25-48

MEGALOBLASTIC ANEMIA

Macrocytic Megaloblastic Anemia

Anemia :-

- ↓ed Total body Red Cell Mass

practical purposes :

- ↓ed PCV (Hematocrit)
- ↓ed Hb Concentration

(↑ed fluid → Hemodilution → ↓(false) porious Anemia)

Macrocyte → (MCV > 100)

Normal

MCV = 86 ± 10 fL
= 76 – 96 fL

Megaloblast

Erythrogenesis:
Initially cells have more proliferation
As time passes by
Proliferation of cells ↓es
In Erythropoiesis three things happens

(1) Size of Cells are Progressively ↓es.

(2) Nuclear Maturation (Nucleus progressively become condense)

(3) Cytoplasm Maturation (Heamoglobinisation of Cytoplasm)
Basophilic ⟶ Eosinophilic (↑Hb)

for Nuclear Maturation we need a definite No. of Cell division & Cell division occurs by Mitotic Replication & for Replication we Need
Vit B_{12} & Folic acid.
& Normal Erythropoiesis Occurs Due to one or of both of vit B_{12} & folic acid deficiency a cells passes by Nucleus does not Condense. In absence of vit B_{12} & folic acid

Replication is more severly affected while Transcription is not affected more. So Nucleus remains Open & there is Excessive formation of RNA → Excessive formation of protein (Heamoglobin) Wc of Excessive Hb Normoblast becomes Over Hb Normoblast with V.V Mature Cytoplasm & Immature Nucleus

So there is Abnormal Normoblast in Bone Marrow.

Normal	Megaloblast
Normoblast	Dysynchronization in Maturation of Nucleus & Cytoplasm
Cytoplasm & Nuclear Maturation Maturation & Synchronized.	
(In Normal Cases where Nucleus is open Cytoplasm is Pink i.e Initial of 0. & Where Nucleus is Condense Cyto is Pink e.g Normoblast)	Nucleus → Immature Chromatin → Open (loose lacy) Cytoplasm → ↑ Hb

So Normal Large No of Megaloblast accumulate in B.M. Normally they are phagocytosed & don't comes into blood.

Due to def of vit B_{12} & Folic acid there is also Maturation problem in Granulopoiesis

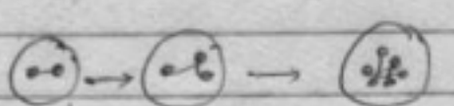
So we found very large cell in Granulopoit pathway.
(2-3 times larger than normal Myelocyte)

So Such a pt Not Only have

Anemia

but also have

Leukopenia (Neutropenia)



(def B_{12} & folic acid)

Such a pt also have ab Maturation of platelate So they also have

Thrombocytopenia.

So the Right Condition is

Megaloblastic Pancytopenia

Thus B_{12} & folic acid deficiency also affects the other rapidly proliferating tissue of body

eg G.I Mucosa

There are larger cells in G.I.T
eg
Cells in Tongues changes
i.e upper Surface of Tongue become more Smooth shiny & glassy (↓ papilla)
↳ Mucosa become thin & Muscle look through Mucosa like BEEF.

