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Amygdalin Toxicity Studies in Rats Predict Chronic Cyanide Poisoning in Humans

GEORGE W. NEWTON, MA; ERIC S. SCHMIDT, BS; JERRY P. LEWIS, MD; ERIC CONN, PhD, *and* RUTH LAWRENCE, MD, *Davis, California*

Significant amounts of cyanide are released when amygdalin (Laetrile), a cyanogenic glycoside, is given orally or intravenously to rats. The amount of cyanide liberated following oral administration is dependent in part on the bacterial flora of the gut and can be suppressed by antibiotic pretreatment of the animals. Bacteria from human feces likewise hydrolyze amygdalin with release of cyanide. Humans taking amygdalin orally in the hope of preventing cancer are likely to be exposed to levels of cyanide in excess of that associated with the development of tropical ataxic neuropathy in people of underdeveloped countries where food containing cyanogenic glycosides is a staple part of the diet.

AMYGDALIN IS A cyanogenic glycoside found in apricot kernels, bitter almonds and seeds of other members of the genus *Prunus*.[1] It is commonly known as Laetrile, a drug that has been advocated variously as (1) a cure for all types of cancer, (2) a cure for some types of cancers, (3) a control for cancer with prolongation of life, (4) a useful drug to reduce the morbidity of cancer and its treatments, (5) a drug to offer some hope to terminally ill patients and (6) a drug to prevent cancer.[2] None of these claims can be substantiated. Throughout the barrage of pro-Laetrile propaganda, with its shifting emphasis from cure to control to prophylaxis, the proponents of Laetrile have staunchly claimed the drug itself is totally without toxicity, stating that "Laetrile is even less toxic than sugar."[3] Some states have passed laws legalizing this unproven cancer remedy, believing if it does no harm it should be available to cancer patients who have faith in it. The question of the fraudulent representation of Laetrile's efficacy and the diversion of cancer patients from an effective treatment to a worthless nostrum has often been overlooked.

To place amygdalin in its proper scientific setting, numerous animal studies have been reported showing the compound's lack of efficacy.[4] No

From the Department of Internal Medicine, Section of Hematology and Oncology (Messrs. Newton and Schmidt, Dr. Lewis), Section of Infectious and Immunologic Diseases (Dr. Lawrence), School of Medicine, and the Department of Biochemistry and Biophysics (Dr. Conn), College of Agriculture and Environmental Sciences, University of California, Davis. Dr. Lawrence is now affiliated with the Department of Medicine, Texas Technological University School of Medicine, Lubbock, Texas.

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Reprint requests to: Jerry P. Lewis, MD, Section of Hematology and Oncology, Department of Internal Medicine, 4301 X Street, Sacramento, CA 95817.

study has shown it to have therapeutic effects. Likewise, clinical studies in man have found no effect by amygdalin on cancer in humans.[4] On the other hand, amygdalin may be hazardous when administered to animals,[5,6] can be toxic when administered to humans,[4,7] has been lethal in at least three cases in humans[8-13] and has produced a near fatality in a child who was given a Laetrile enema.[14]

In an earlier study we showed that amygdalin fed to dogs produced cyanide toxicity in 100 percent of the animals when the compound was administered in conjunction with sweet almonds, a food containing β-glucosidase enzymes which hydrolyze amygdalin. The doses of amygdalin used in our studies were comparable on a gram per square meter basis with doses taken by humans.[5] In addition to signs of respiratory, cardiac and neurologic impairment, 60 percent of the dogs died of cyanide poisoning. These earlier studies focused on the acute toxicity of amygdalin; our current study addresses the potential for chronic cyanide toxicity from amygdalin.

Materials, Methods and Test Subjects

Drugs

Amygdalin for the LD_{50} (lethal dose for 50 percent survival of group) studies had been confiscated by the Fraud Division of the Department of Health, State of California. It had been manufactured in Munich, Germany, by SIDUS Arzneimittel GmbH and was labeled as "Amygdalin 2G for parenteral use." The Department of Health, State of California, had analyzed the drug and determined it was high-quality amygdalin without known impurities and contained 2.07 grams amygdalin per bottle. In subsequent studies following the LD_{50} determinations, we used crystalline amygdalin from Sigma Laboratories, St. Louis (99 percent pure). Both compounds were *(R)*-amygdalin. Neomycin sulfate (Mycrifradin) was obtained from Upjohn Pharmaceutical Company.

