Anaemia and GI Blood Loss

Dr Satish Keshav DPhil FRCP

John Radcliffe Hospital

Nuffield Dept of Medicine

University of Oxford

Blood Management for Medical Patients

OXFORD
Translational Gastroenterology Unit

Case History

- Mr T J, age 85
- Dizzy and unwell – August in France.
- No dyspepsia.
- No wt loss.
- No change in bowel habit.
- On Aspirin 75mg.
- Hb 7 and low MCV.

History

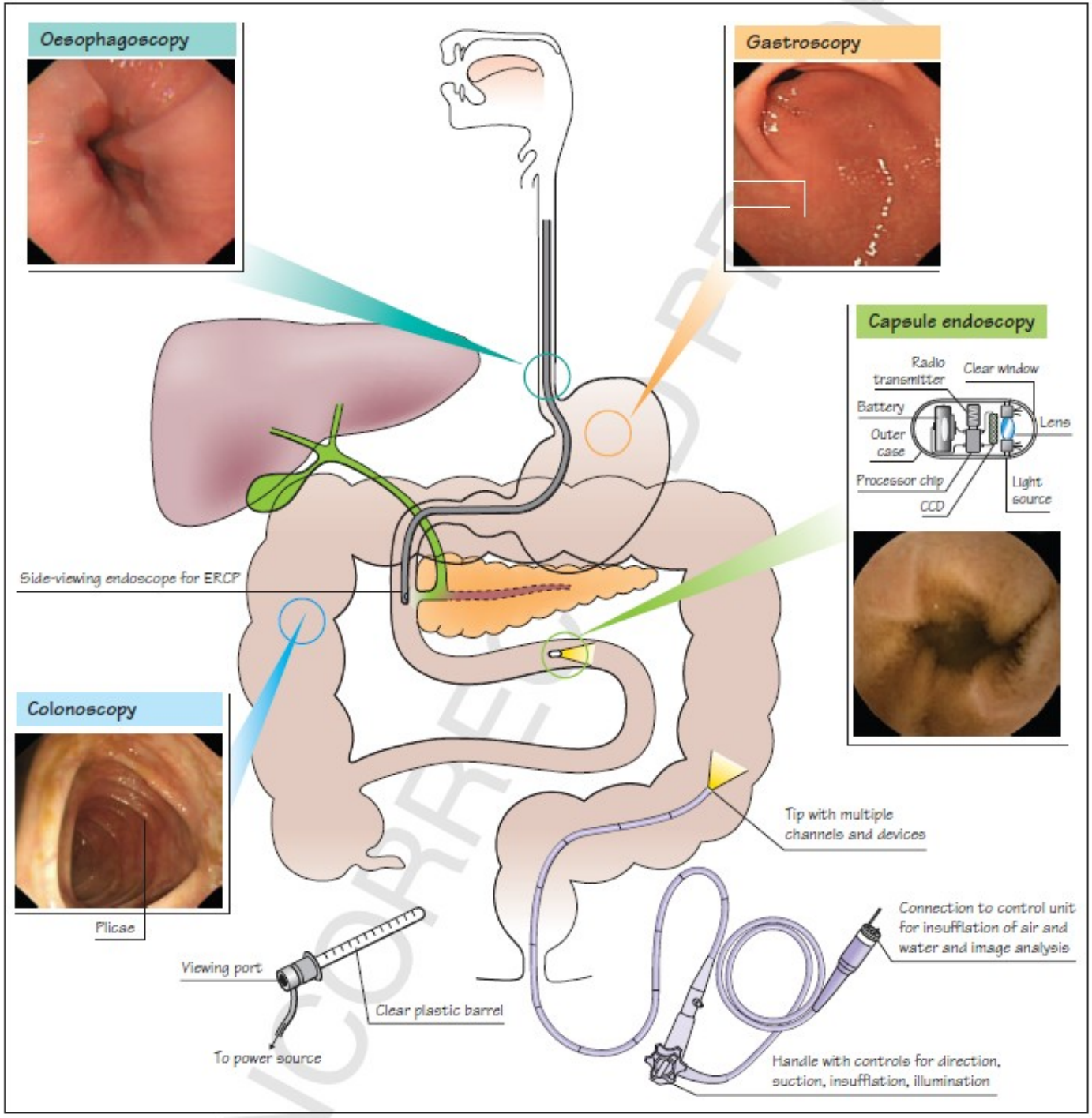
- **Transfused 3 units of Blood.**
- **Symptoms improved.**
- **Aspirin stopped.**
- **Not on any other medications**
- **In UK, noticed melaena intermittently.**

History

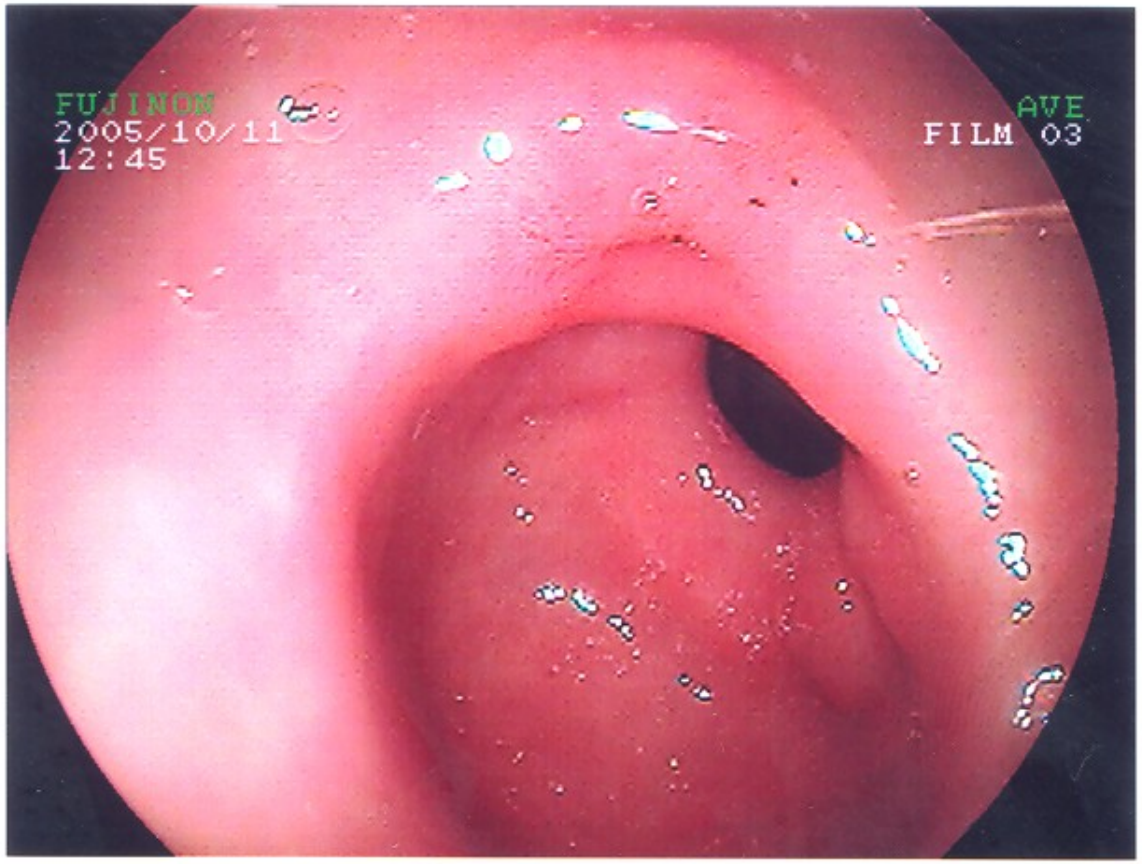
- **Perforated DU in 1940s after the war.**
- **Normal Haematinics- 1993.**
- **Negative U. Breath test for H Pylori-1993.**
- **Normal Ba enema- 1993.**

Examination and Tests

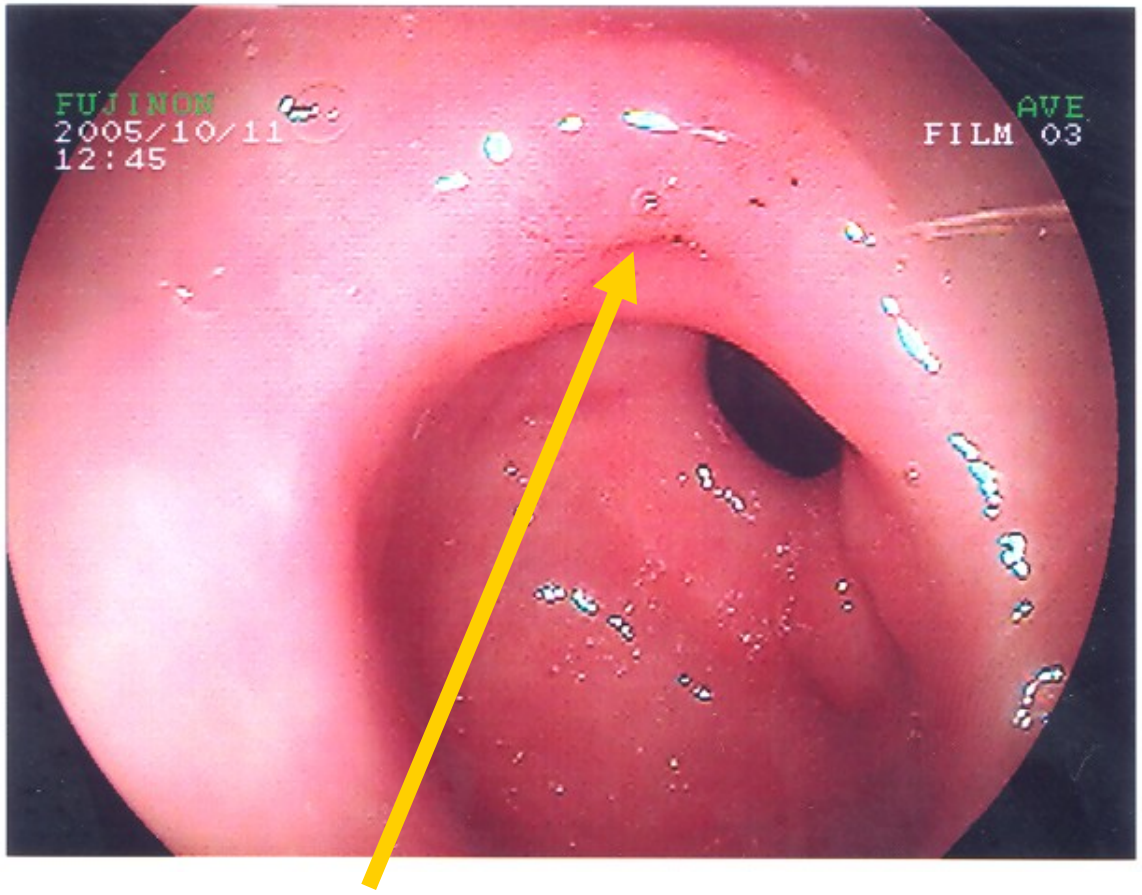
- Unremarkable apart from abdominal scar
- Hb 10.4 MCV 76 MCHC 23 ↓
- Iron 6.8 Sat. 9% Ferritin 14 ↓
- Urea 7 Cr 93 normal LFT INR 1
- TTG Ig A Ab < 1
- GI investigations


Oesophagoscopy
Gastroscopy
Capsule endoscopy
Radio transmitter
Clear window
Battery
Lens
Outer case
Processor chip
Light source
CCD
Side-viewing endoscope for ERCP
Colonoscopy
Plicae
Tip with multiple channels and devices
Viewing port
Clear plastic barrel
To power source
Connection to control unit for insufflation of air and water and image analysis
Handle with controls for direction, suction, insufflation, illumination

