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FOLATE METABOLISM

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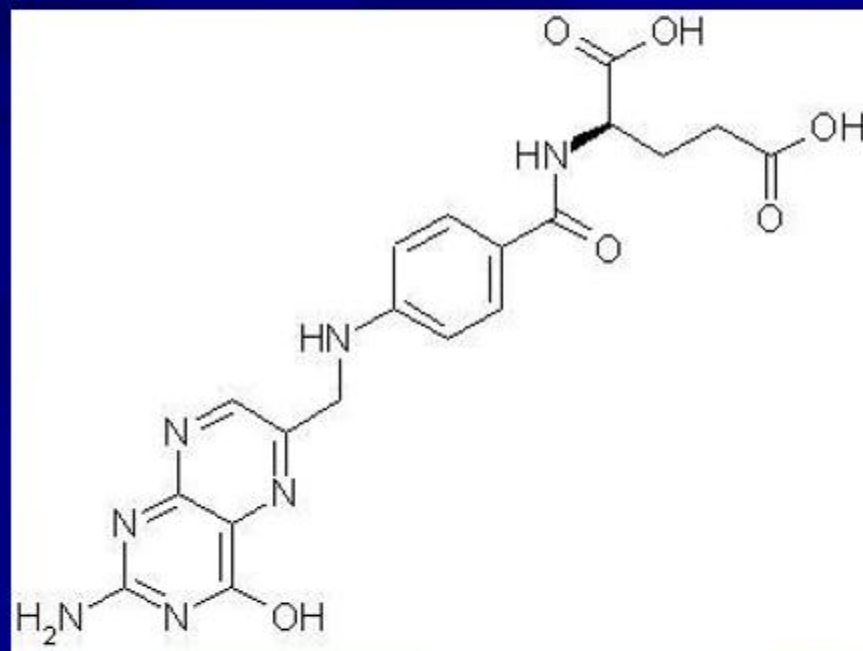
MEDICAL ONCOLOGIST,GUMS,1401/04/16

Take Home Message

- All women should be informed of folic acid.
- All women capable of becoming pregnant could have an NTD-affected pregnancy.
- All women should consume 400 micrograms of folic acid daily in addition to foods high in folate such as fruits and vegetables
- All women should be physically active for at least 30 minutes a day

Folic Acid

FIGURE 1: Chemical Structure of Folic Acid [8]



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WHAT IS FOLIC ACID?

- Folic acid = pteroylmonoglutamic acid, folacin, vitamin Bc, vitamin B9 and Lactobacillus casei factor [8].
- Folic acid is a water-soluble B-vitamin [8]
- MW = 441kDa
- Must be ingested in diet (cannot be synthesized by body)

What is Folic Acid?

- B vitamin
- Involved in DNA synthesis
- Role during pregnancy
 - Prevent certain birth defects of the brain and spine called neural tube defects (NTDs)
 - Supports growth of the placenta and fetus
- Necessary for overall good health

WHY IS FOLIC ACID NEEDED?

- Formation of the coenzyme referred to as tetrahydrofolate (THF) [1]
- Essential for creating heme, the iron containing substance in haemoglobin [1]
- Proper formation of the brain, spinal cord, and nerve cells in the embryo. Closure of the neural tube in the fetus cannot be completed without it ([Northrup H, 2000](#)).
- Essential for synthesis of serine, methionine, ATP, GTP, thymidylate

ABSORPTION

- Natural food source (polyglutamate): conjugase in the small intestine's lumen converts polyglutamates (low absorption) to monoglutamates for absorption [4]
- Monoglutamate is readily absorbed from the gut via energy-dependent, carrier-mediated mechanisms, involving membrane-associated folate-binding proteins [4]

DISTRIBUTION

- Tetrahydrofolate (THF) and its derivatives distribute to all body tissues [4]
- N5-methyl-THF is the major storage form of folate in the body (i.e. ~50% in liver) [4]
- N5-methyl-THF is highly bound to albumin [4]

METABOLISM

- Folate reduced to dihydrofolate (DHF) and then to tetrahydrofolate (THF) within cells, by dihydrofolate reductase (DHFR) and NADH [7]
- Addition of glutamate residues to THF in the cell keep it within the cell to form its active coenzyme in one-carbon metabolism reactions [7]
- 5-methyl-THF is formed by the reduction of N5, N10-methylene-FH4 by N5, N10-methylene-THF reductase [7]
- Normally, folate is excreted in the urine; folate is also excreted in the bile, if not reabsorbed [4]

