One carbon metabolism and its clinical significance

Specific Learning Objectives

- Describe roles of folic acid, cobalamin and S-adenosylmethionine (SAM) in transfer of one carbon units between molecules, and apply their relevance to disease states
- Describe synthesis of S-adenosylmethionine and its role in methylation reactions
- Explain how a cobalamin deficiency leads to a secondary folate deficiency

Introduction

- Human body cannot synthesize folic acid
- Its also called vitamin B_9 give rise to tetrahydrofolate (THF), carry one carbon groups ex. Methyl group
- Intestines releases mostly N^5-methy-THF into blood
- One-carbon (1C) metabolism, mediated by folate cofactor, supports biosynthesis of purines and pyrimidines, aa homeostasis (glycine, serine and methionine)

Table 14.4. One-carbon compounds

Group	Structure	Carried by
Formyl	–CHO	N^5–formyl–THFA and N^{10}–formyl–THFA
Formimino	–CH=NH	N^5–formimino–THFA
Methenyl	=CH–	N^5,N^{10}–methenyl–THFA
Hydroxymethyl	$–CH_2OH$	N^{10}–hydroxymethyl THFA
Methylene	$–CH_2–$	N^5,N^{10}–methylene–THFA
Methyl	$–CH_3$	N^5–methyl–THFA and methyl cobalamin

Table 14.4: DM Vasudevan' s Textbook of Biochemistry for Medical Students 6th edition

Enzyme co-factors involved in aa catabolism

Involves one of three co-factors: Biotin, Tetrahydrofolate (THF) and S-adenosylmethionine (SAM)

- These cofactors transfer one-carbon groups in different oxidation states:

1. Biotin transfers carbon in its most oxidized state CO_2, it require for catabolism and utilization of branched chain aa

- Biotin responsible for carbon dioxide transfer in several carboxylase enzymes

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2. Tetrahydrofolate (THF) transfers one-carbon groups in intermediate oxidation states and as methyl groups

- Tetrahydrobiopterin (BH_4, THB) is a cofactor of degradation of phenylalanine
- Oxidised form of THF, folate is vitamin for mammals
- It converted into THF by DHF reductase

3. S-adenosylmethionine (SAM) transfers methyl groups, most reduced state of carbon

- THF and SAM imp in aa and nucleotide metabolism
- SAM used in biosynthesis of creatine, phosphatidylcholine, plasmenylcholine and epinephrine, also methylated DNA, RNA and proteins

Enzymes use cobalamin as a cofactor

1. Methionine synthase: transfer methyl group from 5-methyl-THF to homocysteine in activated methyl group, requires cofactor methyl cobalamin

- Rate of cobalamin dependent methyl transfer to homocysteine is abnormally low in patients with cobalamin deficiency

2. Methylmalonyl-CoA Mutase: require 5-deoxyadenosyl cobalamin and catalyze reaction in conversion of Propionyl-CoA arises from methionine metabolism,

Loading THF with one carbon groups

- Serine, glycine, histidine and formate are directly contribute to one carbon metabolism

- In irreversible reaction, 5,10-methylene-THF into 5-methyl-THF, by MTHFR (methyl tetrahydrofolate reductase), imp in understanding induction of 2° folate deficiency by a cobalamin deficiency

