CHAPTER I

INTRODUCTION
THIAMINE (VITAMIN B₁)

History:

The first member of the vitamin B complex to be identified was thiamine. Lack of thiamine produced a form of polyneuritis known as beriberi. This disease had become widespread in East Asia in the nineteenth century following introduction of steam powered rice mills which produced polished rice lacking the vitamin rich husk. In 1880 a dietary cause for the disease was first indicated when Admiral Takaki largely reduced the incidence of beriberi in the Japanese Navy by adding fish, meat, barley and vegetables to the sailors' diet of polished rice.

Eijkman, a Dutch physician working in Java where incidence of beriberi was common, demonstrated in 1897 that rice polishings could cure beriberi in human beings. A highly concentrated form of the active factor was isolated in 1911 by Funk who recognized that it belonged to a new class of food factors, which he called vitamines. Later it was shortened to vitamins.

Subsequently, in 1926, the active factor was named vitamin B₁. It was isolated in crystalline form by Jansen and Donath.

Originally, the name 'aneurine' was coined for vitamin B₁ on the basis of its ability to cure or prevent avian polyneuritis. Later, the name thiamine was proposed and accepted as the official name. It derives from the chemical nature of the vitamin which has a thiazole ring attached to a pyrimidine ring with an amine group. Its structure was determined in 1936.
by Williams. The Council on Pharmacy and Chemistry adopted the name thiamine to designate crystalline vitamin B₁.

**Chemical Nature and Constitution:**

Thiamine is an organic molecule containing a pyrimidine and a thiazole nucleus linked by a methylene bridge. Thiamine functions in the body in the form of the co-enzyme thiamine pyrophosphate (TPP). Below is shown the structure of thiamine and its biologically active derivative thiamine pyrophosphate (TPP).

![Thiamine and thiamine pyrophosphate](image)

**Fig.1.** Thiamine and thiamine pyrophosphate

Several modified thiamine vitamers are available. Most of these have an open thiazole ring, and some are lipid soluble. These derivatives seem to give, after oral administration, a more rapid and pronounced increase in blood thiamine concentration than does thiamine itself, presumably because they are not subject to the same regulation of intestinal transport as in the parent thiamine. Thiamine's conversion to its co-enzyme form is carried out by the
enzyme thiamine diphosphokinase with adenosine triphosphate (ATP) as the pyrophosphate (PP) donor. Anti-metabolites to thiamine that inhibit this enzyme have been synthesized. The most important of these are neo-pyrithiamine (pyrithiamine) and oxythiamine. Thiamine is sensitive to photochemical degradation by ultraviolet light (below about 290 nm). It is also destroyed by heat in the presence of water. The rate of destruction increases with the pH, and Cu (a common component of cooking vessels) catalyses this destruction, although other metal ions do not. Under dry conditions thiamine is stable to heating at 100°C for 24 hours or longer without loss.

Physiological Properties and Functions:

i. Absorption

The absorption of thiamine is limited. It occurs mainly in the upper intestine. The evidence that thiamine is absorbed mainly in the upper intestine comes from the observation that absorption is influenced by the quantity of food eaten. Less is absorbed from an empty stomach than following a meal. Possibly this is due to low stability of thiamine in the alkaline conditions of the duodenum.

Thiamine that is absorbed from the small intestine is phosphorylated in the intestinal mucosa. Rindi and Ventura (1972) have reviewed the mechanism of thiamine absorption in the small intestine. It is an active process, but when this is saturated there is also some passive diffusion. The enzyme that carries out this process has been isolated and partially purified. It promotes the reaction between thiamine and adenosine triphosphate with the formation of thiamine pyrophosphate and adenylic acid (Goldsmith, 1964). Rindi and Ventura
(1972) also showed that the rat intestine would absorb thiamine against a concentration gradient, i.e., when the blood concentration was greater than that of the luminal contents.

ii. Storage

The phosphorylation of thiamine to the metabolically active co-enzyme, thiamine pyrophosphate, occurs in all nucleated cells. Most of the newly absorbed thiamine is phosphorylated in the liver, although the kidneys also have an active TPP synthesising system. The same organs also dephosphorylate TPP to release free thiamine for transport in the bloodstream to other tissues.

