Pernicious Anaemia - 2025

B12 (cobalamin) deficiency, Addison-Biermer Anaemia

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NICE NG239 2024
https://www.medicines.org.uk/emc
https://www.medicines.org.uk/emc
https://bnf.nice.org.uk/
BMJ 2024;385:q1019
Pernicious Anaemia Society

What is Pernicious Anaemia ? 1/2

- "Pernicious" = "pernicies" ruin, destruction, detrimental, noxious, deadly.
- Anaemia

	Age	Hb in g/L
Teen	= 12-14	<120g/L.
Men	= 15+	<130g/L
Women	= 15+	<120
Preg		<105 -110
Post Partum		<100

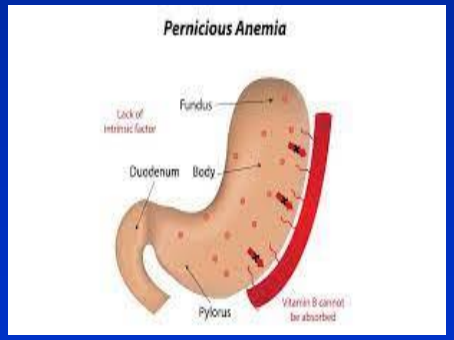
- Cobalamin Level Def <200 / 180pG/L
- Cobalamin Level Normal >300pG/L

Folate deficiency Level <3 mcg/L

What is Pernicious Anaemia 2/2 ?

- AID of gastric mucosa leading to atrophy and reduced number of parietal cells which secrete IF (IF is essential for absorption of dietary B12. This ⟹ leads to megaloblastic anaemia, (macrocytosis of RBCs).

  - ⋆ In PA There are Ab to IF in 50-70% of patients.
    In PA there are Ab to Parietal cells in 90% (False +ve in 16% females >60yo).



With PA there is an increased risk of non-cardia gastric cancer (0.27%/person-years) and carcinoid.

Pathophysiology – 1/2

- B12 (cobalamin), is a water-soluble essential vitamin and its source is animal protein = (red meat, dairy, eggs and fish).
- Dietary B12 binds loosely with R-factor of saliva for transport and haptocorrin in stomach.
- IF (a parietal cell-secreted glycoprotein antibody) binds with B12+ haptocorrin complex and is transported to terminal ileum as IF-B12.
- Here the receptor retains IF and allows absorption of B12 into blood stream.
- Serum B12 = cofactor ⇨ Synthesis of DNA, Fatty Acids and Myelin.
- B12 if in surplus of need, is stored in Liver. Supply can last 3 years.

Pathophysiology – 2/2

This slow processing of DNA leads to megaloblastic anaemia and low PMNLs.

B 12 deficiency takes 2-5 years to develop and leads to accumulation of homocysteine and methylmalonic acid (MMA) which cause myelin damage, neuropathy, ataxia and SCDSC (subacute combined degeneration of Spinal Cord).

Parietal cell Autoantibody = present in 90%. This has high sensitivity but poor specificity.
IF autoantibody = present in 55% cases and has high specificity.

Mohamed M et al. Pernicious anaemia. BMJ 2020;369:m1319
https://www.ncbi.nlm.nih.gov/books/NBK540989/

Prevalence

- Worldwide: (0.1%+ in all ages) and 1.9%+ in over 50.
  UK: 6 mil = B12 Def = <1%.
  USA: 25.5 mil = B12 Def.
  India: 0.5 bil.
- UK, USA and Europe B12 deficiency:

3%	20-39 yo
4%	40-59
6%	60-84
20%	85+yo.

