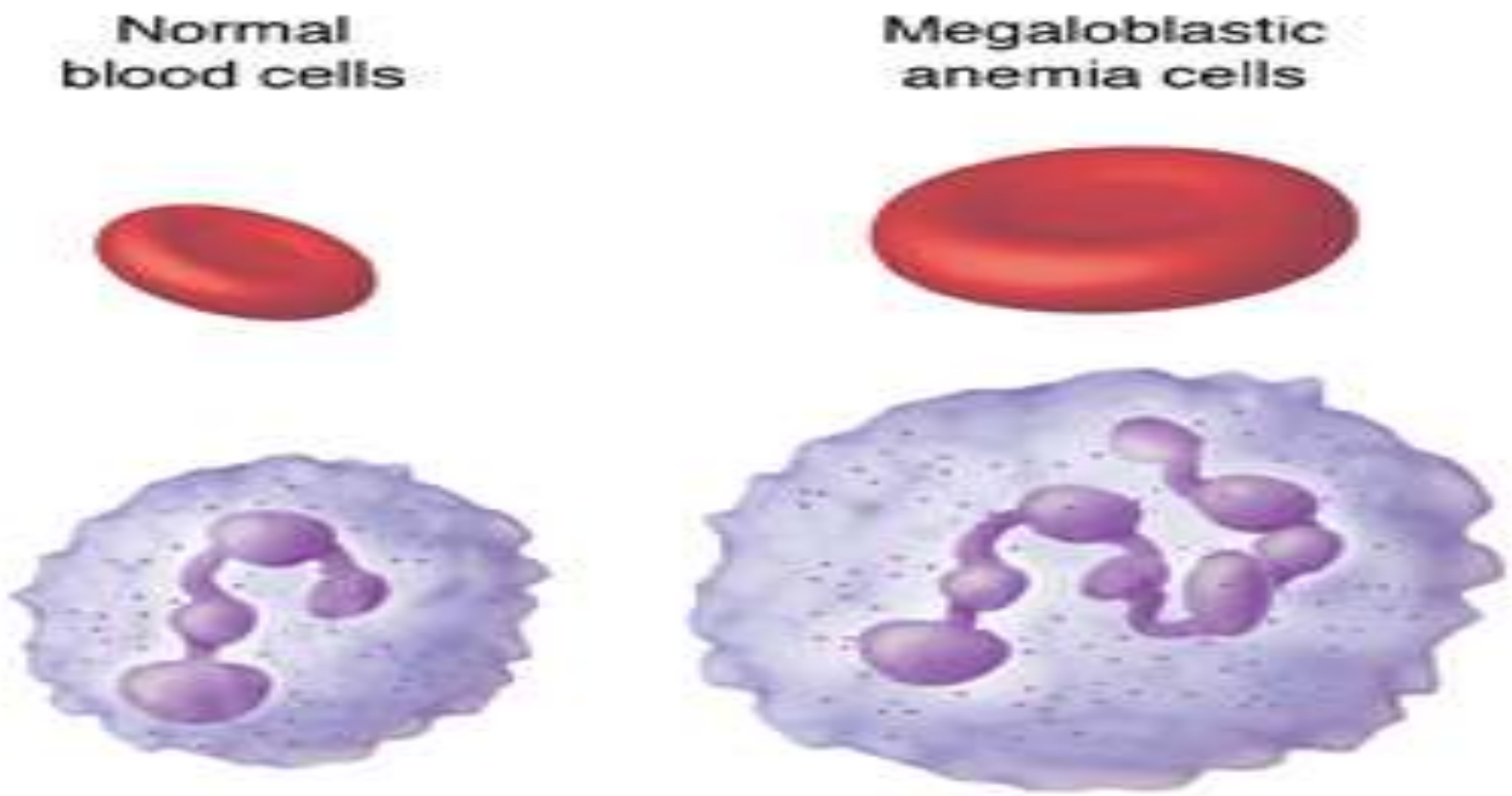
MEGALOBLASTIC ANAEMIA



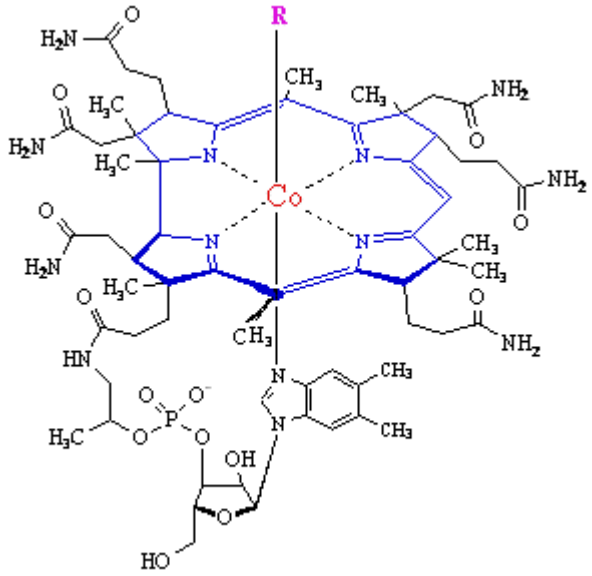
INTRODUCTION

The megaloblastic anaemias are disorders **caused by impaired DNA synthesis** and are characterised by a distinctive abnormality in the haematopoietic precursors in the bone marrow in which the maturation of the nucleus is delayed relative to that of the cytoplasm.

The underlying defect for the asynchronous maturation of the nucleus is defective DNA synthesis due to **deficiency of vitamin B12 (cobalamin) and/or folic acid (folate).** Less common causes are interference with DNA synthesis by congenital or acquired abnormalities of vitamin B12 or folic acid metabolism.

VITAMIN B12

- Vitamin B12 or cobalamin is a **complex organometallic compound** having a cobalt atom situated within a corrin ring.
- In humans, there are 2 metabolically active forms of **cobalamin—methylcobalamin and adenosyl-cobalamin**, which act as coenzymes. The therapeutic vitamin B12 preparation is called **cyanocobalamin**.
- The only dietary sources of vitamin B12 are foods of animal protein origin such as kidney, liver, heart, muscle meats, fish, eggs, cheese and milk.
- The average daily requirement for vitamin B12 is **2-4 µg.**

