputy Assistant Secretary for Health and Scientific Affairs, Department of Health, Education, and Welfare; and Chairman of the Department of Oncology and Director of the Comprehensive Cancer Center at the Mayo Clinic. His professional experience includes over 20 years of involvement in cancer research, particularly with respect to the metabolic effects in cancer patients that occur as cancers grow and metastasize (R 194). Dr. Steinfeld was recognized as an expert in the evaluation of the safety and effectiveness of cancer drugs by the Court in *Durovic v. Richardson*, 479 F. 2d 242, 248 (7th Cir.), cert. denied 414 U.S. 944 (1973). He states that neither

amygdalin nor any other cyanogenic glycoside is generally recognized by himself or by experts generally, to be safe and effective for any medical purpose (id. at 5). Dr. Steinfeld also states: "I have reviewed the clinical records of a number of patients who have received laetrile as treatment for cancer, while I was in California. In that review, there was no evidence to support the view that laetrile was of value to cancer patients. I have reviewed the volumes of material submitted to the FDA in 1970, requesting an Investigational New Drug Application (IND) for laetrile. The application was not approved because of serious flaws or deficiencies in both the animal and human trials" (id. at 8).

Richard H. Lange, M.D., is Chief, Section of Nuclear Medicine, Ellis Hospital, Schenectady, N.Y. He submitted verified testimony (R 385) in which he cited his experience in the field of internal medicine, nuclear medicine, and his particular interests in the problem of cancer. Dr. Lange states: "When one reviews the extensive information presently available from leading experts on cancer, there is no evidence to suggest that Laetrile is in any way an effective cancer drug. * * * The theory that Laetrile is effective because it destroys cancer cells by producing a release of cyanide has never had any scientific support, nor has the newer claim in the prior approach that cancer is caused by a vitamin B-17 deficiency and that Laetrile is vitamin B-17. No scientific group has recognized Laetrile as a vitamin. * * * Evidence of an antitumor effect in animals must be suggested or proven before a drug can be used in human clinical trials. Without such proof of effectiveness, the concept of scientific investigation would be altered; the gates would be open to all sorts of quacks and utter confusion would result. Placebo effects and personal testimonials must be separated from competent objective scientific investigation which is free from bias, personal prejudice or emotional involvement" (R 385 at 1-2).

Michael B. Shimkin, M.D., is Professor of Community Medicine and Oncology, School of Medicine, University of California, San Diego, and has had 40 years of experience in cancer research, teaching, and clinical treatment of patients. He has authored or co-authored over 280 publications on clinical and laboratory cancer research (R 192). Dr. Shimkin states: "My knowledge about amygdalin ('Laetrile') spans some 30 years. At no time, nor now, has there been evidence that this material is useful in the prevention or treatment of cancer in man or in experimental animals. I know of no expert of cancer in chemotherapy who has evidence of usefulness of amygdalin in the treatment of cancer, nor of any recognized journals or textbooks in medicine that indicate such usefulness. I know of no laboratory or clinical studies of amygdalin that demonstrate scientifically any significant, repeatable benefit in animals or in man" (id. at ¶ 12).

Bernard C. Korbitz, M.D., is Chief of the Chemotherapy Section, Department of Oncology at the Radiologic Center,

Inc., Nebraska Medical Hospital, Omaha, Nebr. He has been involved in various aspects of cancer research and cancer therapy since approximately 1954. His professional training and experience includes the authorship or co-authorship of approximately 40 articles relating to cancer hematology and internal medicine (R 181). Dr. Korbitz states: "To date, there has been no bona fide or substantiated evidence that Laetrile has any significant anti-tumor effect in any of the rodent animal systems evaluated. I have reviewed reports by Dr. Navarro in the Philippine Medical Journal who purported to have produced good results in cancer patients using larger doses. In reviewing his studies there is no objective evidence to support these claims that Laetrile is effective in any dose range against cancer" (id. at 3). Dr. Korbitz also states, "There is no objective evidence of any sort from pre-clinical or sketchy clinical reports to indicate that Laetrile has any benefit in the treatment of cancer patients" (id. at 4).

Susan J. Mellette, M.D., is Associate Professor of Medical Oncology, Medical College of Virginia and has had over 20 years experience in a private practice essentially limited to patients with metastatic malignant diseases. In 1975 she was President of the American Association for Cancer Education, an organization of medical and dental school faculty interested in cancer teaching in professional schools (R 420). Dr. Mellette states, "My views on the substance Laetrile are based on reports of the ineffectiveness of amygdalin which have been published in the standard scientific literature and also on two books and other printed materials put out by proponents of Laetrile which I have read. In the latter, I have found only unsubstantiated testimonials and hearsay in the patient reports and so-called scientific arguments which reach unwarranted conclusions without appropriate experimental methodology" (R 420 at 1).

Daniel S. Martin, M.D., has been involved in general cancer research since 1946. Since 1950, he has worked in cancer chemotherapy, and since 1958 in cancer immunology as well. His professional bibliography includes over 100 publications, the vast majority of which resulted from research in cancer immunology and chemotherapy (R 185). Dr. Martin states, "The proponents of Laetrile claim that their clinical studies in cancer patients demonstrated that Laetrile often reduced the size of a malignant tumor and caused some tumors to completely regress. Evidence—none; i.e., no objective evidence to support such a claim. No 'hard' patient data, no tumor measurements of the progress of the disease state, no biochemical data, no survival data, etc. The pro-Laetrilists do not present any competent scientific evidence that Laetrile is effective for the treatment of cancer. Only testimonials—'anecdotal' evidence—are presented that the Laetrile-cancer patients and their doctors 'believe' in its efficacy. Belief, however, is not adequate for reliance of drug effi-

cacy. Only strict scientific standards should be employed; namely, adequately documented scientific, well-controlled, evidence of objective antineoplastic effects in humans. The fact that a great many cancer patients have received Laetrile and attest to its benefits is not evidence. Mere clinical experience *per se* is not a substitute for lack of appropriate objective documentation of clinical efficacy" (emphasis in original) (id. at ¶ 20e).

Harold James Wallace, Jr., M.D., is Director of Cancer Control and Rehabilitation at Roswell Park Memorial Institute, Buffalo, N.Y. He has had extensive training in the clinical pharmacology of cancer drugs and has participated directly in the clinical testing of a number of new anti-cancer drugs. He has, over the past 20 years, conducted and published the results of controlled clinical trials of drugs, radiation therapy, and other treatments of cancer (R 199). He is a cured cancer patient (Tr. at 170). Dr. Wallace states: "There is no evidence in either animal models or in the large numbers of patients who have received amygdalin that it is effective in any way in preventing cancer, causing a regression or remission of cancer, or improving the life expectancy of the cancer patient. Neither has there been any evidence that it decreases the symptoms of pain, weakness, or depression from cancer in any direct way. It is not analgesic or antiemetic in character. The anecdotal evidence claimed by amygdalin proponents has not been presented to me or to any scientific forum for critical review and these claims have not been substantiated by documentation in medical records available for review" (R 199 at ¶ 14).

John T. P. Cudmore, M.D., is a Board-certified surgeon whose professional experience includes the practice at oncology for the past 20 years. Dr. Cudmore stated that his work requires him to be acquainted with the literature related to drugs used in the treatment of cancer published in professional journals, and that he regularly attends meetings of experts at which drugs used in the treatment of cancer are discussed and evaluated (R 178). Dr. Cudmore states (id. at ¶ 10): "In my practice of oncology in San Diego since 1956, I have examined numerous patients after their treatments with amygdalin or Laetrile in nearby Tijuana, Mexico. I have never seen any evidence of cure or palliation with Laetrile. I can conclude from my personal experience that Laetrile or amygdalin is ineffective in the treatment and prevention of cancer." In support of these statements, Dr. Cudmore discusses in his affidavit the case histories of nine patients who have received Laetrile, all of whom in his opinion received no benefits therefrom. Dr. Cudmore states (id. at ¶ 8): "The composition of amygdalin is such that I do not recognize it, nor is it generally recognized by experts qualified through scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for the use in treatment or prevention of cancer."

Sidney Weinhouse, Professor of Biochemistry at Temple University School of Medicine, is a researcher in the field of cancer for the past 30 years, editor of the journal, *Cancer Research*, and a member of the Board of Directors of the American Cancer Society (R 384). He made the following statement regarding Laetrile: "Although widely touted for its curative effects on cancer for many years, there is no shred of evidence from any reputable cancer researcher that this substance has any therapeutic value. I know of no reputable scientist who has published evidence for the effectiveness of Laetrile" (id. et 1).

Bryant L. Jones, M.D., is a Medical Director in the Commissioned Corps of the United States Public Health Service (R 431). Since 1960, first in the pharmaceutical research industry and then in government, he has worked with the design and evaluation of clinical investigations, the purpose of which were to determine the safety and effectiveness of drugs (id. at ¶ 2). Dr. Jones states, "I am presently responsible for the review and evaluation of protocols and reports concerning the use of drugs subject to New Drug Applications (NDA's) and Notices of Claimed Investigational Exemption for New Drugs (IND's). I review such protocols and reports for the purpose of determining whether or not they provide scientifically acceptable standards of safety and effectiveness. I would estimate that I have reviewed several thousands such reports, most of which were and are directly related to and involve drugs intended for use in the field of oncology, which is the management of cancer" (id. at ¶ 3). Dr. Jones states, "I have made a careful review of the statements which are part of the record in this proceeding identified as:

1. Comments: C0001 through C0247.
2. Testimony: TS 01 through 14.
3. Letters: Let No. 1 through 49.
4. Oral arguments: OR 01 through 11.

(When submissions were received by the Hearing Clerk, they were assigned both a number-letter code (used here by Dr. Jones) and an R number, utilized for purposes of citation in this opinion.) I have evaluated each statement and report which purports to show that Laetrile, amygdalin, or any of the cyanogenic glycosides are safe or effective in the treatment of cancer, as a palliative, as an analgesic, or for any medical purpose. None of the statements or reports are adequate, well-controlled scientific studies. The reports I have examined fail to measure up to the principles applicable to adequate, well-controlled scientific studies in every particular. The studies not only fail to measure up to minimum standards applicable to adequate, well-controlled scientific studies, but also fail to present any scientifically acceptable, objectively documented clinical evidence of safety and effectiveness for amygdalin, Laetrile, or any cyanogenic glycoside" (id. at ¶ 6).

George J. Hill, II., M.D., is Professor and Chairman of the Department of Surgery and Associate Dean for Clinical Affairs of the Marshall University School

of Medicine, Huntington, West Virginia (R 170). His professional duties involve the medical management of cancer and require that he be familiar with drugs that are generally recognized as safe and effective in treating cancer. He keeps abreast of the consensus of informed opinion by reading medical literature concerning cancer and its management, by attending meetings of experts where methods of treatment that are recognized as safe and effective are described and discussed, and through teaching, conducting research, and exchanging views with his colleagues who are experts in the field (id. at ¶ 12). He has himself conducted studies on amygdalin, the reports of which have been published and are attached as Exhibits 2 and 3 to his affidavit. He states, "In the course of my investigation of amygdalin's potential as an antitumor agent, an extensive review of both popular and scientific literature relating to it and Laetrile was conducted. Most reports in the scientific literature supporting Laetrile have appeared in foreign medical journals. Only one preliminary report purporting to support use of Laetrile was found in an American journal. The favorable reports concerning clinical use of Laetrile or amygdalin were testimonials based on individual case reports. There were no adequate, well-controlled clinical studies which demonstrated or purported to demonstrate that amygdalin or Laetrile were safe and effective for use in the medical management of cancer. Neither were there any favorable clinical reports in which an attempt was made to measure any objective parameters for adequate periods of followup to determine any possible drug-induced effect. The literature also contains reports concerning a limited number of carefully monitored clinical cases in which use of amygdalin failed to result in any objective benefit in the management of cancer" (id. at ¶ 9-10). Dr. Hill also states, "The composition of amygdalin is such that I do not recognize it, nor is it generally recognized among experts qualified through scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use in cancer management, or for any other known medical use. I know of no medical school where use of amygdalin for treatment or prevention of cancer is taught. I know of no medical expert qualified through scientific training and experience in the control of cancer who advocates use of amygdalin" (id. at ¶ 13).

Vincent T. DeVita, Jr., M.D., is Professor of Medicine at the George Washington University School of Medicine, Washington, DC, and is a diplomate of the American Board of Internal Medicine, with subspecialty certification in Hematology and Medical Oncology (R 169). Dr. DeVita has been Director of the Division of Cancer Treatment, National Cancer Institute, since 1974. His job requires that he regularly attend meetings of experts at which drugs used in the treatment of cancer are discussed and evaluated and that he be acquainted with

the literature published in professional journals relating to drugs used in the treatment of cancer (R 169 at ¶ 1-16). Dr. DeVita states (id. at ¶ 18-19), "The composition of amygdalin is such that I do not recognize it, nor is it generally recognized by experts qualified through scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use in the treatment or prevention of cancer. I know of no adequate, well-controlled clinical study which shows it to be safe and effective for use in the treatment or prevention of cancer in humans. I know of no medical school where use of amygdalin is taught, and of no recognized medical text which prescribes, recommends, or suggests its use. Neither do I know of any expert in cancer chemotherapy who is of the opinion that it is useful in the treatment or prevention of cancer, or that there is evidence that it is useful in the medical management of cancer."

R. L. Meckelnburg, M.D., is Director, Department of Nuclear Medicine, Wilmington Medical Center, Wilmington, Delaware, and a physician concerned with the care and treatment of cancer patients by means of chemotherapy (R 154). He described his limited experience with treating patients with Laetrile in the years 1963-1967. Although Dr. Meckelnburg states (and the Commissioner agrees) that the study was not a clinically controlled series, he reports that "the results of these treatments were uniformly unsuccessful." Dr. Meckelnburg noted, "The individuals who were most interested in promoting the use of Laetrile failed to administer the drug in a manner consistent with good clinical investigative methodologies, particularly the use of the double blind control and crossover models of study." He concluded, "The promulgation of the drug as a preventive for cancer in the light of today's knowledge is totally absurd" (id.).

Robert C. Eyerly, M.D., is a physician and surgeon on the staff of the Geisinger Clinic in Danville, Pennsylvania, and a diplomate of the American Board of Surgery (R. 167). He currently serves as Chairman of the Committee on Unproven Methods of Cancer Management, American Cancer Society. This Committee's chief concern is, "With methods that are promoted as having established value in diagnosis, prevention, treatment, or control of cancer, despite a lack of competent scientific evidence to support claims made for them. The Committee reviews material assembled by its staff, mostly from published sources, to find out what kind of claims are made, and they evaluate scientific literature to see if it contains evidence to support such claims" (id. at ¶ 5-7). Dr. Eyerly states, "The composition of amygdalin is such that I do not recognize it, nor is it generally recognized by experts qualified through scientific training and experience to evaluate the safety and effectiveness of drugs as safe and effective for administration to humans for the treatment or

prevention of cancer, or for any other purpose" (id. at ¶ 10).

Several experts qualified by scientific training and experience in the field of cancer research and cancer treatment submitted similar statements attesting that they knew of no cyanogenic glycoside that is generally recognized as safe and effective for the treatment, prevention, or cure of cancer, for the relief of pain associated with cancer, or for any medical purpose. They also stated that the composition of these cyanogenic glycosides, in general, and of amygdalin, in particular, is such that they do not recognize them, and the cyanogenic glycosides are not generally recognized among experts qualified through scientific training and experience to evaluate drugs, as safe and effective for the treatment of cancer, for prophylaxis against cancer, for relief of pain associated with cancer, or for any medical use. These experts further stated that the scientific literature contains no reports of adequate, well-controlled, scientific studies or other evidence upon which recognition of safety and effectiveness may be predicated. They did not know of any recognized medical text in which the use of amygdalin or any other cyanogenic glycoside is recommended for the treatment of cancer. They did not know of any medical school where use of these substances for such purpose is taught. They did not know of any expert in cancer chemotherapy who is of the view that there is evidence that these substances have any useful effect in treating cancer. They did not know of any report in the scientific literature describing an adequate, well-controlled study which demonstrates that amygdalin or any other cyanogenic glycoside is safe and effective (Dr. Daniel S. Martin, R 185; Dr. Joseph F. Ross, R 190; Dr. Charles G. Moertel, R 186; Dr. Jesse L. Steinfeld, R 194; Dr. C. Chester Stock, R 195; Dr. Harold James Wallace, R 199; Dr. Peter H. Wiernik, R 200; Dr. Emil J. Freireich, R 390; Dr. David T. Carr, R 176). The qualifications of the individuals not previously discussed are set forth in the following paragraphs:

Joseph F. Ross, M.D., is Professor of Medicine at the University of California School of Medicine at Los Angeles, California, and Director of the United States Public Health Service-funded Research Training Program in Hematology and Hematologic Oncology at UCLA. He submitted an affidavit (R 190) in which he described his educational background and experience in teaching medical students and physicians. He is actively involved in the medical care of cancer patients. Dr. Ross listed his membership in several societies and councils which deal with cancer treatment and his membership on the editorial boards of several scientific publications.

Charles G. Moertel, M.D., is Chairman of the Department of Oncology at the Mayo Clinic, Director of the Mayo Comprehensive Cancer Center, and Professor of Medicine at the Mayo Medical School, Rochester, Minnesota. He described his educational background and experience

which have included serving as Editor of Cancer Yearbook, Associate Editor of Cancer Medicine, serving on the editorial board of Cancer, serving on a number of cancer committees, being involved in clinical research in pharmacology concerning cancer chemotherapy and clinical oncology, and publishing as author or co-author over 200 articles, abstracts, and editorials in recognized medical and scientific journals (R 186).

C. Chester Stock, Ph.D., is Vice President and Associate Director for Administrative and Academic Affairs of the Sloan-Kettering Institute for Cancer Research, New York, New York, and Professor Emeritus in Biochemistry at Cornell University. He described his educational background and experience as including serving as a member of several boards and societies concerned with cancer research and serving as Chief of the Division of Experimental Chemotherapy at Sloan-Kettering, where for many years he has had a major responsibility in the development of new drugs for the treatment of cancer (R 195).

Peter H. Wiernik, M.D., is Professor of Medicine, University of Maryland School of Medicine and Chief, Clinical Oncology Branch, National Cancer Institute, Baltimore Cancer Research Center. His educational background and experiences include duties as a reviewer for 9 medical-scientific journals, co-editor of 2 journals and the author or co-author of over 140 articles, editorials, and abstracts which have appeared in medical-scientific literature most of which deal directly with cancer (R 200).

Emil J. Freireich, M.D., is Head of the Department of Developmental Therapeutics and Professor of Medicine, and Chief, Division of Oncology at the University of Texas Medical School at Houston, Texas. His educational background and experience includes membership in several societies and committees concerned directly with cancer treatment. In addition, Dr. Freireich serves as a member of editorial boards of medical and scientific journals concerned with cancer research and, as such, reviews and evaluates scientific papers relating to the causes, treatments and control of cancer. He has published in internationally recognized journals over 250 articles, the majority of which have been concerned with cancer (R 390).

David T. Carr, M.D., is Professor of Medicine at the Mayo Medical School, Associate Director for Cancer Control and Community Relations of the Mayo Comprehensive Cancer Center, and a member of several professional societies and committees concerned with the treatment of cancer. His professional education and experience include the responsibility for a program of public education about cancer. His special interests are internal medicine and medical oncology, and he is regularly engaged in the medical management of cancer (R 176 (see also Tr. at 180-89)).

Several other experts submitted testimony in which they stated that, in their experience, Laetrile was not effective in the treatment of cancer. Their qualifi-

cations are set out in the following paragraphs:

James F. Holland, M.D., Professor and Chairman, Department of Neoplastic Diseases; Chief, Division of Medical Oncology; and Director, the Cancer Center, Mount Sinai School of Medicine, is a physician who has worked exclusively in cancer medication for over 26 years, specializing in cancer chemotherapy. He states, in his verified testimony, that he is thoroughly familiar with the action of drugs on cancer (R 396).

Carl M. Leventhal, M.D., is Deputy Director of the Bureau of Drugs, Food and Drug Administration. He holds the rank of Medical Director in the Commissioned Corps of the Public Health Service and is Assistant Professor of Neurology and Pathology at Georgetown University. As Deputy Director of the Bureau of Drugs, he participates in meetings in which the status of Laetrile is discussed and evaluated (R 184).

William A. Nolen, M.D., is Chief of Surgery at the Meeker County Hospital, Litchfield, Minnesota. He has served on the board of editors of the Minnesota State Medical Journal and has written a number of articles, editorials, and books on subjects of public health interest, including a book entitled *Healing: A Doctor in Search of a Miracle*, in which he describes his personal experience with a patient who lost her life because she chose Laetrile for treatment of an early cancer, thereby delaying conventional medical treatment (R 188).

Thomas H. Jukes, Ph.D., is Professor of Medical Physics and Research Biochemist at the University of California, Berkeley, California. He is a member of several professional societies, serves on the editorial boards of several scientific publications, has written three books and over 250 articles in scientific journals and has conducted research in the vitamin and cancer fields (R 416 (see also R 41)).

Robert S. K. Young, M.D., Ph.D., is a physician and has a doctorate in pharmacology. He serves as adjunct Assistant Professor of Pharmacology at Georgetown University School of Medicine and Dentistry and is group leader for the Oncologic Drug Class, Bureau of Drugs, Food and Drug Administration (R 201 (see also R 430)).

(b) *Supporters of Laetrile*.—In contrast to the great amount of evidence that experts in drug evaluation do not generally recognize Laetrile (or amygdalin) as effective, the evidence in the record to the contrary is meager. The Commissioner will outline qualifications of those persons who claim any modicum of training or experience in the area of drug evaluation whose support for the use of Laetrile appears in the record. The submissions of the following three physicians are discussed under I.A.1.c. above, "The 'Evidence' of Laetrile's Effectiveness":

John A. Richardson, M.D., stated in testimony (Tr. at 462-463) that he had been in general practice for 25 years and since 1971 had been engaged in nutritional using Laetrile, amygdalin, or

vitamin B-17 and that he had treated, over the past 6 years, between 4,000 and 5,000 cancer patients. Dr. Richardson made no claim to special training or board certification in the area of oncology or of training or experience in the evaluation of the safety and effectiveness of drugs. Dr. Richardson's license to practice medicine has been revoked (R 183 at 13).

