Pangamic acid ("'vitamin B\textsubscript{15}''\)\textsuperscript{1}

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A cover story in the March 13, 1978 issue of New York Magazine (1) lauded B\textsubscript{15} "as a possible cure for everything short of a transit strike." The article, according to a note on the masthead page of New York Magazine on April 3 "made it impossible to find the vitamin on any dealer's shelf in the metropolitan area for a full week."

"Vitamin B\textsubscript{15} is the latest rage in health food stores in the United States (1). Numerous articles have appeared in lay publications and on radio and television extolling this substance. Yet, according to the Food and Drug Administration (2), vitamin B\textsubscript{15} is "not an identifiable substance . . . not a vitamin nor a provitamin . . . no accepted scientific evidence establishing any nutritional properties of the substance or any deficiency . . . in man or animal . . . no medical, nutritional, or other usefulness for these substances has been established.""

Background

In 1943, Ernst Krebs, Sr. and Jr., applied for a patent for material similar to that previously discovered by Krebs, Sr., and isolated from apricot kernels, which they named "pangamic acid" (3). Krebs, Sr. and Jr., then \textit{trade-named} such material vitamin B\textsubscript{15}, just as Krebs, Jr. \textit{trade-named} amygdalin, another chemical also isolated (in 1830) from apricot kernels (4, 5), first as "laetrile" and subsequently as "vitamin B\textsubscript{17}.") The B\textsubscript{15} patent claimed pangamate is "a preparation for the immunization of toxic products present in the human or animal system" which has "the property of detoxifying toxic products formed in the human system . . . . This invention relates to a preparation for relief and immunity to persons afflicted with asthma and allied diseases . . . affections of the skin, respiratory tract, painful nerve and joint affec-

tions, and even cell proliferation . . . eczema . . . arthritis, neuritis . . . ." Not a sliver of data is present in the patent application (3) to support any of these snake-oil panacea claims it suggests.

Two decades ago, pangamic acid was promoted for horses (1, 6), but it has been heavily promoted for humans since publication of a review by the stepson of Ernst Krebs, Jr. in World Review of Nutrition and Dietetics (7). Without citing supporting evidence from any country's national nutrition policy body, the review alleged that "pangamic acid has been widely studied and accepted in many countries as a necessary food factor with important physiological actions." It dated the history of pangamic acid from 1951 and did not mention the earlier work by Krebs, Sr. or the pangamic acid patent sought in 1943 by Krebs, Sr. and Jr. (3), in which they claimed pangamate had the property of providing relief for everything from eczema to cancer. The review also failed to note the backgrounds of the American creators and promoters of pangamate or their difficulties with the health authorities and the law in connection with it, and in connection with their concurrent promotion of laetrile (4, 8). The review acknowledged that "this work was funded in part by a grant from the McNaughton Foundation." The author was formerly a Research Associate at the McNaughton Foundation\textsuperscript{3} in Mill Valley, Cali-

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\textsuperscript{3} As indicated elsewhere (4, 8), Andrew McNaughton appears to be a laetrile factory owner with two criminal convictions, and Krebs appears to be a medical school...
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ifornia (9), and had previously published related material in that capacity (9). The McNaughton Foundation publishes lay booklets which promote pangamate (B₁₅) and laetrile (B₁₇) as if they were vitamins. Among their booklets sold to the public at health food conventions are the “Physician’s Handbook of Vitamin B₁₇ Therapy,” published 18 October 1973 ($2.00), and “Vitamin B₁₇, Vitamin B₁₅ and Vitamin B₁₃,” published 12 June 1975 ($1.50). The latter booklet states on page 17, “A review, ‘Pangamic Acid (Vitamin B₁₇)’ will shortly be published by Dr. Peter Stacpoole in The American Journal of Clinical Nutrition and lists over 125 references to studies on pangamic acid, most of them clinical.” In fact, The American Journal of Clinical Nutrition rejected the review as inadequately scientific for the following reasons:

