Journal of the Malaysian Pharmaceutical Society, 6(1):22-27.

PANGAMIC ACID (VITAMIN B15)

I. The Actual State of Research

By

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INTRODUCTION

The subject of vitamins has always aroused the interest of researchers. There has sometimes been over-enthusiasm in this research, and the values of vitamins at times over-emphasized. The story of the vitamin B complex is a particularly interesting one: it is one of an ever-growing family. One of the latest to be added to this already large family of the B vitamins is vitamin B_{15}. Krebs *et al.*, in 1951, added the 15th member and called it pangamic acid. However, after 27 years, vitamin B_{15} has not been given much attention. Besides a brief mention in the *Journal of the American Medical Association* (1968), one finds very few reports in scientific publications from the "west" on this vitamin. Much of the work on this vitamin was carried out by investigators in the Soviet Union and other East European countries.

Lately, there appears to be attempts to renew interest on this vitamin B_{15} by some quarters. At least two publications have appeared, presumably to publicise and boost this neglected vitamin. One of these is a translation of the monograph edited by E.D. Michlin (1965), containing some 35 reports by Soviet investigators on studies into the possible physio-pharmacological properties of pangamic acid. E.T. Krebs Jr., co-discoverer of vitamin B_{15} in 1951, has contributed a foreword to this publication by the McNaughton Foundation. The second publication, from the John Beard Memorial Foundation, has been compiled by E.T. Krebs Jr. himself (Krebs Jr., 1966). After a lapse of about 10 years, Krebs has again brought up the subject of vitamin B_{15} (the last report from this investigator was in Krebs and Krebs, 1955). It is noted that these two publications mentioned have projected a rather important and useful role for the vitamin. Krebs Jr. (1966) even has a very attractive title for his publication, namely *"Physician's New Weapon"*, a connotation he took from Toddes (1964).

It is not known what is the exact impact and attitude of investigators in America and the other "western" countries towards these two publications. Nevertheless, there appears to be some reaction towards these publications in Indonesia. It is probably due to the availability of these publications in Indonesia that vitamin B_{15} has currently attracted the attention of several investigators and physicians here. The vitamin has even won a place in the local newspapers and magazines (e.g. articles by Liem, 1976, 1977 and 1978). However, due to the difficulty of obtaining literature, there has been a rather mistaken view on this vitamin. It is thus felt important to point out the actual state of research on this "new" vitamin, not only to investigators in Indonesia, but also to others in this region.

NATURAL OCCURRENCE OF VITAMIN B_{15}

Krebs *et al.*, in 1951, reported their discovery of pangamic acid in the kernel of apricot (*Prunus armeniaca*). This water-soluble factor was said to have been isolated in crystalline form by Krebs and Krebs from rice bran and polish. It was reported that because of its "ubiquity" and "relatively high concentrations" in seeds, this acid was named pangamic acid ("pan" meaning 'everywhere', and "gami", 'family'). This acid was also said to have been extracted from brewer's yeast, ox-blood, and horse liver. According to these American investigators, "all existing evidence" suggests that it occurs in nature whenever all other members of the vitamin B complex exist. For this reason — and because of its definite physical, chemical and bioligical properties — it was suggested that pangamic acid be tentatively

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assigned the fifteenth position in the vitamin B complex and be tentatively designated vitamin B_{15}. However, it must be pointed out that there was no mention by these investigators of the amounts of this vitamin in the foods from which they isolated the vitamin. Further, besides this report in 1951, there was no further publications from Krebs *et al.* providing further evidence on the occurence of vitamin B_{15}

In fact, there has been no reports, except for the one to be described below, from other investigators on the natural occurrence of pangamic acid. Telegdy-Kovats and his associates (1970) are the only group of investigators who reported on the quantity of pangamic acid in some foods. As may be seen from Table I, the reported values of vitamin B_{15} in the cereals studied are very much higher than other members of the vitamin B group, i.e. thiamine, riboflavine and niacin. However, it must be noted that no other investigators have done parallel studies to confirm these values or to extend to the list of pangamic acid content in foods. For this reason, and because of other reasons to be described in subsequent chapters, it is felt that these reported values must be taken as tentative and need to be verified.