Philip E. Binzel, Jr., M.D., stated that he has been a family physician since 1955 and currently serves as scientific advisor to the Committee for Freedom of Choice (Tr. Ex. 13). He stated that he has treated over 400 patients in the last 3 years with a "metabolic therapy" for cancer (Tr. at 360-361). No special training in oncology or in the evaluation of drug safety or effectiveness is claimed.

Lawrence (Larry) Patton McDonald, M.D., who stated that he has been a urologist since 1963, is a former member of the State of Georgia Medical Education Board, and is currently a member of the U.S. House of Representatives. He stated that he was a member of several societies and associations, including the American Society of Clinical Urologists, the Southeastern Section of the American Urological Association, and the American Association of Physicians and Surgeons (R 509). No showing has been made that Dr. McDonald has a specific expertise in cancer treatment or in the evaluation of the safety and effectiveness of drugs.

Dr. Edward M. Arana, who spoke at the oral argument in this proceeding, identified himself only as a practicing dentist in Carmel, California (Tr. 472-A).

Ernst T. Krebs, Jr., spoke at oral argument in this proceeding (Tr. at 228-248). While he is referred to as Doctor, he did not complete his medical training and is a doctor only by virtue of an honorary degree. No special training in the area of cancer therapy or in the evaluation of safety and effectiveness of drugs has been shown for Mr. Krebs, Jr.

Paul Hart, M.D., spoke at oral argument. He described himself as having been employed at a pathology laboratory that dealt with the effects of radiation from atomic bombing in Japan and that was associated with Deaconess Hospital in Boston (Tr. at 457-58), and as being a diplomate of the National Board of Medical Examiners (Tr. at 457). He stated that he has an interest in "the Carl O. Simonton, M.D., psychotherapeutic approach to cancer therapy * * *" (Tr. at 458). While he indicated a personal respect for various Laetrile proponents, he did not give an opinion as to whether or not Laetrile is generally recognized by experts qualified to evaluate the safety and effectiveness of drugs as safe and effective for use in cancer therapy.

Dr. Mario Soto spoke at oral argument. He described himself as being former head of the chemotherapy departments of two different Mexican hospitals. He stated that he is an independent investigator for the National Cancer Institute and a conventional oncologist and chemotherapist. He is medical direc-

tor of a Laetrile clinic in Tijuana, Mexico (Tr. at 478-479).

Dean Burk, Ph. D., who spoke at oral argument and provided a written submission (R 302), is a biochemist and is president of the Dean Burk Foundation, Inc. He stated at oral argument that he had spent 50 years in research on cancer and vitamins, 35 of which were with the National Cancer Institute (Tr. at 402). His position is that Laetrile is not a drug but a vitamin.

An affidavit of Chauncey D. Leake, Ph. D., prepared for another proceeding, was submitted to this record (R 302, Ex. K). The affidavit indicates that he is Senior Lecturer in Pharmacology at the University of California School of Medicine, San Francisco. His curriculum vitae showed that he has a history of teaching, participation in organizations dealing with medicine and pharmacology, editing of journals, and authorship of books and articles.

An affidavit of Charles Gurchot, also apparently prepared for another proceeding, was submitted as Exhibit L to R 302. His degree is in chemistry and physiology. Now semi-retired, he has taught pharmacology, biochemistry and chemistry at several schools of medicine and is a member of a number of scientific societies.

James Cason, Ph. D., submitted a statement in which he states that he has been a chemistry professor for some 35 years, has published over 100 research papers in scholarly journals and has served on the editorial boards of *Organic Syntheses*, and the *Journal of Organic Chemistry* (R 217). He is currently a professor of chemistry at the University of California, Berkeley (id.). While he states his opinion that a diet high in nitriloxides leads to a low incidence of cancer, he gives no opinion as to whether or not Laetrile (or Amygdalin) is generally recognized by qualified experts to be a safe and effective cancer drug.

The statute requires that "general recognition" be among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs (21 U.S.C. 321 (p) (1)). Few of the proponents of Laetrile who have made submissions to this record possess the necessary training and experience to qualify them as such experts. The Commissioner has, however, for purposes of completeness, considered as coming within the category of "experts" for this purpose, persons, including those listed above, who have exhibited even a small modicum of scientific experience or experience in the area in which they have offered submissions. The weight to be given the testimony of such persons, of course, must correspond to their expertise, cf. *United States v. 1,048,000 Capsules, More or Less, Etc.*, 347 F. Supp. 768, 771 (S.D. Tex. 1972), aff'd 494 F.2d 1158 (5th Cir. 1974).

The Commissioner concludes that, the lack of adequate and well-controlled clinical investigations published in the scientific literature aside, the record clearly demonstrates that the overwhelming majority of experts in the

evaluation of the safety and effectiveness of drugs do not recognize Laetrile as effective. Even the proponents of Laetrile, while they may argue that the majority is wrong, could hardly be heard to argue this point. Laetrile is thus a new drug within the meaning of the act.

B. GENERAL RECOGNITION OF SAFETY

As noted above, for a drug to be exempt from new drug status under 21 U.S.C. 321(p) (1) it must be recognized by "experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs" to be both safe and effective under the conditions of its intended use. While lack of such recognition of Laetrile's effectiveness has already been shown, the Commissioner will discuss in addition the evidence on the question of general recognition of the drug's safety. He finds that such recognition does not exist.

1. Lack of Adequate Testing

As has been discussed above, for a drug to be generally recognized as safe it must have accumulated at least the amount of evidence of safety that would be required for approval of a new drug application and that evidence must be generally available to the community of experts through publication in the scientific literature. In order for a new drug application for a drug to be approved, there must exist as to that drug "adequate tests by all methods reasonably applicable" that show the drug's safety (21 U.S.C. 355(d); cf. 21 CFR 314.111 (a) (1)).

An attempt to show that Laetrile had been proven by adequate testing to be safe for use in man was made in 1970 when the McNaughton Foundation submitted to FDA a notice of claimed investigational exemption for a new drug (IND) for Laetrile. The FDA terminated that exemption because of a lack of evidence of safety. Subsequent to the termination, the IND was referred to an Ad Hoc Committee of Oncology Consultants. The report of this committee is submitted with R 184 as Exhibit 2. This report states, "The Committee concurs with the action of the Commissioner in termination of IND 6734." Addressing the toxicity question, the Committee concluded: (id. at 2), "Although it is often stated in the IND that amygdalin is non-toxic, data to demonstrate this lack of toxicity are absent, particularly with respect to the oral route."

The animal studies done to show Laetrile's safety did not justify use of the dosage suggested in the IND. "[T]he sponsor wishes to begin oral studies in patients at 2.95 mg/kg (oral); this is to be compared with a documented safe oral dose in dogs of 7.5 mg/kg daily for 6 months * * *. On the basis of documented data, if substantiated, then a proper starting dose that might be considered in man, would be 1/10 of 7.5 mg/kg or 0.75 mg/kg (oral). The proposed starting dose of 2.95 mg/kg is 1/100 of the oral acute LD₅₀ in mice. It is considered to be dangerous to base the starting dose for a chronic (6 + weeks) study in man on a single dose

study in mice. It is also dangerous to initiate human studies while the nature of the toxicity has not been elucidated in large animal species. No documented data are presented in the IND to permit a higher starting dose" (id. at 3-4).

Dr. W. Sherwood Lawrence, Executive Secretary for the State of California Cancer Advisory Council states (R 183 at 17), "An extensive review of the world's scientific literature has been made by the Council. The evidence available for the determination of the recognition of safety of the compound is characterized by the lack of a body of scientifically sound information such that experts qualified by experience and training to make such determinations are unable to do so. In the absence of such a determination by qualified experts Laetrile (amygdalin) cannot be considered to be generally recognized as safe."

There is thus an absence of scientifically sound data upon which experts qualified by training and experience to evaluate the safety and effectiveness of drugs could base an opinion that Laetrile is safe for use in man. In the absence of such data the Commissioner must conclude that the safety of use of Laetrile in man has never been, and is not now, "generally recognized" by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs.

2. Testimony of Experts

The Commissioner's conclusion of lack of general recognition among experts of Laetrile's safety is supported by testimony of such experts in the administrative record. (The qualifications of the experts whose statements are quoted have been discussed above.)

As one expert notes, while the toxicity of injected Laetrile has not been studied, there is evidence that amygdalin when ingested (eaten) is harmful to humans, evidence that has led to cautions on the part of Laetrile promoters themselves: In discussing the use of Laetriles, Dr. W. Sherwood Lawrence states (R 183 at 16), "There has never been a formal evaluation of the safety of these compounds to determine their safety. Although the proponents claim Laetriles are non-toxic, there are bonafide reports of clinical toxicity on oral intake (California Morbidity Reports, Ankara), and even fatality (Bitter Almond Poisoning, Zmedzinfrul). Furthermore the proponents themselves are aware of this toxicity as evidence by the proposed labeling submitted in an application for an exemption for an Investigational New Drug which warned: 'CAUTION: Laetrile is not to be taken orally. It is extremely toxic by this route of administration * * *'. There are no studies adequately showing the distribution, activity and metabolic fate of the parenterally administered compound. Chronic effects are not studied and reported in depth. There is cause for the concern as other similar beta-cyanogenetic compounds cause serious toxic effects when ingested on a chronic basis, e.g., Tropical Ataxic Neuropathy in Nigeria (Attachment 20).

Effects of industrial poisoning from chronic low concentration exposure are well-known." (See also, for discussion of toxicity of Laetrile, section V.B.3. below, "Dangers of Ingestion of 'Vitamin B-17'".)

Dr. Robert C. Eyerly reports, "One of the unproven remedies for cancer management which the committee (on Unproven Methods of Cancer Management) investigated is the drug Laetrile. Other names for Laetrile include amygdalin and prunasin. These compounds are classified as cyanogenic glycosides. Cyanogenic glycosides, including amygdalin, are generally regarded as toxic substances, rather than as foods, because when they break down they liberate hydrogen cyanide, one of the most toxic substances known" (R 167 at ¶ 8).

Dr. Robert S. K. Young states (R 430 at ¶¶ 4, 5, and 7), "The FDA does not have authenticated or validated data on the toxicity of amygdalin in humans. It does not have scientific studies or the data upon which scientific studies might be constructed, in humans receiving amygdalin which would allow it to define the toxic effects of this drug. There are no such reports in the medical literature. Nevertheless, Dr. Nepier from Germany has reported that amygdalin causes hypotension and hemoglobinuria in humans. There have been reported cases of cyanide poisoning in humans who ate apricot kernels. The symptomatology includes dyspnea, cyanosis, vomiting, prostration, convulsions, stupor, and paralysis. Since these toxic effects are caused by the cyanide, which is a constituent part of amygdalin, amygdalin could cause the same toxic effects. Although it is possible that amygdalin can be given to humans in doses which are non-toxic in man, the drug is unsafe for use in humans. There is no scientific evidence that the drug can cure or is effective as a treatment for any human cancer." Dr. Young also states (id. at ¶¶ 2-3), "There is a difference between a drug's toxicity and a drug's safety. The toxic effects of a drug are those effects which are not beneficial to the person taking the drug, but are deleterious. The safety of a drug is defined by the context of its use and includes consideration of issues such as a disease for which the drug is intended, the alternative remedies which are available and their efficacy and safety, and the possible abuse of the drug by those who do not have the disease for which the drug is intended. Acute toxicity tests of amygdalin have been carried out in animals. It appears that relatively large quantities of amygdalin can be given parenterally. When given by the oral route, however, the toxicity of amygdalin is greatly increased (by a factor of approximately twenty-five times)."

James F. Holland, M.D., indicated that he does not accept the theory of proponents of Laetrile that patients should be allowed to take Laetrile since, even if it is ineffective, it cannot hurt. He states (R 396 at 1), "It can hurt by interfering with patients' acceptance of indicated therapy in the mistaken and false hope of potential benefit from Laetrile. Delayed

operation, refused radiotherapy, skipped chemotherapy all risk an increasing cancer morbidity and mortality because of the premise that Laetrile is active. This is a very dangerous side effect, indeed."

In addressing whether or not Laetrile is safe, Dr. Carl M. Leventhal states (R 184 at ¶ 19), "The question of whether Laetrile is now, or ever was, generally recognized as safe goes beyond the absence of any evidence indicating the lack of toxicity of the drug. The safety of a drug for human use depends, in large measure, on the therapeutic effectiveness of the particular drug. When patients forego effective forms of therapy and turn instead to worthless potions and nostrums, their disease may progress while effective therapies are foresaken. In the case of cancer, treatment with an ineffective drug will inevitably and inexorably lead to the patient's death. Seen in this light, an ineffective cancer drug is inherently unsafe and even lethal, because of the patient deaths which will necessarily ensue."

Dr. Harold J. Wallace, Jr., states (Tr. at 174) that: "The safety of the various forms of amygdalin has not been tested by the usual scientific methods of clinical pharmacology. There is evidence that the crude oral form can and has caused toxicity in humans and may cause death. There has been no documentation of the usual parameters that we require of drugs when used in a clinical situation. We don't have blood levels achieved, activation, clearance, metabolism, distribution or excretion of amygdalin compounds in man, as is usually required in the pre-clinical and clinical evaluation testing of chemotherapeutic compounds or other drugs."

Dr. Frank Rauscher, a former Director of the National Cancer Institute (NCI), and currently associated with the American Cancer Society, said in his statement concerning Laetrile, while he was Director, NCI: "Assertions of the non-toxic nature of Laetrile have not been demonstrated in vigorous clinical studies. Even if this claim is true, there is no basis whatsoever for recommending the clinical use of any non-toxic agent if it cannot be expected to produce objective clinical benefits" (R 173, Att. "Statement Concerning Laetrile" at 2-3).

Dr. Thomas H. Jukes states (R 41 at 1): "Laetrile is not generally recognized by experts as safe. In the presence of the enzyme beta-glucosidase, Laetrile is hydrolyzed to glucose and mandelonitrile. Mandelonitrile readily decomposes with the liberation of hydrocyanic acid, which is extremely poisonous at low levels. The enzyme beta-glucosidase is widely distributed in materials of plant origin. The potential danger that laetrile may be decomposed with liberation of hydrocyanic acid makes it unsafe."

Dr. George J. Hill, II, after noting that ineffective remedies for cancer can lead to delay in treatment and "needless and untimely death," states: "In the absence of scientific evidence of effectiveness, no drug intended for use in treating cancer

can be regarded as safe" (R 170 at ¶ 11).

Dr. Joseph F. Ross noted that that delay in cancer therapy because of use of Laetrile "results in loss of life, tragic suffering, and shortened life span" (R 190 at 8) and that use of the drug is "hazardous to the health of cancer patients" (id. at 7). He states: "Additionally, the use of 'Laetrile,' Vitamin B-17, 'Aprikern' and other such amygdalin containing materials when ingested presents a definite health hazard. The action of gastrointestinal fluids and enzymes releases the C=N (cyanide) radical from the compound and this may produce acute cyanide poisoning" (id. at 8).

Several additional experts submitted affidavits in which they state that neither amygdalin nor any other cyanogenic glycoside has ever been generally recognized as safe (Dr. Charles G. Moerel, R 186 at ¶ 12; Dr. Jesse L. Steinfeld, R 194 at 5-6; Dr. Peter G. Wiernik, R 200 at ¶ 16; Dr. Emil J. Fraireich, R 390 at ¶ 19; and others).

III. THE "GRANDFATHER" ISSUE

Because Laetrile is not generally recognized by qualified experts as safe and effective (see discussion above), it is subject to the Act as a "new drug" unless it is exempted from the statute's provisions under either of the two "grandfather clauses." These two exceptions, described in more detail below, limit the protection provided to the public with respect to certain drugs that fulfill a number of carefully defined conditions. Accordingly, the courts have recognized the narrowness of the exceptions. *United States v. Allan Drug Corp.*, 357 F. 2d 713, 718 (10th Cir. 1966) cert. denied 385 U.S. 899 (1966): "Since we are dealing with a Grandfather Clause exception, we must construe it strictly against one who invokes it."; *Durovic v. Richardson*, supra, 479 F. 2d at 250 n. 6; *United States v. An Article of Drug* * * * "*Bentex Ulcerine*" * * *, 469 F. 2d 875, 878 (5th Cir. 1972), cert. denied 412 U.S. 938 (1973); *United States v. 1,048,000 Capsules, More or Less, Etc.*, supra, 347 F. Supp. at 770.

The Court in *Bentex Ulcerine* held, 469 F. 2d at 878, that any party seeking to show that a drug comes within the grandfather exemptions "must prove every essential fact necessary for invocation of the exemption." Accordingly, the Commission concludes that Laetrile will not qualify for grandfather clause exemption unless each of the essential facts has been proved by evidence submitted in the record.

In the February 18, 1977 FEDERAL REGISTER notice initiating this proceeding, proponents of Laetrile were informed of their obligation to bring forth evidence that would support their claim that Laetrile qualifies for this exception. The notice set forth the provisions of a regulation (21 CFR 314.200(e)(2)) that detailed the format to which submissions directed to the grandfather clause exceptions should conform (42 FR 10069). Failure to submit formulas, labeling and

evidence of marketing in that format was stated to constitute a waiver of any contention that Laetrile was exempt from new drug provisions of the act. Failure to submit evidence in the format has resulted in such a waiver.

Despite the waiver, the Commissioner, in order to fully address the issue remanded by the courts, has culled the entire record for evidence that might arguably be relevant to the grandfather status of Laetrile. He has considered this evidence in determining whether the essential facts necessary to invoke the grandfather clause exemptions have been proved. Moreover, against the chance that it should later be held that those contending that Laetrile's use is illegal must prove the nonexistence of the essential facts necessary for the invocation of the grandfather clause exemptions, the Commissioner has considered the evidence in the record in light of this possibility.

The essential facts necessary to invoke the two exemptions are discussed, together with the evidence relevant to each, below. The Commissioner's conclusions on these issues may be summarized as follows:

(1) Contentions that Laetrile qualifies for either grandfather clause exception are waived.

(2) Evidence presented does not prove the existence of each essential fact necessary for the invocation of either grandfather clause.

(3) While it is of course not possible to prove a negative with regard to the existence of each of the essential facts involved, the record assembled contains substantial evidence, constituting a clear preponderance of the evidence submitted, that these essential facts do not exist.

A. THE 1938 GRANDFATHER CLAUSE

To qualify for exemption from the definition of a new drug under the 1938 grandfather clause, it must be shown that the drug "at any time prior to the enactment of this chapter [1938] . . . was subject to the Food and Drugs Act of June 30, 1906, as amended, and . . . at such time its labeling contained the same representations concerning the conditions of its use; . . ." 21 U.S.C. 321(p) (1).

Thus, to qualify for this exemption, it must be proved that (1) the identical drug (2) bearing labeling containing the identical representations concerning the conditions of its use (3) was introduced into interstate commerce in the United States (or was manufactured in a Federal territory or the District of Columbia) after June 30, 1906 and prior to the enactment of the act in 1938. The exemption applies only to drugs whose labeling with respect to representations as to conditions of use has undergone no changes whatsoever from the labeling utilized prior to the passage of the 1938 act, and whose composition is completely identical to its composition prior to this passage. If any change in representations for conditions of use in labeling or any change in composition has occurred since the enactment of the 1938 act, such

change precludes the applicability of the 1938 exemption. The proof required would necessarily involve the production of quantitative formulas, labeling, and evidence of marketing both for the pre-1938 use and for the present use. While submissions to the administrative record contained a number of references to use of Laetrile or its predecessors before 1938, no proof was submitted to show that what was termed "Laetrile" or "amygdalin" as used before 1938 was the same drug which is now being marketed. Nor is there any indication whatever that the labeling of the various drugs claimed to have been marketed before 1938 contained representations concerning conditions of use which are identical to the representations associated with the presently marketed drug. It should be noted that the term "labeling" is defined in the act to include not only "all labels" but also, "other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article," 21 U.S.C. 321(m). This definition has been given a broad interpretation, see, e.g., *Kordel v. United States*, 335 U.S. 345, 347-50 (1948); *United States v. Urbucit*, 335 U.S. 355, 357 (1948).

A number of submissions in the record referred to use of substances claimed to be related to Laetrile or amygdalin in ancient times. While each of these statements was hearsay unsupported by any sort of corroborating evidence and thus cannot be considered trustworthy, it is apparent that even if accepted at face value these claims would not justify invocation of the 1938 grandfather clause. Examples of such claims in the record include those found in a McNaughton Foundation article entitled "Information for Physicians: Amygdalin, The Non-Toxic Analgesic" which cites use by the Chinese 3,500 years ago as well as use by the Greeks and the Romans (R 183, Att. 106 at ¶ 1). See also *Hanson v. United States*, 417 F. Supp. 30, 36 (D. Minn.) aff'd 540 F.2d 947 (8th Cir. 1976) (copy of opinion attached to R 173), noting that plaintiffs in that court action had introduced hearsay concerning the use of amygdalin by ancient Egyptians, evidence upon which the court did not rely; affidavit of Chauncey Leake, Ph.D.—recommendation of almonds for various purposes (not to cure cancer) by a first century Greek surgeon (R 302, Ex. K); statement by John J. O'Conner, Jr., in support of a Maryland State bill on Laetrile—bitter almond used by Chinese for the treatment of tumors 3,500 years ago; use by Greeks and by Romans (Tr. Ex. 4, Att. at 22).