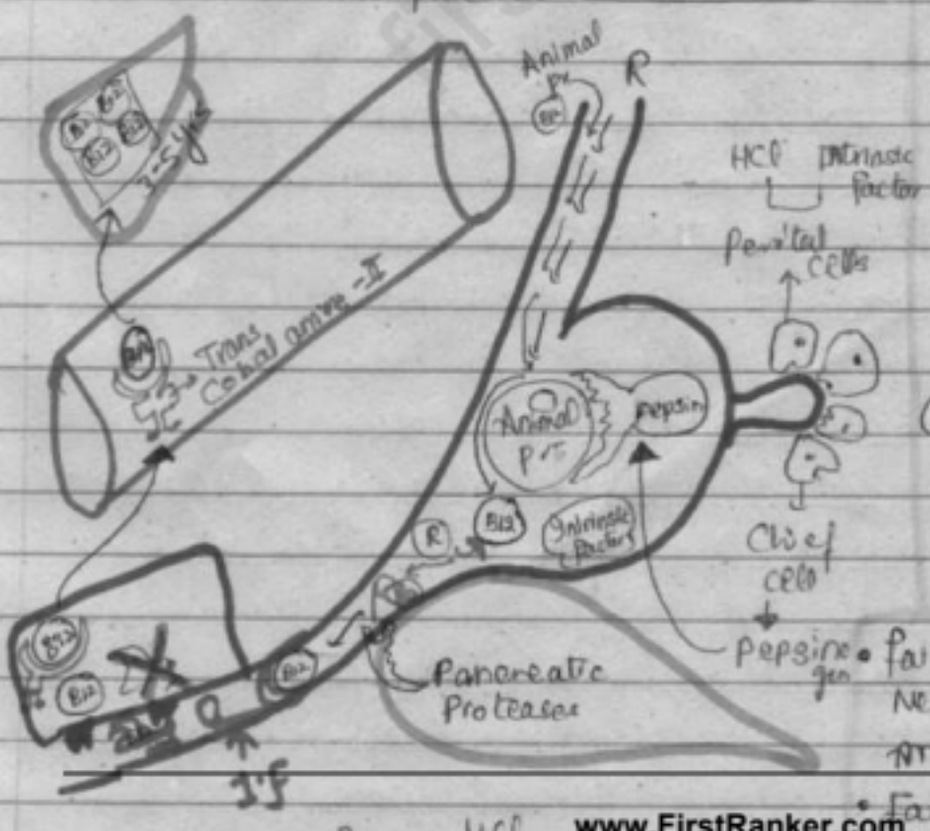
SOURCES OF VIT B12 & FOLIC ACID

- 2-3 g/dl.
- Animal product

B12 Cobalamine

Folic acid

- Green leafy vegetables
- Citrus fruit (but it is destroyed by Cooking (Its def also cause Neural tube defects)



- failure of ant Neuropore → Anencephaly
- Failure of post Neuropore → Spina bifida

Anterior Neuropore → closes at day 25th
Posterior " → Closes at day 27th

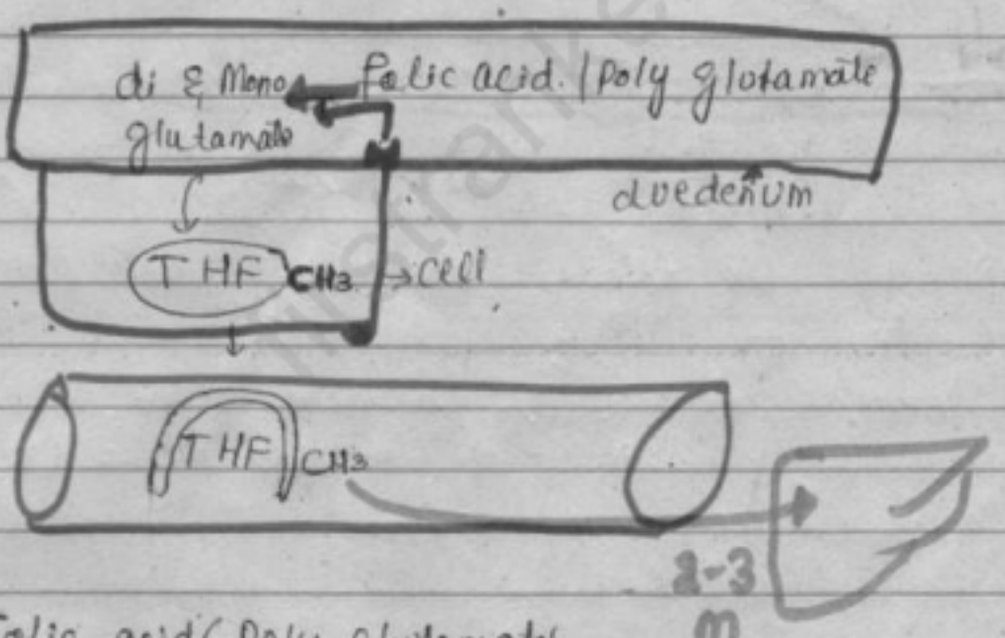
Every day = 50–100 gm/day.

R Protein present in plasma they are Cobalamine philic i.e why they are called Cobalophilic
R binds bind with B12 in stomach after stomach Enzyme have acted upon Animal protein.