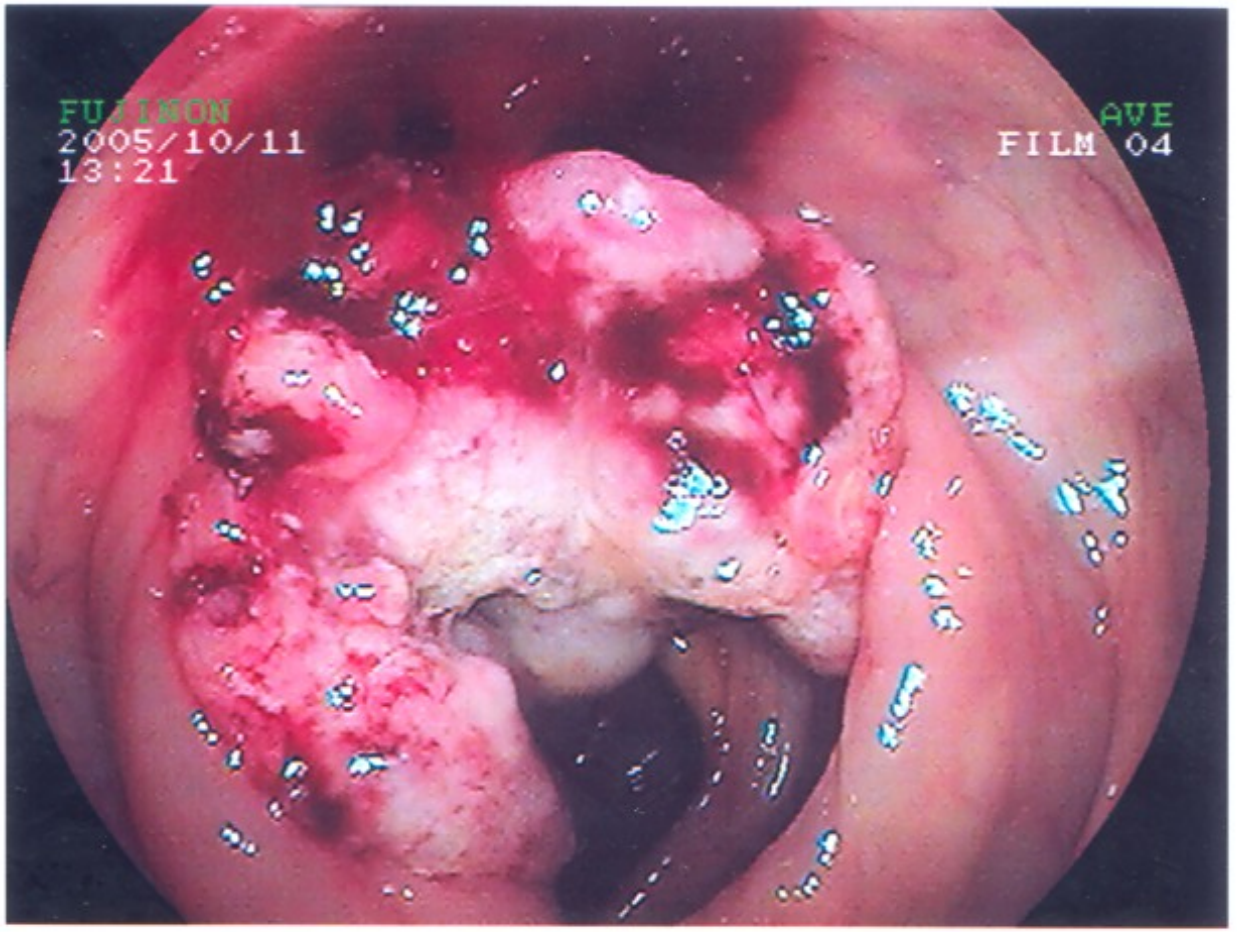
Upper Endoscopy



Healing antral ulcer



Colonoscopy



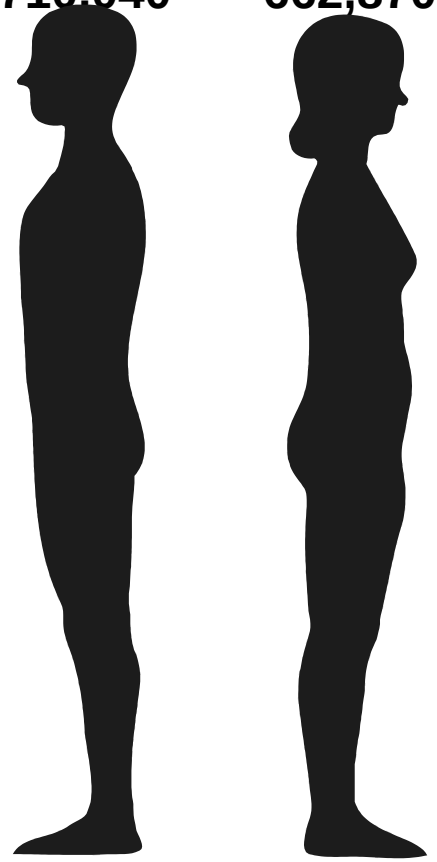
Evaluation of Iron Deficiency

- 89 patients with Occult blood loss.
- 34 had Oesophagitis, Gastritis or gastric erosions
- 13 had colon cancer
- No diagnosis was established in 14 patients.
- 8 patients had concurrent upper GI and Ca Colon
- Most of them had no symptoms of colonic disease.
- The presence of proximal lesion should not preclude evaluation of the colon.

- BMJ 1997 Jan 18;314(7075):206-8

Estimated US Cancer Cases*

Men 710,040	
Prostate	33%
Lung and bronchus	13%
Colon and rectum	10%
Urinary bladder	7%
Melanoma of skin	5%
Non-Hodgkin lymphoma	4%
Kidney	3%
Leukemia	3%
Oral Cavity	3%
Pancreas	2%
All Other Sites	17%



Women 662,870	
32%	Breast
12%	Lung and bronchus
11%	Colon and rectum
6%	Uterine corpus
4%	Non-Hodgkin lymphoma
4%	Melanoma of skin
3%	Ovary
3%	Thyroid
2%	Urinary bladder
2%	Pancreas
21%	All Other Sites

***Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.**
Source: American Cancer Society, 2005.

Probability of CRC

CRC	Birth to 39 (%)	40 to 59 (%)	60 to 79 (%)	Birth to death
Males	.07(1 in 1484)	.90 (1 in 111)	3.96 (1 in 25)	5.90 (1 in 17)
Females	.06(1 in 1586)	.69 (1 in 145)	3.04(1 in 33)	5.54 (1 in18)

Modified from American Cancer society, Surveillance research, 2005

Screening Guidelines 2003

- Beginning at age 50, men and women should follow one of the following examination schedules:
  - A fecal occult blood test (FOBT) every year
  - A flexible sigmoidoscopy (FSIG) every five years
  - Annual fecal occult blood test and flexible sigmoidoscopy every five years*
  - A double-contrast barium enema every five years
  - A colonoscopy every ten years
- *Combined testing is preferred over either annual FOBT, or FSIG every 5 years alone.
  - People who are at moderate or high risk for colorectal cancer should talk with a doctor about a different testing schedule

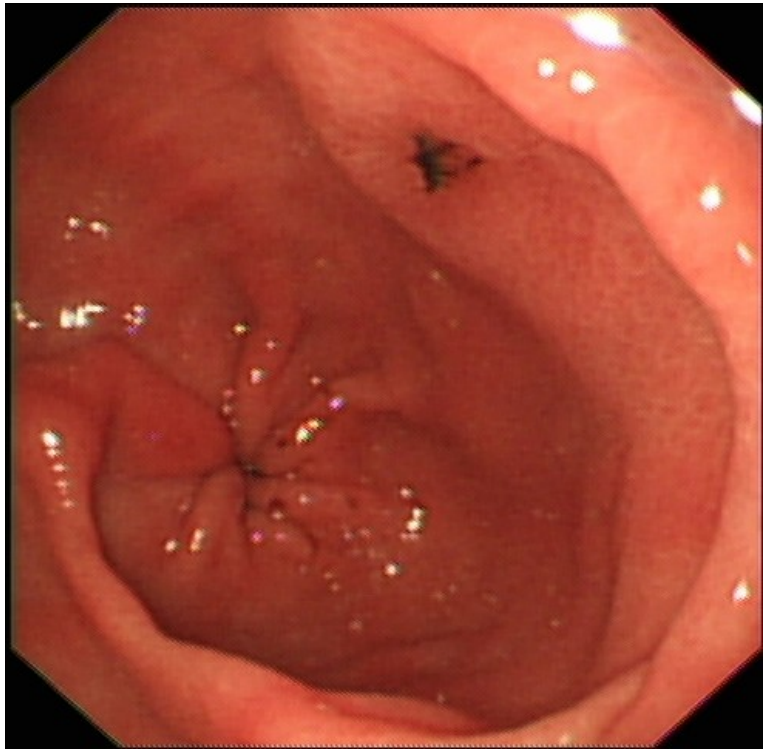
GI Bleeding

•GI bleeding may originate anywhere from the mouth to the anus and may be overt or occult.
•**Hematemesis** or emesis with red blood indicates an upper GI source of bleeding (almost always above the ligament of Treitz) that is often brisk, usually from an arterial source or varix.
•**"Coffee grounds"** result from bleeding that has slowed or stopped, with conversion of red Hb to brown hematin by gastric acid.
•**Hematochezia** usually indicates lower GI bleeding but may result from vigorous upper GI bleeding with rapid transit of blood through the bowels.
•**Melena** typically indicates upper GI bleeding, but a small-bowel or right colon bleeding source may also be the cause.
•About 100 to 200 mL of blood in the upper GI tract is required to produce melena, which may continue for several days after severe hemorrhage and does not necessarily indicate continued bleeding.

Causes of GI Bleeding

Upper GI tract			
Duodenal ulcer	(20–30%)	Mallory-Weiss tear	(5–10%)
Gastric or duodenal erosions	(20–30%)	Erosive esophagitis	(5–10%)
Varices	(15–20%)	Angioma	(5–10%)
Gastric ulcer	(10–20%)	Arteriovenous malformation	(< 5%)
Lower GI tract (percentages vary with the age group sampled)		**Small-bowel lesions**	
Diverticular disease		Meckel's diverticulum, tumors, angioma, arteriovenous malformations	
Colonic carcinoma			
Colonic polyps			
Inflammatory bowel disease: ulcerative proctitis/colitis, Crohn's disease, infectious colitis			
Colitis: radiation, ischemic			
Angiodysplasia (vascular ectasia)			
Internal hemorrhoids			
Anal fissures			

Causes of GI Bleeding



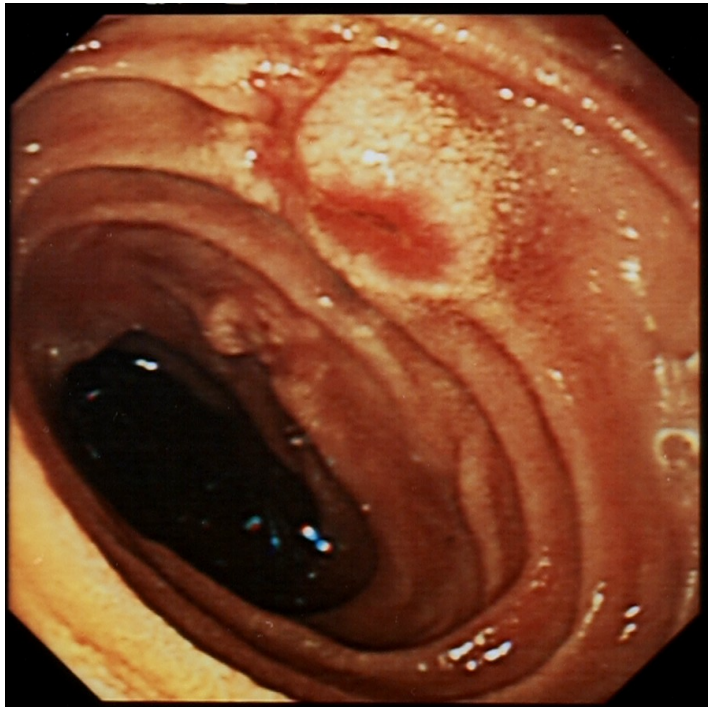
Causes of GI Bleeding

Age	<60yr	**0**
	60-79 yr	**1**
	>80 yr	**2**
Shock		
	None	**0**
	Pulse >100 and syst BP >100	**1**
	Syst BP <100	**2**
Co-morbidity		
	None	**0**
	Cardiac failure, or any major comorbidity	**2**
	Dissemin. Malignancy	**3**
Endoscopic diagnosis		
	M-W tear, no lesion seen **and** no SRH	**0**
	All other diagnoses	**1**
	Malignancy of upper GI	**2**
Stigmata of recent haemorrhage (SRH)		
	None, or dark spots only	**0**
	Blood in upper GI tract	**1**
	Adherent clot, visible or spurting vessel	**2**

Predicted Mortality

Initial Risk Score	**Final Risk Score**
Pre-endoscopy	Post-endoscopy
0 0.2%	0.0%
1 2.4%	0.0%
2 5.6%	0.2%
3 11.0%	2.9%
4 24.6%	5.3%
5 39.6%	10.8%
6 48.9%	17.3%
7 50.0%	27.0%
8+ -	41.1%

Causes of GI Bleeding



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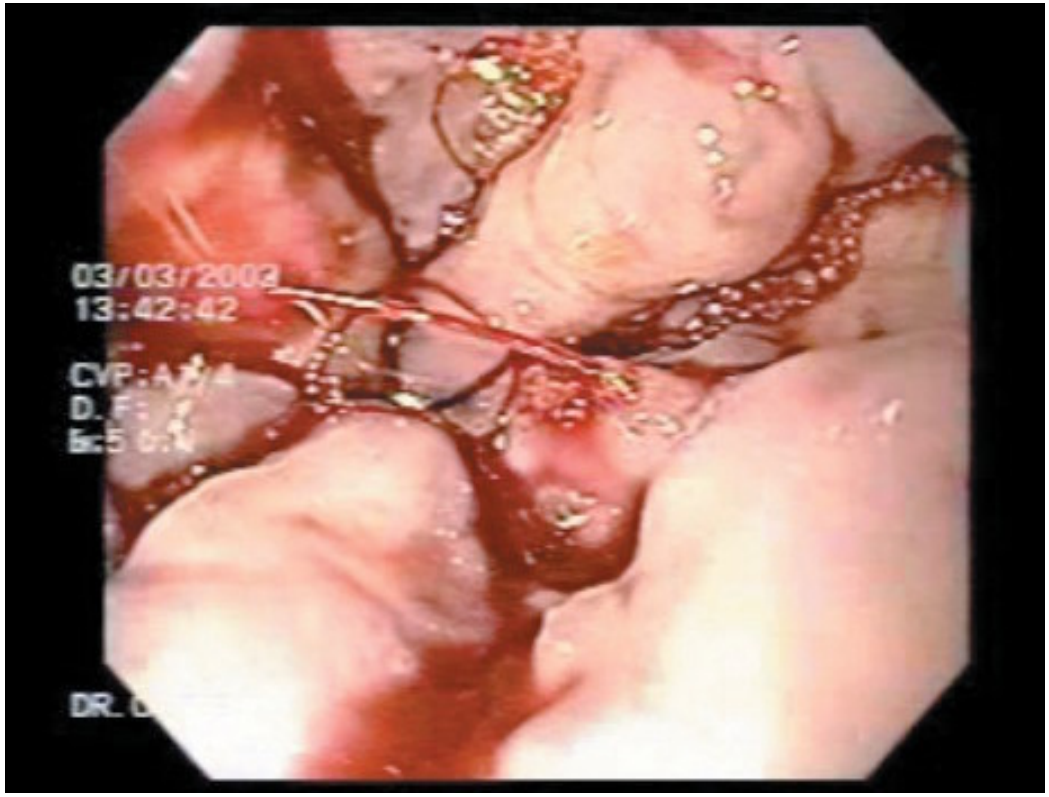

