Anémies

(Anémies régénératives du sang)

Tableau 1: Classification des anémies

A. Anémies régénératives	
1. Par déperdition sanguine aiguë	
2. Hémolytiques	
B. Anémies hyporégénératives	
1. Les insuffisances quantitatives de l'érythropoïèse	*
a) les érythroblastopénies	
b) les insuffisances médullaires globales	
— par aplasie médullaire	
— sur envahissement médullaire	
2. Les insuffisances qualitatives de l'érythropoïèse	
a) les anomalies de l'hémoglobinogénèse	
— par carence en fer	
— par déviation du fer	
— par défauts de l'utilisation du fer	**
— hémoglobinopathies	
— anémies sidéroblastiques	
b) les anomalies de synthèse de l'ADN	
— par carence en vitamine B_{12}	
— par carence en folates	***

* Anémies normocytaires normochromes.

** Anémies microcytaires hypochromes.

*** Anémies macrocytaires.

Tableau 2: Distribution et rôles biologiques du fer

Pigments/enzymes	Localisation	Teneur (g)	%	Rôles biologiques
Hémoglobine	Erythroblastes et globules rouges	2.5	60	Transport de l'oxygène
Ferritine et hémosidérine	Foie, rate, moelle osseuse	1.3	30	Réserves de fer
Myoglobine	Muscles	0.5	9	Mise en réserve de l'oxygène
Cytochromes	Mitochondries	0.02	0.5	Phosphorylation oxydative
Catalase	Peroxysomes	0.005		Dégradation de H_2O_2
Transferrine	Plasma	0.004	0.1	Transport du fer

Synthèse journalière = 7 g d'Hb

≈ 24.5 mg de Fe

vie des GR ≈ 110 jrs

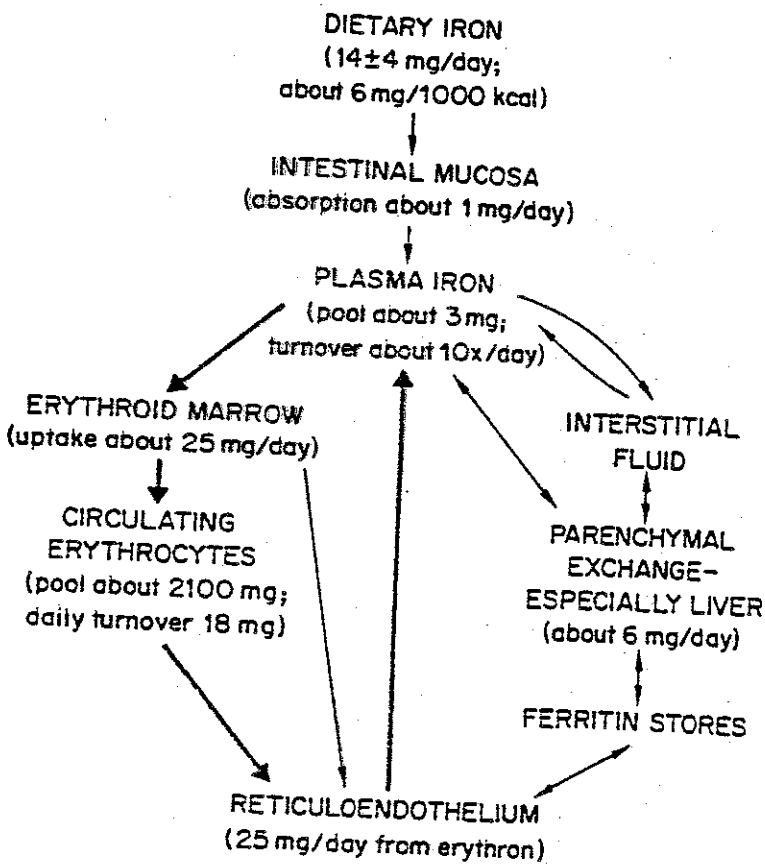


Figure 54–2. *Pathways of iron metabolism in man (excretion omitted).* (*See* text for explanation.)

Table 69.8 Equations for Calculating the Dose of Iron Dextran for Patients With Iron Deficiency Anemia and Anemia Secondary to Blood Loss

Iron Deficiency Anemia

$$\text{mg of iron} = [W \times (100 - \%\text{Hb}) \times 0.3] / 2.2$$

where W is the patient's weight in pounds and %Hb is the patient's observed hemoglobin expressed as a percentage of the normal hemoglobin concentration (assuming that 14.8 g of hemoglobin per 100 mL is equivalent to 100% concentration)

If the patient weighs 13.6 kg (30 pounds) or less, the dose is 80% of the calculated amount.

Anemia Secondary to Blood Loss (hemorrhagic diathesis or long-term dialysis)

$$\text{mg of iron} = \text{blood loss} \times \text{hematocrit}$$

where blood loss is in milliliters and hematocrit is expressed as a decimal fraction

Table 54–3. IRON REQUIREMENTS FOR PREGNANCY

	AVERAGE	RANGE
	mg	*mg*
External iron loss	170	150–200
Expansion of red-blood-cell mass	450	200–600
Fetal iron	270	200–370
Iron in placenta and cord	90	30–170
Blood loss at delivery	150	90–310
Total requirement *	980	580–1340
Cost of pregnancy †	680	440–1050

* Blood loss at delivery not included.
† Iron lost to the mother; expansion of red-cell mass not included.

(After Council on Foods and Nutrition. 1968. Courtesy of the *Journal of the American Medical Association*.)

