Vitamin B15
A Review and Update

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During the past several years, a great furor has arisen over the promotion and sale of pangamic acid also known as Vitamin B15. This was stimulated to some extent by an article in **New York** magazine (Nobile, 1978) extolling this "vitamin", resulting in near exhaustion of supplies in local retail outlets, a phenomenon which eventually spread to other areas of the country. This article presents some of the evidence supporting the claims of efficacy by the proponents of B15 as well as some pertinent history and facts surrounding the recent court decision regarding sale of this controversial substance. Vitamin B15 has been particularly touted as an "energiser, a natural metabolite which increases the efficiency of certain metabolic oxidative processes, thereby being recommended for use by athletes to increase their performance and endurance", for example. Vitamin B15 and pangamic acid are used synonymously in this article. However, this substance is not specifically defined because studies noted in this article have used various chemical entities, all designated as B15. Most of these substances contained dimethylglycine alone or mixed with gluconic acid.

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Brief History

Until recently, Vitamin B15 was quietly being sold in health food stores and, despite the controversy it later aroused, it attracted relatively little attention from the medical profession, the regulatory authorities represented by the FDA, or the consumer. Nevertheless, pangamic acid was stigmatized at the outset. It was introduced and promoted by the same Dr. Krebs who was responsible for Laetrile, the anti-cancer agent the use of which is considered quackery and pseudoscience by the established medical community. Despite the provocative claims made by Krebs, virtually no substantial research was conducted in this country following the initial 1951 publication of the announcement of its isolation from apricot pits and its chemical structure (Krebs, 1951) as shown in Figure 1.

According to Dr. Krebs, B15 could be found in rice bran, brewer's yeast, horse liver, barley, wheat seeds, oats and corn, being a companion to the recognized members of the B Complex vitamins, also found

in these natural sources. The structure in Figure 1 shows B15, a crystalline, water-soluble material, to be the gluconic acid ester of dimethylglycine, the latter compound being an intermediate in the choline cycle, a metabolic cycle involved in energy transformation.

Krebs, in an effort to improve upon his initial "discovery", announced an alternative to the original B15 which was a diisopropyl ammonium dichloroacetate (DIPA) derivative. DIPA (Figure 2) was not new despite its promotion as the "real" B15 (Beard and Woffard, 1956). It had been included in several OTC products for its vasodilator effect.

It is now known that the ester structure with gluconic acid is very unstable (Aspit, 1980) and to isolate the intact structure from natural sources would be very difficult. The procedure, as described by Krebs (1951) has yet to be reproduced by other scientists. Also, if it does exist naturally in foods as the ester, it would undoubtedly be broken down by the gastric juices into free gluconic acid and DMG or DIPA. In this country, the designation, "Vitamin" is now unanimously considered by both FDA and the manufacturers to be a misnomer. There is no deficiency disease associated with it and minimum daily requirements cannot be defined. Therapeutic doses range from 50 to 150 mg daily.

Clinical Indications — The Russian Research

The lack of clinical research in this country was made up for by studies performed overseas. Much of this work was done in

Figure 1. Structure of Vitamin B15 (Pangamic Acid) — an ester of Dimethylglycine (DMG) and Gluconic Acid.

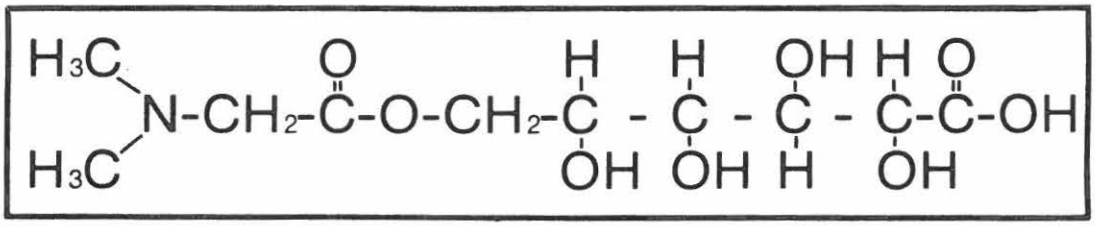
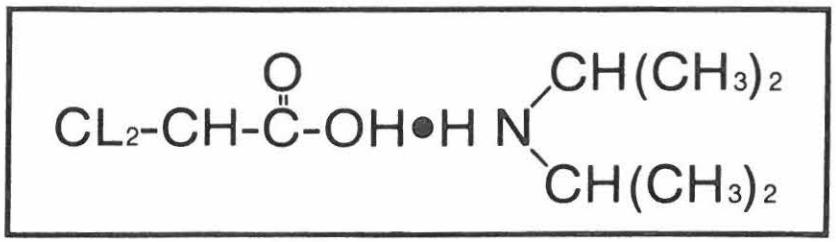


Figure 2. Structure of Diisopropylammonium Dichloroacetate (DIPA), an ingredient formerly found in B15 products.