Normal = >300pG/L

Marginal B12 deficiency – What is it ?:

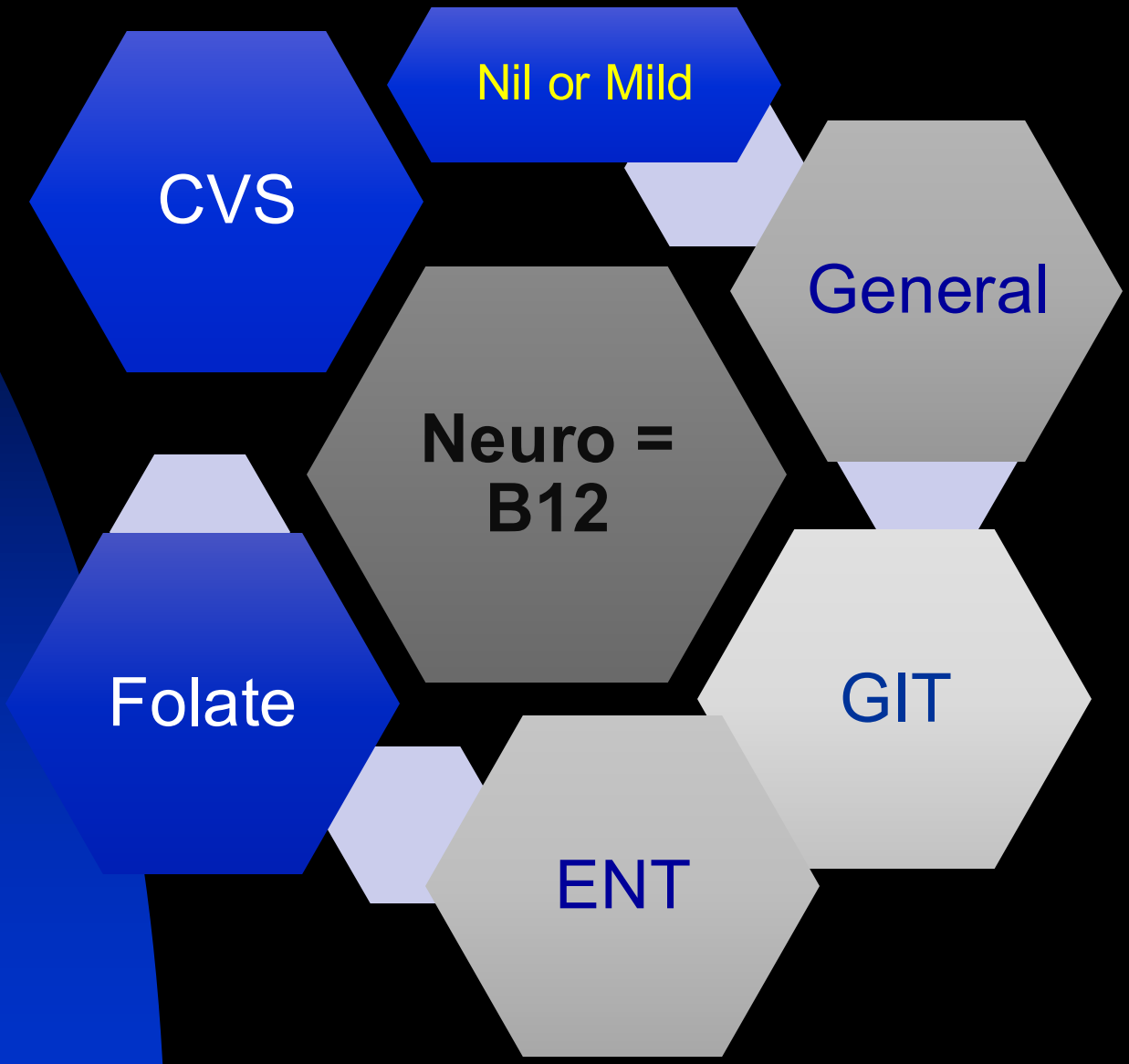
- Marginal Depletion 15% in 20-59 yo = B12 = 148-221 pmol/L
  Marginal Depletion 20%+ >60yo = B12 = 148-221 pmol/L
  Marginal Depletion with vegan diet 11% deficient in B12
  Folate deficiency unknown.
  https://cks.nice.org.uk/topics/anaemia-b12-folate-deficiency/references/

RFs (Causes) of B12 or Folate Def

Risk Factors for PA

- Old age, 0.1% (43yo) ⟹ 1% (60+)
- Low B12 diet excluding animal-source foods.
- Low intake of eggs, milk, fish or supplement.
- Food allergy.
- Eating disorder.
- Family h/o B12 def or Autoimmune disorder.
- Co-morbidity with atrophic gastritis, CD, Thyroid.
- Weight reduction surgery or ileal disease.
- Recreational drugs (NO).