Other submissions mentioned that amygdalin was prepared by two Frenchmen in 1830 and analyzed by two Germans shortly thereafter. (See R 183, Att. 10b at ¶ 1; R 302, Ex. K; R 168, Att. at 345; R 80, Att.) No claims were made that these 19th century experimenters used amygdalin to treat cancer. There is a claim, however, that a Russian physician used amygdalin for that purpose in 1845. The reference is to a report in

the *Gazette Medicale De Paris*, Tome XIII, Samedi, Le 13 Septembre 1845, by Dr. Inosentzeff. This article is referred to in a number of submissions. (See, e.g., R 259, Att. at 1.) It was not, however, itself submitted and in thus not part of the record available for analysis by the Commissioner. According to the description in the "Listing of Documents Relative to . . . Laetrile" attached to R 259, a submission by Mr. Wynn Earl Westover, the author of the 1845 article was a professor of surgery at the Imperial University of Moscow, and his article described two cases of cancer apparently successfully controlled for 11 years and 3 years, respectively, by the use of amygdalin (for other references to this article, see R 260, Att. at 1; R 302, Ex. L at ¶ 5).

As is obvious, this "evidence" relating to ancient and 19th century use is irrelevant to the 1938 grandfather clause issue for the following reasons: (1) It does not indicate that the drug was used in the United States after June 30, 1906 and before 1938. (2) It gives no indication that the drug used was the same as Laetrile. Most of the references in fact indicate that the substances used were either some extract of almonds, or, as in the case of the alleged Russian physician, simple amygdalin. (3) No suggestion that any drug was to be used in accordance with the indications now associated with treatment with Laetrile may be found in these references. Again, where the submissions go into detail concerning the historical uses of almonds or amygdalin, it is apparent that different conditions of use are involved.

A number of claims purporting to be relevant to the 1938 grandfather issue dealt with the appearance of almond extract in various Pharmacopoeia. (See, e.g., Tr. at 250; R 302, Ex. K and Ex. L, ¶ 9-12 Tr. Ex. 9.) The opinion in *Hanson v. United States*, *supra*, indicates that plaintiffs in that case relied upon a listing of amygdalin in the Merck Index of 1896. The references in the Pharmacopoeia involve in each case some sort of almond extract. There is no indication that that extract was to be used as an injection to cure, control, or prevent cancer. The references to the Pharmacopoeia, as is the case with other general, unsupported references indicating use in cancer patients in previous centuries (see, e.g., R 509 at 2) are for the reasons detailed simply not probative of grandfather status.

Of more direct relevance to possible grandfather status is the information in the record regarding the work done with what was apparently Laetrile's predecessor by Dr. Ernst Krebs, Sr. A great deal of conflicting information regarding the dates of Dr. Krebs' work was submitted to the record. There are numerous instances in the record of statements that Dr. Krebs developed a drug related in some way to modern day Laetrile either in 1920 or shortly thereafter, while a new and allegedly nontoxic form of Laetrile was developed by Ernst T. Kerbs, Jr., in 1952 or in the early 1950's. See e.g., the American Cancer Society Committee on

Unproven Methods of Cancer Management's article on Laetrile (R 167, Ex. 2); A Report on the Treatment of Cancer with Beta-Cyanogenetic Glucosides ("Laetriles") by the Cancer Advisory Council, State of California (1963) at 2 (R 183, Att. 16). The latter report may be the genesis of the 1920 date, though the former indicates that it is reporting the date "According to" Dr. Krebs. At any rate, the 1920 date appears in or is alluded to in a number of submissions (see R 173, Att., "Questions Most Frequently Asked," and Att., "Laetrile: The Making of a Myth," FDA Consumer (Dec. 1976-Jan. 1977) at 6; R 184 at ¶ 6; Tr. at 272; Tr. at 41; R 250 at 2-3; R 170, Ex. 3 at 2104; R 258, Ex. 16; R 386; Tr. Ex. 10; R 183, Ex. 3 at 33). There may have been some basis for the original statement that Dr. Krebs had begun to work or had achieved results on a substance containing amygdalin in 1920 or in the early 1920's, but nothing has been submitted to indicate what that basis is. The apparent manner in which one submission has relied upon another on this question illustrates the undersirability of relying on hearsay accounts to prove a fact of this kind. None of these statements indicate, in any case, that the materials with which Dr. Krebs was experimenting were identical to, and were used under conditions indicated in labeling which were identical to, the composition and indications for present day Laetrile.

Michael L. Culbert, representing the Committee for Freedom of Choice in Cancer Therapy at the oral hearing, stated: "Dr. Krebs, Sr., both publicly and privately and in numerous different ways, has published not only results but some labels of material that goes back to the 1920's when Dr. Stohl in Switzerland and a number of Japanese scientists and Dr. Krebs, Sr., and others were working with the original extract" (Tr. at 41). If Mr. Culbert or his group have in their possession such publications, they have not submitted them.

A document submitted which would seem, questions of credibility aside, to be the most reliable on the question of the dates of Dr. Krebs' work and that of his son is an affidavit signed and sworn to by Dr. Krebs on April 28, 1965. This affidavit, taken by an FDA employee, appears as Exhibit 6 to R 184 and as attachment 13 to R 183. Since this affidavit is under oath and is by the person most likely to know of the dates in question, the Commissioner concludes that where the dates in the affidavit are different from those appearing elsewhere, chief reliance should be placed on the affidavit. In the relevant paragraphs, Dr. Krebs says:

2. In 1926, I made an extract from apricot kernels which I called Sarcocarpinase. This extract contained Amygdalin and 1-glucosidase. When I injected this product into rats it was toxic and killed some of them.

3. In 1936, I changed the composition of the preparation resulting from the extract of apricot kernels so that the only active principle which remained was Amygdalin.

4. During the period between 1936 and 1960, I perfected the purification process so

that the purity of the Amygdalin rose from 66 percent in 1936 to 99.8 percent by 1960.

5. In 1955, I began to lyophilize the Amygdalin and I have been lyophilizing it in its final form ever since when I produce it in my laboratories.

6. In 1949, my son, Ernst T. Krebs, Jr., gave the name Laetrile to the Amygdalin I was producing and I have used the name of Laetrile ever since that time for the final form of the Amygdalin which I produce.

7. As early as 1926 and up through 1962, I first began to ship and have done so continuously thereafter the Sarcocarpinase extract (cf 2), then the amygdalin (cf 3), then the purified amygdalin (cf 4), then the purified and lyophilized amygdalin (5), and then since 1949 (cf 6) the latter under the name of Laetrile to persons in other States outside of the State of California and in many other countries. Many of these persons have reported their studies in scientific and medical journals and in private communications over several decades. The above shipments were for investigational use only.

As the dates cited by Dr. Krebs illustrate, the substance with which he experimented in the 1920's and 1930's was not the same substance as that which he was using in 1962. The pre-1938 use is, for that reason alone, not sufficient to qualify Laetrile for exemption from coverage of the act under the 1938 grandfather clause.

In another document upon which the Commissioner would ordinarily place reliance, a December 15, 1962 report by FDA inspectors describing their conversations with Dr. Krebs, Sr. (R 184, Ex. 5), Dr. Krebs is reported to have stated that "he began experimenting some 10 months ago with the extraction of Cyanogenetic Glucoside from a mixture containing apricot pits. The purification of this glucoside was effected in the laboratories of Dr. Krebs and used in the treatment of his patients with, according to him, satisfactory results. This material assertedly liquefies malignant growths by the release of cyanide in the area. Injections are made around the area and the case of lung cancer injections are made in the apex of the trapezei." It may be that Dr. Krebs in his statement to the inspectors was speaking of his efforts to purify Amygdalin, referred to in paragraph 4 of his affidavit. On the second page of the inspectors' report, they indicate that "E. T. Krebs, Jr., stated that Dr. Harry Pincus Jacobson, M.D., was the first to use 'Laetrile' on humans and that this was in June 1952. Up to the present time (December 1952) he has used the product on approximately 14 cases."

This last quotation from the inspection report comports with statements elsewhere indicating that in 1952 Mr. Krebs, Jr., developed a new product, related to the products with which his father had been working, which he called Laetrile. While the failure of the affidavit of Dr. Krebs, Sr., to mention this "improvement" by Mr. Krebs, Jr., might lead one to question whether such an improvement had taken place, an article by the senior Krebs and Dr. Arthur Harris, copyright 1955, entitled, "The Treatment of Breast Cancer with Laetrile by

Iontophoresis" (R 183, Att. 7) at 23-24, states as follows:

In 1952 the senior author's biochemist son, Ernst T. Krebs, Jr., became interested in the preparation his father had used on cancer for so many years in his laboratory—the John Beard Memorial Foundation—he tore the drug apart and came to the conclusion that it was not only the glucoside but more particularly the cyanogenetic glucoside that had benefited cancer patients. He succeeded in separating the enzyme Emulsin from the cyanogenetic glucoside and advised their administration separately, in order to avoid the premature trigger-off of HCN from the chemical breakdown in the somatic (or normal) tissue, for this gas—HCN—was the active agent in destroying the cancer cell.

Again the senior author tried each purified preparation—the cyanogenetic glucoside and the enzyme Beta-glucosidase—separately. He administered the cyanogenetic glucoside parenterally (by injection) and followed it in fifteen minutes or so with an injection of the enzyme Beta-glucosidase. The cancer victims so treated tolerated both the drug and the enzyme excellently—and were immeasurably improved. Using the chemical and the enzyme separately, therefore, gave a high degree of safety as well as enhancing its cancerolytic effect.

Because this apricot kernel preparation was "Laevorotatory" (left-handed) to polarized light, and because Amygdalin was chemically a "mandelonitrile," Krebs, Jr., united the first and last syllables to invent a name for the new cancericidal drug—LAETRILE.

Krebs Jr. uncovered the vital link that united Laetrile with the Unitarian or Trophoblastic Thesis of Cancer. In the previous chapter we emphasized the known fact that most malignant lesions are focally characterized by high concentrations of the enzyme Beta-glucuronidase—one of the main attributes common to both the trophoblast cell and the cancer cell. The Beta-glucuronidase of the animal kingdom is the equivalent of Emulsin in the vegetable kingdom, and Emulsin is the very enzyme that Krebs, Jr. separated from Amygdalin to make the empirical apricot formula safe for parenteral (injection) administration to humans!

This was an epochal milestone. Krebs, Jr., worked and experimented feverishly now: he was on the brink of cataclysmic discoveries, discoveries which, if substantiated, could mean victory over invincible Cancer!

He found that when he added Emulsin to Laetrile and incubated the mixture, hydrocyanic acid gas (HCN), one of the deadliest of gaseous poisons, was given off. He found that when he added animal Beta-glucuronidase (or prepared enzyme Beta-glucosidase) to Laetrile and incubated the mixture, HCN was again given off. This, he knew then, was the reaction that took place within the body—IN THE CANCER CELL!

The need for Krebs, Jr.'s improvement was related to the lack of safety of his father's original preparation. As this article co-authored by the senior Krebs states, the original "preparation proved so toxic that he and his colleagues who were experimenting with him were reluctant to continue its use, except in dire circumstances" (id. at 23; cf R 167, Ex. 2; R 170, Ex. 3 at 2014; R 386, Att. at 2-3). Again, it is apparent that the improvement in the substance used by the Krebs (father and son) after 1938 made the drug different in composition, and

also in indications for use, from the drug which was used before 1938. The 1952 date appears at several points in the record. (See e.g., R 167, Ex. 2; R 173, Att. "Laetrile: The Making of A Myth" supra; R 173, Att. 3; R 184 at ¶ 6; R 189; Tr. at 272; R 250 at 2-3; Tr. Ex. 10 at 3.)

In the submission of Mr. Wynn Earl Westover (R 259) (see also R 260), in a document entitled "Listing of Documents Relative to the Krebs Enzyme Extracts Later Known as Laetrile," at 13, there is a list of registrations of trademarks and issuances of letters patent allegedly granted for Sarcarcinase during the years 1930 through 1935. These documents have not all been submitted. Apparently submitted as representative of the patents is a patent specification from the Government of Ireland. As the above discussion indicates, the material covered in these patents is different from the material now known as Laetrile. A submission by Eric E. Conn, Professor of Biochemistry at the University of California, Davis (R 424) discusses this patent application and states that if the procedure set out in the patent is followed, "much or all of the amygdalin in the intact kernels may be destroyed by enzymes set in action by the grinding" of the kernels to produce the extract. Most of the amygdalin remaining would be lost in processing. The extract produced "would be a mixture of glycerides, esters, certain pigments and other fat-soluble compounds that might or might not also contain a small amount (less than 5 percent) of the amygdalin remaining in the finely ground kernels." Compare the claims by Robert W. Bradford, President of the Committee for Freedom of Choice in Cancer Therapy, Inc., at the oral argument, that "Laetrile was first offered for sale in a trademark assigned in 1934, that it was sold at that time in three different forms: tablets, capsules, and injectables, (and that it) pharmaceutically was the same substance used today in cancer therapy. There can be no disagreement on this point" (Tr. at 346). Mr. Bradford submitted nothing to support his claim, which is at odds with the factual information submitted in the record and discussed above.

The Westover submission (R 259) also includes copies of a number of letters by various doctors who indicate that they have used the senior Krebs' formulation in the treatment of tumors or cancer. The letters bear dates in the 1930's. Mr. Westover's submission claims that there are a large number of other letters, not submitted, which are of generally the same type. Ernst T. Krebs, Jr., appearing at the oral argument, testified that amygdalin had been used as early as 1932. He indicated that the product then in use was labeled Sarcarcinase. (See Tr. at 232, 238, 246.) Sarcarcinase is the name of the product which was, according to Mr. Westover, granted a United States trademark in 1934. (See also Tr. at 446-48.) Two affidavits, apparently prepared for some court action, by Charles Gurshot, Ph.D., and Chauncey Leake, Ph.D., indicate that the affiants were involved in the

treatment of patients with Krebs, Sr.'s product in the 1930's (R 302, Ex. K and L).

The Commissioner has carefully surveyed the entire administrative record brought together for this proceeding. While it appears that Dr. Krebs, Sr., was utilizing some substance, which apparently had the trademark name of Sarcarcinase, before 1938, there is no evidence that that substance is identical in its formulation, or in its indications for use, to present day Laetrile (cf R 416 at ¶ 27(I) (7) (pg. 23)). In fact, as discussed above, the record is clear that the substance with which Dr. Krebs, Sr., experimented in the 1930's is different from the drug now being used by Laetrile proponents. The evidence suggests that the substance used by Dr. Krebs, Sr., in the 1930's was too toxic for general use. This toxicity appears to have been the reason for the work of Mr. Krebs, Jr., which, apparently, culminated in a substantial change in the formulation around 1952.

The Commissioner thus concludes that (1) no proof has been offered which shows that Laetrile was used and labeled before 1938 in a manner identical to its present use and labeling, and that (2) the evidence in the record demonstrates that present day Laetrile was not developed until after 1938. Thus, regardless of where the burden of proof lies in an administrative proceeding of this type, the Commissioner must conclude that Laetrile is not eligible for exemption from the protection to the public provided by the new drug provisions of the act because of use prior to 1938 involving identical labeling as to conditions of use.

B. THE 1962 GRANDFATHER CLAUSE

The provision that has been characterized as the "1962 grandfather clause" is set forth at section 107(c) (4) of Pub. L. 87-781 (note following 21 U.S.C. 321):

(4) In the case of any drug which, on [October 9, 1962] the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of the Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

The "basic Act as then in force" read in relevant part as follows:

Sec. 201. For the purposes of this Act—

(p) The term "new drug" means—

(1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and " at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

The Commissioner has previously admitted that one of the conditions for 1962 grandfather status does exist—Laetrile (or amygdalin) was not covered by an effective NDA on October 9, 1962. (See 42 FR 10069). The Commissioner concludes on the basis of the information in the administrative record that Laetrile (or amygdalin) fails to meet all of the other requirements for qualifying for the 1962 grandfather clause exemption: (1) No showing has been made that a drug was used or sold on October 9, 1962 which has the same composition as a drug used or sold, or sought to be used or sold, today. (2) The record is clear that any use of drugs called "Laetrile" or "amygdalin" in cancer therapy in 1962 was for investigational use. Investigational use can not provide the basis for exemption from new drug status on October 9, 1962 (see section 201(p) (2) of the act as then in force, set forth above) and of course does not constitute commercial use or sale. (3) No showing has been made that conditions of use recommended in labeling of a drug used or sold on October 9, 1962 are the same as those now recommended in labeling for the same drug. In fact, neither present labeling nor labeling in use on October 9, 1962 has been submitted to the record. Review of labeling available for "Laetrile" before and after October 9, 1962 reveals substantial changes in the prescribed conditions of use. (4) Laetrile (or amygdalin) was not generally recognized, by experts qualified by scientific training and experience to evaluate drug safety, as safe for use in cancer therapy on October 9, 1962.

As has been noted above, the Commissioner has concluded that the proponents of the proposition that Laetrile is exempt from the act because of "grandfather" status must bear the burden of proving that it is exempt. As has also been previously noted, however, the Commissioner has made a determination based on the alternative theory that the Government must prove that at least one of the essential facts leading to exemption does not exist. Proof of a negative is obviously more feasible in some instances than in others. The record leaves no doubt that use of Laetrile (or amygdalin) on October 9, 1962 was for investigational purposes and that use of the drug in cancer therapy was not "generally recognized" by qualified experts to be safe on that date. Since neither the present composition nor the present labeling of the drug appears in the record, it may not be conclusively determined that that composition and the conditions of use suggested in that labeling are not the same as the composition and suggested conditions of use of some drug in 1962. Nonetheless, the Commissioner is able to conclude, based upon substantial evidence which constitutes the prepon-

derance of the evidence in the record, that neither of those essential facts (i.e., identical formulation and identical conditions of use) do exist as to Laetrile (or amygdalin).

1. Composition

Clearly, for the 1962 grandfather clause to apply, the identical drug must have been used or sold in 1962 as is presently used or sold. The fact that a drug with the identical name (or names) was being used is irrelevant. Similarly, the fact that a drug in commercial use on October 9, 1962 has ingredients (such as amygdalin) in common with drugs in use today would not be sufficient under the grandfather clause if any of the ingredients of the drug, or the proportions in which those ingredients appeared in the drug, had changed (see generally 21 CFR 310.3(h)). Even a change in an inactive ingredient will make a drug a "new drug," (see 21 CFR 310.3(h)(1); *United States v. Article of Drug "Entrol-C Medication,"* 513 F.2d 1127, 1130 n. 7 (9th Cir. 1975)).

The discussion earlier in this opinion of the identity of drugs characterized at different times as "amygdalin" or as "Laetrile" illustrates the wide variation in composition of these drugs. There is no evidence in the record of the present formulation of Laetrile or of amygdalin medication. Neither is there evidence of the composition of such a drug on October 9, 1962. The Commissioner thus concludes that there has been no showing that Laetrile or amygdalin as presently constituted was in use on October 9, 1962. The Commissioner also concludes, based upon the evidence of wide variation in the drugs' composition, both before and after 1962 (discussed below), that the 1962 versions and the versions of the drugs currently in use are not identical.

It should be noted that the Commissioner's decision on this point is in accord with a statement by Andrew McNaughton of the pro-Laetrile McNaughton Foundation, discussed earlier, that data on Laetrile obtained prior to 1968 are frequently not reliable because of the variability in composition of early preparations (R 173, Att., "Report of Ad Hoc Committee of Oncology Consultants"). Other evidence on the question of composition of the drugs consists of (1) analyses done of Laetrile products and (2) representations made as to the products' composition. (The discussion of the 1938 grandfather issue sufficiently catalogues and disposes of claims that drugs similar to Laetrile or amygdalin were marketed prior to 1938, and this section will thus discuss evidence post-dating 1938.)

Analyses. As discussed previously, the results of analyses of drugs called "Laetrile" have often been at variance with their labeled composition. Analyses by Canadian investigators, reported in 1965, found that two versions of the drug, one manufactured in the United States and one manufactured in Canada, had different compositions. The American version contained 98 ± 2 percent amygdal-

in plus .5 percent phenol. The Canadian version contained 87 ± 2 percent amygdalin, 5 percent di-isopropylammonium iodide, and 8 ± 2 percent sucrose (R 189, Att., "Laetrile: A Study of its Physicochemical and Biochemical Properties" at 1059).

Analyses done in 1961 and 1962 for the California Cancer Advisory Council of samples of Laetrile from various different sources—samples obtained in 1951 and 1953, samples obtained from Hale Laboratories, and samples obtained from Dr. Krebs, Sr.—also showed a variation in composition among the drugs (R 183, Att. 16 at 27). Similarities to commercial amygdalin were revealed in some tests. (See, e.g., R 183, Att. 16 at 28 and App. 8.) "The old Laetrile (1951 and 1953) was similar but not identical to amygdalin in the (infra-red examination), while the new Laetrile exhibited certain similarities and certain dissimilarities to both the old Laetrile and to amygdalin" (R 183, Att. 16, App. 8 at 1). Some samples were found to contain inorganic iodine; others did not contain that substance. (See, generally, R 183, Att. 16, App. 7 and 8.)

Claims. A new drug application submitted to FDA by Ernst T. Krebs, Jr., on October 3, 1962, lists the composition of Laetrile as:

L-mandelonitrile-diglucoside [amygdalin] 1,000 mg.

N, N-diisopropylammonium iodide 50 mg.

Inactive saccharides, principally sucrose 176-250 mg.

The drug was to be reconstituted with a sterile isotonic solution (R 201, Ex. B at 101-102).

Dr. Krebs, Sr., in his 1965 affidavit, stated that his preparation contained amygdalin as its only active principle and that that amygdalin, by 1960 at least, was lyophilized and 99.8 percent pure. (See R 183, Att. 13.) It is not clear whether other, inactive, ingredients were a part of the drug he prepared.

A 1953 letter from Ernst T. Krebs, Jr., to California medical authorities states that he was forwarding to Dr. Macdonald "samples of biosynthetically degraded amygdalin in which one dextrose was removed by prunasin and the resulting compound, in the presence of platinum black, was oxidized to the corresponding glucuronoside" (R 183, Att. 14).

In 1965, FDA investigators obtained examples of labeling utilized by the senior Krebs' laboratory. The labeling indicates that Laetrile is "cyanide glucoside type amygdalin." Additional labeling, a pamphlet entitled "Laetrile: Directions for the Administration of Laetrile," states that the drug is to be reconstituted with water, a non-isotonic solution (see R 201 at ¶ 10a and Ex. C).