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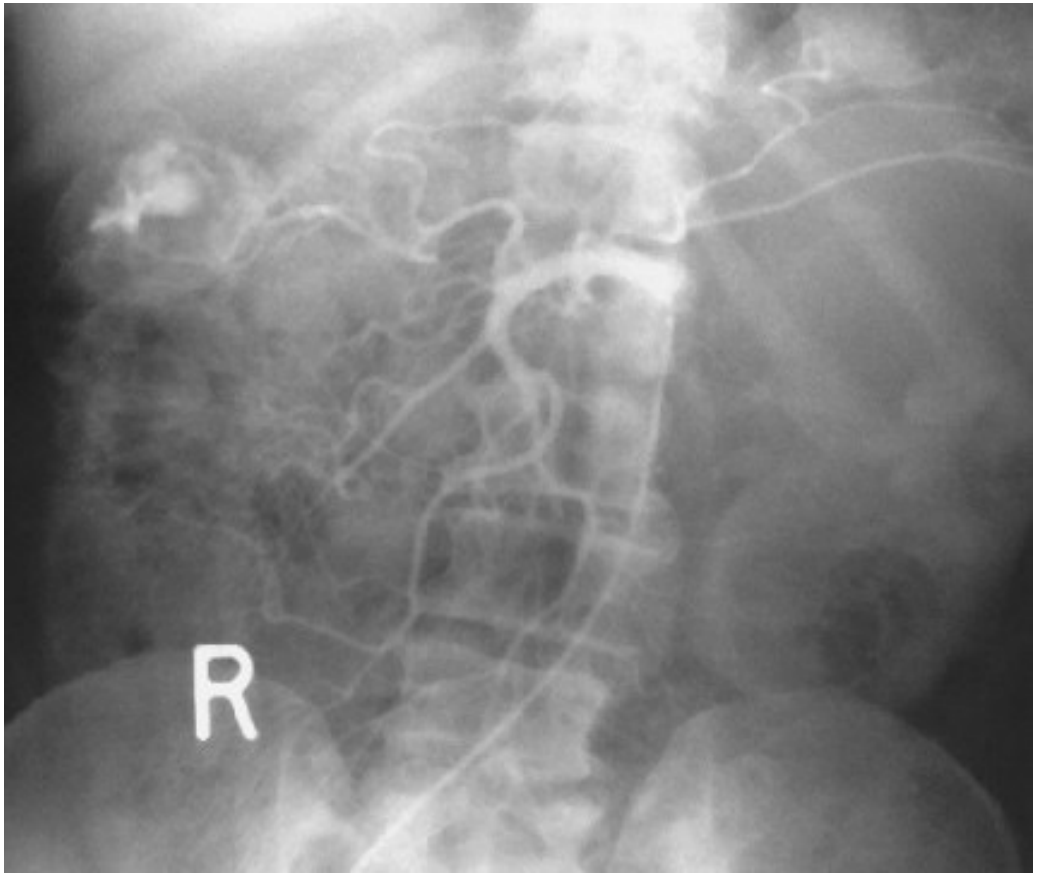

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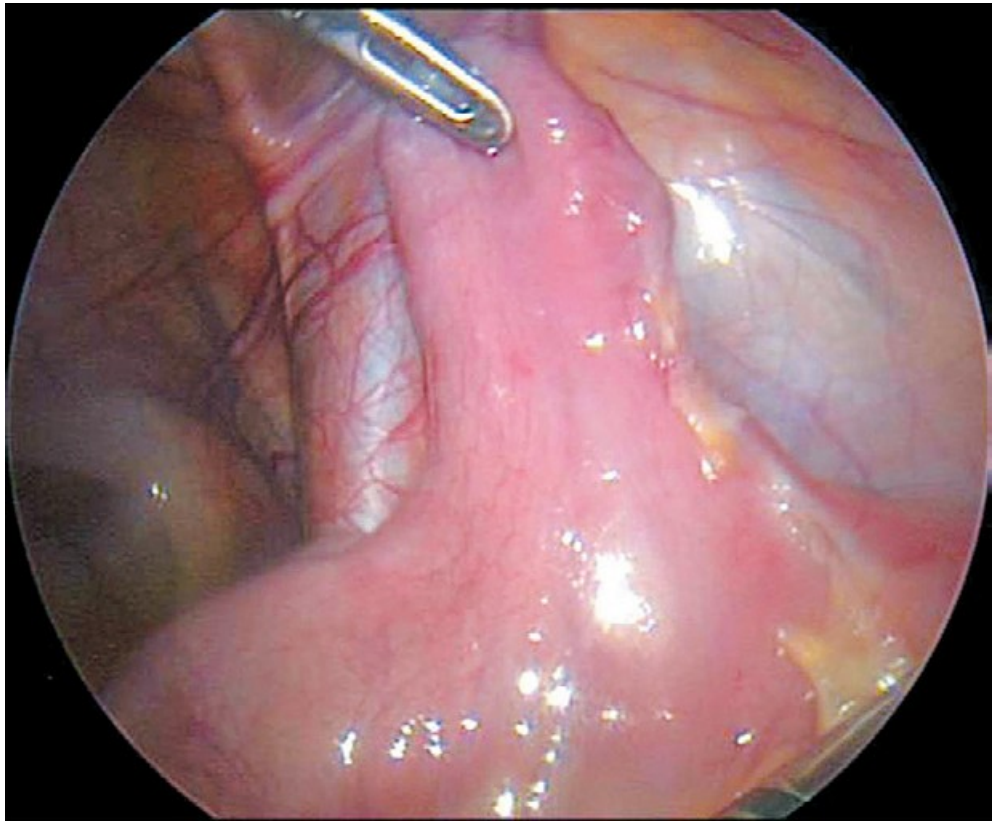
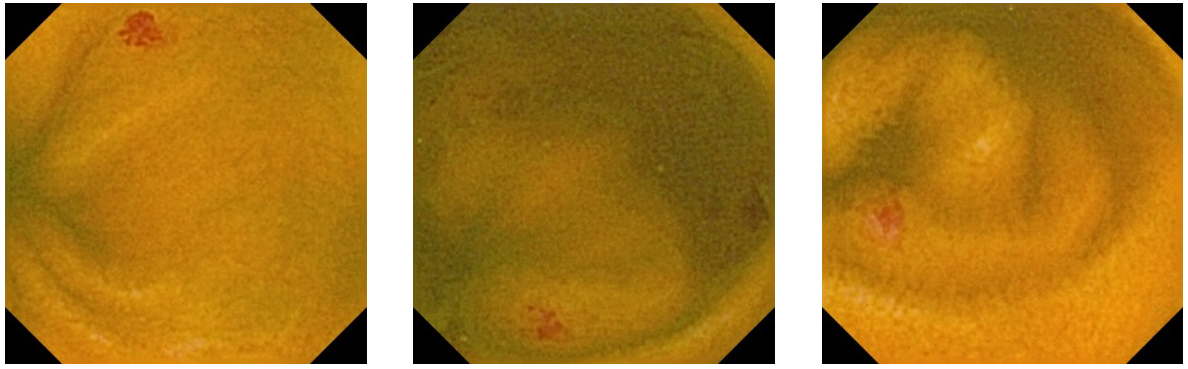


Causes of GI Bleeding

Causes of GI Bleeding



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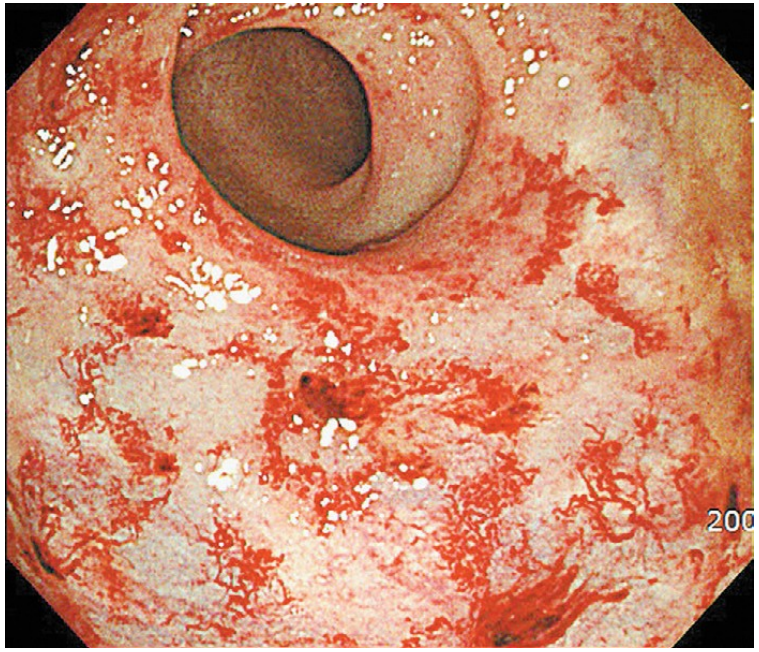
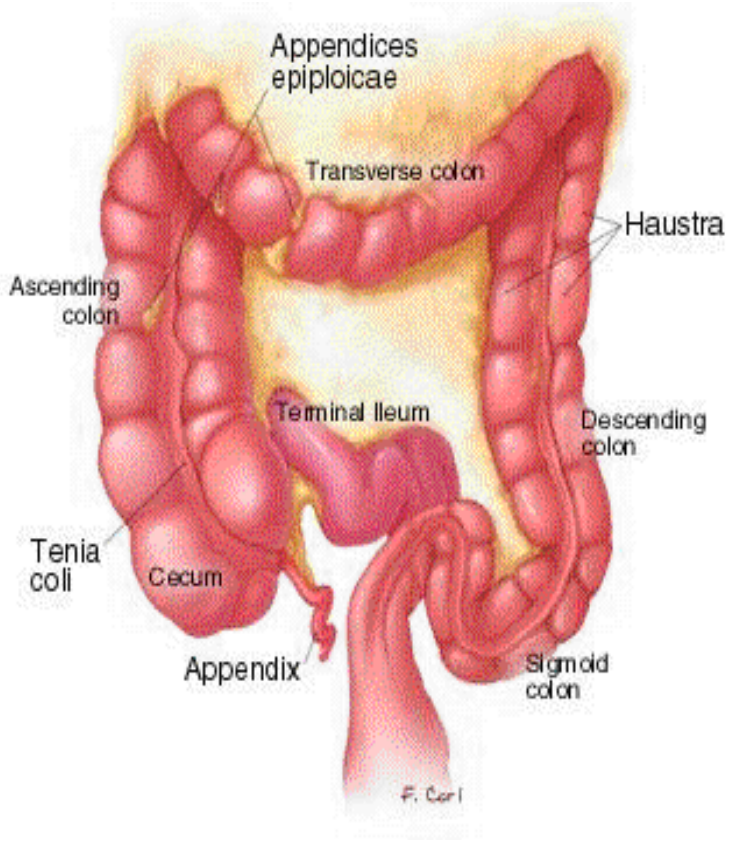
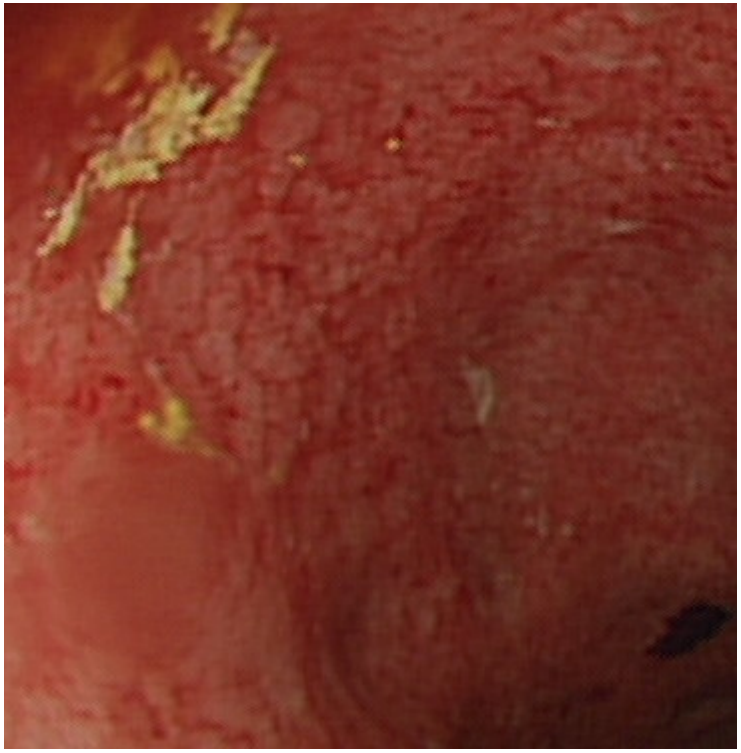