TABLE 1: One-carbon pool: Sources and Recipients of Carbon [7]

<i>Source</i>	<i>Form of THF produced</i>	<i>Recipient</i>	<i>Product</i>
Formate	N10-Formyl	Purine precursor	Purine (C2)
Histidine	N5, N10-Methenyl	Purine precursor	Purine (C8)
Serine, Glycine, Formaldehyde	N5, N10-Methylene	dUMP Glycine	dTMP Serine
Reduction of N5, N10-methylene- THF	N5-Methyl	Vitamin-B12	Methyl-B12

HOW DOES FOLIC ACID WORK?

- Folic acid is converted to its active coenzyme form, THF, which behaves as a donor or receiver of a one carbon entity in different oxidation states (formyl, methylene, or methyl)

FIGURE 2: FOLATE MECHANISM OF ACTION [9]

Main Folate Metabolism Pathways

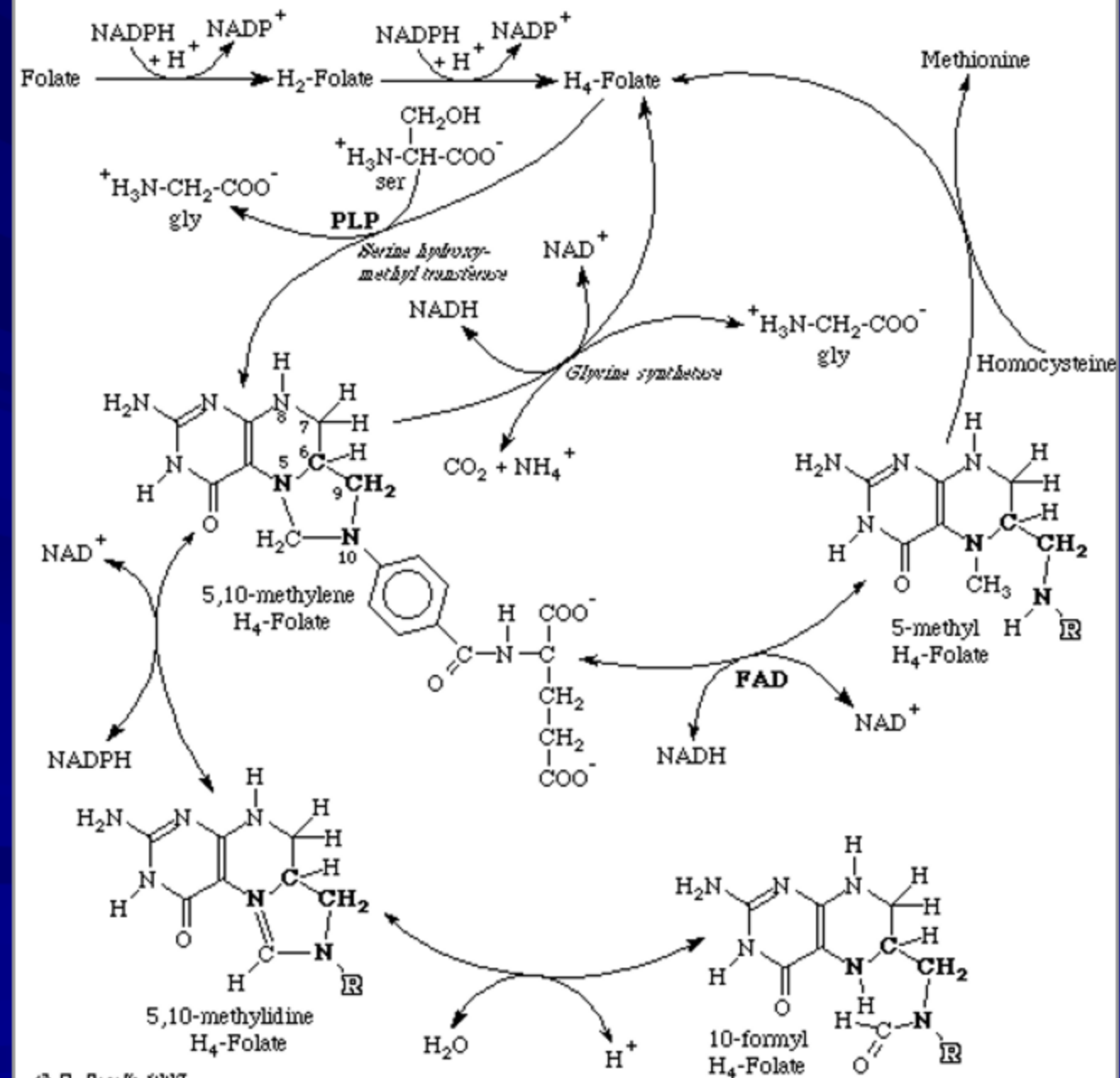


FIGURE 3: MECHANISM OF ACTION – EXAMPLE [9]

