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A bibliography of essays and monographs by Dr. Krebs, John Beard and other's involved the metabolic resolution of cancer will be found at: http://www.navi.net/~rsc/krebsall.htm. rsc. (Updated 31 July 1997...see end of file for graphic links; for an essay on suggested mechanisms of action of nitrilosides; Also, certain terms are defined in the text for clarity and are included in brackets.rsc)

THE NITRILOSIDES IN PLANTS AND ANIMALS

Nutritional and Therapeutic Implications

Ernst T. Krebs, Jr.
John Beard Memorial Foundation
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Since the principal objective of this presentation is a study of the clinical use of the Laetriles (nitrilosides) because these substances yield nascent HCN [hydrocyanic acid] when they undergo enzymatic hydrolysis *in vivo*, it will be helpful if one begins with a general study of the nitrilosides in plants and animals.

A *nitriloside* is a naturally occurring or synthetic compound which upon hydrolysis by a beta-glucosidase yields a molecule of a non-sugar, or aglycone, a molecule of free hydrogen cyanide, and one or more molecules of a sugar or its acid. There are approximately 14 naturally occurring nitrilosides distributed in over 1200 species of plants. Nitrilosides are found in all plant phyla from Thallophyta to Spermatophyta.

The nitrilosides specifically considered in this paper are 1-mandelonitrile-beta-diglucoside (amygdalin) and its hydrolytic products; 1-para-hydroxymandelonitrile-beta-glucoside (dhurrin); methylethyl-ketone-cyanohydrin-beta-glucoside (lotaustralin); and acetone-cyanohydrin-beta-glucoside (linamarin). All of these compounds are hydrolysed to free HCN, one or more sugars and a non-sugar or aglycone. For the purposes of this study they may be considered as physiologically and pharmacologically identical and varying essentially only in the per cent of free HCN they produce upon hydrolysis by beta-glucosidase.

The concentration of nitrilosides in plants varies widely and ranges from small traces to as much as 30,000 mg./kg. in some of the common pasture grasses (in the dry state). There is no evidence that animals synthesize nitrilosides under normal conditions. The metabolism of all the higher animals, and most of the invertebrates as well, involves the hydrolysis of plant-derived nitrilosides ingested in the plant components of the diet. This hydrolysis is produced by beta-glucosidase occurring in the gastro-intestinal tract and produced in various tissues of the animal. The enzyme occurring in the intestinal tract is produced by various bacteria or microflora. When the enzyme so produced or that enzyme existing in the organs acts to hydrolyse the nitrilosides to free HCN, sugar and a non-sugar moiety the CN [cyanide] ion released is detoxified or converted by an enzyme normally occurring in the organism and known as *rhodanese* or thiosulfate transulfurase. The product of such

conversion is thiocyanate, a compound found in the tissues of all vertebrates, many invertebrates and a number of plants.

It is one of the objectives of this report to survey extensively but not intensively the indispensable but long-overlooked role of the nitrilosides in the plant and animal kingdoms. The material utilized for this paper comprises, to a large extent, an abstract of a book now in preparation on the subject. The latter carries a bibliography in excess of 3,000 titles. It is not possible in this report to supply an adequate bibliography. We have, therefore, limited the references in this paper, as a rule, to isolated or specific experimental observations; and we have omitted the citation of reference sources for data that are commonplace or unquestioned facts in the universe of the relevant expert. For this reason statements undocumented here may often appear extraordinary to a reader not intimately acquainted with sophisticated data derived from disciplines often distant from his own. For example, even to experts in animal husbandry, agriculture, pharmacology, and toxicology it may come as an almost unbelievable statement that cattle in the course of grazing may daily ingest grasses containing as much as 30,000 mg./kg of nitriloside (carrying over 2.0 gram of derivable HCN) over a period of years without discernible effect. The grasses involved have, however, been repeatedly assayed by reliable and universally accepted techniques and the quantities ingested by sheep and cattle have been repeatedly and carefully measured. The results have been duly published in acceptable journals over the world. For such data the bibliography will be supplied to the reader upon request. We shall offer, often of necessity in a highly abridged form, factual foundations for our study, which foundations have not yet become accessible as a part of any organized discipline. For the often extensive data comprising such foundations, a detailed bibliography is available to the reader upon request.

NITRILOSIDES AND NITRILES IN TERMS OF BIOLOGICAL EXPERIENCE

Nitrilosides are produced by, and HCN enters into the metabolism of, members of the plant kingdom extending from bacteria, moulds and fungi to the common fruits--apricots, peaches, cherries, berries, and the like--comprising the Rosaceae and extends through the Leguminosae--lima beans, vetch, pulses, clovers--to the Graminae with over eighty grasses of the latter family carrying one or more specific nitrilosides.

No area of the earth that supports vegetation lacks nitriloside-containing plants. Over 30 per cent of *all* tropical plants, edible or unedible by man or animals, contains a nitriloside. From the nitriloside-rich salmon-berry or bufallo-berry (Rubus spectabilis) growing on the Artic tundra and the arrow-grass growing in Arctic marshes and supplying the major fodder for the caribou, to the cassava or manioc--the bread of the tropics--plants extraordinarily rich in nitriloside, and serving as food for man and animals, are found in abundance. All life on earth participates directly or indirectly in the chain of nitriloside metabolism. In terms of living forms, the nitrilosides appear as ubiquitous in time as they do in space. There is some evidence that life on earth commenced in conjunction with hydrogen cyanide. The ubiquity of it normally occurring as glycosides in plants was well established before animal evolution had reached the vertebrate level.

A glance at the vegetation about us almost anywhere will disclose nitriloside-containing plants. The common weed and fodder, Johnson-grass, often carries 15,000 mg/kg [milligrams per kilogram] or more of nitriloside. A similar concentration is found in Sudan-grass, Velvet grass, white clover, the vetches, buckwheat, the millets, alfalfa or lucerne, lima beans, even some strains of green or garden peas, the quinces, all species of the passion-flower, the seeds as well as the leaves and roots of the peaches and various cherries are but a few of the natural sources of this essentially non-toxic water-soluble factor.

METABOLIC ROLE

Though the nitrilosides are plant-produced, we are interested here only in their metabolic role in the animal kingdom. We know that they account largely if not exclusively for all the thiocyanate found in the tissue and body fluids of animals. Thiocyanate is found in the serum, urine, sweat, saliva and tears of man and lower animals. Thiocyanate as well as its natural precursor, the HCN derived from dietary nitrilosides, supply the cyanide ion for the nitrilization of the precursor of vitamin B-12 (hydrocobalamin) to vitamin B-12 (cyanocobalamin).

Upon hydrolysis in the intestinal tract of man or animals the nitriloside exerts a variable antibiotic effect through the action of the freed hydrogen cyanide and, in the case of some nitrilosides such as amygdalin or dhurrin, through the antiseptic action of benzaldehyde or p-hydroxybenzaldehyde aglycone [non-sugar]. The latter from Johnson-grass, before and after oxidation to a benzoic acid is about 30 times more antiseptic (in terms of the phenol coefficient) than ordinary benzaldehyde or benzoic acid.

It is now experimentally established that *only* those nitrile compounds that are hydrolyzed to *free hydrogen cyanide* lend themselves to the formation, through rhodanese in the presence of utilizable sulfur, of thiocyanate.

EXCRETION. After metabolism in the animal body, most of the HCN moiety is eliminated as thiocyanate in the urine with possibly some being eliminated in the faeces. In man a small percentage of the nitriloside-derived HCN may be excreted through the lungs and even in the urine. In rabbits the administration of one nitriloside (amygdalin) has been reported as resulting in the elimination of traces of the unchanged nitriloside in the urine. Sorghum and other plants involved in cyanogenesis associated with the synthesis of nitrilosides are known to emit a small percentage of free HCN.