Ulcerative colitis and Crohn's disease = IBD

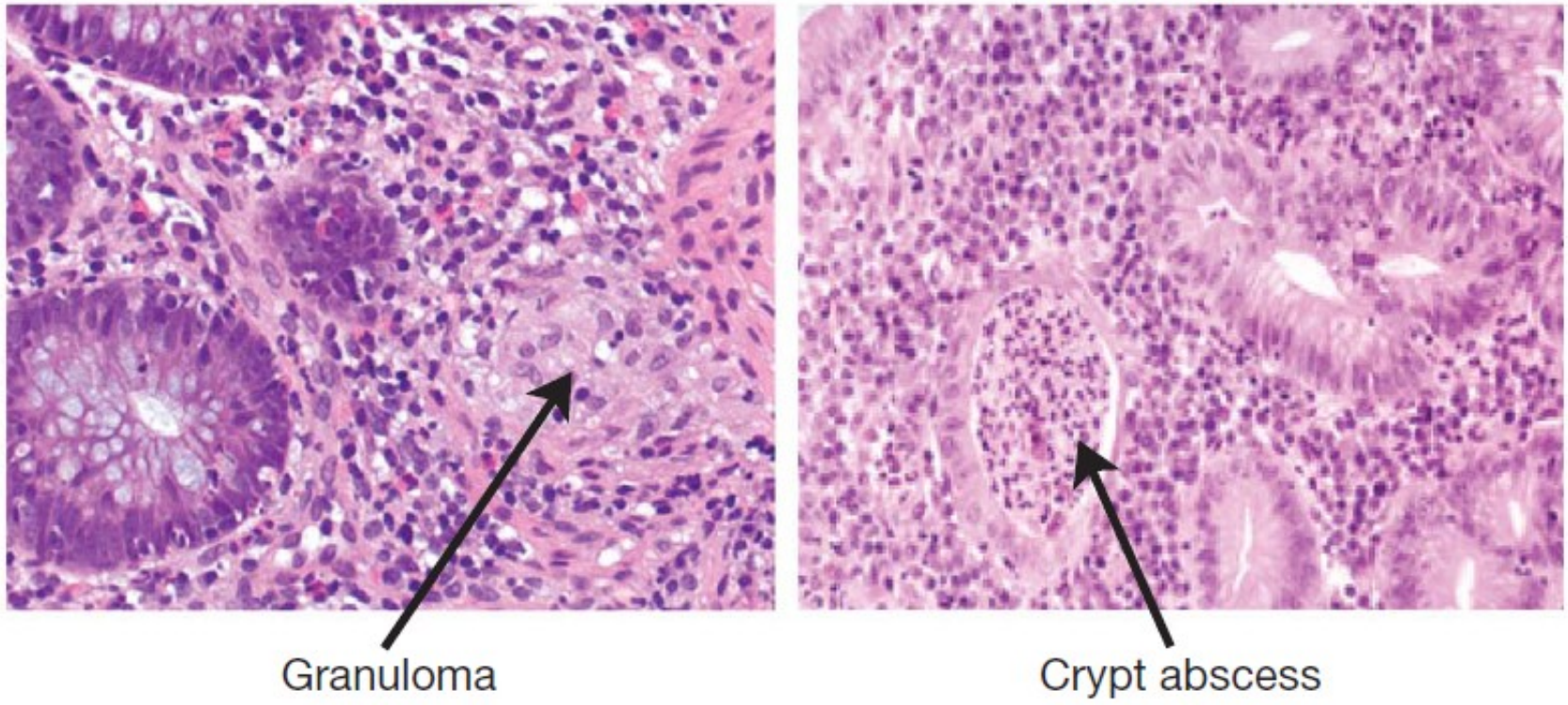


- **Prevalence: 150:100 000**
- **Incidence: 5-15:100 000**
- **Incidence of Crohn's rising year on year**
- **Presents at any age, commonest in 3rd decade**
- **25% diagnosed before age 18 years**
- **Crohn's most prevalent in westernized countries**
- **Ulcerative colitis distributed worldwide**

Ulcerative colitis & Crohn's



Ulcerative colitis & Crohn's



Xavier & Podolsky (2007) Nature 448: 427

Ulcerative colitis & Crohn's

Ulcerative colitis

- From rectum to variable distance proximally
- Mucosal inflammation only
- Neutrophils, eosinophils, lymphocytes
- Antibody responses to colonic antigens
- Moderate systemic inflammatory response

Crohn's disease

- May involve any part of bowel, non-contiguous
- Transmural inflammation
- Lymphocytes and macrophages, granulomas
- Antibody responses to enteric organisms/antigens
- Marked systemic inflammatory response

Anaemia is common in IBD

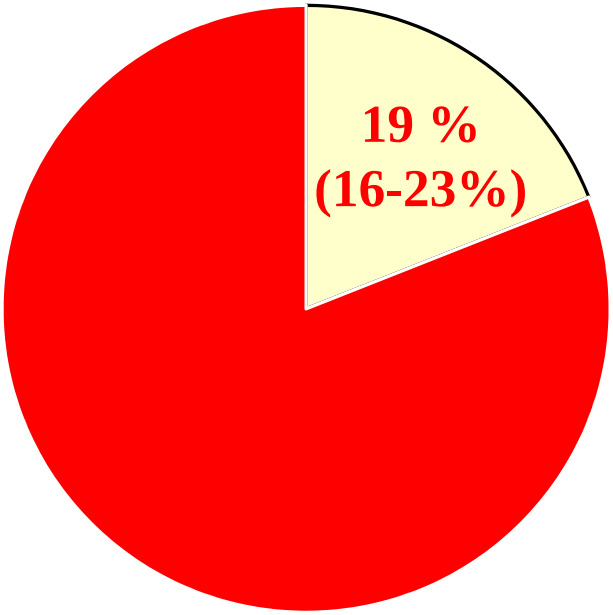
Prevalence at diagnosis 32 %

Sjöberg D et al. *Sv gastrodagarna* 2011:

Anaemia

Hb < 130 g/l ♂

Hb < 120 g/l ♀



Prevalence in outpatients with IBD

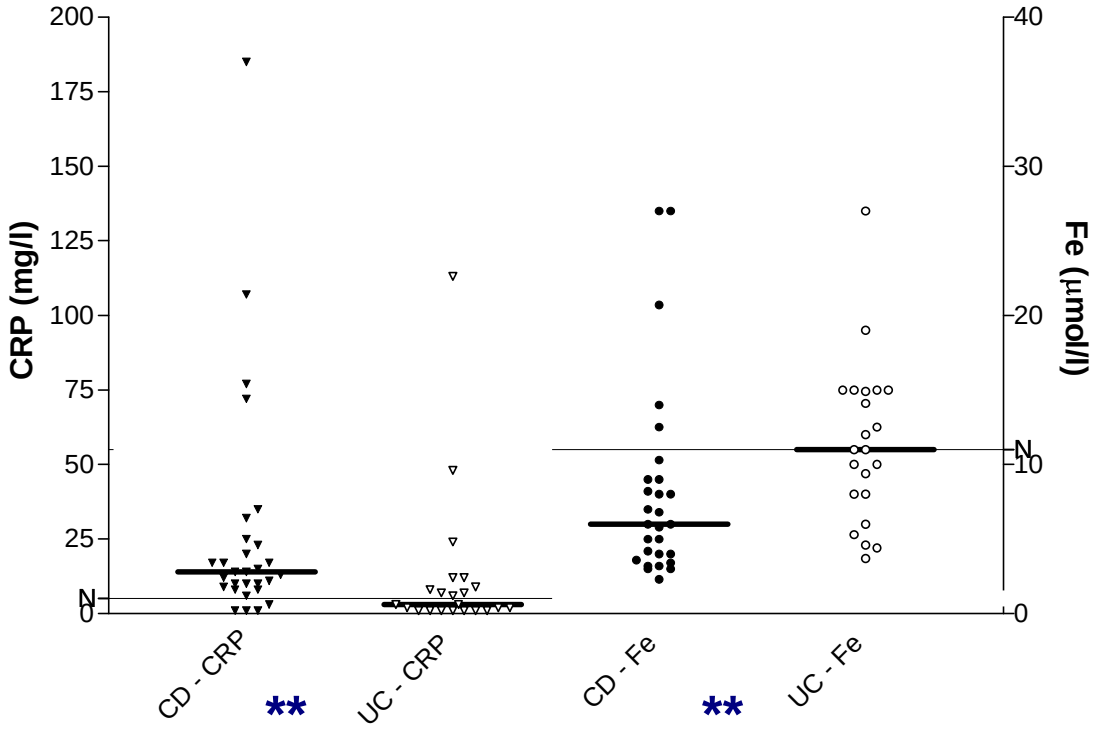
Bager P et al. *Scand J Gastroenterol* 2011;**46:**304-9

Causes of anaemia in IBD

Common	Iron deficiency
	Anemia of chronic disease
Occasional	Vitamin B_{12} deficiency
	Folate deficiency
	Drug-induced (sulfasalazine, thiopurines)
Exceptional	Hemolysis
	Myelodysplastic syndrome
	Aplasia (often drug-induced)
	Inborn hemogobinopathies or disorders of erythropoiesis