However, the body is unable to store thiamine for any length of time. The total amount of thiamine in the body of a healthy subject is about 25 mg. Heart muscle is the richest tissue, followed by brain, liver and kidney, and skeletal muscle. The most immediate loss, when a subject is placed on a thiamine deficient diet, is from skeletal muscle. Liver, nervous system and heart all lose their thiamine more slowly.

The blood level of thiamine is between 40-100 μg/l in healthy subjects (Carleen et al, 1944). Free thiamine is present mainly in the plasma (5-20 μg/l) with the remainder being thiamine pyrophosphate in erythrocytes and leucocytes (Carleen et al, 1944; Sinclair, 1939). The blood thiamine concentration varies considerably in the same individual and appears not to be related to the excretion.

iii. Excretion

Excretion of thiamine in the urine has been widely studied in human subjects. Excretion in 24 hours is linearly related to the dietary intake
except at low levels (Unglaub and Goldsmith, 1954). With a good diet, the excretion in 24 hours is 100 µg or more. If the thiamine intake is decreased to less than 1.0 mg daily, the urinary excretion falls at first rapidly and then more slowly until equilibrium is reached. Minimal excretion is 1 to 10 µg daily and is found when the diet furnishes less than 0.6 mg of thiamine daily in adults.

The excreted thiamine is mostly free but some is excreted as the pyrophosphate. The urinary excretion is reduced in diabetes, during infections, in the aged, during exercise and as a result of injury and haemorrhage. Reduced excretion has also been reported in patients suffering from alcoholism.

Sweat may contain 90-150 µg/l so that losses of thiamine may be important in workers in extremely hot conditions, although under usual conditions this will be an unimportant factor (Cornbleet and Bergeim, 1943).

iv. Function

Considerable information is available on the role of thiamine in intermediary metabolism. Peters' classical work between 1929 and 1936 demonstrated the co-enzyme function of thiamine in the oxidative decarboxylation of pyruvate. He showed that the avitaminous brain contained more lactic acid than normal (Kinnersley et al., 1929), and then that avitaminous brain brei oxidised less glucose than normal (Gavrilescu et al., 1931). If lactate but not succinate was used as the substrate, the same low rate of oxidation was observed. The addition of thiamine in vitro largely restored the rate of respiration — the first report of any action of a vitamin in vitro (Gavrilescu et al., 1932). Peters' work on the biochemical lesion of pyruvate
oxidation in thiamine deficiency was confirmed by Lohmann and Schuster in 1937 who showed that the co-enzyme for yeast pyruvate apo-decarboxylase was the pyrophosphate ester of thiamine, thiamine pyrophosphate or co-carboxylase. Peters (1937) had already shown that thiamine was phosphorylated to TPP by brain preparations.

Handler (1958) has summarized knowledge of the role of thiamine in mammalian metabolism. Thiamine pyrophosphate is necessary for the first step in the reactions which feed into the citric acid cycle. Pyruvic acid is decarboxylated and active acetaldehyde is formed transiently on the thiamine before it is transferred to the oxidized form of lipoic acid. The lipoic acid is reduced thereby and acetyl lipoic acid results. This is the fate of pyruvic acid which is dominant in the oxidative metabolism of mammals. The simple decarboxylation of pyruvic acid to acetaldehyde never occurs in mammalian metabolism. A second reaction analogous to the above is the oxidative decarboxylation of $\alpha$-ketoglutaric acid, a subsequent step in the citric acid cycle. Co-carboxylase (thiamine pyrophosphate) functions as in pyruvic acid decarboxylation. The $\alpha$-ketoglutaric acid is decarboxylated and active succinyl semi-aldehyde exists in transient fashion on the thiamine and then is transferred to lipoic acid. This gives rise to succinyl lipoic acid from which the succinyl group is transferred to the co-enzyme A.

Thiamine pyrophosphate is also a co-enzyme in the transketolase reaction which is part of the so-called direct oxidative pathway of glucose metabolism which occurs not in the mitochondria but in the cytoplasm of cells including those of liver, brain, adrenal cortex and kidney but not skeletal muscle. The combined overall reactions in the pathway can be represented as follows :-
6 glucose + 6 ATP + 12 NAEP $\rightarrow$ 6 ribulose-5-phosphate
+ 6 CO$_2$ + 12 NADPH + 6 ADP ... (1)

6 ribulose-5-phosphate $\rightarrow$ 5 glucose-6-phosphate ... (2)

Transketolase is among the enzymes necessary for the overall conversion indicated in the above reactions. It "catalyzes the general reactions: xylulose-5-phosphate (a ketopentose), ribose-5-phosphate, 3 phosphoglyceraldehyde and sedoheptulose-7-phosphate (a ketopentose)" (Handler, 1958).