Table 1
Pangamic Acid (Vitamin B_{15}) Content of Some Cereals

	(mg per 100 g sample)			
	Thiamine	*Riboflavine*	*Niacin*	*Pangamic Acid*
Rice bran	1.26	0.25	29.8	200
Rice, undermilled	0.20	0.05	2.6	
Corn grits (corn, whole kernel, dried)	0.29	0.11	2.1	150
Wheat germ	2.10	0.60	7.0	70
Wheat bran	0.54	0.80	5.5	31
Oat grits (oats, whole grain)	0.35	0.09	2.2	106
Barley grits (barley, whole grain)	0.31	0.10	5.2	12
Legumes	0.4–0.9	0.1–0.3	1.0–3.0	-

Source:– For vitamins thiamine, riboflavine and niacin: Food Composition Table for Use in East Asia, 1972
For pangamic acid: Telegdy-Kovats *et al.* (1970)

POSSIBLE PHYSIO-PHARMACOLOGICAL PROPERTIES

In their "discovery" paper in 1951, Krebs *et al.* reported some preliminary studies on the possible physio-pharmacological properties of pangamic acid (as its sodium salt) to overcome the effect of anoxic anoxia and histo toxic anoxia in animals (studies on the physiological properties described in the following paragraphs were done on experimental animals). They postulated that the vitamin is able to facilitate cellular oxidation in organisms. Subsequent to this, several reports (mostly by Soviet investigators) appeared, attempting to demonstrate the anti-hypoxic ability of pangamate (e.g. Andreyev *et al.*, 1965; Andreyev & Rode, 1965; Beburishvili & Nersesova, 1972). The studies of Udalov & Chernyakov (1965), Braude *et al.* (1965), and Shamray &. Selezneva (1969), provide insight into the possible influence of pangamic acid on respiratory enzymes, oxidative phosphorylation and the structure of mitochondria.

The presence of the dimethyl group in the vitamin B_{15} molecule prompted several investigators to study the possibility of pangamic acid serving as a methyl donor in the methylation process. Solovyeva & Garkina (1965a) reported the ability of calcium pangamate to methylate guanidoacetic acid to form creatine. They were, however, unable to show that pangamic acid could methylate homocysteine in the biosynthesis of methionine or the methylation of nicotinamide. Udalov & Sokolova (1963) and Nankov (1974) reported demonstrating the lipotropic ability of vitamin B_{15}.

Several investigators had reported that another possible physiological action of pangamic acid is its stimulatory action on the adrenal cortex function. The reports of Udalov (1962 and 1965) and Motova *et al.* (1970) are of relevance. The report of Krebs *et al.* (1951) on the ability of pangamic acid to resist histotoxic hypoxia created by cyanide poisoning probably prompted subsequent studies to be made to further demonstrate the possible detoxication properties of vitamin B_{15}. Alpatov *et al.* (1965), Braude *et al* (1965) and Trofimova (1965) studied the effect of pangamic acid on various toxicants.

Other investigators studied the possible role that pangamic acid may play in various other aspects of metabolism. Yakovlyev *et al.* (1965) and Karpoochina *et al.* (1965) appear to be interested in the effect of pangamic acid on various aspects of metabolism during physical exer-

cise. The possibility of pangamic acid participating in oxidative demethylation in the organism was investigated by Soloveya & Garkina (1965b). The reports of Kutateladze & Jabna (1970) and Andreenko *et al.* (1972) indicated the possible influence of vitamin B_{15} on lipid metabolism.

The possible therapeutic value of this 15th member of the B group vitamins has been studied by several investigators. Krebs *et al.* (1951) in their "discovery" paper said that the vitamin has "definite therapeutic effect in a wide range of cardiovascular diseases, particularly in the condition termed coronary insufficiency, clinically characterised by angina pectoris or coronary thrombosis". No data were provided in this paper. However, these investigators felt that "this agent is destined to become an important factor in cardiac therapy". Various Soviet investigators followed up with several clinical trials, aiming to show the effectiveness of this vitamin in the ameliorating of this disorder. Some examples of such studies are: Milimovka *et al.* (1965), Mikhailova & Solovyeva (1965), Shpirt (1965), and Anisimov & Salikhov (1965).

Bobrova & Oleinik (1965) and Shpirt (1965) reported the successful use of calcium pangamate in the treatment of patients afflicted by atherosclerosis of the vessels of the lower extremities. Shpirt (1965) also studied the use of pangamate in a few cases of diabetes mellitus.