In the case of nitrilosides with an acetone aglycone or an ethylmethyl-ketone aglycone, the ketone aglycones as well as the sugar moiety are probably fully metabolized to carbon dioxide and water with the HCN residue contributing to the production of thiocyanate, some of which may be eliminated from the body in the urine and faeces with the remainder persisting as part of the normal "cyanide metabolic pool".

EVIDENCE FOR BETA-GLUCOSIDASE IN ANIMAL TISSUES. Beta-glucosidase is found in especially high concentrations in the liver, spleen, kidney and intestinal mucosa in animals. Since HCN is eliminated as thiocyanate conversion by rhodanese in the presence of a source of sulfur, the fact that ingested nitrilosides increase the level of thiocyanate in the body fluids proves that they have been hydrolysed to free HCN. This hydrolysis is enzymatically accomplished only by a beta-glucosidase.

Nitrilosides are also hydrolysed to free HCN when injected into the peritoneal cavity of the rabbit. The fluid in this area apparently is lacking in rhodanese activity since free HCN has been observed in the peritoneal fluid of rabbits following injections of large does of amygdalin. Extensive studies have also been published on the hydrolysis of nitrilosides to free HCN by the ruminal microflora of sheep.

EVIDENCE FOR OCCURRENCE OF RHODANESE IN VERTEBRATES. The detoxification of HCN as thiocyanate was first observed by S. Lang in 1894, and the enzymic aspects were first studied in 1933 by K. Lang who gave the name *rhodanese* to the enzyme

concerned. Since thiocyanate is some hundred times or so less toxic than HCN, the rhodanese reaction is a true detoxification.

It appears that the concentration or activity of rhodanese in the tissues of animals varies directly with the normal nitriloside content of the general dietary characterizing each species. The livers of rats, rabbits and cows appear to be more active than those of monkeys, men, dogs, and cats in descending order. Rhodanese activity is as widely distributed in living forms as are nitrilosides. Both have been found in forms as diverse as fish, squids, insects and plants. The enzyme has been isolated in crystalline form by Sorbo and a substantial literature on it has developed.

The action of rhodanese is highly specific. It is limited not merely to nitriles but only to those nitrilosides which surrender free HCN ions upon hydrolysis.

The administration of rhodanese has been found to protect experimental animals from doses of cyanide or its salts ten times or more in excess of normally lethal doses. The concentration of rhodanese in tissue is generally proportional to that of beta-glucosidase and always functionally in excess of the latter. Rhodanese may also appear in the absence of beta-glucosidase as in the case of the brain just as beta-glucosidase may appear in conjunction with cancer or trophoblast cells in the absence of rhodanese. The high sensitivity of cerebral tissue to hypoxia would tend in the course of natural selection to provide a high rhodanese activity against adventitious HCN and to exclude any enzymatic means by which the cyanide ion could be hydrolysed in this area. The rationale for the occurrence of a high beta-glucosidase concentration in the absence of rhodanese in the case of trophoblast is associated with the role the trophoblast plays in hemopoiesis [blood formation], especially as it concerns the nitrilization of hydrocobalamin to active vitamin B-12 (cyanocobalamin).

Rhodanese, beta-glucosidase, nitrilosides, and thiocyanates are found throughout the phyla of the plant and animal kingdoms from bacteria to giant trees, and from protozoa to man.

THIOCYANATES IN PLANTS

Although the normally occurring nitrilosides in plants have never been known to contribute any evidence of chronic or cumulative toxicity from the nitriloside itself nor from the derivable HCN, thiocyanates occurring in plants, notably the *cruciferae* or *Brassicae*, have been identified with goitrogenic properties among peasant populations subsisting on large quantities of such Cruciferae as cabbage, turnips, rutabaga, brussel sprouts, kohli rabi, cauliflower, etc. grown in iodine-deficient soil. Clovers among many other legumes and grasses are rich sources of nitriloside for grazing animals. Recently ewes grazing on nitriloside-rich clover growing in Australian soil deficient in iodine were reported as showing a high incidence of goiter which was identified as apparently arising from the thiocyanate derived from the clover nitriloside and metabolized in the presence of a severe iodine deficiency.

In soils carrying normal concentrations of iodine no such effects have been observed in sheep or cattle despite the fact that some of these animals may ingest as much as 300 grams of nitriloside a day through dry arrow-grass, Johnson-grass, clovers, or other fodder.

It will also be recalled that Wilder Bancroft, Professor of Physical Chemistry at Cornell University, ingested 1,000 mg. of thiocyanate a day for a period of 23 years in the process of studying the cumulative properties of this chemical. He reported no untoward result from the experiment. To the contrary he associated it with some suspected positive benefits that need not be considered at this time.

While prolonged excessive ingestion or development of thiocyanate in the presence of a severe iodine deficiency has apparently been associated with a goitrogenic effect in both human and animal populations, there has never been anything to suggest the possibility of any cumulative toxicity arising from the cyanide ion itself.

It is apparently impossible to develop cumulative toxicity to HCN in animals. The reason for this is that the biological experience with the cyanide ion in metabolism is almost as ancient and extensive as the biological experience with water, oxygen, nitrogen, salt, or the like. All can prove fatal to animals if administered in excessive quantities or in an improper way. As a result of an almost archetypical ignorance of or superstition towards HCN engendered by observations of the swiftness of its lethality made in days when chemistry had barely emerged as a science, a powerful cultural antipathy toward cyanide developed. Cyanide was indiscriminately and falsely classified, because of its toxic potentiality, with protoplasmic poisons utterly foreign to the biological experience of the organism. Unfortunately, this ancient misapprehension has been perpetuated among botanists, physiologists, toxicologists and even pharmacologists. And in their culturally induced fear or antipathy toward cyanide as a poison they have unwittingly foreclosed adequate attention to, and study of, the critically important factors in the physiology of plants and animals. An atmosphere of pure nitrogen or pure carbon dioxide is just as lethal as one of hydrogen cyanide. The major differences among these compounds possessing almost equal biological experience are those of concentrations and rates, and none are capable of producing chronic or cumulative toxicity. As we shall study in a subsequent section, sheep have received as much as 460 mg of HCN in the course of an hour without any evidence of acute toxicity and as much as 210 mg of HCN a day for two years without any evidence of cumulative toxicity or resistance or immunity of any kind to HCN. This biological experience qualitatively parallels that for water, salt, sodium chloride and compounds with similar biological experience.

Though in our early studies on the nitrilosides we attempted because of our then limited knowledge of their basic significance in terms of biological experience to ascertain some evidence of cumulative toxicity for them, we now agree with such students of the problem as Coop and Blakely that it is impossible for compounds that have through nutrition been a part of the biological experience of plants and animals millions of years before the appearance of man, and an inherent part of his physiology since his appearance, to produce any cumulative toxic effect. Whether we are dealing with the first nitriloside to be discovered, amygdalin, or with linamarin or lotaustralin, it would seem vain to expect to find from their hydrolytic products of glucose and HCN and their aglycone of benzaldehyde or benzoic acid in the case of the first, or acetone or methyl-ethylketone, respectively, in the case of the latter, any possibility of cumulative effect. Glucose, thiocyanate, benzoic acid, and even acetone are components normal to the metabolic pathways of the organism, which would have to be susceptible to a development of a cumulative toxicity to itself in order to sustain one to the components which comprise the organism.