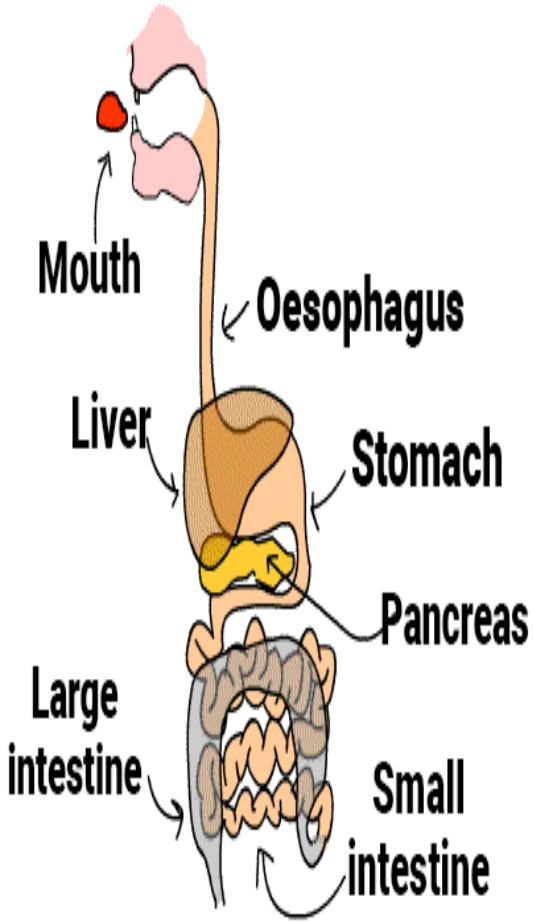


Ingestion

Vit B12 is released

Stable complex with R- binder

In duodenum vitB12-R binder digested

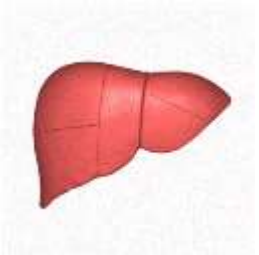


Released vit B12 binds to IF

In distal ileum vit B12-IF complex binds to specific receptors on mucosal brush border

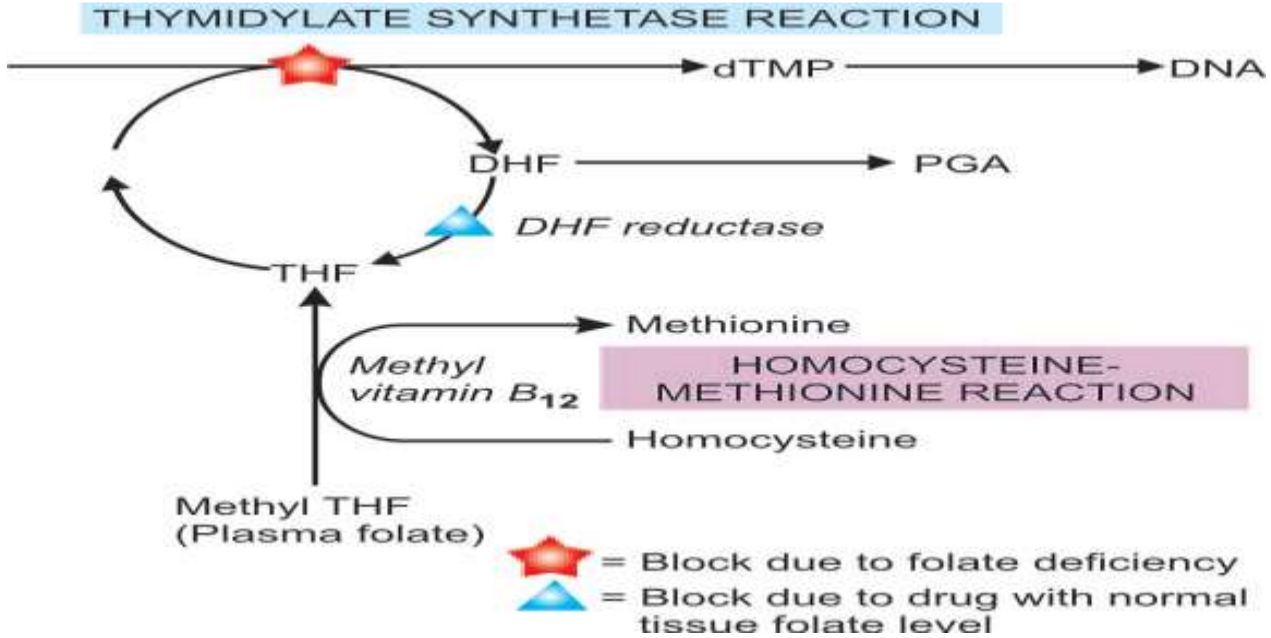
Vitamin is absorbed

- The **liver is the principal storage site** of vitamin B12 and stores about 2 mg of the vitamin, while other tissues like kidney, heart and brain together store about 2 mg.



- The body stores of vitamin B12 are adequate for **2-4 years**.
- Major source of loss is via bile and shedding of intestinal epithelial cells. A major part of the excreted vitamin B12 is reabsorbed in the ileum by the IF resulting in enterohepatic circulation.
- Vitamin B12 plays an important role in general **cell metabolism, particulary essential for normal haematopoiesis and for maintenance of integrity of the nervous system**.
- Vitamin B12 acts as a co-enzyme for 2 main biochemical reactions in the body:

- Firstly, as methyl cobalamin (methyl B12) in the **methylation of homocysteine** to methionine by methyl tetrahydrofolate (THF).