Pepsin act on Animal protein & release Cobalamine R pr bind with B12 as they reach the duodenum Pancreatic lipase act on R & digest the R so B12 will come out.
No Intrinsic factor binds with B12, In Terminal Ileum Surface receptor will be activated & This [I.f + B12] is Internalized (Endocytosis) In these cells I factors is digested B12 is set free.
It is then bind with Trans Co-II & Secreted into blood → B12 → Liver (3–5 yrs)
Some of it is stored there

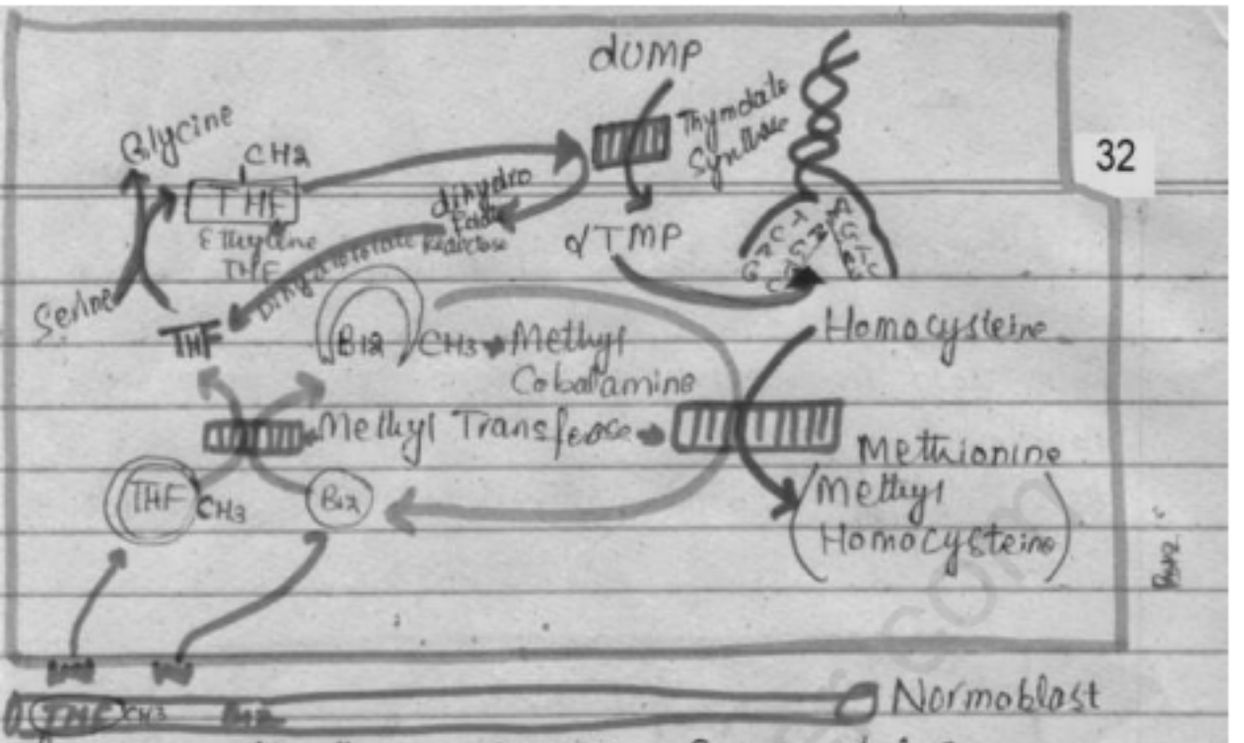
will do important functions.

Folic acid in nature is present in form of poly glutamates.
As these poly glutamates passes through G.I.T



Folic acid / Poly glutamates
↓ Enzyme present in duednum
di / mono glutamate
↓ Circulation
THF CH3 → Liver → 2-3 m

Any cell which divide & Multiply can express surface receptor for vit B12 & folic acid.



through all this process folate helps in Maturation of these cells.

If there is folate deficiency this process does not taken place

(Serine provide 1 C atom to THF & THF provide this to dUMP → dTMP.

① In absence of B12 THF will not be demethylated & remains lipid Soluble & comes out of cell ↓ Intracellular concentration

② THF Can not be Converted to active form.

So all above System is disturbed & there is Megaloblastic Anemia.

Deficiency of both B12 & folic acid produce Similar Complications.

Macrocytic Megaloblastic Anemia with leukopenia / thrombocytopenia & glossitis

~~Monocyte → Anemia → Megaloblast~~

Pt with B_{12} def & folic acid deficiency both have same
bone M picture & pheripheral blood picture.
Folic acid deficiency donot produce
Neurological disorders
Until it is produced Perconceptional
B_{12} deficiency 20% of people have.
Neurological
U.V Severe B_{12} deficiency.