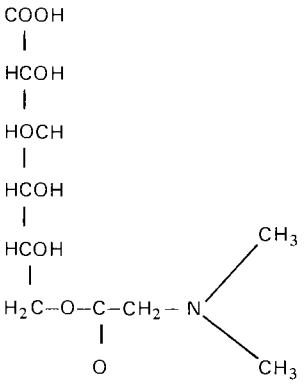
The number of patients suffering from liver diseases (including cirrhosis of the liver and chronic hepatitis) successfully treated by Mikhailova & Solovyeva (1965) and Anisimov & Salikhov (1965) using calcium pangamate are relatively few. On the other hand, the possible use of pangamic acid in geriatric practice had received considerable attention. Yakovleva (1965), Altshuler (1965), Kolosov *et al.* (1965) and Motova *et al.* (1970) had reported the use of vitamin B_{15} in middle-aged and elderly persons.

Krebs & Johnson (1953), Strelchuk (1965) and Goodkova & Sinkevich (1965) reported on the possible use of B_{15} in patients suffering from chronic alcoholism. The efficacy of pangamate in dermatological-venerological practice was reported by Camp & Ponjoan (1959), Vedrova & Chamaganova (1965) and Stoodnitsin & Maslov (1965). Studies on the above disorders were relatively small and isolated.

The above paragraphs represent a rapid survey of the reported physio-pharmacological properties of pangamic acid. It must be pointed out that they are the possible properties, and not to be taken as the established properties. Many aspects of the reported biochemical and therapeutic roles of pangamic acid need to be further evaluated and substantiated. For reasons to be described below, these reported findings must be taken as tentative and their validity verified.

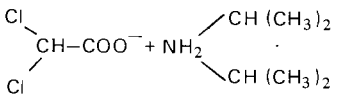
SYNTHETIC VITAMIN B_{15} – PANGAMIC ACID PREPARATIONS.

The so-far reported physiological and therapeutic properties of pangamic acid have been studied using synthetic preparations of the vitamin. However, it has been shown that a large number of these preparations do not contain pangamic acid (see structure below).



Structure of pangamic acid (vitamin B_{15}):
(molecular formula: $C_{10}H_{19}O_8N$; molecular weight: 281)

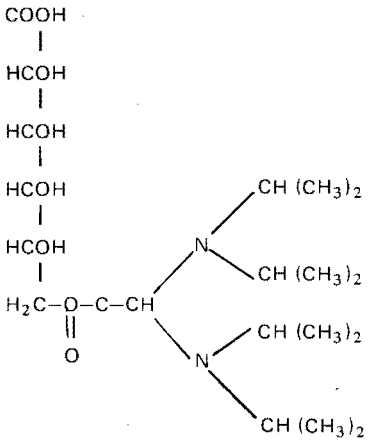
Casu *et al.* (1958), French & Levi (166) and Micheau *et al.* (1972) had separately studied several such synthetic preparations, variously named "vitamin B_{15}", "pangamic acid", "pangametin," "biopangamin", etc. These preparations are supposed to have the therapeutic properties of pangamic acid. It was however obtained that these preparations do not contain pangamic acid, but instead, diisopropylammonium dichloroacetate. The structure of this compound, given below, is totally different from that of pangamic acid:



Structure of diisopropylammonium dichloroacetate
(molecular formula: $C_8H_{17}O_2NCl_2$; molecular weight: 234)

In a study of six synthetic preparations called "pangamic acid-vitamin B_{15}", including one from ICN Pharmaceuticals, Cleveland, Ohio, the authors (Tee & Rasad, 1978) have shown that none of the preparations may be said to contain pangamic acid. They are really mixtures of two or more of the following: diisopropylammonium dichloroacetate, gluconate, dimethylglycine and glucose.

It is clear that if such preparations are used for the study of the biological and therapeutic properties, and the results obtained said to be that of pangamic acid or vitamin B_{15}, the findings reported will be inaccurate and confusing. Therefore one has to scrutinize the report and first determine what compound is actually being used for the study, since the term pangamic acid has been so loosely used. In fact, some studies reported in the literature had used, instead of vitamin B_{15}, an octamethyl derivative of pangamic acid called vitamin $B_{15}H_8$ (structure given below), although the titles of such reports carry the words "pangamic acid-vitamin B_{15}".



Structure of vitamin $B_{15}H_8$.