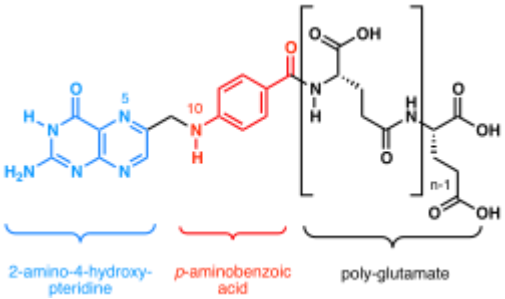


- Secondly, as adenosyl cobalamin (adenosyl B12) in propionate metabolism for **the conversion of methyl malonyl co-enzyme A to succinyl co-enzyme A**:

Adenosyl B12

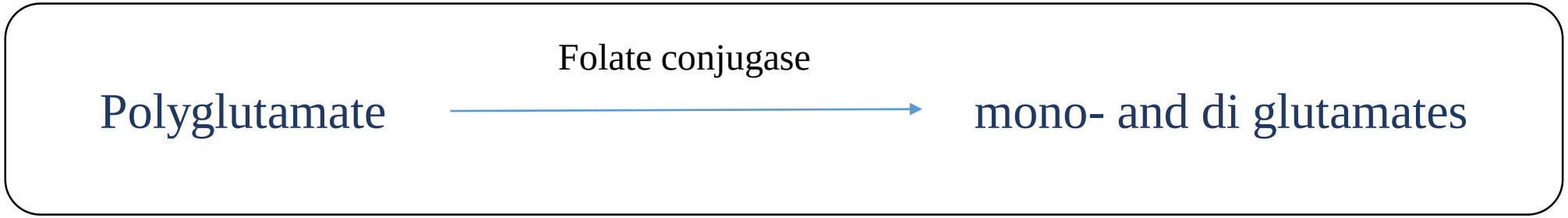
Propionyl CoA → Methyl malonyl CoA → Succinyl CoA

FOLIC ACID



- Folate or folic acid, a yellow compound, is **a member of water-soluble B complex vitamins** with the chemical name of **pteroyl glutamic acid (PGA).**
- Folic acid does not exist as such in nature but exists as folates in polyglutamate form (conjugated folates). For its metabolic action as co-enzyme, polyglutamates must be reduced to **dihydro- and tetrahydrofolate forms.**
- Folate exists in different plants, bacteria and animal tissues.
- Dietary sources are fresh green leafy vegetables, fruits, liver, kidney, and to a lesser extent, muscle meats, cereals and milk.
- Humans are mainly **dependent upon diet** for its supply.
- The average daily requirement is **100-200 µg**.

- Folate is normally absorbed from the duodenum and upper jejunum.
- Absorption depends upon the form of folate in the diet.
- Polyglutamate form in the foodstuffs is first cleaved by the enzyme, folate conjugase, in the mucosal cells to mono- and diglutamates which are readily assimilated.



- Synthetic folic acid preparations in polyglutamate form are also absorbed as rapidly as mono- and diglutamate form because of the absence of natural inhibitors.

- Mono- and diglutamates undergo further reduction in the mucosal cells to form tetrahydrofolate (THF), a monoglutamate.
- THF circulates in the plasma as methylated compound, methyl THF, bound to a protein. Once methyl THF is transported into the cell by a carrier protein, it is reconverted to polyglutamate.
- The **liver and red cells** are the main storage sites of folate, largely as methyl THF polyglutamate form.
- The total body stores of folate are about **10-12 mg enough for about 4 months.**

Folate plays an essential role in cellular metabolism. It acts as a co-enzyme for 2 important biochemical reactions involving transfer of 1-carbon units (viz. methyl and formyl groups) to various other compounds.