Methyl malonyl CoA requires adenosyl Cobalamin in absence of B12 ↓Succinyl CoA doesn't form.

↑ Malonyl CoA → ↑ Propionyl CoA

One of most sensitive marker of B12 def is ↑ Malonyl CoA

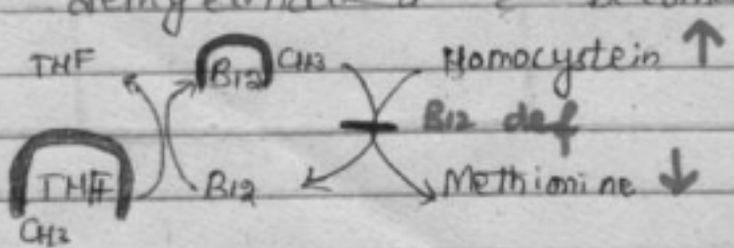
These Malonyl CoA & Propionyl CoA accumulate in CNS & PNS.

When these ab FA accumulates in Myelin sheath then sheath will not be stable & neuron become demyelinated

So Neuron will not conduct more

Neuron which are most myelinated are suffered more.

i.e All rapidly conducting neurons are demyelinated & becomes dysfunctional



We require Methionine for formation of Choline

When Methionine ↓ → ↓ Choline

So Choline Containing phospholipid ↓ which is required for Myelination → led Myelination

Proprioception:
All Sensation generated from Locomotor Systems

↑ Homocystein → damage the Endothelial cells → platelate stuck on damage Endothelial cells → Thrombus formation.
Chronic ↑ Hcystein → ↑ damage of Endo → chronic Inflammation → Atheroma.

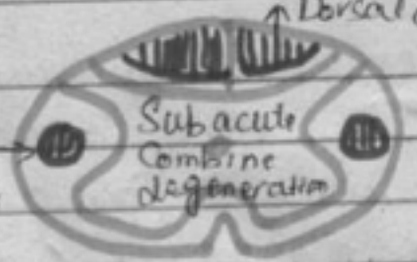
Clinical Features

- Paraesthesia (due to demyelination of pheripheral Sensory Neurons)
  Hyperesthesia Hypoesthesia
  ↑ed Sensation ↓ed Sensation.
- Demyelination of Dorsal Column medial lemniscus system. So there is loss of Sensation of
  - Position
  - Vibration
- Ataxia
- Demyelination of Cortico Spinal pathway Lower motor neuron released from Influence of Upper motor neuron
  So LMN Overfire
  So there is ↑ed Reflexes.

B12 def can cause both UMN & LMN lesions.

- Babensaki Sign → move upward.

Parasthesia → PASED → dementia B12 def
Ataxia Spastic paraplegia



i.e both
degeneration along with Neuropathies.

So most of pt with B12 def there is
Macrocytic Megaloblastic anemia
+
Neurological disorders

- May be pt have Only Macrocytic Megaloblastic Anemia without Neurological disorders.

(Folic acid very effectively absorbed in Jujenum)

- In absence of B12 level of Malonyl CoA les both in Blood & Urine.
- If B12 is at lower limit of Normal value & we want to see whether it is enough for each & person or not

we check Malonyl CoA in blood & Urine If it is still normal it means ↳ is level of B_{12} is sufficient for such a person & Malonyl CoA does not accumulate.

- If in blood of a pt Only Homocysteine level is high It is folic acid deficiency.
- but If in blood of a pt both Malonyl CoA & Homocysteine level is high It is B_{12} deficiency.

- B_{12} is part of Myelin Sheath but folic acid does not.

B_{12} def.

Causes ① Megaloblastic Anemia
(Most common cause of Mild Macrocytoses is Alcohol.)

