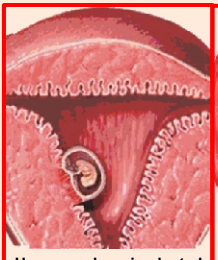
VITAMIN B-12 AND FOLIC ACID

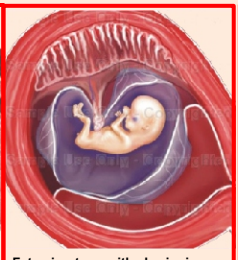
"Halal Nutritional Center Discovers Halal Vitamin B-12 And Folic Acid"

THEY ARE ESSENTIAL FOR THE GROWTH AND DEVELOPMENT OF ALL THE STAGES OF HUMAN LIFE CYCLE[1]

Pregnant Women

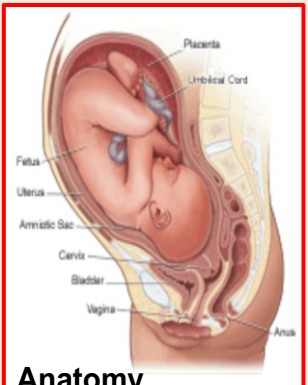


Human embryo implanted in the uterine wall in the early stages of pregnancy.



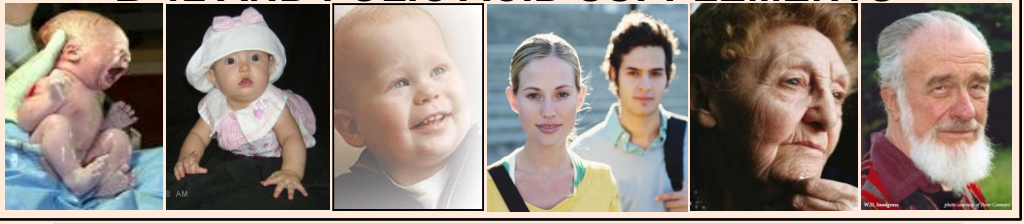
Fetus in-utero, with chorionic sac, villi, cavity and amniotic fluid containing a human embryo in the ninth week of fetal development.

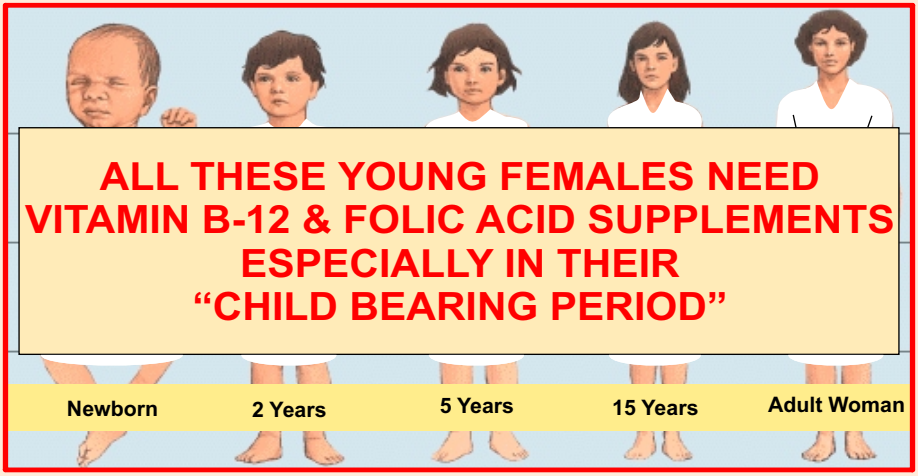
STAGES OF IN-UTERO GROWTH & DEVELOPMENT NEEDING VITAMIN B-12 & FOLIC ACID[2].



Anatomy of the fetus in-utero

DIFFERENT STAGES OF LIFE NEEDING VITAMIN B-12 AND FOLIC ACID SUPPLEMENTS





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Halal nutrition Center (HNC) is established with a mission to revolutionize production process of dietary supplements & off the counter vitamins. We value the importance of Halal quality products. That's why we have invested heavily in quality control system. We make sure that all the ingredients & materials are from vegetable, fish & or Halal bovine sources.

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This manuscript on the role of Vitamin B-12 and Folic acid & the affects of their deficiency is especially prepared for the guidance of General Physicians; Pediatricians & Pediatric Surgeons; Plastic and Reconstruction Surgeons; Gynaecologists; Hematologists; Biochemists; Neuropsychiatrists; Cardiologlsts & Cardiac Surgeons.

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HNC RE-DISCOVERS

FOLIC ACID
VITAMIN B-12

FOLIC ACID & VITAMIN B-12

MOVE ON THE FRONT FOOT

NO → FOLIC ACID VITAMIN B-12 → NO MITOSIS NO DNA SYNTHESIS NO CELLS DIVISION → NO GROWTH NO DEVELOPMENT

IMPORTANCE OF VITAMIN B-12 AND FOLIC ACID

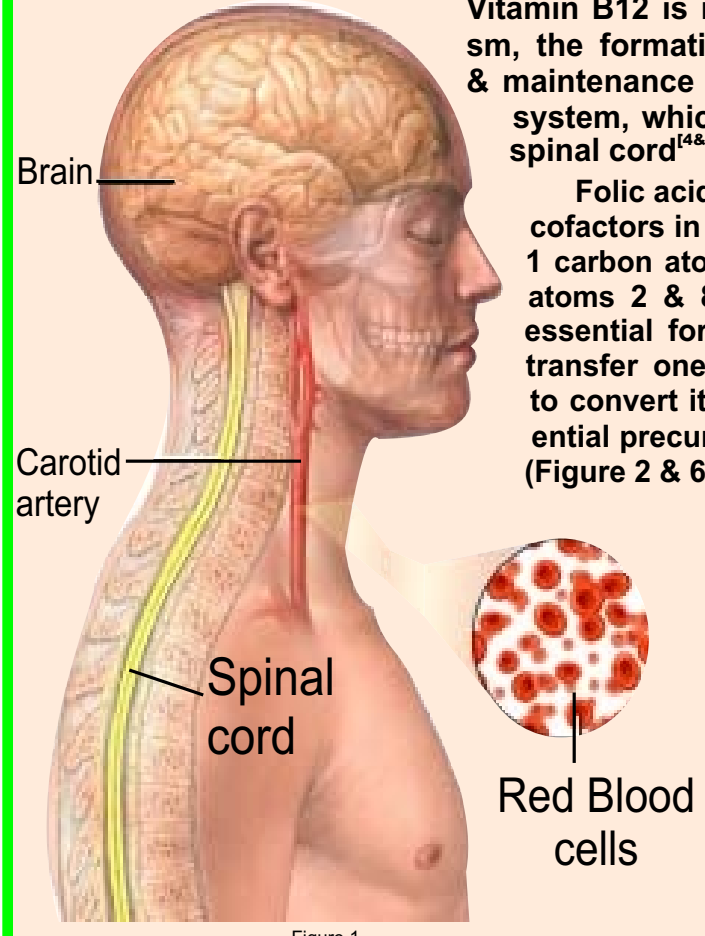


Figure 1

Vitamin B12 is important for metabolism, the formation of red blood cells, & maintenance of the central nervous system, which includes the brain & spinal cord[4&5].(Figure 1)

Folic acid[5] is changed to 2 folate cofactors in the body which transfer 1 carbon atom each to make carbon atoms 2 & 8 of purine heterocycle essential for DNA synthesis & also transfer one carbon atom to dUMP to convert it to dTMP which is essential precursor for DNA synthesis. (Figure 2 & 6)

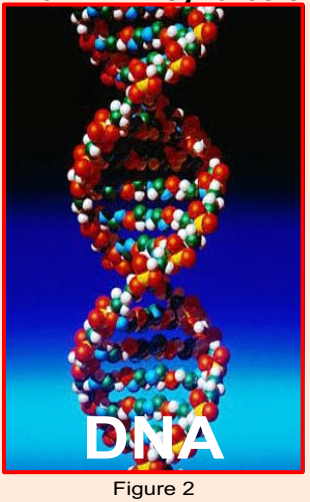
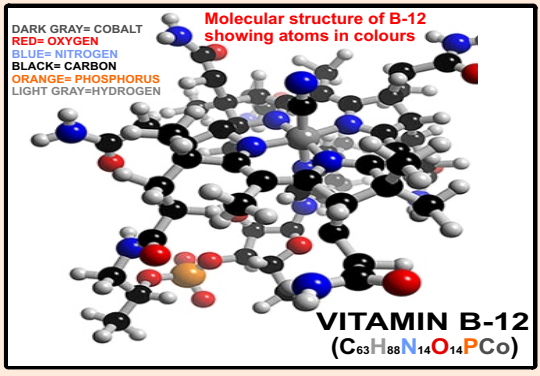


Figure 2

VITAMIN B-12 AND FOLIC ACID ARE ESSENTIAL VITAMINS FOR NORMAL GROWTH AND DEVELOPMENT AS THEY PROMOTE MITOSIS, DNA SYNTHESIS & MATURATION OF CELLS.