CRP and Fe levels distinguish anaemia in CD and UC

Scattergram and medians of CRP and Fe in CD and UC

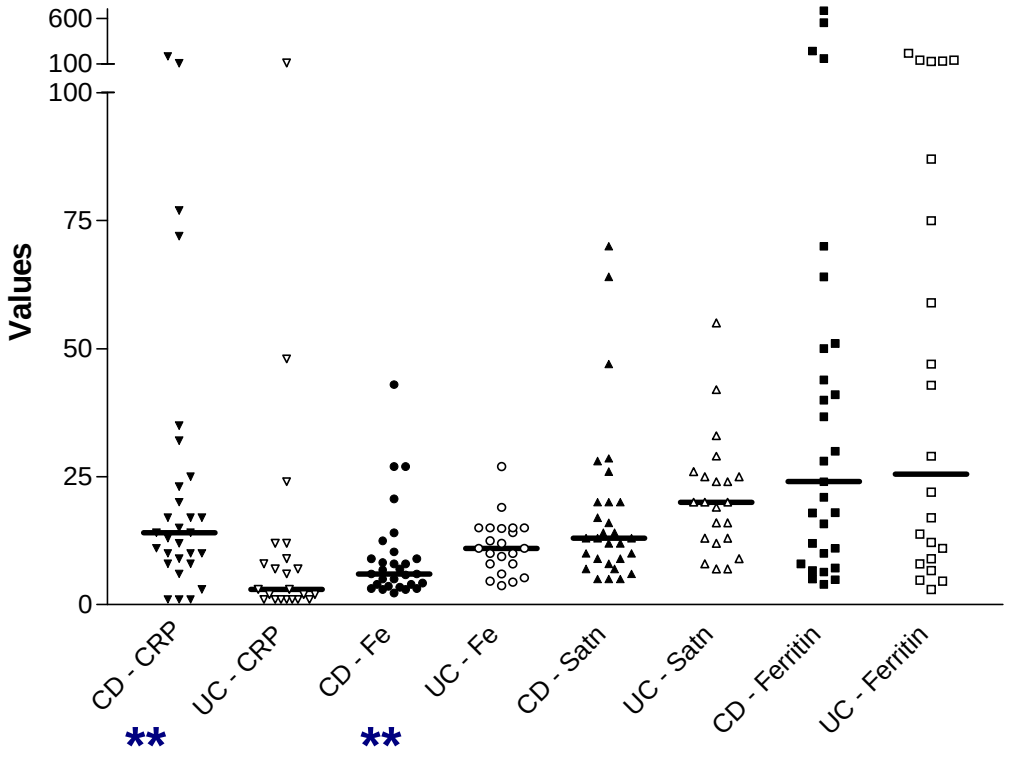


** P<0.05

Sivanesan S et al unpublished data

CRP, Fe, %Saturation, Ferritin in CD and UC

Scattergram and medians of CRP, Fe, %Satn, Ferritin in CD and UC



** P<0.05

Sivanesan S et al unpublished data

Anaemia in Ileo-anal Pouch

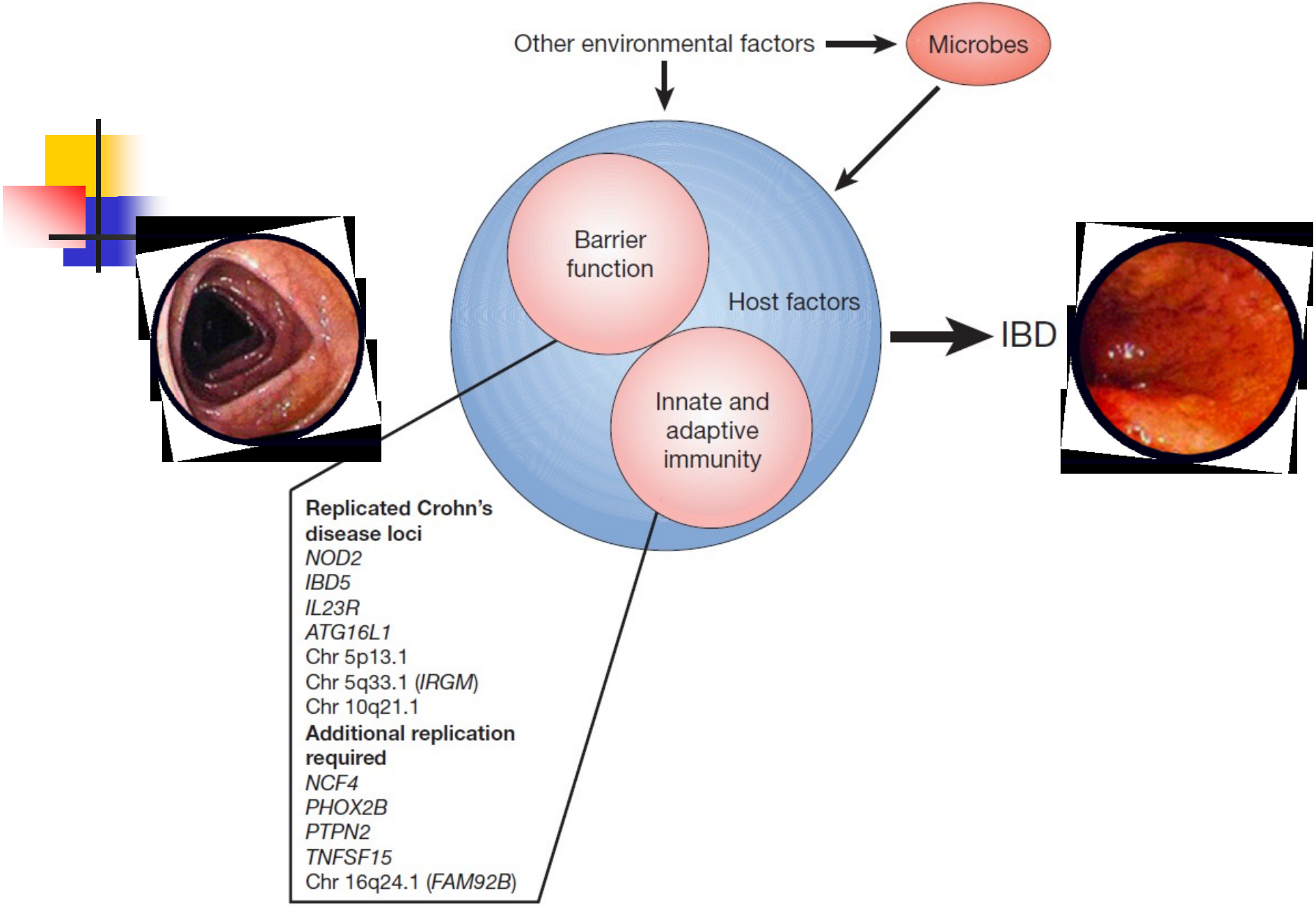
117 Patients with ileo-anal pouches, >12 months after surgery

Mean Hb:	12.8g/dl (+/-1.9)	(range: 6.6 - 16.4)
Mean ferritin:	64.0μg/l (+/-86.1)	(range: 2.9 - 433.5)

Anaemia:	35.9% (42/117)
Microcytosis:	17.1% (20/117)
Hypoferritaemia:	21.6% (16/117)

B12 deficiency:	5.3%
Folate deficiency:	12.1%

Gilchrist J, Amin, I et al unpublished data



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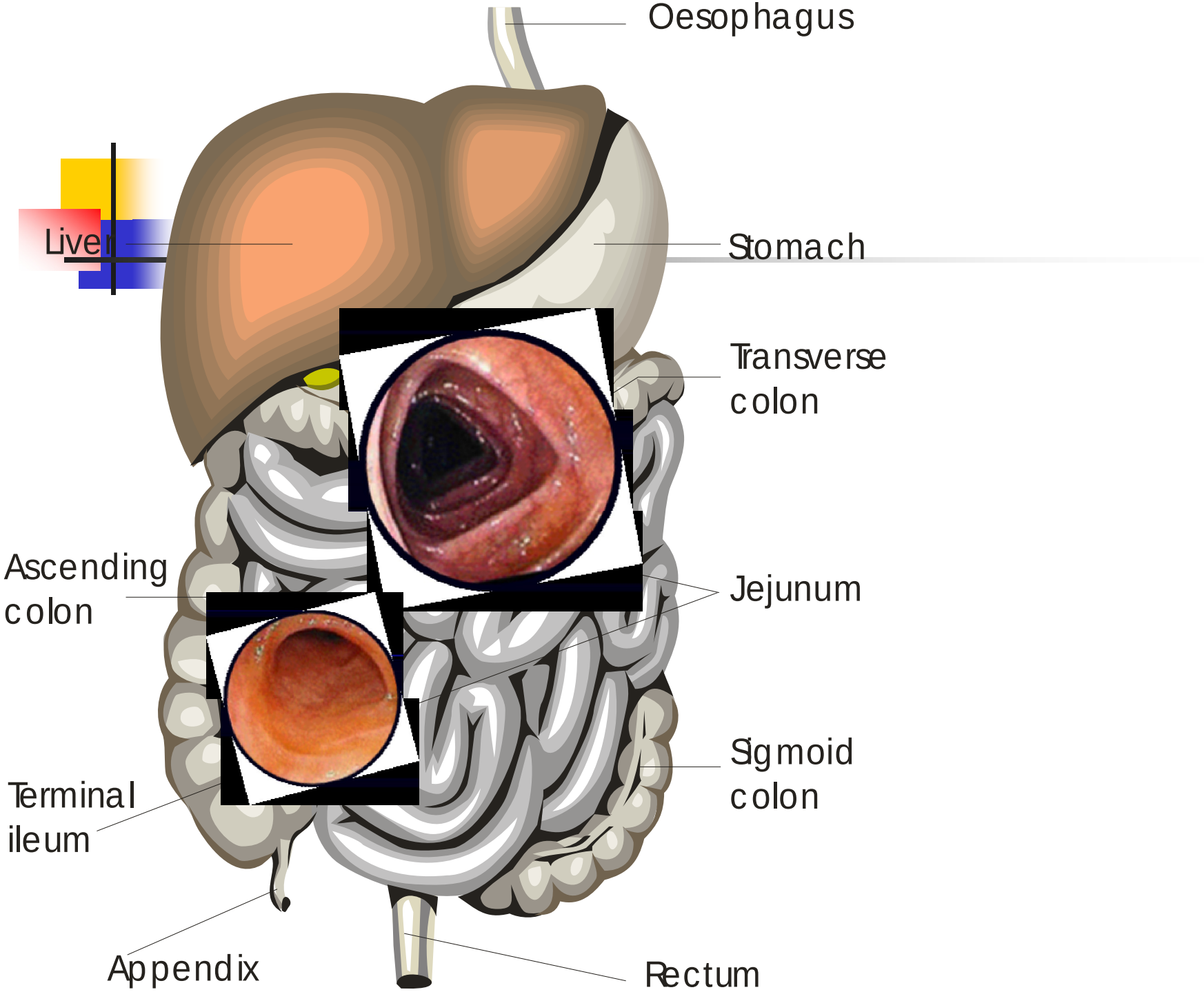
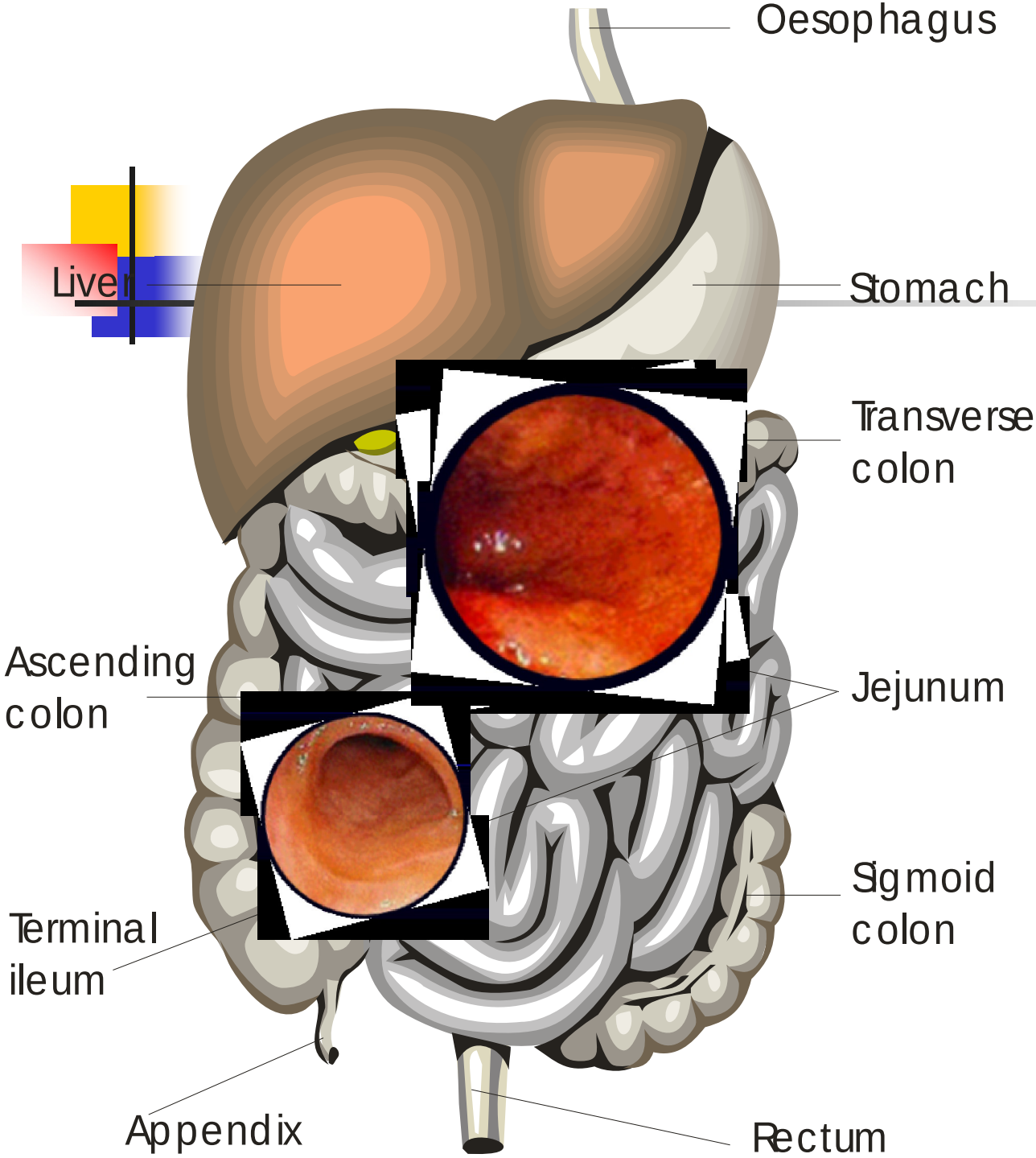
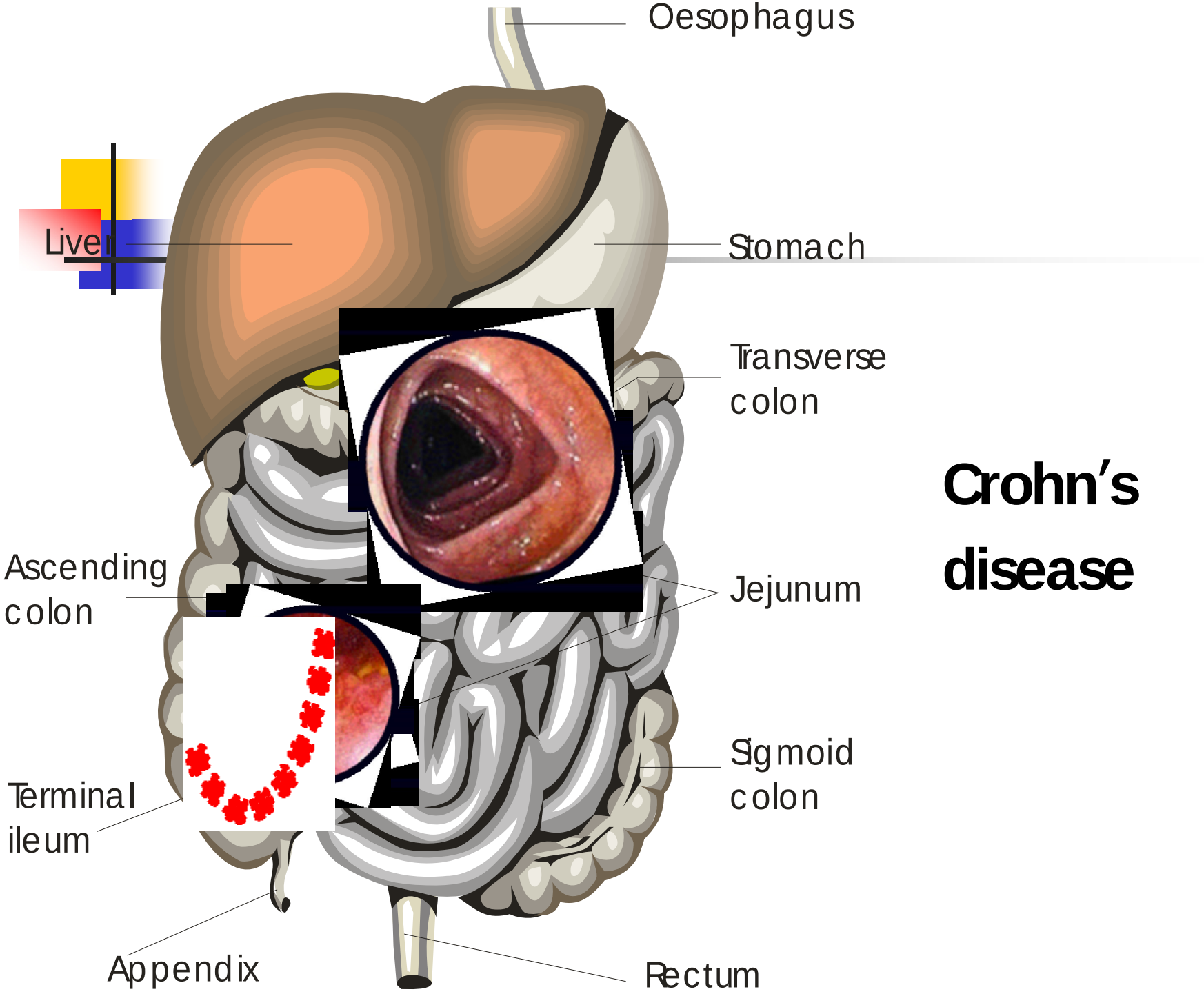