Russia and two volumes of research reports resulting from symposia on this substance have been published, available in English translation (Anismov, 1965). It should be noted that it is not always clear as to the exact composition of the B15 substance referred to in those papers, although it probably contained DMG mixed with calcium gluconate or gluconic acid for the most part.

B15 seems to be a safe substance despite the lack of published long-term toxicity studies; no untoward effects have been reported to date. Doses as high as 200 mg/kg given s.c. to rats caused no toxic effects (Alpatov et al., 1965). The lack of toxicity is not surprising since DMG is a natural metabolite, a simple glycine derivative.

The Russians feel that pangamic acid is a valuable therapeutic agent, and they have studied it clinically in many disease states. The conclusions of efficacy as a result of this research should be tempered by the fact that most of these studies were not controlled, often lacking adequate comparable control groups, or including other drugs with the B15 therapy. DMG, a component of the Russian B15, is purported to contribute methyl groups in the transmethylating process which results in improved energy utilization. Methionine, choline and betaine are some other common substances capable of donating methyl groups in certain metabolic synthetic processes occurring in the body. It is suggested, based on experimental evidence in rat experiments, that the DMG component of pangamic acid acts similarly, a participant in transmethylation processes (Beard and Woffard, 1956). This possible mode of action is often proposed as the basis of its activity, such as the observation that various animal species — rats, mice, cats and dogs — have increased tolerance to altitude, asphyxia, hypoxia (particularly that induced in brain and heart tissue), and fever induced by certain pathogens (Udalov and Skibnew, 1961; Udalov, 1965; Dokukin et al., 1962; Tromiva, 1965; Andreyev and Rode, 1965).

The action of B15 which has received the most attention is that of its effect in stress and on athletic and physical effort. B15 has been purported to increase the magnitude and endurance of physical activity. Rats, when stressed, showed higher glycogen, lipid, phospholipid and creatine phosphate levels in skeletal and heart muscle following administration of B15 (Leshkevich and Kolomeitseva, 1967; Samodanova and Yakovlev, 1967; Krasnova, 1968).

Cytochrome oxidase activity was also increased when animals were put under stress in swimming tests. Lower lactate levels were observed in both plasma and muscle. Muscle glycogen was utilized more efficiently. This action was particularly noted during hypoxic states, which results from strenuous exercise during a short time span, and is related to dose, lasting a few days after dosing is stopped, if pangamic acid is administered over a period of time. (Yakovlev, 1965).

In one of the human studies, athletes were given 100 or 300 mg of calcium pangamate for three days. Serum lactic acid and glucose were lowered after exercise as compared to control treatments which included glucose, glycine and methionine (Karpukhina, Areshchenko and Stolyarva, 1967).

Russian research has shown that B15 exerts a protective effect on coronary artery occlusion and myocarditis in animals (Dokukin et al., 1962; Andreyev et al., 1965; Tromiva, 1965). Oxygen utilization was improved. Animal studies have also shown B15 to have a detoxifying effect, particularly with regard to the liver (Anismov, 1965). Animals subjected to liver stress showed less degenerative effects when dosed with B15. The stress included administration of chloroform, carbon tetrachloride, 5-fluorouracil and dichloroethane. This hepatoprotective action has been the subject of a great deal of Russian research (Damir et al., 1964) and they have reported profound effects in this regard, using in vivo animal experiments. One study showed that fatty infiltration of the liver caused by starvation was inhibited by administration of B15. Other positive benefits were also observed in these starved animals including effects on fat metabolism and serum glucose. B15 protects against the adverse effects of high cholesterol diets in rats. This was evidenced by less fat deposition in liver, adrenal, kidney and heart tissue, as well as a decrease in evidence of atherosclerosis. (Nakanishi et

al., 1960; Khomulo and Dzeranova, 1970; Andreenko et al., 1972, Dzeranova, 1974; Anismov, 1965).

It has also been suggested that B15 may show anti-tumor properties (Beskroonyi, 1971). For example, animals subjected to dimethylbenzanthracene, a mammary tumor-inducing agent, fared better when given B15.

The Russians also have conducted numerous clinical studies (Passwater, 1976; Stacpoole, 1977; Beard, 1956, 1962), reporting positive results in diverse disease states, with particular success in cardiovascular diseases. B15 has been approved by the U.S.S.R. Health Ministry as an effective agent in several diseases.