If the obvious is belaboured to *reductio ad absurdum*, it is because even at this late date there are apparently some unacquainted with the fact that the hydrolysis *in vivo* of a nitriloside by one or more endogenous beta-glucosidases with the production of free HCN, detoxified as thiocyanate by the enzyme rhodanese in order to protect the organism, or sometimes left undetoxified by cells or organisms lacking or deficient in rhodanese, comprises biological phenomena that were commonplace in organisms aeons before the advent of man who inherited such mechanisms. As a result of a deficient rhodanese mechanism some organisms have been destroyed by the HCN emitted by other organisms rich in beta-glucosidase and rhodanese.

Blum & Woodring (*Science*, 138:513, 1962) in a paper on "Secretion of Benzaldehyde and Hydrogen Cyanide by the Millipede *Pachydesmus crassicutis* " describe how this large millipede

whose known distribution is limited to Louisiana and southern Mississipi protects itself against its natural prey, the imported fire ant (*Solenopsis raevissima* v. *richteri* Forel) by secreting a mixture of benzaldehyde and hydrogen cyanide against the predator when disturbed by it. The millipede is equipped with paired glands located on eleven of the notal projections; from these glands benzaldehyde and HCN are ejected. The water-clear secretion of *Pachydesmus* was collected by touching the dorsal surfaces of the notal projections with a small square filter paper which rapidly absorbed the liquid discharge. This discharge was then analysed by gas chromatography and infra red photospectroscopy. The major component was found to be benzaldehyde. HCN and glucose were also found together with a disacharide which appears to be the sugar moiety of the nitriloside amygdalin. The millipede secretes its own beta-glucosidase which hydrolyses the nitriloside in the notal glands to free HCN, benzaldehyde and sugar. While the millipede protects itself from the HCN through its endogenous rhodanese, this HCN is emitted against a predator relatively deficient in rhodanese.

David A. Jones, Department of Genetics, and John Parsons, Department of Pharmacology, Oxford University, in a paper on "Release of Hydrocyanic from Crushed Tissues in All Stages of the Life-Cycle of Species of the Zygaeninae (Lepidoptera)" (*Nature,* 193 (4810), p.52, 1962) reported that 50 crushed eggs (weight of about 50 eggs 2.6 mg-4.0 mg) of this moth release up to 150 microgram of HCN, which HCN thus accounts for about 5 per cent of the weight of such eggs.

The foregoing examples were selected from a comprehensive body of similar data for the purpose of adumbrating the ubiquity of the biological occurrence and experience among all forms of life not only in terms of nitriloside but also in terms of beta glucosidase, rhodanese, thiocyanate, and the selective susceptibility of rhodanese-deficient cells to the noxious effect of adventitious HCN. Some of the data briefly reviewed in the two papers just cited concern the occurrence of rhodanese in the parasites of the gastro-intestinal tract of animals ingesting nitriloside-rich foods. Such rhodanese is, of course, necessary as a protection against the free HCN released from the ingested nitrilosides by the beta-glucosidase produced by the intestinal flora and possibly also by the intestinal mucosa of the host.

NUTRITIONAL IMPLICATIONS

Tribes in the Karakorums of West Pakistan, the aboriginal Eskimaux, tribes of South Africa and South America living on native foods, the North American Indian in his native state, the Australian aborigines, and other native or so-called primitive peoples rely upon a diet carrying as much as 250 to 3,000 mg of nitriloside in a daily ration. All populations living close to a Neolithic level appear to be characterized dietarily by a similarly high consumption of nitriloside-rich foods.

Civilized, Westernized or Europeanized man, on the other hand, relies on a diet that probably provides an average of less than 2 mg of nitriloside a day.

It is noteworthy that no case of cancer has ever been reported among the peoples of one tribe in the Karakorums over a period of about 60 years of medical observation. For a period of at least 80 years the Eskimaux have been observed with even greater scrutiny by medical men, missionaries, teachers, traders and others for the specific purpose of attempting to discover the possible incidence of cancer among them. Despite such observations, no case of cancer has yet been reported among these two native populations while they lived on their native diet; however, in the case of the Eskimaux a number of cancer victims have been found among those who left their aboriginal dietary habits for a Westernized diet.

The medical scrutiny by which such cancer cases were noted was no less intense than that given a large proportion of the natives not having access to modern foods.

The observations made of Eskimaux on this subject are recorded in Vilhjalmur Stefanson's book on "CANCER: Disease of Civilization? An Anthropological and Historical Study" (Hill and Wang, N.Y. 1960. Philip R. White, M.D., has written an interesting preface to the book while Rene Dubos' introductory chapter is most instructive.)

The remarkable freedom primitive populations show to dental caries is, of course, a commonplace to students of anthropology. Many of the nutritional reasons for such freedom from caries among these people are not difficult to find in terms of the food they eat, and especially of the food they do not eat. In the similar freedom of these populations from cancer the possible role of nutrition has been at best vague and general---as it was in the case of pellagra and the anemias prior to the discovery of the specific factor involved in the deficiency.

Major General Sir Robert McCarrison, before and during his appointment as Director of Nutrition Research in India under the Research Fund Association, treated and studied the people of Karakorum. From the perspective of 20 years of observation he reported that he had failed to find a single case of cancer among this population. Later John Clark, M.D. served in a medical mission to this population. He was properly critical of the tendency of some to romanticize the allegedly perfect health of these long-lived people. He described, as had McCarrison, a relatively high incidence of goiter among these people as well as certain skin diseases and a substantial incidence of dental caries. The nutritional basis for the high incidence of goiter among them is clear in the relative iodine deficiency of their diet, their incidence of dental caries likewise has a clear nutritional basis. The tendency to goiter though resting on an iodine deficiency is exacerbated by the presence in their diet of an abundant quantity of nitriloside, which contributes a corresponding quantity of thiocyanate that in the absence of adequate iodine is goitrogenic, as we have seen in the case of human populations eating vegetables of the thiocyanate-rich Cruciferae grown in areas deficient in iodine or in the case of ewes grazing on nitriloside-rich (i.e., thiocyanate-producing) clover grown in iodine deficient soil.

At any rate, John Clark while recognizing and describing the many pathological conditions to which these people, like all others, are subject did add that he, too, had never observed a single case of cancer among them.

While cancer may elude diagnosis in some cases, early cases ultimately become terminal cases, and when the latter involve the skin, breast, the lymphatic glands, mouth, tongue, lungs, or rectum they do not go unrecognized even by the medically naive---certainly not by medical observers.

DIETARY SOURCE FOR NITRILOSIDES

KARAKORUM TRIBE. A number of reliable works have reported the general diet of the people of the Karakorum. Buckwheat, peas, broad beans, lucerne, turnips, lettuce, sprouting pulse or gram, apricots with their seeds, cherries and cherry seeds, berries of various sorts---these are among the seemingly commonplace foods that comprise the bulk of the diet of these people. With the exception of lettuce and turnips, each of these plants contains some nitriloside. Turnips contain thiocyanate, a substance to which nitrilosides give rise.

Over a dozen books and articles that we have read on these people are unanimous in the report that the apricot is the major staple in their diet. In view of our work of the nitrilosides in relation to human cancer, the predominance of the apricot in the nutrition of these reportedly cancer-free

people was frequently called to our attention over the years. We originally dismissed the matter on the basis of pure coincidence, especially since the meat or flesh of the apricot contains little or no nitriloside, which is concentrated in the seed that resides in the pit. The seed is the size of a small almond and may be mistaken for a shelled almond.

Finally, upon investigating the diet of these people we found that the seed of the apricot was prized as a delicacy and that every part of the apricot was utilized. We found that the major source of fats used for cooking was the apricot seed, and that the apricot oil was so produced as inadvertently to admit a fair concentration of nitriloside or traces of cyanide into it. The apricot seed is so prized among these people that there are experts chosen among them for the purpose of testing the seeds of new apricot trees for their bitterness, since occasionally there appears strains that produce apricot seeds carrying extraordinary and toxic concentrations of nitriloside and beta glucosidase. These trees are destroyed.