Dietary fat is known to exert a thiamine-sparing action. One explanation for this might be that thiamine pyrophosphate participates in the oxidation of fat only in the oxidation of $\alpha$-ketoglutarate. If fatty acids, rather than glucose, were the prime source of calories, there might be just enough thiamine pyrophosphate for this one enzyme. It is known that the activity of pyruvic decarboxylase declines before that of $\alpha$-ketoglutarate decarboxylase. It is also possible that some toxic product might be derived from carbohydrate metabolism but not from fat metabolism.

In thiamine deficiency blood pyruvate and often blood lactate rises sharply. It is not certain whether the central nervous system effects of thiamine deficiency should be attributed to these effects on carbohydrate metabolism or to the resulting decrease in active acetate component for production of acetylcholine.

1B. RIBOFLAVIN (VITAMIN $B_2$)

History:

From 1879 onward, a series of yellow pigmented compounds have been isolated from time to time from a variety of sources and designated as flavins; prefixed
to indicate the source. It was finally demonstrated that these various flavins were identical in chemical composition.

Meanwhile, water soluble vitamin B had been separated into a heat labile antiberi factor (B<sub>1</sub>) and a heat stable growth promoting factor (B<sub>2</sub>), and it was eventually appreciated that concentrates of the so-called vitamin B<sub>2</sub> had a yellow colour.

Warburg and Christian described in 1932 a yellow respiratory enzyme in yeast. In 1933 the yellow pigment portion of the enzyme was identified as vitamin B<sub>2</sub>. All doubt as to the identity of vitamin B<sub>2</sub> and the naturally occurring flavins was removed when lactoflavin was synthesized and the synthetic product was shown to possess full biological activity. The vitamin was designated riboflavin because of the presence of ribose in its structure.

**Chemical Nature and Constitution:**

Riboflavin is a yellow pigment with green fluorescence. It has the chemical formula C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub> or 6,7-dimethyl-9-isoalloxazine. The structural formula is shown below:

![Chemical Structure of Riboflavin](image-url)

*Fig. 2. Riboflavin*
The isoalloxazine nucleus gives riboflavin certain chemical properties of a substituted benzene, an azine dye and a pyrimidine. The ribityl side chain relates it to the pentose sugars. Riboflavin is water soluble to some extent, solubility being 10 to 13 mg per 100 ml at 25°C and 235 mg per 100 ml at 100°C. It is quite stable in strong mineral acids and oxidizing agents, but it is sensitive to alkali. In neutral aqueous solutions it is relatively heat stable if protected from light.

Riboflavin is irreversibly decomposed on irradiation with ultraviolet rays or visible light. No appreciable destruction occurs during the cooking of food, but exposure of milk in bottles to sunlight leads to destruction of more than half of the riboflavin in 2 hours.

Physiological Properties and Functions:

1. **Absorption**

Riboflavin is absorbed by the mucosa of the small intestine. Gastric hydrochloric acid is probably needed for its absorption. The absorption rate appears to be related to the intake. Phosphorylation is thought to occur in the intestine and from there it is transmitted via the portal blood to the liver. Phosphorylation of riboflavin may be due partly to the transferase action of the phosphomonoesterase of the small intestine (Yogi et al, 1958). In the liver, conversion to flavin adenine dinucleotide takes place.

ii. **Storage**

The bulk of the riboflavin in the body is stored in the liver, heart and kidneys. Human blood contains about 32 μg of riboflavin per litre; about 25%
is as free riboflavin and the rest bound to plasma proteins. Muscle contains about 2-3 μg/gm. Tissue stores become saturated with riboflavin readily when the intake is high but the reserve stores are not great and may be lost quickly. A relationship has been demonstrated between the retention of riboflavin and the retention of protein and with protein breakdown there is concomitant loss of riboflavin from the tissues.

iii. Excretion

Excretion of riboflavin is influenced by many factors. Riboflavin is excreted in the urine, the output varying with the intake and the degree to which tissue stores are saturated. In normal persons, urinary excretion of riboflavin ranges from 150 to 2000 μg daily. In man the administration of large doses of thiamine (1 to 10 mg) over a period increases the excretion of riboflavin in the urine, although such a dosage does not produce clinical riboflavin deficiency. The protein intake also influences riboflavin excretion (Sarett et al., 1942; Sastri et al., 1950). An increased protein intake causes diminished excretion and increased retention of riboflavin. In man the excretion falls after exercise. The output of this vitamin is increased in acute starvation, in diabetes mellitus, in conditions in which nitrogen balance is negative and after administration of certain antibiotics.

