Thrombophilia and the risk of arterial thrombosis

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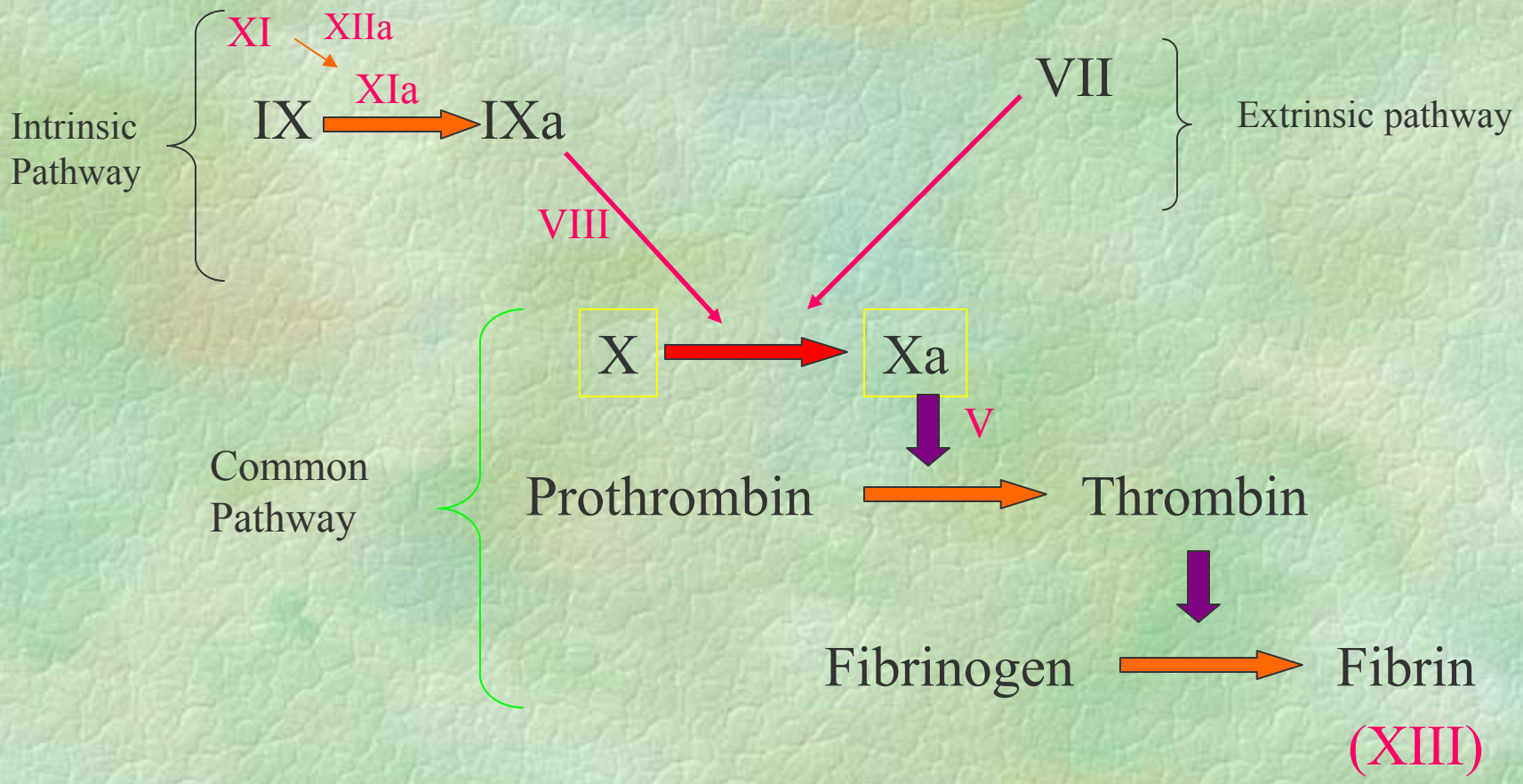
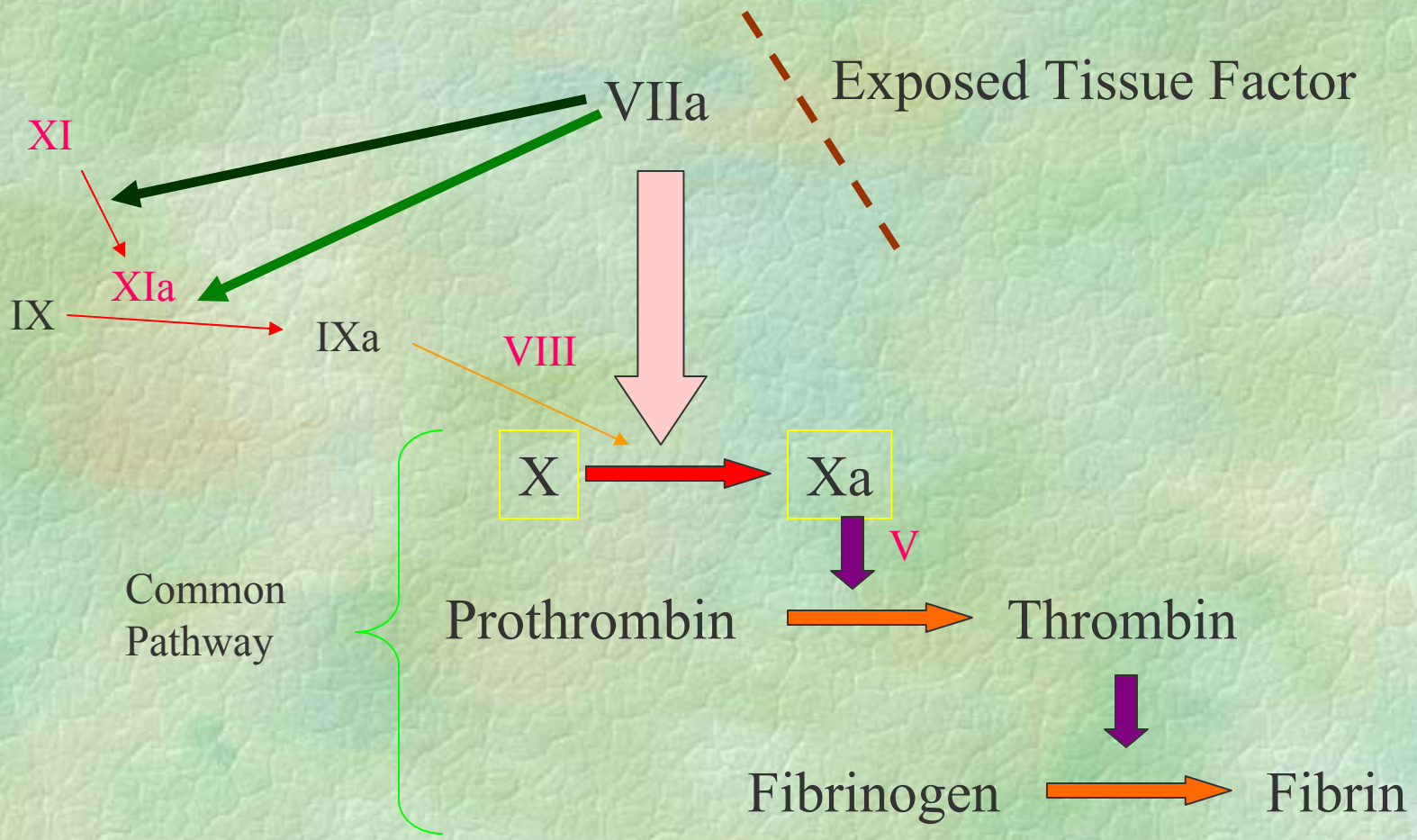
Summary