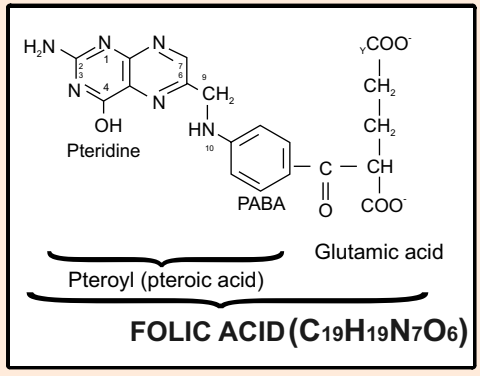


Figure 3 shows the molecular structures and chemical formulae of Vitamin B-12 and Folic acid.

BOTH VITAMIN B-12 & FOLIC ACID ARE ESSENTIAL FOR THE DIFFERENT PHASES OF GROWTH OF HUMAN LIFE.

1. **Vitamin B-12 & folic acid are needed for normal mitosis, normal DNA & protein synthesis to achieve the normal production, maturation & function of cells, which are basic steps for growth and Development[4&5].**

2. **Vitamin B-12 & folic acid are needed most in tissues where cells undergo rapid cell division, such as the bone marrow & the gastro-intestinal tract epithelium.**

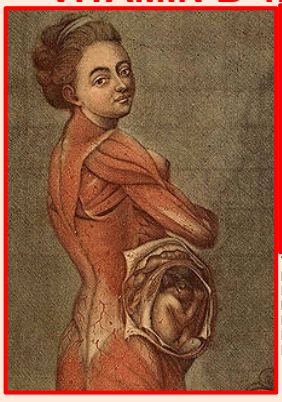
3. **Vitamin B12 and folic acid are essential for the synthesis of normal fatty acids which incorporate in synthesis of myeline sheath and the membranes of cells of central nervous system. In case of their deficiency the substrate methylmalonyl Co. A (MMA) accumulates in the body and damages both myeline sheath and CNS cells[6].**

4. **The Succinyl Co. A which is produced by the action of Vitamin B-12 and enzyme methymalonyl Co. A Mutase on MMA, is an important metabolic step for the extraction of energy from protein and fats and is involved in beta oxidation of fatty acids.**

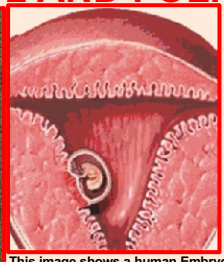
5. **During pregnancy, Vitamin B-12 and folic acid are essential for the cells of the embryo and fetus which are rapidly dividing and becoming the infant's muscles, bones, and organs. The growth and development of the normal perinatal life will require, normal DNA synthesis, mitosis, normal cells maturation & proportionate Development of both nucleous and cytoplasm[7&12].**

THE ABOVE ROLES OF B-12 & FOLIC ACID WILL BE BETTER UNDERSTOOD AFTER WE DISCUSS THEIR PHARMACODYNEMICS.

THE FOLLOWING IMAGES SHOW THAT THE WHOLE CYCLE OF HUMAN LIFE IS DEPENDANT ON VITAMIN B-12 AND FOLIC ACID[8 & 12] (FIGURE 8,9,10)



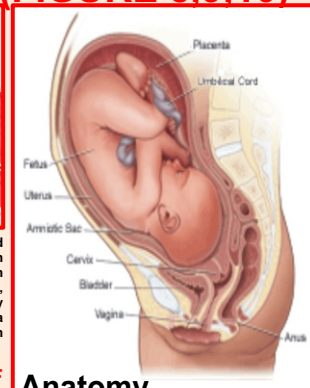
Pregnant Women



This image shows a human Embryo Implanted in the Uterine wall in the Early Stages of pregnancy. Updated by: Melanie N. Smith, M.D., Ph.D., Dept. of Obstetrics & Gynecology, Brigham and Women, Hospital, Boston, MA. USA.

Embryology Nine (9) Week Old Fetus in Utero, This illustration features a side cut view through the uterus, Chorionic villi, chorionic sac, choroinic cavity and amniotic sac containing a human embryo in the ninth week of fetal development.

FIGURE 8 SHOWS: DIFFERENT STAGES OF IN-UTERO GROWTH & DEVELOPMENT NEEDING VITAMIN B-12 AND FOLIC ACID.



Anatomy of the fetus inutero

DIFFERENT STAGES OF LIFE

FIGURE 9 shows different stages of human life

They all need Vitamin B-12 & Folic acid Supplements for their growth & development. In old age 30% of people over 70 need Supplements of Vitamin B-12 and Folic acid[9 & 25].

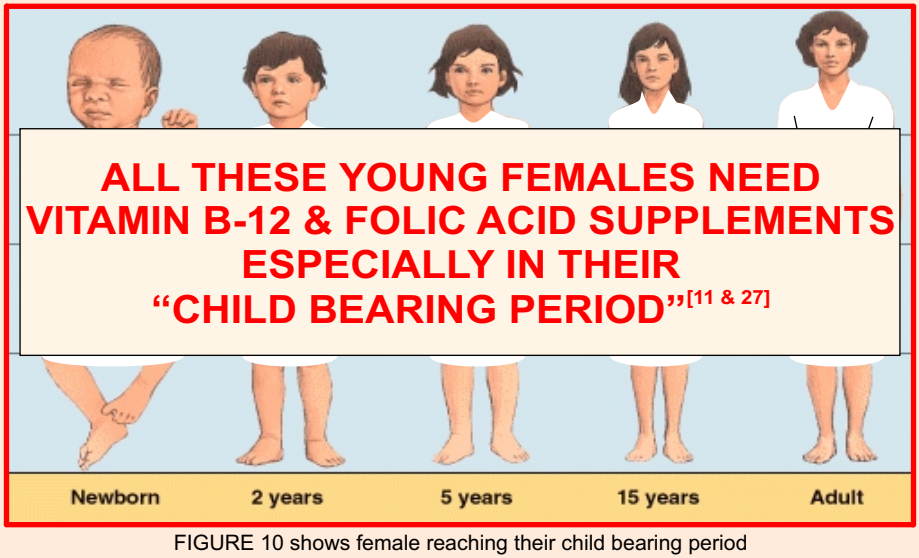


FIGURE 10 shows female reaching their child bearing period

PHARMACODYNAMICS[5] OF VITAMIN B-12 & FOLIC ACID

Reader should keep in mind the followings :

1. Many of the affects of deficiency of Vitamin B-12 can be replaced by sufficient quantities of folic acid (another B vitamin), but B-12 is necessary to regenerate folate in the body.
2. Most "B-12 deficient symptoms" are actually folate deficient symptoms, since they include all the effects of pernicious anemia and megaloblastosis. These are due to the poor synthesis of DNA, when the body lacks proper supply of folic acid for the production of thymine.
3. When sufficient folic acid is available, all known B-12 related deficiency syndromes normalize, except the 2 reactions narrowly connected with the B-12 dependent following coenzymes.

A) Methylmalonyl coenzyme A mutase (MUT) enzyme is narrowly dependent & connected with vitamin B-12 which is in adenosylcobalamine form of vitamin B-12, & there is the built up of the respective substrate methylmalonic acid (MMA) in case of deficiency of vitamin B-12. This is an important step in the extraction of energy from proteins & fats.

B) 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), also known as methionine synthatase; and there is the build up of the respective substrates homocysteine in case of deficiency of vitamin B-12.