Riboflavin is also excreted in the sweat. The estimates of the amount lost in this way are variously given as from 5 to 120 μg/l and 10 μg per hour (Cornbleet et al., 1943; Mickelsen et al., 1943).

It is secreted by the mammary glands. About 10% of the daily intake can be recovered in the milk.
In studies of adults on restricted diets which supplied 0.55 to 1.1 mg daily the average excretion of riboflavin has been reported to range from less than 10 to 14% of the dietary intake. When diets furnished 1.3 to 1.6 mg daily, excretion ranged from 21 to 26% of the intake. When very large amounts of riboflavin were given, 50 to 85% of the intake was excreted in the urine in 24 hours (Sebrell et al., 1941).

In man the faecal excretion is greater than the urinary and on a low intake can be three times the intake (Denko et al., 1946). The amount of riboflavin excreted in the faeces is determined largely by the amount of intestinal synthesis, which is affected by the nature of the diet but is largely independent of its riboflavin content. The faecal excretion of riboflavin appears to be proportional to the number of viable bacteria in the faeces and presumably to the amount of riboflavin they synthesize. There is no evidence that riboflavin synthesized by the bacteria in the colon can be absorbed.

iv. Function

Riboflavin is found in tissues chiefly in the form of flavin adenine dinucleotide (FAD) with a smaller amount of riboflavin-5-phosphate or flavin mononucleotide (FMN). These in turn can form the prosthetic groups of several different enzyme systems. The dinucleotide (FAD) forms the prosthetic group of some hydrogen transport enzyme systems.

The flavoprotein functions as important enzymes for tissue respiration:

a. Acting as a link between the pyrimidine nucleotide systems and the cytochromes.
Two of these are specific systems for the reoxidation of the reduced forms of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP).

b. Acting as a link between the intermediary metabolite and the cytochrome systems.

Flavoproteins containing enzymes thus have an integral role in the biological oxidation reactions of the electron transport chain at various stages; both FAD and FMN are involved. During these reactions the hydrogen released by the dehydrogenases is converted to water with energy production which is stored as ATP. A number of flavoprotein enzymes (oxidase flavoproteins) have been isolated which catalyze the direct oxidation of substrates by oxygen with no requirement for pyridine nucleotide co-enzymes. These include D and L amino acid oxidases, glycine dehydrogenase, xanthine oxidase, aldehyde oxidase, glucose oxidase, diamino oxidase and fumaric hydrogenase.

Whereas vitamin B₂ is present in most animal organ as a phosphate or a flavin adenine dinucleotide, the retina of the eyes contains free vitamin B₂ in relatively large amounts. The function it fulfills there, however, is still not clear. In avascular tissues such as the cornea it is thought that oxidation takes place by means of a riboflavin containing enzyme. In deficiency of the vitamin, the body attempts oxygenation by vascularization. In both animals and man riboflavin is essential to growth and life.

1C. PYRIDOXINE (VITAMIN B₆)

History:

Gyorgy (1964) and Harris (1968) have extensively reviewed the history of the isolation, identification and synthesis of vitamin B₆ with details of some
of the methods used.

In 1934 Gyorgy reported the presence of a factor in water soluble vitamin B that was distinct from other activities reported previously and would cure the signs of acrodynia in the rat. Acrodynia is a vitamin deficiency dermatitis seen in rats. This factor was called vitamin B\textsubscript{6} to differentiate it from the vitamin B\textsubscript{2} complex from which it was isolated.

Five separate groups of workers isolated the vitamin in 1938 (Barker and Bender, 1980) from rice and yeast in pure form and its chemical structure was determined the following year (Kuhn et al., 1939). Working from the observation that different methods for estimating the vitamin B\textsubscript{6} activity of various foods gave widely differing results, Snell and coworkers discovered pyridoxal and pyridoxamine in 1942.