The peoples of the Karakorum share with most Western scientists an ignorance of the chemistry, toxicology and physiology of the nitrilosides and nitriles. Emperically, however, they have apparently discovered the value of these factors to nutrition, though recognizing the very toxic potential of the cyanide of apricot kernels when improperly used. They prepare a solution of HCN (prussic acid) by allowing the apricot kernel nitriloside to react, in the presence of a little water added to defatted meal, with the endogenous beta-glucosidase (emulsin) to release free HCN. The resulting solution of HCN is then maintained as a form of bitters that is added drop-wise, because of its recognized toxicity, to wines immediately before they are drunk. It is held that this solution is contributory to health and even longevity.

THE ESKIMAUX.

The diet of the Karakorum is of necessity essentially a vegetable diet; that of the Eskimaux is essentially a meat diet. Superficially no two diets could probably appear more divergent; yet the Eskimaux shares with many other primitive peoples, most of whom are dominantly vegetarian, a remarkable freedom from malignant disease. On this basis we were at first inclined to dismiss the high concentration of nitrilosides in the diet of Karakorum people and others relying mainly on plant food as simply another coincidence, contradicted by the situation among the meat-eating Eskimaux.

Upon further investigation of the Eskimau diet we found that one berry grew abundantly in the Arctic areas and that this berry is extraordinarily rich in nitriloside. This is the salmon-berry, cloud-berry, or buffalo-berry *(Rubus spectabilis)* . It is eaten by birds, animals and men. It is also incorporated into pemmican, which is eaten during all seasons of the year. It was noted also that animals such as the caribou are important in the diet of these people. In eating the caribou the frozen contents of the rumen or paunch are utilized as a salad and considered a delicacy. In view of this we investigated the forage upon which the caribou feeds. Among the grasses that grow in Arctic marshes, arrow-grass *(Triglochin maritima)* is very common. Studies made by the United States Department of Agriculture on the nitriloside content of arrow-grass (Triglochin maritima) show it to be probably richer in nitrilosides than any common grass. On a dry weight basis, one kilogram of arrow-grass was found to contain over 30,000 milligrams of nitriloside. One teaspoonful of such rumenal salad might be expected to carry 100 mg or more of nitriloside. This nitriloside is p-hydroxymandelonitrile-beta-glucoside; whereas the dominant one among the Karakorum is l-mandelonitrile-beta-diglucoside, though both nitrilosides occur in the diet of both groups.

A quick glance at native populations in tropical areas, such as South America and South Africa, discloses a great abundance of nitriloside-containing foods. Over one-third of all plants in these areas contain nitrilosides. Cassava or manioc, sometimes described as "the bread of the tropic", is one of the most common as well as richest sources of nitriloside. As eaten by primitive populations, the bitter and nitriloside-rich manioc is preferred. People in the cities on Westernized diet favor the sweet cassava. Even in the case of these the cassava is so processed as to eliminate virtually all nitriloside or nitrile ions. The cassava eaten by those still near a Stone Age culture, on the other hand, retains a large quantity of nitriloside and nitrile ions. When these primitive and relatively cancer-free people move to the cities, the incidence of cancer among them rises as they assume the nitriloside-free Westernized diet. Like the rest of civilized mankind, they then show a cancer incidence of one in every three or four individuals if they live for a sufficiently long period.

RELATIVE FREEDOM OF SHEEP, GOATS, AND WILD HERBIVORES FROM CANCER

The relative freedom of wild and most domestic herbivores from cancer as contrasted to its higher incidence among at least domesticated carnivores has been the subject of considerable attention. The nitriloside content of much pasturage, fodder and silage is, of course, often striking. White clover *(Trifolium repens),* alfalfa or lucerne *(Medicago sativa),* vetch, certain millets, the various sorghums, lupines, broad beans, velvet grass, and at least 80 other grasses, the leaves of Rosacae, berries, etc.---all are common and often rich sources of nitrilosides. The two most common of the pasture grasses, Johnson and Sudan, in many parts of the United States carry as much as 15 to 20,000 mgs nitrilosides per kilogram of dry grass. A 10 kilogram ration a day is not uncommon for freely grazing animals. Such a ration would supply from 150 to 200 grams of nitriloside a day, which would upon hydrolysis yield over 10,000 mg of free hydrogen cyanide. As studies on fistulated sheep have proved, over 95 per cent of all nitrilosides ingested by herbivores in plant foods are hydrolysed within about an hour with the release of the free HCN into the organism.

Domesticated horses, however, may be deprived of a variety of plant foods and be limited more or less to fodder completely deficient in nitriloside. In such animals the incidence of cancer appears to be reasonably high, though no formal statistics are obviously available.

WILD CARNIVORES.

Carnivorous animals in their natural state treat animal food similarly to the Eskimaux of a Stone Age culture. Such animals eat the viscera, especially the rumen, and often do so before eating the muscle tissue of the animal. When carnivorous animals are domesticated as pets or maintained in zoological gardens they often show a relatively high incidence of cancer. For example, in the great San Diego Zoo 5 bears have died in one grotto in the last 6 years. All have died from cancer of the liver. These bears were maintained on a diet almost completely free from nitrilosides. Many speculations were advanced as to the cause of their malignancy, all explanations or suggestions sharing in common a version of the virus theory of cancer. These speculations are reminiscent of those made by Sir William Osler in 1906 on the etiology of pellagra as he studied a report of about 20 per cent of the population of an asylum for the colored insane dying from pellagra during one winter. To Osler this was almost conclusive evidence for the infectious or viral or bacterial origin of pellagra.

The liver cancer which killed the captive bears in San Diego is suggestive of the liver cancer which kills 95 per cent of all Bantus who die from cancer in the hospitals of one area of South Africa. In their native state, liver cancer is virtually unknown among these people. When they migrate to urban areas or to the mines their diet is changed to one consisting, for economic reasons, almost

exclusively of low grade carbohydrates completely devoid of nitrilosides. A staple of this diet is fermented milk and corn meal in a mixture known as mealie meal. When this ration was fed for a prolonged period to rats, most of the rats developed cirrhosis of the liver and the pre-cancerous changes observed in the male Bantus.

Bears in the wild state eat nitriloside-rich berries, such as choke berries, salmon berries; grasses also rich in this factor; wild fruits---apricots, peaches, apples, cherries, plums---the seeds of which are all rich in nitriloside with often the leaves and roots carrying a high concentration of the factor; and barks, roots, twigs, and flowering plants rich in nitriloside. Since bears are omnivores, they also eat game. Peter Krott, Ph.D. in his "Bears in the Family", (E. P. Dutton & Co., Inc., N.Y., 1962) describes the predatory habits of the bear as follows:

"**Isolated footmarks** showed the shepherds where to go and it was not long before they found the remains of the sheep in the undergrowth. The body was carefully cleaned out---a butcher could not have done better. While we roasted a leg of mutton, I asked the men why they did not leave the carcass in place, as the bear would surely return to finish it".

The significance of the rumenal contents of sheep in terms of nitrilosides and nitriles will become increasingly clear in the next section. The nutritional pattern in civilized man as well as in omnivores in captivity is reversed from what obtains in nature: the viscera is largely discarded and that which the animals in the wild state treat as second rate is utilized to the exclusion of a rich source of nitrilosides.

Krott also reported the fondness of bears for whole cherries. He described feeding two bear cubs 20 pounds of cherries. Like all the non-human primates and most primitive men, the bears eat the seeds as well as the meat of the cherries.