S/S

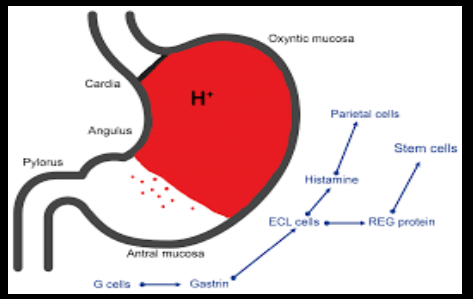


S/S – B12 (or Folate) Deficiency

- Nil or Mild: Insidious, PA can cause s/s without anaemia or low B12, or no symptom.
- Gen: Anorexia, weight loss, Mild pyrexia, fatigue, fractures due to B12 def and BMD - Osteoporosis.
- GIT: Angular cheilosis, Tongue, diarrhoea, Liver enlargement, Mild jaundice.
- CVS: Angina, CCF / murmurs.
- Neuro: Symm Neuropathy, ataxia, paraesthesia, muscle weakness, optic lesions, lack of mental and physical drive, psychiatric disturbances = MCI dementia and sphincter incontinence.

Untreated complications of PA, B12 def

- Neurological (40%), some are irreversible.
- Increased risk of gastric cancer (0.27%) and carcinoid.
- Increased risk of fractures (hip, spine and forearm).
- Gait, incoordination ⟹ falls.
- Neural tube defects in pregnancy.
- False positive pap smear and Infertility.
- Heart failure, anaemia and renal function impairment.
- MCI and Dementia.
- Vision disorder due to optic nerve lesions.
- Fatigue, tiredness = common symptom.