Table 54–4. DAILY IRON INTAKE AND ABSORPTION

SUBJECT	IRON REQUIREMENT (*μg/kg*)	AVAILABLE IRON IN POOR DIET–GOOD DIET (*μg/kg*)	SAFETY FACTOR (*Available Iron/ Requirement*)
Infant	67	33–66	0.5–1
Child	22	48–96	2–4
Adolescent (male)	21	30–60	1.5–3
Adolescent (female)	20	30–60	1.5–3
Adult (male)	13	26–52	2–4
Adult (female)	21	18–36	1–2
Mid-to-late pregnancy	80	18–36	0.22–0.45

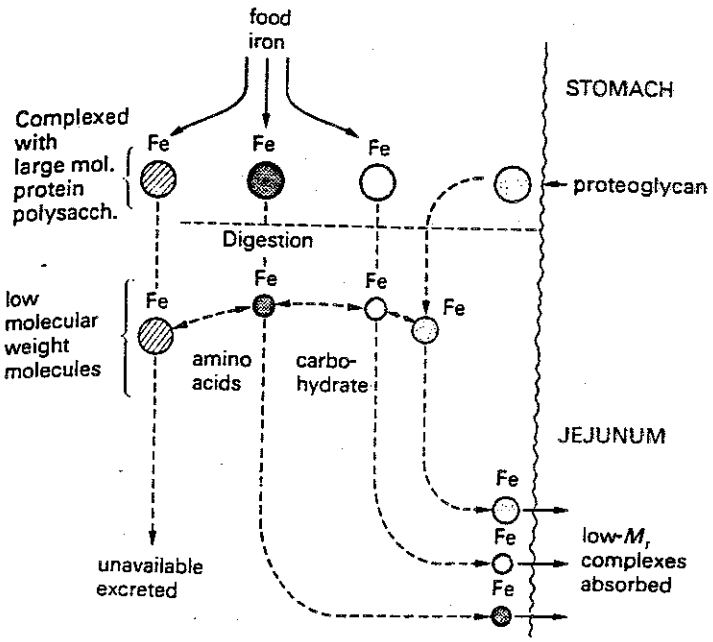


Figure 28.2 **Role of complexes in iron absorption**

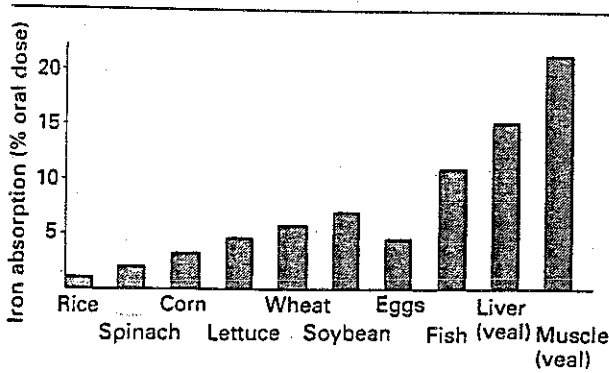


Figure 28.1 **Absorption of iron from vegetable and meat foods in human subjects; 11–137 subjects used in each test**

Table 28.5 **Iron content of alcoholic beverages**

Beverage	*Iron content (mg/l)*
US beer	0.1
Gin, whisky	0.6
US wines	2.3–2.6
Red and white French wines	6.2
Cider and wine from Rennes (France)	10–16

From R.A. McDonald (1963) *Arch. Intern. Med.*, 112, 184.

Tableau 4: Formes pharmaceutiques de sels ferreux (II) et ferriques (III)

	Fer élémentaire (%)	Fer élémentaire* (mg)	Voie d'administration	Choix de spécialités (B, CH, F)	Présentation et/ou dosage (mg)
A. Sels de fer					
fumarate (Fe-II)	33	66	orale	Ferumat (B)	sirop 100/5 ml
		100	orale	Ferrum Hausmann (B, CH)	caps. 305
		66	orale	Fumafer (F)	compr. 200
sulfate (Fe-II hydraté)	20	105	orale	Fer-In-Sol (B)	gttes 125/ml
		105	orale	Fero-Grad (B), Kendural (CH)	compr. 525
		105	orale	Ferro-Gradumet (B, CH, F)	compr. 525
	30	37.5	orale	Résoféron (B, CH)	compr. 125
sulfate (Fe-II ferro-glycocolle)		100	orale	Ferrosanol (CH)	caps. 567.7
aspartate (Fe-II anhydre)	15	37.5	orale	Sideryl (B)	amp. buv. 250/10 ml
				Spartocine (B)	sachets gran. 105 et 350/2 g
ascorbate (Fe-II)	12	33	orale	Ascofer (CH, F)	caps. 275
Fe(III)-dextran			parentérale: — i.m.	Ferrum Hausmann (B, CH) Fer Lucien (F), Imferon (B)	100/2 ml
Fe(III)-saccharate			— i.v.	Ferrum Hausmann (CH)	100/5 ml
B. Chélateur spécifique du fer					
déferoxamine			orale et parentérale (i.m., i.v., s.c.)	Desféral (B, CH, F)	Flacons-amp. subst. sèche 500

* On utilise la quantité de fer élémentaire d'une préparation pour évaluer la durée d'un traitement oral. Par exemple: déficit en fer 2 g; appo de 100 mg de fer élémentaire par jour; absorption moyenne: 20%; durée de la substitution: 100 jours.

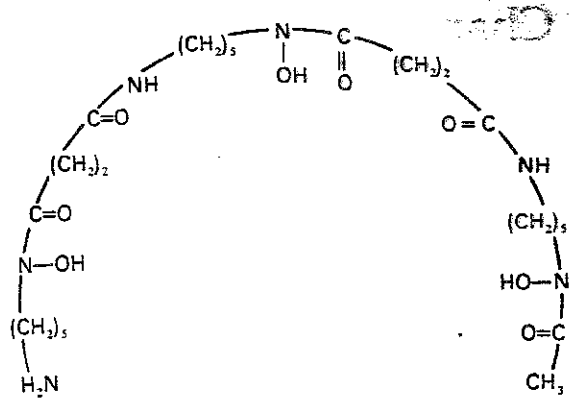


Figure 28.16 **Structure of desferrioxamine.** Desferrioxamine is a very powerful iron-chelating agent which has been used extensively to remove excess iron deposits from the body. It is a naturally occurring compound synthesized by the mould *Streptomyces* sp.