- Basic physiology
  - coagulation vs. anticoagulation
- Venous thrombosis and thrombophilia
- Arterial disease and thrombophilia

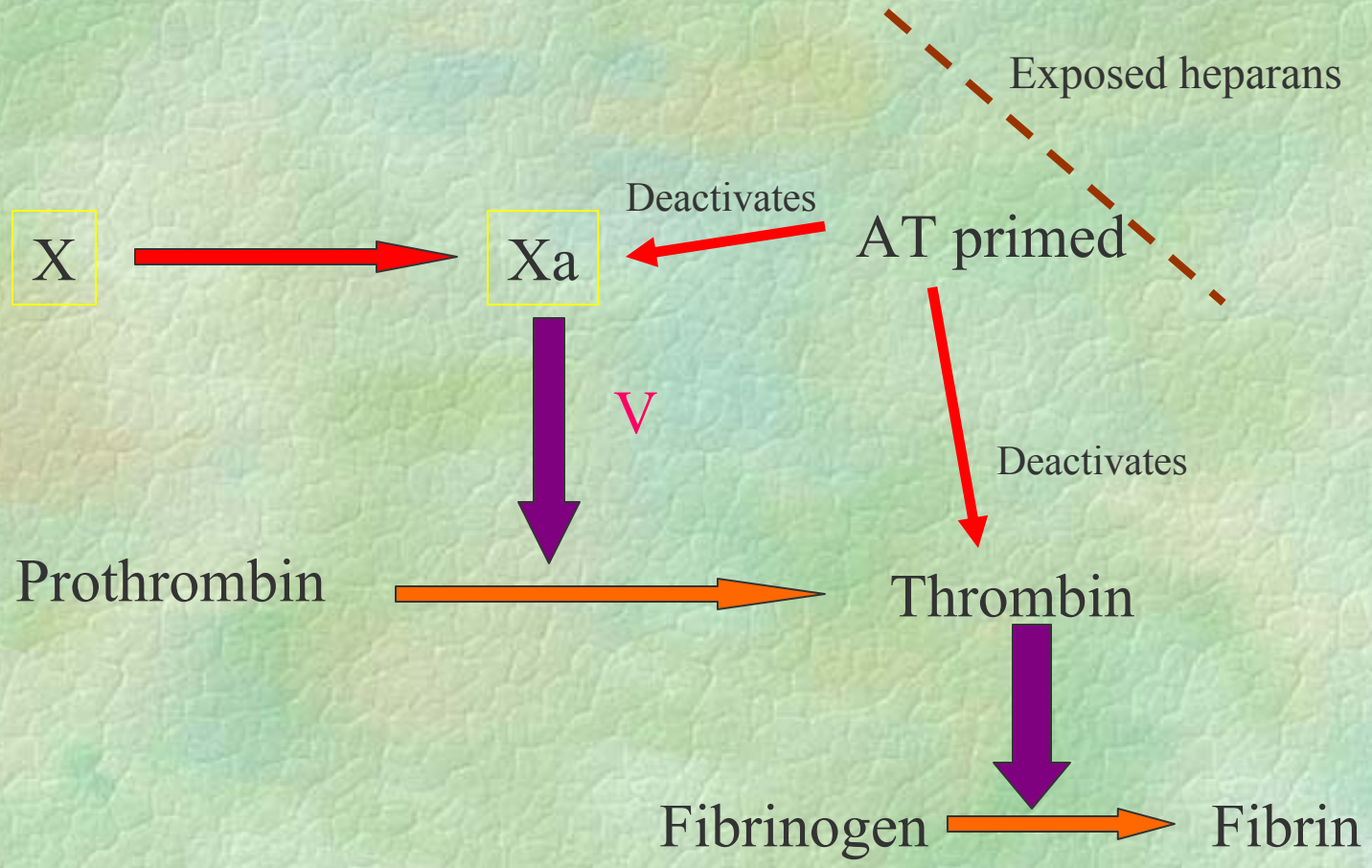
Basic Physiology



Basic Physiology



Natural Anticoagulants



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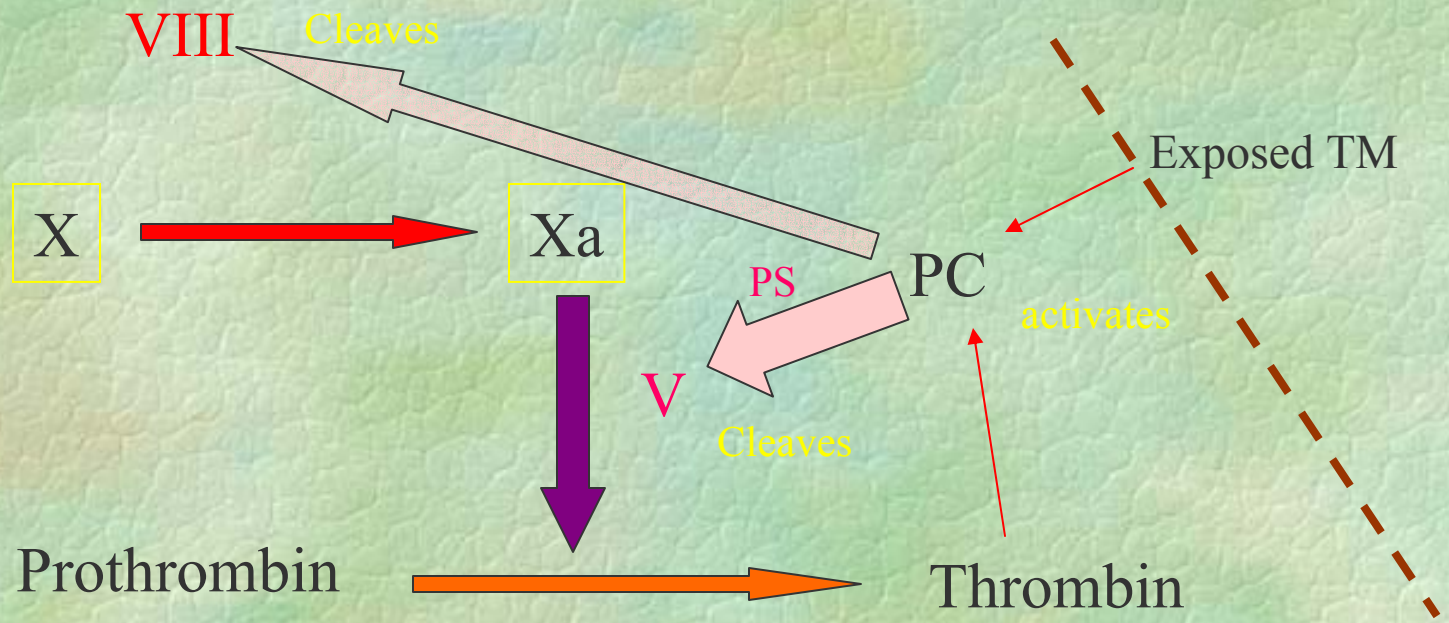

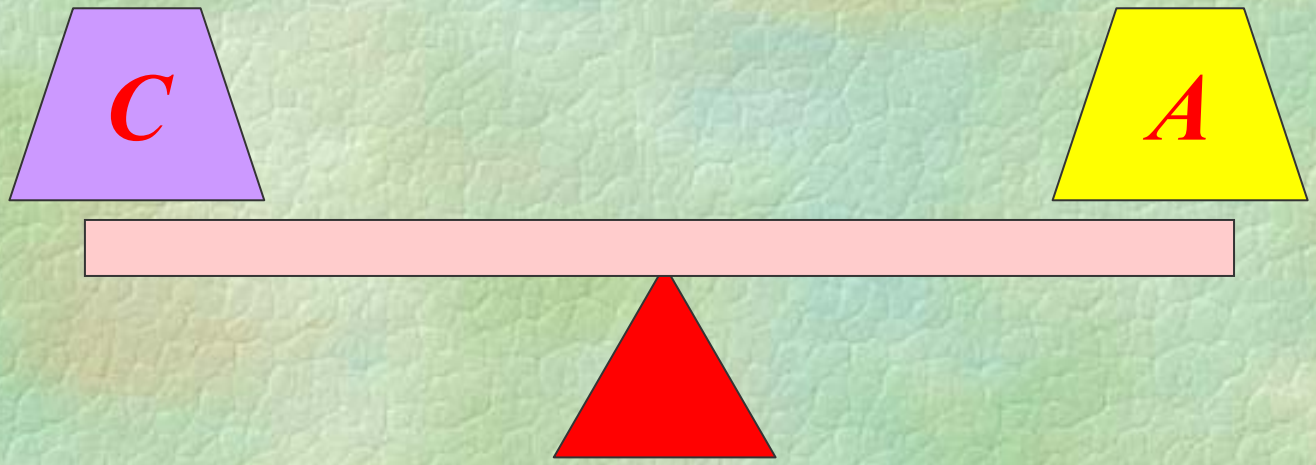
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The Concept of Thrombophilia

"A disorder of haemostasis that increases the probability of thrombosis"

70% of venous thromboses have an identifiable precipitant

30% do not and are "spontaneous"

Circumstantial Triggering

The interaction of two or more intrinsic or extrinsic influences as the “trigger” for thrombosis.