Macrocytoses

Without Megaloblast
- Alcohol
- Hypothyroidism
- Cirrhosis
- Hemolytic Anemia
- ↑ Erythropoiesis (↑ Reticulocytoses)

With Megaloblast
- ↓ B_{12} def
- ↓ folic acid
- Methotrexate (distrupt DNA Syn)
- 5F-U

Macrocytosis in Cirrhosis b/c
In such a case some of
RBC becomes the target cells.

e.g

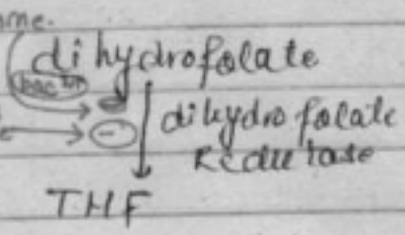
Normally more Hb. is at pheripby so Center is pale

Cirrhosis
Hb also present in the center

Target cell

Hemolytic Anemia → As large No of RBC is destroyed So B.M undergo compensation by ↑ing the Erythroparsee So releasing large No of Reticulocyte into blood
(Reticulocyte size is greater than Mature RBC)

Pyrimethamine.



(Inhibit DNA synthesis)

B_{12} & folic Acid deficiency

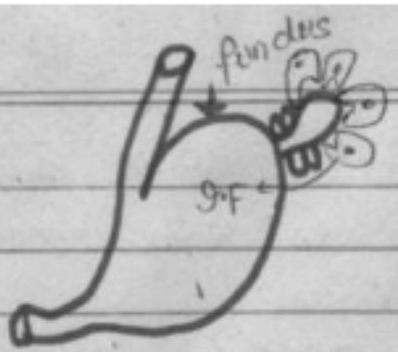
vitamines deficiency
↓ Intake
↓ absorption
↑ Requirment

Normally we need 2-3 mg/dl of B_{12}
In most of pt B_{12} deficiency occurs who are strict vegetarians.
So B_{12} not commonly occurs due to ↓ed Intake.
& also B_{12} def is not due to ↑ed demand (b/c of B_{12} stores in body)

Most Common deficiency is due to Malabsorption.

Most of patient who have folic acid def is due to
↓ed Intake
↑ed demand.
less commonly due to Malabsorption

In gastrectomy Macrocytic Megaloblastic Anemia occurs due to def of Intrinsic factor this is not known as Pernicious Anemia.
Pernicious Anemia:-
Macrocytic Megaloblastic Anemia due to B_{12} def
which is due to Intrinsic factor deficiency which must be due to Auto Immune dysfunction of Gastric Mucosa.



Pernicious anemia is Most Common after the age of 40yrs

B12 def

1. Strict Vegetarians
2. Breast feeding Mother.
3. Achyloridia
4. Drugs e.g Omeprazole (↓HCl Secretion)

Auto Immune reaction which occurs against parietal cells in pernicious Anemia is both T Cell mediated Response.

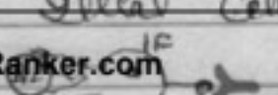
Ab response

Anti parietal Ab

Anti Intrinsic factor Ab (binds at B12 Binding Site)

Anti Intrinsic F. Ab + B12 (binds with Complex of (IF + B12))

So this Complex can not enters into Ileal Cells.