In 1944, Gunsalus ascribed the first metabolic role to vitamin B\textsubscript{6} when he reported that pyridoxal phosphate was the co-factor in the enzymic non-oxidative decarboxylation of amino acids (Gunsalus, 1944).

The first chemical synthesis of pyridoxine was carried out by Harris and Folkers in the United States and by Kuhn and coworkers in Germany in 1939.

Kuhn proposed in 1938 that 'adermine' would be a suitable name for vitamin B\textsubscript{6} in view of its biological effect in curing the dermatitis of acrodynia in rats. However, Gyorgy and Eckhart proposed in 1939 that, on the basis of its chemical relationship to pyridine, a more suitable name would be pyridoxine, and this was the name that was accepted by the Council on Pharmacy and Chemistry of the American Medical Association in 1940. The systematic nomenclature now accepted was adopted by the Commission on Biological

Physiological Properties and Functions:

i. Absorption

On most natural diets most of the vitamin B₆ is ingested as pyridoxal or pyridoxamine. Very little is known about the factors influencing absorption of B₆ although it is rapidly absorbed from the digestive tract of man, dog and the rat.

ii. Storage

Pyridoxine is distributed throughout the animal tissues but in the form of the co-enzyme. Little is known about the destruction of vitamin B₆ in the tissues. The storage of vitamin B₆ as such is not known. There is no evidence that vitamin B₆ is stored in the body.

iii. Excretion

Small amounts of pyridoxine, pyridoxal and pyridoxamine may be excreted in the urine, but the major product of metabolism is 4-pyridoxic acid (Huff and Perlzweig, 1944). This pyridoxic acid is the chief metabolic product of pyridoxine, pyridoxal or pyridoxamine. Rabinowitz and Snell (1949) studied the excretion products of three male subjects on a normal diet after administering the different forms of vitamin B₆. Regardless of whether pyridoxine, pyridoxal or pyridoxamine were given the chief excretion product was pyridoxic acid. Pyridoxal gave rise to significantly larger quantities of this compound than did pyridoxine or pyridoxamine. Neither pyridoxal nor pyridoxamine were...
converted to pyridoxine. When pyridoxamine was administered, both pyridoxal and pyridoxamine were excreted in approximately equal amounts and the administration of pyridoxine greatly increased the amount of pyridoxal and pyridoxamine excreted. The excretion of all products was at a peak at 2 to 5 hours after administration of the compound and returned to normal values after 8 to 12 hours. The highest recovery was 70%. When pyridoxal was given, 45% of the pyridoxine was recovered but only 30% of the pyridoxamine. All forms of vitamin B₆ give rise to pyridoxal, which suggests that this is the form used in metabolic processes, i.e. as pyridoxal phosphate. A major portion of each form is eventually oxidized to 4-pyridoxic acid which is an inactive metabolite. Women with an average daily intake of 1 mg excrete about 75 to 85% of the ingested vitamin as pyridoxic acid.

iv. Function

The B₆ group is rapidly converted in the body into co-enzymes pyridoxal phosphate and the pyridoxamine phosphate. These co-enzymes play an essential role in protein metabolism. Pyridoxal phosphate forms the prosthetic group of the following enzymes:

a. Transaminases: The mode of action is probably as an amino group transfer mechanism by the formation of pyridoxamine. The reaction allows the transfer of amino groups from glutamic and aspartic acid to certain α-keto acids. Thus, synthesis of amino acid is possible from carbohydrate intermediates, e.g.

\[
\text{aspartate} + \text{ketoglutarate} \xrightarrow{\text{transaminase}} \text{oxaloacetate} + \text{glutamate.}
\]
In other transaminase reactions either glutamine or asparagine can act directly as the amino donor to pyridoxal phosphate containing enzymes. Transamination plays an essential role in urea formation by providing aspartic acid one of the amino donors.

b. **Decarboxylation Reaction**: Pyridoxal phosphate dependent enzymes specific for the decarboxylation of amino acids have been found in animal tissues. These decarboxylases convert them into the physiologically important amines.

