Haemostasis & Coagulation

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Girl dies after tooth extraction at KMC hospital

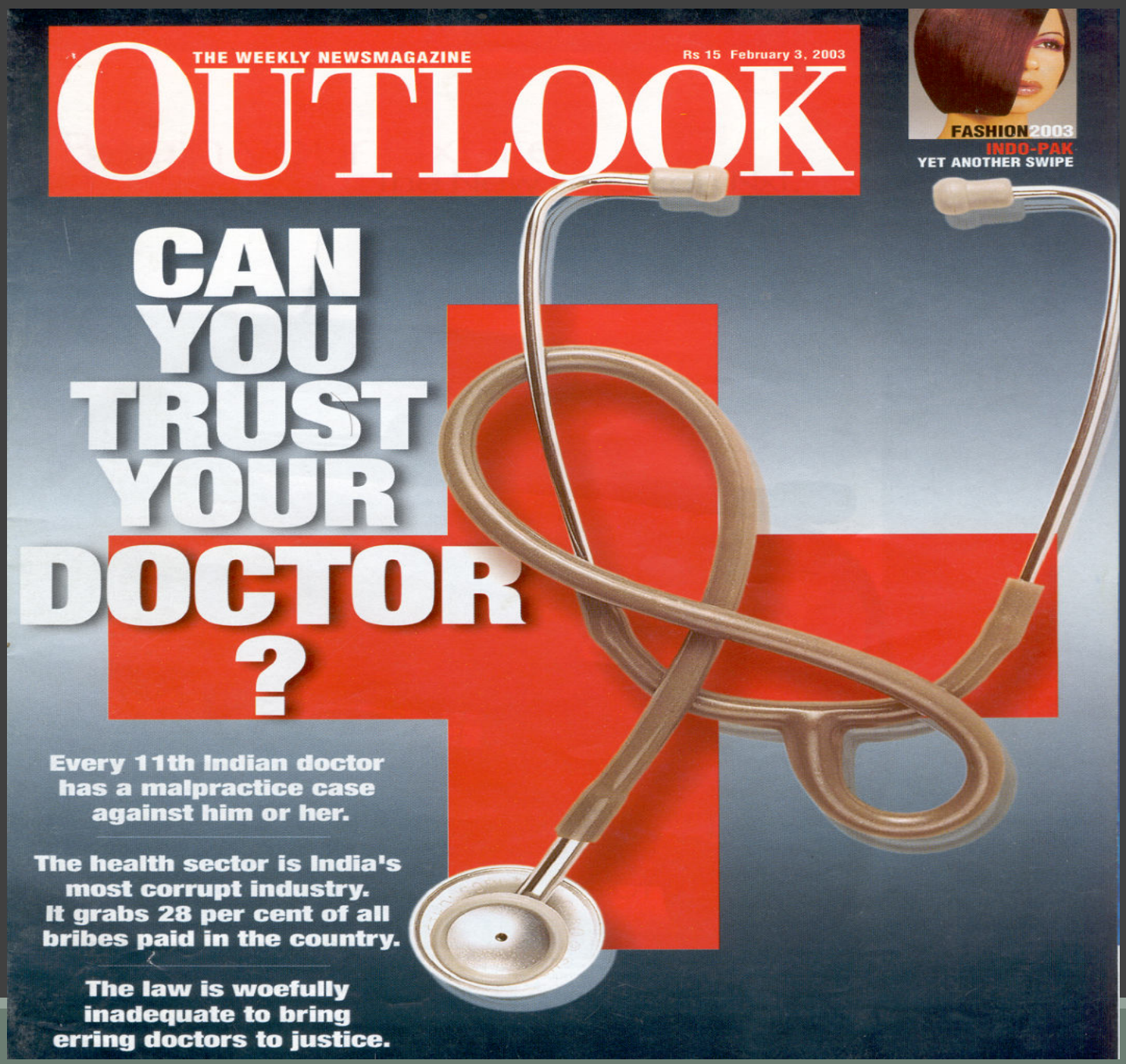
By Ramya Kannan

CHENNAI, DEC. 30. What promised to be a simple tooth extraction procedure turned out to be fatal for a 12-year-old girl of Ambattur at the Kilpauk Medical College hospital here today.