Oesophagus
Liver
Stomach
Transverse colon
Ascending colon
Jejunum
Sigmoid colon
Terminal ileum
Appendix
Rectum



Ulcerative colitis

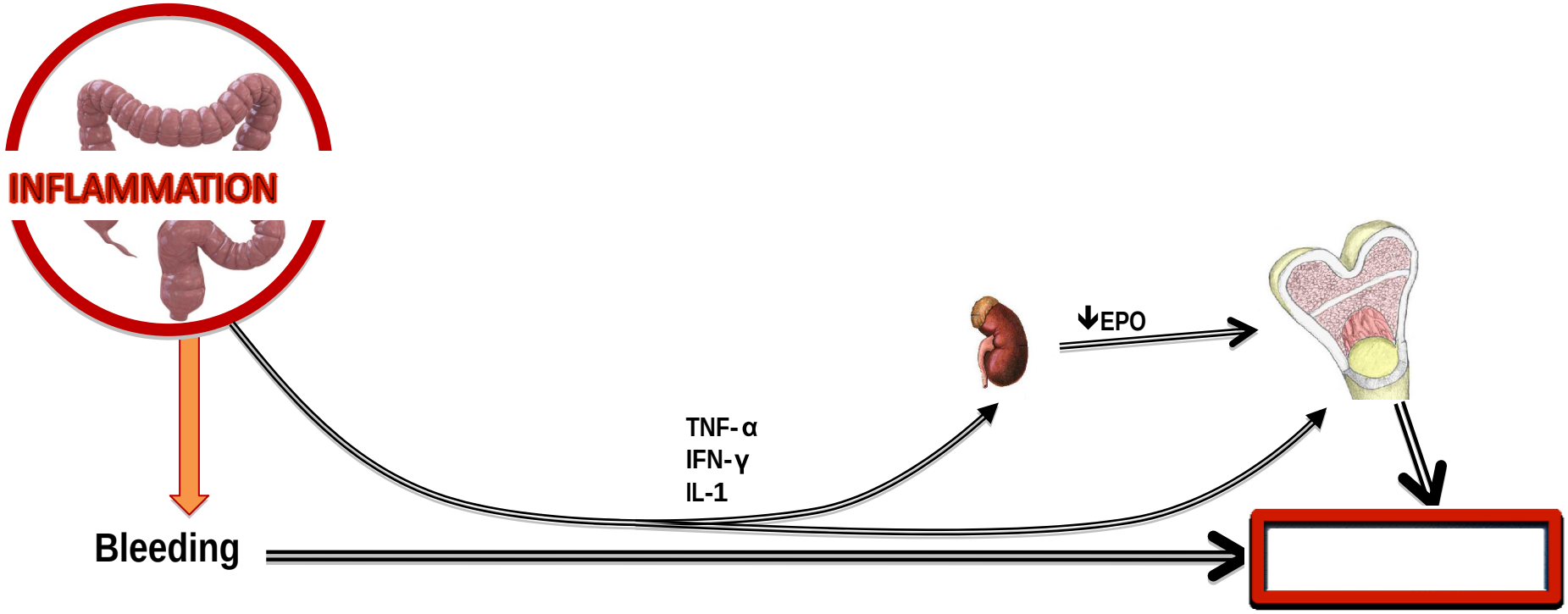


Crohn's disease

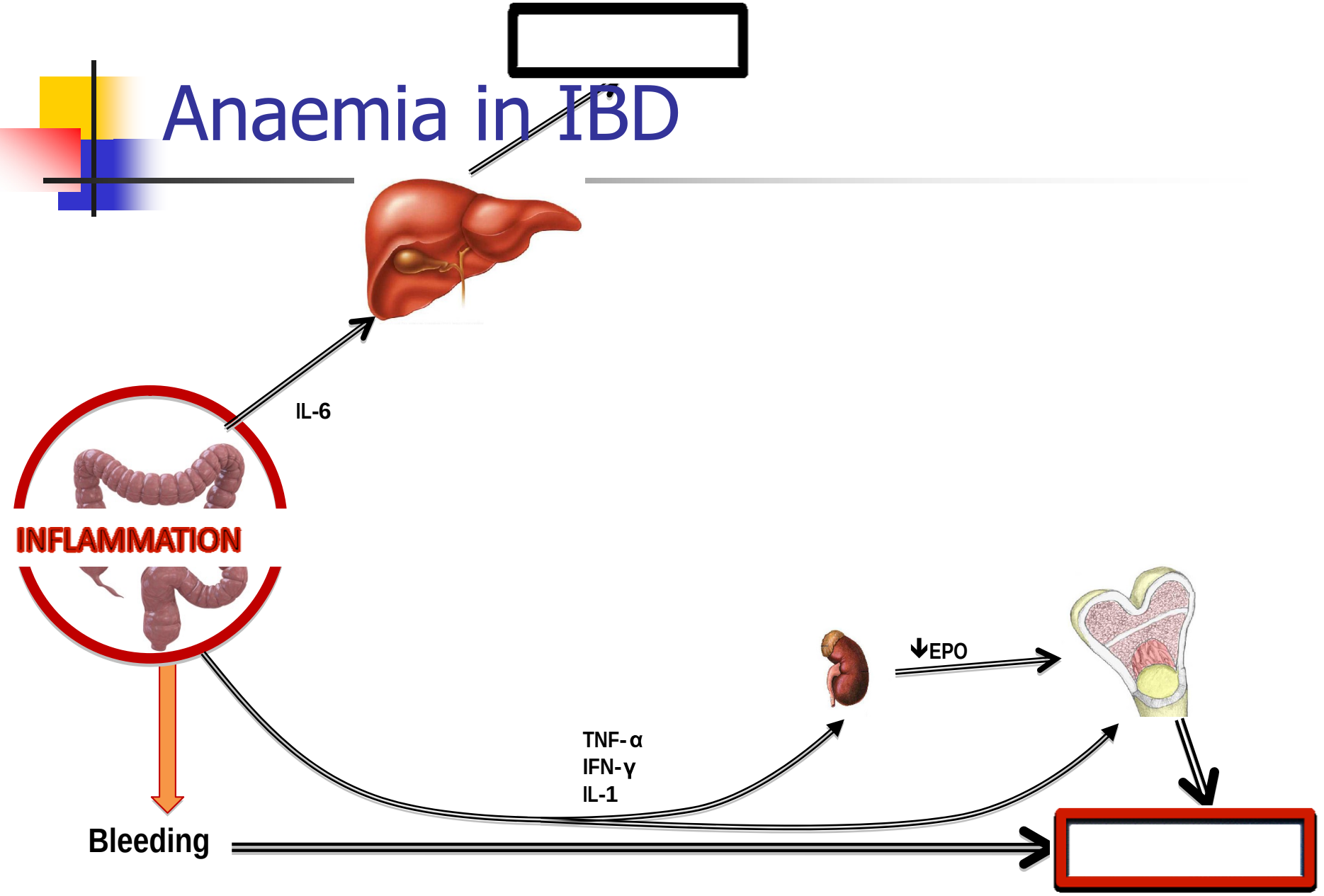
Anaemia in IBD

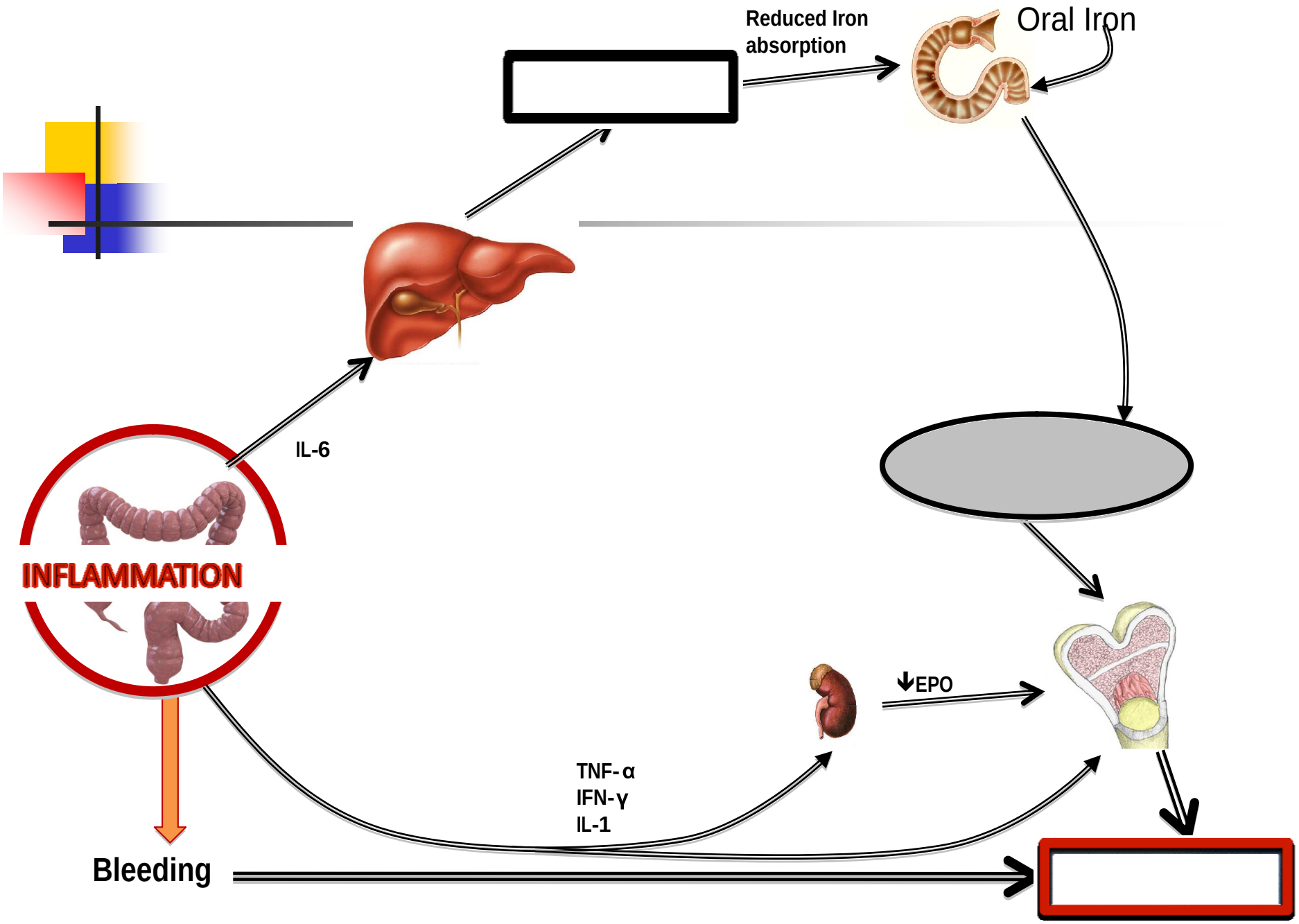
Bleeding

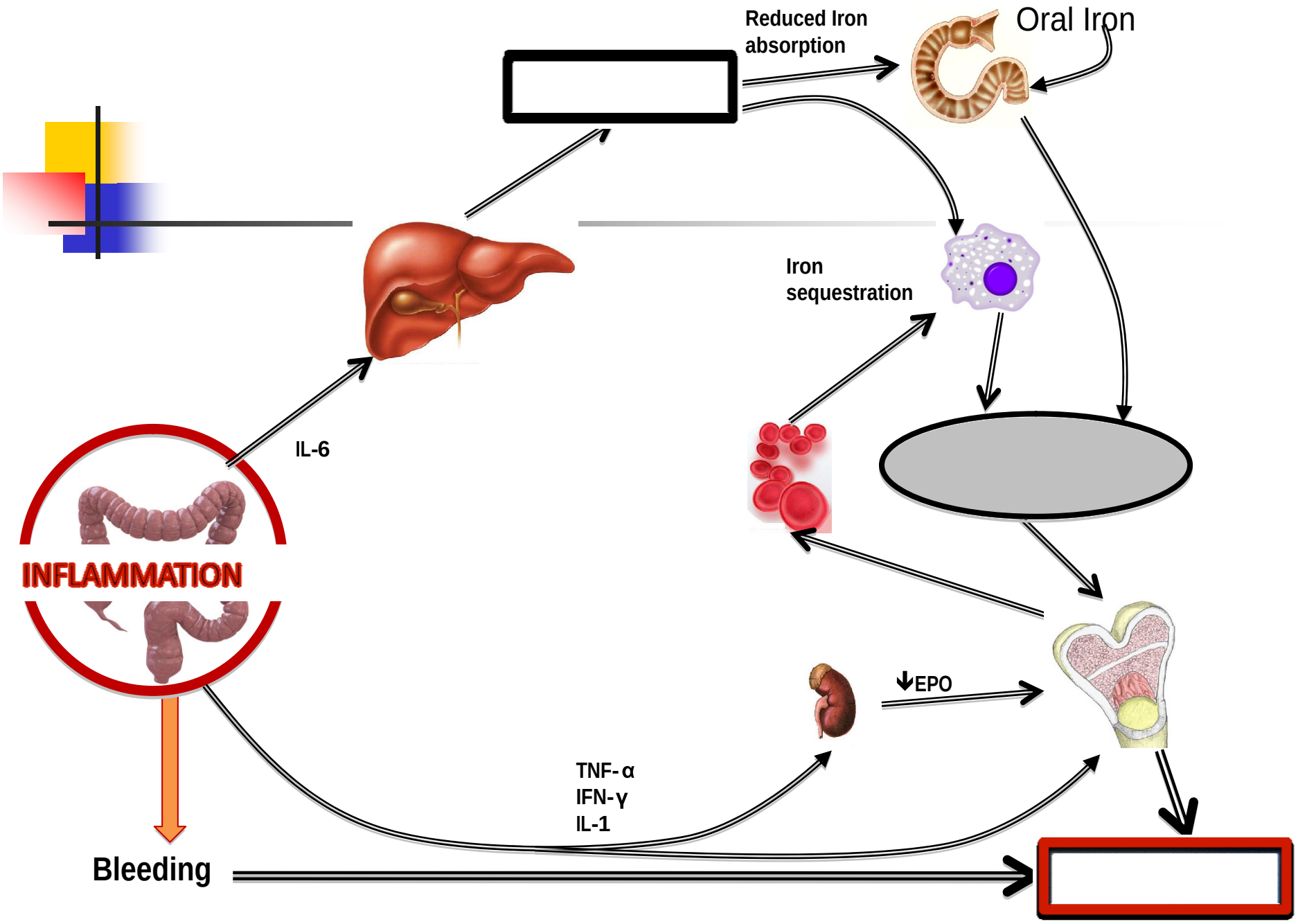