Mr. Krebs, Jr., in a 1970 article in the *Journal of Applied Nutrition* (R 183, Att. 10c) in which he explained his theory that Laetrile and similar substances make up Vitamin B-17, suggested the drug use of a substance clearly different from all other Laetrile drugs previously in use. While what had been used pre-

viously had apparently been a manufactured drug containing either the "Laetrile" of his own formulation or amygdalin in a more or less purified form, in this article he advised that "one gram of defatted apricot seed or kernel carries about 30 milligrams of nitrilioside. Six or seven teaspoonsful will supply what our clinical investigators consider an adequate oral dose—one gram. It is best that the (beta)-glucosidase enzyme be completely heat inactivated in such material" (id. at 84). As discussed previously, this advocacy of the use of apricot kernels rather than a manufactured drug represents a change in the formulation of the product which is of particular importance because of the danger of toxicity associated with oral ingestion of apricot kernels.

The Commissioner concludes that drugs called variously Laetrile and amygdalin have no set composition, their makeup varies depending upon the manufacturer and the time of manufacture. It thus appears that any drug in use on October 9, 1962 was different in composition from Laetrile as used, or proposed to be used, today.

2. Investigational Use

The record is clear that use of Laetrile (amygdalin) on October 9, 1962 was for investigational, not commercial, purposes. This fact is borne out by legal documents concerned with each of the two major figures in its development—Dr. Ernst T. Krebs, Sr., and his son, Ernst T. Krebs, Jr.—and by other information in the record. Much of the evidence relating to the 1962 grandfather issue, like that relating to the 1938 grandfather issue, is not of the type which would be considered reliable evidence in a court of law. In many cases the "evidence" consists of hearsay which is not substantiated by any documentation. The record does contain, however, a sworn affidavit of Ernst T. Krebs, Sr. In this affidavit (R 183, Att. 13 at ¶ 7) Dr. Krebs describes his shipment in interstate commerce of various versions of his cancer cure, including amygdalin which he stated to have been sold after 1949 under the name of Laetrile, "up through 1962." Dr. Krebs states, "The above shipments were for investigational use only."

Ernst T. Krebs, Jr., and the John Beard Memorial Foundation were convicted in 1962, upon pleas of guilty, of charges of introducing and delivering for introduction in interstate commerce a new drug without an approved new drug application (R 183, Att. 16, App. 17). The drug involved there was another unproved remedy, called by Mr. Krebs "pangamic acid" or "Vitamin B-15." Sentence of imprisonment on those charges was suspended and the defendants placed on probation for 3 years on the condition that they not manufacture, sell, offer for sale, hold for sale, or deliver or give away any "new drug." Mr. Krebs, Jr., obtained a special order which allowed him to ship 400 vials of Laetrile to the McNaughton Foundation in Canada, "for investigational use" pro-

vided the Canadian Food and Drug Directorate acquiesced in that shipment. In a supplemental order of June 28, 1962, Ernst T. Krebs, Jr., was permitted, under certain detailed conditions, to deliver Laetrile to experts qualified by scientific training and experience to investigate the safety of drugs. The drug was not to be administered to any patient except one with extensive malignancy who was receiving Laetrile under Krebs's direction as of June 15, 1962. Thus, if Laetrile were in commercial use on October 9, 1962, and if the Laetrile involved were supplied by Mr. Krebs, Jr., he was in violation of this court order. Copies of the court papers involved in this criminal prosecution are found at appendix 17 to attachment 16 to R 183.

Use of a drug is investigational, as contrasted with commercial, when that use is for the purpose of determining whether, or demonstrating that, the drug in question is safe and effective. The record contains no evidence to suggest that, contrary to the affidavit of Dr. Krebs, Sr., or to the court order binding Ernst T. Krebs, Jr., Laetrile (or amygdalin) was being used on October 9, 1962 for other than investigational uses.

"In 1953 the Cancer Commission of the California Medical Association investigated the claims made for the use of Laetrile in cancer treatment and condemned its use" (R 168, Att. "Vitamin Fraud"). The activities that led to the Medical Association action were apparently based upon Dr. Krebs' use of Laetrile. As shown by labeling collected during a 1952 FDA inspection, the Laetrile then in use was labeled, "Caution: New Drug limited by Federal Law to investigational use." (See R 184, Ex. 5.)

A submission to the record which contains much information about the use of Laetrile at about the crucial date of October 9, 1962 is the 1963 report of the California State Cancer Advisory Council entitled "Treatment of Cancer with Beta-cyanogenetic Glucosides (Laetriles)" (R 183, Att. 16). While the Council concluded that use of Laetrile was not warranted in any context, its report does not contradict Krebs' claims that use was investigational at that time.

Other references to the use of Laetrile prior to 1962 do not specify whether or not the use mentioned was investigational, see R 183, Atts. 5, 6; R 307 at 1; R 64; R 174, Ex. 2; Tr. at 81-82.

A pamphlet entitled *Information for Physicians, Amygdalin The Non-Toxic Analgesic* provides information about what it states to be the experience of various doctors around the world in administering amygdalin to patients. Some of the statements indicate use by doctors before 1962—that use appears to be investigational and was not, with the exception of 10 cases reported by a New Jersey doctor, in the United States (R 183, Att. 10 (b)).

The article by Levi et al., "Laetrile: A study of its Physicochemical and Biochemical Properties," discussed above, refers to Laetrile as "a drug manufactured and distributed until recently for

clinical trial in Canada and the United States to determine its value as a palliative in cancer therapy" (R 189, Att. at 1057).

In 1970 the McNaughton Foundation submitted an IND for Laetrile, which was disapproved by FDA (R 184 at ¶ 9). An IND is a notice, filed by persons interested in the development of a drug product, which seeks permission to distribute an unapproved new drug for the purpose of conducting clinical investigations of it in humans. Such clinical investigations must be completed to form the basis for an NDA for the drug. The fact that Laetrile's proponents were still seeking to investigate its use in 1970 is additional evidence that any use of the drug on October 9, 1962 was investigational.

3. Conditions of Use in Labeling

In order to qualify for the 1962 grandfather clause, Laetrile (or amygdalin) would need to "be intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on" October 9, 1962 (section 107(c)(4) of Pub. L. 87-781). Conditions of use include, among other things, what the drug is recommended for, how it is to be administered, and in what quantities it is to be administered. Under the statute, any change in those conditions from October 9, 1962 to the present disqualifies the drug from exemption. (See *United States v. Allan Drug Corp. supra.*) Here, no submission contains either labeling now in use or proposed for use, or labeling used on October 9, 1962.

Since no labeling in use on October 9, 1962 has been submitted, the indications found in labeling in use in years prior to that time will be discussed as illustrative of the variation in proposed conditions of use apparent in the record. The Commissioner will then review labeling from dates after October 9, 1962. As the following discussion demonstrates, not only do the proposed conditions for use of Laetrile (amygdalin) vary from before October 9, 1962 to after that date, no two sets of labeling propose the same conditions.

Before October 9, 1962

A new drug application (NDA) submitted to FDA by the John Beard Memorial Foundation and Ernst T. Krebs, Jr., on October 3, 1962 indicates that Laetrile was a lyophilized water-soluble powder for use in the palliation of human cancer. Excerpts from the NDA, attached as Exhibit B to R 201, provide information concerning its intended uses: It was to be administered by injections of 1 gram each, which were to be either every day or every second day and either intravenously or intramuscularly. Intravenous administration was stated to be preferred. The average administration was stated to be every other day for a total of 10 injections. Apparently, a total of 20 grams of Laetrile were expected to be administered. Dosages, frequency, and route of administration are described as varying widely with each individual case. The

application indicated that Laetrile often produces a temporary hypotensive reaction shortly after injection, especially in hypertensive patients. Laetrile is not indicated for use to the exclusion of surgery, radiation, or other chemotherapeutic substances where those find any indication.

The proposed labeling in the NDA is, of course, not an example of labeling in commercial use at the time of the NDA's submission. The NDA does, however, state the indications which Mr. Krebs, Jr., thought to be most appropriate for the use of Laetrile at that time. Thus, if Laetrile had been commercially used at that time, it is reasonable to believe that the indications proposed in the NDA would be the ones proposed in any labeling used for such a commercial product.

An article by Dr. Krebs, Sr., and Dr. Arthur T. Harris, entitled "The Treatment of Breast Cancer With Laetrile By Iontophoresis" (copyright 1955 by the John Beard Memorial Foundation) (R 183, Att. 7) proposes three different methods of utilizing Laetrile. At page 30, the three main methods of administering Laetrile and its auxiliary Beta-glucosidase are described as: (1) Parenteral administration (injection into the muscle), (2) iontophoresis, discussed below, and (3) tamponade.

Perhaps the most bizarre of the proposed methods of administration for Laetrile is "Iontophoresis". This new procedure developed by the senior Krebs for treatment of cancers "especially in the breast" is described as "infinitely more effective and thorough." The procedure is described as follows:

It is to force by galvanic current the Laetrile through the skin and into as well as between the individual cancer cells. The apparatus we use is a simple galvanic instrument (or, preferably, one of the modern instruments with resistors instead of tubes). The positive pole lead goes to the tumor site—the breast—the negative to the back. The solution of Laetrile is soaked in gauze and covered by a block tin electrode, then positioned firmly over the tumor. The negative pad, well moistened, is positioned on the back, and the current turned on. Slowly the amperage is raised to 10 milliamperes then 15, never more than 20 except in a very thick chest wall. In fifteen to thirty minutes, depending on the size of the growth, the pad has become almost dry: the Laetrile has been driven into—not around—the cancer cells (id. at 26-27).

The action of iontophoresis is described in more detail on pages 30-31. Apparently it is expected that the iontophoresis therapy will liquify the tumor mass, and a physician will thus be able to draw out, with an aspirating needle, the "cancer-juice" before administering the next iontophoresis treatment (id. at 32). Iontophoresis therapy involves administration every 2 to 5 days (id. at 31).

This article, which has been quoted and referred to previously, explains some of the history and theories of Laetrile's use. The article promotes the "Howard Beard Anthrone Test" for the diagnosis of cancer (id. at 34). This test involves analysis of the urine of the patients (see id. at 16-19). The authors recommend against biopsies to determine whether tumors are malignant (id. at 27-28). The

authors state their opposition to surgery prior to "control" of the cancer by Laetrile (id. at 35).

Laetrile (amygdalin) is apparently currently in use as an oral medication. Nothing in the record, other than conclusory statements of the most general kind, indicates that any version of the drug was in use as an oral medication on October 9, 1962. The only statement that such a drug was ever used orally before that date which purports to be based on first-hand knowledge is the statement of Charles Gurchot, Ph.D. (R 302, Ex. L at ¶ 8), that between 1933 and 1934 a Dr. Lewis administered amygdalin orally as well as intramuscularly and intravenously. Dr. Gurchot states that use in California, in which he participated between 1934 and 1945, involved administration intramuscularly and intravenously (id. at ¶ 14). As discussed above in the section on the 1938 grandfather clause, the "amygdalin" Dr. Gurchot states he was involved in using is different from that used at later dates.

After October 9, 1962

Variations in the conditions for use of Laetrile (or amygdalin) proposed in its labeling continued after the critical October 9, 1962 date. In 1965, an FDA inspection of Krebs' Laboratories produced labeling for Laetrile which suggested a new set of conditions for its use (see, generally, R. 201, Ex. C.). The labels on the packages of the drug stated "For raising hemoglobin index and red count[;] relieves pain due to malignancy." (Similar labels were obtained by California State health officials in 1971 (R 183, Att. 9).)

In a pamphlet published by Krebs' Laboratories, obtained in the 1965 inspection, injections at various sites were indicated for various types of cancer—brachial vein for cancer of lungs; brachial vein and innominate artery for breast cancer; external carotid or one of its branches for cancer of the neck, thyroid, face, and temple area; brachial vein for cancer of liver, gastro-intestinal tract and the spleen; the vault of the vagina, the abdominal aorta, or the internal iliac arteries for cancer of the uterus and ovaries; the scrotal sac for cancer of the prostate and testicle (R 201, Ex. C, II).

Two pamphlets obtained in the 1965 inspection are in fact inconsistent with each other in some instances, though the similarities in printing style indicate that they were printed at about the same time. One states the dose of Laetrile to be administered to be "(g)enerally speaking 10 mgs. per pound of patient's weight, with "occasionally" 15 mgs. per pound and "very rarely" 20 mgs. per pound (id.). The second states that: "The usual daily dose of Laetrile now is 20 mgs. of the glucoside Amygdalin for every pound of the patient's weight, or even twice this, particularly in bone cancer." Three gms. are recommended for a 150-pound person and 4 gms. for a 175-pound patient, i.e., over 20 mgs. per pound (id. at Ex. C, III). (While no labeling indicating such conditions was

submitted, it should be noted that Dr. Binzel, at oral argument, talked of injections of from 9 to 15 grams of amygdalin at one time (Tr. at 363). The page proofs of Dr. Richardson's book indicate that he uses intravenous injections of "6-9 gms. or more" of Laetrile during the first month of treatment with intravenous or intramuscular injections of 3 grams thereafter (Tr. Ex. 1 at 124).)

More important, however, are the differences between the conditions recommended in the labeling collected in 1965 and those in that submitted with the 1962 NDA. In the 1962 NDA, Laetrile was to palliate, not to cure; in the 1965 labeling it is stated: "Laetrile does not palliate, it acts chemically to kill the cancer cells selectively without injury to the normal tissues of the body" (R 201, Ex. C). While the 1962 NDA stated that Laetrile was not indicated to the exclusion of other recognized cancer therapies, the labeling collected in 1965 states: "The less drugs and medicines given, during the Laetrile treatment the better. What should be especially avoided is sulphur and sulphur drugs and other cancer therapies, * * ." (emphasis added) (id.). Even more frightening to those who are concerned that utilization of therapies of proven effectiveness will be delayed until too late because of use of Laetrile is the statement in the pamphlet in use in 1965 that: "Being harmless * * * Laetrile should be used first instead of last as generally has been done when everything else has been tried and hope is gone" (id.). An affidavit submitted by Dr. Robert S. K. Young describes the medical importance of the numerous variations between the 1962 labeling and that of 1965 (see ¶ 11 of R 201).

The labeling discussed, which bears the name of Krebs Laboratories and of Dr. Krebs, Sr., appears as Ex. C to R 201. It should be noted that there is no copyright or other date on the labeling that was found in Dr. Krebs' establishment in 1965. One of the pamphlets, that which contains some of the statements quoted above, is described as a "pre-1963 pamphlet" in the affidavit of Dr. Sherwood Lawrence (R 183 at 4). It appears as attachment 8 to that affidavit.

A pamphlet published by the McNaughton Foundation suggests intravenous dosages of amygdalin of from 3 to 6 grams a day administered over a 24-hour period (R 183, Ex. 10b at 5). That pamphlet, which cites references dated May 11, 1970 and thus must have been published thereafter, described the use of amygdalin as an anlygesic, yet also indicates that the drug inhibits the growth of malignancies (id. at 1).

The record contains labeling for Laetrile (or amygdalin), which was in use after October 9, 1962, which clearly recommends oral administration of the drug. See R 183, Att. 10a—capsules, 400 mg.; R 183 Att. 4c—capsules, 400 and 500 mg.; R 183, Att. 10b—amygdalin tablets which may be broken up and added to drinking water or food (½ to 2 grams per day recommended); R 183, Att. 10d—"Magydalin" capsules with 500 mgs. of "pure crystalline LAETRILE (amygdalin)".

While in 1962 Laetrile was proposed in the NDA as a palliative, the labeling in the record makes clear that it has been touted since that time as a treatment for cancer (see R 183, Att. 10a.; see also R 201, Ex. C, discussed above). Mr. Krebs, Jr., claims Vitamin B-17, which may be or may contain Laetrile, to be "antineoplastic" and to be instrumental in "therapy" for cancer (Journal of Applied Nutrition, Vol. 22, "The Nitrilosides (Vitamin B-17)—Their Nature, Occurrence and Metabolic Significance (Antineoplastic Vitamin B-17)," at 75, 81 (R 183, Att. 10c).

In a transcript dated November 18, 1974, prepared by FDA, of a film entitled "World Without Cancer", produced by the proponents of the use of Laetrile, the claim is made that 15 percent of persons with advanced metastasized cancer will be saved by "vitamin therapy," which from the context includes vitamin B-17 (Laetrile). The film claims that, of those with cancer diagnosed early, at least 80 percent will be saved by vitamin therapy. Of those who are healthy with no clinical evidence of cancer, the film's narrator states that close to 100 percent can expect to be free from cancer as long as they utilize vitamin B-17. The use of the term "vitamin B-17" indicates that the film was made after 1962, since Laetrile was not claimed to be a "vitamin" until after that time (see, generally, exhibit 2 to R 198).

As discussed above, to qualify for exemption from the "new drug" definition of 21 U.S.C. 321 (p) pursuant to the "1962 grandfather clause," the proponents of Laetrile (or amygdalin) would need to show among other things that the drug in question is now "intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on" October 9, 1962. No evidence in the record shows either that the drug was used or that any conditions of use were recommended for it on that date. Evidence in the record indicates that conditions of use recommended prior to the critical date not only conflict with each other, but also conflict with recommendations after that date, which themselves conflict with each other. The Commissioner concludes, on the basis of the evidence in the record, that Laetrile as now known is not intended solely for use under conditions recommended in labeling on October 9, 1962.

4. Lack of General Recognition of Safety in 1962

As discussed above, a drug could not escape new drug status under the "1962 grandfather clause" if it were a "new drug" on October 9, 1962. To have been exempted from new drug status on that date, Laetrile (or amygdalin) would have to have been "generally recognized among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof" (21 U.S.C. 321(p)(1) (1962)), and that general recognition would have to be based upon use other than investigational use

(21 U.S.C. 321 (p) (2) (1962)). The Commissioner has elsewhere discussed the evidence that demonstrates that Laetrile and amygdalin (to the extent that they are different) are not now generally recognized by qualified experts as safe for use under the conditions prescribed, recommended or suggested in their labeling. While the present lack of general recognition of the substances would not necessarily demonstrate that they were not so generally recognized in 1962, that fact does provide evidence of the earlier lack of recognition.

The evidence in the record provides a number of independent grounds upon which the Commissioner concludes that Laetrile (or amygdalin) was not generally recognized by experts in drug safety evaluation as safe on October 9, 1962. That conclusion is supported (1) by the proven lack of a number of prerequisites to such general recognition: lack of knowledge among such experts generally of Laetrile's use, of Laetrile's formulation, and of the proposed conditions of Laetrile's use; lack of data published in the scientific literature supporting Laetrile's safety as a cancer drug; and lack of scientific testing sufficient to show safety; (2) by statements in the record by experts in the evaluation of the drug safety that Laetrile was not generally recognized as safe as a cancer drug by themselves and their peers on October 9, 1962; and (3) by abundant evidence that Laetrile was not generally recognized by appropriately qualified experts to be effective in cancer therapy on October 9, 1962. The Commissioner concludes that the showing in the record on each of these points is itself sufficient to demonstrate that Laetrile (or amygdalin) was a new drug in 1962.

(a) *The Prerequisites.* (i) *Lack of General Knowledge of Use.*—A number of submissions to the administrative record indicated that the use, and the details of the use, of Laetrile or amygdalin were simply not generally known to the community of experts in the safety evaluation of drugs on October 9, 1962. Thus, there could not be any sort of "general" recognition of the substances' safety in 1962. (See, e.g., the oral testimony of Dr. Rhoads, the national chairman of the National Cancer Advisory Board (Tr. at 110-111; Tr. Ex. 5); oral testimony of Dr. Carr, professor in medicine at the Mayo Medical School (Tr. at 181).)

(ii) *Lack of General Knowledge of formulation.*—The variability in, and uncertainty about, the composition of the drug in use at that date (discussed in detail above) means that "general recognition" of the drug's safety by experts in drug safety evaluation would be impossible. The fact was recognized in *Durovic v. Richardson*, *supra*, 479 F. 2d at 251, in which another unproven cancer remedy was ruled not to be exempted from regulation by the 1962 grandfather clause.

(iii) *Lack of General Knowledge of Conditions of Use Suggested.*—Equally important, the variation in and uncertainty about the conditions of use suggested in the labeling of Laetrile (or amygdalin) on October 9, 1962, also dis-

cussed in detail above, means that such general recognition could not have existed. The law as of that date is clear that general recognition must be of safety "for use under the conditions prescribed, recommended, or suggested in the labeling" of the drug (21 U.S.C. 321(p) (1) (1962)). If experts throughout the country could not have known of those conditions of use, recognition of safety by them could not have existed.

(iv) *Lack of Safety Data in Scientific Literature.*—The existence of published data available in the scientific literature on the safety of a drug is a prerequisite to general recognition by experts of that drug's safety within the meaning of 21 U.S.C. 321(p). *Weinberger v. Bentex Pharmaceuticals, Inc.*, *supra*, 412 U.S. at 652; see *United States v. 41 Cases, More or Less*, 420 F. 2d 1126, 1130 (5th Cir. 1970); *United States v. 1,048,000 Capsules, More or Less*, *supra*, 347 F. Supp. at 771. The record lacks any reference to any such published data available to experts on October 9, 1962.

In fact, the record demonstrates that, while data showing the lack of Laetrile's effectiveness have been published in the scientific literature, data upon which an expert in the evaluation of drug safety could make a judgment that Laetrile was safe for use in cancer therapy do not exist in the scientific literature available to experts generally even today.

(v) *Lack of Showing of Safety by Adequate Testing.*—As noted in the sections of this opinion dealing with the new drug issue, the Supreme Court has held in *Weinberger v. Bentex Pharmaceuticals, Inc.*, *supra* that "general recognition," as those terms are used in 21 U.S.C. 321(p), requires the same type of showing of safety and efficacy necessary for approval of an NDA pursuant to 21 U.S.C. 355(d). For approval of an NDA prior to October 9, 1962, the application was required to contain "adequate tests by all methods reasonably applicable to show whether or not such drug is safe" for its intended uses, and those tests were required to in fact show that the drug was safe (21 U.S.C. 355(d) (1962)). It appears from the record that no such tests existed for Laetrile (or amygdalin) on October 9, 1962. Were there a question about the lack of such studies, that question could be resolved by the fact that, at approximately the time in question, NDAs for Laetrile and for a combination of Laetrile and iodine were submitted to the FDA. Both applications were declared to be incomplete because of the lack of required data to show safety and effectiveness. (See, generally, the letter from John L. Harvey, FDA Deputy Commissioner, to K. F. Ernst, M.D., April 30, 1963 (R 183, Att. 16, App. 18).)