In both A & B, the two vitamin B-12 enzymes serve as cofactors for 2 important reactions in humans. In both of these reactions, coenzyme B-12's reactive C-Co (carbon-cobalt) bond participates in these enzyme-catalyzed reactions:-

PHARMACODYNAMICS OF VITAMIN B12

THE VITAMIN B-12 HAS 2 ULTIMATE ROLES IN THE CELLULAR METABOLISM[10]:

A. In its first role the vitamin B-12 causes conversion of:

Deoxyadenosylcobalamine(B-12)
L-Methylmalonyl -Co. A ---------- Succinyl Co. A
Enzyme methyl malonyl Coenzyme A Mutase (MUT)

(FIGURE 4.)

Normally L. Methylmalonyl Co. A (MMA) is converted to Succinyl Co. A in the presence of cofactor of (B-12) Deoxyadenosylcbalamine and enzyme methyl -malonyl Co. A Mutase.

In Vitamin B-12 deficiency this conversion does not take place and it results into 2 things:

1). Succinyl Co. A is not formed. This is an important step in the extraction of energy from protein and fat, and is involved in beta oxidation of fatty acids in the mitochondria.
2). The substrate MMA is not converted to Succinyl Co. A and accumulates in the body and It's urinary excretion as methylmalonic acid (MMA) provides a means of assessing vitamin B-12 nutritional status. MMA elevation is seen in 90 – 98% of vitamin B 12 deficient people. It is elevated in 25-33% of people over 70 years of age[13]. For this reason MMA test is not recommended in old people. The "gold standard" test for vitamin B-12 deficiency continues to be low blood levels of the vitamin.

Methylmalonyl Co. A (MMA)

May produce following damage to the body:-

a). The MMA is myelin destabilizer and it destabilizes the myeline sheath.
b). Excessive MMA will prevent normal fatty acids synthesis and may form abnormal fatty acids. If these abnormal fatty acids are incorporated into myelin sheath, the myelin sheath will be too fragile and demyelinization will occur. This results in subacute combined degeneration of central nervous system, both brain and spinal cord[14 &15].
c). These fatty acids are also incorporated in the membrane of cells making central nervous system, thus they result in the neurological manifestations of vitamin B-12 (Table 1).
d). Vitamin B 12 deficiency causes neuropathies, even if folic acid is present.

B) In its 2nd role, the vitamin B-12[16] in the presence of cofactor 5-methyl-tetrahydrofolatehomocysteine methyl transferase(MTR) causes conversion of:

a). 5-CH_3-H_4 folate (inactive form) ⟶ H_4 folate (precursor folate cofactor)

b). Homocysteine ⟶ Methionine

Cofactor (enzyme) (5-CH_3-H_4 folate homocysteine methyl transferase)

OR

5 methyl tetra hydrofolate homocysteine methyl transferase (MTR)
also known as (methionine synthetase))

a). CH_3-tetrahydrofolate(inactive form) (5-CH_3-H_4 folate) ⟶ tetrahydrofolate(active form of folic acid)

b). Homocysteine ⟶ Methionine

B12 (methylcobalamine) is a cofactor

(Cobalamine and methylcobalamine are interconverted in this reaction)

FIGURE 5.

This reaction transfers the methyl group of 5- CH_3-tetrahydrofolate to homocysteine.

As a results of this reaction two things happen:-

(i). Homocysteine + methyl group from CH_3-tetrahydrofolate make Methionine.

(ii). The methyltetrahydrofolate (the inactive form of folic acid, after giving CH_3 group) becomes tetrahydrofolate (the active form of folic acid).

Normally Methyltetrahydrofolate homocysteine methyl transferase (MTR) also known as Methionine synthetase, in the presence of B12 cofactor methylcobalamine, converts CH_3-tetrahydrofolate (inactive form) to tetrahydrofolate(active form of folic acid). The homocysteine is also converted to methionine.

In the deficiency of vitamin B-12[17 &18], both of the reactions do not take place & result into:

a). The substrate CH_3-tetrahydrofolate will not change to tetrahydrofolate and deficiency of folate cofactor necessary for DNA synthesis develops. The accumulation of the body's folate as 5-CH_3-H_4folate and the associated inability to form folate cofactor in vitamin B- 12 deficiency have been referred to as the "methyl folate trap". This is the step whereby vitamin B-12 and folic acid metabolism are linked together and also explain why the megaloblastic anemia of vitamin B-12 deficiency can be partially corrected by folic acid.

b). In addition the homocysteine is accumulated in the body because it is not converted to methionine because of the absence of above mentioned cofactor and enzyme. The failure of this step results in 2 things[19]:

i). **On one hand,** the methionine will not be produced, hence it will not be available for very important metabolic steps in cellular metabolism including its conversion to s-adenosyl methionine (Adomet).

Methionine & S-adenosyl-Methionine

Methionine is very important amino acid and independently serves as:

a). An essential amino acid for protein synthesis.

b). Methionine also serves in the formation of s-adenosylmethionine as the major methyl donor in numerous important enzymatic reaction.

c). Methionine is also used for the formation of myelin sheath, metabolism of brain and production of neurotransmitters.

d). Methionine is required for protein synthesis and it is the precursor of s-adenosyl-Methionine (Ado-Met) which is required in polyamine synthesis and in the numerous transmethylation reactions[20]. In relation to birth defects, it is particularly s-denosylmethionine (AdoMet) & its role in the transmethylation reactions that plays the most important role.

e). S-adenosyl-methionine (AdoMet) is used in the methylation of phospholipids, proteins, DNA, RNA, amino acids, neurotransmitters and a number of other small molecules.

f). In addition, the methylation of ribosomal RNAs plays an important role in mRNA function & Integrity. Thus, a disturbed methylation activity may interfere with normal fetal growth & development in a number of different ways. In the absence of methionine, all these important steps will not take place.

ii). **On the other hand,** as homocysteine is not converted to methionine, it will accumulate in the body[19].

Homocysteine:

Homocysteine accumulation may have multiple biological effects and they are discussed in detail in heart section.

The interrelationship of affects of Vitamin B-12 and Folic acid should be kept in mind while treating their deficiencies. The deficiency of Vitamin B-12 can be partially compensated with folic acid supplementation. Several affects of B-12 deficiency can be compensated by excessive doses of folic acid in diet.

It should be kept in mind that in the deficiency of Vitamin B-12 two things can not happen: 1). Methyltetrahydrofolate, the inactive form of folic acid can not be changed to tetrahydrofolate (H_4 folate), the active form of Folic acid. 2). Homocysteine will not be changed to methionine.

The significance of this information is that excessive doses of dietary folic acid will mask certain symptoms and defer the diagnosis of Vitamin B-12 deficiency. Hence it is suggested that in the case of vitamin deficiency, Folic acid should not be given alone, because it can cause more damage than benefit. The total clinical picture of the patient will not improve until the Vitamin B-12 is essentially given.

PHARMACODYNAMICS OF FOLIC ACID

THE ULTIMATE ROLE OF FOLIC ACID IN THE CELLULAR METABOLISM[20]

Various numbers of glutamic acid moieties may be attached to the pteroyl portion of the molecule, resulting in monoglutamates, triglutamates, or polyglutamates. The fully oxidized pteridine ring of folic acid can undergo reduction, catalyzed by the enzyme dihydrofolate reductase, to give 7.8-dihydrofolic acid. (H_2folate) and then to the fully reduced 5,6,7,8-tetrahydrofolic acid (H_4folate).

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Full Reduction of Folic Acid in Two Different Steps in the Presence of Folate Reductases

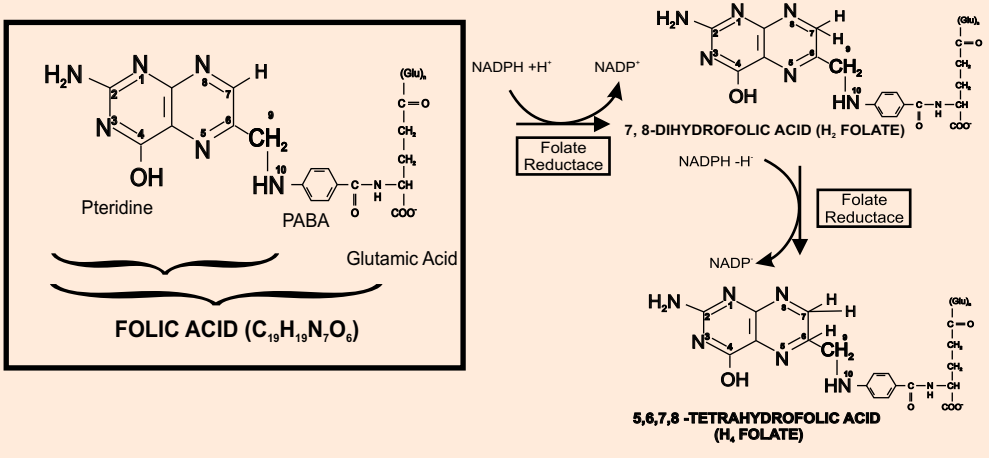


Figure No 6.1: Shows full reduction of Folic Acid to H_4 folate

H_4folate is subsequently transformed to 2 folate cofactors possessing one-carbon units attached to the 5-nitrogen (5-CH_3-H_4folate and 5-CHO-H_4folate), the 10-nitrogen (10-CHO-H_4folate), or both positions (5,10-CH_2-H_4folate and 5,10-CH^+-H_4folate) The folate cofactors are interconvertable by various enzymatic reactions and serve the important biochemical function of donating one carbon units at various levels of oxidation.