Extrinsic Influences

- General anaesthesia/surgery
- Trauma
- Oestrogen therapy
- Air travel
- Intravenous injection/cannulation
- (Smoking)

Intrinsic influences

- Congenital
  - AT deficiency
  - PC/PS deficiency
  - Dysfibrinogenaemia
  - APCR/FVLM
  - PTGM
  - others
- Acquired
  - Antiphospholipid syndrome
  - Obesity
  - Pregnancy
  - Malignancy
  - Myeloproliferative disorders
  - others

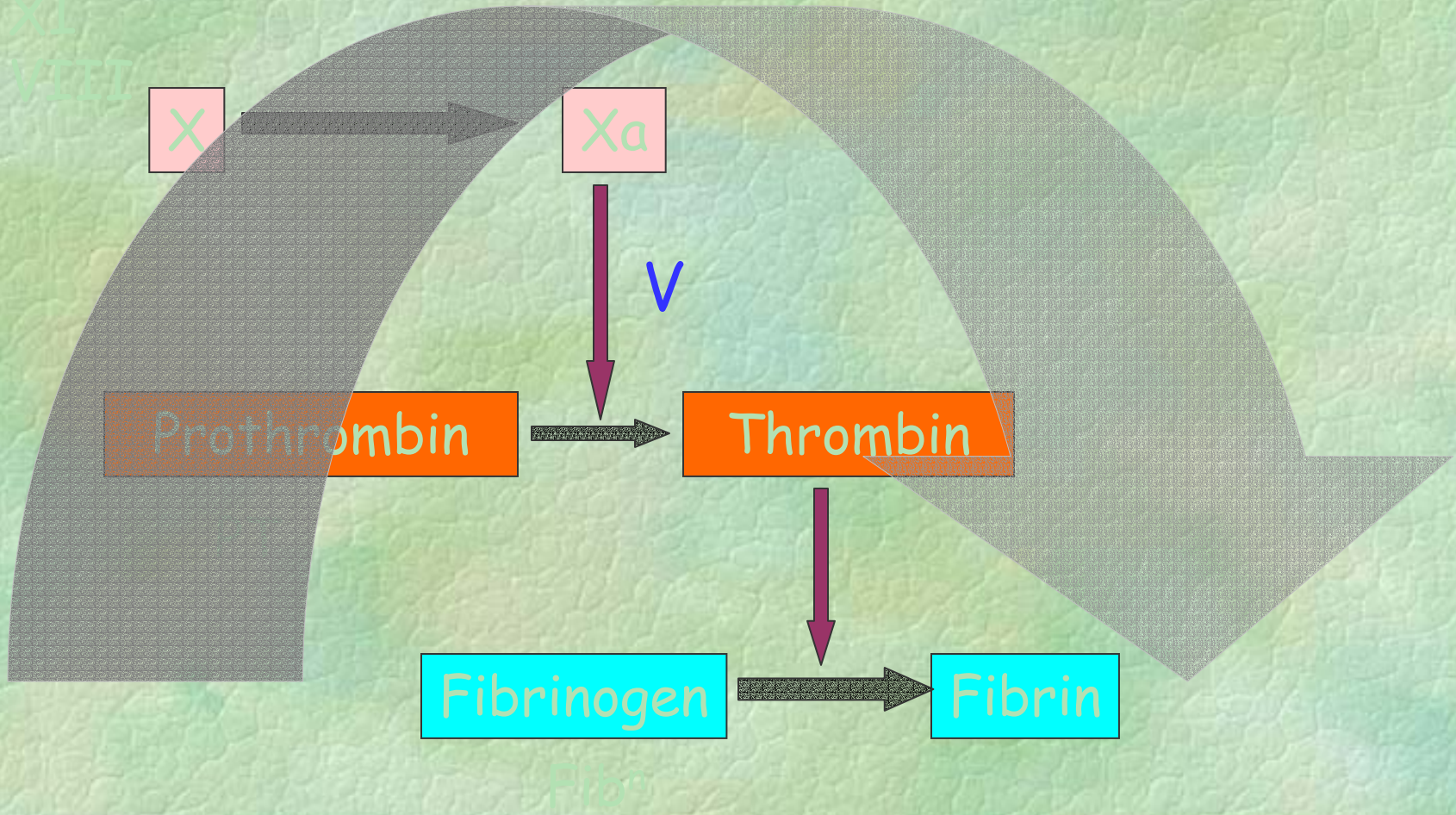
Natural anticoagulant deficiencies

DISORDER	Homozygous state?	Overall gene prevalence	Frequency in thrombotics	Relative risk of VTE
Anti-thrombin deficiency	(no)	0.02%	0.5-1.0%	25-50
Protein C deficiency	Yes	0.2-0.3%	3.0%	10-15
Protein S deficiency	Yes	1.3-2.1%?	3.0%	Mild?