As distraught family members struggled to come to terms with the sudden expiry of Guna, doctors are foxed by the tragic turn of events themselves. Having been brought to the dental unit of the hospital for a 'routine' extraction procedure, Guna is said to have collapsed after the procedure, following 'excessive bleeding'.

According to hospital sources, the patient was immediately rushed to the operation theatre, but the bleeding could not be controlled and she died. Shocked family members protested at the way the things were being handled in the hospital. Initially they refused to allow a postmortem. Later they agreed for the same at the intervention of senior hospital authorities. The authorities claimed that all precautions were taken during the extraction, which was handled by a senior professional and preliminary investigation ruled out medical negligence.

While initial examination revealed that the cause of death was 'haemorrhagic shock', the Director of Medical Education, C. Ravindranath, said a postmortem was ordered and samples from the bone marrow and spleen were taken, as physicians suspected an 'unidentified bleeding disorder'. The results, which would be available in 48 hours, would confirm the actual nature of the problem. A senior physician would conduct an enquiry.



'THE DOCTOR WAS IN SUCH A HURRY TO OPERATE ON MY FATHER, LIKE A CHILD WANTING A LOLLYPOP'

When an incision is made , the blood clots

A 68 year old woman with a history of a 12 kg weight loss over the past six months presents to the emergency room with a history of passing bright red blood per rectum. Her pulse is 95, her blood pressure 120/70. She has not seen a physician in 40 years.

Study Questions:

What history and physical exam information would you gather to assess this patient's coagulation system?

If there is a problem present, what would be the most likely?

What laboratory tests would you order to assess this patient's coagulation system?

A 24 year old man is in the operating room for a massive liver injury sustained when his motorcycle hit a truck. After one hour of surgery he has received 15 units of packed cells and has developed diffuse oozing from the surface of his liver. Clots are no longer forming. His body temperature is 34oC.

Study Question:

What are the most common coagulation difficulties associated with massive transfusion? What is the management of each?

HAEMOSTASIS

OBJECTIVES

Mechanism of coagulation

Tests

Abnormal thrombosis

Abnormal bleeding

HAEMOSTASIS

Keeps blood in fluid state & in circulation

Prevents blood loss

Haemostasis

Four interconnected mechanisms form the basis of hemostasis:

(a) blood vessel contraction

(b) platelet plug formation (primary hemostasis)

(c) clot stabilization with fibrin cross-linking (secondary hemostasis)

(d) endogenous fibrinolysis.

What is involved in Haemostasis?

Blood vessels

Platelets

Plasma coagulation factors

Inhibitors

Fibrinolytics

Events in Haemostasis

Vascular spasm

Formation of platelet plug

Formation of fibrin plug - Blood clot

Re-establishment of endothelium

Haemostasis

Vasoconstriction

Clean cut vessels > crushed vessels

Partially transected > completely cut

Veins are easily compressed

Danger areas of bleed

Haemostasis

Platelet plug - White bodies or microthrombi

Contact with subendothelial collagen

swell

irregular with pseudopods

release ADP, thromboxane A2 , phospholipids , HMWK

sticky & aggregate

Haemostasis

Fibrin clot:

Severe trauma - 15-20 secs

Minor trauma - 1-2 mts

Retraction - 20-60 mts

Haemostasis

COAGULATION

3 steps:

Prothrombin activator

Prothrombin → Thrombin

Fibrinogen → Fibrin

Haemostasis

Pathways

Intrinsic - XII = slow

Extrinsic - VII = fast

Common pathway

factor V

Xa → Prothrombin activator

phospholipid, calcium

Haemostasis

Extrinsic

Tissue extract factor VII factor X

Intrinsic

surface contact VII

XII XII a XI a IX a X

HMWK phospholipid
calcium

BOTH ARE ESSENTIAL

HAEMOSTASIS

ACTIVATED PLATELETS

Prothrombin activator **{rate limiting factor}**

{THROMBOPLASTIN}

CALCIUM

PROTHROMBIN THROMBIN

FIBRINOGEN FIBRIN MONOMERS

CALCIUM XIII

FIBRIN POLYMERS STABLE CLOT

HAEMOSTASIS

PRODUCTION OF CLOTTING FACTORS

Fibrinogen → liver

II, VII, IX, X → liver with vit K

VIII, V, XII → endothelium

XIII → platelets

HAEMOSTASIS

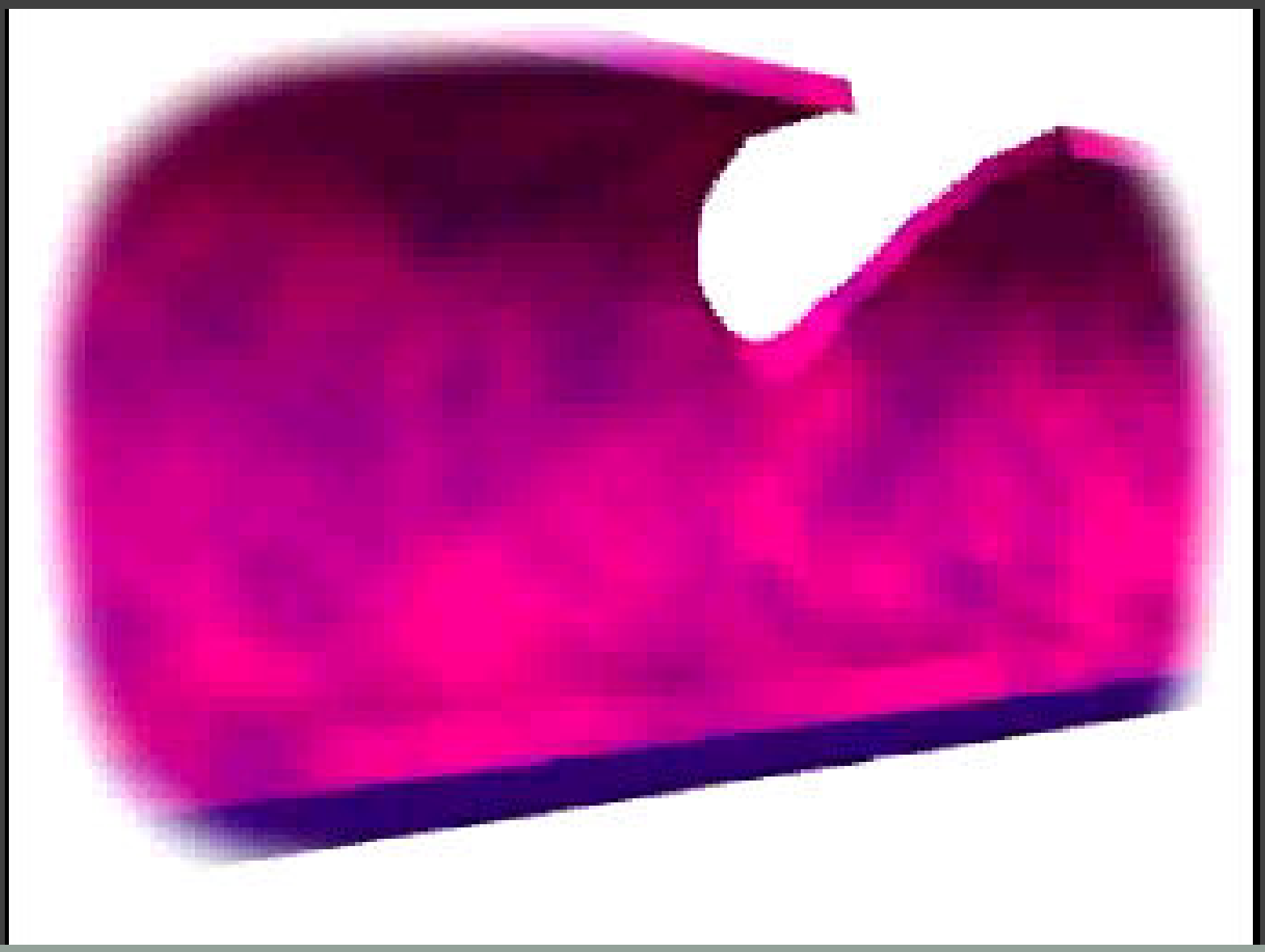
THROMBIN

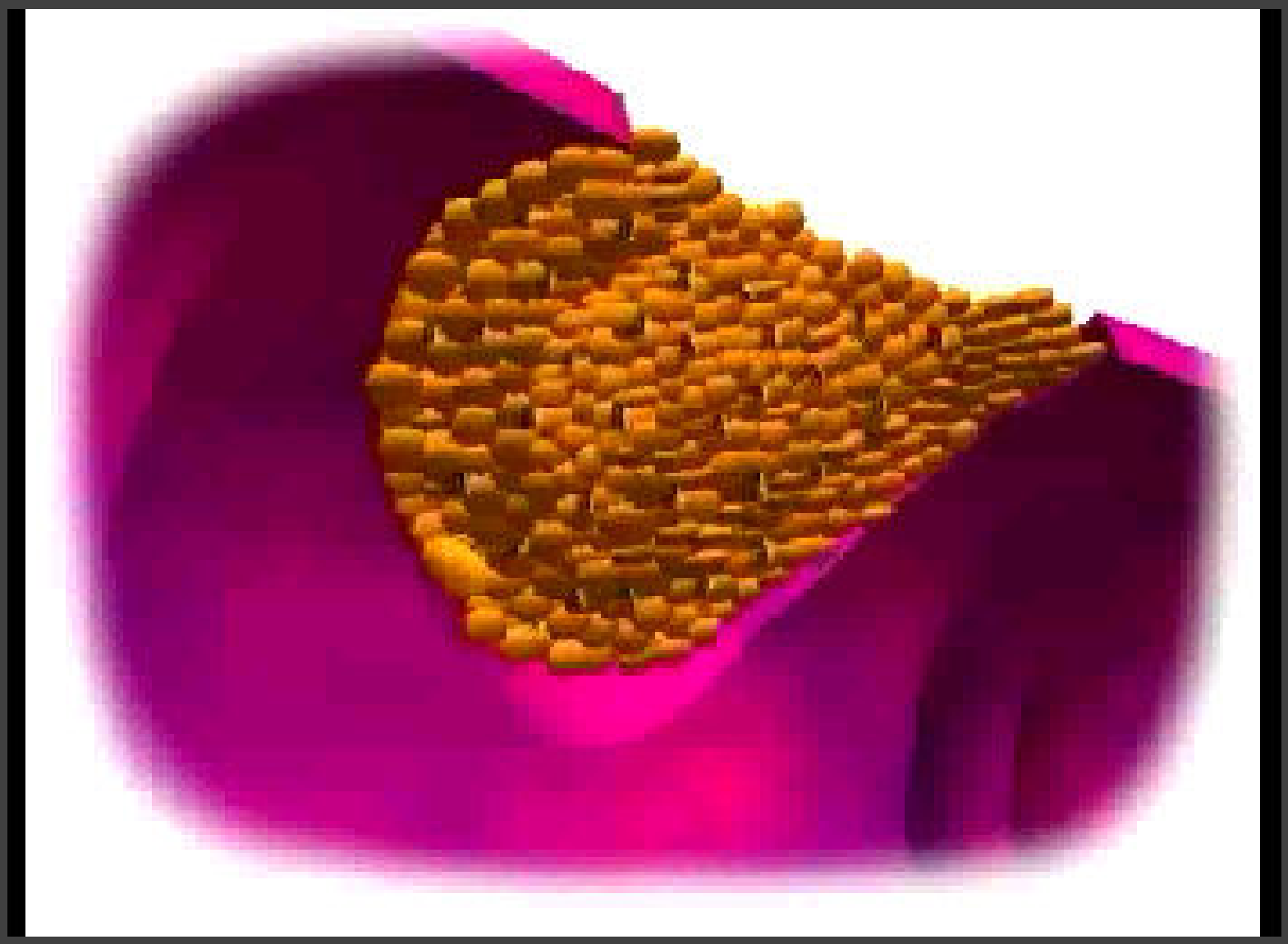
Intensely proteolytic

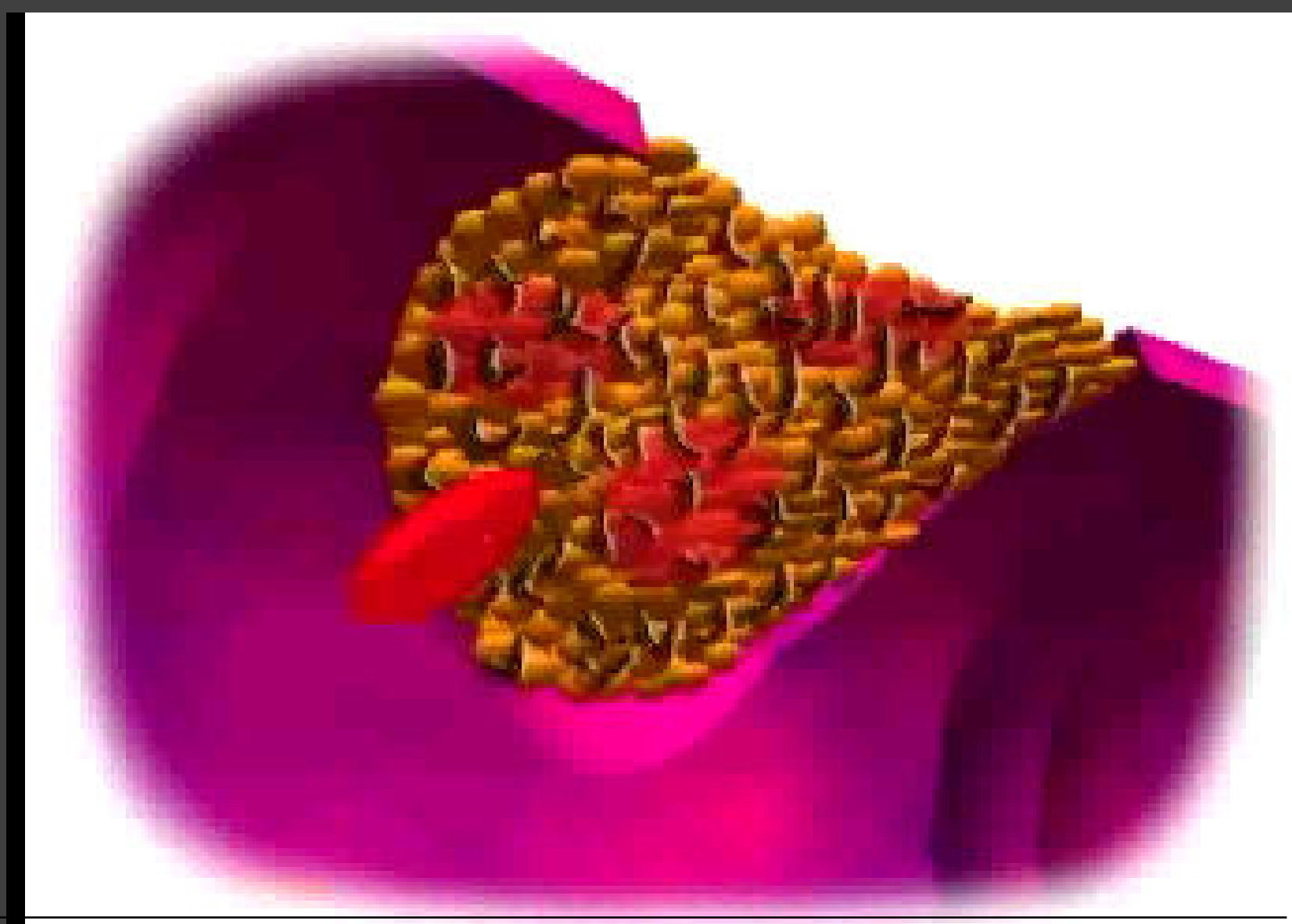