The title of the review declared pangamate a vitamin (with no qualifying quotation marks). The review did not cite the position of either the Canadian or United States food and drug authorities that not only was there no evidence pangamate was a vitamin, but also no acceptable scientific proof it had any therapeutic benefit or was safe for human use (2, 6, 7). In the review, none of the biochemical data gave any description of biochemical or chemical reactions that take place physiologically. Data on absorption, blood levels, urine levels, excretion, degradation, etc., of pangamic acid were not provided. The usual toxicological studies were not described. No dose response data were provided. The clinical data were not obtained under controlled conditions. There was not a critical evaluation of the literature, which might help the reader assess the various claims of different investigators. It was not convincing that the claims had any foundation in fact. Most of the claims were conclusory statements extracted from uncontrolled anecdotal observations published in Russia. What was provided were general statements with no controlled data. No negative or contradicting data were cited. Although no amount of uncontrolled or anecdotal studies nor the number of papers published determine whether or not a substance is a vitamin or whether it has physiological functions, the author took all of these deficient studies and attempted to derive meaningful positive information from quantity instead of quality, appearing not to heed the humorous but valid scientific dictum, “Garbage in, garbage out.” The poorly designed studies with conclusions not derived from the data, studies lacking adequate controls, could not produce meaningful positive information.

Chemistry

Krebs et al. (10) and a number of Russian workers cited by Stacpoole (7), used the term pangamic acid to describe a product, claimed isolated from various plant sources, and also obtained by laboratory synthesis, which had the empiric formula C₁₀H₁₉O₅N, d-gluconodimethyl aminoacetic acid (an ester of d-gluconic acid and dimethylglycine (glycine is aminoacetic acid)), molecular weight 281 daltons, has an unstable ester bond, and does not crystallize (11). The synthetic Russian preparation of calcium pangamate crystallizes with a water molecule and has a molecular weight of 618.7 and four methyl groups (from its two pangamate monomers) (11). It is described as a mixture consisting of no less than 70% of the calcium salt of gluconic acid ester and dimethylglycine, no more than 25% calcium gluconate, and no more than 6% calcium chloride (11), (which can be a poison (15)). It is slightly hygroscopic and must be stored dry and sealed to retain stability (11). It is a white powder, soluble 1:1 in water, relatively stable in acid, and resists heat to 100°C when dry (11). It has a characteristic weak amine odor and a slightly bitterish taste (11). The Merck Index, 8th edition, 1968 (5), notes pangamic acid as a mixture of sodium gluconate, glycine, and disisopropylamine dichloroacetate. The 9th edition of the Merck Index (12) gives the structure as (d-gluconic acid 6-bis (1-methylethyl) amino acetate. The editor of the Merck Index indicated to this reviewer that “pangamic acid” and “vitamin B₁₅” will be deleted from the 10th edition, since they were deceived into listing it. Products marketed as B₁₅ or pangamic acid, or calcium pangamate could contain any or all of the above materials, plus other materials, since there is no standard of identity for the product. The term pangamic acid appears to be used indiscriminately regardless of which of various adducts are on the ester linkage.

flunk-out with at least one criminal conviction. They appear to interact closely in promoting B₁₅ and B₁₇.
Those B₁₅ products containing the chloride ion may be synthetic, and for them the designation “derived from natural sources” is meaningless. The Russian preparation is also synthetic, as appear to be the American equivalents of it.

The Food and Drug Administration has repeatedly seized B₁₅ tablets that include mixtures of calcium gluconate and dimethyl glycine marketed under various names such as calcium pangamate, Aangamik and Caldia- mate, and default decrees have ordered their destruction. The chemical composition varies from product to product⁴ and its various promoters and vendors designate its chemistry differently from year to year and from article to article, hence the FDA statement that it is “not an identifiable substance” (2, 5–7). Krebs appears to have been selling a product containing calcium gluconate, because testimony in his probation revocation case (4) included that “. . . there were three probationary searches . . . on each occasion there were empty barrels of calcium gluconate . . . these were all 200 pound drums . . . sales records . . . 1975 . . . $10,310 passed from Mr. Bradford to Mr. Krebs for the B₁₅.”