The general reaction is:

\[ RCHNH_2COOH \rightarrow RCH_2NH_2 + CO_2 \]

c. Desulphydrase and transulphurases in the interconversion and metabolism of sulphur containing amino acids.

d. **Enzyme for the Synthesis of δ Aminolevulinic Acid**: Pyridoxal phosphate is required among other co-factors in the synthesis of aminolevulinic acid, an important intermediate in the synthesis of porphyrin (δ aminolevulinic acid is formed from succinyl CoA and glycine).

e. **Kynureninase**: In pyridoxine deficiency the production of nicotinic acid from tryptophan is impaired at the hydroxykynurenic stage. Instead of being converted to hydroxyanthranilic acid, this compound forms xanthurenic acid, the urinary excretion of which has been used as a biochemical index of inadequate pyridoxine.
f. In the conversion of linoleic to arachidonic acid in the metabolism of essential fatty acids.

g. Glycogen phosphorylase which catalyzes the breakdown of glycogen reserves to give glucose-1-phosphate in muscle and liver.

As a result of these reactions pyridoxal phosphate forms an essential enzyme for energy production (supplying metabolites to the Kreb’s cycle), fat metabolism, central nervous system activity and haemoglobin production.

From the foregoing, it is obvious that pyridoxine deficiency involves a number of non-oxidative metabolic changes of amino acids as well as some pathways not involving amino acids, such as -

1. Degradation of γ-aminobutyric acid (GABA) in brain mediates through transaminase reactions.

2. B₆ deficiency results in accumulation of oxalate due to lack of transaminase necessary in the conversion of oxalate to glycine.

3. Many important neurohormones require these specific enzymes in their synthesis, viz. the formation of serotonin, γ-amino butyric acid, epinephrine and histamine all require pyridoxal phosphate.

4. Immune response is impaired in B₆ deficient animals as is shown by the decrease of participating hemagglutinin antibody levels and increased tolerance of skin homograft.
2. CONCEPT OF PHYSICAL EXERCISE

Study of muscular exercise in detail began in the 18th century when Antonie Laurent Lavoisier and Pierre Simon de Laplace discovered that the process consumes oxygen and produces carbon dioxide. As investigation progressed it became clear that exercise involved not only the muscles but also the other tissues, that it depended indeed on an extraordination of the respiratory, circulatory and nervous systems, all working together under a highly integrated control.

Eggleton (1936) tried to bring together the knowledge that had been accumulating about the way our bodies did physical work, how muscles contracted, how they were made to contract at the right moment, how all the organs of the body were made to adjust their activities and other tempo so that exercise could be performed with minimal disorganisation.

Man, in the interior working of his body, is subject to the same constraints as any inorganic mechanism for converting one form of energy into another. The body of man is, in fact, a machine whose unique properties are the result not of unique resources but of an organisation unique in its complexity and perfection. The task of finding out what is happening inside a man's body during exercise is an integrating effort in ingenuity, for we cannot cut him open for observation. Yet, in spite of this limitation, there is a great deal to be learned from indirect measurements.

Probably the most fascinating side of muscular exercise is a group of mechanism which coordinate all the organs of the body so as to make possible the abrupt change from rest to violent activity and back again.
Muscular work may be divided into -

1. thermodynamic aspect;
2. physiologic aspect.

The thermodynamic aspect is concerned mostly with energetic efficiency and the physiologic aspect is concerned especially with anaerobic oxidative metabolism in muscular work, hormonal, nutritional, temperature and humidity aspects and oxygen transport as an index of the work capacity. The physiology of muscular work and exercise is basically a matter of transforming bound energy into mechanical energy. The physicist defines work rigidly as the product of force times the distance through which a force acts. This may be expressed in the following equation:

\[ \text{work} = \text{force} \times \text{distance} \]

Thus, lifting 5 pounds to a height of 5 feet will constitute 25 foot-pounds of work. Pushing an object horizontally for a distance of 5 feet and applying 5 pounds of constant pushing force throughout this distance will also result in 25 foot-pounds of work. In the case of the metric system, if an individual weighed 80 kilograms and climbed up to stand on a 3 meter diving board, he would have performed 80 kilograms times 3 meters, or 240 kilogram-meters of work.

The physicist's definition of work is unsatisfactory and unfair from the standpoint of the horizontal position - he is not doing any work, since the distance is zero, yet he quickly gets fatigued. It is common to express this as static or isometric work.