Activates factor V ,VIII, XIII

Releases phospholipid from endothelium & platelet

Activates protein C







HAEMOSTASIS

CONTROL

Fibrinolysin or Plasmin

Plasminogen activator

DIGESTS	**ACTIVATES**
fibrin	factor XII
fibrinogen	kinin
factor VII	complement
factor V,XII	
prothrombin	

Inhibited by- alpha 2 plasmin inhibitor .

HAEMOSTASIS

Why does not blood clot normally ?

Endothelium	Fibrin & Antithrombin
smooth	thrombin fibrin **[85-90%]**
glycocalyx	antithrombin →
thrombomodulin	
prostacyclin	
heparin sulfate	
tissue plasminogen activator	
ADP ase	

HAEMOSTASIS

Why does not blood clot normally?

Heparin → Thrombin

Alpha 2 macroglobulin → Thrombin

C 1 inhibitor → XII a, Kallikrein

Alpha 1 antitrypsin → XI a, Elastase

Protein C → Va, VIIIa

Tests of blood coagulation

1. Bleeding time:

{modified Ivy's method}

N = 1-6 mts

platelet plug

Prolonged in:

Thrombocytopenia

Thrombasthenia

Von-Willebrand's disease

2.Clotting time:

{Lee & White method}

N = 6-10 mts in glass

N = 20-60 mts in

siliconized tubes

Measures intrinsic &

common pathway

Tests of blood coagulation

Prothrombin time: { Quick's one stage test }

oxalated blood from patient —(calcium; tissue thromboplastin)→ clot

N = 12 secs

extrinsic & common pathway

Prothrombin time contd...

Prolonged in:

1. Oral anticoagulant drugs
2. Liver disease, obstructive jaundice
3. Vit K deficiency
4. D I C
5. Deficiency of factor VII , X, V, II

SPECIFIC FOR FACTOR VII

[With X & V APTT is also prolonged]

PARTIAL THROMBOPLASTIN TIME
[activated]

Contact activation

KAOLIN

\+ of factor XII + pt's = **Clot**

CEPHALIN

phospholipid

blood

Intrinsic & Common pathway

Partial thromboplastin time [activated] contd.....

Prolonged in:

1. D I C
2. Liver disease
3. Massive transfusion of stored blood
4. Heparin
5. Circulating anticoagulants
6. Deficiency of clotting factors other than VII
7. Haemophilia

THROMBIN TIME

PLASMA + THROMBIN → CLOT

Assesses fibrinogen

Prolonged in :

1. Hypofibrinogenemia

   DIC → CONGENITAL

2. ↑ FDP

3. Heparin [assess with REPTILASE test]

4. Dysfibrinogenaemia

PLATELET COUNT

N = 150 - 300 x 10^9 / L

80 x 10^9 / L → **Bleeding may follow trauma**

< 40 x 10^9 / L → **Spontaneous haemorrhage**

< 10 x 10^9 / L → **Lethal haemorrhage**

PRIMARY SCREENING TESTS

Bleeding time

Platelet count

P T

A P T T

Specific tests- Factor VIII, XIII, fibrinogen

Tests for fibrinolysis

ABNORMAL HAEMOSTASIS

	PT	APTT	TT	Platelet count	
1	n	n	n	n	Normal haemostasis
2	long	n	n	n	Disorder of platelet function. Mild coagulation disorder
3	n	long	n	n	Factor VII deficiency Early oral Anticoagulation 12-36 hrs
					Factor VIII, IX, XI, XII deficiency Prekallikrein, HMWK Deficiency, vWD, circulating anticoagulant