Because of lack of any proof that pangamic acid is either a definite chemical entity, safe for human use, or of any therapeutic benefit, its distribution in Canada is prohibited by that country’s Food and Drug Directorate (6). The pangamic acid (vitamin B₁₅) sold by one corporation for chemical and investiga- tional use proved to be a mixture of diisopropylammonium dichloroacetate, sodium gluconate, and glycine (6). Correspondence in 1978 with their successor organization has not revealed what is packed under the pangamic acid (vitamin B₁₅) label of the material purchased in 1978 from them. In the course of our correspondence with them, they attempted unsuccessfully to get additional specifications or analysis from their European supplier, and then discontinued sales.

Pharmacology

The gluconic acid, glycine, and acetate in some of the formulations are essentially inert. One pharmacologically active agent is diisopropylamine, which has been studied by Kraushaar and others (12, 13). This amine acts on smooth muscle to lower blood pressure and decrease body temperature (13). Acute toxic doses cause death in rodents by cyanosis and respiratory failure (13). The material is nutritionally worthless and may be one of the “toxicants occurring naturally in foods,” others of which are described in the book of that name published by the National Academy of Sciences, Washington, D.C., 1973 (15). It is pertinent that the term “pangamic acid” (Gr. pan = universal; gamic = seed) was coined to describe the claim that the substance is frequently found in seeds, which is also the case for cyanide (15). Stacpoole et al. (14) reported on certain acute metabolic effects of dichloroacetate, and state “the efficacy and safety of chronic dichlo- roacetate administration are unknown.” Their findings made a case for its use in the short-term treatment of acute life-threatening lactic acidosis, hitherto often fatal. One can, of course, legitimately use poisons to save lives in acute emergencies (such as the use of nitroprusside in acute hypertensive emer- gencies). However, question has been raised as to whether dichloroacetate offers anything over bicarbonate in treatment of lactic acidi- dosis (16). Additionally, the substance has been shown to inhibit the pyruvate transporter in rat liver mitochondria in vitro, which would be an undesirable effect if reproducible in humans (16, 17). Adverse effects noted by Stacpoole et al. (14) included mild sedation and increased serum uric acid levels in diabetic patients. Crabb and Harris suggest that dichloroacetate (DCA) may produce oxalic acid stone formation and renal dysfunction, because DCA converts to gly- oxylate which is a precursor of oxalate (17a).

Aliphatic halogenated hydrocarbons have recently begun to cause concern regarding

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⁴ Claimant’s Answer to Government’s Written Interro- gatories (Interrogatory No. 2) in U.S. v. Aangamik 15 Calcium Pangamate, etc. (Consolidated Cases Nos. 77C 662, etc., U.S. Dist. Ct., N. Dist. Ill., E. Div.) states the seized calcium pangamate was a blended mixture of N, N-dimethylglycine hydrochloride, calcium gluconate, di- calcium phosphate, stearic acid, and avicel. Claimant’s Answer to Interrogatory no. 9 stated there are about 20 mg of dimethylglycine in 100 g of meat eaten by man, but did not state whether any of it was free (as in claimant’s product) rather than bound, or whether any of it was dimethylglycine hydrochloride (as in claimant’s product). In his order of December 5, 1978 denying defense motion for rehearing in U.S.A. v. . . “B₁₅ (so- dium pangamate) 50 mg . . . .” Civil Action no. 76-1860, U.S. Dist. Ct., Dist. of N.J. Judge Curtis Meanor stated: “the chemical composition of the articles under seizure is 64% calcium gluconate, 16% glycine, and 20% of the salt formed from di-isopropylamine and dichloroacetic acid.”
their carcinogenic potential because of the ease with which they can form free radicals (18). The potential of dichloroacetate for carcinogenesis therefore requires evaluation. We recently found it mutagenic by Ames test (19). It should be noted that toxic cataracts frequently appear months or years after chemical or drug exposure (20), and the connection to prior drug or chemical exposure may not be made in the absence of adequate alertness. A year ago this reviewer requested information from Stacpoole on possible mutagenicity and cataract production by DCA. Subsequent to our preliminary report on DCA mutagenicity (19), Stacpoole et al announced the suspension of chronic oral administration to patients on the basis of serious toxicity to animals and at least one human (20a). There was dose-related hind limb paralysis, germinal epithelial degeneration of the testis and vacuolation of the myelinated tracts of the cerebrum in rats and dogs. Dogs also showed severe ocular lesions including irreversible lenticular opacities. A man developed polyneuropathy. DCA may be more toxic orally than parenterally (20a), as is the case for laetrile (4).