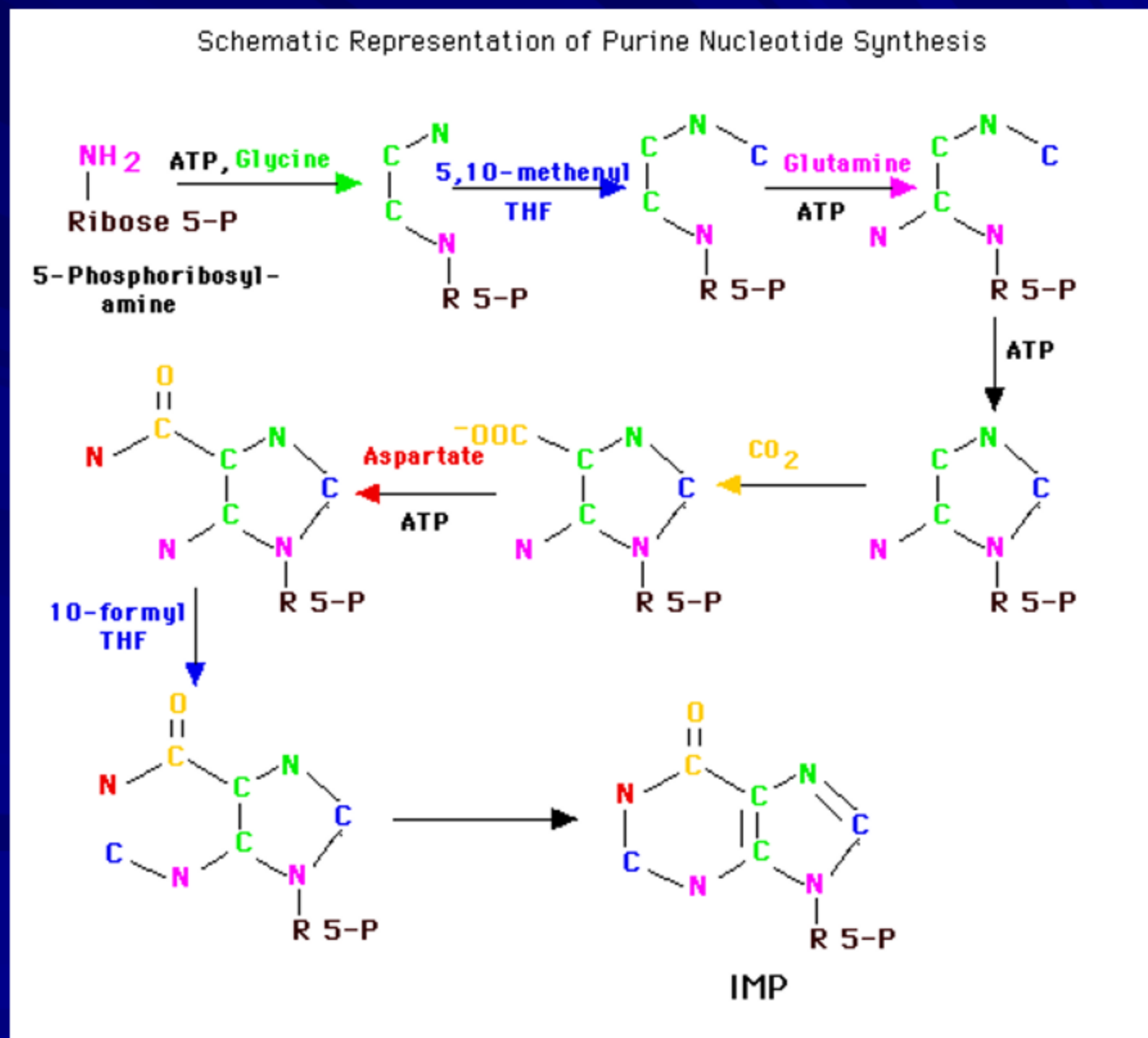
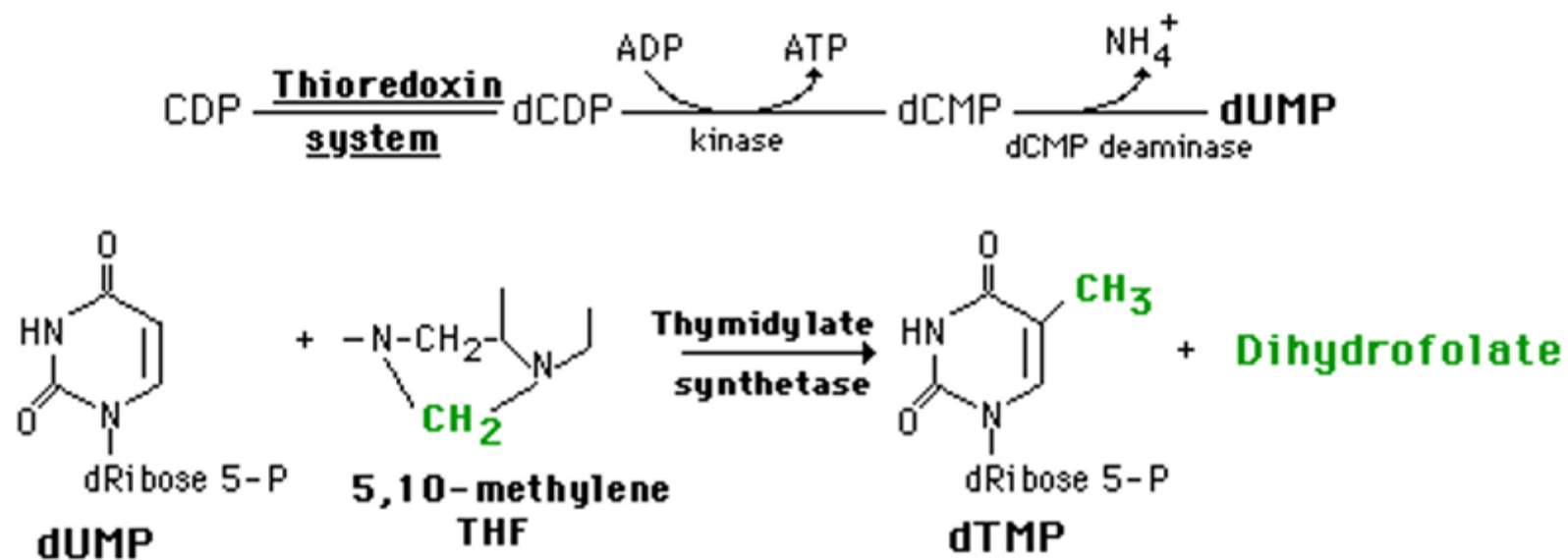


FIGURE 4: MECHANISM OF ACTION – EXAMPLE [2]