(b) *Statements by Experts.* Even setting aside the above important prerequisites to general recognition, the evidence in the record that Laetrile was not generally recognized as safe by experts in the evaluation of drug safety on October 9, 1962 is extremely strong.

The plethora of statements of experts in drug evaluation that Laetrile (or amygdalin) is not now generally recog-

nized as safe is discussed elsewhere. Some of the experts focused upon the October 9, 1962 date. (See affidavit of Dr. Emil J. Freireich: "Neither amygdalin nor any other cyanogenic glycoside was generally recognized as safe for any (use in the treatment of cancer or prophylaxis against cancer or relief of pain associated with cancer, or for any medical use) on October 10, 1962" (R 390 at ¶ 19; accord affidavit of Dr. Daniel T. Carr, (R 176 at ¶ 15).) For a similar statement that Laetrile was not generally recognized as safe by appropriately qualified experts in 1962, see affidavit of Dr. Carl M. Leventhal (R 184 at ¶ 13).

Even more compelling evidence on this question can be gleaned from statements of experts in drug safety evaluation made near the October 9, 1962 date. Fortunately, at just about that date the State of California Cancer Advisory Council was polling just that type of expert concerning Laetrile (R 183, Att. 16 at 37-38). (Since the Krebs Laboratory was located in California, it would seem that experts in the California area would be most likely to be aware of recognition of Laetrile or amygdalin's safe use as cancer therapy.) The experts polled, representing each of the medical schools in the California university system, were asked about the drug's efficacy rather than their views on the question of the safety of Laetrile's use in cancer therapy. Clayton G. Loosli, M.D., Dean of the University of Southern California School of Medicine, speaking for the members of the school's faculty, indicated that Laetrile, while extensively investigated, was in the unanimous opinion of the faculty without value in the treatment of human cancer. He stated that "further, we consider its use not only not valuable even as a placebo but harmful in that use of Laetrile prevents patients from receiving what otherwise might be an effective modality of treatment" (id., App. 10). J. B. deC. M. Saunders, M.D., Dean of the University of California School of Medicine at San Francisco, speaking for the clinical staff of his medical school, gave their opinion that the use of Laetrile was of no value in the treatment of cancer. He said "(i) t may not only delay or interfere with conventional therapy (surgery and radiation) but indeed could seriously jeopardize whatever chances the patient may have for cure. The unscrupulous use of unproven cancer 'remedies' such as Laetrile tragically increases the human suffering already associated with cancer (id.)."

The only evidence submitted by proponents of Laetrile that experts qualified to evaluate the safety of drugs generally recognized the drug as safe when used in cancer therapy were two affidavits by Charles Gurchot, Ph.D., and Chauncey D. Leake, Ph.D., (R 302, Exs. K and L). The Gurchot affidavit states in paragraph 14 that amygdalin in liquid and solid form was used prior to 1962 (between 1934 and 1945) by Gurchot, under the supervision of five named medical doctors at the University of California Medical School at San Francisco (R 302, Ex. L). This amygdalin

was, according to his statement, administered "on patients intramuscularly and intravenously" (id.). At the same time, the amygdalin preparation he used, he states, was used by "about a dozen physicians throughout California through the University of California Medical Schools and as recommended by members of the Hospital Staff of the University of California Medical School at San Francisco" (id.). Gurchot states that these physicians were qualified by medical and scientific training and professional experience to evaluate the safety of substances such as amygdalin and that they recognized it as safe (id.). The Gurchot affidavit should be compared, in the first instance, to the 1962 statement, already discussed, of the Dean of the University of California Medical School at San Francisco, which states, "Laetrile is not, nor has it been, in clinical use or in experimental trials in this institution * * *" (emphasis added) (R 183, Att. 16, App. 10 at 8).

Even were the Commissioner to credit Dr. Gurchot's statement, he would have to conclude that, whatever had happened in the years 1934-1945, that experience did not form a basis for general recognition by qualified experts of safety in 1962, since even the faculty of the medical school in which Gurchot claimed the experiments had taken place had no knowledge of them. It should also be noted that, as discussed in the section on the 1938 grandfather clause, the "amygdalin" Gurchot could have been using would not have been the same substance in use today. His evidence, in addition, speaks only of investigational, as opposed to commercial, use of the drug—an improper basis for "general recognition" (see discussion above). In light of these facts, and of the other information in the record on this issue, Gurchot's statement in paragraph 16 of his affidavit indicating his belief that the general recognition of safety requirement for exemption from new drug status did exist for amygdalin on or prior to October 10, 1962 must be questioned.

The affidavit of Chauncey D. Leake, Ph.D., indicates that he is familiar with Dr. Gurchot's use of amygdalin in the mid-1930's and 1940's at the University of California Medical School Hospital in San Francisco. He states that at that time, i.e., in the 1930's, "it was generally held by physicians and other scientists familiar with it, that amygdalin was safe when used in the treatment of cancer as well as in its use as an expectorant or cough suppressant" (R 302, Ex. K at ¶ 6). This conclusion does not, however, indicate recognition by anybody in 1962; it does not, as demonstrated elsewhere, deal with the drug presently being used (see affidavit of Dr. Krebs, Sr., (R 183, Att. 13)); it refers only to physicians and scientists "familiar with it", thus not addressing the question of whether recognition was general.

(c) *Lack of General Recognition of Effectiveness in 1962.*—Experts in the

evaluation of the safety of a drug do not conclude that a drug is safe, if that drug is intended for the treatment of a life-threatening disease, if it has not been shown to be effective. The record illustrates a broad consensus of cancer researchers and physicians that Laetrile presents a grave danger to patients who might be helped by orthodox therapy. The concern is that such patients may be induced to turn instead to this ineffective drug, their disease may progress while effective therapies are foresaken, and the use of the ineffective cancer drug will inevitably and inexorably lead to the patient's death. (See, e.g., R 396 at 1; R 384; R 170 at ¶ 11; R 183 at 18; R 266, Ex. 3 at 865; R 192 at ¶ 14; R 193 at 1; and R 195 at ¶ 13.) Thus, even if it were shown, as it has not been, that experts in 1962 generally were aware of the drug, its formulation, its conditions of use, and of toxicity data concerning it published in the scientific literature, the alleged nontoxicity of Laetrile (or amygdalin) would not form a sufficient basis for general recognition of safety in 1962.

At the time of the 1962 amendments to the act, it was made clear that, where drugs utilized for life-threatening diseases are involved, evidence of effectiveness is essential to proof of safety. The Senate report on the amendments stated:

The Food and Drug Administration now requires, in determining whether a "new drug" is safe, a showing as to the drug's effectiveness where the drug is offered for use in the treatment of a life-threatening disease, or where it appears that the "new drug" will occasionally produce serious toxic or even lethal effects so that only its usefulness would justify the risks involved in its use.

(S. Rep. No. 1744, 87 Cong. 2d. Sess., 1962 U.S. Code Cong. Ad. News 2884, 2891.) The report made it clear that the amendments were "in no way intended to affect any existing authority of the (FDA) to consider and evaluate the effectiveness of a new drug in the context of passing upon its safety" (emphasis added) (id. at 2892).

As the Court held, when dealing with a similar unproven cancer remedy, in *Durovic v. Richardson, supra*, lack of general recognition of the effectiveness of a drug intended for treatment of a life-threatening disease on October 9, 1962 means that general recognition of its safety could not have existed:

(A) drug offered for use in the treatment of cancer is now, and was before the amendments, a new drug unless it has achieved general recognition among the experts, as safe and effective for such use (479 F. 2d at 250).

The evidence in the record overwhelmingly demonstrates that, among experts in the evaluation of the safety and effectiveness of drugs, Laetrile (or amygdalin) is not recognized as effective (see discussion above). It is a fair inference, absent any indication to the contrary, that a drug not recognized as effective now was not so recognized on October 9, 1962.

Again, however, the record supplies evidence of opinions of such experts given at almost exactly the time in question. As noted above, the medical schools in California were asked their opinions of Laetrile's effectiveness. Each of the medical schools contacted stated that Laetrile was never used in their institutions and that they concluded that it was not effective and had not been shown by testing to be effective. (See, in addition to the letters discussed above, letters from Dean David B. Hinshaw, M.D., Dean of Loma Linda University Medical School, Dr. M. H. Simmers, Coordinator, Cancer Training, California College of Medicine, Sherman M. Mellinkoff, Dean, University of California, Los Angeles Medical School.) These letters are printed as appendix 10 to R 183, Att. 16; see also R 183, Att. 16 at 38. The report states that Robert H. Alway, M.D., Dean of Stanford University School of Medicine, also indicated that Laetrile was of no value in cancer treatment and was not part of the treatment program at his medical school (R 183, Att. 16 at 38). The report also states that two other professors involved with cancer therapy and research concurred in this evaluation (id.). The report of the California Cancer Advisory Council itself constitutes convincing evidence that at about the time of the crucial date, October 9, 1962, experts did not generally recognize Laetrile as safe for the treatment of cancer, in particular because it was considered to be a worthless treatment for a life-threatening disease. As has been pointed out elsewhere, no adequate and well-controlled clinical investigations, the prerequisite for general recognition by experts of a drug's effectiveness (*Weinberger v. Hynson, Wescott and Dunning, Inc., supra*) exist as to Laetrile. Thus, even were the testimony in the record on this question less conclusive than it is, it would be necessary to find that there was no general recognition by experts that Laetrile was safe for use for any purpose on October 9, 1962.

The Commissioner thus concludes that Laetrile (or amygdalin) does not qualify for exemption from the new drug provision of the act by virtue of compliance with the 1962 grandfather clause.

IV. THE POPULARITY OF LAETRILE

A. LAETRILE AND OTHER UNPROVEN REMEDIES

Laetrile, as far as is known, has nothing in common scientifically with any of the other "unproven" cancer remedies of the past.⁶ Yet the method of promotion of the drug and the arguments advanced for its use are markedly similar to those of past cancer frauds.

1. *The History of Cancer Quackery in the United States*

Through the ages there have been literally thousands of supposed remedies

⁶ Dr. Ernst Krebs, Sr., though he thought people should be allowed to use his Laetrile, and a number of other remedies since forgotten by the public, is on record as stating that he could see no rationale for Krebiozen, the last of the highly publicized "unproven" cancer remedies (R 183, Att. 14 at 2).

for cancer, generally so outlandish that it seems incredible that people once believed in them. One historian of health quackery pointed out that the promotion of "unproven" cancer cures has a long history in this country:

Cancer quackery appeared in America during colonial times, one example being the alleged "Chinese Stones" vended by a purported Frenchman, Francis Torres, who hawked his cures from town to town. During the nineteenth century, an alert physician, Caleb Tichnor, bemoaned the breed of cancer quack, (each of whom offers) his "secret specific" to the panicked citizenry who, "like a drowning person grasping at straws seize upon the frail hope that is offered by the hand of ignorant charlatany!" "Dr. Johnson's Mild Combination Treatment for Cancer" offered the first serious legal challenge to the 1906 Pure Food and Drug Act, requiring the Congress to enact the Sherley Amendment of 1912. At this same time, Dr. Arthur J. Cramp of the American Medical Association devoted fifty pages in his first *Nostrums and Quackery* volume to a detailed account of ten major cancer 'cures' deceiving the American people. Compiling a third volume in 1936, Dr. Cramp pointed to twenty-nine purported cancer cures, stating that "hardly a week has passed when the Bureau of Investigation of the American Medical Association has not received one or more letters in which the writers stated that they had discovered, or had in their possession, a 'sure cure' for cancer."

Nor has cancer quackery diminished as the twentieth century has progressed. Indeed, with the decline of contagious diseases, due mainly to the chemotherapeutic revolution, and the consequent rise of cancer into second place as a cause of death, cancer quackery has expanded. The 1971 edition of *Unproven Methods of Cancer Management*, published by the American Cancer Society, described fifty-four promotions offering hope to cancer sufferers but deemed devoid of value by ACS. The 1976 edition of *Unproven Methods of Cancer Management* cites in its appendix seventy-one such methods (R 400 at 1-2; see also R 400, Ex. 2).

Evaluation of approximately 60 of these methods may be found as attachments to R 400, Ex. 2.

Each decade seems to have an unproven cancer remedy that is promoted so effectively that it attracts a large following and becomes a cause celebre. In the 1940's and early 1950's, the Koch Antitoxins were heavily promoted as a specific cure for cancer. The Koch Antitoxins thesis, promoted by William F. Koch, M.D., advanced "the theory that cancer is caused by a microorganism resembling the spirochete of syphilis, which could be destroyed by a differential poison of his invention" (R 183, Att. 3 at 43). "The Koch medications, known collectively as Koch's Synthetic Antitoxins or oxidation catalysts, were individually packaged in 2 ml ampules. Malonide and glyoxylyde (were) claimed to be present in a concentration of one part in a trillion parts of water, and parabenzoquinone one part in a million parts of water" (id.). "Glyoxylic acid, of which glyoxylyde is the anhydride (the resulting element after water is removed), is a normal constituent of the human body. About two grams are formed daily—at any given time there are about five milligrams in the human body, whether healthy or diseased. It would take a tril-

lion 2 ml ampules of Koch's glyoxylyde to equal the amount produced daily by the body, and two and one half billion ampules to equal the amount present in the body at any one time" (id. at 44). Even so, cancer patients paid as much as \$300 per injection for this worthless remedy (R 400, Ex. 2, ACS "Koch Antitoxins").

Another unproven cancer remedy whose promotion reached substantial proportions in the 1950's was the medications of Harry Hoxsey. Two liquid mixtures played the central role in the Hoxsey remedy. The "brownish black liquid" contained potassium iodide and "some of all of the following inorganic substances as the individual case may demand: Licorice, red clover, burdock root, stillingia root, berberis root, poke rot, cascara, Aromatic USP 14, prickly ash bark, (and) buckthorn bark (R 400, Ex. 2, ACS "Hoxsey Method"). The "pink liquid" was composed of lactate of pepsin and other ingredients (R 416, Ex. 6 at 368).

Hoxsey and his spokesmen were frank to confess that they did not completely know why his colored mixtures cured cancer. They asserted that they had been kept too busy treating cancer patients and fighting court battles to keep their clinic open "to spare the time, personnel, and facilities for objective study" (id. at 369). Hoxsey's hypothesis "held that a major chemical imbalance in the body caused normal cells to mutate into a cancerous form, and his medicines restored the original chemical environment, checking and killing the cancerous cells" (id. at 369). The proponents of the Hoxsey remedy, like the Laetrile proponents of today, condemned the only treatments then recognized as having value in cancer therapy. The Hoxsey proponents held that "X-ray and radium (had) no place in the treatment of cancer They further upset basic cell metabolism rather than do anything to correct it" (id. at 369).

Harry Hoxsey promoted his unproven cancer remedy for more than 30 years until 1960, when after years of numerous local, State, and federal court actions, the sale of the Hoxsey medicines was stopped in the United States. At the time of the 1960 permanent injunction banning the sale of Hoxsey remedy at the Taylor Clinic, more than 10,000 patients were receiving the remedy. (See, generally, R 400, Ex. 2, ACS "Hoxsey Method"; R 416, Ex. 6.)

In 1964 a California State government report stated that, at that time, "Possibly no other unproven treatment for cancer has received so much public attention or approbation as Krebiozen. This agent has been the subject of intense scrutiny by scientists and government officials, and loudly discussed by the press and by the general public. The events surrounding the introduction of Krebiozen as a potential cancer cure and the subsequent trials to test its capabilities produced an air of notoriety seldom seen in the medical world" (R 183, Att. 3 at 59).

Unlike Harry Hoxsey's backwoods herb remedy, Krebiozen, the most heavily pro-

moted unproven cancer remedy of the 1960's, had an aura of high scientific prestige. The drug's principal proponent in the United States was Dr. Andrew C. Ivy, then Vice-President in charge of the Chicago Professional Colleges, Distinguished Professor of Physiology and Head of the Department of Clinical Science, University of Illinois (id.). Krebiozen was reportedly produced originally in Argentina by Stevan Durovic, M.D., a Yugoslavian physician, and brought to the United States in 1949 (R 400, Ex. 2, ACS "Krebiozen and Carcalon"). "According to Dr. Durovic, the original 2 grams of powder, from which he said 200,000 doses were prepared, was obtained as an extract of the blood of 2,000 Argentinian horses which had previously been injected with a sterile extract of *Actinomyces bovis*, a microorganism which causes a disease called 'lumpy jaw' in cattle" (id.). "Food and Drug Administration analyses of Krebiozen ampules (showed) that those sold before 1960 (were) different from those sold in 1963, and that neither contain(ed) any of the powder identified in July 1963 by Dr. Stevan Durovic as Krebiozen, and found to be creatine monohydrate, which will not dissolve in mineral oil. . . . analyses of Krebiozen ampules shipped before 1960 showed they contained nothing but mineral oil, while ampules shipped since then contained mineral oil plus minute amounts of amyl alcohol and 1-methylhydantoin, a derivative of creatine which will dissolve in mineral oil" (id.).

In 1963, a committee of 24 cancer experts was appointed by the Director of the National Cancer Institute to review clinical records on 504 patients treated with Krebiozen, and to recommend whether the Institute should sponsor clinical trials of Krebiozen. The committee unanimously concluded that Krebiozen was an ineffective cancer drug and strongly urged that no clinical trial be undertaken (id.).

In November 1964, Drs. Ivy and Durovic and other proponents of Krebiozen were indicted on 49 counts for violations of the Federal Food, Drug, and Cosmetic Act, mail fraud, mislabeling, making false statements to the government, and conspiracy. All of the defendants were acquitted in January 1966, after a 9-month jury trial (id.). Although the acquittal meant that the government did not prove its case beyond a reasonable doubt, it did not have any bearing on the question of whether Krebiozen was a safe and effective cancer drug. As an unapproved new drug, its distribution in interstate commerce remained illegal in spite of the acquittal, the Krebiozen boom collapsed shortly thereafter.

2. Similarities Between Laetrile Promotion and That of Other Recent "Unproven" Cancer Remedies

The promotion of Laetrile in the 1970's is completely in character with the historical pattern of the promotion of other unproven cancer remedies such as the Koch Antitoxins, the Hoxsey method, and Krebiozen. These characteristics include the following:

(1) The proponents "don the mantle of science while at the same time traducing the reputable scientists of their day" (R 400 at 3).

(2) The proponents claim that "prejudice of organized medicine hinders their efforts" and they "challenge established theories and attack prominent scientists with bitter criticism" (R 400, Ex. 2 "Unproven Methods of Cancer Management—1976" at 3) (hereinafter cited as "Unproven Methods").

(3) The proponents "cite examples of physicians and scientists of the past who were forced to fight the rigid dogma of their day" (id.).

(4) The proponents rely mainly on testimonials and anecdotes as evidence that their remedy is a safe and effective cancer therapeutic agent (see R 400 at 4).

(5) The proponents "do not use regular channels of communication (current, reputable scientific journals) for reporting scientific information" (R 400, Ex. 2 "Unproven Methods" at 2-3). The main channels of communication are the mass media, popular journalism, and word of mouth (see R 400 at 4-5).

(6) The proponents' "chief supporters tend to be prominent statesmen, actors, writers, lawyers, even members of state or national legislatures—persons not trained or experienced in the natural history of cancer, the care of patients with cancer, or in scientific methodology." (See R 400, Ex. 2 "Unproven Methods" at 3.)

(7) The proponents often offer a simplistic theory for causation of the disease frequently involving claims that dietary management can counteract virulent pathologic processes (R 266, Ex. 3 at 865).

(8) The proponents' remedy is "easy and pleasant, compared with the frightening therapies wielded by orthodoxy, the surgical knife, harsh chemical drugs, poisonous radiation" (R 400 at 8).

(9) The proponents claim that the mode of administration of the drug and the method of treatment can only be learned from them (R 400, Ex. 2, "Unproven Methods" at 3).

The record illustrates the remarkable conformity of the Laetrile promotion to this pattern:

(a) *Mantle of Science.*—Throughout history, promoters of unproven cancer remedies have couched the explanation for the remedies in pseudoscientific terms. "Impressive and plausible to the layman, such arcane explanations, to true scientific specialists, came off as nonsensical balderdash" (R 400 at 3). The promoters of Laetrile have presented a series of shifting theories to explain the alleged anticancer activity of Laetrile. These theories have been examined in detail above. (See, generally, R 318.)

(b) *Attacks on the "Establishment."*—The proponents of Laetrile have often accused government agencies and organized medicine of making untruthful and irresponsible statements regarding the experimental evidence of Laetrile's anticancer activity. (See, e.g., R 302, Ex. A at 14-16; R 509 at 3-4.) In other instances, proponents of Laetrile have chastized the orthodox methods of cancer treatment and management, i.e., surgery, radiation, and chemotherapy. (See, e.g., Tr. at 16-27, 297-316, and 417-426.)

The most vocal arguments challenging established orthodox treatments have been concerned with the issue of freedom of choice, discussed elsewhere in this opinion. These arguments, many of them

from cancer patients or their relatives and friends, hold that the "bureaucracy" has no right to interfere with the physician-patient relationship by withholding from them a treatment in which they believe and which they want. (See, generally, Tr. at 55-56, 255-256, and 454-456.)

(c) *Claimed Parallel with Scientific Pioneers.*—To combat criticism from the established medical societies and government agencies that Laetrile had not been shown to be safe and effective, its proponents compare the originators of the drug and physicians who prescribe Laetrile with earlier scientists who were persecuted and ostracized for their scientific theories: Copernicus, Newton, Freud, Galileo, and Semmelweis. (See, e.g., R 318 at 61-63; R 198, Ex. 2 at 3-5).