Experimental Animals

Female Fischer 344 rats were obtained from Simonsen Laboratories, Inc., Gilroy, California. These animals weighed between 150 and 200 grams when entered in the study. Animals were housed in pairs for the LD_{50} study and singly in metabolic cages for other experiments. The diet was similar to that used by others in investigating the effects of other cyanogenic glycosides in rats.[15] The diet did not contain β-glucosidase. We modified the diet used by Barrett and co-workers such that it was barely sufficient in methionine (0.01 percent rather than 0.3 percent), because excess sulfur from methionine might have altered the LD_{50} data and because this dietary modification closely mimics the meat-free diet advocated by proponents of Laetrile. We found this level of methionine (which perhaps is the most important amino acid that serves as a donor of sulfur for thiocyanate production) to be the lowest compatible with normal growth.

LD_{50} Studies of Amygdalin

We first determined the oral dose of amygdalin that was lethal to 50 percent of our rats (that is, LD_{50}). This study was necessary to be certain that our subsequent investigations would be carried out with minimal loss of animals.*

The LD_{50} dose of orally administered amygdalin was determined in a series of five experiments, each utilizing 60 rats. Amygdalin was introduced via gastric tube to rats lightly anesthetized with ether. This level of anesthesia permitted the rats to recover in five minutes. In the last two experiments a small amount of blue food coloring was added to the amygdalin as a tracer. The gastrointestinal tracts of these latter animals were examined after death to assess how far the drug had passed down the alimentary tract. All rats were observed for six hours and then followed daily for 14 days. Doses of amygdalin ranged from below 400 mg per kg of body weight to above 1,100 mg per kg of body weight. Blood specimens were collected at the time of death by intracardiac puncture and immediately frozen for blood cyanide determinations. Whole blood cyanide determinations were done according to the technique of Rieders.[16]

Kinetic Studies of Amygdalin

Urinary amygdalin and thiocyanate excretion following the oral administration of the drug was investigated in 20 rats. These studies, which were replicated once, were designed to document the effect of orally administered amygdalin on cyanide release and excretion of amygdalin. In these studies the rats were housed individually in metabolic cages. Again, the rats had free access to a balanced diet marginally sufficient in methionine.

*Mr. David Lewis assisted in carrying out the LD_{50} studies.

The animals were divided into two groups. After 10 to 15 days of subsistence on the controlled diet, half received 1 ml containing 12 mg of neomycin via gastric tube followed on the subsequent three days by 1 ml containing 9 mg of neomycin. Rats not given the antibiotic received 1 ml of distilled water on each of these days by gastric tube. The antibiotic was well tolerated by the rats and did not produce diarrhea. Urine was collected from all study rats at 24-hour intervals.

The day following the last dose of neomycin or distilled water, amygdalin in a concentration of 250 mg per kg of body weight (approximately an LD_{10} dose) was administered orally to the rats. Urine was collected from each rat daily and frozen until assayed for amygdalin and thiocyanate by technique of Ames (Flora, Cradock and Ames[17]) and a modified Lambert[18] method, respectively. Amygdalin, when hydrolyzed, is broken down to benzaldehyde, cyanide and two glucose molecules. The technique of Ames measures benzaldehyde. Cyanide is detoxified primarily by conversion to thiocyanate which is then excreted in the urine.

In a similar fashion, the urinary amygdalin and thiocyanate excretion following the intravenous administration of the drug was carried out.

Hydrolysis of Amygdalin, In Vitro Studies

The ability of various segments of the rat gastrointestinal tract to hydrolyze amygdalin was studied by incubating portions of the tract and its fecal contents with amygdalin and measuring cyanide generation.