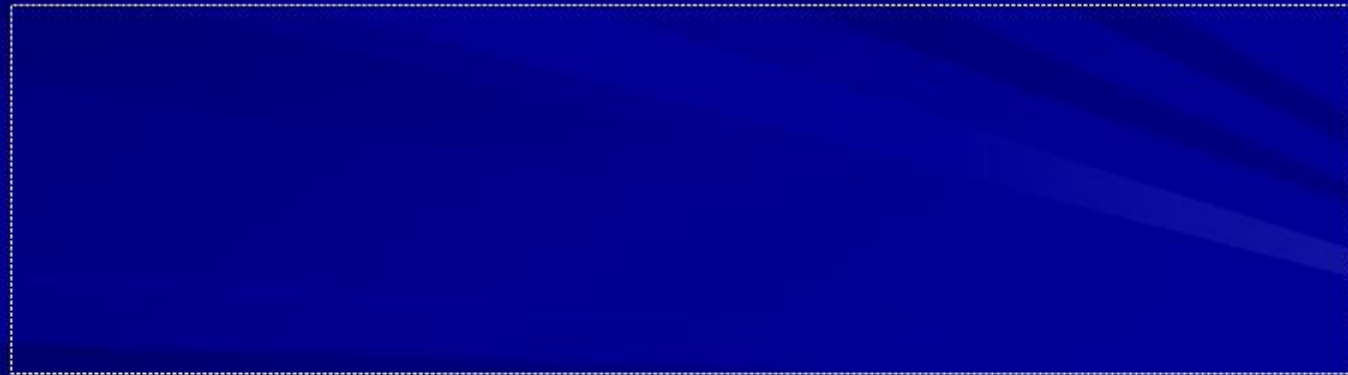


Dihydrofolate must be subsequently reduced to the tetrahydro form.

Sources of Folic Acid

- Cereals (100-400 mcg), dark green vegetables (120-160 mcg), citrus fruits (50-100 mcg) [10]
- Folic acid may also be found in supplements and multivitamin combinations sold at pharmacies

Folate Deficiency



Causes of Folate Deficiency

- Decreased intake (diet, malabsorption)
- Increased need (pregnancy)
- Also, consider decreased availability (antifolate drugs etc.)

WHAT ARE NEURAL TUBE DEFECTS (NTDs)?

- The neural tube forms in the embryo and then closes (between the 2nd and 4th week of gestation)
- A neural tube defect occurs when the neural tube fails to close properly
- The two most common NTDs are anencephaly and **spina bifida**

How do NTDs Occur?

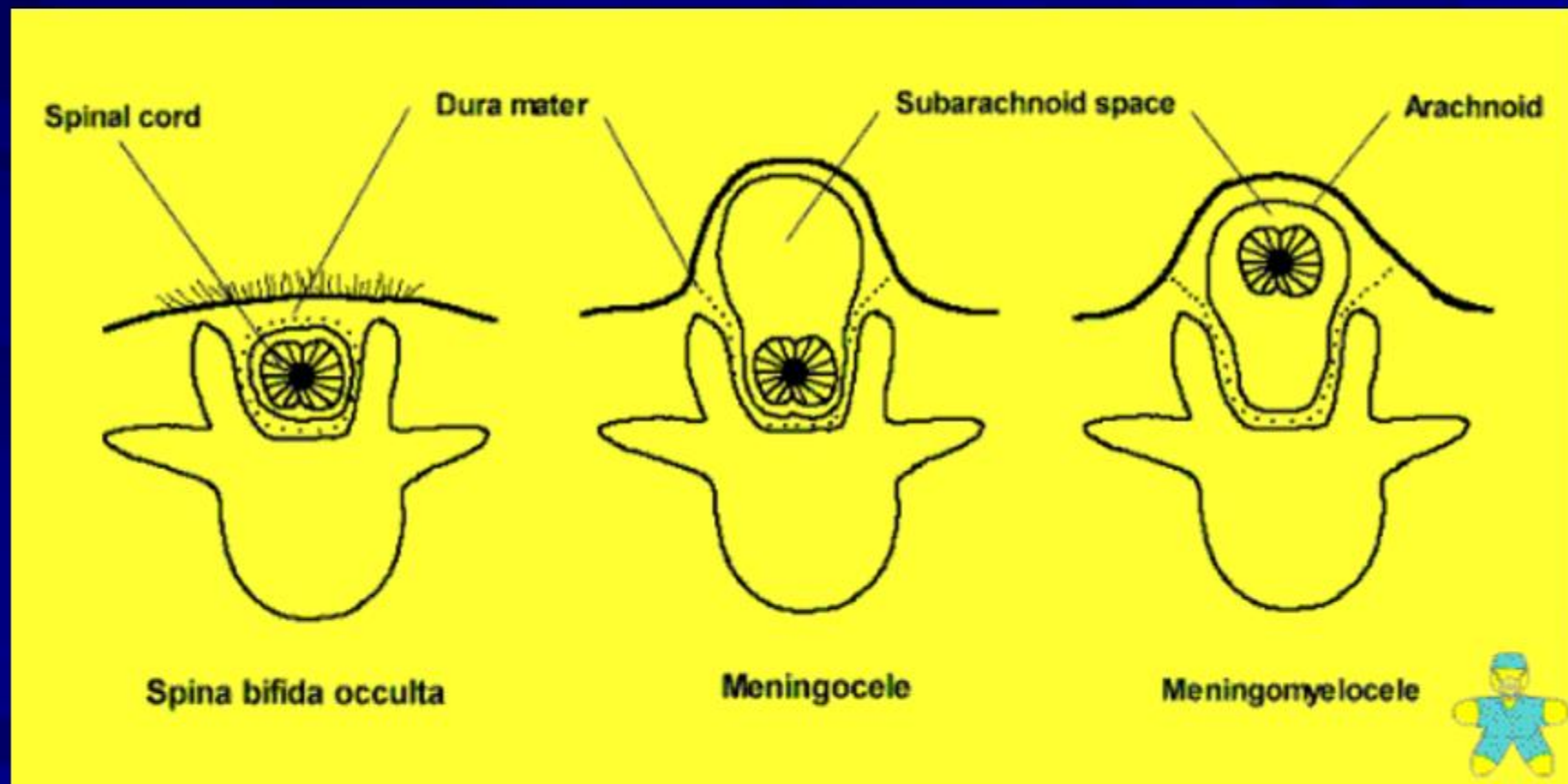
- Neural tube starts as a ribbon of tissue in embryo.
- Folds in on itself and forms a tube within first month of pregnancy
- Ultimately forms the spinal cord, spine, brain and skull