Table 28.6 **Treatment of iron overload with desferrioxamine and ascorbate**

Condition	*Increase of iron excretion in urine produced by ascorbate (%)*
Large number of blood transfusions to combat anaemia	88
Haemochromatosis (genetic)	60
Haemochromatosis (excess dietary intake by Bantu subjects)	350

Patients are treated with desferrioxamine and then with desferrioxamine + 1.5 g ascorbate per day.
From R.W. Charlton, T.H. Bothwell and H.C. Seftel (1973) *Clinics in Haematology*, 2, 383.

Tableau 5: Causes des carences en vitamine B_{12} et en folates

A. **Carences en vitamine B_{12}**

1. Défaut d'apport alimentaire
2. Troubles de l'absorption
   - — par manque de facteur intrinsèque (gastrectomie, maladie de Biermer)
   - — par atteinte de l'intestin grêle (sprue)
3. Par compétition intestinale (anse borgne, bothriocéphale).

B. **Carences en folates**

1. Défaut d'apport alimentaire
2. Troubles de l'absorption
3. Augmentation des besoins (grossesse, lactation, anémies hémolytiques)
4. Ethylisme
5. Médicaments (antifoliques, anti-épileptiques).

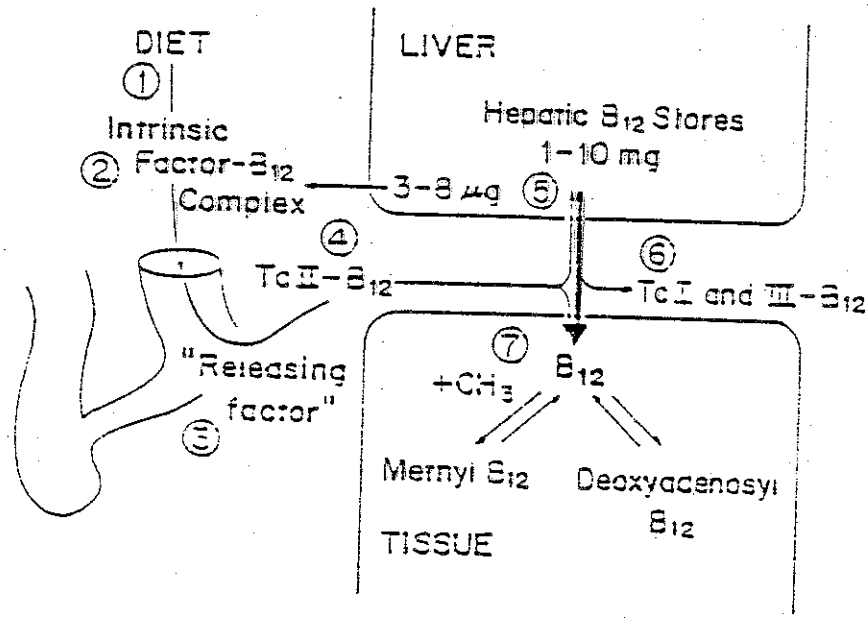


Figure 54–8. *The absorption and distribution of vitamin B_{12}.*

Tableau 6: Choix thérapeutique de vitamine B_{12}

Principes actifs	Voies d'administration	Spécialités (B, CH, F)	Dosage (mg/ml)
hydroxocobalamine	parentérale (i.m.)	Forta B 5.000 (B)	5.0/1
		Forta B_{12} (B)	12.0/3
		Hydroxo 5.000 (B, CH, F)	5.0/2
		Novobédouze (B)	5.0/1
		(B, CH, F)	10.0/2
		Dodécavit (F)	10.0/2
cyanocobalamine	parentérale (i.m.)	B_{12} Aguettant (F)	0.1/1
			1.0/2
		B_{12} Delagrange (F)	1.0/2
		B_{12} Labaz (F)	1.0/4
		B_{12} Lavoisier (F)	5.0/2
		Betoivex (CH)	1.0/1
		Vitarubin (CH)	0.03; 0.2; 1/1
			0.2; 1/10
		Vitarubin-Dépôt (CH	0.5; 1/1