Other heritable thrombophilias

DISORDER	Homozygous state?	Overall gene prevalence	Frequency in thrombotics	Relative risk of VTE
Factor V Leiden mutation	Yes	2-15%	20-50%	3-8 (80 if HZ)
Prothrombin gene variant	Yes	2.0%	6.0%	3

Coagulation Factor excess



Antiphospholipid Antibodies

- Common finding
  - significant proportion of healthy (esp. elderly) population
  - most never thrombose
  - may be transient
- Uncommon cause of severe thrombophilia
- Complex physiology

Antiphospholipid Antibodies

- As most APL antibodies are not pathogenic, and many are transient, be strict about the diagnostic criteria
  - 1-5% of healthy controls
- *Possibly* the only thrombophilia which makes a difference to management of a *first* thrombosis

Antiphospholipid syndrome

- Association of a thrombotic tendency
  - venous or arterial thrombosis
  - recurrent (3+) miscarriages
- with the persistence of one or more antiphospholipid antibodies
  - LA confirmed by two different tests, or IgG or IgM ACA by ELISA
  - repeated after 6 weeks

Factor VIII

- Raised FVIII levels are associated with an increased risk of venous thrombosis
- If FVIII >150iu/dl, relative risk of VTE is 4.8 compared with if FVIII <100iu/dl
- Is this the commonest thrombophilia?
- Need to exclude acute phase reaction as a cause of raised FVIII
- Genetic determinant?

Hyper*homocystein*aemia

- Non-protein forming amino acid
- Product of the metabolic processing of methionine

Fibrinogen

- No clear cut association with venous thrombosis
- Possible association between raised FIX and XI levels and venous thrombosis
- No evidence of a genetic element as yet

What difference does a positive test make?

- First thrombosis - does it influence immediate management?
- Does it influence duration of therapy?
- Does it make a difference to advice regarding high risk exposure?
  - i.e. surgery, OCP/HRT, pregnancy, LHAF

What difference does a positive test make?

- Screening asymptomatic patients
  - a positive test is not an indication for anticoagulation
  - most will never thrombose
- Would a positive test modify lifestyle/risk management advice?
  - controversial

So why do it?

- Patient curiosity
- Future reference
- *Possibly* will influence advice
  - COCP/HRT
  - surgery
  - pregnancy
  - ?duration/intensity of anticoagulation

Is thrombophilia screening of value when investigating arterial disease?