The d-gluconodimethyl aminoacetate formulation has been reported to have neuro-muscular blocking activity in rabbits and chickens and to produce hypotension in dogs (21). Russian calcium pangamate of this formulation is contaminated with up to 6% calcium chloride (11), and all calcium pangamate of similar formulation should be considered contaminated with calcium chloride until proved otherwise. It is possible that contamination with dichloroacetate may also occur, and this possibility should be evaluated in each preparation.

Some formulations of pangamic acid contain methyl groups, but these are not labile. Furthermore, there is no published data that the large promoted doses of such formulations normally are found in the diet, concentrate in human tissues, or play a salutary physiologic role not due to folate or choline present in the diet (and not carried out with less energy loss by choline and methionine). None of the formulations of pangamate appear from available data to be lipotropic, or to be methylating or transmethylating agents. One-carbon compounds can be oxidation products of some of the formulations, and those products can then enter the one-carbon pool, as do similar oxidation products of many substances. The Krebs patent “N-substituted glycine esters of gluconic acid” (22) states “a particular object is to provide synthetic compounds . . . which are more effective methyl donors than known methyl donors such as methionine and choline,” but no data are presented to support the claim that any of the “pangamates” in the patent is labile. Indeed, the diisopropylamino product cannot be a methyl donor because its methyl groups are on C, and only methyl groups on an N or an S can serve as methylating agents, and then only when there is no need for an added energy source. This is not the case for dimethylglycine, a product of choline catabolism, which is synthetically attached in an ester linkage to gluconic acid in some pangamate formulations. Its methyl groups, like those of sarcosine, are not labile, and so must be removed by oxidation and only then can enter the one-carbon unit pool (23, 24). It was established in 1946 that dimethylglycine was not lipotropic (24). It enters one-carbon metabolism at the oxidation level of formaldehyde, and worsens methyl depletion of rats on diets creating methyl deficiency who are given nicotinamide supplements, resulting in renal cortical necrosis in mature females and damaged growth and development of fetal rats (24a). Alkali-metal (Na, K, NH₄) salts of dimethylglycine are claimed to chelate alkaline earth metals (Mg, Ca), thereby rendering absorbable certain sulfated polysaccharides claimed to be lipemia-clearing (24b). The safety and efficacy of such claimed effect requires evaluation before use (see Addendum).

Dimethylglycine (N-methylsarcosine), a tertiary amine, reacts with nitrites (which are formed de novo in the intestine) (25) to form both the potent carcinogen, dimethylnitrosamine, and the weaker carcinogen, nitrososarcosine (26). Nitrites that effect this reaction occur in human saliva (27), and nitrososarcosine induces cancer of the oral pharyngeal cavity and esophagus in the rat (27). Thus, dimethylglycine ingested in concentrated free form in a tablet appears much more likely carcinogenic than the same amount bound in 100 g of meat, since only the former is presented to the oral cavity and esophagus in high concentration, and the dimethylglycine in human muscle as a catabolic product of choline is not presented at all to the oral
cavity and esophagus. Additionally, what purveyors of pangamate" and B15 appear to be selling is not dimethylglycine, but dimethylglycine hydrochloride, of different composition and reactivity.

Hundreds of compounds found in seeds and plants have chemical and pharmacological effects. This does not make them nutrients or physiological. Many are poisons (15), as is DCA (20a), described by Krebs in the June 1978 issue of the laetrile industry magazine "Choice" as a "sister compound" of B15 (19).