Cancer is generally considered a chronic disease. So far no chronic or metabolic disease has ever found prophylactic or therapeutic resolution except through normally occurring accessory food factors. Certainly none has ever been known to have a viral or bacterial etiology. Pellagra, scurvy, beri-beri, rickets, the anemias, a wide range of neuropathies, etc., etc.--all have found total prophylactic and therapeutic resolution only in factors accessory to normal food. No chronic or metabolic disease has found any other resolution. It is not probable that cancer will prove the first exception.

SYSTEMATIC STUDIES OF THE NITRILOSIDE CONTENT OF VEGETABLE FOODS

It is not practicable to attempt to list here concentrations of nitrilosides in the vegetable foods of man and all the animals. This listing is provided in our book together with a number of specimen diets or rations from the people of the Karakorum and elsewhere who live on a nitriloside-rich diet and these diets are contrasted with the inadvertently nitriloside-free diets or rations advanced by some modern nutritionists as ideal examples of the balanced diet.

Botanists, like agricultural and other experts, share our cultural antipathy toward cyanide. As a result of this antipathy relatively slight attention has been paid the nitriloside-containing plants, and what has been paid has been largely negative. The standard botanical technique in identifying such plants has involved a qualitative test utilizing a test tube containing a piece of filter paper moistened with a picrate solution. The suspect plant is crushed between the fingers of the botanist and then placed in the tube. A color change in the picrate paper indicates the presence of "prussic acid". In order for this color change to occur it is necessary, of course, that the plant contain not only the

nitriloside nut also the beta-glucosidase necessary to hydrolyse it. Many plants contain a relatively large concentration of nitriloside with little or no beta-glucosidase while other plants may contain only the enzyme without the nitriloside. The sweet almond is a classical example of the latter.

Agricultural experts have concerned themselves with the nitrilosides only when these have appeared in fodder and other plants in association with such high concentrations of beta-glucosidase that the plant upon being crushed immediately releases large quantities of HCN and thereby offers a threat to cattle. Such plants are labeled as "poisonous" by botanists and agricultural experts alike, and plant geneticists direct their efforts toward breeding "the cyanide" out of the plant. This incidentally, is probably what occurred in the case of the sweet almond which, different from the bitter almond, carries only the beta-glucosidase and not the nitriloside (amygdalin).

The grasses and clovers have been virtually ignored so far as their nitriloside or nitrile content is concerned, since they seldom carry sufficient of the associated enzyme to present a toxic threat to food animals. In Australia, however, a wild fuchsia is often found in areas containing grasses very rich in the nitrilosides. The wild fuchsia is relatively low in nitriloside but rich in beta-glucosidase. Occasionally sheep or cattle grazing upon the nitriloside rich grasses will turn to such fuchsia plants while they are in bloom and ingest the beta-glucosidase-rich foliage. As a result of this, hydrolysis of the grass nitriloside has been so accelerated that HCN has been released at a rate beyond that of the capacity of the animal to detoxify it as thiocyanate and death has quickly ensued. This situation in Australia brought about the excellent studies by Coop and Blakely of New Zealand on the physiology of nitrilosides and nitriles through the use of sheep with artificially fistulated rumen.

METABOLISM AND TOXICITY OF CYANIDE AND NITRILOSIDES IN SHEEP

Coop and Blakely *(New Zealand Journal of Science and Technology,* 31 February 1949, page 277; *Ibid,* 31:(3) 1; *Ibid,* February 1950, page 45) prepared sheep with permanent rumen fistulas for the study of the production of HCN from nitrilosides and nitriloside-containing plants in the rumen. They found:

1. When HCN is introduced into the rumen absorption is very rapid. On the average 75 per cent of the administered HCN is absorbed within 15 minutes.
2. Hydrolysis of nitriloside-containing plants in the rumen is rapid and may be completed within 15 minutes.
3. Naturally occurring beta-glucosidase is not required because the ruminal bacteria supply this enzyme.

The ruminal bacteria supply under self-regulating conditions a source of beta-glucosidase sufficient to bring about the complete hydrolysis of nitrilosides in the ingested plant material. Regardless of the concentration of nitrilosides in the ingested plants, no toxic level of HCN is achieved because of the "self-regulating" condition under which hydrolysis is produced. Only if the nitriloside-rich vegetation is accompanied by other plant material extremely rich in beta-glucosidase is the release of HCN brought about at *a toxic rate* . Toxicity can not occur if the rate of beta-glucosidase hydrolysis is maintained at a slightly lower rate than that of rhodanese detoxification of HCN in the presence of available sulfur.

The presence of H_2S in the rumen of sheep and its rapid absorption suggest that it is probably the important sulfur donor for HCN conversion to thiocyanate by rhodanese. While some of this conversion occurs in the rumen, probably through ruminal bacteria producing rhodanese, most of it occurs in the tissues of the animal.

Over 50 per cent of the HCN released by nitrilosides in the rumen was accounted for by thiocyanate recovered from the urine. A small quantity of free HCN is excreted by the lungs, a quantity that does not exceed 10 per cent of that produced. Additional cyanide is lost through the thiocyanates of the saliva, tears, and faeces.

For all practical purposes the release of free HCN occurred at almost the same rate for nitrilosides residing in ingested plants as it did for the corresponding nitrilosides administered in the pure form.

QUANTITY OF HCN DETOXIFIED BY SHEEP

Franklin and Reid (*Aust. Vet. J.*, 100: 92, 1944) showed that normal sheep could consume the equivalent of 8 to 10 mg of HCN/kg. per day as linseed meal (containing the nitriloside linamarin) without mortality. In a 70 kg sheep this would be equivalent to about 700 mg of HCN. The authors found that the only way enough HCN could be administered through plant food to produce a fatal effect was to force feed the animals.

Fistulated sheep weighing 66 kg were given over a period of three hours a dose of 2.7 grams of nitriloside yielding 300 mg HCN. Coop and Blakely reported that "at no time during the experiment were even the slightest symptoms observed". A total of 568 mg HCN was given a 76 kg sheep in the course of an hour. The only symptoms the animal showed was a "general sleepiness for an hour".

"What Is the 'Toxic Dose' of Nitriloside or HCN?"

The toxicity of nitrilosides or the CN ion is obviously not absolute but relative to two factors:

1. The rate of hydrolysis of nitrilosides and the rate of absorption of the CN ions by the organism.
2. The rate of detoxification of the CN ion by rhodanese, in the presence of utilizable sulfur, to thiocyanate.

So long as rate (2) continues in excess of that rate (1), toxicity from cyanide or the nitrile aspect of the nitrilosides is apparently not possible.

"Though some authors", Coop and Blakely write, "believe that chronic cyanide poisoning is possible, it is generally recognized that provided free HCN or cyanogenetic plants are ingested at a moderate rate throughout the course of the day animals can tolerate amounts well in excess of the M.L.D. for a single dose. Van der Walt (Onderspoort J., 19:79, 1944) failed to produce chronic poisoning in sheep even after administering 3.2 mg HCN/kg daily for two years. Worden (*Vet.Records,*52:857, 1940) showed that in rabbits repeated dosing does not produce a cumulative effect and that the animal is capable of eliminating 1/2 M.L.D. in 2 1/2 hours.

On the other hand, there is no evidence that continued sublethal dosing or ingestion causes any resistance or acclimatization to HCN poisoning".

In the 70 kg sheep the dose of HCN that van der Walt gave was 214 mg a day. This was repeated every day for two years so that the animal received a total of about 150 grams or 1/3 of a pound. No suggestion of any toxicity was found during this period and no trace of cumulative toxicity was found after two years.