Some of the Russian successes are in atherosclerosis, coronary insufficiency, and hypertension. In one study, as an example, a dosage regimen of 150 mg given for 20 to 30 days resulted in an improved condition in patients with ischemic heart disease. The author claimed that oxygen consumption in heart muscle was stimulated (Aspit, 1965).

In addition to the above, claims of success in other pathological states include conditions involving abnormal lipid metabolism, liver diseases, alcoholism, dermatological disorders, diabetes, rheumatism and asthma.

Unfortunately, all of these studies were conducted far from this country, mostly under uncontrolled conditions. Therefore, they would not be acceptable as evidence of efficacy based on current FDA regulations. If a U.S. pharmaceutical company submitted such studies as evidence that B15 was an effective therapeutic agent, its application would most probably be rejected. (Table 1 presents a summary of therapeutic claims for B15).

Yet there seems little reason to doubt the sincerity of the Russian research. It would be difficult to conceive of any motivation other than the development of B15 as a potentially useful pharmacologically active agent. Also, studies in other countries, including Japan, tend to confirm some of the Russian findings.

The positive results reported by the Russians are complicated by the vague definition of the chemical composition of B15. Most of their literature does not precisely define B15, but it is apparent that they had difficulty in producing a stable DMG-gluconic acid ester and settled for a calcium pangamate (which they patented), a mixture of the ester, uncombined DMG and calcium gluconate.

Despite this lack of definition, there is little doubt based on the many diverse studies reported in the literature, that B15, pangamic acid, or the defined chemical entity, DMG, has physiological activity.

The FDA Position and the Case Against Vitamin B15

From a regulatory point of view, two problems emerged from the sale of Vitamin B15. One was that the designation B15 or

Table I

Conditions in which B15 is Purported to be Effective

- Hypoxia — B15 increases the efficiency of oxygen utilization
- Increased physical endurance and capacity — used by Russian and some American athletes
- Heart disease — Myocarditis and coronary artery occlusion
- Fatty infiltration of liver
- Atherosclerosis
- Alcoholism

pangamic acid did not refer to a specific definable chemical activity. A bottle of B15 could contain one of several quite distinct and pharmacologically different products; the public would find it impossible to make an educated choice among these products. The second problem was that the definition of Vitamin B15 was unclear from a legal perspective. Was it a food, a drug, or, as the FDA claimed, a "food additive"? If it were the latter, an application to the FDA and a proof of safety would be needed. According to Federal regulations, a food additive is defined as follows:

The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food) if such substance is not generally recognized among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use . . .

The FDA expressed some of its views in an article in **FDA Consumer** (Hopkins, 1978). The author, Harold Hopkins, stated its position that pangamic acid was a food additive, not a food supplement, and noted that "no application has been filed with the agency" and no evidence of safety or efficacy had been received by it.

FDA claimed that B15 was not a vitamin, and was without nutritional benefit. They said that the substance should be defined as a food additive. Safety data was needed and it could not be marketed as a dietary supplement (**New Scientist**, 1978). From this point of view, the problem was a case of mislabeling.

The basic question was one of definition, according to **Science Digest** (1978). Could a natural substance such as DMG be regulated by the FDA? The FDA obviously felt it could. That institution deployed its forces, confiscating the substance from retail outlets, initiating legal action.

There have been claims that all B15 products are potentially contaminated with the likes of calcium chloride or DIPA. It was stated that the methyl groups present in B15 substances do not make B15 formulations lipotropic, methylating or transmethylating, which are assumed to be the basis of its action. Those opposed to B15 claim that the clinical data presented by the Russians is anecdotal, uncontrolled and of no value; the composition of the B15 used is not clearly specified.

Still, there is no documented evidence of toxicity or adverse effects in humans.

On June 12, 1978, in Newark District Court, pangamic acid (DIPA) was deemed to be a food additive and the FDA's seizure action was upheld. The FDA declared the sale of pangamic acid illegal as either a drug or a food additive. The government's case rested on its classification of B15 as an "unsafe food additive." This designation was apparently only a way of allowing the FDA to take legal action.