Overview of reactions that donate one-carbon groups to tetrahydrofolic acid

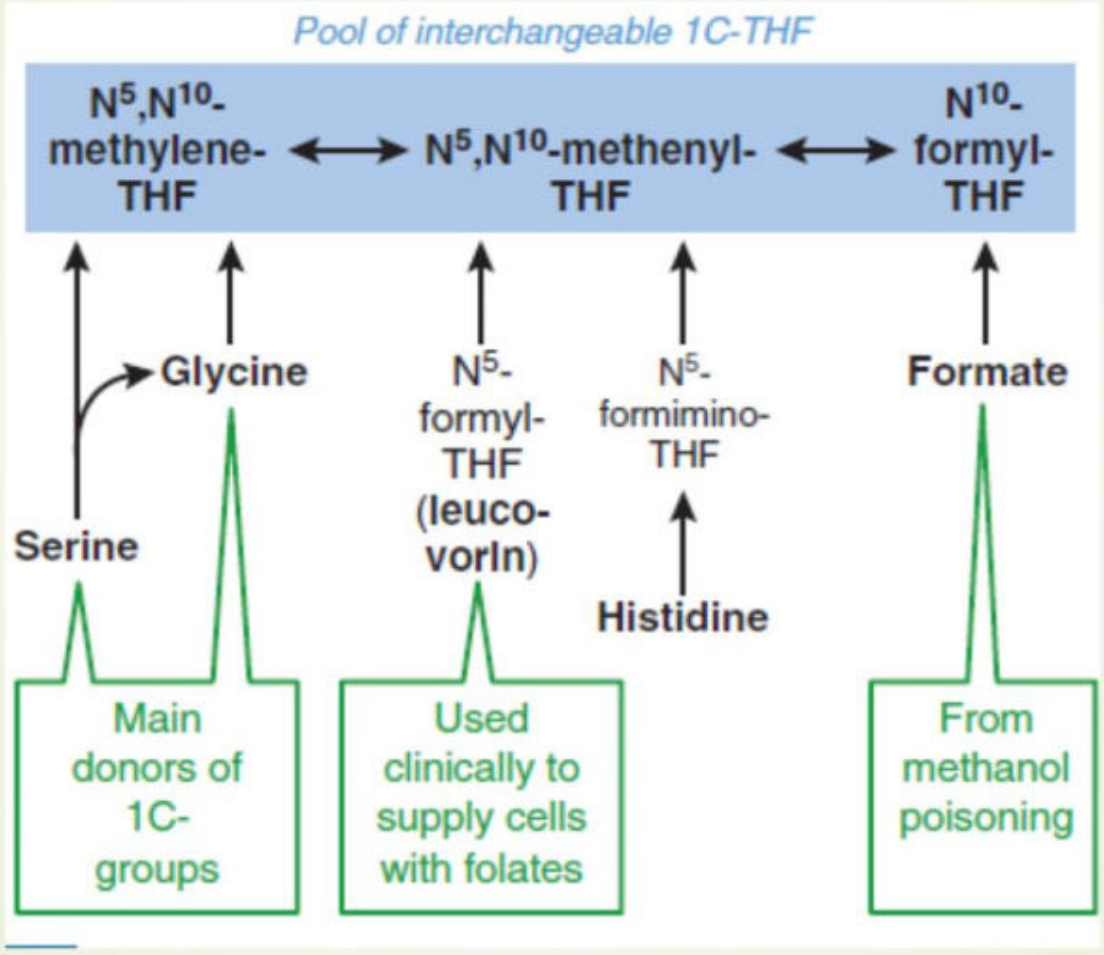

Fig 36.3. Netter's Essential Biochemistry, 1st Ed

Overview of the use of one-carbon groups from folates

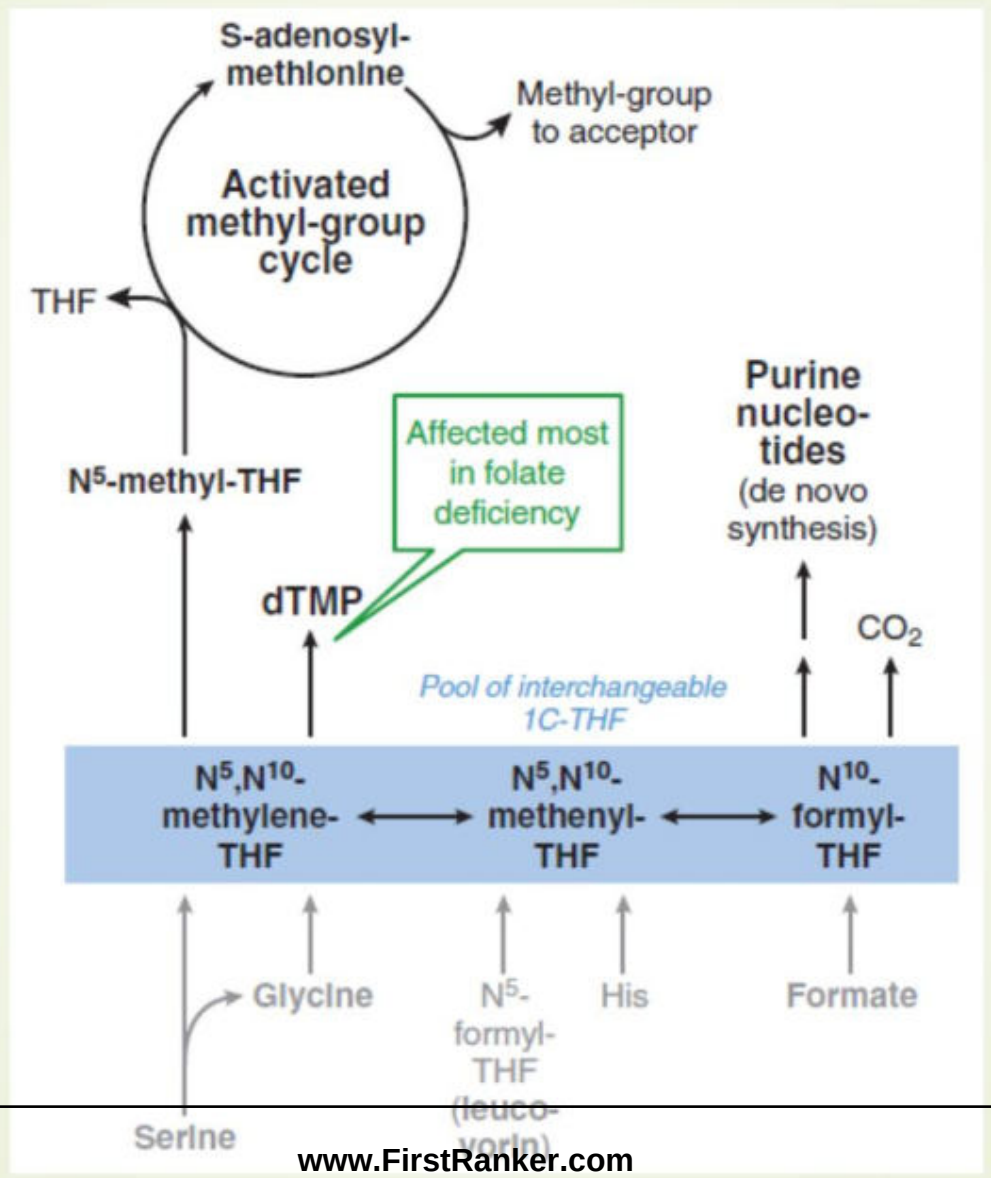

Fig 36.4. Netter's Essential Biochemistry, 1st Ed