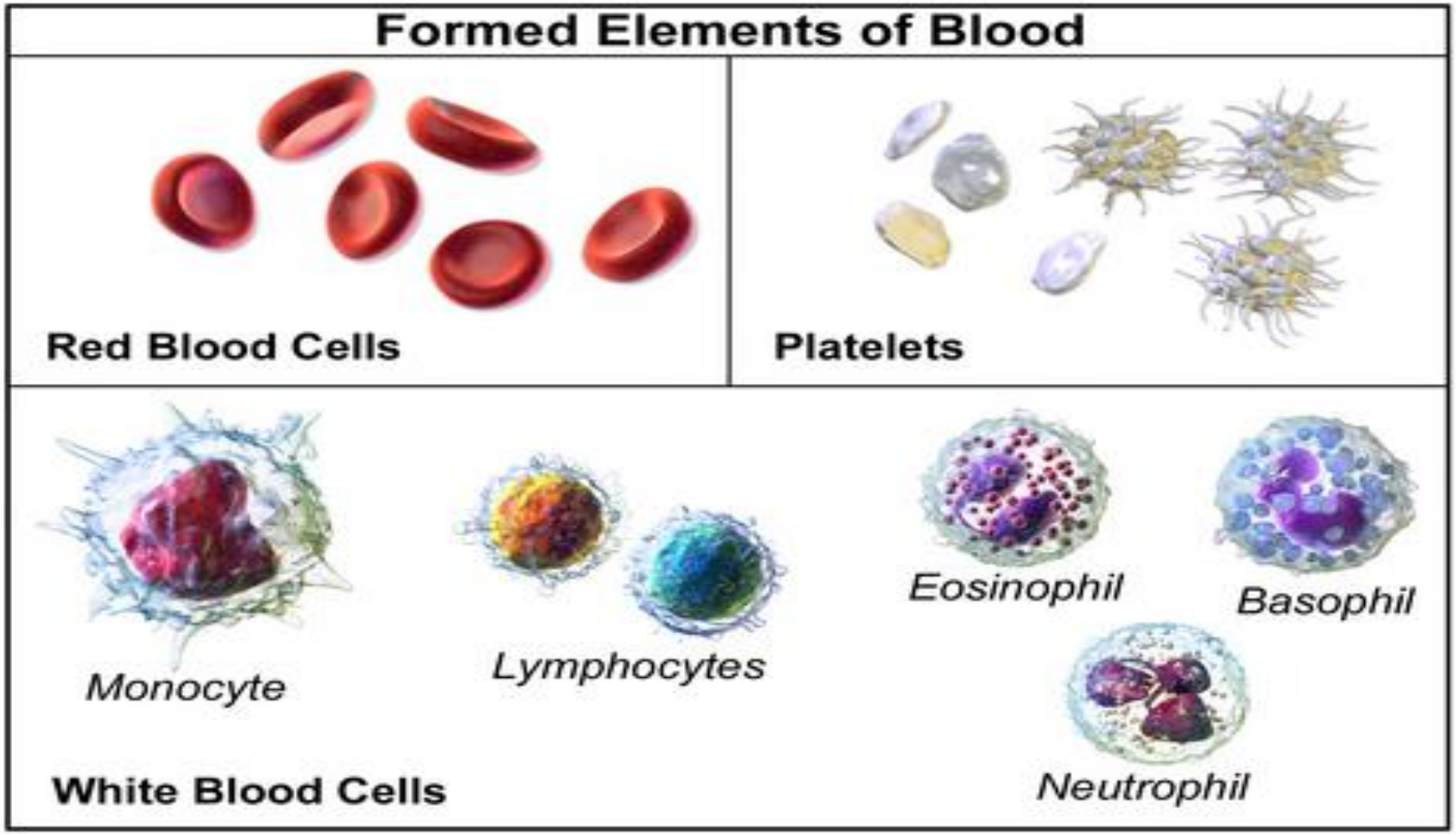


Basic GP Investigations

- Do not delay B12 replacement awaiting test results.
- Take note of OTC meds.
- FBC (MCV, Hct and Hb and a blood film).
- LFT including GGT, TFT, CRP, UE and eGFR.
- Total Serum B12 and / or Active B12= (holotranscobalamin), even in pregnancy).
- If there is h/o recreational NO check MMA or plasma homocyseine (hosp lab).
- S Folate level.
- MMA (methylmalonic acid) level rises with B12 deficiency (neuro damage).

Homocyseine without B12 is not converted to other amino acids so its level rises and this risen level indicates B12 deficiency. Hct Men = 40-54% Hct women = 36 – 48%