National Clinical Guidelines for Stroke

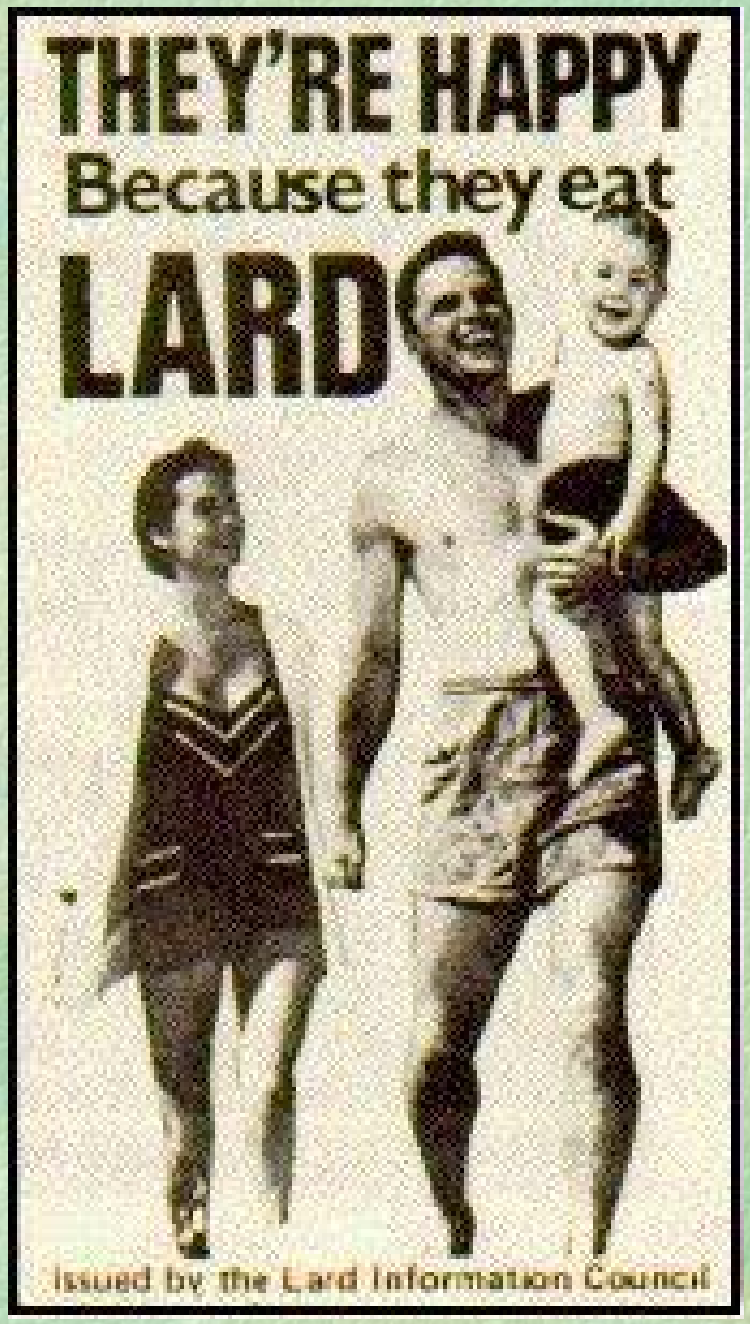
" It is likely that local services will wish to develop local guidelines for:

5. investigation of the underlying cause of stroke; "


Marlboro

Diabetes UK

The charity for people with diabetes


THEY'RE HAPPY
Because they eat
LARD
Issued by the Lard Information Council

Natural Anticoagulant Pathway

- AT, PC and PS deficiencies, APCR/FVLM, PTGV
- Any evidence of an association with stroke or ischaemic heart disease is *anecdotal*
- No genuine justification for testing

Antiphospholipid Syndrome

- Clear association between presence of antiphospholipid antibodies and first VTE, first MI and recurrent stroke
  - VTE>CVA>MI
- Enough to justify primary prophylaxis?
- Enough to justify secondary prophylaxis?

Hyperhomocysteinaemia

- Association between homocystinuria and atherosclerosis reported in 1969
- Is there an association between moderately raised homocysteine levels and CVA and IHD?
- Relative risk of MI 1.7, CVA 2.5, PVD 6.8
- Increase in plasma homocysteine of 5μmol/l associated with 33% increase in vascular risk

Hyperhomocysteinaemia

- Genetic influence
  - MTHFR or CBS heterozygosity
  - Not independently associated with vascular risk
- Dietary influence
  - B12, B6 and Folate supplementation will lower homocysteine levels moderately (2μmol/l)
- Is this reduction associated with a reduced risk?
  - VISP and VITATOPS studies in stroke

Coagulation factor excess

- Raised clottable fibrinogen appears to be associated with increased mortality from CHD
- Clauss assay
- Due to effect on whole blood viscosity?
  - Haematocrit also associated
- No evidence of a genetic effect

Summary of thrombophilia and arterial disease

- Limited thrombophilia screening may be of value in investigation of stroke, IHD and PVD in selected patients
- “Young” patients
  - under 40(?) for MI, under 60(?) for CVA
  - esp. if no other risk factors
  - only in non smokers for PVD

Summary of thrombophilia and arterial disease

- Some tests of no value
  - PC, PS and AT assays, APCR/FVLM, PTGV, factor VIII assay
- Others more valuable?
  - Lupus anticoagulant/anticardiolipin antibodies
  - Homocysteine

So choose your patients (and tests) carefully...

- Venous thromboembolic disease
  - Under 55
  - PC, PS, AT, VIII assays
  - APCR +/- FVLM
  - PTGV
  - VIII
  - LA/ACA
  - Homocysteine
- Arterial disease
  - under 40 for IHD
  - under 60 for CVA
  - ?PVD if non smoker
  - LA/ACA
  - Homocysteine