ABNORMAL HAEMOSTASIS

	PT	APTT	TT	Platelet count	
4	long	long	n	N	Vit K deficiency Oral anticoagulants
5	long	long	long	N	Heparin, Fibrinogen Deficiency, Liver disease, Fibrinolysis
6	n	n	n	Low	Thrombocytopenia
7	long	long	n	Low	Massive transfusion Liver disease
8	long	long	long	low	DIC

SURGICAL SCREENING

GROUP - I	GROUP - II	GROUP - III
No history	No history	History ++
Minor operations	Major operations	High risk procedures
↓	↓	↓
No screening	Screening questionable	Screening required

HAEMOSTASIS

In a patient who bleeds:

LIVER
IMMUNOLOGIC
RENAL
CARDIAC
SEVERE INFECTION
DRUGS

COMPLETE
WORK UP

Best screening test - HISTORY

NATURAL ANTICOAGULANTS

Antithrombin III

Protein C and protein S

NATURAL ANTICOAGULANTS

Antithrombin III

This is an inhibitor of thrombin, its action being potentiated by heparin.

Congenital antithrombin III deficiency is inherited as an autosomal dominant.

Heterozygotes may suffer from recurrent DVT, pulmonary embolism, and mesenteric thrombosis.

Homozygotes present in childhood with severe arterial and venous thrombosis.

NATURAL ANTICOAGULANTS

Protein C and protein S

These are synthesised in the liver and are dependant on vitamin K.

Protein C degrades factors Va and VIIIa and promotes fibrinolysis by inactivating plasminogen-activator inhibitor I.

Protein S is a cofactor for protein C and enhances its activity.

Hereditary protein C defciency may occur, patients being more susceptible to DVT, PE, superficial thrombophlebitis, and cerebral venous thrombosis

ANTICOAGULANT DRUGS

Warfarin

Warfarin is a coumarin derivative which is administered orally.

It is a vitamin K antagonist and in effect induces a state analogous to vitamin K deficiency.

It interferes with the activity of factors II, VII, IX and X. It delays thrombin generation, thus preventing the formation of thrombi.

Warfarin is usually administered for 3–6 months following DVT or PE

Lifelong warfarin is required for recurrent venous thromboembolic disease,some prosthetic heart valves, congenital deficiency of antithrombin III, deficiency of protein C or protein S,

ANTICOAGULANT DRUGS

Heparin

Heparin potentiates the action of antithrombin III.

Standard unfractionated heparin is administered i.v. or s.c. and has a half life of about 1 h.

Low molecular weight heparin is used subcutaneously and has a longer biological half life..

Heparin does not cross the placenta and is, therefore, the drug of choice when anticoagulation is required during pregnancy.

Bleeding due to overdose is managed by stopping the heparin and administering protamine sulphate intravenously.

Side effects of heparin include thrombocytopaenia,hypersensitivity reactions, alopecia, and osteoporoi

DISORDERS OF HAEMOSTASIS AND COAGULATION

CONGENITAL

HAEMOPHILIA A and B.

Von WILLEBRAND'S disease.

Defencies of factorXI and XII,prekallikrien,HMWkininogen.

Defencies of factorVII,V and thrombin.

Disorders of fibrinogen like a or hypofibrinogenemia or dysfibrinogenemia.

Factor XIII defeciency.

ACQUIRED

VITAMIN K DEFECIENCY.

ANTICOAGULANT DRUGS.

HEPATIC FAILURE.

RENAL FAILURE.

THROMBOCYTOPENIA.

THROMBOCYTOPATHY.

HYPOTHERMIA.

DIC.

APPROACH

HISTORY

H\O bleeding,easybruising.

Frequent or unusual mucosal bleeding.

Metromenorrahgia.

Haematuria.

Epistaxis.

Previous h\o prolonged bleeding asso with invasive procedures.

Positive family history.

Drug history like intake of NSAIDS,aspirin,etc.

EXAMINATION

Ecchymotic patches or petechiae on skin.

Joint deformities.

Adenopathy.

Hepatospleenomegaly.

Hypermobility of joints.