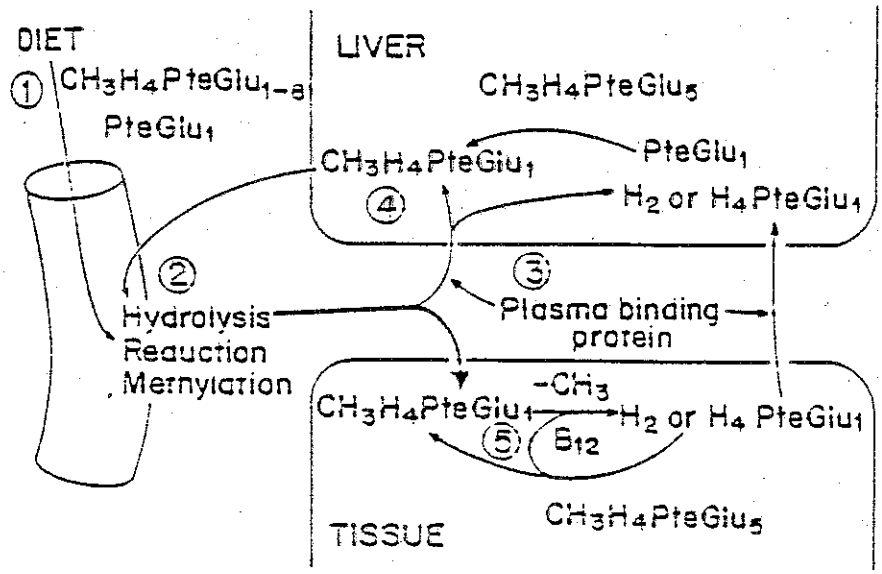
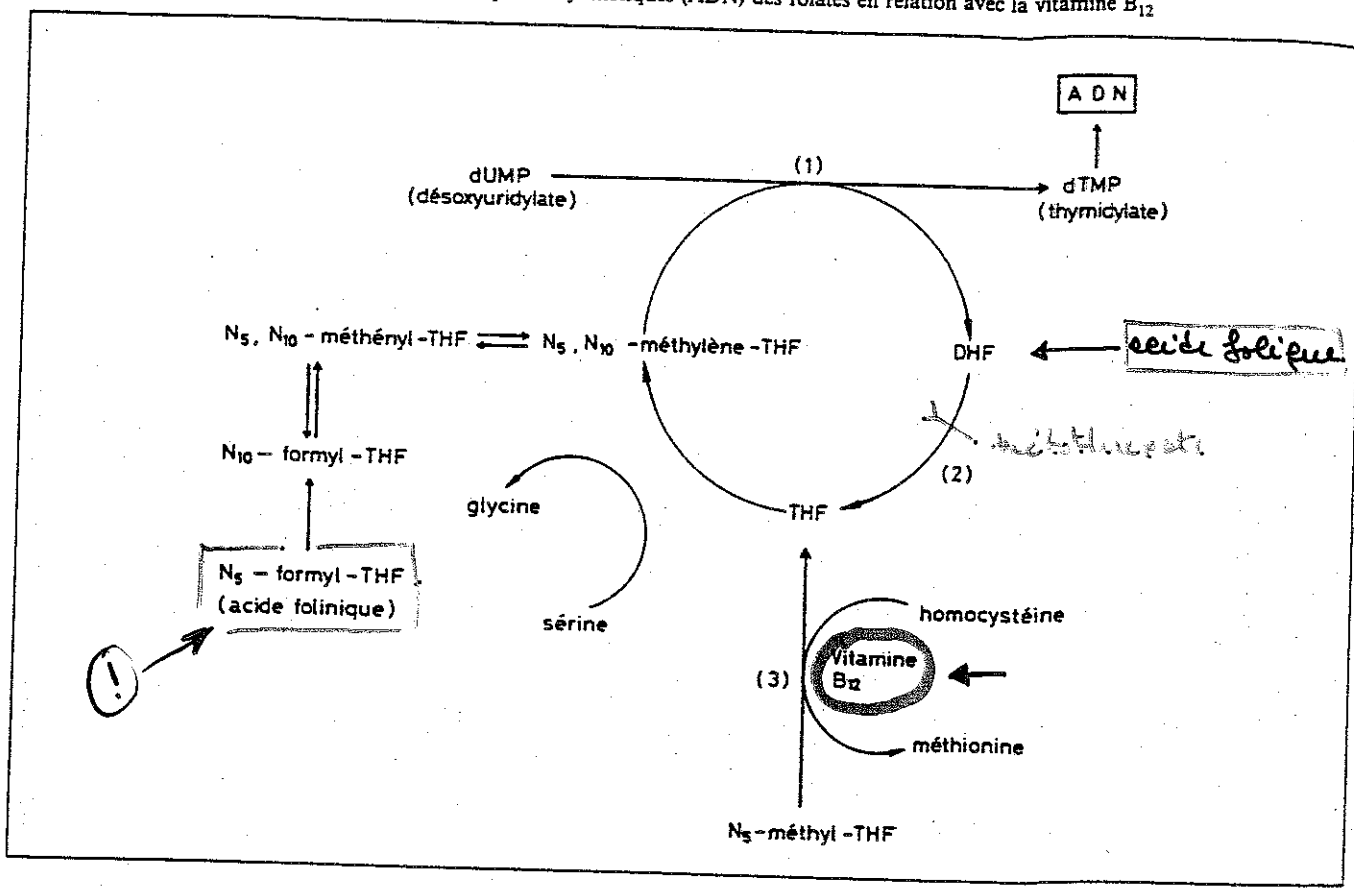


Figure 54–10. *Absorption and distribution of folate derivatives.*

Figure 3. Rôles métaboliques et synthétiques (ADN) des folates en relation avec la vitamine B_{12}



Enzymes:
(1) thymidylate-synthétase
(2) dihydrofolate-réductase
(3) méthionine-synthétase

Folates:

N_5-méthyl-THF
N_5, N_{10}-méthylène-THF

N_{10}-formyl-THF
N_5, N_{10}-méthényl-THF
N_5-formimino-THF
N_5-formyl-THF (acide folinique)

Actions:

synthèse de la méthionine
synthèse de thymidylate
conversion sérine-glycine
synthèse des purines
synthèse des purines
catabolisme de l'histidine
conversion en formes actives