(d) *Reliance on Testimonials.*—As previously discussed, the proponents of Laetrile rely on testimonials and anecdotes as evidence that the drug is safe and effective in the treatment of cancer. In reviewing the administrative record, the Commissioner has not encountered even one study that meets the legal and scientific standards for making a determination that Laetrile is safe and effective. Proponents claim that physicians using Laetrile are too busy treating patients to be able to maintain the records needed to document adequately the case histories they present. (See, e.g., Tr. Ex. 1 at 117.)

(e) *Lack of Scientific Publication.*—Good science demands that evidence that a drug is safe and effective be presented in a manner whereby that evidence can be reviewed and evaluated by other scientists. Usually this evidence is published in scientific journals and presented for discussion at symposia and other meetings. Historically, "the main reliance of unorthodox promoters rests on the anecdotal evidence of testimonials from laymen, and the main channel for reaching an audience is through the mass media. In earlier days newspaper advertising trumpeted the promise of cancer cures, bolstered by the faces and words of grateful testifiers, not infrequently already dead of the disease" (R 400 at 4-5). The proponents of Laetrile have relied heavily on popular journalism, advertisements, radio and television, "health" organizations and word of mouth to spread their claims that Laetrile is a safe and effective anticancer drug. (See, e.g., R 318; R 302, Ex. A and H; R 198, Ex. 2.) A number of experts active in the management of cancer have submitted testimony stating that the scientific literature contains no reports of adequate, well-controlled studies upon which Laetrile can be regarded as generally recognized as safe and effective. (See, e.g., R 185 at 5; R 186 at 4; R 390 at 6.)

(f) *Noneexpert Supports.*—The proponents of Laetrile are well-organized and, through organizations such as the Committee for Freedom of Choice in Cancer Therapy, have conducted active campaigns to move the discussion of the safety and effectiveness of the drug from the scientific to the political arena. These organized efforts have encouraged cancer patients and others to write their

local, state, and congressional representatives demanding that Laetrile be "legalized." These efforts are addressed not to discussions of the scientific merits of Laetrile as a cancer drug, but rather to the issue of "freedom of choice" discussed elsewhere in this opinion. Such action on the part of the Laetrile proponents is typical of other unproven cancer remedies. Failing to win acceptance in the established medical community, proponents seek sympathetic allies in places of political power. (See R 400 at 6-7.)

(g) *Simplistic Theories of Causation and Reliance on Diet.*—The latest claims being made for Laetrile are that it is a "vitamin," and that cancer is a vitamin deficiency disease. The basis for these claims is discussed elsewhere in this opinion. It is sufficient to note here only that this simplistic theory of cancer prevention and treatment is common to other unproven cancer remedies. Cancer patients are told that they can cure or control their cancer by strict adherence to a special diet that includes a special "vitamin" even through this "vitamin" is not recognized by nutritional experts. (See R 266, Ex. 3 at 865-66.)

(h) *A Painless Cure.*—Laetrile, like other unproven cancer remedies, is promoted as a harmless cancer remedy free of the side effects associated with orthodox methods of treatment such as radiation and chemotherapy. Many of the statements submitted by cancer patients and their relatives and friends reflect the proponents' claims that Laetrile is free of side effects. (See, e.g., R 17; R 48; R 137.)

(i) *Only Proponents Can Effectively Use the Drug.*—In common with the supporters of other unproven cancer remedies, the proponents of Laetrile stress, as did Robert W. Bradford of the Committee for Freedom of Choice in Cancer Therapy, that "you" do not and cannot expect to get results from Laetrile treatment unless you are a trained metabolic physician" (Tr. at 349). These arguments are used to explain why orthodox physicians (i.e., those not trained in the proper use of Laetrile) do not see any evidence of Laetrile's effectiveness as a cancer drug.

B. WHY DO PEOPLE USE LAETRILE?

Throughout history persons afflicted with cancer have turned away from the medical establishment to a series of what most euphemistically might be called "unproven remedies." Laetrile is the most recently publicized of these remedies, but, as the discussion above illustrates, it follows on the heels of other widely publicized therapies such as Krebiozen and the Hoxsey cure. Thoughtful persons have questioned the reasons for this troubling phenomenon. Why do people bet their lives, or the lives of their loved ones, on a therapy which is rejected by almost everyone trained and experienced in cancer research and treatment?

Much evidence in the record addresses this question. The answer lies in the fear that cancer engenders—and that proven therapies for cancer engender—and the need of patients and families for hope in a situation where the hope offered by

the legitimate therapies is often modest. The use of "unproven remedies" is, in the opinion of observers, in large part attributable to the loved ones of the cancer victim, in whom both fear and the need for hope are magnified by sympathy and by the guilt that one feels at being unable to relieve the suffering of a person one loves. This situation is, unfortunately, skillfully exploited by the purveyors of "unproven" cancer remedies, of which Laetrile is only the most publicized.

1. The Emotional Reaction to Discovery of Cancer

"[W]hen cancer afflicts an individual, he is frequently faced with a circumstance which is virtually without hope. First of all, the cancer patient must be terrified by the diagnosis * * *. It would be enough to terrify any lay person to simply be told that he has cancer. But more important than that is the fact that once he is told that he has cancer, he is told by the doctor that the treatments that we have available are very often disfiguring; they can be painful; they can be unpleasant; they can even be risky" (Tr. at 204).

The cancer patient must thus cope with two wounds simultaneously. The first is to the body itself (R 423 at 1). "The other wound is to the psyche, reflected in the loss of the feeling of being invulnerable, a feeling which is basic to ordinary day by day living" (id.). The cancer patient senses suddenly that the future is limited. Social and work mobility are seen as curtailed; so are the patient's functional role in the family and the community. In addition, the patient senses a new dependence on others and may fear that he or she will become a burden on the family (id. at 2). "The initial psychological status of the patient and family is characterized by disorientation, anxiety, guilt, fear of pain and suffering" (R 421 at 1).

Dr. Robert C. Eyerly, Chairman of the American Cancer Society's Committee on Unproven Methods of Cancer Management, states that, "Indeed, we've found that the major reason cancer patients use Laetrile is fear * * * fear that the disease is incurable, that surgery or other therapy is mutilating, and that the medical profession is not to be trusted" (R 173, Att. "Laetrile: Focus on the Facts").

In this climate of anxiety and fear, the medical establishment—which, unlike the proponents of "unproven" remedies, feels an obligation to be honest with the patient and his family—cannot always offer hope: "[P]robably the most important factor (explaining why cancer patients choose to use Laetrile) has been the failure of modern medicine and technological advances to cure or adequately control some cancers. These unfulfilled expectations lead patients to disappointments in standard medicine and to attempt a cure of their disease by pseudoscientific methods" (R 398 at ¶ 9).

Physicians, trained in the saving of life and the alleviation of suffering but unable, in some cases, to do either with

cancer patients, may contribute to the frustration. "Many patients sense a feeling of frustration and hopelessness conveyed, perhaps unconsciously, by the physician who tells them the nature and probable outcome of their disease—a natural feeling on the part of the physician who is discouraged by his recognition that he cannot cure the patient. Patients sensing this hopelessness frequently are unwilling to 'abandon hope' and therefore seek (unorthodox therapies)" (R 190, Ex. 4, Editorial at 327). Glen W. Davidson, Ph.D., Chairman of the Department of Medical Humanities, Southern Illinois University School of Medicine, testified that, "* * * when primary emphasis for treatment is placed on 'cure' and the physician's abilities, rather than on 'coping' and the patient's abilities, the patient is placed in an inappropriate and ineffective dependency relationship. When the physician can no longer promise 'cure' and then attempts to refer the patient out of his practice, or leaves the patient to institutional care of others, the patient feels abandoned. The patient has already had his coping abilities undermined. And many patients react to unfulfilled expectations and violated trust with anger and panic" (R 387 at 2).

A patient facing cancer and the lack of positive assurance from the physician that the cancer can be cured may simply give up hope that what the physician can do for the patient can work. This lack of confidence in proven remedies is tragic in an era when, in the case of many cancers, a significant percentage of patients can be cured or have their lives extended. See, e.g., R 173, Att. ACS, 1977 Cancer Facts at 3. Laetrile's proponents expend great efforts to encourage this feeling. Much of the oral argument of Laetrile proponents in this proceeding was addressed not to the effectiveness of Laetrile but to the ineffectiveness of proven remedies (see, e.g., Tr. at 16 et seq.; Tr. at 228). With real hope extinguished, the use of Laetrile or other unproven remedies is a way of avoiding an acceptance on a conscious level of the consequences of the disease: "The decision to use Laetrile indicates that, at the subconscious level, patients and their families have given up on conventional therapy and, in fact, have accepted the inevitability of death. On the more superficial level, patients choosing Laetrile are persons who believe that they do not require the use of sophisticated, anti-cancer treatments. This reflects an ambivalence which many patients feel at the time they are required to make decisions about cancer therapy. If patients can maintain denial about the seriousness of their cancer, then they can permit themselves to experiment with a bizarre apricot-extract, such as Laetrile" (R 433 at ¶ 13). "Human beings have become accustomed to using the psychological techniques of denial in dealing with real problems" (R 390, Ex. 3 at 386). "The decision to use Laetrile is, in essence, an attempt 'magically' to avoid the reality of cancer" (R 433 at ¶ 9).

2. The Role of Loved Ones

Patients with a diagnosed malignancy frequently encounter ostracism in their private, social, and vocational roles (R 387 at 1). At this point, the caring of loved ones and their sympathetic willingness to continue to associate with and to share the suffering of the cancer patient assume great importance to the patient. This caring relationship, quite understandably, leads to a dependence by the patient on the loved one and a corresponding feeling of responsibility in the nonpatient: "Many patients in their initial response to cancer diagnosis surrender control to those closest to them, further complicating the issue of informed choice. Highly anxious relatives with little or no medical understanding of cancer as a disease entity fall prey to the emotional appeal of the proponents of Laetrile" (R 421 at 2). "Cancer patients are most vulnerable to the manipulations of others when they feel they are (1) being abandoned, (2) unable to control pain, and (3) unable to maintain a 'sense of dignity' by being able to make decisions for themselves. Attempts at guarding oneself from all three fears are often incompatible. Many cancer patients feel they are in a 'double-bind.' If they don't follow their physician's treatment plan, the disease process won't be arrested. If they don't follow the competing, and often contradictory advice from relatives and friends, they will be abandoned. And if they assert their own feelings they will be ostracized by others at the very time they most need support from others" (R 387 at 1-2). Thus, some patients pay the price of what benefits are available from orthodox treatments in order not to be abandoned by family and friends—"a psychological analogue to the theological concept of being 'cast into Hell' * * *" (id. at 2). In many cases, it is family and friends who, amplifying the patient's feelings, try to get their anger and panic under control by manipulating the patient into use of medically unacceptable remedies. (See id. at 2.) The families of cancer patients, particularly parents of children with cancer, are understandably desperate for anything that will cure cancer. They often are beset by irrational feelings of guilt, and seek to assuage these feelings with the assurance that "* * * 'we did everything for our child' even to the point of foolishness in going after an unproven cure * * *" (R 394 at 2).

The shared responsibility of the loved one of cancer patients for the patients' involvement with Laetrile (or other unproven remedies) helps to explain why these families have been among the most vociferous proponents of Laetrile. "This reaction can be understood because such persons, whether they are family members or friends, have to justify the deceased's use of Laetrile by suggesting that the patients were considerably helped by the drug, that their lives were prolonged to a significant extent, or, at the least, that they did not suffer a great deal of pain during treatment with the drug. To do otherwise would require them to acknowledge that they made a mistake

and misled the patients or that they went along with decisions which were clearly erroneous. Living with that kind of guilt is very difficult and the advocacy of Laetrile is a way of avoiding it" (R 433 at ¶ 15). It is only those family members who did not participate in, or dissented from, the decision to use Laetrile who, after the patient's death, raise their voices against the drug's use (see, e.g., R 47; R 429; R 300; R 348).

3. Methods of Promotion of Laetrile

As is obvious from the above discussion, the cancer victim and his or her family are extremely vulnerable to the kind of persuasion used so skillfully by Laetrile's promoters. This persuasion may take the form of highly polished and thus convincing films and books (see Tr. at 331) or of personal visits. The fact that many persons involved in Laetrile promotion believe strongly in the drug makes their presentations, because sincere, all the more compelling. In his affidavit, one cancer patient, speaking from his own experience, stated that "immediately after a diagnosis of cancer, most patients and family members are susceptible to something such as Laetrile, which offers a painless treatment with certain results" (R 388 at 2). The patient also stated that, somehow, the names of cancer patients in his area had been obtained by certain persons helping to spread the Laetrile theory. He indicated that Laetrile proponents exerted constant pressure on him and his wife to quit orthodox medical treatment and try Laetrile. Testimonials from patients who spoke in glowing terms of their recovery or successful treatment with Laetrile were offered to support the proponents' claim (id.). Laetrile promoters are diligent in searching out persons with reported cancer to offer their product. One physician noted that he had a patient who, within 24 hours of his being diagnosed as having lung cancer, received information in the mail telling him he ought to take Laetrile and where and how to get it (Tr. at 184).

Laetrile proponents are keenly aware of the involvement of family members and friends in decisions to accept unproven remedies and actively seek to persuade them of the drug's benefits. One woman who had had surgery and chemotherapy for treatment of breast cancer commented: "My biggest problem has been coping with well-meaning relatives and friends who swallow this propaganda of unprofessionals and then try to make me feel guilty because I don't take their advice . . ." (R 96).

Laetrile proponents play upon the victim's frustration with a medical establishment that cannot offer the certainty of a cure. Some patients reportedly turn to Laetrile precisely because it is "illegitimate," behavior that appears to be "an anger reaction toward legitimate medicine" (R 387 at 3). This antagonism toward the medical establishment is fanned by Laetrile proponents (as it has been by the purveyors of previous "unproven" remedies) to a pitch that most observers would consider absurd. When a speaker at the oral argument asked the

audience, which consisted predominantly of Laetrile supporters, if "you really think that a quarter of a million physicians across the country can let people die because they want to make a profit off of them?" the audience response was a loud chorus: "Yes" (Tr. at 191).

Laetrile proponents also play upon and build the cancer patient's fear of legitimate cancer therapies. (See R 421 at 2: "The promise of a painless cure through Laetrile, as opposed to orthodox medical methods with their side effects capitalizes on the fear of pain and suffering".) "Slash (or cut), burn, and poison" are the code words of the Laetrile supporters for the proven remedies of surgery, radiation and chemotherapy (see, e.g., Tr. at 291, 357, 463). A videotape of an interview with a cancer patient (R 419, Ex. B; see also R 197 at ¶ 7) that is part of the record shows graphically the costs of this sort of propaganda. The victim is a woman who, at the time her breast cancer was discovered, was given a reasonably good prognosis of recovery after surgery. Out of fear of surgery she tried Laetrile therapy. Though the tumor grew to involve her whole breast she continued to avoid conventional therapy, even trying, after Laetrile did not help, an "asparagus" diet cure, garlic, and finally a fruit and vegetable diet with hot baths. When, nearly at death's door, she returned to the surgeon, it was too late for surgery to be effective. She then was convinced to try radiation therapy, which she testified she had avoided because the negative descriptions of it in *Prevention* magazine, to which she had long subscribed. The radiation therapy helped reduce the size of her tumor and make her more comfortable, but her expected survival was greatly diminished by her delay in obtaining effective treatment. This kind of disparagement of conventional therapy, a bulwark of the campaigns of Laetrile proponents, is perhaps the most morally reprehensible aspect of the pattern of the drug's promotion.

4. The Sampson Survey

While the conclusions about the reasons for use of Laetrile expressed in the record are based upon a multitude of experiences by various witnesses with patients taking Laetrile, it is interesting to note the conclusions of the one attempt to survey Laetrile patients about their reasons for using the drug.

Based upon about 20 interviews with cancer patients who abandoned orthodox therapy in favor of Laetrile, Dr. Wallace I. Sampson, Clinical Associate Professor of Medicine, Stanford University School of Medicine, stated that about 75 percent of the patients reported that they had serious problems with their physicians. About 75 percent believed in Laetrile's therapeutic rationale and effectiveness. About 75 percent of the patients were involved in other methods of therapy that included high doses of Vitamin C, megavitamin therapy, and immunotherapy given by unqualified individuals. Dr. Sampson is of the opinion that the patients receiving Laetrile were involved in other types of unorthodox

therapy because of their outlook on life (i.e., they seek nonrational, magical solutions to the problems of dread and often incurable illness) or perhaps because of difficulties in relating to a standard physician. A large majority of the patients believed that there is a conspiracy to keep Laetrile off the market. Less than 10 percent of the patients tried to inform themselves about Laetrile from non-Laetrile sources. (See Tr. at 118-119; R 398 at 4.)

C. THE LAETRILE TESTIMONIALS

Unproven cancer remedies like Laetrile are invariably supported by numerous testimonials of persons who pronounce themselves satisfied with the results they, or their deceased friends and relatives, have achieved with the drug. The present widespread use of Laetrile as an alternative to remedies of proven effectiveness illustrates the problems to which such "evidence" of a drug's effectiveness leads, and it is a legitimate question to ask why there are so many such testimonials.

The Commissioner does not doubt the honesty or the sincerity of the many testimonials for Laetrile, but many of the positive experiences reported may be accounted for by explanations other than the claimed effectiveness of the drug. The placebo effect discussed above undoubtedly accounts for some of the reports, particularly those claiming decrease in pain and increased sense of well-being. Experts interested in the question have provided other explanations. Most of the patients reporting Laetrile "cures" appear actually to have had the benefit of other, proven effective therapies. Some of those who believe themselves cured may never have had cancer at all. Others may simply not be cured, despite their belief.

Many of the testimonials and anecdotes concerning the effectiveness of Laetrile replay the same scenario. The cancer patient is told he has cancer and agrees to surgery, radiation, and/or chemotherapy. After some time, the patient, feeling nauseous, weak, and general malaise, in desperation turns to Laetrile. Within a few days or weeks after stopping orthodox treatment and starting to use Laetrile, the patient feels better, has an appetite, and is able to move about on his own. The patient in all sincerity attributes his recovery and feeling of well-being to his decision to reject orthodox medical treatment and to choose Laetrile. (See, e.g., R 9; R 35; R 223; R 267; R 315; R 391; R 483.) Many families of deceased cancer patients who had orthodox therapy and who then used Laetrile believe that the patient benefited from the Laetrile and might still be alive if they had turned to Laetrile earlier. (See, e.g., R 19; R 208; R 279.)

It is easy to understand how such a situation could develop. A doctor may prescribe 10 applications of a proven cancer drug, perhaps after surgery. The cancer may have been totally removed by the surgery or it may have been totally destroyed by, for instance, the 7th

of the 10 applications of the effective drug. Because the physician cannot know this, and because he cannot risk the chance that some cancer remains, he has prescribed the recognized treatment regimen. Use of cancer drugs (referred to as chemotherapy) or of radiation may involve unpleasant side effects. The patient, sickened by the side effects of the drug and importuned by Laetrile proponents, may stop the chemotherapy before the prescribed regimen is completed. As the side effects clear up, the patient feels better. If a full cure has been accomplished, it will be attributed to Laetrile. If it has not, the surviving family may well believe that, since the patient felt better after stopping chemotherapy and starting Laetrile, the therapy was only received "too late." See R 184 at ¶ 7:

Testimonials attesting to a feeling of general improvement and cessation of pain in patients upon abandonment of radiation and chemotherapy in favor of Laetrile treatment do not indicate that Laetrile is effective in curing cancer or in relieving pain. The feeling of well being experienced by these patients derives from two phenomena, one physical and the other psychological. Chemotherapy and radiation treatments produce unpleasant side effects in most patients. When such therapies are stopped, the side effects they produce disappear. This natural physical effect in the case of these patients is reinforced when Laetrile is administered because of the patients' expectation that the treatment will have a beneficial effect.

Dr. John A. Richardson, himself a major proponent of Laetrile therapy, stated that 85 percent of the 4,000 to 5,000 patients treated with Laetrile at his clinic had previously received some type of orthodox medical treatment (Tr. at 463).

Sometimes conventional and Laetrile therapies are administered simultaneously, with any beneficial effects attributed by patients to the latter. Dr. Emil J. Freireich is involved in the development of cancer drugs. He stated that:

(W)e have numerous patients who are receiving developmental therapy drugs which have at the time, real promise, and subsequently prove to be useful and are introduced into practice, who unbeknownst to us, were also taking therapy with laetrile and when their disease responds to therapy, (they) inadvertently ascribe it to the effectiveness of the unproven remedy, whose administration is revealed to us subsequently. When we compare the responses of patients on a given therapy who have received laetrile at the same time, with those who received none, there is no significant difference, which indicates clearly that those observed responses were due to the cancer chemotherapy drugs which were being administered by us and not by the additional use of laetrile (R 390 at ¶ 20.)

For other testimony on the propriety of attributing to Laetrile cures that may be caused by other, proven effective, drugs, see, generally, R 174 at ¶ 9 and R 185 at ¶ 20e.

"Some people who believe that Laetrile cured them never had cancer to begin with" (R 174 ¶ 9). In a number of the "case histories" submitted to show Laetrile's effectiveness, there is no accepta-

ble showing that the patient ever had cancer. (See, e.g., R 183, Att. 16, App. 2; R 184, Ex. 2; R 378, Att. "Supplementary Report," cf. evaluation of case histories above.)

In one 1955 pamphlet, Dr. Krebs, Sr., discouraged biopsy, the procedure often used to determine whether a tumor is malignant (cancerous) (R 183, Att. 7 at 14). He urged instead that a special urine test, not generally accepted by the medical community as useful, be the means for diagnosing cancer (id. at 16). Even where the diagnosis has been done by someone other than a Laetrile proponent, a mistake is possible. Some cancers which are discussed in reference to Laetrile are very difficult to diagnose histologically. Thus, a diagnosis of cancer may often on later review be reversed. (See Tr. at 141.)