To ascertain whether human fecal flora were also capable of hydrolyzing amygdalin, we tested the ability of certain common human fecal bacteria to hydrolyze amygdalin using purine cultures of *Escherichia coli, Bacteroides fragilis, Enterobacter aerogenes, Streptococcus fecalis* and *Clostridium perfringens*. Each organism was incubated overnight in thioglycolate broth medium supplemented with vitamin K and hemin. The final culture was adjusted to yield bacterial counts of 10^9 per ml. Cell-free culture filtrates of each culture were prepared by passage through a 0.4 μ Millipore filter. Both the broth cultures and the cell-free culture filtrates were incubated with amygdalin and the release of cyanide measured. To further explore the possibility of amygdalin hydrolysis by human fecal material, approximately 1 gram of fresh human feces was incubated with 1 mg of amygdalin, and hydrolysis of amygdalin with the release of cyanide was determined

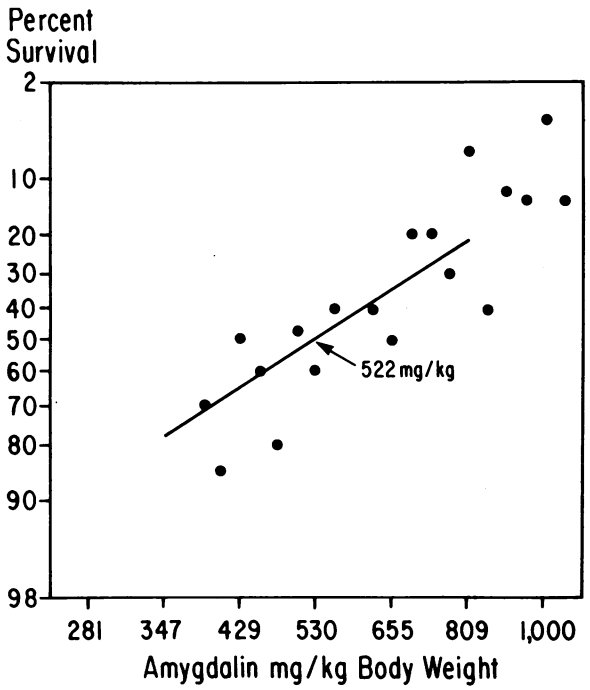

Figure 1.—Survival data of rats administered amygdalin orally. The 50 percent lethal dose (LD_{50}) in these studies is 522 mg per kg of body weight. Each dot represents the results in 5 to 20 rats. A lower number of animals per dose was used at the extremities of the range, a higher number of animals per dose was used in the midportion of the survival curve.

The ability of human gastric juice to hydrolyze amygdalin was investigated using 10 specimens of gastric juice with pH's ranging from 2.2 to 6.8. Gastric aspirate specimens were collected from patients undergoing gastric analysis at the University Medical Center, Sacramento, for diagnostic purposes and were made available for our studies by Dr. Lee Chen. The specimens were centrifuged at 5,000 rpm for five minutes to remove particulates, 1 ml supernatant was removed, added to 1 ml solution of 4 mM amygdalin and incubated at 37°C for one hour. Any cyanide released was captured in a 0.1 M sodium hydroxide solution. Analysis of the sodium hydroxide trap solution was carried out according to the Lambert method.[18]

Results

LD_{50} Studies

The results of the LD_{50} study are shown in Figure 1. Although great variability exists between groups of rats, we calculate the LD_{50} of amygdalin to be approximately 522 mg per kg of body weight. The first sign of neurologic damage appeared 80 minutes after administration of amyg-

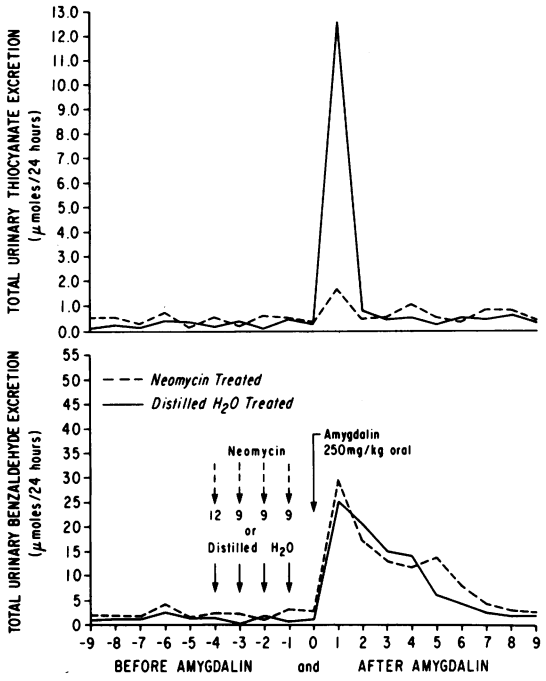

Figure 2.—Twenty-four hour urinary clearance of thiocyanate **(top panel)** and benzaldehyde **(lower panel)** before and after the oral administration of amygdalin. One standard error of the mean at all points on this figure is equal to or less than 8 percent.