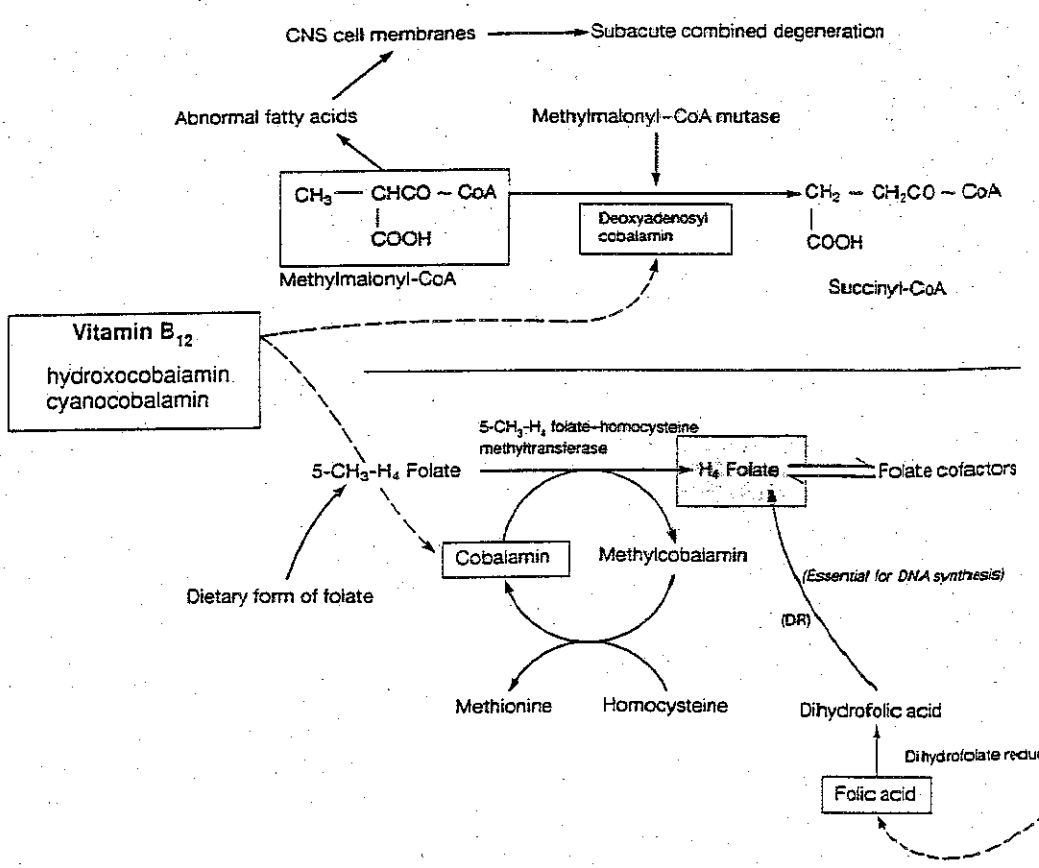
Tableau 7: Choix thérapeutique d'acide folique, d'acide folinique et de pyridoxine

Principes actifs	Voie d'administration	Spécialités (B, CH, F)	Dosage (mg); amp. mg/ml
acide folique	orale	Folvite (CH)	compr. 1
		Speciafoldine (F)	compr. 5
	parentérale (i.m., i.v., s.c.)	Folvite (CH)	amp. 5/1
acide folinique *	orale	Ledervorin-Calcium, Rescuvolin (B)	compr. 15
		Leucoverin-Calcium, Leucoverin (CH)	compr. 15
		Lederfoline (F)	compr. 5/15
		Folinoral (F)	sol. buv. 50 mg*/5 gél. 5
		Osfolate (F)	gél. 5/25
	parentérale	Folinate de calcium Roger Bellon (F)	amp. 2.5/1
		Lederfoline (F)	amp. 5/2 amp. 50*
		Ledervorin-Calcium (B)	amp. 3 amp. 30*
		Rescuvolin (B)	amp. 15* et 50*
		Leucoverin-Calcium (CH)	amp. 3 amp. 30*
		Leucoverin (CH)	amp. 3 et 30*
pyridoxine	orale	Bedoxine 300/Beom 6 (B)	drag. 300/250
		Pyridoxine Labaz (B, F)	compr. 250
		Bécilan (F)	compr. 250
		Bénadon (CH)	compr. 40/300
	parentérale	Bécilan (F)	amp. 250/5
		Bénadon (CH)	amp. 100/2

* Substance sèche.

* pour trait. des antagonistes de l'acide folique (méthotrexate).

20 Agents used in anaemias



Iron preparations

ORAL
- ferrous sulphate
- ferrous gluconate
- ferrous fumarate
- ferrous glycine sulphate

PARENTERAL
- iron dextran
- iron sorbitol

Table 69.6 Laboratory Changes in Anemias

	Parameter[a]	
	Increased	**Decreased**
Iron deficiency anemia	TIBC Free erythrocyte Protoporphyrin	Hemoglobin Hematocrit MCV MCHC Ferritin Iron
Vitamin B_{12} deficiency	MCV Unconjugated bilirubin Lactate dehydrogenase Transferrin saturation	B_{12} (but may be normal) Reticulocyte count
Folic acid deficiency	MCV Unconjugated bilirubin Lactate dehydrogenase Transferrin saturation	Folate Reticulocyte count
Anemia of chronic disease	Transferrin saturation Bilirubin Protoporphyrin Marrow sideroblast iron	Hemoglobin MCV MCHC Iron (may be normal) TIBC
Hemolytic anemia	Reticulocyte count Unconjugated bilirubin Urinary urobilinogen Fecal urobilinogen Spherocyte count Urinary hemosiderin	

[a] MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; TIBC, total iron-binding capacity.

Compiled from References 26, 27, 31, and 32.

Table 54–1. HEMATOPOIETIC GROWTH FACTORS

INTERLEUKIN-3 (IL-3 or Multi-CSF)
- —Stimulates colony formation of most hematopoietic cell lines
- —Acts synergistically with GM-CSF to increase number of neutrophils, monocytes, and eosinophils in blood
- —Acts with erythropoietin to expand the BFU-E compartment and stimulate CFU-E proliferation
- —Directly stimulates pulmonary macrophages to proliferate and, with CSF-1, stimulates high proliferation potential forming cells (HPP-CFC), blood monocytes, and peritoneal macrophages
- —Influences functions of eosinophils and basophils

GRANULOCYTE/MACROPHAGE COLONY-STIMULATING FACTOR (GM-CSF)
- —Acts synergistically with IL-3 to stimulate colony formation and proliferation of granulocytes, monocytes, macrophages, and megakaryocytes
- —With erythropoietin, promotes formation of BFU-E
- —Increases phagocytic and cytotoxic potential of mature granulocytes, but reduces motility and clearance from circulation
- —Increases cytotoxicity of eosinophils and leukotriene synthesis
- —Stimulates proliferation of small cell carcinoma in culture

GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF)
- —Stimulates granulocyte colony formation and production of neutrophils
- —Acts synergistically with CSF-1 to stimulate HPP-CFC, with GM-CSF to stimulate granulocyte/macrophage colonies, and with IL-3 to induce formation of megakaryocytes
- —Induces release of granulocytes from marrow
- —Enhances phagocytic and cytotoxic activities of mature granulocytes
- —Stimulates proliferation of small cell carcinoma in culture

COLONY STIMULATING FACTOR (CSF-1 or M-CSF)
- —Stimulates monocyte/macrophage colony formation alone and synergistically with GM-CSF and IL-3
- —Induces synthesis of G-CSF and IL-1 and enhances the production of interferon and tumor necrosis factor
- —Enhances functions of monocytes and macrophages

ERYTHROPOIETIN
- —Stimulates proliferation, maturation, and hemoglobin formation by committed erythroid progenitors (CFU-E)
- —Acts synergistically with IL-3 and GM-CSF to expand the BFU-E compartment
- —Stimulates the early release of reticulocytes from marrow into the circulation

THROMBOPOIETIN
- —Acts in conjunction with megakaryocyte colony-stimulating factor to regulate megakaryocytopoiesis and hence production of platelets

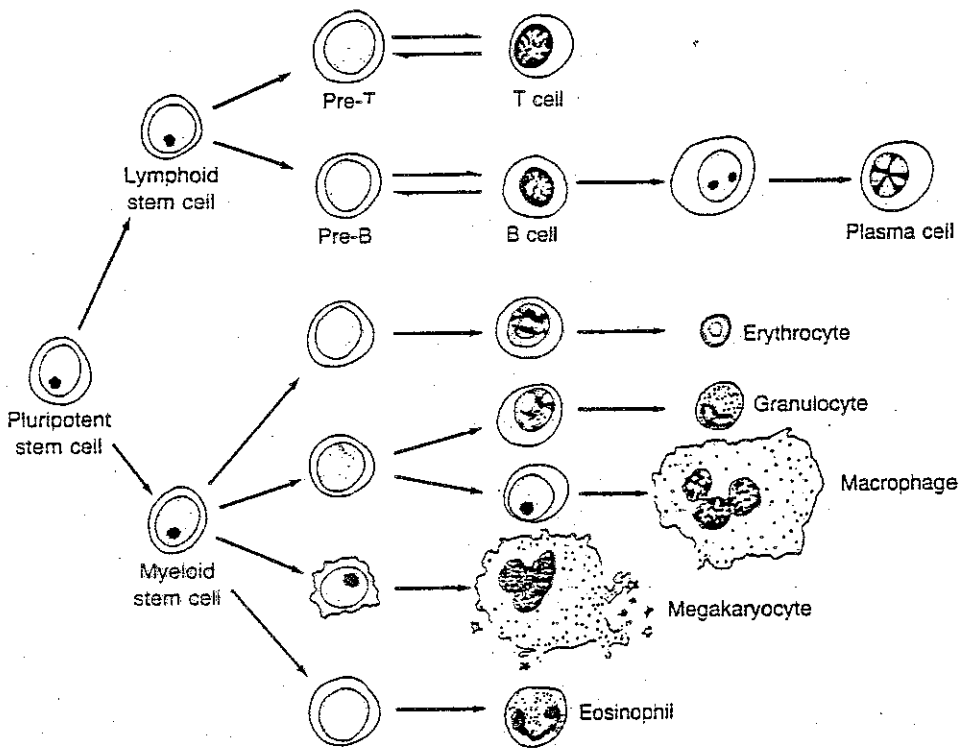


Figure 72.1 The process of maturation of blood cellular components from pluripotent stem cells to mature granulocytes, erythrocytes, and other cells. *(From Cline MJ, Golde DW: Controlling the production of blood cells. Blood 1979;53:159, with permission.)*

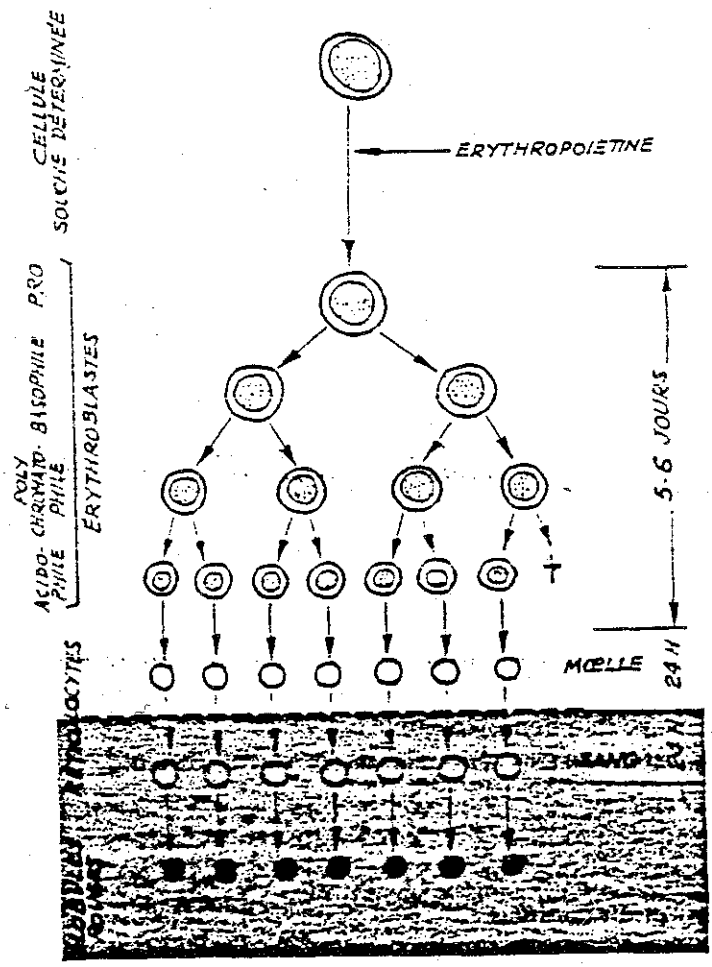
Médicaments agissant sur la myélopoïèse

I. – Erythropoïèse

Physiologie

l'érythropoïèse normale comprend :
- une réduction de taille de l'érythroblaste.
- une diminution du rapport nucléocytoplasmique.
- une synthèse progressive de l'hémoglobine.
- une expulsion de noyau.
- une mort intramédullaire de 5 à 10 p. 100 des érythroblastes : c'est l'érythropoïèse inefficace physiologique.