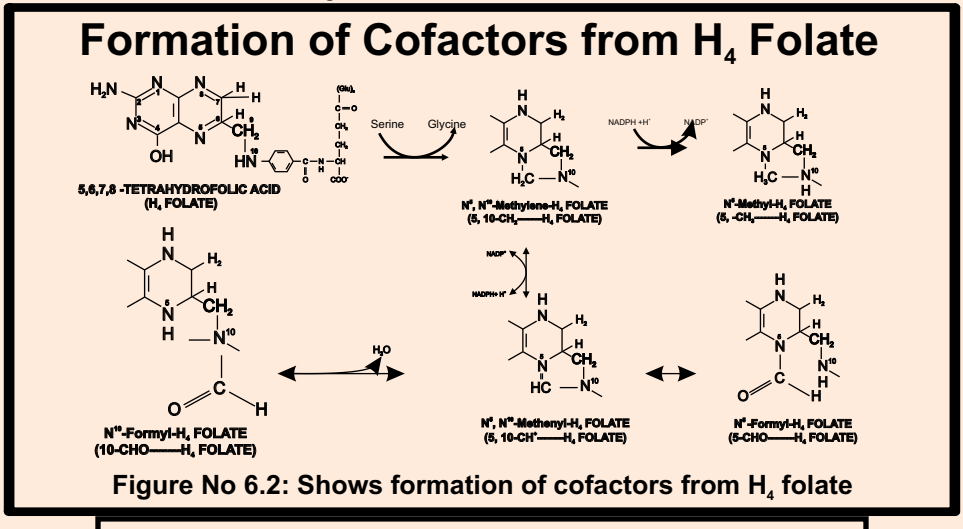


Figure No 6.2: Shows formation of cofactors from H_4 folate

H_4 FOLATE IS TRANSFORMED INTO 2 COFACTORS:

2 Cofactors

1. 10 -CHO-----H_4 folate (N^{10} -Formyl-H_4 folate)

OR

5,10-CH^+-------H_4 folate (N^5,N^{10}-Methenyl-H_4 folate)

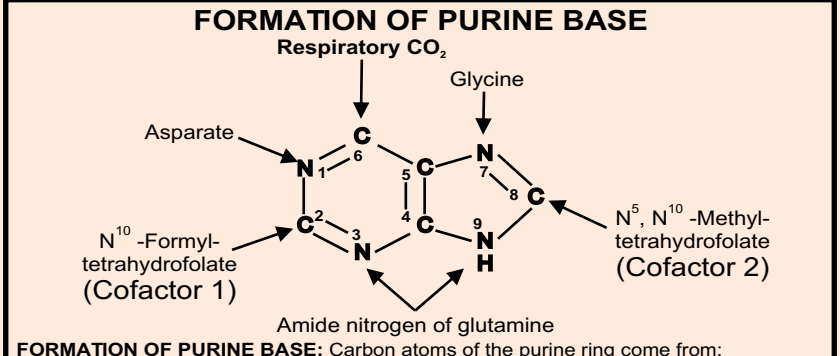
2. 5-CH_3----------H_4 folate (N^5 -methyl-H_4 folate)

OR

5,10-CH_2--------- H_4 folate(N^5,N^{10}-Methylene-H_4 folate)

Figure No 6.3: Shows the formation of cofactors 1 & 2.

One of the two essential ultimate roles of the folate after the formation of folate cofactors, is the one-carbon transfer reaction, which is necessary for DNA synthesis. The de novo synthesis of the purine heterocyclic involves two enzyme reactions that use folate cofactors. In these, 10-CHO-H_4 folate and 5,10-CH^+-H_4 folate, donate their one carbon unit to ultimately form carbons 2 and 8 of the purine hetrocycle.



FORMATION OF PURINE BASE: Carbon atoms of the purine ring come from:

i. Atoms 2 and 8 come from cofactor 1 and cofactor 2 which are derived from fully reduced form of H_4 folate-(5,6,7,8-tetrahydrofolic acid, the active form of Folic Acid).

ii. Whereas carbon 4, 5 and 7 are derived from glycine.

Figure No 6.4: Shows the formation of purine base and incorporation of atoms 2 & 8 coming from cofactor 1 & cofactor 2.

In the underneath, we summerize these important steps:

i. **Conversion of folic acid to completely reduced folic acid which is the active form of folic acid (H_4folate).**

ii. **Transformation of H_4 folate into 2 cofactors, which give carbons 2 & 8 each, for the formation of purine ring (Figure 6.4).**

Iii. **Cofactor 2 provides methyl moity for the synthesis of thymidylic acid by converting dUMP into dTMP . Both purine base & dTMP are essential for the synthesis of DNA and proteins (Figure 6.5 & 6.6).**

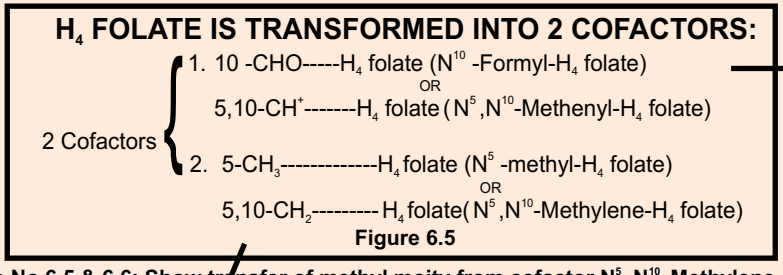


Figure 6.5

Figure No 6.5 & 6.6: Show transfer of methyl moity from cofactor N^5, N^{10} -Methylene H_4 folate to deoxyuridine monophosphate to form Deoxythymidine monophosphate

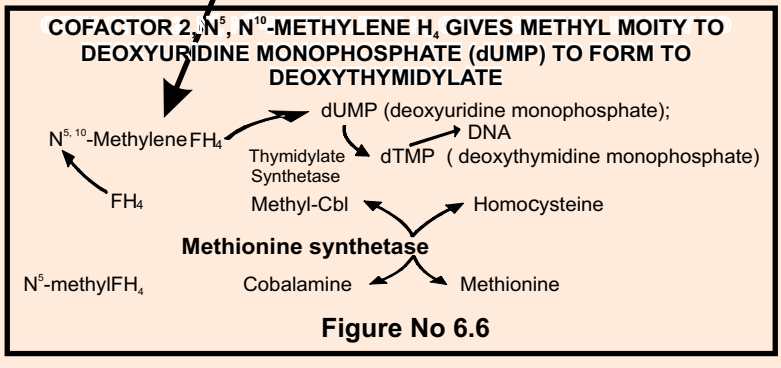
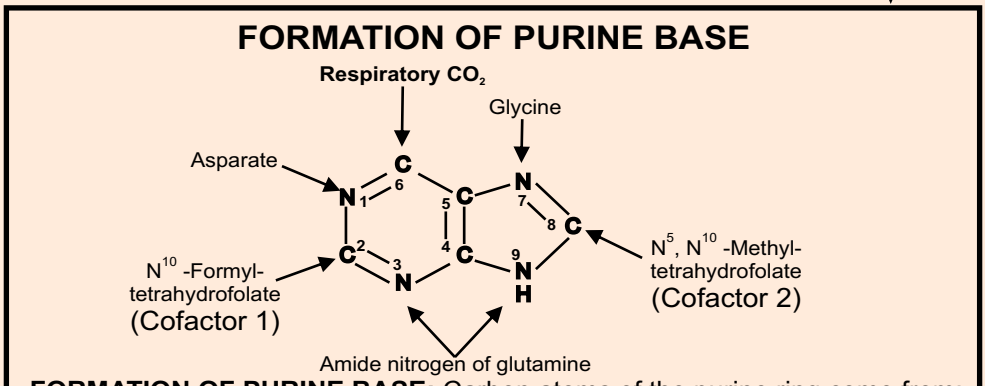


Figure No 6.6



FORMATION OF PURINE BASE: Carbon atoms of the purine ring come from:

i. Atoms 2 and 8 come from cofactor 1 and cofactor 2 which are derived from fully reduced form of H_4 folate-(5,6,7,8-tetrahydrofolic acid, the active form of Folic Acid).

ii. Whereas carbon 4, 5 and 7 are derived from glycine.