When a muscle shortens whilst performing work against a constant load, the contraction is described as isotonic. It is a straightforward matter
to calculate the external work performed and the power exerted. When a muscle shortens as it develops tension, the work is said to be concentric. When a muscle lengthens at a controlled rate activity resting the lengthening tension, the work is said to be eccentric. Lowering a weight with forearm at a slow controlled speed is an example of eccentric work of biceps allowing extension of the elbow. The work performed in this case is called negative work, whereas lifting against gravity is positive work.

When a muscle contracts and generates a force which does not produce any shortening of it, or movement at the joint is involved, the contraction is described as isometric (same length). In this case the work performed is the development of force and its maintenance for the duration of the contraction. No external physical work is performed and the energy balance is impossible to study.

Since work rate combines three factors into one, namely, load, distance, time or speed, it is possible to do work by muscles only and it will require oxygen to maintain its continuity. Oxygen will be supplied by haemoglobin of the blood. The need of $O_2$, however, will vary with the changes in the organic constituents like glycogen and lactic acid and it has got a definite quantitative relation according to chemical reactions. On the basis of this need a definite amount of haemoglobin can supply the requisite amount of oxygen. The increment of haemoglobin requirement can be maintained by the activity of heart.

Muscular exercise calls for an integrated action of many functions, any one of these may become limiting in the work capacity complex. Maximal $O_2$ consumption, maximal pulmonary ventilation, rapidity of functional adjustment
from rest to work and from work to rest are good capacity indices. The $O_2$ consumption per heart beat per unit weight ($O_2$ pulse per unit weight) is taken as the index of work capacity applicable to man regardless of the body weight.

In recent years investigations of exercise have concentrated on processes in the cell and on physiological systems involved in controls (Chapman and Mitchell, 1965). In order to ensure an adequate oxygen supply for the working muscle cell the body must coordinate the interaction of the lungs, the blood, the heart and the circulatory system and, finally, the muscle cell itself.

3. RELATION BETWEEN EXERCISE AND B VITAMINS (THIAMINE, RIBOFLAVIN AND PYRIDOXINE)

It has been said that an athlete is no better than the adequacy of his nutrition. But a balanced diet alone cannot compensate for poor skill development and training. Diet, conditioning and training should be regarded as mutually complementary. Manipulating the diet and taking extra quantities of various vitamins and minerals seem to be a relatively harmless method to make the body at its best.

Vitamins are essential for normal body function. Unfortunately, athletes have no way to judge their vitamin level until they become deficient when the rather unpleasant symptoms appear. A number of studies have found, on the other hand, increased endurance with megadoses of vitamin C, E and B complex.

The practice of vitamin supplementation has long been popular among athletes. However, few controlled studies have been conducted on athletes to assess the vitamin needs and the effects of supplementation. It is an established fact that the vitamin needs can increase a great deal in active
athletes. That men doing hard physical labour needed adequate daily intake of thiamine and probably of the whole of B complex vitamins to maintain fitness was pointed out by Johnson and coworkers back in 1942. Corroboration came also from experiments on effects of diets deficient in thiamine (vitamin B₁), or low in B complex generally but otherwise adequate. Egana and coworkers (1942) noted that such diets produced in healthy subjects symptoms like fatigue, loss of ambition and efficiency in daily work within a period of four weeks. Several other workers have also reported that vitamin requirements of an individual might increase several times in severe exercise (Bicknell and Prescott, 1945; Bourne, 1948; Bro-Rasmussen, 1958; Tucker et al, 1960; Souberlich et al, 1970; Belko et al, 1983; Vander Beek, 1991).

In view of the above it seems natural that a lot of discussion goes on at present on whether or not supplementation of additional vitamins, especially of B complex vitamins (thiamine, riboflavin and pyridoxine), has beneficial effects in exercise and sports.