- **Thymidylate synthetase reaction.**

Formation of deoxy thymidylate monophosphate (dTMP) from its precursor form, deoxy uridylate monophosphate (dUMP).

Methylation of homocysteine to methionine.

This reaction is linked to vitamin B12 metabolism.

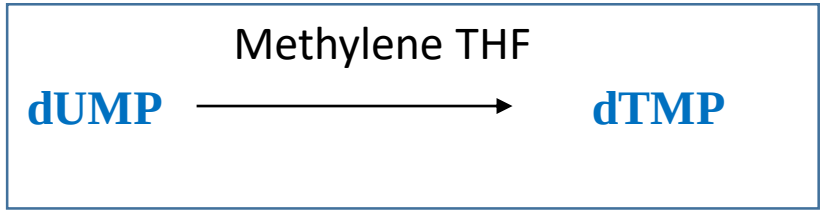
BIOCHEMICAL BASIS OF MEGALOBLASTIC ANAEMIA

The basic biochemical abnormality is a **block in the pathway of DNA synthesis** and that there is an inter-relationship between vitamin B12 and folate metabolism in the methylation reaction of homocysteine to methionine.

Folate as co-enzyme methylene THF, is required for transfer of 1-carbon moieties (e.g. methyl and formyl) to form building blocks in DNA synthesis. These 1-carbon moieties are derived from serine or formiminoglutamic acid (FIGLU).

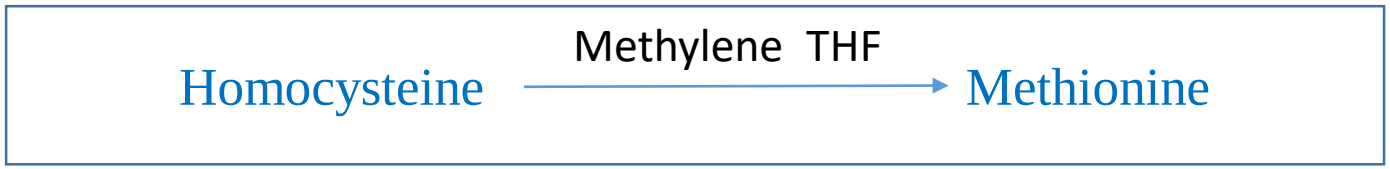
Two of the important folatedependent (1-carbon transfer) reactions for formation of building blocks in DNA synthesis are,

1. **Thymidylate synthetase reaction.**



After the transfer of 1-carbon from methylene-THF, dihydrofolate (DHF) is produced which must be reduced to active THF by the enzyme DHF-reductase before it can participate in further 1-carbon transfer reaction. Drugs like methotrexate (anti-cancer) and pyrimethamine (antimalarial) are inhibitory to the enzyme, DHF-reductase, thereby inhibiting the DNA synthesis.

2. Homocysteine-methionine reaction.



After transfer of 1-carbon from methylene- THF, THF is produced. This reaction requires the presence of **vitamin B12 (methyl-B12).**

Deficiency of folate from any cause results in reduced supply of the coenzyme, methylene-THF, and thus interferes with the synthesis of DNA.

Deficiency of vitamin B12 traps folate as its transport form, methyl-THF, thereby resulting in reduced formation of the active form, methylene-THF, needed for DNA synthesis. This is referred to as ***methyl-folate trap hypothesis.*** An alternative hypothesis of inter-relationship of B12 and folate is the ***formate-saturation hypothesis***. According to this hypothesis, the active substrate is **formyl-THF.** Vitamin B12 deficiency results in reduced supply of formate to THF causing reduced generation of the active compound, formyl THF.