Figure No 6.4

Another essential reaction in which a folate cofactor is necessary is the synthesis of thymidylic acid (2´-deoxy thymidine monophosphate; dTMP), an essential precursor of DNA. In this reaction thymidylate synthetase catalyzis the transfer of methyl moity of 5,10-CH_2-CH_4 folate to the 5-position of 2-deoxyuridinemonophosphate to form 2-deoxythymidinemonophosphate(dUMP to form dTMP). Unlike all the other enzymatic reactions that utilize folate cofactor, in this reaction the cofactor is oxidized to H_2 folate & for each molecule of dTMP produced, a molecule of H_4 folate is consumed.

Normally 2 folate cofactors perform 2 important roles:

A). The 10-CHO-H_4-folate and 5, 10-CH_4-H_4 folate, donate their one carbon units to ultimately form carbon 2 and 8 of the purine heterocycle.

B). Thymidylate synthetase catalyzis the transfer of methyl moity of 5,10-CH_2- CH_4 folate to the 5- position of 2´-deoxy uridine monophosphate to make to deoxy thymidine monophosphate, (dUMP to form dTMP)[20 &21].

In case of folic acid deficiency neither of the above reactions will take place

a). Neither carbon units will be available for the synthesis of purine necessary for the synthesis of DNA.

b). Nor 5,10-CH_2-CH_4 folate will transfer methyl moity to the 5- position of 2´-deoxyuridine monophosphate to convert it to deoxythymidine monophosphate (dUMP to form dTMP), the step which is necessary for the synthesis of DNA and proteins.

The figures 6 & 7 shows the continuing series of reactions in rapidly proliferating tissues[5].

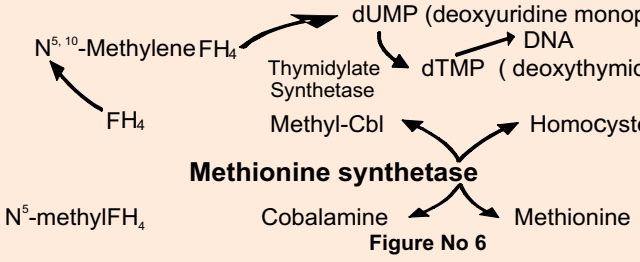


Figure No 6

Figure 6 shows The combined catalytic activities of the three important enzymes, dTMP synthetase, dihydrofolate reductase and serine transhydroxymethylase. These are referred to as dTMP synthesis cycle. It also shows the relationship between N^5-methyl FH_4, methionine synthetase and thymidylate synthetase. This assures continued regeneration of H_4 folate, ontinued synthesis of dTMP, & DNA.

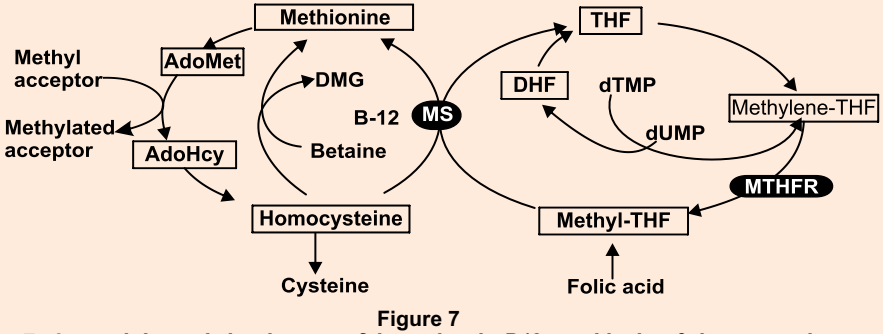


Figure 7

Figure 7 shows: i. Interrelation between folate, vitamin B12, methionine & homocysteine metabolism. ii. Transmethylation of methionine to AdoMet, & adenosylhomocysteine; iii. Conversion of homocysteine to cysteine and to methionine. iv. Reduction of folic acid to H_2 folate (7, 8 dihydrofolic acid) and then to fully reduced form H_4 folate (5,6,7,8- tatrahydrofolic acid v. Action of MS, methionine synthase, MTHFR methylenetetrahydrofolate reductase & the role of $N^{5\text{-}10}$-Methylene FH_4 in the conversion of dUMP to dTMP and DMG, dimethylglycine.

The pharmacodynamics of Vitamin B-12 & Folic acid and the above images from the early weeks of conception and intrauterine life to old age, indicate the essential roles, the both vitamins play in the fetal growth, development and also maintenance of health[25].

In case of their deficiency all the systems of the body suffer. In the underneath are shown the different manifestations and symptoms of the systems that become victims of their deficiency:

1. Hemotologic Abnormalities[22]
2. Gastrointestinal & Other Symptoms
3. Neurological & Psychiatric Symptoms
4. Neural Tube Defects (NTDs)
5. Cardiovascular abnormalities
   (A) Hyperhomocystenomia
   (B) Congenital Heart Defects
6. Cleft Lip & Palate

1. HEMATOLOGIC & OTHER ABNORMALITIES THAT MAY BE DUE TO DEFICIENCY OF VITAMIN B-12 & FOLIC ACID. MEGALOBLASTIC ANEMIA[23]

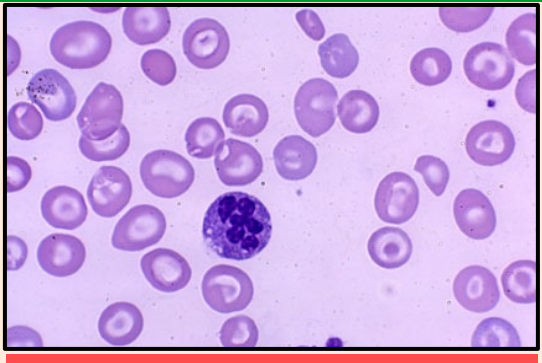


Fig. 11 shows the Blood slide with poikilocytosis. Hypochromia. Oval macrocytes and premature hypersegmented (six-lobed) neutrophil. The changes shown in the slide are defined as magaloblastic changes. They are produced from different causes including deficiency of Folic acid and Vitamin B-12[34].

HEMATOLOGIC CHANGES
Anemia
Reticulocytopenia
Macrocytosis increased (MCV)*
Neutropenia
Thrombocytopenia

PERIPHERAL BLOOD SMEAR
Neutrophil
(Hypresegmentation)
Erythrocyte
Variation in size
Variation in shape
Macro- ovalocytes

SERUM
Elevated lactate
Dehydrogenas
Elevated bilirubin
Elevated iron
Decreased heptoglobin

BONE MARROW
Hyper cellular
Megaloblastic morphology
Giant bands and metamyelocyte

2. GASTROINTESTINAL & OTHER SYMPTOMS

Megaloblastic abnormalities[22] may occur in other proliferating body cells, all of which share the underlying defect in DNA synthesis. These changes have been documented in the epithelial cells of the buccal mucosa, stomach, intestine, and vagina and account for phenomenon such as glossitis, stomatitis, and secondary malabsorption. Similar changes may account for the infertility that some times is seen.

Glossitis	Infertility
Stomatitis	Orthostatic Hypotension
Gastrointestinal symptoms	Weight Loss
Hyperpigmentation	

3.NEUROLOGICAL & PSYCHIATRIC ABNORMALITIES[25]

Cobalamin deficiency[22 & 26], in contrast to folate deficiency and other causes of megaloblastic anemia, produces a wide variety of neuropsychiatric abnormalities as shown in table 1. These symptoms are unrelated to the presence of megalo-blastic anemia. Vitamin B-12 deficiency can potentially cause severe & irrever-sible damage, especially to the brain and nervous system in addition to megal-oblastic anemia. As shown in discussion on pharmacodynamic of Vitamin B-12 & Folic acid, we have seen that in case of their deficiency, MMA accumalates[15] & produces damage to central nervous system. The same way homocysteine is not converted to methionine and accumulates in the body & causes intrautrine growth retardation & perinatal death[35]. In addition, the deficiency of methionine[23 & 24] & S-adenosyl-methionine produces different way as explained in the discussion on pharmacodynamics.