étapes et morphologie de l'érythropoïèse



Facteurs impliqués : synthèse ADN : Vit B12 - ac folique
synthèse Hb : Fer
hormones : Erythropoïétine

Régulation :

production

REIN • [redacted] : la sécrétion d'un Facteur Erythropoïétique Rénal ou FER contrôlée par la P_{O_2} tissulaire;

FOIE • [redacted] : la sécrétion d'un profacteur plasmatique est probable; l'interaction du F.E.R et du profacteur plasmatique aboutit à la production d'érythropoïétine.

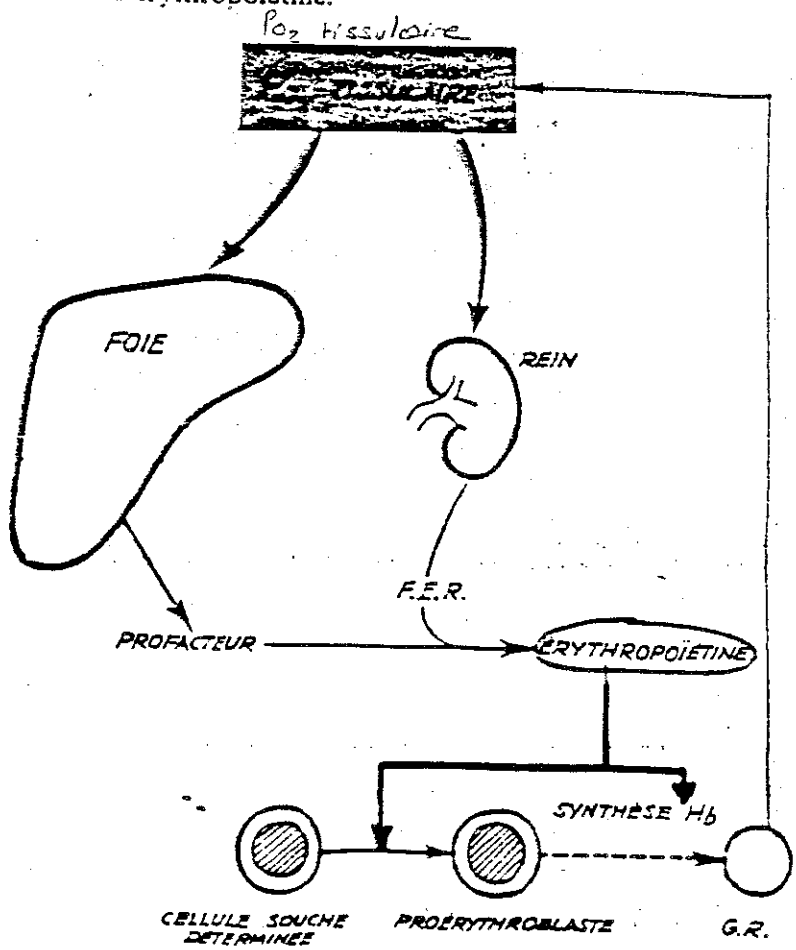
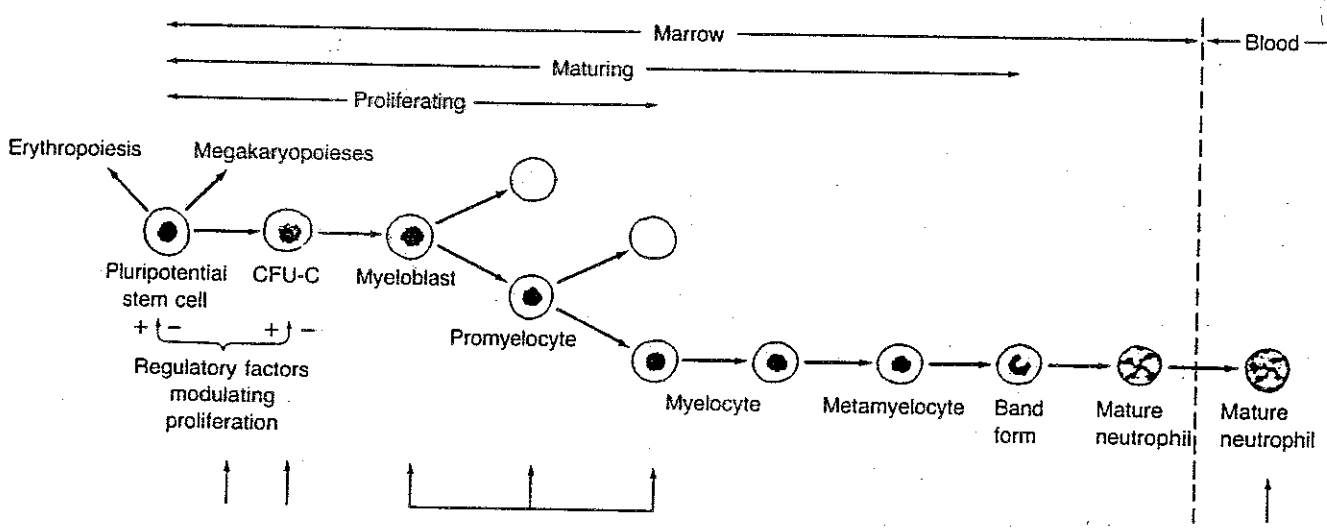