FBC, Haemogram

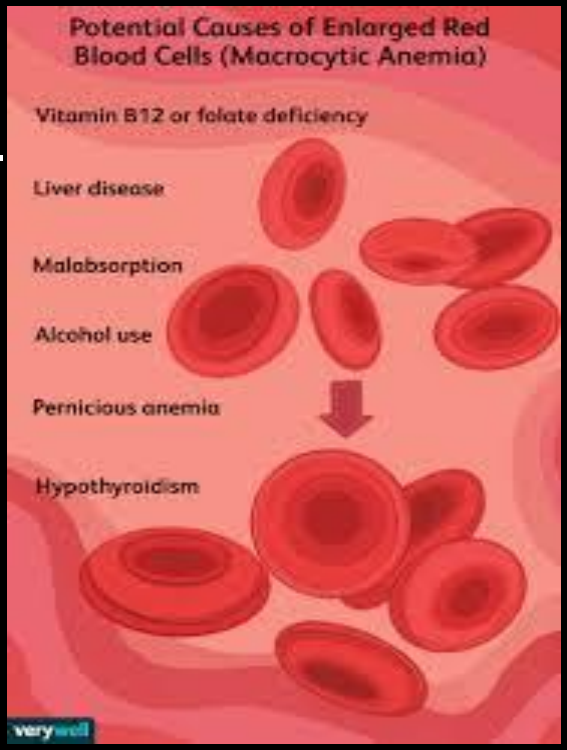


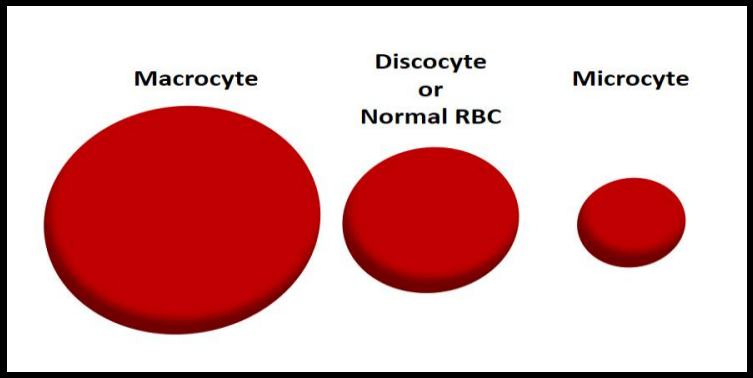
FBC, Haemogram

Parameter		Male	Female
Haemoglobin	g/L	135 - 180	115 - 160
WBC	$x10^9/L$	4.00 - 11.00	4.00 - 11.00
Platelets	$x10^9/L$	150 - 400	150 - 400
MCV	fL	78 - 100	78 - 100
PCV		0.40 - 0.52	0.37 - 0.47
RBC	$x10^{12}/L$	4.5 - 6.5	3.8 - 5.8
MCH	pg	27.0 - 32.0	27.0 - 32.0
MCHC	g/L	310 - 370	310 - 370
RDW		11.5 - 15.0	11.5 - 15.0
Neutrophils		2.0 - 7.5	2.0 - 7.5
Lymphocytes		1.0 - 4.5	1.0 - 4.5
Monocytes		0.2 - 0.8	0.2 - 0.8
Eosinophils		0.04 - 0.40	0.04 - 0.40
Basophils		< 0.1	< 0.1

D/D – Macrocytosis

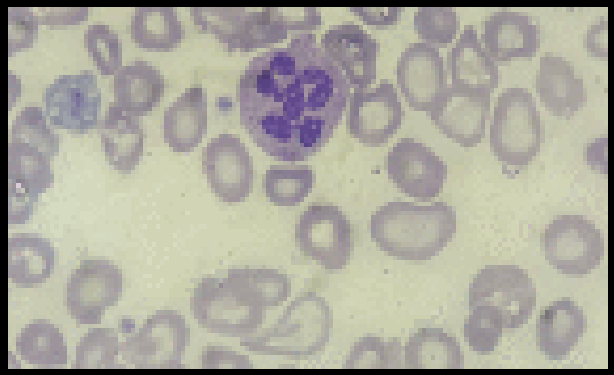
- B12 and Folate deficiencies (any cause).
- Alcohol:with no anaemia or LFT changes.
- Drugs: Antimetab (hoxycarb, MTX, AZT.
- Haematological abnormalities:
  - Myelodysplasia, Aplastic anaemia.
  - Paraprotein cancers e.g. myeloma.
  - Reticulocytosis.
- Liver disease — chronic liver disease.
- Pregnancy and the neonatal period.
- Severe untreated hypothyroidism (MCV falls with treatment).
- Smoking.
- RBC >110 fL = macrocyte
  1 fL = 10^{-15} L





Diagnostic pitfalls

- FBC and Film.
  PA has macrocytes (>100) but if patient also has Iron-def anaemia (small RBCs and low plat) then MCV may be NAD.
- Normal neutros are oval but with PA or Folate Def 5% neutros have 4-5 lobes = PA or Folate deficiency.



- B12 level.
- B12 in normal pt = approx. 200 nG = 148pmol/L.
- NICE B12 def = Total B12 <180nG = 133pmol/L.
- NICE B12 def = Active B12 (holo) = <25pmol/L.
- NICE B12 Suspected def = Total B12 180-350
  = Active B12 25-70

Medication linked to causing PA

- Colchicine
- H_2-receptor antagonists (Cimetidine).
- Metformin.
- Pregabalin.
- Primidone (AED).
- proton pump inhibitors.
- Topiramate
- Oestrogen containing pills

Treatment of PA without Neurological S/S

Initial treatment

- I/M Hydroxocobalamin 1mg alternate days for 2w.
- No tests, watch out for allergy.