NTDs result when the neural tube doesn't properly close.

What is Spina Bifida?

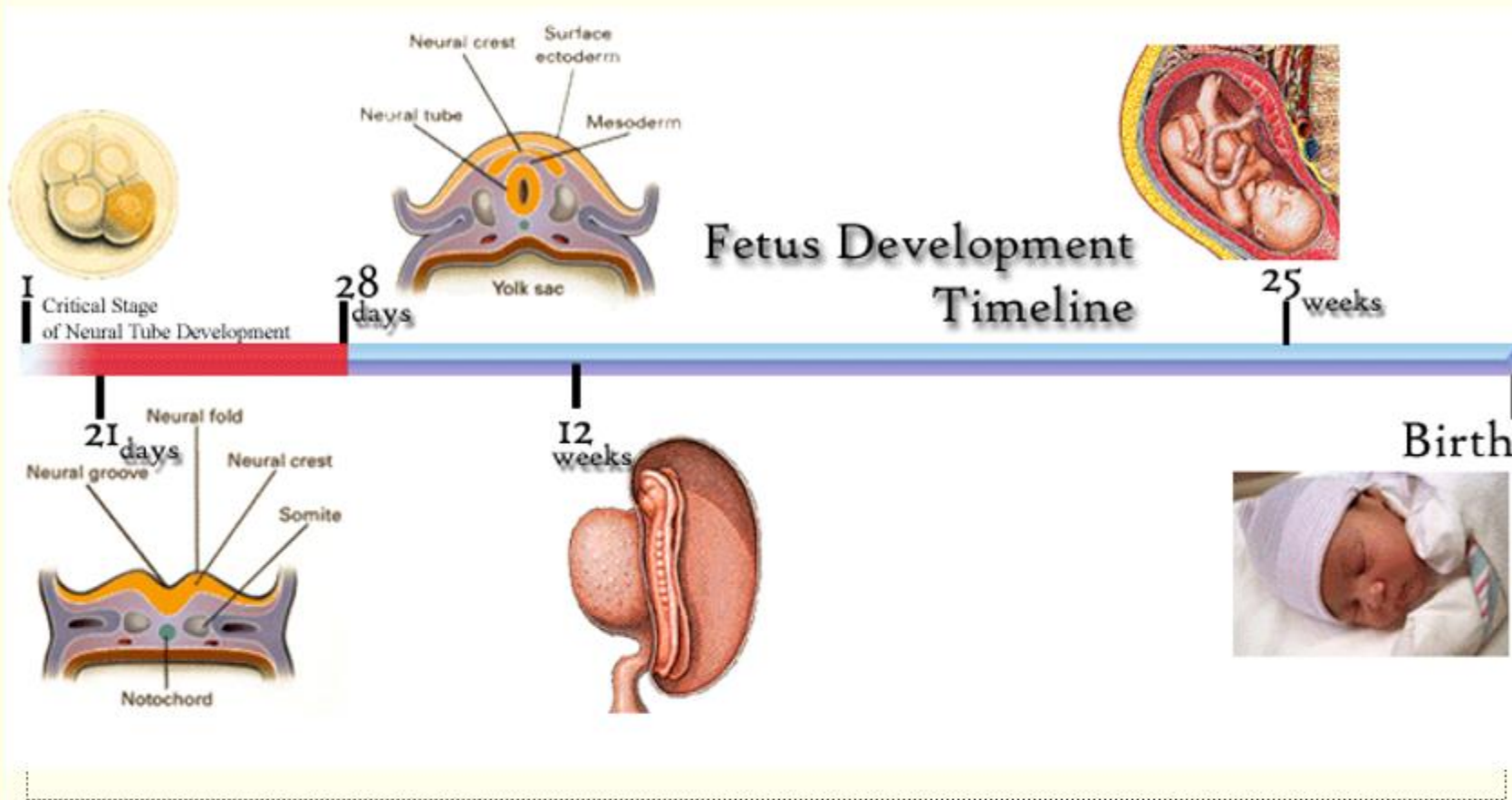
- Occurs when the two sides of the spine fail to close and protect the spinal cord
- There are two forms of spina bifida:
 - 1) Spina bifida **occulta** (mildest form)
 - 2) Spina bifida manifesta which includes two types of spina bifida: **meningocele** and **myelomeningocele**