"Many cancer patients have given testimonials believing themselves cured, only to discover later that they still have the disease" (R 174 at ¶ 9). Since he is involved in the testing of cancer drugs, Dr. Emil J. Freireich is in a good position to follow up on patients who leave his program to use Laetrile. Dr. Freireich reports that "(I)n virtually every instance, (Laetrile patients treated in our department and subsequently followed by our tumor registry, have been) found to have evidence, not only of progressive disease, but to have expired after receiving such unsuccessful treatment, and a significant fraction eventually return to our clinic for more developmental therapy" (R 390 at ¶ 20).

An illustration of what, in all likelihood, explains most Laetrile testimonials appears in the record:

Testimonials fail to provide objective evidence that there has been control or regression of a tumor which is attributable to the use of Laetrile To illustrate why such data are important, let us examine two typical versions of testimonials from women who state that their cancer of the breast was cured by Laetrile. The first testimonial is from Jane Doe. She discovered a lump in her breast and based upon the urging of friends has consumed on her own initiative a number of Laetrile tablets. It is also possible that she saw a doctor who administered injections and prescribed a special diet. In a month, the lump has disappeared, and Jane Doe sings the praises of Laetrile. "It cured my cancer; I am living proof." This is not credible evidence. The lump detected may have been caused by a variety of conditions. Without laboratory confirmation that a malignant condition existed, there is no basis to assume that it was cancer and that Laetrile contributed to its disappearance. The second testimonial is from Dorothy Doe. She had objectively diagnosed cancer, underwent a mastectomy, and postoperative chemotherapy or radiation treatments. The physician informs Dorothy that an additional surgical procedure may be necessary. Dorothy decides against further unpleasant treatment and takes Laetrile. Now, six months or three years later—time makes little difference—she, too, sings the praises of Laetrile. Dorothy's experience does not constitute evidence. It is possible that her orthodox treatment was successful; it is possible that she still has cancer, but that it will not manifest itself for another year or, indeed, as is sometimes the case, for another dozen years. The point is that there are no objective data upon which to assess Doro-

thy's condition at the time Laetrile was administered and the effects of Laetrile. In the absence of such data, there is no basis for a claim that Laetrile was effective (R 191 at ¶ 14).

As another affidavit states,

. . . . It is a certainty that any substance without significant toxic or harmful effect, including mystical activities, faith healing and all other types of non-toxic or non-harmful remedies will be effective in a small fraction of the very large population of patients with hopeless terminal cancer. Those individuals who fail to respond to such treatment, that is, who have the expected outcome, which is progression of their cancer and death, are no longer living and those rare individuals who have the exceptional or miraculous outcomes frequently live for long periods of time. It is obvious that a large number of individuals can be identified who have unusual outcomes. These individuals are of course easily convinced of the effectiveness of such treatments and are free to testify to their effectiveness for as long as their disease remains in control. Such testimonials contribute no significance toward our understanding of the effectiveness of any treatment for cancer. Evidence accumulated in the proven, objective, medical and scientific fashion is the only evidence that can be of use in evaluating the potential of any treatment for influencing the course of malignant disease (R 390 at ¶ 21).

Dr. Melvin Krant, Professor of Medicine and Psychiatry and Director of Cancer Programs at the University of Massachusetts Medical Center, reviewed a number of the testimonials submitted to the record from patients and relatives and friends of patients who have been treated with Laetrile. He stated that the testimonials "do not offer evidence for effectiveness because frequently the treatments with Laetrile were taken after other treatments such as surgery, radiation, or chemotherapy. At times, the Laetrile was taken in conjunction with other modes of therapy such as chemotherapy. In such instances, it is impossible to know whether the Laetrile added anything to the patient's response. There are no objective ways to measure the patient's response. In many instances, it seems like the main emphasis of the testimonials is on the patient's emotional reaction to being treated. Because the testimonials are not presented in a scientific manner, it is also impossible to determine if there were any side effects from Laetrile administration" (R 453 at 1-2).

V. OTHER ISSUES REGARDING LAETRILE

A. USE OF LAETRILE OUTSIDE THE UNITED STATES

Laetrile's proponents have sometimes sought to give the impression that Laetrile is in use around the world and that it is only the United States' overly restrictive drug laws or an evil conspiracy among drug companies, physicians, and bureaucrats that is preventing marketing of the drug in this country. (See, e.g., the claim, in a 1963 publication, Control for Cancer by Glenn D. Kittler, that Laetrile was being studied in several countries in addition to the United States: Canada, the Philippines, Japan, England, Belgium, Italy, Union of South Africa,

and Mexico (R 318 at 31.) The book also reported that the drug was registered in Iran in 1962 (id.). (See also the reference to the use of Laetrile (or Amygdalin) in West Germany in the late 1960's (R 302, Ex. G).) (Cf. R 198, Ex. 2 at 24, (transcript of film World Without Cancer); Tr. at 424.)

The record reflects no international recognition or use of the drug. The State Department and the United States Mission to the World Health Organization made an effort to determine whether Laetrile, Amygdalin, Vitamin B-17, or such drug under any other name was known and approved elsewhere in the world. The State Department sent inquiries to all American embassies instructing embassy officials to ascertain the status of the drug in their respective host countries, and the mission to the World Health Organization made telephone inquiries of member states throughout Western Europe. The following information was obtained:

The American Embassy in Mexico advised that in 1974 the Mexican government gave provisional approval, contingent upon the presentation of evidence of Laetrile's effectiveness in treating cancer, to two laboratories in that country to manufacture the drug. This approval was cancelled in late 1976 because no positive results were obtained in research carried out at the Medical Center General Hospital. The decision to ban Laetrile has been appealed by Laetrile proponents and is now in the Mexican courts (R 426; see also Tr. at 430).

The mission to the World Health Organization had been told by some European contacts that "Laetrile" can be "purchased across the counter in Geneva without prescription" (R 426). The American Embassy in Switzerland, upon inquiry, was told that Laetrile is not sold on the Swiss market and is not approved there. One company does sell "small quantities of Laetrile," "exclusively to cancer research scientists" primarily in Western Europe. The company told the American embassy in Bern that "Laetrile is not made available commercially, nor is it sold as a cancer 'cure'" (id.).

In Madagascar, Laetrile is known as Amygdalin and is considered a poison by health authorities. Its use is prohibited. In Chile, Laetrile is also known as azaribina and its use is prohibited under any circumstance. This prohibition followed receipt of Newsletter 172 from the World Health Organization which described the potential dangers of use of the drug. The importation or use of Laetrile (Amygdalin) is illegal in the Republic of Korea (id.).

Health officials in Guyana reported that Laetrile has been used there. The Minister of Health indicated that he was not aware of FDA's prohibition of the use of Laetrile, however, and that, since the United States standards are closely followed in that country, his country would also ban the drug (R 426).

The State Department inquiry drew 69 responses from around the world. Each of the countries not already mentioned responded by indicating that

"Laetrile," "Amygdalin," and "Vitamin B-17" were unknown or were not approved for use for treating cancer or any other use. The responding countries included the Philippines, Japan, the United Kingdom, Belgium, Italy, South Africa, and the Republic of Germany, as well as France, Korea, Taiwan, Hong Kong, India, and others from every part of the globe (id.). The United States Mission at the World Health Organization confirmed that Laetrile "is not registered and by definition, unavailable," in any of WHO's member states throughout western Europe (id.).

B. CLAIMS THAT LAETRILE IS A VITAMIN OR FOOD

Proponents of Laetrile (or amygdalin) have in recent years contended that their product is a vitamin or that it is a natural food substance rather than a drug. These claims are properly irrelevant to the questions this administrative proceeding was intended to address. However, in light of the interest in the vitamin issue demonstrated by the submissions to the record, the Commissioner will take this opportunity to discuss it. The potential safety problems presented by this concept will also be discussed.

1. A Vitamin or Food May Be a Drug As Well

This question is irrelevant to the issues in this administrative proceeding because, even if Laetrile (or amygdalin or "laetrile") were a vitamin (or a food), it would still be a drug. Any substance, including a vitamin or food, is a drug and subject to regulation as such if it is intended for use in the "diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals * * *" (21 U.S.C. 321(g)(1)). (See *Rutherford v. United States*, supra, 542 F. 2d at 1140; *United States v. General Research Laboratories*, 397 F. Supp. 197, 200 (C.D. Cal. 1975).⁷ As the previous discussion illustrates, there is no question that Laetrile or amygdalin has been recommended in the treatment of cancer. In fact, in the very article in which Ernst T. Krebs, Jr., explained his theory that his product was "Vitamin B-17", he promoted it for cancer treatment. (See R 183, Att. 10c.)

⁷ Section 411 of the act (21 U.S.C. 350) deals specifically with vitamins and minerals. Section 411(a)(1)(B) does limit the authority of the Secretary to classify a vitamin as a drug "solely because it exceeds the level of potency which the Secretary determines is nutritionally rational or useful." The vitamin provisions do not, however, affect FDA's authority to classify and regulate vitamins as drugs if they are represented to be for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. The conference committee report states, "Except as specifically provided, the conference substitute does not alter the drug or food provisions of the Federal Food, Drug, and Cosmetic Act. If a product containing vitamins, minerals or other ingredients is a drug within the meaning of Section 201(g) of the Act, the Secretary may, with regard to such product, exercise his authority under Chapter V of the Act" H. R. Rep. No. 1005, 94th Cong. 2d Sess. (April 2, 1976); (see also, 122 Cong. Rec. H3244-H3248, April 12, 1976).

It has been suggested that the claims that Laetrile (or amygdalin) is a vitamin or a food are simply an effort to establish that the substance is covered by the food requirements of the Federal Food, Drug, and Cosmetic Act and its regulations rather than those requirements applied to drugs. (See, generally, Tr. at 216, 225, 405; R 173, Att. "Questions most frequently asked about 'Laetrile,'" at 1; R 416 at ¶ 16.) One court has called the attempts by Laetrile proponents to represent Laetrile as something other than a drug, "a patently absurd and transparent attempt to avoid the drug labeling provisions of the Federal Food, Drug, and Cosmetic Act." *United States v. Spectro Foods Corp.*, Civil No. 76-101 (D.N.J., Jan. 29, 1976) (R 173, Att.). The Commissioner does not agree that Laetrile is a vitamin. (See discussion below.) It is clear, however, that even if Laetrile were a vitamin (or a food) it would be subject to the drug provisions of the act.

2. Is Laetrile a Vitamin?

This administrative proceeding was not intended to address the issue of whether Laetrile is a vitamin, and testimony on that issue was not solicited. Nevertheless, a considerable amount of evidence in the record addresses this issue. It appears that (a) Laetrile proponents classify amygdalin and certain related substances as a vitamin under their own definition of that term and (b) experts in the vitamin area, utilizing the criteria against which each of the legitimate vitamins have been assessed, conclude that amygdalin and other nitrilosides are not a vitamin.

(a) *Proponents' Claims.*—The idea that Laetrile could be considered a vitamin first appears in a pamphlet, in use in 1965, published by Krebs Laboratories and entitled "Cancer Is A Deficiency Disease: The Deficiency of Cyanide Sugars" (R 201, Ex. C, No. IV). In that pamphlet, amygdalin and other "cyanogenetic glucosides" are characterized as pro-vitamins for vitamin B-12. This means that they participate in the formation of vitamin B-12. It is stated that "during the process of formation the liver is thoroughly fumigated and rendered sterile (id.). The real anticancer effect of amygdalin is said to be not this formation but the release of cyanide in the cancer cells by the mechanism discussed above under "Theories of Action." It is interesting to note that another Laetrile proponent, Dr. Navarro of the Philippines, states that vitamin B-12 should never be administered to cancer patients (R 318 at 165).

The pro-vitamin theory had apparently been set aside by 1970 when an article by Ernst T. Krebs, Jr., referred to previously, "The Nitrilosides (Vitamin B-17—Their Nature, Occurrence and

⁸ The Krebs were no strangers to the "vitamin" area. Ernst T. Krebs, Jr.'s, marketing of another of his inventions, "Vitamin B-15" ("pangamic acid"), led to his plea of guilty to a charge of causing the introduction into interstate commerce of an unapproved new drug in 1962 (R 185, Att. 16, App. 17 at 7).

Metabolic Significance (Antineoplastic Vitamin B-17)," was published (R 183, Att. 10c). In this article, Krebs, Jr., uses the term "vitamin B-17 (nitriloside)" as "a designation proposed to include a large group of water-soluble, essentially non-toxic, sugary compounds found in over 800 plants, many of which are edible" (id. at 75). He indicates that the compounds "are collectively known chemically as beta-cyanophoric glycosides. They comprise molecules made of sugar, hydrogen cyanide, a benzene ring or an acetone" (id.). These compounds could be hydrolyzed by beta-glucosides to a sugar, free hydrogen cyanide, and benzaldehyde or acetone (id.). He states that amygdalin is one of the most common of the nitrilosides and that it "occurs in the kernels or seeds of practically all fruits" (id.).

Mr. Krebs, Jr., in this article, attempts to build a theory that vitamin B-17 is a specific dietary factor that could be used to prevent and to cure cancer. He explains that prevention and cure occur through the cytotoxic (toxic to cells) compounds of vitamin B-17—hydrogen cyanide and benzaldehyde—through mechanisms discussed elsewhere in this opinion (id. at 80). He concludes that: "In nitriloside or vitamin B-17 we have a new vitamin in which all of us are severely deficient" (id. at 84). The theory that Laetrile (or laetriles) constitutes a vitamin has found another proponent in the person of Dr. Dean Burk, a biochemist and president of the Dean Burk Foundation, Inc. (see, generally, R 302; Tr. at 401 et seq.).

Clearly, whether or not a given substance comes within the definition of vitamin depends upon the definition chosen. In his affidavit, Burk defines a vitamin as a substance which is "virtually non-toxic, water-soluble, an exogenous nutrient or food factor, and active in relatively small, essentially catalytic, non-calorific amounts, and is essential or beneficial in normal metabolism and/or physiologic functioning to overcome deficiency lesions and symptoms of nutritional disease" (emphasis in original) (R 302 at 4). Dr. Burk continues that in animal experimentation " * * * the deficiency lesions and symptoms of nutritional disease are best illustrated by the action of amygdalin in lengthening of animal lifetime or decreasing development of metastases, or both, and increase in health and well-being * * * " (id.). (See also Tr. at 408 and 465.)

Thus, even by the Burk definition, the claim that Laetrile is a vitamin depends in large part on the substance's ability to combat cancer, an ability not shown by testing convincing to drug experts in general. Proponents of the vitamin theory claim that the higher the everyday diet is in nitrilosides, the lower the incidence of cancer (R 73 at 36). Others claim that it may not be only high nitriloside levels that account for this observation but that other dietary elements (e.g., vitamin C) may play a role. (See, generally, R 318). These claims are based upon assertions that in some geographical areas, where the normal diet con-

tains nitrilosides in abundance, cancer does not exist. Evaluation of the prevalence of cancers requires careful studies by competent epidemiologists and suitable cancer registries, which contain reports by professional pathologists (R 399 at ¶ 9). What evidence does exist in this area indicates a complete lack of the correlation between high nitriloside diet and low cancer incidence that the Vitamin B-17 proponents claim. The record contains citations to numerous reports showing that a variety of cancers do occur in populations consuming nitriloside-containing diets. These include findings that cases of most of the recognized cancers appear in the Kampala Cancer Registry, Uganda (id.). There are also references to published papers from the Ibadan Cancer Registry, Nigeria on Burkitt's lymphosarcoma, Kaposi sarcoma and breast cancer, cancer of the bladder in Kenya, and the cancer incidence in Bantu (id.). Some cancers that are rare or absent in North America and Western Europe occur in the populations which consume high levels of nitrilosides (id.).

In the film "World Without Cancer," the people of the Kingdom of Hunza in the Himalayan mountains are said to eat a diet containing over two hundred times more nitrilosides than the average American diet and to prize above all other foods the apricot seed. It is stated that "[v]isiting medical teams from the outside world report that there never has been a case of cancer in Hunza" (R 198, Ex. 2 at 8). However, in 1955, a Japanese medical expedition studied the Hunza people and reported that they have many diseases, including cancer (R 173, Att. "Questions Most Frequently Asked" No. 6; Tr. at 338).

Similarly, the film claims that the Eskimos eat a high nitriloside diet and are "found to be totally free of cancer" (R 198, Ex. 2 at 8). The Eskimos have also been found to have cancer (R 173, Att. "Questions Most Frequently Asked" No. 6; Tr. at 339). In commenting on another reference to "the diets of the cancer-free population" (R 217 at 2), Thomas H. Jukes, Ph.D., states correctly: "There are no cancer-free populations" (R 416 at ¶ 28(C)).

(b) *Vitamin Experts' Position.*—Numerous nutrition experts and organizations concerned with nutritional science provide support in the record for the Commissioner's conclusions that "Laetrile," or "amygdalin," or "nitriloside," is not a nutrient or vitamin. (See, e.g., R 173, Att. "Questions Most Frequently Asked" (American Cancer Society); R 168, Att. "The Vitamin Fraud" and R 399 at ¶ 12(C) (David M. Greenberg, Ph.D.); R 416 (Thomas H. Jukes, Ph.D.); R 378, Att. Editorial; Att. American Institute of Nutrition letter; R 169 at ¶ 17 (Vincent T. DeVita, Jr., M.D.); R 191 at ¶ 11 (Philip S. Schein, M.D.); R 227 at 3 (National Council on Drugs).) The steps which are necessary to establish that a substance is a vitamin are described in the record. These steps include the publication in reputable journals of a complete description of the

research procedures, and confirmation, by other scientists, of the results obtained. If the work cannot be repeated, the existence of the vitamin is not recognized (see R 416 at ¶ 15). Additional steps include demonstrating the presence of the purported vitamin in foods, determination of its exact chemical molecular structure, the demonstration of its effectiveness, and its chemical synthesis. After these steps are completed, the Food and Nutrition Board of the National Academy of Sciences sets up Recommended Daily Allowances for the vitamin which then must be adopted by the Food and Drug Administration (id.).

The lack of scientific evidence of any effect, which has prevented Laetrile from being recognized by experts as a safe and effective drug, also prevents recognition of its claimed status as a vitamin. (See e.g., R 416 at ¶ 16: "(T)here are no data available to show that a disease state is produced or alleviated by the exclusion from (or) addition to the diet of amygdalin.") Other experts emphasize that there is no evidence that (1) laetriles (*beta*-cyanogenic glucosides, vitamin B-17) are essential nutritional components nor that (2) they promote any physiological process vital to the existence of any living organism. (See R 168, Att. at 347; R 395.)

A compelling point made by experts in this area is that if there were a vitamin B-17, and if cancer were a vitamin B-17 deficiency disease, then every animal deprived of the vitamin would get cancer while no animal given the vitamin in sufficient amounts would get cancer. It is noted, that "No person given adequate vitamin C, for example, ever gets scurvy" (R 198 at 5). Stated another way: "The key to the term 'vitamin' is that the absence of vitamins from the diet in an experimental animal or a human being must lead to the appearance of a nutritional deficiency disease, which is prevented or cured by adding the vitamin to the diet. Laetrile has no such property" (R 416 at ¶ 14).

It is further stated that "(no vitamin has) the property of destroying tissue, such as cancer tissue, that is claimed of Laetrile. Such a property would be incompatible with the action of vitamins" (Tr. at 223). Other experts in this area rejected the claimed vitamin status in part on the grounds, discussed below, that amygdalin is, or can be, harmful to the body. It is pointed out that, amygdalin properly belongs to the class of compounds termed "toxigens occurring naturally in foods". (R 416 at ¶ 27(A)(1)).

3. Dangers of Ingestion of "Vitamin B-17"

As has been demonstrated above, the presence of *beta*-glucosidase, oxynitralase, and amygdalin together in apricot pits presents the potential for a combination that would release cyanide and cause poisoning of the individual consuming an extract of the pits. Additionally, though *beta*-glucosidase is not present in animal tissues, it, and other substances capable of breaking down amygd-

daline, may be present in the digestive track and thus may break down orally consumed amygdalin to release cyanide in the body. It is therefore with great concern that the Commissioner views the emergence of the theory that human beings should step up their consumption of "naturally occurring" nitrilosides such as amygdalin.

In his vitamin B-17 article, Ernst T. Krebs, Jr., notes that while the "stupidity" of "political power" may keep prepared vitamin B-17 off the market, six or seven teaspoonsful of defatted apricot seed or kernel would supply what is considered to be an adequate oral dose of nitrilosides (R 183, Att. 10c at 84). He suggested, "It is best that the beta-glucosidase enzyme be completely heat inactivated in such material" (id.). He does not indicate how much heat inactivation should be accomplished, nor does he cite any support for the idea that it can be.

There are documented cases of poisoning, some fatal, due to the consumption of apricot pits or kernels. The toxic element in these cases is the hydrogen cyanide which is released from the cyanogenic glucosides by the action of the enzymes (including beta-glucosidase) present in apricot kernels (R 378, Att. "California Morbidity Reports," Att. "Hazards to Health"). The suggestion by Mr. Krebs, Jr., that the beta-glucosidase be "inactivated" can be taken as tacit—too tacit—acknowledgement that the kernels and/or pits present a hazard when consumed unless the enzymes are first destroyed. The Commissioner notes that other proponents of Laetrile clearly state that amygdalin products should never be given by mouth because the hydrochloric acid in the stomach is capable of hydrolyzing the drug (R 318 at 158). A 1954 document, "The Rationale and Clinical Evaluation of Laetrile-Beta-Glucosidase Palliative Therapy" states, "CAUTION: Laetrile (1-mandelonitrile-beta-glucuronidase) is NOT TO BE TAKEN ORALLY. It is extremely toxic by this route of administration, since the gastric hydrochloric acid acts to hydrolyze the glucoside with the release of hydrogen cyanide" (R 388, Ex. 5).