Different groups of workers have studied the role of vitamins B₁, B₂ and B₆, individually and in combination, in athletic performance. Gounelle (1940) and McCormick (1940) reported that supplementation of diet with vitamin B₁ improved the performance of cyclists and swimmers respectively. Bacinskij (1959) made the observation that persons taking physical exercise needed extra vitamin C and probably extra vitamin B₁ also. From a study of effects of vitamins on physical performance including swimming, Maksjutinskaja et al (1967) favoured supplementation of additional vitamins A, B₁, B₂, B₆ and C for improvement of performance. An increase of performance by 3% due to application of vitamin B₁, B₂ and B₆ was observed by Van Dam (1978) in a study on high performance fencers.
To assist in correcting deficiency in vitamin B₁, PP, and C in topclass athletes, Podorozhnyi and coworkers (1979) suggested some dosages of the vitamins and duration of administration. Buskrik and Hayness (1981) noted that B vitamins had become extremely popular with athletes for improving endurance, strength and recovery from fatigue. The findings of Vander Beek et al (1988) that a combined restricted intake of vitamins B₁, B₂, B₆ and C resulted in decrease in physical performance were also a confirmation of the beneficial role of these vitamins in physical performance. Bhatia (1989) observed that nutrition supplements could become a promising tool in optimizing performance of men required to do heavy physical and mental work.

There is evidence that supplementation of vitamins has effects also on cardio-respiratory functions. Harper et al (1943) found that mixed vitamin supplementation increased the vital capacity, breath holding time and endurance time of a group of military cadets. Chatterjee and coworkers (1978) observed an improvement of the working capacity and endurance time in terms of $V_O^{2\text{max}}$ of athletes who were supplemented with vitamin B₁ one hour before exercise. Increase of maximal aerobic power by 6% of trained subjects supplemented with pyridoxine and α-ketoglutarate was recorded by Marconi et al (1982). Tremblay and coworkers (1984), however, from their experiments with some top swimmers, concluded that riboflavin supplementation did not affect the performance of swimmers. Vander Beek and coworkers (1988), on the other hand, observed decrease of aerobic power by about 9.8% due to restricted intake of vitamins B₁, B₂, B₆ and C.

These roles of B vitamins in exercise performance are related to the specific metabolic roles of these vitamins, especially their highly specific
roles as micronutrients in facilitating energy transfer. In general, B vitamins are essential in metabolism of carbohydrates and amino acids, the formation of active acetate, the synthesis of fatty acids and the formation of nucleic acids for RNA and DNA.

Vitamin B₁ (thiamine) is, in its physiologically active form, the co-carboxylase which is essential for the breakdown of dextrose and is thus of great significance for any endurance performance with caloric demands.

Vitamin B₂ (riboflavin) functions among other forms in FAD, a part of many hydrogen transferring enzyme. The B₂ need mainly increases with fatty nutrition, because of the participation of FAD in the catabolism of fatty acids.

Vitamin B₆ (pyridoxine or other forms) is concerned with the metabolism of amino acids. It acts as a co-enzyme of transaminases. Increase of protein intake always implies increased B₆ need.

It is well-known also that vitamin B₁ is concerned with decarboxylation and carboxylation of pyruvic acid which is one of the intermediary degradation products of carbohydrate metabolism. This accounts for the fact that maximal work output and mechanical efficiency are the most sensitive indices of decrease in dietary thiamine. Horvitt et al (1948) found that administration of thiamine decreased the lactic acid concentration in blood after exercise. They showed that in endurance exercises thiamine pyrophosphate was the rate limiting enzyme.

In experimental studies on B vitamins deficient states and on effects of supplementation of B vitamins on physical performance, blood lactic acid and
blood pyruvic acid concentrations have been used as biochemical indices. Increase in the concentrations of pyruvic and lactic acid in the blood has been observed particularly after exercise and administration of glucose (Beaton and McHenry, 1964). Williams and Wilder (1950) found that the levels obtained 30 minutes after administration of glucose were most informative. From evidence of increased blood pyruvic acid following exercise, Vitchikova (1958) suggested that thiamine content should be increased in the rations of athletes. A study by Marconi et al. (1982) showed that lactate accumulation in blood after short supramaximal workloads decreased following daily administration of pyridoxine and α-ketoglutarate. But pyridoxine alone did not cause such effects. But riboflavin supplementation to a group of swimmers, Tremblay et al. (1984) pointed out, did not affect the biochemical indices. In concluding that thiamine appeared to be an effective physiological support for the endurance athletes, Knippel et al. (1986) also employed blood lactate level as a biochemical index to study the effects of thiamine supplementation in competitive cyclists. Decrease in onset of blood accumulation as a result of combined restriction of vitamins B₁, B₂, B₆ and C was observed also by Vander Beek et al. (1988).
REFERENCES