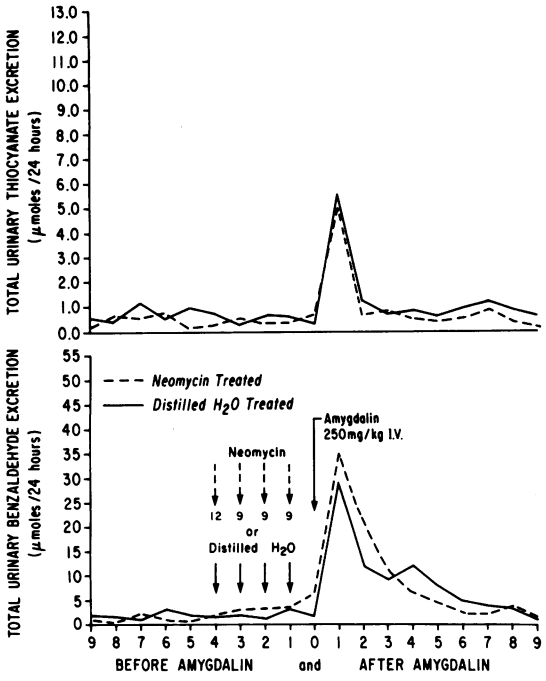

Figure 3.—Twenty-four hour urinary clearance of thiocyanate **(top panel)** and benzaldehyde **(lower panel)** before and after the intravenous administration of amygdalin. One standard error of the mean at all points on this figure is equal to or less than 5 percent.

dalin and was exemplified by hind-quarter ataxia. For those animals that progressed to death, ataxia increased until the rats were unable to right themselves. The rats' noses and paws then became cyanotic, the animals had labored respirations, urinated and defecated, lapsed into coma, convulsed and died. Autopsy of those animals given blue coloring showed the dye confined to the stomach with the exception of two animals in which the dye had extended into the duodenum.

There was no linear correlation between the amount of amygdalin administered and the blood cyanide level in those animals that died; however, all blood specimens assayed were either in the range of toxicity (greater than 50 μg per dl) or lethality (greater than 100 μg per dl).[16] Cyanide levels in blood specimens from 57 deceased animals ranged from 64.8 μg per dl to 425 μg per dl. This compares favorably with blood cyanide levels reported in rats that died following the intraperitoneal administration of amygdalin.[6]

Kinetic Studies of Amygdalin

The pattern of excretion of thiocyanate and amygdalin (expressed as benzaldehyde) following the oral administration of the drug is shown in Figure 2. The excretion of thiocyanate was greatly dependent upon whether or not the rats had previously been given neomycin. There was a minimal rise in urinary thiocyanate in those rats receiving neomycin and a 40-fold rise in those not receiving the antibiotic.

The data from rats given amygdalin intravenously are shown in Figure 3. There was a pronounced rise in 24-hour urine output of thiocyanate following intravenously given doses, and this result was independent of pretreatment of the animals with neomycin, suggesting that neomycin had no effect on cyanide release in those animals given the intravenous preparation. Following intravenous dosing, approximately 6 percent of the available cyanide from amygdalin was released. This is roughly 50 percent of that which is released following the oral administration of amygdalin in rats not previously given neomycin. The urinary amygdalin excretion continued for five to seven days and did not depend upon the route of amygdalin administration or the pretreatment of animals with neomycin. In these studies we accounted for 70 percent to 85 percent of the amygdalin injected as either amygdalin cleared through the kidneys or amygdalin hydrolyzed to cyanide and subsequently converted to thiocyanate before

renal clearance. Following the oral administration of amygdalin, we accounted for 89 percent to 97 percent of amygdalin.

Hydrolysis of Amygdalin, In Vitro Studies

Results of these studies are shown in Table 1. We found that all segments of rat gut tested were capable of hydrolyzing some amygdalin. Our in vivo studies show that this hydrolysis is blocked partially by neomycin. Therefore, it is quite likely that hydrolysis is accomplished primarily by bacterial action. The fact that hydrolysis occurred even in the gastric segment is compatible with our findings with the marker dye in our LD_{50} studies in which there was sufficient cyanide released while the drug was in the stomach to cause cyanide toxicity, including death.