NEUROLOGICAL & PSYCHIATRIC ABNORMALITIES[25]

Neurological Abnormalities		Psychiatric abnormalities	
Paresthesia	Romberg's sign	Depression	Paraphrenia
Impaired vibration sense	Increased reflexes	Paranoia	Mania
Impaired position sense	Spastisity	Listlessness	Personality changes
Impaired touch sensation	Babinski's sign	Acute confusional state	Panic attack
Impaired pain perception	Lhermitte's sign	Hallucination	Suicide
Ataxia	Urinary incontinence	Delusions	
Abnormal gait	Fecal incontinence	Insomnia	
Fatigue	Urinary urgency or nocturia	Apprehensiveness	
Memory loss	Impotence	Psychosis	
Disorientation	Abnormal smell or taste	Slow mentation	
Obtundation	Decreased vision		
Decreased reflexes	Optic atrophy		
Weakness	Decreased muscular strength		

Table 1

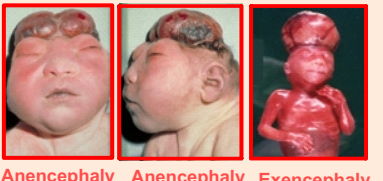
4. NEURAL TUBE DEFECTS (NTDs)[25,27,34 &36]

NTDs develop during the third to fourth week of gestation and are due to a combination of genetic & environmental causes (multifactorial). However, the rapidly dividing cells of the neural tube probably require a large amount of folate for DNA synthesis. Supply of folate may be inade-quate because of gene defects that result in subtle abnormalities of folate metabolism. Defective closure of the neural tube results in neural tube defects (NTDs). These are classified as anterior NTDs (anencephaly, encephalocele & exencephaly) & posterior NTDs as spina bifida Fig. 12&13.

ANENCEPHALY

In anencephaly, the brain initially protrudes through a defect in the cranial vault (exencephaly) and is gradually destroyed because of mechanical injury and vascular disruption. Eventually, all that is left is a small, vascular mass of disorganized neural tissue (cerebrovasculosa) mixed with choroid plexus. Anencephaly is incompatible with survival. (FIGURE 12)

NTDs

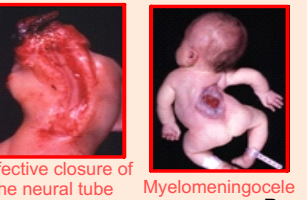


Anencephaly Anencephaly Exencephaly

FIGURE 12

SPINA BIFIDA

Spina bifida is a set of malformations of the spinal cord caused by failure of closure of the neural tube and lack of fusion of the vertebral arches, soft tissues, and skin that cover the back. The lesion is usually in the lumbo-sacral area but sometimes it can be more extensive and may involve the entire spinal cord. Anencephaly is often accompanied by spina bifida. (FIGURE 13)



Defective closure of the neural tube Myelomeningocele

FIGURE 13

5. CARDIOVASCULAR ABNORMALITIES

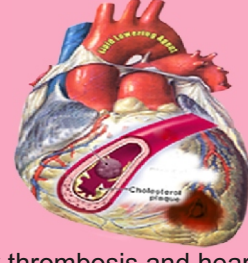
A. HYPERHOMOCYSTINEMIA

The B12 cofactor methylcobalamine, in the presence of enzyme methyltetra - hydrofolate homocysteine methyl transferase (MTR) or (methionine synthetase) converts (i). CH_3-tetrahydrofolate (inactive form) to tetrahydrofolate (active form of folic acid). (ii). Homocysteine is converted to methionine.

In the deficiency of Vitamin B-12 homocysteine is not converted to methionine & accumulates in the body[19]. It's accumulation may have multiple biological affects. It may impair the methylation activity in brain. In addition, a high plasma total hyperhomocysteinemia (tHcy) level is believed to be atherogenic & thrombogenic[28] (Fig 14 & 15). The mechanisms behind these vascular affects are platelet abnorm-alities, stimulated coagulation or inhibited fibrinolysis, smooth muscle cell proli-feration, LDL oxidation & endothelial dysfunction. Increasing evidence suggests that oxidative stress is a mediator of endothelial cell dysfunction and that it may contribute to the vascular complications of pregnancy and coronary artery disease[29 & 30]. In this regard, it is particularly interesting that hyperhomocysteinemia causes an acute endothelial dysfunction through mechanisms involving oxidative stress. A recent clinical study clearly demonstrated that Homocysteine interferes with nitric oxide function through its pro-oxidant effects. By doing so, the relation between hyperhomocysteinemia and the pregnancy complications involving placental ischemia[33]; & also hyperhomocysteinemia & cardiac effects involving coronary ischemia can be explained. The homocysteine will accumulate and cause atherosclerosis, cerebral stroke (FIG. 14) & myocardial infarction (FIG 15).

Atherosclerosis caused by Hyperhomocysteinemia[31]

CEREBRAL STROKE FROM ATHEROSCLEROSIS FIG 14



Atherosclerosis causing coronary thrombosis and heart attack (FIGURE 15).

This type of atherosclerosis[37] is indistinguishable from the general atherosclero-sis & it increases the morbidity & mortality from myocardial infarction & cerebral stroke. Homocysteine blood level should be done to determine if this is the cause of atherosclerosis. In positive cases vitamin B-12 will benefit the patients.

B. CONGENITAL HEART DISEASES AND VITAMIN B-12 AND FOLIC ACID DEFICIENCY[32]

Congenital heart disease is estimated to involve less than 1% of all live births. As some defects are not found until later in life, or may never be diagnosed, this number may actually be higher.

CONGENITAL HEART DISEASE (continued)

Many congenital defects are often incompatible with life leading to miscarriage & stillbirths[33, 41 & 42]. During a child's first year of life, the most common defects that are symptomatic include ventricular septal defect (VSD), transposition of the great vessels (TGV), tetralogy of Fallot, coarctation of the aorta, & hypoplastic left heart syndrome. Premature infants have an increased presentation of VSD and patent ductus arteriosus (FIGURE 16 shows congenital heart defects) .

These congenital heart defects are detected after birth according to the following age schedule.

1).Atrial septal defects: during the preschool years. 2).Patent ductus arteriosus: between ages one & two. 3).Coarctation of the aorta in infancy at age 4 years. 4).Tetralogy of Fallot: age varies. 5).Transposition of the great arteries: often in the first weeks after birth, but before the patient is 12 months old.

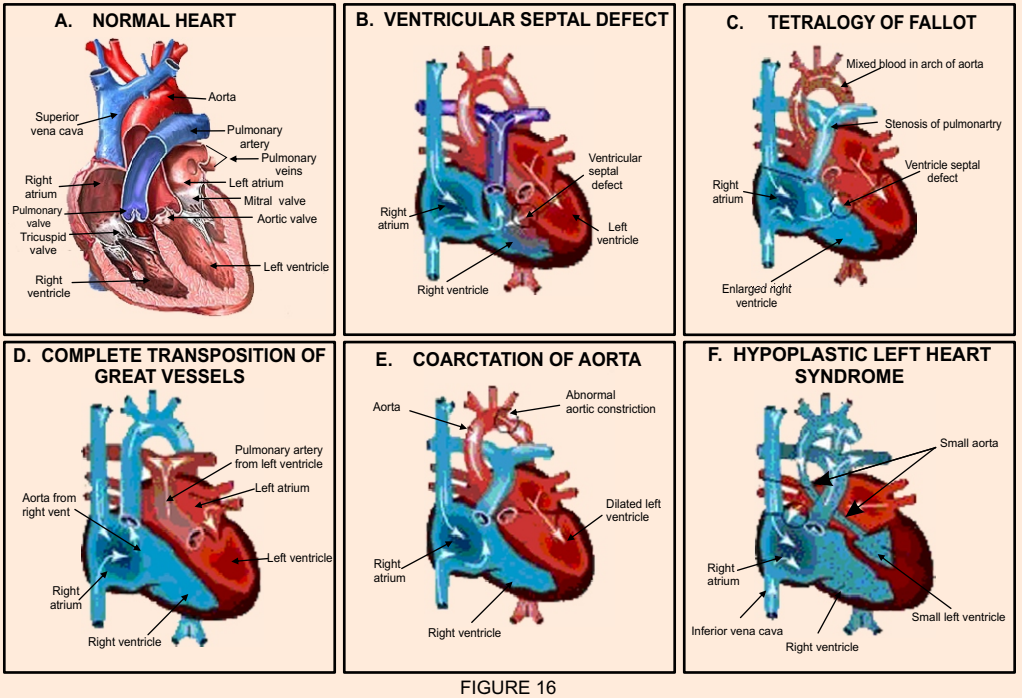


FIGURE 16

This diagram shows: (A).Normal Heart. (B).Ventricular Septal Defect. (C).Tetralogy of Fallot. (D). Complete Transposition of Great Vessels. (E).Coarctation of Aorta. (F).Hypoplastic Left Heart Syndrome.