To obtain the equivalent amount of nitriloside represented by the HCN, multiply the amount of HCN by the applicable nitriloside factor. For amygdalin this would be 16.92; for dhurrin, 11.51; linamarin, 9.11; lotaustralin, 9.66 In addition to the free HCN component, these nitrilosides yield

glucose and as an aglycone either benzoic acid or acetone, all of which are either normal foods or normal metabolites devoid of toxicity. They account for the fact that, like free HCN itself, the nitrilosides are devoid of any chronic cumulative toxic properties.

Brown, Wood and Smith in a paper on "Sodium Cyanide as a Cancer Chemotherapeutic Agent...Laboratory and Clinical Studies" (*Am. J. Obst. & Gynec.*, 80: 907, 1960) observed a similar freedom of cyanide from cumulative toxicity both in mice and human patients:

"The recovery and convalescence of these patients treated with sodium cyanide was indistinguishable from that of patients who had not received cyanide. *There was no observable delayed clinical toxicity*. All patients recovered promptly from the cyanide treatment and no latent or residual effects could be noted" (emphasis, ours)

Though Brown, et al. reported evidence of therapeutic effects in terms of life-extension, reduction in tumefaction, loss of pain, etc. in laboratory animals, in dogs, and in man, they were limited strictly by the safe peak level of 0.8 to 1.5 mg/kg of cyanide ion that can be safely presented at one time to animal tissue. Were the cyanide ion administered in such a way that a level of 0.8 mg/kg of free HCN might be approached but never exceeded---through the action of self-limiting enzyme systems on a stable source of free HCN---the period of exposure to the cyanide ion could have extended indefinitely instead of being limited to a few minutes as a result of rhodanese detoxification of CN ions not immediately replaced by other CN ions. While a 70 kg sheep was observed to capable of receiving 506 mg of HCN over a period of four and a half hours without any suggestion of acute or chronic toxicity, a smaller dose of cyanide ion given very rapidly in a way to overwhelm the capacity of the rhodanese detoxifying system would have proved fatal. In another instance a sheep absorbed 360 mg HCN within 75 minutes whilst showing only minor symptoms. This would indicate that the capacity of the animal for HCN detoxification was about 300 mg per hour so that the sheep absorbing 506 mg of HCN within four and a half hours without any sign of toxicity fell well within the rate limits for the rhodanese system.

That parenterally administered nitrilosides are likewise subject to the self-limiting and protective capacities of the beta-glucosidase and rhodanese systems in the metabolism of free HCN is evident from numerous studies reporting the absence of parenteral toxicity for the nitriloside amygdalin. In studies conducted by our group the LD50 for this nitriloside in rats was found to be 4.5 G./Kg. This toxicity apparently reflects that of the whole molecule rather than that of the -CN component. Such a dose would be equivalent to 315 G. of the nitriloside (intravenously administered) in a 70 Kg subject. This "toxicity" compares favorably with that of dextrose.

The fact that HCN is a substance with fundamental physiological significance to plant and animal organisms is indicated not only by the normal occurrence of the ion in such organisms but also by the fact that, different from such true or foreign toxins as carbon monoxide, (HCN does not combine with hemoglobin unless it is first reduced to methemglobin) and even under conditions in which HCN combines with such molecules as cytochrome oxidase this combination is highly reversible as evidenced by the fact that experimental animals even when unconscious from cyanide toxicity may be restored to consciousness (without any residual toxicity) through the administration of large quantities of rhodanese and other factors involved in the normal thiocyanate detoxification of this ion.

These facts serve to explain how cattle grazing on dry arrow-grass that may run 40,000 mg HCN per kilogram may during a 24 hour period ingest about 10 kilograms and safely metabolize over 400 grams of nitriloside (about a pound) in this period which produces about 40 grams of free HCN.

Given an adequate source of iodine, there is no evidence suggesting that even a goitrogenic excess of thiocyanate would develop in cattle consuming grasses as rich in nitriloside as arrow-grass.

Johnson-grass and Sudan-grass are among the most common fodder grasses and a nitriloside content equal to 75 per cent that of Arrow-grass is not uncommonly found among them. That the thiocyanate produced from them presents no problem is further suggested in the fact Professor Wilder Bancroft of Cornell ingested 1,000 mg of thiocyanate a day for 23 years and lived to the age of 88 without any sign of cumulative toxicity from the chemical. Such an amount of thiocyanate would represent the detoxification of about 450 mg of HCN a day which would be equivalent to the quantity of HCN released from the *in vivo* hydrolysis of 7650 mg of the amygdalin nitriloside a day. The dextrose released from such a quantity of the nitriloside would not be sufficient to raise the dextrose level from a normal 120 mg per cent in the blood to 121 mg per cent. The benzoic acid released would be equivalent to a little over a gram, which is about the quantity of benzoic acid produced through a moderate ration of certain plant foods.

It is not practicable to attempt to review here the great number of papers published during the past 164 years since L.N. Vauquelin first reported the identification of HCN in apricot seeds in his paper---"Experiences qui demontrent la presence de l'acide prussique tout forme dans quelque substances vegetales", *Ann. Chim.,* 45:206,1800).

From the appearance of Vauquelin's first paper in 1800 to the present no one in the course of hundreds of papers on the subject has advanced any experimental evidence suggesting the possible cumulative toxicity of the nitrilosides such as amygdalin. Authoritative works over the world, including many editions of the *United States Dispensatory,* have properly described amygdalin as non-toxic when parenterally administered and devoid of cumulative toxicity. Certain populations have ingested in their foods up to a gram of this nitriloside a day for spans in excess of 50 years; yet such is the cultural antipathy toward the cyanides, and the misunderstanding of them there from resulting, that some authoritative groups have urged that the nitriloside amygdalin be studied for a period of three or four months for its possible cumulative toxicity when administered to rabbits parenterally in doses of 15 mg/kg body weight. This despite the fact that these animals may already be ingesting plant material carrying a nitriloside content well in excess of the suggested parenteral levels. Davison ("Synopsis of Materia Medica, Toxicology and Pharmacology", 3rd Edition, C.V. Mosby, St. Louis, 1944, p.33) expresses the unanimous opinion of informed authority in stating: "The glucoside amygdalin, given by injection, produces no harmful effect".

Such common foods as lima beans may contain over a gram of nitriloside to the pound.

IN WHAT CLASSIFICATION DO THE NITRILOSIDES FALL?

We have seen that cattle may metabolize almost a pound of nitriloside a day through their fodder, and continue to ingest large rations of nitriloside throughout the span of their life. Indeed, the better the fodder the more nitriloside it is likely to contain.

Can the water-soluble non-toxic nitrilosides properly be described as food? Probably not in the strict sense of the word. They are certainly not drugs per se. They are non-toxic, and they do contribute the essential nitrile radicals to what students of physiology describe now as the "metabolic cyanide pool" in the animal organism. They foster the production of thiocyanate, are involved in the nitrilization of hydrocobalamin to active vitamin B-12 or cyanocobalamin, and they exert a physiological effect that when sufficient is reflected in a hypotensive reaction They do no depress any vital function such as hemopoiesis. To the contrary, their CN ion has been repeatedly reported as raising both the red cell count and the total hemoglobin in animals and humans given small quantities of cyanides or various quantities of the nitrilosides.

Since the nitrilosides are neither food nor drug, they may be considered as accessory food factors. *Another term for water-soluble non-toxic accessory food factors is vitamin.*

THERAPEUTIC IMPLICATIONS

We gave glanced briefly at populations almost or entirely free from cancer under dietary conditions native to them. One such population was seen to be almost exclusively vegetarian, the other, almost exclusively meat-eating. These populations shared in common a high consumption of nitrilosides. We live in a civilization in which one out of every 3 or 4 of us will develop cancer. Our population is characterized by a dietary pattern almost devoid of nitrilosides.