Clinical use

The allegations of long-term medicinal value for pangamic acid in cancer, alcoholism, hepatitis, heart disease, allergies, diabetes, schizophrenia, glaucoma, retarding aging, purifying air, and increasing respiratory ability by providing "instant oxygen" are anecdotal and testimonial stories rather than studies, and lack comparison for effectiveness in controlled studies to other treatments or to "the doing of nothing" (6, 28, 29). A number of these stories, either totally uncontrolled or lacking the crucial choline control, originate in Russia. The authors often claim spectacular results from pangamic acid or vitamin B15 without identifying which of the many chemicals and chemical combinations which go by that name they are using, without distinguishing drug effect from placebo effect, and without reporting any evaluation of patients for short-term or long-term toxic effects. The Food and Drug Administration regards the products as illegal whether used as a food or as a drug, and has made a number of seizures of them (2, 30). On June 12, 1978, in the New Jersey seizure case, Newark District Court Judge Curtis Meanor upheld the Food and Drug Administration contention that B15 is essentially an untested "food additive" that is not generally recognized by scientific experts as safe for human consumption and cannot be sold legally on the market (30). Pangamate has been prohibited in Canada for more than a decade (6). Because of these facts, any physician who prescribes it should first secure an Investigational New Drug number for it, describing which of the many different chemical mixtures called "pangamate" is the one to be used, should submit his proposal to a Human Studies Committee, and should get informed consent from his patients after informing them that it is not a vitamin, has no known nutrient value, no known value in the long-term treatment of any diseases, its safety has not been established, and it may be mutagenic. The claim that "B15" supplies calories is deceptive and misleading. Carbohydrates and proteins supply 4 cal/g and fats supply 9 calories per g, so the most a 50 mg tablet of "B15" could supply, regardless of its ingredients, is less than half a calorie.

As noted elsewhere (4, 29), there are four basic scientific canons for evaluating medical information:

1) Does it go beyond "personal observation" to stand the test of scrutiny and criticism by other scientists, i.e., is it a study or a story? Is it science or anecdote?
2) Was it compared for effectiveness in double blind controlled studies to other treatments and to suggestibility or to the "doing of nothing," i.e., to a placebo? What is the natural history of the disorder in the absence of therapy? Was the observed result of cause and effect, placebo effect or coincidence due to the natural history of the disorder?
3) Has it been proved safe? Safe compared to what? Is the risk justified? What is the risk:benefit ratio? (Note that if there is no benefit, the risk:benefit ratio is infinity, which is not tolerable.)
4) The burden of proof is on those who propose doing or giving something, especially if it involves a remedy or procedure not well established in medical practice. Valid weapons against disease are forged in the crucible of these canons. After three decades, B15 has yet to successfully meet any of these basic scientific challenges.

Conclusion

Pangamic acid, pangamate, and B15 are synonyms for an alleged entity that in fact is a number of different products of variable composition which do not constitute a definite chemical entity. The label originally described what may have been partly Na or Ca d-glucosodimethyl aminoacetate. However, the label more often describes a product which is one part sodium (or calcium) gluconate, one part glycine (or dimethyl glycine); often also one part disopropylamine dichloroacetate. Often still other synthetic mixtures are sold as B15 and calcium pangamate. Pan-
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Gamic acid is trade-named vitamin B₁₅ but it has no known nutritional worth, has no vitamin properties, and no such vitamin exists. In fact, pangamic acid can be said not to exist, since there is no standard of chemical identity for products sold under that label. There is no proof that it has any therapeutic benefit or is safe for human use, and it may be mutagenic. All of the B₁₅ and pangamate products being sold, including those in health food stores, appear to be at least partly synthetic. The use of pangamate may violate the primary ethical rule of medicine—above all, do no harm (31, 32).

In the Middle Ages, anecdotal claims of efficacy and safety of nostrums were automatically accepted, and it was for science to disprove them. This required science to prove a negative, often difficult or impossible to do. The Age of Reason began with recognition that to protect the public health and safety required adopting the rule that it is for the proponent to prove his claim, rather than for science to disprove it, and that nostrums should be considered inefficacious and unsafe until proved efficacious and safe. With laetrile and pangamic acid, we are in danger of returning to the age when anecdote substituted for science. Both products appear to meet the criteria that define a quack remedy (4, 29, 33–37), and both appear to be more toxic on oral than parenteral administration (4, 20a).