The Manufacturer's Position

The principal U.S. manufacturer of B15, (a DMG product), FoodScience, contested the FDA's position, claiming that their product, then a mixture of DMG and calcium gluconate, should not be considered to be a drug or a food additive, but rather a food in the absence of therapeutic claims (Aspit, 1980). They agree with the FDA that DMG is not a vitamin, having long since removed that designation from their label. They contend that it is DMG, and DMG alone, which is responsible for B15's activity (Kendall, 1981) and that gluconic acid is considered an unnecessary component of their DMG formulation. The safety of DMG is defended by virtue of its wide use with no reports of adverse effects, along with some short-term animal studies, and yet unpublished chronic animal studies. Some definitive studies in animals to settle this issue once and for all would be welcome. According to Dr. Roger Kendall of DaVinci Laboratories, publication of such studies is imminent. Dr. Kendall also promises, along with these publications, evidence of DMG's

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role as a metabolic enhancer. One of these studies, investigating the potential mutagenicity of DMG, has recently been completed. DMG was subjected to the standard Ames/Salmonella mutagenesis assay and there was "no evidence of mutagenicity . . . either alone or after incubation with NO_2 or saliva," (Graber et al., 1981).

The question of the physiological effects of DMG and its role in nutrition is still being sorted out. It is a natural metabolite which appears to have some physiological effects when given in so-called "therapeutic doses." Again, firm evidence in this area, other than overseas data, would be helpful. A recently published article in the **Journal of Infectious Disease** is a step in this direction (Graber et al., 1981). This report showed that DMG given orally in a double blind clinical study in humans increased the immunological response to pneumococcal vaccine by a factor of four, a highly significant result. This appears to be a bona fide well controlled study and supports similar data reported in animals in the Russian literature where "calcium pangamate" was used.

Two studies of the effects of DMG on (a) the performance of greyhounds and (b) the performance and blood chemistry of race horses have recently been completed. The latter study showed that DMG treatment resulted in substantially lower blood lactic acid levels compared to controls. This was reflected in a shorter running time of 2.5 seconds in the mile and a quarter. It is not clear whether or not the study was "blinded" or if the decrease in running time is statistically significant. However, the decrease in lactic acid is impressive.

The first study was conducted on twenty greyhound sprinters and twenty strayers given either DMG or DIPA (Gannon et al., 1981). Each of the forty dogs had increased "endurance" resulting in a faster performance compared to the running time before the substances were administered. The benefit was manifest during the latter part of the run, suggesting increased "energy reserves." This study was not controlled or blinded. It is unfortunate that these newer studies suffer the defects of most of the clinical studies reported to date, not being controlled according to FDA standards.

Recent Developments

The case involving FoodScience and the FDA came to court in Chicago during December 12 to 19, 1979. From the court's point of view the question concerned the definition of DMG. Was it a "food" or a "food additive?" The problem of its therapeutic effect was not addressed since its use as a drug was not in question.

Earlier this year, the court made its "final" decision. DMG is legally a "food additive," even though the court recognized that it functions as a metabolite in the body. This case is currently under appeal. The strained quality of the court's logic highlights the arbitrariness of the FDA's classification. The court reasoned that if DMG is combined with other substances, whether inert or active, it must be considered a food additive, even if combined with just a small amount of inert lactose. Although the court stated that DMG is a food, they noted that it is without historical precedence, according to Dr. Kendall, Research Director at DaVinci Labs. If DMG were marketed as the pure, unadulterated, identifiable chemical substance, the "food additive" designation would not apply and the product could be freely sold in interstate commerce, no matter what alias it may carry. What is found on the shelves of retail outlets now is either there illegally or was legally stocked and available before the court decision. In order for DMG to be legally sold as a food additive, extensive safety studies must be submitted to FDA to ensure that regulatory body that the substance is non-toxic. Da Vinci Laboratories currently has such studies underway, but they must be submitted before the approval process can begin.

The court's strange decision, the scientific basis of which is not obvious, allows only the sale of the pure substance. Since the dose of DMG in the previously marketed equimolar 50 mg mixture with calcium gluconate was relatively small, a pure 15 mg DMG tablet would be difficult to manufacture. A "legal" higher strength product composed of pure DMG, to be taken not two or three tablets three or four times a day, but perhaps one tablet two or three times a day, is now on the market.

Implications for the Practitioner

With research continuing and some anticipated reports forthcoming, time will tell if DMG, or B15, will live up to its promises. The FDA has won the first battle. However, if DMG is approved as a food additive, it will be more readily available to the general public. If a drug claim were to be obtained, much more work, time and money, and carefully controlled studies in humans would be required. So far, it appears that no one is fully committed to this course of action. Since DMG, per se, is not a patentable item, such studies may never come to fruition in this country. Perhaps this work will be fulfilled elsewhere, accomplished in a manner that would satisfy FDA requirements if, in fact, DMG possesses the activity that its proponents claim.

For the present, it appears that the only legal B15 product is the pure DMG tablet (no added excipients). Although this may be sold, no drug claims may legally be made for the product. Under these circumstances, recommendation of B15, or DMG, for therapeutic or physiological effects should be carefully considered by the practicing physician and pharmacist.

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