Surgical procedures seek to repair the defects and restore normal pulmonary & systemic circulation. Sometimes, multiple, serial surgical procedures are necessary. Repair for simple cardiac lesions can be performed in the cardiac catheterization lab. Catheterization procedures include balloon atrial septostomy & balloon valvuloplasty. Surgical procedures include arterial switch, Damus-Kaye-Stansel procedure, Fontan procedure, Ross procedure, shunt procedure, and venous switch or intraatrial baffle.

6. CLEFT LIP AND PALATE

Cleft lip and cleft palate are birth abnormalities of the mouth and lip. These abnormalities affect about one in every 1,000 births and are more common among Asians and certain groups of American Indians than among Caucasians. A child can have cleft lip, cleft palate, or both. Cleft lip and cleft palate together are more common in boys. It is also important to know that most babies born with a cleft are otherwise healthy with no other birth abnormalities.

CAUSES OF CLEFT

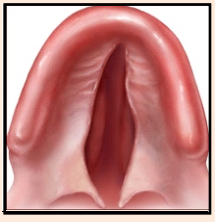
During the first six to eight weeks of pregnancy, the shape of the embryo's head is formed. Embrologicaly five primitive tissue lobes grow: a) one from the top of the head down towards the future upper lip; b-c) two from the cheeks, which meet the first lobe to form the upper lip; d-e) & just below, two additional lobes grow from each side, which form the chin & lower lip.

If these tissues fail to meet, a gap appears where the tissues should have joined (fused). This may happen in any single joining site, or simultaneously in several or all of them. The resulting birth defect reflects the locations and severity of individual fusion failures (e.g., from a small lip or palate fissure up to a completely malformed face).

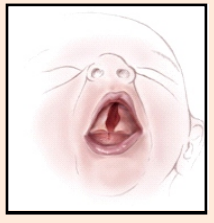
CLEFT PALATE

Cleft palate occurs when the roof of the mouth does not completely close, leaving an opening that can extend into the nasal cavity (Figure 17). The cleft may involve either side of the palate. It can extend from the front of the mouth (hard palate) to the throat (soft palate). Often the cleft will also include the lip.

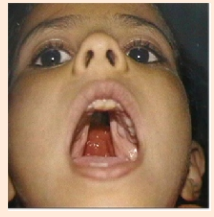
FOLLOWING ARE THE EXAMPLES OF CLEFT PALATE BEFORE AND AFTER SURGERY



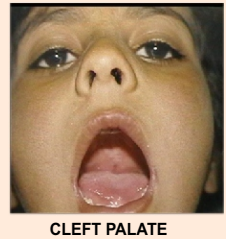
CLEFT PALATE



BABY WITH CLEFT PALATE



COMPLETE CLEFT PALATE GOING UP TO PHARYNX

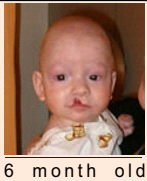


CLEFT PALATE AFTER REPAIR

FIGURE 17 shows cleft palate before and after surgical repair.

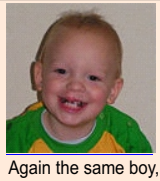
CLEFT LIP

Cleft lip is an abnormality in which the lip does not completely form during fetal development (Figure 18). The degree of the cleft lip can vary greatly, from mild (notching of the lip) to severe (large opening from the lip up through the nose). Cleft lip and cleft palate may occur together in an infant, or separately. The most common early problem associated with these abnormalities is feeding the baby.

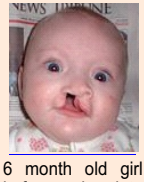


6 month old boy before going into surgery to have his unilateral incomplete cleft lip repaired.

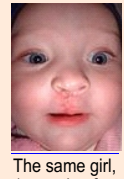
The same boy, 1 month after the surgery.



Again the same boy, age 1.5 years old. Note how the scar gets less visible with age.



6 month old girl before going into surgery to have her unilateral complete cleft lip repaired.



The same girl, 1 month after the surgery.

Again the same girl, age 5.4 years old. Note how the scar gets less visible with age.

FIGURE 18 shows cleft lip before and after surgical repair.

Abbreviated Prescribing Information

VITAMIN B-12

Cobalamin exists in four forms, two naturally occurring and another two in the form of cofactors. Their roles in the cellular metabolism are already discussed in pharmacodynamics: i. Cyanocobalamin; ii. Hydroxycobalamin & finally, the two naturally occurring cofactor forms of B-12: iii. 5-deoxyadenosylcobalamin (ado B-12) the cofactor of methylmalonyl coenzyme A mutase (MUT), and iv. Methylcobalamin (me B-12), the cofactor of 5-methyltetra-hydrofolate-homocysteine methyltransferase (MTR).

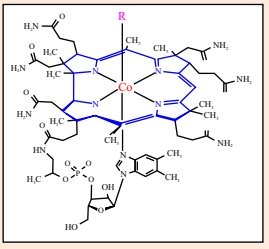


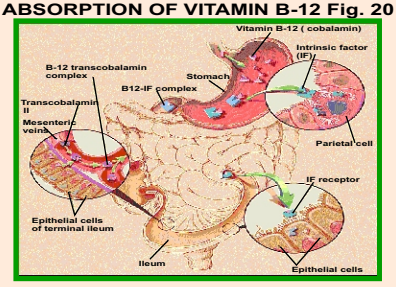
FIGURE 19

Pharmacokinetics of vitamin B-12

Vitamin B-12 cannot be made by plants or animals as only bacteria have the enzymes required for its synthesis. The average diet in the United States contains 5 to 30 µg of vitamin B12 daily, 1- 5µg of which is usually absorbed. It is present in all foods of animal origin. Its deficiency is rare except in vegans who avoid all diary products as well as meat and fish. The daily requirement is of the order of 2 to 3 µg. It would take 5 years for all the stores of vitamin B-12 to be exhausted before megaloblastic anemia develops.

Absorption: Vitamin B-12 is absorbed only after it complexes with intrinsic factor. Intrinsic factor is a glycoprotein with a molecular weight of about 50000, that is secreted by the parietal cells of the gastric mucosa. Intrinsic factor combines with B-12 liberated from dietary source in the stomach and duodenum, and the intrinsic factor-vitamin B-12 complex a subsequently absorbed in the distal ileum by the highly specific receptor-mediated transport system (FIGURE 20).

ABSORPTION OF VITAMIN B-12 Fig. 20



Once absorbed vitamin B-12 is transported to the various cells of the body bound to plasma glycol protein, transcobalamin II. Excess vitamin B-12 is transported to the liver for storage.

Indications: Indicated in Cases of vitamin B12 deficiency :

1). Inadequate diet which must be present for many years to deplete the reserves. **2).** Lack of intrinsic factor have a decreased ability for absorption; **3).** Malabsorption states: the absorption of vitamin B-12 may be impaired by disruption of any one of the steps outlined earlier.**4)**. With achlorhydria and loss of pepsin secretion (which occurs in some elderly individuals), vitamin B-12 is not readily released from its protein-bound form. **5)**. With gasterectomy and pernicious anemia, intrinsic factor is not available for transport to the ileum. **6).** With loss of exocrine pancreatic function, vitamin B-12 deficiency occurs because the vitamin can not be released from the r-vitamin B-12 complexes. **7).** Ileal resection. **8)**. Diffuse ileal disease can remove or damage the site of intrinsic factor-vitamin B-12 complex absorption. **9).** Competitive parasitic uptake like tape worm infestation, by competing for the nutrient, can induce a deficiency state. **10).** Under some circumstances, there may be increased demand for example, pregnancy, hyperthyroidism and disseminated cancer, the demand for vitamin B-12 can be so great as to produce a relative deficiency, even with normal absorption. **11).** Coronary artery disease and atherosclerosis when caused by high serum concentrations of Homocysteine. **12).** Cyanide poisoning: Recent studies show that hyroxocobalamine is an effective complexing agent for cyanide ions if administered soon enough. Cyanocobalamin is of no value in this application. **13).** Pernicious anemia. **14).** Prevention of fetal neural tube defects.