As shown in Table 1, four of the bacterial species found in human feces were capable of hydrolyzing amygdalin; the most efficient bacteria in this regard were *Bacteroides fragilis,* a major constituent of human stool. On the other hand, cell-free filtrates of the broth cultures failed to hydrolyze amygdalin. Not shown in Table 1 is the fact that on incubating amygdalin with approximately 1 gram of human feces, 53 percent of the available hydrocyanic acid was released by hydrolysis.

The results of the human gastric acid studies are also given in Table 1 and show that no cyanide was released in acid gastric juice, but as the pH rises above 5—a level at which colonization of the stomach by bacteria has been documented—some cyanide is released. These findings vary somewhat from those in our investigations with rat gastrointestinal tracts in that much less amygdalin was hydrolyzed on incubation with the gastric contents of humans than was released on incubation of gastric segments of rats. We postulate that in humans with high gastric acidity, hydrolysis of amygdalin may be delayed until the glycoside leaves the stomach and enters the intestines.

TABLE 1.—*In Vitro Hydrolysis of Amygdalin (CN^- Recovered)*

	CN^- Recovered (nmoles/gram tissue)
Rat gastrointestinal segment	
Stomach	0.049
Duodenum	1.065
Ilium	2.121
Cecum	3.165
Colon	1.112
pH	***nmoles CN^- Released***
Human gastric juice	
2.2-4.1 (5 samples)	0
5.0	34
5.4	35
5.8	53
6.1	0
6.8	64
	nmoles CN^- Released*
Human fecal bacteria	
Escherichia coli	0
Enterobacter aerogenes	43
Streptococcus fecalis	43
Clostridium perfringens	62
Bacteroides fragilis	1,700
Filtrates	0

CN^- = cyanide

*10^9 bacteria

Comments

Discussion of Test Results

It has been known that the harmful effects of amygdalin are directly related to the toxicity of cyanide, which is released following hydrolysis of the parent compound.[1,2,4,5] Our current investigations verify this and show that there is great variability in the effects of amygdalin on rats and that the slope of the LD_{50} curve is not steep. The calculated LD_{50} for rats is somewhere in the range of 15 to 75 times the usual dose of amygdalin recommended for humans by Laetrile advocates. In brief, the oral dose of amygdalin as proposed by its advocates is 500 to 2,500 mg per day. For a 70-kg man, this is 7 to 36 mg per kg of body weight per day, or approximately 1/15 to 1/75 of the LD_{50} dose for rats.

Because humans are seven times more sensitive to the lethal effects of standard chemotherapeutic agents than rats,[6] the difference between the usual dose of amygdalin for man and the theoretical LD_{50} dose for man may vary by a factor of only two to ten. Based upon the rather flat LD_{50} curve, it is reasonable to assume that the toxicity of orally given amygdalin in humans will vary greatly from person to person. This may explain why presumably some have ingested amygdalin and noted no toxic effects, whereas others have become symptomatic and a few have died of cyanide poisoning, one adult dying after ingesting as little as 10.5 grams of amygdalin.[9]

These studies suggest that the status of the bacterial content in the gastrointestinal tract will

have a significant impact on the amount of cyanide released by hydrolysis of amygdalin. Thus, one may postulate that in persons with any gastrointestinal disorder predisposing to proximal colonization of fecal bacteria—such as achlorhydria[19] or spontaneous or surgically induced intraintestinal fistulas—toxicity may be increased following the oral administration of amygdalin. On the other hand, patients on a regimen of orally given antibiotics, especially extended spectrum antibiotics, may have reduced gastrointestinal flora and be less susceptible to amygdalin's toxicity. Results from our studies on the hydrolyzing ability of some human enteric bacteria show that the ability to release cyanide from amygdalin exists in the gastrointestinal tract even in the absence of food stuffs containing the hydrolytic enzymes.