Effects of folate deficiency on one-carbon metabolism

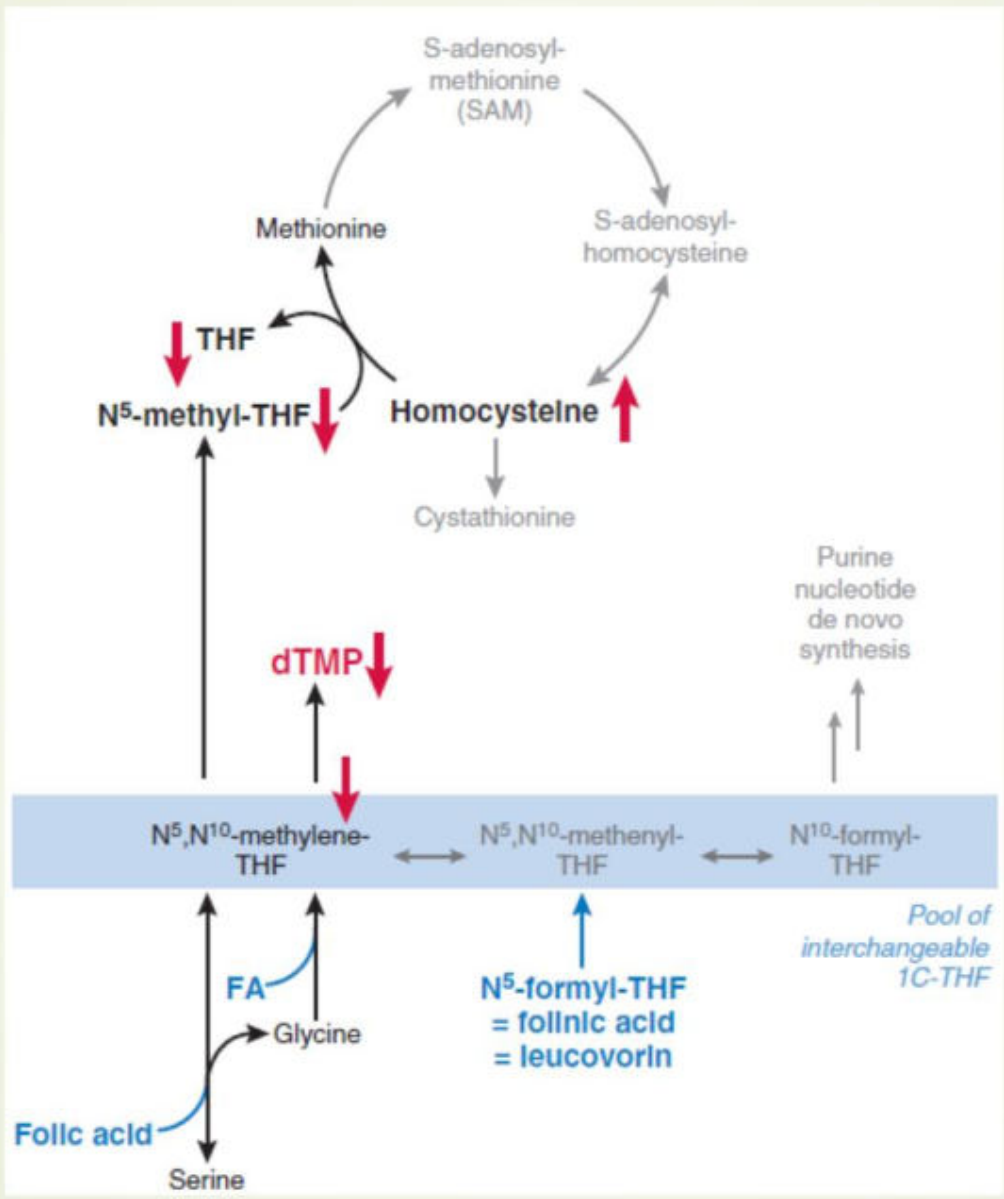

Fig 36.11. Netter's Essential Biochemistry, 1st Ed

Synthesis of methionine and S-adenosylmethionine in an activated-methyl cycle

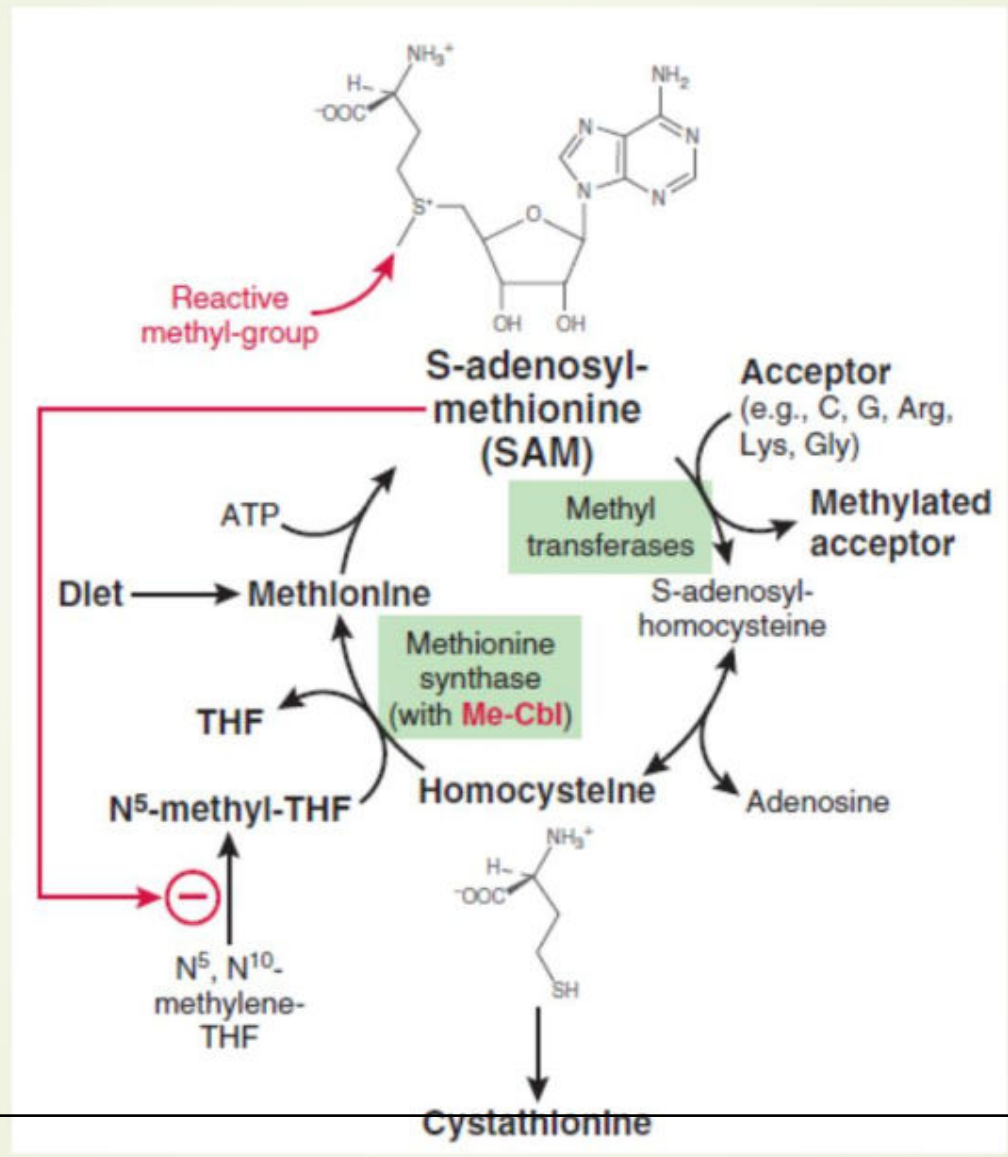

Fig 36.6. Netter's Essential Biochemistry, 1st Ed

Conversion of one carbon units on THF

- 1° source of one-carbon units for THF is carbon removed in conversion of serine to glycine, produce 5,10 methyleneTHF
- SAM synthesized from ATP and methionine by methionine adenosyl transferase
- Transfer of methyl group from SAM to S-adenosyl-homocysteine, broken down to homocysteine and adenosine

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- Methionine regenerated by transfer of methyl group to homocysteine in reaction catalyzed by methionine synthase
- Methionine synthase activity depends on two vit: N^5-methy-THF and cobalamin
- In fasting state, homocysteine stays in activated methyl group cycle.
- Methionine reconverted to SAM to complete activated methyl cycle