This appearance of numerous preparations, loosely called "pangamic acid" or "vitamin B_{15}", but really do not contain pangamic acid is probably due to the misconception among some investigators on the actual structure of pangamic acid. *The Merck Index* (1968), for example, stated that "Bigi (1966) gives the structure of pangamic acid as (6-0-(N,N-dimethylglycyl) D-gluconic acid." It is also mentioned in this Index that according to Casu *et al.* (1958) and Kraushaar *et al.* (1963), pangamic acid is a mixture of sodium gluconate, glycine and the physiologically active diisopropylammonium dichloroacetate. It is noted that in the same paragraph in this Index, two different structures of pangamic acid have been given. The pamphlet distributed by Sankyo, Japan, marketing a product called "Liverall", and available in drug stores in Jakarta, states that "a mixture of diisopropylammonium dichloroacetate and a gluconate represents the active portion of pangamic acid".

It must be emphasized that the accepted structure for pangamic acid is 6-O-(N,N-dimethylglycyl)-D-gluconic acid, and preparations containing compounds with other structures must be said to be non-authentic preparations of pangamic acid or vitamin B_{15}.

CONCLUSION

It is thus clear that research on vitamin B_{15} leaves much to be desired. The natural occurrence of this so-called vitamin must be of primary concern to all investigators. It must be pointed out that the statement: "all existing evidence suggests that it occurs in nature where all other members of the vitamin B complex exist" (Krebs *et al.*, 1951) need to be further proven. It must be borne in mind that unless this compound is shown to be present in foods, it may not be called a vitamin at all!

The existing contradictions on the structure of pangamic acid is regrettable since this is another fundamental aspect of the subject. This disagreement among investigators on the structure gives rise to much confusions. One direct consequence is the appearance of numerous synthetic preparations called "vitamin B_{15}" or "pangamic acid", but they do not actually contain 6-O-(N,N-dimethylglycyl)-D-gluconic acid. The marketing of such preparations can certainly lead to confusions, and are detrimental to the progress of research on the subject. It is believed that there are numerous reports in the literature that had been studied using preparations that do not contain authentic pangamic acid. One wonders how many authentic preparations of pangamic acid exist. One must therefore cast doubts on the validity of the so-far reported properties of vitamin B_{15}, be it the chemical and physical properties, or the physio-pharmacological properties, and its reported concentrations in foods.

This existence of synthetic preparations loosely labelled as pangamic acid or vitamin B_{15} is perhaps the reason for the non-recognition by the authorities of the "western" countries of the existence and usefulness of this vitamin. This availability of various products claimed to be pangamic acid or vitamin B_{15} is perhaps the reason why investigators have not been able to obtain uniform results, since the preparations they studied may be of totally different structures!

From this discussion, it is perhaps clear why "western" investigators have avoided doing research on this still controversial vitamin. It is hoped that we in this region will be aware of the facts concerning this currently much talked about, but yet unproven "physician's new weapon" that has been claimed to be a "life saviour in Russia" (Liem, 1976).

SUMMARY

After its discovery in 1951 by Krebs *et al.*, pangamic acid has been given little attention, espe-

cially by investigators in the "western" countries. Most of the studies on this "new" water-soluble accessory food factor, also called vitamin B_{15}, were carried out in the Soviet Union and East European countries. Today, a quarter century after its discovery, little data has been accumulated. The natural occurrence of this vitamin itself has not been sufficiently proven. Reports on its possible physiological and pharmacological properties have come forth, mainly from Russian investigators. These properties have been studied using synthetic preparations of the vitamin B_{15}. However, various investigators, including the authors, have shown that these synthetic preparations, although called "vitamin B_{15}" or "pangamic acid", may not have the required structure for this vitamin. Hence, these properties reported to be attributable to pangamic acid must be treated with caution. The marketing of such synthetic preparations loosely labelled "vitamin B_{15} pangamic acid" had come about due to the misconception of the structure of pangamic acid. Research on this so-called vitamin B_{15} is thus scanty; contradictions and confusions surround the subject. An attempt will be made to present here the actual state of research on vitamin B_{15}.

ACKNOWLEDGEMENTS

The authors are grateful to the following for their assistance in the obtaining and translating of articles on this subject: staff members of the National Documentation Centre, Jakarta; dr. G.H. Lie, Unit Diponegoro, Jakarta; dr. Gunawan and dr. Harijanto of the Cisarua Sanatorium; staff members of the Nutrition Division, Institute for Medical Research, Kuala Lumpur; P. Unchumchoke, Chulalongkorn Hospital, Bangkok; Professor Telegdy-Kovats, Budapest Technical University, Hungary; and Dr. J.C. Micheau, University of Toulouse, France.

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