The ability of bacteria to release cyanide from amygdalin has been demonstrated by others. Coop and Blakeley noted cyanide production from amygdalin and from two other cyanogenic glycosides, linamarin and lotaustralin, by the microflora of sheep rumen.[20] In their studies, as in our investigations, hydrolysis was decreased by reducing bacterial numbers, which they accomplish by mechanically washing out the sheep rumen. Human feces have been reported to hydrolyze 45.2 percent of amygdalin as compared with 0.47 percent by mouse feces and 0 percent by monkey feces.[21] In our studies, human stool hydrolyzed 53 percent of amygdalin. The capability of human feces to hydrolyze such a large amount of amygdalin probably explains why a Laetrile enema was nearly fatal to one patient.[14]

Amygdalin administered in conjunction with foods rich in β-glucosidase yields toxic levels of cyanide.[4,5] From our current investigations, we conclude that when amygdalin is given orally or intravenously to rats, even in the absence of food stuffs containing β-glucosidase, appreciable quantities of cyanide are released. In the case of orally given amygdalin, we feel this release of cyanide is due to a great extent to bacterial action in the gastrointestinal tract. In rats fed amygdalin, up to 12.7 percent of the available cyanide in amygdalin was released. Reduction of fecal flora by neomycin reduced the release of cyanide to 1.7 percent.

The Potential for Chronic Poisoning by Cyanide

The pro-Laetrile movement has inappropriately labeled amygdalin as a vitamin (Vitamin B_{17})—a vitamin that is presumably lacking in our diet. They imply that cancer is a nutritional deficiency disease of dietary amygdalin. Using this rationale, the prophylactic administration of amygdalin has been advocated to prevent cancer. Our studies, showing 12.7 percent of available cyanide being released following the oral administration in rats and 53 percent of available cyanide being released following exposure of amygdalin to human feces, suggest that orally given daily doses will expose persons to chronic levels of cyanide. The clinical implication of this becomes staggering when one considers that chronic cyanide poisoning is reported in humans in the tropics and subtropics among natives whose main dietary food is cassava root, which contains linamarin, another cyanogenic glycoside.[22]

Osuntokun and co-workers have shown the association of a degenerative disease in Nigeria, tropical ataxic neuropathy, with chronic cyanide poisoning from the dietary intake of cassava.[23] The most common neurologic damage reported was sensory and motor ataxia, optic atrophy and nerve deafness. Osuntokun states approximately 8.25 mg of cyanide is ingested daily by those who subsist on cassava diets prepared as *gari* meals. The possibility of chronic cyanide poisoning from daily ingestion of Laetrile is overwhelming when one compares this with 30 mg of cyanide ingested with every 500 mg tablet of Laetrile. It is clear that the amount of cyanide contained in the recommended one to five tablets of Laetrile per day is considerably higher than that found in the Nigerian *gari* diets. Some 300,000,000 people eat cassava regularly. Reports of neurologic damage secondary to cyanide are frequent from those countries where these people live. In addition, deaths have been reported following meals of cassava due to cyanide poisoning.

Smith and associates were the first to describe neurologic symptoms consistent with chronic cyanide poisoning in patients ingesting amygdalin.[7] One of their patients was described as having pronounced neuromuscular disorders, including paralysis of both eyelids and lower and upper extremity muscle paresis. The patient had been taking only a single 500 mg amygdalin tablet daily for seven months. When this drug was discontinued, his neurologic symptoms improved dramatically over the subsequent six days. Should some people continue to believe that amygdalin has therapeutic benefits and ingest this cyanogenic glycoside, our studies suggest that signs of chronic cyanide poi-

soning will develop in some. In addition, persons having altered gastrointestinal physiology, such as achlorhydria or spontaneous or surgically induced intestinal fistulas, may sustain acute cyanide toxicity, even death.

The results of our studies have answered the original question we addressed: Is it possible for amygdalin usage to place a person at risk of chronic cyanide exposure? This has been answered in the affirmative, and in so doing a number of additional questions have arisen. These include the following: (1) Why is urinary excretion of amygdalin similar in rats regardless of the route of administration? (2) Why does hydrolysis of amygdalin occur only in the first day of intravenous and oral administration despite the fact that amygdalin's renal clearance continues for five to seven days? (3) Where does conversion of amygdalin to thiocyanate in vivo take place?

While the above questions remain unanswered, we are able to conclude from our studies that Laetrile remains a hazardous drug, lacking not only therapeutic benefit in patients fearing cancer or having cancer, but possessing harmful effects related to cyanide poisoning. We can predict from our studies that if amygdalin is taken chronically, it will produce neurologic damage in humans similar to that seen in persons suffering from tropical ataxic neuropathy, a disorder attributed to chronic cyanide exposure.

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