Because of its usual content of dichloroacetate or dimethylglycine hydrochloride, persons buying pangamate in the erroneous belief they are purchasing nutrition may be purchasing mutagenesis or other unknown harms.

The United States Food and Drug Administration “Statement on Pangamic Acid”, dated August 18, 1978, concludes:

“FDA considers ‘vitamin B₁₅’ to be a food additive for which no evidence of safety has been offered. It therefore is illegal for the substance to be sold as a dietary supplement. No new drug application for ‘Pangamic Acid’ has been submitted or approved by FDA and the substance legally cannot be marketed as a drug.”

References

11. BUKIN, V. N. Calcium pangamate (vitamin B₁₅). A. N. Bakh Institute of Biochemistry, Academy of Sciences of the U.S.S.R. (45 page manuscript sent in June 1978 by U.S.S.R. Ministry of Health to V. Herbert, in response to request to Russian ambassador to the U.N. for Russian view of pangamate. Forwarded by V. Herbert to Food and Drug Administration and available from the F.D.A. V. N. Bukin and I. N. Garkina hold United States Patent no. 3,907,869 (Sept. 1975), for “Method of Producing Calcium Pangamate” (“vitamin B₁₅”), consisting in esterification of gluconic acid or the lactone thereof with dimethylglycine hydrochloride in an aqueous medium in the presence of hydrogen chloride or sulfuric acid at a temperature of from 30° to 70°C. The esterification product is concentrated and neutralized with calcium carbonate to obtain almost non-hygroscopic calcium pangamate in a high yield (up to 80%).

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HERBERT


Addendum

Regarding the patent of dimethylglycine to enhance absorption of heparin (24b), the Manager of Professional Services of the corporation to which the patent is assigned informed this reviewer by letter dated 2 May 1979 that, "We never carried out any long term animal studies with this particular agent, and therefore I am unable to answer your question about toxicity. Also, dimethylglycine was never tested in humans. We never marketed any products of this type since the extent of absorption (of heparin) never reached levels greater than five percent of the administered dose."

Despite the U.S. government position that pangamate is illegal, worthless, and possibly unsafe, in 1979 it was still being vigorously promoted and sold in every "health food" store in the United States visited by this reviewer, including those of the multimillion-dollar General Nutrition Center chain. Mr. Paul Sage, of the Bureau of Enforcement of the FDA, informed this reviewer that the FDA lacked enough personnel to seize pangamate from these thousands of stores, and was doing its best to fight the huge and lucrative pangamate industry by bringing court cases against producers. However, while the cases grind through the courts, the producers of pangamate such as Aangamik (4) continue to promote and sell, and others spring up and do likewise. Where there is money to be made, there are those who will make it.

With respect to the misleading health claims, the government has no power to stop them, unless they are stated on the labeling of the product (34), and the multimillion dollar nutrition cultism industry (4, 33-35) and its pangamate arm are too legally sophisticated to do that. The claims are made in nutrition cultism literature sold in "health food" stores and elsewhere, which is protected "free speech" (34). Many "health food" stores were selling in 1979 the General Health and Nutrition Centers, Inc. vitamins and minerals placemat which misleadingly claims panagamic acid as a vitamin which facilitates "cell oxidation and respiration, metabolism (protein, fat, sugar), glandular and nervous system stimulation," whose "deficiency symptoms" are "heart disease, nervous and glandular disorders," and whose "therapeutic applications" are "alcoholism, asthma, atherosclerosis, cholesterol (high), emphysema, heart disease, headaches, insomnia, poor circulation, premature aging, rheumatism, shortness of breath."

Parenthetically, victims have just brought the first civil suit against the author and publisher of a nutrition cultism book sold in "health food" stores and elsewhere which made a misleading nutrition claim which they say led them astray and thereby caused the death of their child (4). The misleading claim was that large doses of potassium can help against colic.

On June 18, 1979 the United States Supreme Court ruled 9-0 against laetrile in Rutherford v USA (4). Many of the same interests promote both laetrile and B12 (4).