ETIOLOGY

I. VITAMIN B12 DEFICIENCY

A. Inadequate dietary intake e.g. strict vegetarians, breast-fed infants.

B. Malabsorption

1. Gastric causes: pernicious anaemia, gastrectomy, congenital lack of intrinsic factor.

2. Intestinal causes: tropical sprue, ileal resection, Crohn's disease, intestinal blind loop syndrome,

fish-tapeworm infestation.

II. FOLATE DEFICIENCY

A. Inadequate dietary intake e.g. in alcoholics, teenagers, infants, old age, poverty.

B. Malabsorption e.g. in tropical sprue, coeliac disease, partial gastrectomy, jejunal resection, Crohn's disease.

C. Excess demand

1. Physiological: pregnancy, lactation, infancy.

2. Pathological : malignancy, increased haematopoiesis, chronic exfoliative skin disorders, tuberculosis, rheumatoid arthritis.

D. Excess urinary folate loss e.g. in active liver disease, congestive heart failure.

III. OTHER CAUSES

A. Impaired metabolism e.g. inhibitors of dihydrofolate (DHF) reductase such as methotrexate and pyrimethamine; alcohol, congenital enzyme deficiencies.

B. Unknown etiology e.g. in Di Guglielmo’s syndrome, congenital dyserythropoietic anaemia, refractory megaloblastic anaemia.

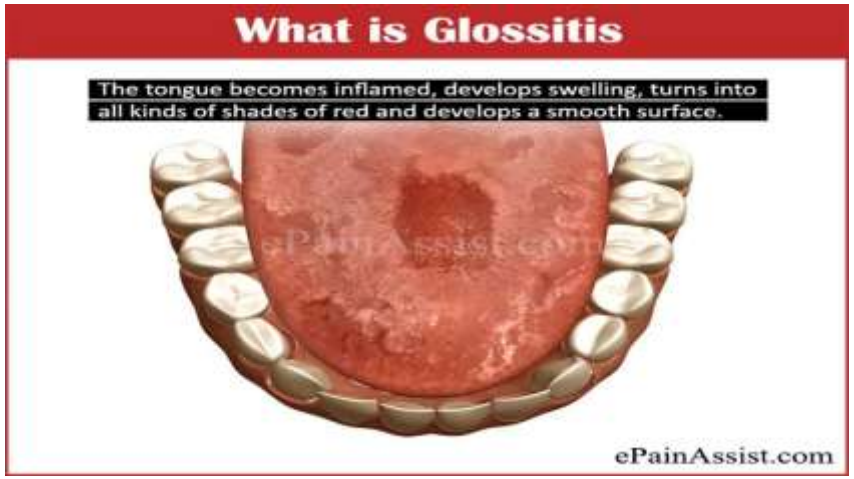
CLINICAL FEATURES

The following clinical manifestations which may be present singly or in combination and in varying severity:

1. Anaemia

Macrocytic megaloblastic anaemia is the cardinal feature of deficiency of vitamin B12 and/or folate.

The onset of anaemia is usually insidious and gradually progressive.



2. Glossitis

Typically, the patient has a smooth, beefy, red tongue.

3. Neurologic manifestations

Vitamin B12 deficiency, particularly in patients of pernicious anaemia, is associated with significant neurological manifestations in the form of subacute combined, degeneration of the spinal cord and peripheral neuropathy while folate deficiency may occasionally develop neuropathy only.

Signs and symptoms include numbness, paraesthesia, weakness, ataxia, poor finger coordination and diminished reflexes.