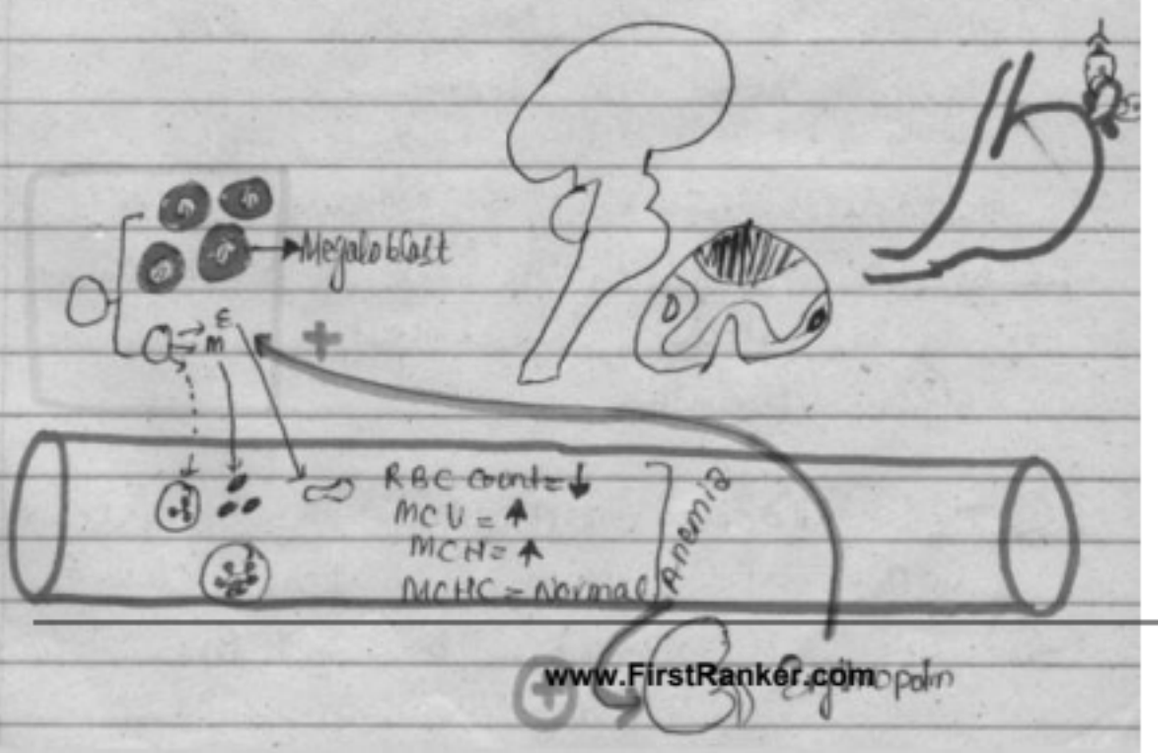


Most Common of these Ab which is dx. of pernicious Anemia is "Anti Intrinsic factor antibody."

If blood is taken from 100 person above age of 70yrs 10-15% will have Antiparietal Antibody but do not have pernicious Anemia so still they have enough I.F to abp B_{12}.

Pernicious Anemia

↓ B_{12} → ↑ Homocysteine
→ ↑ Melonic Acid



BM

In pernicious Anemia there is ① hypercellular B.M
In B_{12} All
dep Erytroid
Granulopoid
Thromolyoid
↑ed in Size.

② Megaloblastic R in Erythropoitic pathway
③ Giant cells.
④ Circulation → Anemia
→ Neutropenia (Leuckopenia)
(Hypersegmented Neutrophil lobes)
→ Thrombocytopenia

How Anemia occurs while BM is hypercellular bc most of cells are destroyed within B.M & whatever cells are produced are Macrocytic & large RBC undergo hemolysis easily.

↓ Production → RBC ↓ Survival → RBC

CNS: ① demyelination of pheripheral Nerves.
② Sub acute Combined degeneration
③ Dementia.

GIT: Mucosa destruction & Infiltration with lymphocyte these changes can not be reversed by wt B_{12} Injection

i.e GIT cells will become megaloid & do not absorb well. Same changes in GIT also occur in def of folic acid but Auto Immune reaction does not takes place.

So there is deficiency of other vit in body also b/c of Malabsorption.

- ↑ level of Homocystein → Endo damage ↑ risk of Arterial & Venous thrombi.

Vit B12 def.

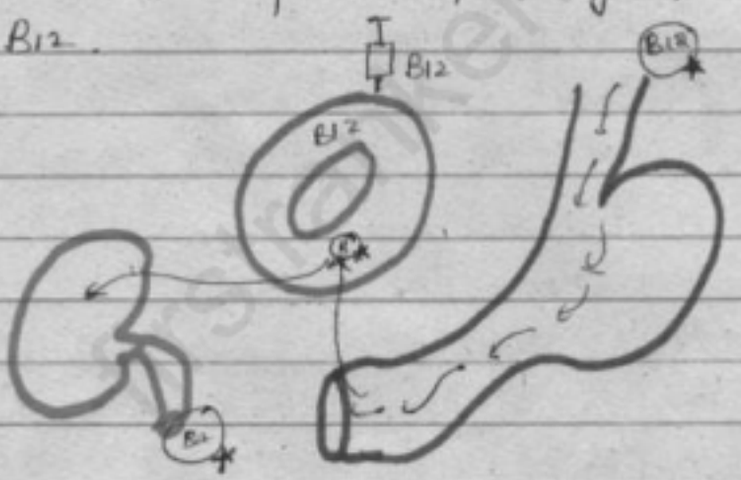
1. Strict Vegetarian
2. Pernicious Anemia (Most Common)
3. Achlorydia
4. Fish tapeworm
5. Pancreatic failure.
6. Bacterial Overgrowth in GIT
7. Gastrectomy
8. Malabsorption Synd. (Tropical Sprue → attack the villi of Small Intestine)
9. Non tropical Sprue.

(there are certain substances in food & GIT develops allergic reaction to that substance.