We have seen animals that in their native state are almost devoid of cancer. Observing these animals in captivity we see an alarming increase in the incidence of cancer in them. These animals whether they be the 5 bears in the San Diego Zoo that died from cancer over the past six years or cats and dogs in our household share one common dietary experience: an almost total deficiency in nitrilosides in contrast to the abundance of this factor in their natural diet. To these generalizations on the increased incidence of cancer in domestic animals we find a remarkable exception in sheep and cattle. But when we examine their ration we find it extremely rich as a rule in the nitrilosides. An exception sometimes is found to this in work horses. Here we find the incidence of cancer strangely elevated. Such animals are usually maintained on a nitriloside-free ration of oats and timothy hay and the like.

We frequently observe cats and dogs that under domestication are provided with a variety of rich foods seek out a garden or a weed patch and commence to eat Johnson-grass, even certain species of crab-grass, and other grasses. These grasses have in common a high nitriloside content. In the wild state we see even the omnivorous bear eat first the nitriloside and nitrile filled rumen of sheep while leaving the mutton legs and the remainder of the carcass for a period of hunger.

Among the poor of rural Turkey the incidence of cancer is substantially lower than in the West. Professor Sayre in the May 1960 issue of the *New England Journal of Medicine, 270* published a paper on "Health Hazards, Cyandide Poisoning from Apricot Seeds Among Children in Central Turkey". The children involved had mistaken the wild apricot for the domestic variety. The wild apricot variety carries seeds containing 2,000 mg of HCN per Kg, equivalent to about 35 grams of the nitriloside. The nitriloside existing in the presence of a rich concentration of beta-glucosidase in these seeds renders them toxic. But adults and children in Central Turkey prize these seeds as a delicacy, and parents believing they are "good for the health" do not dissuade their children from eating them.

In the June 1964 issue of *Gourmet Magazine* there appeared a letter that since China does not have a true almond the nut of the apricot is used in its place. This letter caused a physician's wife to write in alarm warning the Editor against the food use of apricot kernels. The Editor for a time shared her alarm until he consulted with the U.S. Food and Drug Administration, the Poison Control Center of New York City Department of Public Health, and others. The consensus was that the seeds were safe for human consumption because the quantities used are usually small and cooking provides and additional safeguard (through destroying the beta-glucosidase).

All this despite the fact that all the sub-human primates that eat apricots, plums, cherries, peaches, apples, and the like also eat the seeds. All the primates fed these fruits in zoos are seen tediously to extract and eat the seeds from pits as resistant even as the apricot. All people of the Stone Age culture, so far as we have been able to ascertain, eat the seeds of all fruits--almost all of which are extremely rich in nitrilosides.

ORIGINAL STUDIES

Over a decade ago clinical investigation of then empirical extracts from apricot kernels (*Prunus armeniaca*) was commenced because of evidence of some anti-neoplastic activity in animals. In humans this extract proved to be palliative in human cancer. Further study showed the responsible factor to be the nitriloside amygdalin. This nitriloside (Laetrile) was then chosen as the subject for systematic clinical investigation after its lack of immediate or cumulative toxicity was demonstrated on experimental animals.

The doses of the nitriloside standardized for human use range from about 12.5 mg/kg to 37.5 mg/kg of the nitriloside. These doses supply from 0.8 mg/kg of the HCN ion. Doses as high as 20 grams or more intravenously have been shown to be without toxic effect in healthy human subjects, though a mildly hypotensive effect is produced through thiocyanate engendered by such large doses. It appears that the 0.8 mg/kg (equivalent to a dose of 1.0 gram of the nitriloside in a 70 kg patient) is generally optimal.

Brown, Wood and Smith in their studies on sodium cyanide in mice bearing Sarcoma 180 found experimentally that 0.8 mg/kg of the CN ion was the optimal dose in contributing a life-extension of as high as 70 per cent to not only these mice but to another strain bearing Ehrlich's ascites cell tumors. Not only did such doses lack cumulative toxicity; but the controls not receiving the cyanide obviously experienced a 70 per cent shorter life-span.

Brown et al. were unaware of any work on nitriloside during the period they made their studies; yet the optimal dosage of the nitrile ion they arrived at from studies on cancer animals is identical to the optimal dose determined for clinical use for nitriloside (Laetrile) by many clinical investigators working over the course of a decade while gradually scaling their original doses of 50 mg of the nitriloside to the present dose of 1,000 mg and altering the route of administration from an intramuscular one to an intravenous one.

Brown et al observed---

"Because the action of...cyanide is almost instantaneous and since normal tissues and cells are capable of recovering from its noxious effects, it could be anticipated here that there would be no cumulative or latent complications in the bone marrow, the gastrointestinal tract, or the renal apparatus."

Clinical experience with approximately 100,000 parenteral doses of nitriloside in man over a decade of study have sustained Brown's original findings on the non-toxicity of the -CN ion administered within the capacity of the rhodanese system. Administration of the ion in the form of nitriloside, of course, provides an optimal concentration of the ion in a safe and self-limiting fashion --- self-limitation being the characteristic of the action of accessory food factors.

Maxwell and Bischoff in 1933 (*J. Pharmacol. & Exper. Therap., 49:*270) in studying the possible cumulative effect of HCN in mice reported:

"After twenty-one days of exposure to HCN, the red blood cell count and the hemoglobin rose in the mice 12 to 15 per cent, and in the rats, 20 to 25 per cent."

Their experience has been confirmed repeatedly by clinicians studying the action of Laetrile (nitriloside) in advanced cases of human cancer where the nitriloside-derived HCN has produced a substantial stimulation in hemopoiesis even in some terminal patients.

In 1935 Isabella Perry of the Department of Pathology, University of California Medical School, reported on the study of "The Effects of Prolonged Cyanide Treatment on the Body and Tumor Growth Rate" (*American Journal of Cancer, 25:*592). Reporting the action of prolonged inhalation of cyanide fumes in young tumor-bearing rats, she wrote:

"..Retards the growth of Jensen sarcoma implants. A considerable percentage of the animals so treated showed complete regression of the tumor. Both regressing and growing tumors in treated animals had little capacity for transplantation..The dose was given on strips of blotter paper..It seems that the range of the effective dose is limited and too close to the lethal dose to be practical".

The administration of the -CN ion through non-toxic nitrilosides eliminates the limitation. Perry observed that --

"In the treated animals the tumors grew slowly and necrosed early. Ten days after the inoculation the tumors in 9 treated rats averaged 0.5 cm in diameter, while 8 control rats had tumors averaging 2.2 cm in diameter. On the twenty-fifth day after the tumors had been inoculated and fifteen days after the cyanide treatment was discontinued, 5 treated survivors had tumors averaging 2.5 cm in diameter while the tumors in the control animals averaged 8 cm in diameter".

Of the control rats bearing Jensen sarcoma 8 had died and only one was surviving on the 34th day after inoculation. By the 105th day 6 treated rats that had received the same implantation were still alive and showed extensive tumor regression. Such residues which remained were untransplantable. Thus treated by the inhalation of HCN gas, with all its attendant dangers, rats bearing Jensen sarcoma transplanted often showed not only complete tumor regression but an average life extension in excess of 300 per cent.

These observations have been substantiated clinically with the nitriloside-derived CN ion of Laetrile and without any evidence of toxicity and no side-effect except the increase in red blood cell count and hemoglobin first observed in 1933 by Maxwell and Bischoff in mice receiving cyanide ions.