DIAGNOSIS

Same as for IDA

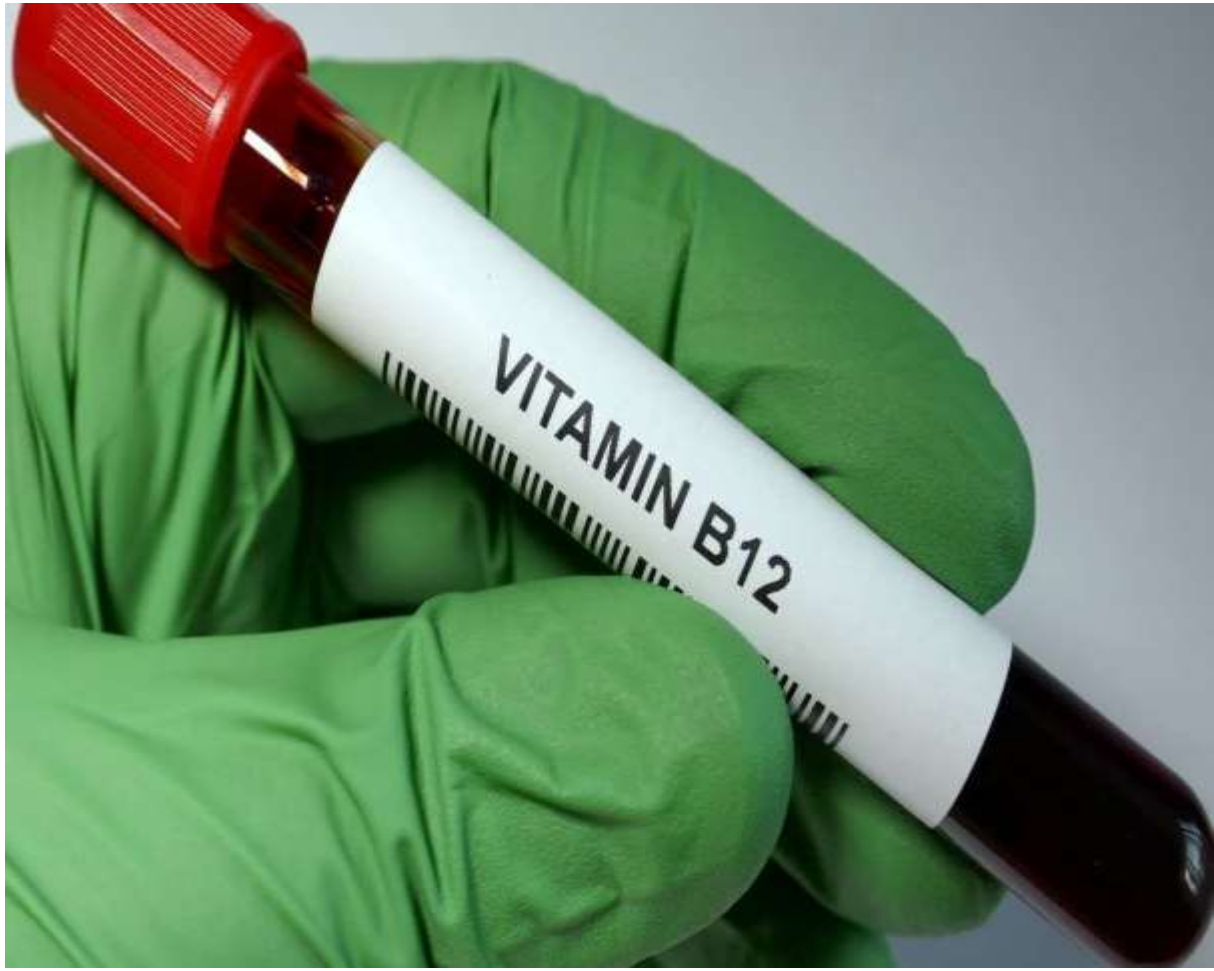
Specific tests to determine vit B12 and folic acid deficiency