Doses & mode of administration: pernicious anemia is treated with parenteral I/M injections of 100µg daily for a week, weekly for a month & then monthly for life.

HNC HALAL Oral lozange containing Vitamin B-12 1000 micrograms and Folic acid 100 microgram should be used regularly daily as supplement.

Toxic effect: vitamin B-12 has no toxic effect. Cyanocobalamin has no cyanide poisoning.

FOLIC ACID

Vitamin B_9; Vitamin M; Folacin) Formula **($C_{19}H_{19}N_7O_8$)** PTEROYL GLUTAMIC ACID (Compound composed of pteridine heterocycle, *p*- aminobenzoic acid & glutamic acid*)*.

Folic acid (pteroylglutamic acid) is a compound composed of a pteridine heterocycle, P-aminobenzonic acid, and glumatic acid. Various numbers of glutamic acid moieties may be attached to the pteroyl portion of the molecule, resulting in monoglutamates, triglutamates, or polyglutamates. The fully oxidized pteridine ring of folic acid can undergo reduction, catalyzed by the enzyme dihydrofolate reductase, to give 7.8-dihydro-folic acid. (H_2folate) and then to the fully reduced (H_4folate). The 5,6,7,8-tetrahydrofolic acid (H_4folate) can subsequently be transformed to folate cofactors possessing one-carbon units attached to the 5-nitrogen (5-CH_3-H_4 folate and 5-CHO-H_4folate), the 10-nitrogen (10-CHO-H_4folate), or both positions (5,10-CH_2-H_4folate and 5,10-CH^+-H_4folate). The folate cofactors are interconvertable by various enzymetic reactions and serve the important biochemical function of donating one carbon units at various levels of oxidation. In most instances, H_4folate is regenerated in these reactions and is available for reutilization. Various forms of folic acid are present in a vide variety of plant and animal tissues, the richest sources are yeast, liver, kidney and green vegetables.

Abbreviated Prescribing Information

Folic acid (Continued)

Pharmacokinetics of Folic acid

Folic acid is present in most fruits and vegetables especially citrus and green leafy vegetables. The average diet in USA contains 500 to 700µg of folate daily, 50 to 200µg of which is usually absorbed, depending on the metabolic requirement (pregnant women may abs orb as much as 300 to 400µg of folic acid daily).

The average daily requirement is 50-100µg. Normally 5 to 20 mg of folate is stored in the liver & other tissues. Folates are excreted in the urine and stool, and destroyed by catabolism, so serum level falls within a few days when intake is diminish. Since body stores are low & body requirements high, folic acid deficiency & megaloblastic anemia can develop within 1 to 6 months after the intake of folic acid stops.

Unaltered folic acid is readily and completely absorbed in the proximal jejunum. Dietary folates consist primarily of polyglutamates form of 5-CH_3-H_4 folate. Before absorption all but 1 of the glutamyl residues of the polyglutamates must be hydrolyzed by the enzyme, a-L glutamyl transferase within the brush border of intestinal mucosa. The monoglutamate 5-CH_3-H_4 folate is subsequently transported into the blood stream & then widely distributed throughout the body.

Indications: Indicated in Cases of folic acid deficiency :

1). Indicated in inadequate diet, alcoholics, anorectic patients, lack of fruits & vegetables in diet and over cooked food. **2)**. When there is decreased absorption as in tropical sprue, Drugs: phenytion, sulphasalazine, trimethoprim- sulfamethoxazole **3)**. When there is increased requirement as in Chronic hemolytic anemia, Pregnancy and Exfoliative skin disease **4)**. Indicated in dialysis because there is loss of folates. **5)**. When there is inhibition of reduction to active form as by Methotrexate. **6)**. Folic acid is indicated for the prevention of fetal neural tube defects. Folic acids suppplementation during pregnancy reduces the incidence of fetal neural tube defects. The USA Public Health recommends that all women capable of becoming pregnant should consume a minimum of 0.4 mg of folic acid daily.

Dosage and mode of administration: folic acid deficiency is treated with folic acid,1 mg/day orally, the response is very rapid as shown by sense of well being & reticulocytosis in five to seven days.

HNC HALAL Oral lozanges containing Vitamin B-12 1000 micrograms and Folic acid 100 microgram should be used regularly daily as supplement.

Toxic e effects: Folic acid has no toxic effects.

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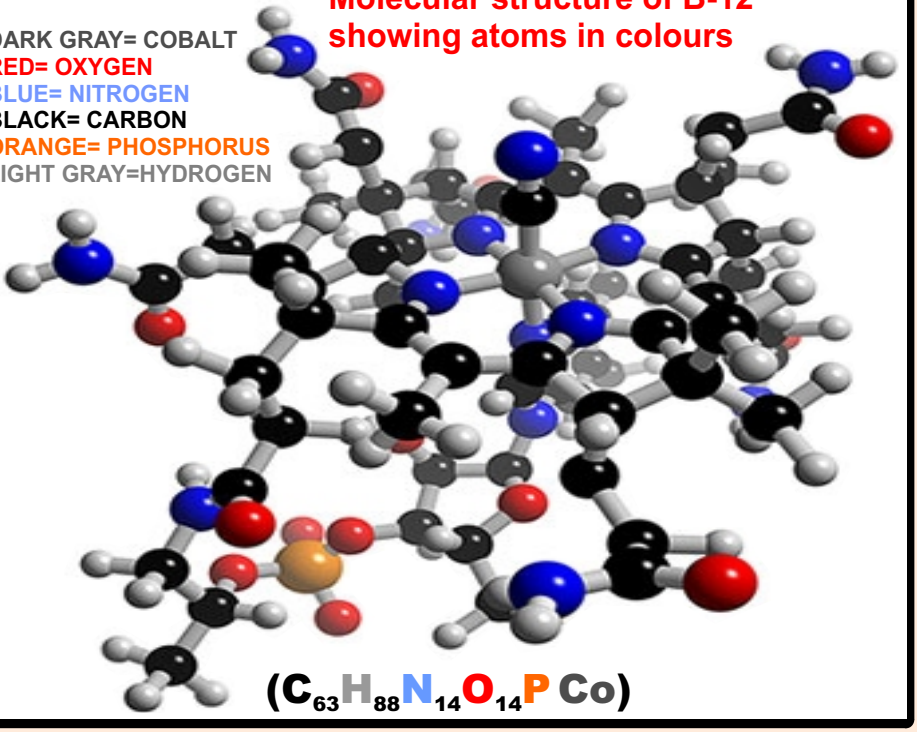
“HALAL LIFESTYLE IS HEALTHY LIFESTYLE”

HALAL VITAMIN B-12

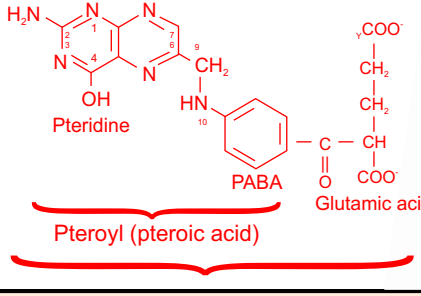
Molecular structure of B-12 showing atoms in colours

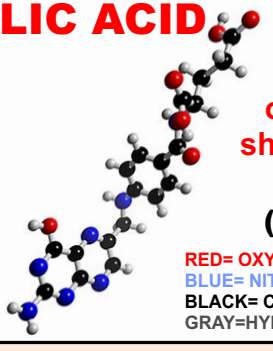
DARK GRAY= COBALT
RED= OXYGEN
BLUE= NITROGEN
BLACK= CARBON
ORANGE= PHOSPHORUS
LIGHT GRAY=HYDROGEN



$(C_{63}H_{88}N_{14}O_{14}P\,Co)$

HALAL FOLIC ACID





Molecular structure of Folic Acid showing atoms in colours

$(C_{19}H_{19}N_7O_6)$

RED= OXYGEN
BLUE= NITROGEN
BLACK= CARBON
GRAY=HYDROGEN