Folate mediated one carbon metabolism

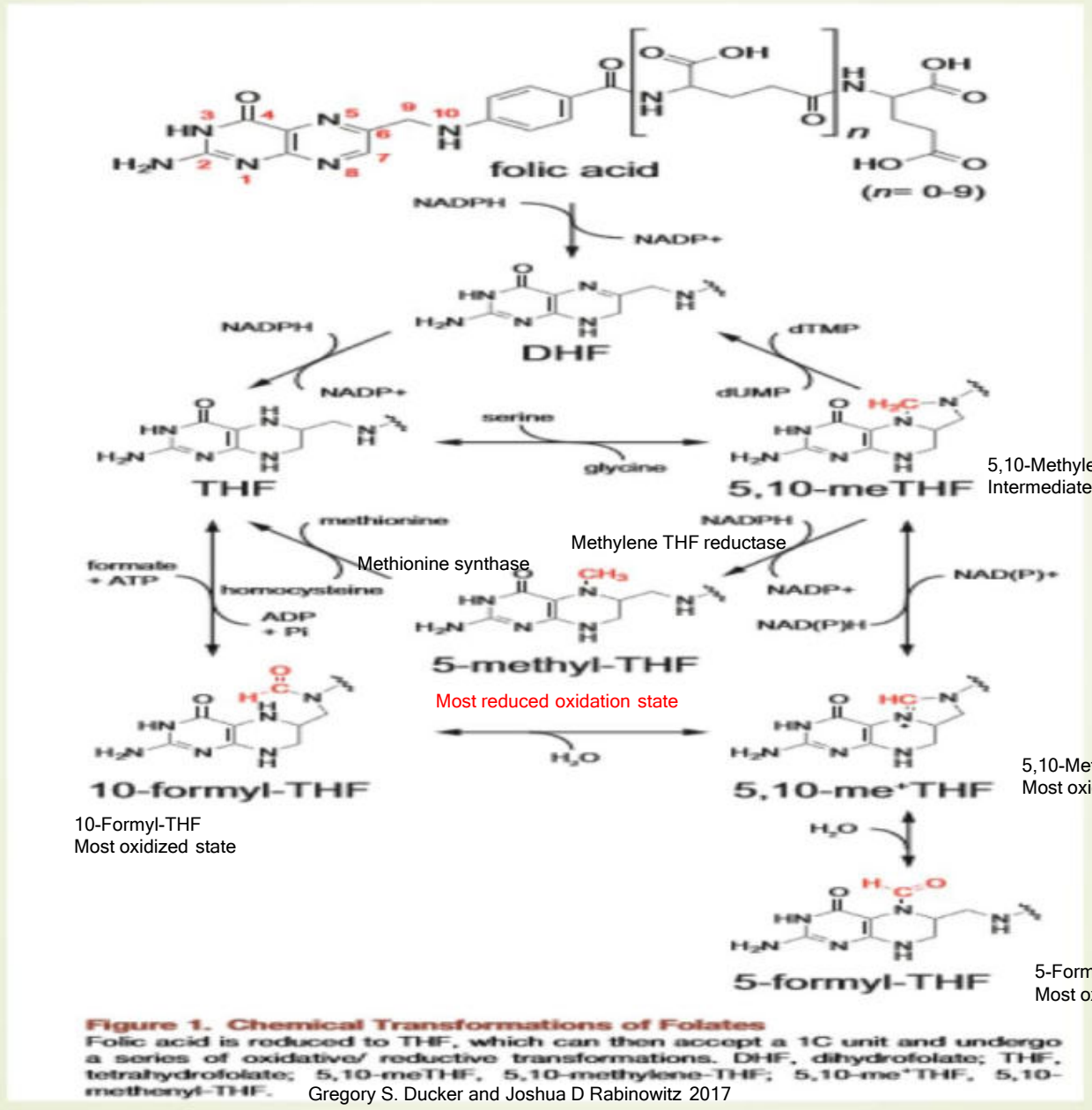

Figure 1. Chemical Transformations of Folates
Folic acid is reduced to THF, which can then accept a 1C unit and undergo a series of oxidative/ reductive transformations. DHF, dihydrofolate; THF, tetrahydrofolate; 5,10-meTHF, 5,10-methylene-THF; 5,10-me+THF, 5,10-methenyl-THF.

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Folate Trap

- Conversion of 5,10-methylene-THF into 5-methyl-THF, by MTHFR (methyl tetrahydrofolate reductase), is irreversible
- Use of 5-methyl-THF and to maintain folate cycle consists in vit-B12-dependent remethylation of homocysteine to methionine (regenerating THF)
- Methyl group transfer is dependent on 5-methyl-THF and availability of vit-B12

Cont--

- In vit B_{12} deficiency, in spite of sufficient availability of folates (and 5-methyl-THF), deficiency of active THF arises, this situation is called a 'folate trap'

- Because concentration of 5-methyl-THF continues to rise due to it being prevented from releasing methyl groups, a 'metabolic dead-end situation' develops, which leads to blockage of methylation cycle.

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- Co-factors for C1-transfers decrease and replication as well as cell division rate are reduced

- Hence, decreasing activity of methionine synthase under vitamin-B12 deficiency with secondary disorders affecting folate metabolism and insufficient de-novo synthesis of purines and pyrimidines

- Deficiency in active folic acids first affects quickly dividing and highly proliferating haematopoiesis cells in bone marrow and lead to pancytopenia

Folic acid deficiency

- It may result from limited diets, when food is cooked at high temperatures for long periods, which destroys vitamin
- Intestinal diseases (celiac disease), are characterized by folic acid deficiency caused by malabsorption
- Inability to absorb folate is rare.
- Folate deficiency is usually in newborns and produces symptoms of megaloblastic anemia

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- Besides anemia, mental and other CNS symptoms are in patients with folate deficiency, and all respond to continuous therapy although permanent damage appears to be caused by delayed or inadequate treatment

Megaloblastic anemia

1. Folate deficiency:

- Vit B_{12} and folate linked in metabolic pathways

- Vit B_{12} deficiency leads to pernicious anemia, seen in individuals having defect in intestinal absorption pathways due to lack of intrinsic factor for this vitamin

- It causes symptoms like anaemia and neurological disorders

Cont--

- Conversion of 5,10-methylene-THF into 5-methyl-THF, by MTHFR (methyl tetrahydrofolate reductase), is irreversible

- If coenzyme B_{12} not available for synthesis of methyl-cobalamin, then metabolic folates becomes trapped in 5-methyl form.

- This anemia associated with Vit B_{12} deficiency called megaloblastic anemia

- Treat pernicious anemia by Vit B_{12} and folate

Clinical-cases discussed

Thank you