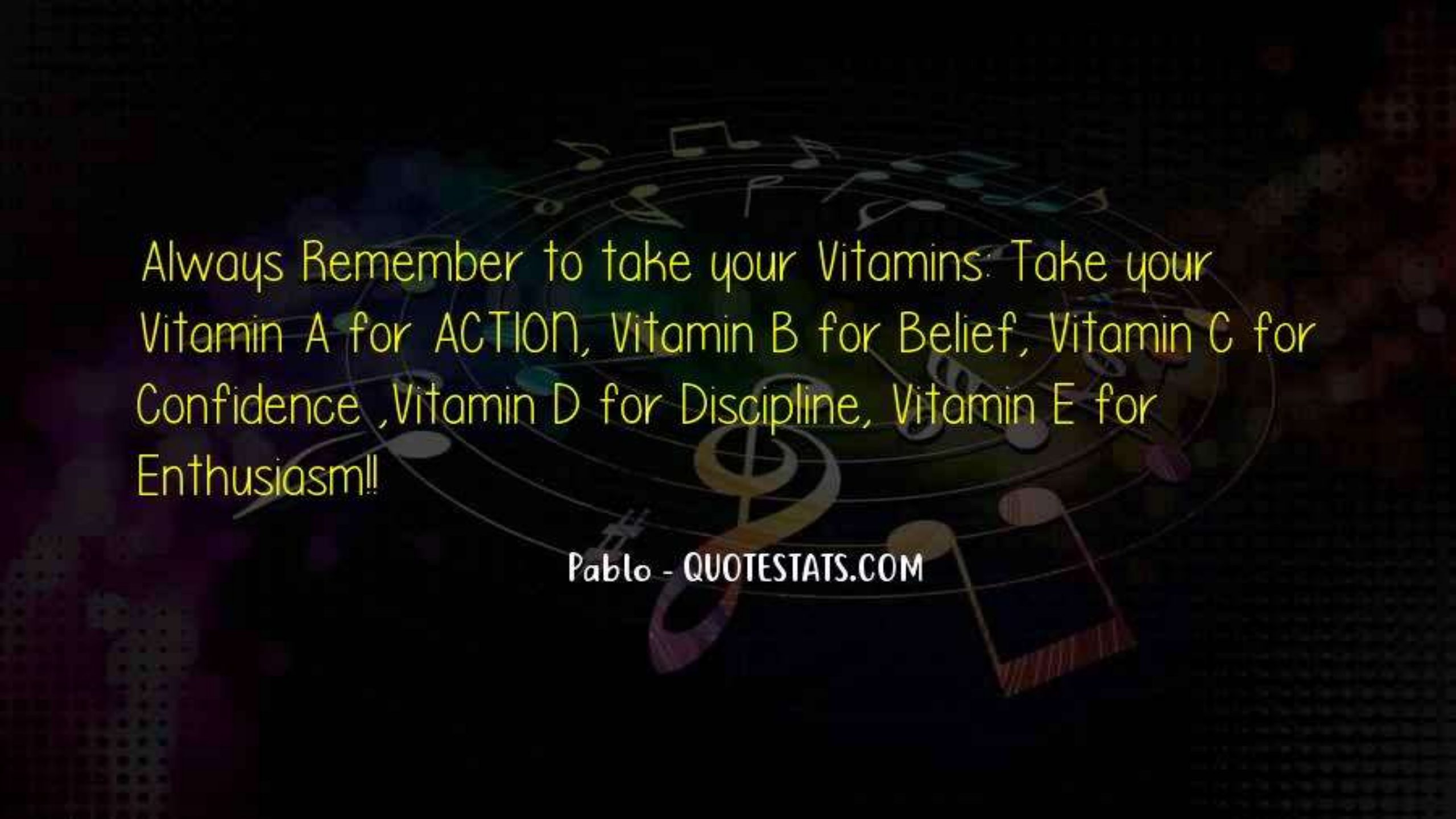
Vitamin B12 deficiency

1. Serum vit B12 assay
2. Schilling test
3. Serum enzyme levels

Folic acid deficiency

1. Urinary excretion of FIGLU
2. Serum folate assay
3. Red cell folate assay




Always Remember to take your Vitamins: Take your Vitamin A for ACTION, Vitamin B for Belief, Vitamin C for Confidence ,Vitamin D for Discipline, Vitamin E for Enthusiasm!!
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THANK YOU