Clinical investigation of parenteral nitriloside (Laetrile) at four universities medical schools over the past decade have confirmed the animal studies reporting a specific chemotherapeutic effect of the CN ion in cancer. Professor M.D. Navarro of the University of St. Thomas Medical School has observed such effects for Laetrile (nitriloside) over a period of twelve years.

One gram of Laetrile (nitriloside) treated with beta-glucosidase derived from the tissues of experimental animals (with or without cancer) supplies 56 gm of HCN. This HCN may be administered through inhalation to cancer animals as in the case of Perry's studies. It may be neutralized with NaOH to form sodium cyanide and then so administered as in the case of the work by Brown et al who found that 0.8 mg/kg of the cyanide ion provided a 70 per cent life extension in experimental animals and an apparently complete regression in spontaneous cancer in dogs as well as substantial palliation in some human cases. Under experimental conditions Laetrile (nitriloside) has been hydrolysed by a few drops of beta-glucosidase to a solution of free HCN, sugar and benzaldehyde. In this state the material, of course, becomes as toxic as the materials used by Brown et al, Perry, Maxwell and Bischoff and others, and provides the same action as such.

FOCAL ACTION OF LAETRILE (NITRILOSIDE).

Some of the findings reporting a selective action for CN on a diversity of malignant tumors in various animals have been briefly reviewed. In all these cases the administration of the -CN ion was presented to the tissues of the organism diffusely and at an uniform concentration whether through

injection of a cyanide salt or through inhalation. We have pointed out that by the prior hydrolysis of Laetrile (nitriloside) *in vitro*, the injection of the hydrolysed material (before and after neutralization with NaOH) or its administration through the vaporization of HCN would present the organism with precisely the same chemicals in the same quantities as in the described experiments.

When the nitriloside, however, is parenterally administered as such it enters the blood stream as an intact molecule. Malignant lesions are focally characterized by an especially high and selective concentration of beta-glucosidase and beta-glucuronidase. An extensive literature describes the high focal concentration of beta-glucuronidase that characterizes most malignant lesions. This concentration is often in excess of 300 times that of the contiguous somatic tissues. There is also a substantial literature describing the deficiency of the definitively malignant cell in rhodanese. The occurrence of beta glucuronidase appears to be paralleled by an equal concentration of beta glucosidase. Both enzymes are described generically as *beta-glycosidases.* Synthetic glucuronosidic nitrilosides (Laetrile) have been synthesized to exploit the beta-glucuronidase system in the same manner in which the natural nitrilosides are used against the beta-glucosidase system at the malignant lesion. In comparative studies it has been found that both the natural and synthetic nitrilosides are active against their respective enzyme systems. The simple natural nitriloside, however, has been chosen for our routine investigation at this time.

This nitriloside is selectively hydrolysed at the malignant lesion by the beta-glucosidase in the rhodanese-deficient lesion. In this way the CN ion is brought to the malignant cell in an highly concentrated and selective manner. It is true that there are a number of normal tissues in the body that carry both beta-glucosidase and beta-glucuronidase but they also carry a countervailing concentration of rhodanese, which completely protects such normal somatic tissue from the action of any cyanide ion that the beta-glucosidase or beta-glucuronidase component of the tissue causes to be released from the hydrolysed nitriloside. In each instance the rhodanese capacity in such tissues is proportional to, though in excess of, the diffusion of the hydrolysed CN and accounts for the fact that Laetrile (nitriloside) is completely non-toxic to somatic or non-malignant tissue while being extremely and selectively toxic to the specific malignant cells that provide a situation in which nitriloside is hydrolysed at a rapid rate in the absence of an adequate rhodanese system. While the studies by Perry, Brown et al., Maxwell and Bischoff have shown in experimental animals, in domestic pets bearing spontaneous cancer, and in man that the malignant cell is selectively susceptible to cyanide ions diffusely and uniformly distributed among all body cells, the clinical work on Laetrile (nitriloside), as well as the early animal work, has shown that the selective susceptibility of the cancer cell to HCN may further be exploited through the phenomenon of selective lysis at the malignant lesion.

The equivalency of the derivable HCN of nitriloside to that of NaCN and HCN used by Brown et al and Perry, respectively, has been stressed almost to an absurdity for the purpose of emphasizing that in non-toxic water-soluble accessory food factors normal to the adequate diet of the higher animals and man there exists a component that will bring about the total regression of a variety of cancers in experimental animals, reduce the size of other malignant lesions 8-fold or more, prevent by 10-fold or more the rate of malignant growth as compared to that seen in control animals bearing the same tumor, and render the treated tumors insusceptible to transplantation and the treated animals resistant to the implantation of cancer as compared to controls showing full transplantability as well as full receptivity to malignant transplants.

The effect of rendering the malignant tumor untransplantable and rendering the treated animal insusceptible to the transplantation of a malignant tumor are expressive of *prophylactic effects*. Like all other non-toxic water-soluble accessory food factors that have been identified as specific in a

given chronic or metabolic disease, the specificity of nitriloside is also accompanied by a specific prophylactic effect.

To emphasize again the equivalency of the cyanide ion in nitriloside as compared to the free ion or its salt, we may point out that many nitriloside-rich food plants need merely be mashed in their native state and allowed to stand awhile in their own fluid to cause them to surrender the free HCN that can duplicate what has already been achieved by this ion in experimental animals bearing transplanted or spontaneous cancer. This is the non-toxic water-soluble accessory food factor that is as important to adequate nutrition as ascorbic acid, thiamine, riboflavin and similar non-toxic water-soluble accessory food factors that appear in plants in a lower concentration, as a rule, than does nitriloside.

UNIFORMITY OF EFFECT

It will be noted that the CN ion did not produce a total regression of all tumors in all animals. It brought about a total regression of a good variety of tumors in four or more species of animals. It also accounted for an average life-extension of 70 per cent in one group and extension as high as 300 per cent in another group. Of all achievements, failure is the most facile to attain. There have been several investigators who sought to prove that Laetrile (nitriloside) had no action in experimental animals bearing cancers. The longest study done involved less than six weeks and a transplanted Jensen sarcoma. The investigator failed to achieve "objective results" in this period, and discounted the soundness of the experiment on the declared grounds that animal tissue contained no means to hydrolyse nitriloside to free HCN---that animal tissue does not contain beta-glucosidase. Such incompetence of a presumably honest nature has characterized many of the mistaken notions that experimental demonstration is gradually eliminating from this area.

CLINICAL STUDIES.

We have written nothing about the very extensive and very successful clinical investigation of nitriloside (Laetrile) that has been conducted by a number of highly competent workers over the world. Without exception all of these men have reported one degree of success or another in advanced or terminal cases. No one who has actually used and studied the material has failed to report positive results, though many who have neither used nor studied the material have criticized it. Such critics have described the provable positive results, and even recoveries that have followed the use of nitriloside (Laetrile) in late or terminal cancer patients as an expression of "the delayed therapeutic effects of prior radiation, surgery or other chemotherapy". Since only advanced cases in which such measures have already failed have so far been given Laetrile (nitriloside), all such cases are theoretically subject to the critical explanation described. One clinician has pointed out that if nitriloside itself does not directly produce the results that usually follow its application, it does greatly increase the percentage of "delayed therapeutic effects" that follow seemingly unsuccessful prior measures. One can but anticipate that, when the nitrilosides are finally used in the treatment of those cancers previously untreated by other methods, the incidence of spontaneous remissions will be found by such critics to have increased beyond reasonable statistical expectations.

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This partial bibiliography is appended as found in another article by Dr. Krebs: The Nitrilosides (Vitamin B-17)--Their Nature, Occurence and Metabolic Significance (Antineoplastic Vitamin B-17). A link to that paper is appended below.

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