Maintenance treatment

- I/M Hydroxocobalamin1mg every 2 months for life
- Or
- Oral Cyanocobalamin 500 – 1000 mcg daily for life.
- Enhance oral supplements.
- Re-test 6-12 months

Treatment of PA with Neurological S/S

Initial treatment

- I/M Hydroxocobalamin 1mg alternate days for 3w.
- No tests, watch out for allergy.

Maintenance treatment

- I/M Hydroxocobalamin 1mg every 2 months for life.
- Seek Neurology advice.
- Re-test 6-12 months

B12 injections - Varieties

https://uk.images.search.yahoo.com/search/images;_ylt=Awr.rN3ehx9p.wEA44wM34IQ;_ylu=Y29sbwNpcjIEcG9zAzEEdnRpZAMEc2VjA3Nj?type=E210GB384G0&p=hydroxocobalamin+injection&fr=mcafee&th=790&tw=474&imgurl=https%3A%2F%2Fempower-images.s3.us-east-1.amazonaws.com%2Fimages%2FWebsite%2520Images%2FInjections%2Fempower-pharmacy-hydroxocobalamin-b12-injection-2mgml-10ml-294x490.jpg&rurl=https%3A%2F%2Fwww.empowerpharmacy.com%2Fcompounding-pharmacy%2Fhydroxocobalamin-vitamin-b12-injection%2F&size=80KB&name=Compounded+Hydroxocobalamin+%28Vitamin+B12%29+Injection+%7C+Empower+Pharmacy&oid=1&h=980&w=588&turl=https%3A%2F%2Ftse1.mm.bing.net%2Fth%2Fid%2FOIP.ks2dzLI_ElUaZQIqqOvmDAHaMW%3Fpid%3DApi&tt=Compounded+Hydroxocobalamin+%28Vitamin+B12%29+Injection+%7C+Empower+Pharmacy&sigr=CnDIRuzgdFeH&sigit=mlYbzlS2.0xB&sigi=1LunMeExV.IB&sign=Ijx6bVSpRSBx&sigt=Ijx6bVSpRSBx

Oral cyanocobalamin - varieties

https://www.google.com/search?q=Cyanacobalamin+images&sca_esv=7ad43583249a6c5a&source=hp&ei=4TMgaaLXE-m7hbIPpdmpuQs&iflsig=AOw8s4IAAAAAaSBB8c_epObV2Sy8PF-tUOI4Guy_qb3l&ved=0ahUKEwjiy4P9-YKRAxXpXUEAHaVsKrcQ4dUDCA8&uact=5&oq=Cyanacobalamin+images&gs_lp=Egdnd3Mtd2l6IhVDeWFuYWNvYmFsYW1pbiBpbWFnZXMyBxAAGIAEGA0yBhAAGBYYHjIGEAAYFhgeMgsQABiABBiGAxiKBTILEAAYgAQYhgMYigUyCxAAGIAEGIYDGIoFMgsQABiABBiGAxiKBTIIEAAYogQYiQUyCBAAGIAEGKIEMgUQABjvBUiHqwFQAFjepAFwAHgAkAEAmAHKA6AB_BKqAQoxNS40LjEuMC4xuAEDyAEA-AEBmAIVoAKcFMICCBAAGIAEGLEDwgIREC4YgAQYsQMY0QMYgwEYxwHCAgsQABiABBixAxiDAcICDhAAGIAEGLEDGIMBGIoFwgILEC4YgAQY0QMYxwHCAgsQLhiABBixAxiDAcICCBAuGIAEGLEDwgIFEAAYgATCAgwQABiABBixAxgKGAvCAgUQLhiABMICCRAAGIAEGAoYC8ICBxAAGIAEGAqYAwCSBwoxMi43LjEuMC4xoAfnsAGyBwoxMi43LjEuMC4xuAecFMIHBjItMTYuNcgHeA&sclient=gws-wiz

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Thank you.

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