10. Chronic disease (autoimmune disease invoke granuloma formation of terminal ileum)

(11) G.I.T T.B (most common site is Illeum)
(12) Lymphoma in Illeum
(13) (Removal) Resection of Illeum.
(14) ↑ NO Intake.

Schilling Test:
Determine the cause of deficiency of B_{12}.



Pt - 1

(1) Give the pt Radiolabelled Cobalamine orally (B_{12}^*)
(2) B_{12} IM injection → all the binding sites are loaded
(3) If in GIT there is no any obstruction to B_{12}^*, B_{12}^* enters into Circulation → As there are fed binding sites for B_{12}^* So this Radioactive B_{12} enters into Kidney & Appears in Urine.

④ When $(B_{12})_A$ present in Urine It means abs is about the Primary Problem is

↓ Intake

Pt - 2

Orally → Radio labeled B_{12}^*

IM → B_{12}

B_{12}^* → does not appears in Urine

Now

Give B_{12}^* + I. factor

Now It appears in Urine so the problem was Intrinsic factor.

Pt -3

Orally → Ra. B_{12}^*

IM → B_{12}

B_{12}^* does not appear in Urine

Orally → B_{12}^* + I.F

does not appears in Urine

Now also, give

Antibacterials

Now B_{12}^* appears in Urine.

So the problem is

Bac Overgrowth

Pt -4

Orally → Rad B_{12}^* Not appear in Urine

Rad B_{12}^* + IF " " "

+ Anti bac " " "

B_{12}^{*} + ~~9f~~ + ~~Antibac~~ + Pancreatic Extract

B_{12}^{*} appears in Urine

Problem is Chronic Pancreatitis Cleads to Steatorrhea heavy, bulky V.V bulky offensive Smelly Stool float on pot & difficult to flush Such a pt can be dx from Steatorrhea)

Pt – 5

$RadB_{12}^{*}$ ⟶ B_{12}^{*} not appear in Urine.

Rad B_{12} + 9f ⟶ " " " " "

" + Antibac ⟶ " " " " "

" + Pan. extrate ⟶ " " " " "

Problem is any Ileal disease

Folic Acid deficiency

(1) ↓ Intake (green leafy vegetable)

(2) Alcohol (most Common)

(Alcohol does not allow Absorption of ⓐN Ionoglutamate)

(3) Contraceptive pills (does not allow Abp of N Imoglutamate)

* Alcohol also cause N Multivitamine def bc Alcohol fulfill the need of food So proper food will not be taken

③ Alcohol disrupt the liver function & does not allow the stores of folic acid to secrete d.

④ Phenytoin Na → block the Enzyme Conjugase

⑤ ↑ed demand
- pregnancy
- lactation
- Cancer in body
- growing age
- Hemolytic Anemia
- Iron deficiency Anemia

} ↑ Erythropoiesis

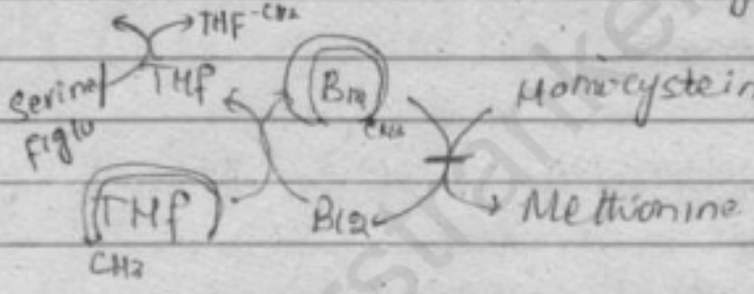
Pt with Macrocytic Megaloblastic Anemia Donot give folic acid alone. b/c folic acid recover the Hematological & B.M abnormalities but ppt the Neurological disorders b/c whatever Small Rx is also used in Hematopoitic pathway & there are CNS disturbances.

Test for Folic acid def
① Serum F.A ↓ed
② RBC.F.A → ↓ed (more reliable) b/c

Serum F.A most rapidly fluctuate with food but RBC F.Acid does not fluctuates more.

③ ↑ Homocystein (b/c in def of folic acid B12 is not Metylated

So



↑ Homocysteine

(Homocystein level goes up both in B12 & folic acid deficeency)

④ No affect on Malonyl CoA

⑤ ↑ed figlu in Urine

(formino glutamic acid)