Anaemia in IBD



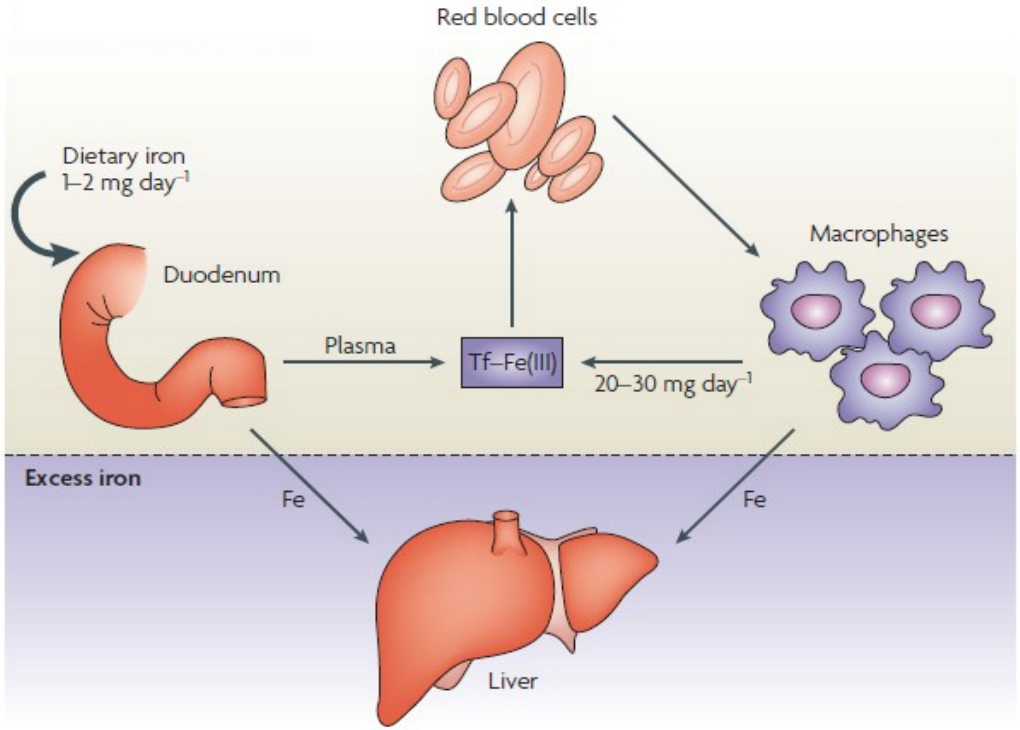
Anaemia in IBD

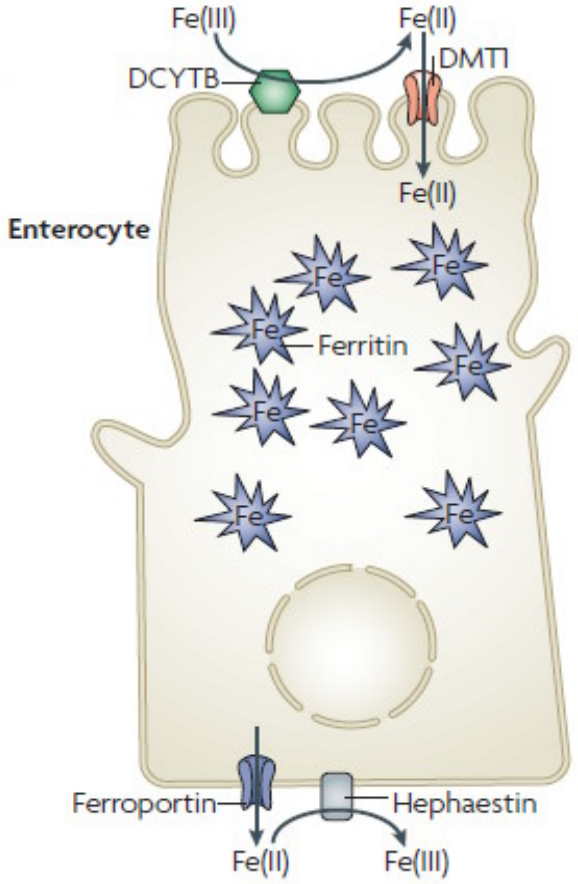



Reduced Iron absorption
Oral Iron
IL-6
INFLAMMATION
↓EPO
TNF-α
IFN-γ
IL-1
Bleeding

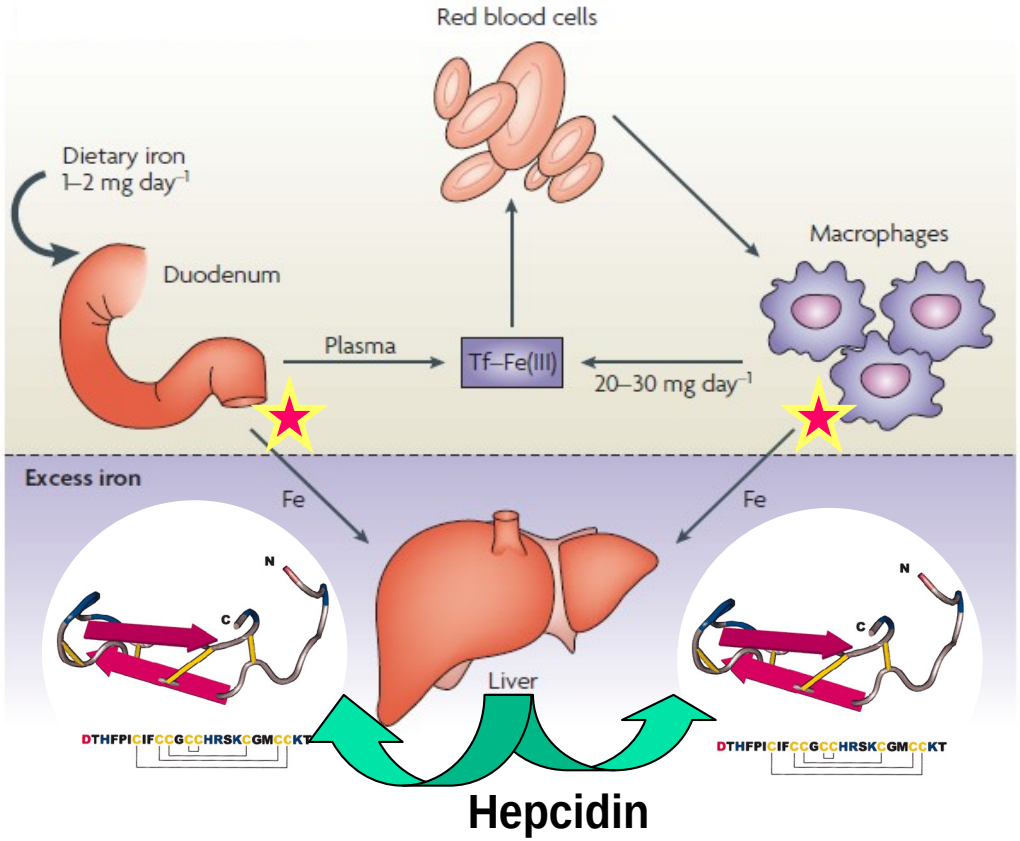

Reduced Iron absorption
Oral Iron
Iron sequestration
IL-6
INFLAMMATION
↓EPO
TNF-α
IFN-γ
IL-1
Bleeding