Dr. Burk seeks to support the idea that Laetrile or amygdalin is a food and, among other things, may be safely consumed by an allegation that " * * * laetrile is listed in the HEW-FDA GRAS list (foods 'Generally Regarded (sic) as Safe') under the heading of natural extractive from bitter almond, apricot or peach kernels" (R 302 at 3; see also Ex. B). The material to which Dr. Burk refers is "Bitter almond (free from prussic acid)" which does appear on the generally recognized as safe (GRAS) list, 21 CFR 182.20. (Prussic acid is another name for hydrogen cyanide.) The material on the GRAS list, however, is an oil extracted from peach, almond, or apricot kernels. After cold pressing the oil from its source, it is processed to effect enzymatic hydrolysis of amygdalin. There is no amygdalin present after the hydrolysis step. The final product is essentially benzaldehyde. "Thus the material listed for flavor use * * * is not

amygdalin and thus neither is it Laetrile" (R 415 at 2). Dr. Burk's contention is thus incorrect and has no basis in fact.

The idea that foods containing nitrilosides may be safely consumed is also supported by stories of "non-toxic" nature of nitrilosides which are found in the diets of various peoples. This claimed nontoxicity is not borne out by reality. In some parts of Africa two important human diseases—human ataxic neuropathy and endemic goitre—appear to be associated with high cassava intake (R 183, Att. 20 at 161; R 378, Att. 6). (Cassava contains linamarin, a commonly consumed nitrilose (R 217, Att. "Sickle Cell Anemia" at 51).) It is also reported that cows have been killed by eating large amounts of young millet, which is particularly high in nitrilosides, and intoxication of other animals has been reported. (See R 416, Ex. 5 at 302.) There have been reports in this country of toxicity and, in some cases fatalities, in humans from consumption of amygdalin-containing substances (See, e.g., R 378, Att. "California Morbidity"; see also R 378, Att. "Hazards to Health; Cyanide Poisoning from Apricot Seeds Among Children in Central Turkey," Sayer et al.). Thus there is ample and clear indication that the consumption of "nitrilosides" is not without hazard. To urge the public to consume "apricot pit milkshakes" or similar foods in order to be sure to get an ample supply of amygdalin or "vitamin B-17" or "nitrilosides" is irresponsible and foolhardy.

C. FREEDOM OF CHOICE

The administrative record contains many comments not directed to the legal issues of Laetrile's "new drug" or "grandfather" status or even to the question of whether the drug is safe or effective for use in cancer therapy. Rather these comments support the proposition that a person should be free to choose his or her own cancer therapy, at least if the drugs involved are not overtly toxic (see, e.g., Tr. at 33; R 231; R 238; R 242; R 209; R 211; R 283; R 500; R 155; R 272). The issue of "freedom of choice" is irrelevant to the issues remanded to the agency by the Rutherford courts. Nevertheless, because of the demonstrated public interest in this issue, the Commissioner has given it, and submissions addressing it, careful consideration.

The very act of forming a government, of course, necessarily involves the yielding of some freedoms in order to obtain others. In passing the 1962 Amendments to the act—the amendments that require that a drug be proved effective before it may be marketed—Congress indicated its conclusions that the absolute freedom to choose an ineffective drug was properly surrendered in exchange for the freedom from the danger to each person's health and well-being from the sale and use of worthless drugs. This is in fact the same decision made by those in government who have decided over the years that only those persons may practice medicine who have been certified by experts to be qualified to actually help the patients who would choose to seek their assistance.

Some would argue that the law-makers' well-considered decision to prohibit the use of drugs not shown to be effective was the wrong one. One alternative suggested is that a drug such as Laetrile should be marketed with labeling which indicates that experts do not consider it to be effective. The present use of Laetrile vividly illustrates the impracticability of such a solution. There can be few patients taking Laetrile in this country today who do not know that the government and most experts consider it worthless. Yet the drug continues to be used, to the detriment of cancer patients who might otherwise be helped by conventional treatment.

The choice to use Laetrile is seldom, in any case, a free one. As the discussion above (Why Do People Use Laetrile?) illustrates, a cancer patient is a person beset by immense stresses, physical, psychological, emotional and societal; and the persuasion that the patient and his family are subjected to by Laetrile proponents is seldom limited to a rational laying out of competing arguments. The information that the proponents of Laetrile provide is false—that the drug cures, palliates, relieves pain, "controls" cancer. As Dr. Sampson's survey, discussed above, indicates, few Laetrile patients make an effort to hear the argument against Laetrile therapy. The idea that a reasoned free choice is involved in the selection of Laetrile rather than legitimate therapy is thus ultimately an illusion. (See R 421 at 1.)

The record contains the views of many persons who have considered the issue of "freedom of choice" in cancer therapy. Each represents a thoughtful attempt to deal with this question, which, while irrelevant to the legal issues which are the subject of this opinion, is troubling to those concerned with the Laetrile problem. These comments may be grouped roughly as supporting the two responses to the "freedom of choice" argument set forth above: (1) The surrender of an absolute freedom to choose among cancer remedies in order to obtain the greater freedom from the suffering associated with use of ineffective remedies is a rational decision; and (2) the "choice" of unproven cancer remedies cannot fairly be characterized as "free."

1. Balancing Freedoms

Reverend Allan W. Reed, Director, Department of Pastoral Services and School for Pastoral Care, Massachusetts General Hospital, considered the ethical side of the "freedom of choice" question. He states "The ethical issues of a group of legislating for an individual, thereby threatening the principal (of) freedom of choice, contrasts with the ethical principal of a government protecting its citizens from fraud and abuse. In the case of a drug for which there is no proven efficacy, the ethical weight is on the side of protection of the citizens" (R 148).

Leroy G. Kerney, Chief of the Department of Spiritual Ministry at the Clinical Center, National Institutes of Health, pointed out that, "Freedom of the indi-

vidual is important. But when the freedom to accept any drug for treatment and the freedom to injure oneself collide, a judgement must be made: Stop signs or restrictions on turning at certain corners restrict my freedom in driving, but, at the same time, they protect my freedom from hurting myself and others in traffic" (R 414 at 3).

J. Philip Wogaman is Dean and Professor of Christian Social Ethics at the Wesley Theological Seminary and past president of the American Society of Christian Ethics. He noted an "initial presumption" in favor of freedom from governmental prohibition but concluded that Laetrile should be banned for three reasons: (1) The ban prevents fraud in the medical marketplace; (2) "[M]isrepresentation in the field of medicine is particularly serious because it undermines public confidence in medicines that are of real value"; (3) "(T)here is a real danger that persons may be led by false hopes in a worthless drug to neglect treatment at a time when it could be most effective" (R 417 at 2-3).

Dr. James F. Holland of the Mount Sinai School of Medicine points out that the freedom achieved by regulation of drug products is often the freedom to live: "For the patient ignorant of the inertness of Laetrile as an anticancer drug, there is an overriding concern that he not be denied his individual freedom by untimely death from cancer from having relied on Laetrile to help. This is a cruel deprivation of individual freedom, since the patient does not get a second chance" (R 396 at 2).

James Harvey Young, Ph.D., a historian of health quackery, discussed the past use of the freedom of choice concept and phrased his conclusions concerning the validity of application of that concept to health care in colorful terms. He states that acceptance of the primacy of the freedom to choose medical therapies "leads only toward the license of those ancient days, when 'the toadstool millionaires,' preaching religion and spouting patriotism, operating without restraint, fleeced and often killed their gullible victims. That is a fate from which seven decades of constructive legislation, beginning with the Pure Food and Drugs Act of 1906, has somewhat rescued the nation. Complex, modern, industrial, urbanized society, with standards of medical judgment far more precise than those existing in the nineteenth century, cannot afford to let the nation's health concerns be governed by a distorted definition of that great symbol, 'freedom,' which would return piratical anarchy to the realm of health" (R 400 at 11-12).

2. The Choice Is Not Free

The discussion above of "Why People Use Laetrile?" describes the many pressures that induce cancer patients and their families to make the decision to use Laetrile. Orville Eugene Kelly is a cancer patient who has founded an organization called "Make Today Count," which now has 103 chapters in 30 states, to help other cancer patients and their families

deal with the problems that discovery of cancer entails. He addressed the question of "freedom of choice" in an affidavit submitted to the record (R 389). He notes from personal experience that patients and their families are often susceptible to arguments that a painless drug like Laetrile can cure them (id. at 2) and describes the persistence with which those arguments are made. He himself has tried to present the counter-arguments to other cancer patients. "But it is difficult to convince some of these people that the substance Laetrile is ineffective as a therapy for cancer when they have watched a film, listened to tapes, and heard testimonials from other patients, quite sincere in their beliefs that Laetrile has helped them" (id. at 3). He asks: "(I)s it a fair choice if (the cancer patients) are being pressured by Laetrile proponents?" (id.).

The constant efforts of Laetrile proponents are emphasized by those dealing with cancer patients. See, e.g., statement of Helene Brown, Executive Director of Community Cancer Control, Los Angeles, "that far from exercising a free and informed choice patients are confronted with enormous pressures to use Laetrile instead of conventional forms of therapy and that representatives attesting to the worth of Laetrile make untrue, misleading and unsubstantiated claims" (R 393 at 5).

The presentations of the Laetrile proponents are made, as discussed in more detail elsewhere, to patients and families deprived of their normal decisionmaking abilities. See statement of John J. Dawson, M. Div., Director, Patient and Family Support, Mountain States Tumor Institute: "Research conducted at the Mountain States Tumor Institute and elsewhere indicates that the emotional trauma of a cancer diagnosis severely impairs the patient's and families' ability to engage in rational decisionmaking processes" (R 421 at 1).

Other submissions reflect a similar conclusion, see the statement of Rev. Reed: "The ability of (cancer patients and their families) to protect themselves is often severely limited by the emotional situation in which they find themselves" (R 418). (See also R 414 at 4; R 433 at ¶ 14.)

The Commissioner thus concludes as follows:

(1) To the extent that any freedom has been surrendered by the passage of the legislation which bans from the marketplace drugs that have not been proven to be effective, that surrender was a rational decision which has resulted in the achievement of a greater freedom from the dangers to health and welfare represented by such drugs.

(2) The choice of Laetrile therapy, by persons under the severe stresses associated with discovery of cancer and in response to misinformation presented persuasively by Laetrile's proponents, cannot be regarded as a choice which is free.

D. ALLEGATIONS OF BIAS

Several submissions charged that FDA is too biased against Laetrile to conduct

a fair hearing. Aside from general allegations of bias (R 313; R 248; R 353; R 507, R 302; R 73, Att. at 43; Tr. at 44-45), these submissions fall into two general categories: (1) the administrative rulemaking proceeding should have been conducted by someone other than FDA (R 144; R 505; R 222; Tr. at 12, 29, 75, 444-45); and, (2) the drug approval process administered by FDA is wrong (R 235; R 258; R 144; R 509; Tr. Ex. 1).

It is difficult for an agency charged with bias to rebut such charges persuasively. Nonetheless, the Commissioner feels that a complete decision requires some rebuttal of charges that he regards as erroneous and misdirected. Insofar as comments suggesting that the proceedings should have been conducted by someone other than FDA, it should be noted that FDA was required by court order to assemble an administrative record and make appropriate determinations therefrom. The task could not have been delegated to anyone else, and, even had the agency been able to do so, it is not likely that any tribunal chosen by FDA would have satisfied those persons who are convinced that the agency is biased. The FDA is, of course, the agency designated by Congress to evaluate the safety and effectiveness of drugs and, as such, it is the agency with expertise in this area.

The comments charging that the requirements for drug approval administered by FDA are wrong contained statements to the effect that testimonial evidence should be accepted as adequate proof of safety and effectiveness or that the cost of a clinical trial is too great a burden for the proponents of Laetrile to bear. Laetrile proponents place particular emphasis on the cost factors, stating that because clinical trials are expensive, FDA somehow favors only large drug companies.

As has been discussed above, FDA is bound by the requirements of law regarding drug safety and effectiveness. Those requirements have been challenged in court before, by the very drug companies toward whom Laetrile proponents allege FDA has a positive, favorable bias. These "favored" groups did not prevail, and the safety and effectiveness provisions were upheld.

In *Pharmaceutical Manufacturers Ass'n v. Richardson*, supra, a trade association whose membership includes major drug firms sought to enjoin the FDA regulations establishing the standards of evidence necessary to demonstrate the effectiveness of drug products (21 CFR 314.111). Pointing out that Congress could not have had testimonial evidence, clinical impressions, practical experience, or the unsubstantiated subjective views of medical practitioners in mind when it defined "substantial evidence," the court upheld the regulations. As one witness in the case pointed out, the approach which assumed that a collection of impressions would furnish the truth, "did not prevent doctors from having unbounded faith in the curative powers of leeches for hundreds of years before scientific evaluation became the pre-

ferred means of judging efficacy of therapy" (318 F. Supp. at 307).

In *Upjohn Company v. Finch*, 422 F.2d 944 (6th Cir. 1970), a drug manufacturer sought review of an FDA order revoking marketing approval for seven combination antibiotic drugs. Stating that testimonial evidence was not enough to meet the standard of substantial evidence, the court held that "the record of commercial success of the drugs in question and their widespread acceptance by the medical profession, do not, standing alone, meet the standards of substantial evidence, prescribed by 21 U.S.C. 355(d)" (422 F.2d at 954). Although the cost of developing the proper scientific evidence of safety and effectiveness is high, placing this burden upon those who wish to sell drugs is more than justified by the need to protect the consumer from harmful, useless, and fraudulent drugs.

The Commissioner acknowledges that the FDA is biased in one sense; the agency is committed to requiring that drugs meet the standards of safety and effectiveness required by law. The standards are designed to protect the public from drugs which are not both safe and effective. While the standards are rigorous, they are not mysterious. They are accepted by the scientific community and can be applied by any scientists who seriously wants to prove the value of a drug. The proponents of Laetrile choose to attack the standards. They have not attempted to meet them.

E. LIMITING USE TO TERMINAL PATIENTS

There has been concern expressed in the submissions to the record that Laetrile might be approved for use by "terminal" cancer patients. Such an approval would be theoretically justified only on the grounds that since such patients might be considered beyond the help of other therapies, Laetrile cannot hurt them. Approval of a drug for use by terminal patients is not possible under the act; however, in light of the interest in this issue the Commissioner will discuss the evidence relating to it.

One submission objected to the possible use of Laetrile by terminal patients on the grounds that approval of such use constitutes sanction of an inhumane fraud upon the patients involved, one which wastes the financial resources of the patients and their families uselessly (R 190 at ¶ 17). Two other arguments were expressed by a number of submitters: (1) there is no such thing as a "terminal" patient and (2) allowing use by a subgroup of cancer patients would lead to increased use by patients who could be helped by legitimate therapy.

1. Who is Terminal?

Dr. Peter H. Wiernik, Chief of the Clinical Oncology Branch of the National Cancer Institute's Baltimore Cancer Research Center, states, "One major difficulty in making a particular chemical available for terminal patients only, is that no one can prospectively define the term 'terminal' with any accuracy. A patient can be said to be terminal only after he dies. Many patients who are

critically ill respond to modern day management of cancer" (R 200 at ¶ 18).

D. Joseph F. Ross, Professor of Medicine at the University of California School of Medicine at Los Angeles, is actively involved in the medical care of cancer patients. He states, "[T]he distinction of 'terminal' patients from 'non-terminal' patients may not be reliably determined and an assumption that Laetrile may be given to such patients with impunity may deprive such patients of therapeutic measures which could help them" (R 190 at ¶ 17). Cf. R 393, Ex. 1 at 2: "Medical history is full of miracles." "No one knows if and when any patient is going to die." (Helene Brown, Executive Director of Cancer Control/Los Angeles); see also R 173, Att. "Questions Most Frequently Asked * * *" at 2).

2. Effects on Other Patients

Approval for use of Laetrile by "terminal" patients, assuming some way could be found to define that class of individuals so as to exclude all those who might be helped by legitimate therapy, would still pose a risk to other patients who could be helped. This effect would, the evidence in the record shows, occur in two ways. First, approval for even this limited use would encourage illegitimate use of the type now occurring in this country.

Historian James Harvey Young, based upon his study of past "unproven" medical cures, states, "Permitting Laetrile's use in terminal cases gives it a credence among the public at large that will expand its use in early cases, for people will prefer taking a 'vitamin' to confronting the surgeon's knife" (R 400 at 11).

Dr. Samuel C. Klagsbrun, a psychiatrist who works with cancer patients at St. Luke's Hospital in New York, states, "Permitting Laetrile to be used by any population of cancer victims would have the correlative effect of creating the misimpression in the minds of other cancer victims that the drugs is, in fact, safe and effective for a broader population" (R 433 at ¶ 12).

A second danger from such a limited approval of Laetrile is that the limitation would be extremely difficult to enforce. Kenneth A. Durrin, Acting Director, Office of Compliance and Regulatory Affairs, Drug Enforcement Administration, submitted an affidavit describing the detailed and costly regulation of "controlled substances" under the Controlled Substances Act (CSA) and then considered the possibility of approval of Laetrile "for terminal patients only" (R 435). He stated his conclusion as to the practicality of preventing the diversion of Laetrile from "terminal" patients, if approved for such patients, to others who might be helped by legitimate therapy: "Absent the kinds of controls available under the CSA—and indeed even with such controls—it is my opinion that a drug such as Laetrile could not effectively be restricted to a class of terminally ill cancer patients. For example, absent a quota on production, manufac-

turers would not be limited to producing an amount of Laetrile sufficient only to provide a source of supply for terminally ill cancer patients. Manufacturers would not be restricted in the channels in which they could permissibly distribute the drug. They would not be required to report transactions in Laetrile. The amount of Laetrile which could be imported into this country would be unlimited.

"Given such unrestricted and unfettered availability of Laetrile, it is my opinion that there would be no practical way of limiting access to the drug to terminally ill cancer patients only. It is completely unrealistic to suggest that any other result would occur" (id. at ¶ 18-19).

The Commissioner concludes that approval of Laetrile restricted to "terminal" patients would lead to needless deaths and suffering among (1) patients characterized as "terminal" who could actually be helped by legitimate therapy and (2) patients clearly susceptible to the benefits of legitimate therapy who would be misled as to Laetrile's utility by the limited approval program or who would be able to obtain the drug through the inevitable leakage in any system set up to administer such a program.

F. USE CONCURRENTLY WITH OTHER THERAPY

Some persons not familiar with the problem of drug interactions have suggested that Laetrile might be approved for use concurrently with legitimate cancer therapy. This theory would logically extend to allow any worthless drug to be used as long as effective therapy was also utilized. Such a limited use program would, of course, involve the problems of administration discussed in the previous section. Particularly in light of the Laetrile proponents' practice of dissuading patients from what they characterize as the "cut, burn, and poison" techniques of legitimate therapy, any seeming government sanction of Laetrile would inevitably involve encouragement of use of "painless" Laetrile therapy alone and thus would result in needless suffering and loss of life (cf. R 191 at ¶ 17).

More important, it simply has not been shown by any sound scientific evidence that the administration of Laetrile along with other therapy may not either make such therapy more dangerous or interfere with its effects. Dr. James F. Holland states (R 396 at 2), "That Laetrile is inert as an anticancer drug does not mean it may not interfere with the metabolism of and compromise the effects from known anticancer treatments. This would require years of study to elucidate, and it is not a worthwhile undertaking since Laetrile itself has no anticancer activity. One does not seek further information on why not to use Laetrile. If there is no good reason to do something, the best reason exists not to do it" (emphasis in original). Thus, the same reasons that justify the law's ban on use of drugs not shown to be effective form an equally strong basis for

the ban on that use where the use will be concurrent with other therapy.

VI. CONCLUSIONS

The Commissioner, after careful review of the administrative record amassed in this rule making proceeding, makes the following conclusions:

(1) Although the terms "Laetrile," "laetrile," "amygdalin," "Sarcarcinase," "vitamin B-17," and "nitroside" have been used interchangeably, the chemical identity of the substances to which these terms refer has varied over the years. The identity of material referred to or called by any of those names is often not known. All too frequently terms have been used haphazardly or imprecisely by proponents, as well as opponents, of Laetrile:

"Laetrile," as described by Ernst T. Krebs, Jr., is: 1-mandelonitrile-beta-glucuronic acid.

"Amygdalin" is: D-mandelonitrile-beta-D-glucosido-6-beta-D-glucoside.

"Sarcarcinase" is the name given by Dr. E. T. Krebs, Sr., to a mixture of 6, possibly more, enzymes extracted from apricot pits.

(2) Neither Laetrile nor any other drug called by the various terms mentioned above nor any other product which might be characterized as a "ni-

triloside" is generally recognized by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs to be safe and effective for any therapeutic use.

(3) Animal studies conducted to date show that Laetrile has no anticancer activity in laboratory animals. Even if such activity were shown, the data would not be relevant to the issue of whether Laetrile is generally recognized by qualified experts as a safe and effective anticancer drug in humans.

(4) Neither Laetrile, amygdalin, nor any other drug called by the various terms set out in conclusion (1) is exempted from the "new drug" definitions of the act (21 U.S.C. 321(p)) by virtue of compliance with either the "1938 grandfather clause" (21 U.S.C. 321(p)(1)) or the "1962 grandfather clause" (section 107(c)(4) of Pub. L. 87-781).

(5) The history and promotion of Laetrile are characteristic of other unproven cancer remedies. Laetrile's popular acceptance by laymen lies not in credible proof of its effectiveness, but rather in the fears of orthodox medical treatment and the false hope, fostered by Laetrile's proponents, that suffering and eventual death can be avoided through Laetrile.

(6) Laetrile is not in general use as cancer therapy anywhere in the world.

(7) There is no evidence that "Vitamin B-17" is generally recognized among experts in the field of nutrition or nutrition research as a vitamin. Even if there were such recognition, "Vitamin B-17" would still be subject to regulation as a drug under the Federal Food, Drug, and Cosmetic Act because of the claims made for its use in cancer therapy.

(8) The safety of ingesting amygdalin, Laetrile and/or apricot or peach kernels or pits has not been established. There is, in fact, evidence of frank toxicity from ingestion of the kernels or pits.

(9) There is no basis in law or in fact for the use of Laetrile or related substances in the treatment of cancer.

The foregoing opinion in its entirety constitutes the Commissioner's findings of facts and conclusion of law. Distribution of Laetrile, amygdalin, or any other substance called by the various terms set out in conclusion (1) in interstate commerce is in violation of the Federal Food, Drug, and Cosmetic Act and subject to regulatory action.

Dated: July 29, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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