Figure 72.2 Differentiation of the stem cell to the mature neutrophil. The arrows indicate possible sites of drug-induced agranulocytosis. *(From Young GAR, Vincent PC: Drug-induced agranulocytosis. Clin Haematol 1980;9:483–504, with permission.)*



G-CSF

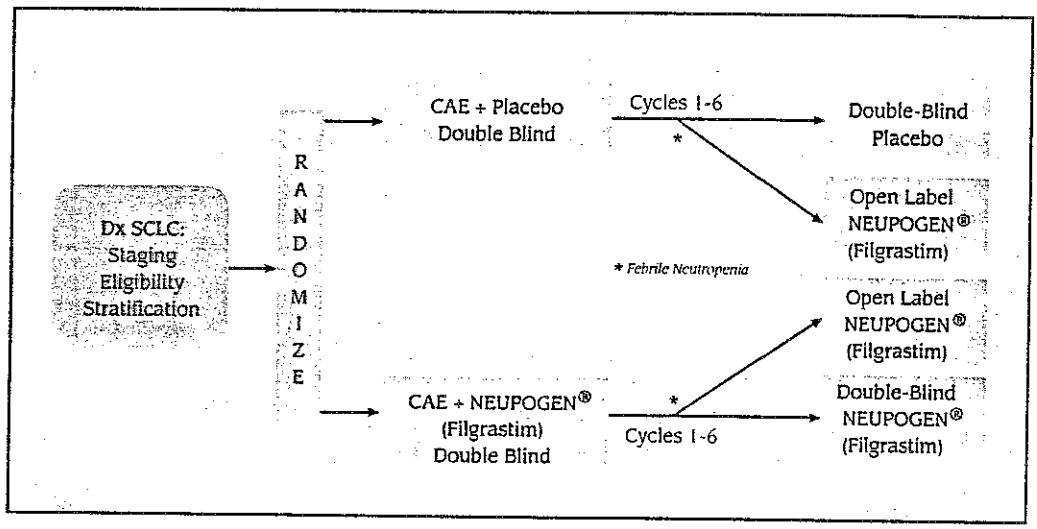


Figure 4. Design for Phase III study investigating NEUPOGEN® (Filgrastim) as an adjunct to CAE chemotherapy in patients with small cell lung cancer. NEUPOGEN® (Filgrastim) or placebo was administered daily by subcutaneous injection for up to 14 days, starting 24 hours after the last chemotherapy dose (i.e., day 4 of each 21 day cycle). Patients were eligible to receive open label NEUPOGEN® (Filgrastim) for subsequent cycles if they experienced febrile neutropenia during any blinded cycle in the study.

Each cycle of CAE chemotherapy consisted of cyclophosphamide (1,000 mg/m^2 IV), doxorubicin (50 mg/m^2 IV), and etoposide (120 mg/m^2 IV) administered on day 1. Additional doses of etoposide (120 mg/m^2 IV) were administered on day 2 and 3. Cycles were repeated every 21 days. NEUPOGEN® (Filgrastim) (230 mcg/m^2/day) or placebo was administered by SC injection from day 4 to 12 of each cycle. If ANC levels were <10,000 cells/mm^3 on day 12 of the cycle, study medication could be continued through day 17 (i.e., up to 14 days; see Figure 5).

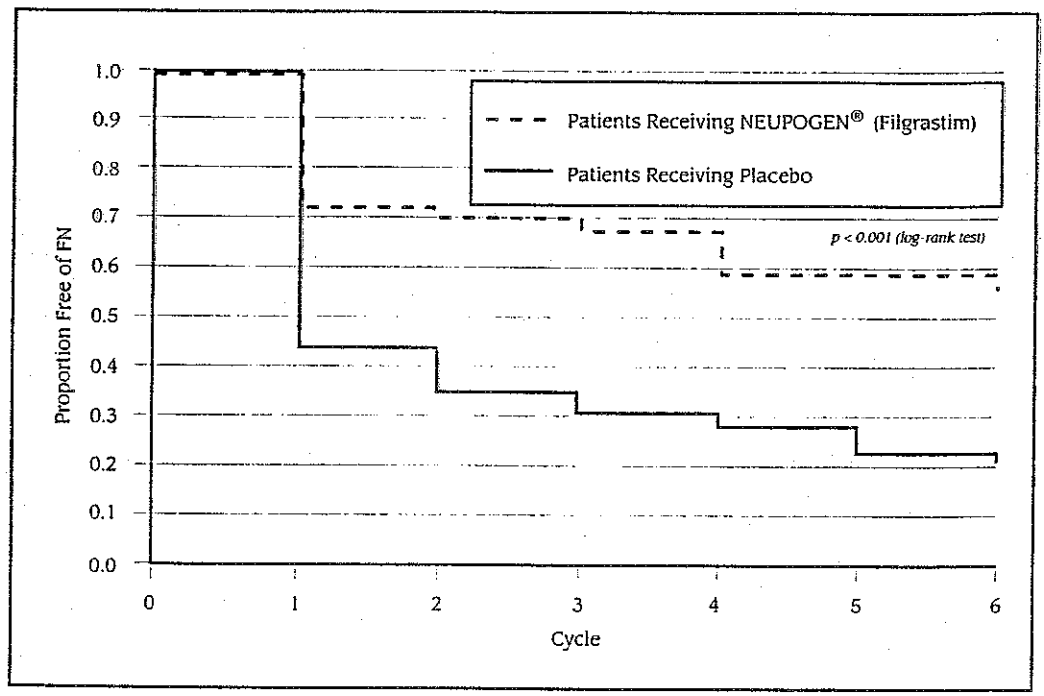


Figure 8. Kaplan-Meier time to event curve demonstrating proportion of patients (n = 194) in the Phase III study free of febrile neutropenia (ANC < 500 cells/mm³ and temperature ≥ 38.2°C).