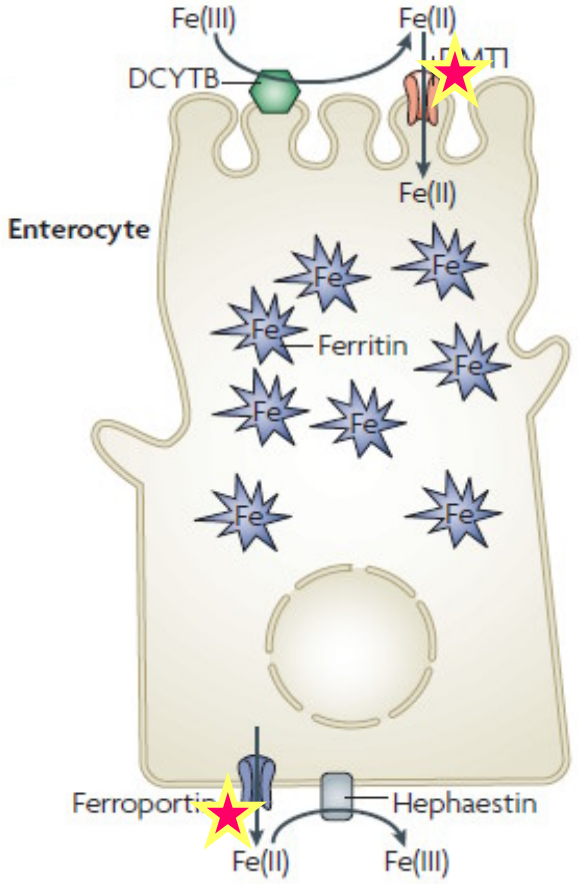
Iron uptake and use



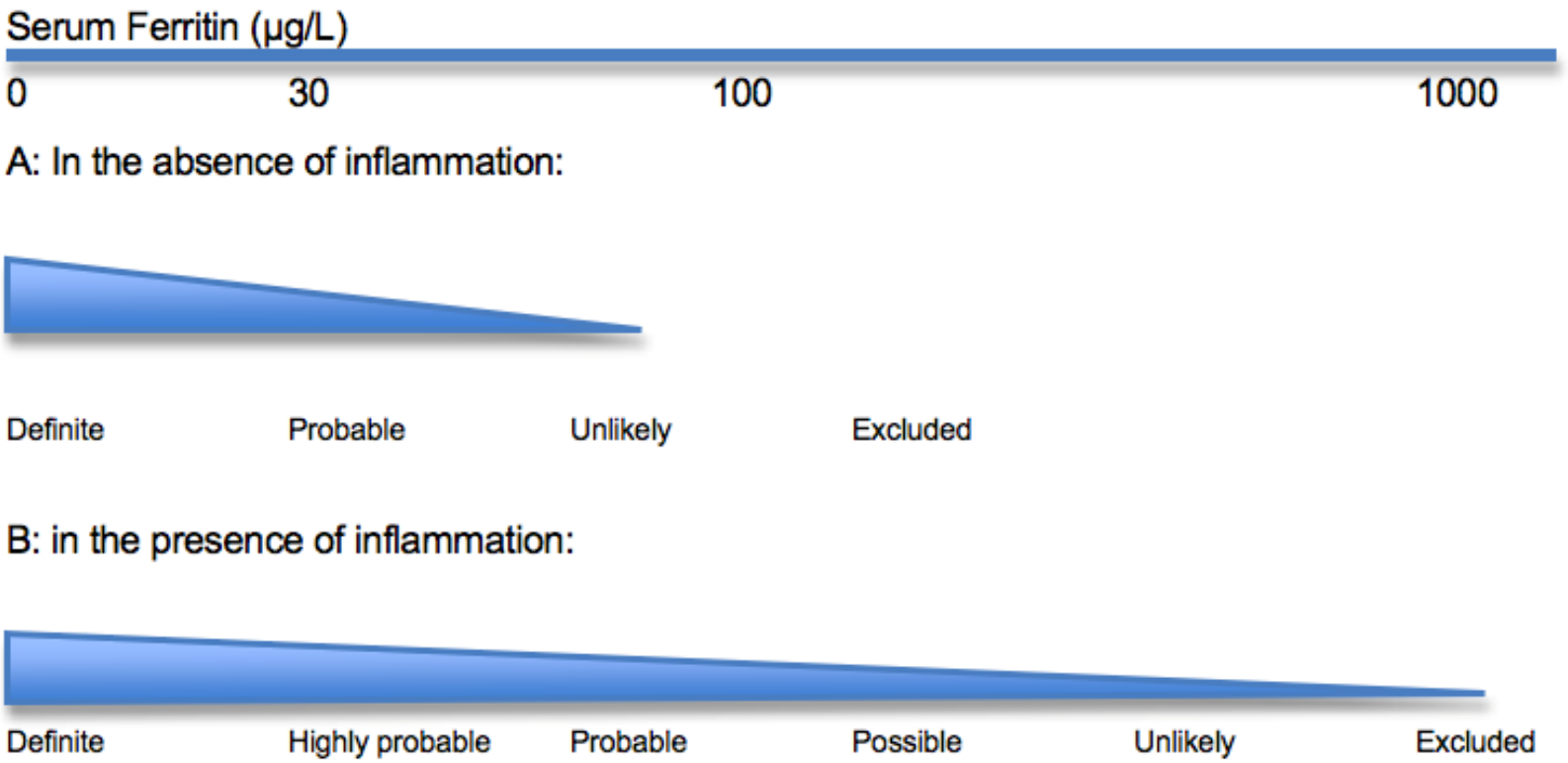


Iron uptake and use blocked





Serum Ferritin in IBD



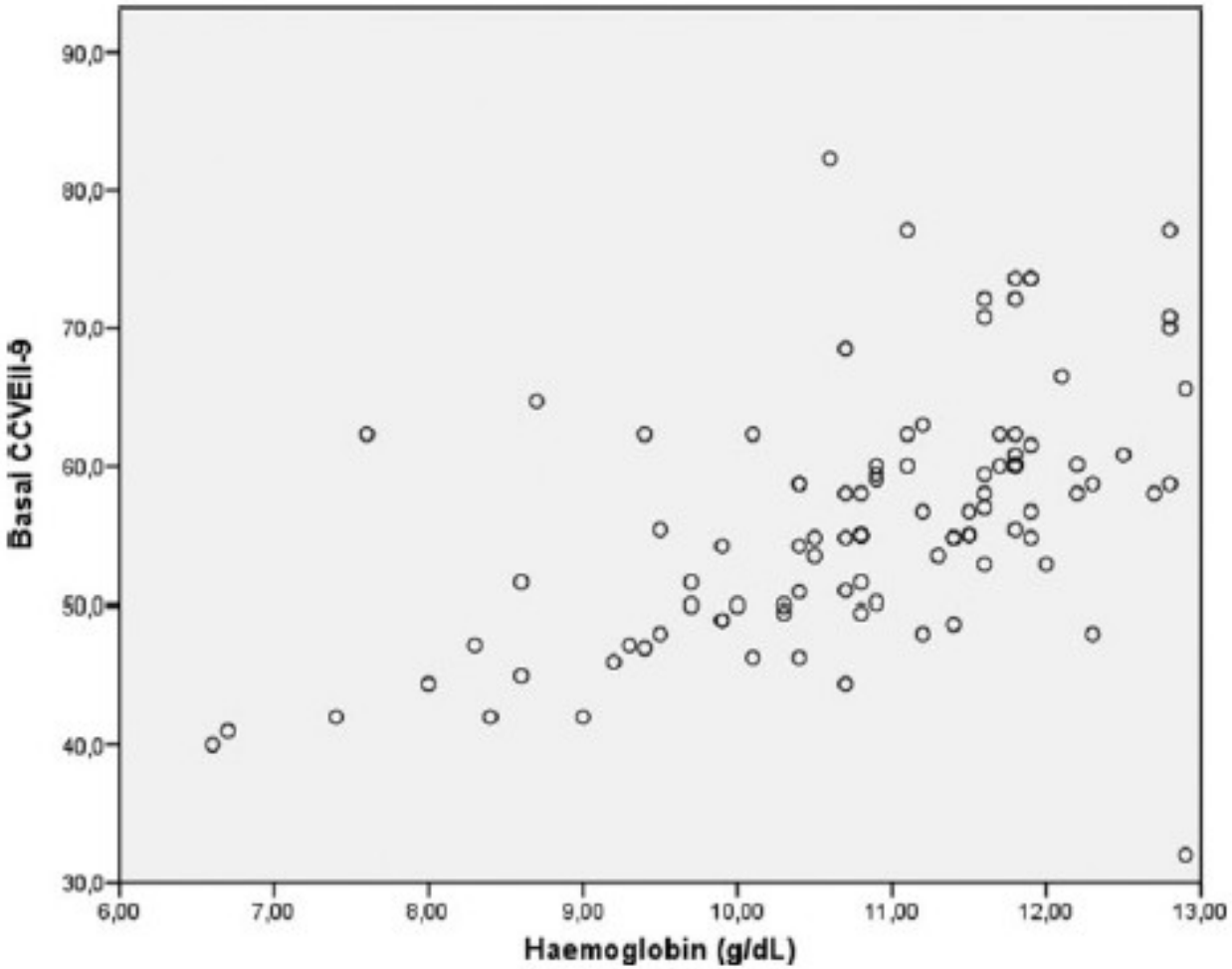


FIGURE 2. Correlation between hemoglobin concentrations and quality-of-life questionnaire (CCVEII-9) score.

Gisbert JP et al (2009) Inflamm Bowel Dis epub ahead of print

Intravenous Iron Therapy

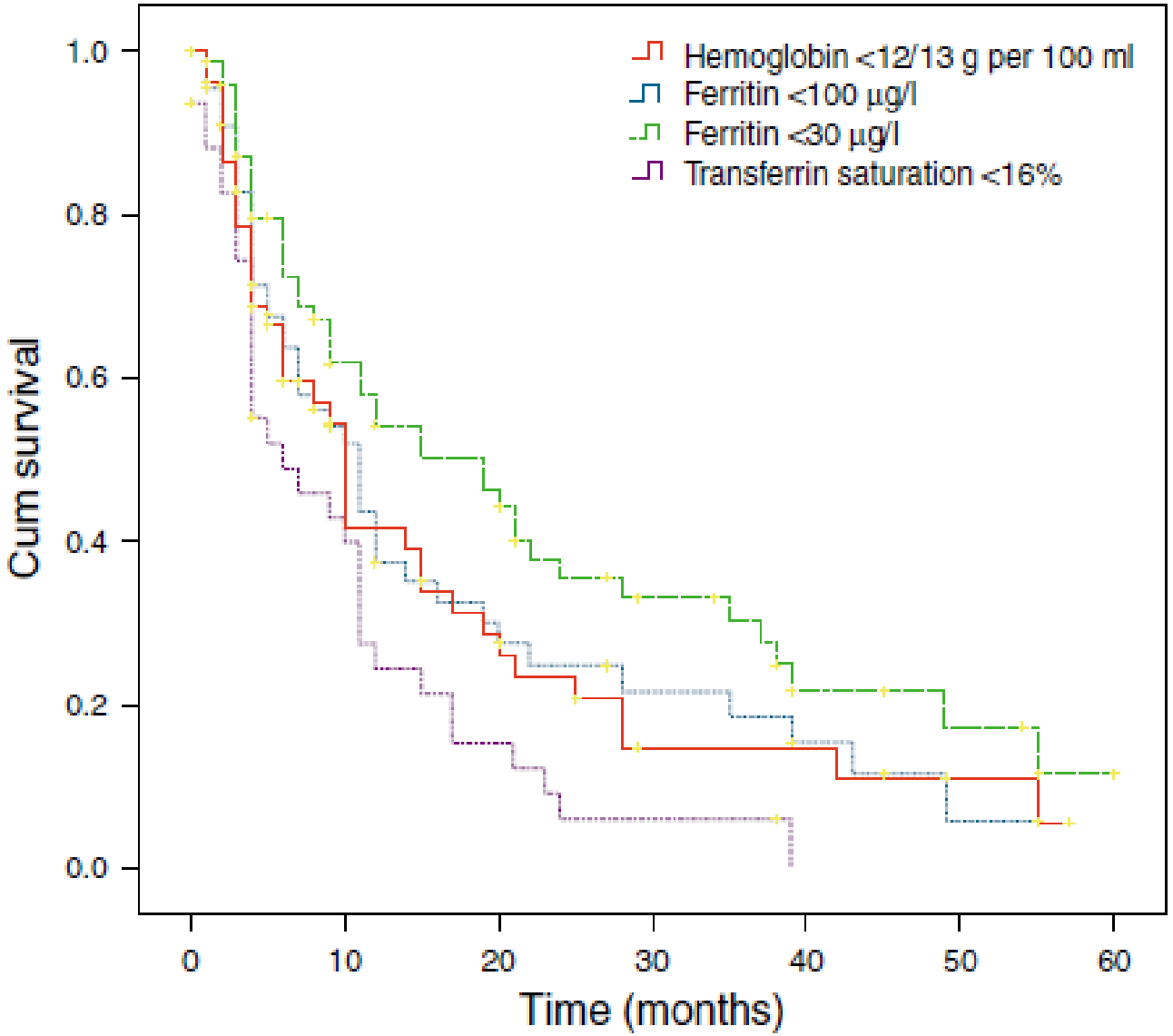
	High MW Iron Dextran	Low MW Iron Dextran	Iron Gluconate	Iron Sucrose	Ferric Carboxy-maltose[a]
Trade names[b] (US, Europe)	Dexferrum	Infed, Cosmofer	Ferrlecit	Venofer	Injectafer, Ferinject
Manufacturer	Luitpold Pharmaceuticals	Pharmacosmos	Sanofi-Aventis	Vifor Int.	Vifor Int.
Chemical properties[c]					
MW [kD]	265	165	< 50	30–100	> 100
Complex stability	[redacted]	[redacted]	Low	Moderate	[redacted]
Acute toxicity	[redacted]	[redacted]	High	Medium	[redacted]
Dosing[b]					
Test dose required	Yes	Yes	[redacted]	Yes*/No	[redacted]
Maximal dose	[redacted]	[redacted]	62.5–125 mg	200–500 mg	[redacted]
Max. infusion time	360 min	360 min	60 min	30–210 min	[redacted]
Max. injectable single dose	100 mg	100 mg	125 mg	[redacted]	[redacted]
Max. injection time	[redacted]	[redacted]	10 min	10 min	[redacted]
Safety profile[d]					
Risk of dextran-induced anaphylaxis	Yes	Yes	[redacted]	[redacted]	[redacted]
Relative risk of serious adverse events	High	Moderate	Low	Lowest	n.a.

Table 2. Number (%) of patients with normal levels of hemoglobin, serum ferritin, or transferrin saturation after iron replacement therapy

	Hb ≥12/13 g per 100 ml	Ferritin ≥100 µg/l	Ferritin ≥30 µg/l	TfS ≥16%
Crohn study	31 (79.5)	37 (94.9)	39 (97.5)	30 (76.9)
Colitis study	14 (70.0)	14 (70.0)	16 (80.0)	6 (30.0)
Predict study	11 (37.9)	25 (86.2)	29 (100.0)	5 (17.9)
Combined	56 (63.6)	76 (86.4)	84 (95.5)	41 (47.1)

Hb, hemoglobin; TfS, transferrin saturation.
Data are presented as *n* (%).

Kullnig S et al (2009) Am J Gastroenterol 104 1460-7



Kullnig S et al (2009) Am J Gastroenterol 104 1460-7

Conclusion

- **Iron deficiency anaemia in GI disease is potentially serious:**
  - **Always consider Colon Cancer, especially in those over 50**
  - **Consider unusual causes**
  - **Consider specialist referral**

- **Iron deficiency in GI disease is not only due to bleeding:**
  - **Inflammation may reduce iron absorption**
  - **Consider coeliac disease!**
  - **Is the diet adequate?**

- **Therapy of iron deficiency is evolving:**
  - **Iron deficiency is not corrected by blood transfusion**
  - **Intravenous iron is a viable option**
  - **Monitor and maintain treatment**