What is Spina Bifida?



Source: http://www.surgical-tutor.org.uk/default-home.htm?system/hnep/neural_tube.htm~right

Neural Tube Development



What Causes Spina Bifida?

- Largely unknown
- Some evidence suggests that genes may be involved. (Northrup H et al, 2000)
- A high fever during pregnancy or epileptic women who have taken the drug valproic acid to control seizures may have an increased risk of having a baby with spina bifida. (Lewis DP et al, 1998)

Spina Bifida

- Baby's spine is not completely formed.
- May cause paralysis of the lower body, bladder and bowel control problems, and learning disabilities.
- Affects approximately one in every 1,000 newborns
- Average lifetime cost for child with spina bifida is in the hundreds of thousands.



Source: Centers for Disease Control and Prevention, Spina Bifida Association of America.

Anencephaly

- Top part of the brain and skull doesn't completely form
- Affected pregnancies either result in miscarriage, stillbirth, or death shortly after birth



Who is at risk for NTDs?

- All women capable of becoming pregnant
- 95% of NTDs occur in women with no family history of NTDs
- There are some known risk factors



Some Risk Factors for NTDs

- Previous NTD-affected pregnancy
- Maternal insulin-dependent diabetes
- Obesity
- Race/ethnicity
- Some anti-seizure medications
- High temperatures early in pregnancy (e.g., prolonged fevers, hot tub use)
- Lower socio-economic status

Source: Centers for Disease Control and Prevention.

The Role of Folic Acid

- Can reduce the risk of NTDs by 50 to 70 percent

HOWEVER...

- Folic acid must be consumed before and early in pregnancy to lower your chance of NTDs

The Challenge

- NTDs happen in the first month of pregnancy – before most women know they are pregnant.
- Half of all pregnancies in the US are not planned.



Be prepared!

Recommended Daily Value of Folic Acid

Non-pregnant women and men aged 14 yrs and older	400 mcg
Pregnant women* and women planning a pregnancy	600 mcg
Breastfeeding women	500 mcg
9-13 years (boys and girls)	300 mcg
4-8 years (boys and girls)	200 mcg
1-3 years (boys and girls)	150 mcg

* Women with previous NTD-affected pregnancy should talk to their doctor

How Can NTDs be Prevented?

- **All** women of childbearing age should receive 0.4 mg (400 micrograms) of folic acid daily prior to conception of planned or unplanned pregnancies and continue thru 1st trimester
- Women with a history of NTD and should receive daily supplementation of 4 mg (4000 micrograms) of folic acid starting three months prior to conception and continuing thru the 1st trimester

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