Increased elaticity of skin.

SCREENING TESTS

CBC.

Platelet count.

PT.

aPTT.

Bleeding time.

Fibrinogen level.

Thrombin time.

Platelet function tests.

Specific factor assays.

PROTHROMBIN TIME

Measures function of factor VII,X, prothrombin and thrombin,fibrinogen and fibrin.

Prolongation occurs when levels of factor V,VII or X fall.

Seen in warfarin therapy and vit.k defeciency.

aPTT

Detects decreased levels ofHMWkininogen,prekallikrien,XII,XI,IX,VIII,V,X.

Increased in heparin therapy.

CONGENITAL DISORDERS

HAEMOPHILIA A

HAEMOPHILIA A

Deficiency of factor VIII.

X linked recessive disorder with males being affected exclusively.

Severe bleeding if factor level<2%.Moderate bleeding with levels b\w 2%-5%.Mild bleeding with factor levels b\w 5%-30%.

Patient has large haematomas and haemarthroses.

Bleeding is prolonged for hours or days after injury.

Lab tests show a prolonged Aptt with decreased factor VIII level,normal PT,bleeding time and vWF levels.

HAEMOPHILIA A

Desmopressin may temporarily raise factor VIII levels in mild disease.

Can be given intranasally or iv and is ineffective in treating severe disease.

Antifibrinolytic therapy with EACA and tranexemic acid with or without desmopressin is also effective in dental extarctions or paediatric patients.

CRYOPRECIPITATE is a good source of factorVIII.

One bag contains 80 units of factor VIII and 1U\kg increases levels by2%.

Specific factor VIII concentrates are more popular now.

Give 50U\kg stat then 30U\kg every 8 hrs for the first 2 days after surgery or injury.

CONGENITAL DISORDERS

HAEMOPHILIA B

HAEMOPHILIA B

Xlinked bleeding disorder with a deficiency of factor IX.

Patient presents with deep bleeding and haemarthroses.

Lab tests show increased Aptt with decreased factor IX levels, normal PT, BT,platelet count and factor VIII.

Tt is by prothrombin complex concentrate which contains factor IX and all of the vit k dependent factors.

HighPurity factor IX concentrate is also available.

CONGENITAL DISORDERS

VON WILLEBRAND'S DISEASE

Von WILLEBRAND'S DISEASE

Most common congenital bleeding disorder.

vWF is an important stimulus for platelet aggregation and carrier protien for factor VIII.

Type 1 is inherited as autosomal dominant and is characterized by quantitative defect in vWF.

Type 2 has variable inheritance and there is qualitative defect in vWF.

Type3 is autosomal recessive disease with absent levels of vWF.

Patients present with mucosal bleeding,petechiae,epistaxis and menorrhagia.

Tt is by desmopressin or cryoprecipitate.

ACQUIRED DISORDERS

VITAMIN K DEFECIENCY

Platelet disorders

Thrombocytopaenia

This may be due to a failure of platelet production or increased destruction or sequestration of platelets, and abnormal platelet function.

Abnormal platelet function may cause bleeding despite a normal platelet count.

Abnormal platelet function may occur with: drugs, e.g. aspirin, non-steroidal antiinflammatory drugs carbenicillin, and ticarcillin; uraemia;septicaemia; and von Willebrand's disease.

Blood vessel wall abnormalities

Blood vessel wall abnormalities

These are rare and may be due to scurvy, steroids, Cushing's syndrome, or Henoch-Schonlein purpura.

VITAMIN K DEFICIENCY

Vit k is required for the reaction that attaches a carboxyl gp to glutamic acid.

Causes of def are inadequate dietary intake,

Malabsorption,obstructive jaundice,biliaryfistula,

Oral antibiotics and TPN.

Tt is parenteral administration of vit k if there is no active bleeding.

Administration of FFP rapidly corrects the coagulation deficit and is given in patients with ongoing bleeding.

Correction of the etiology.

ACQUIRED DISORDERS

HEPATIC INSUFFICIENCY

HEPATIC INSUFFICIENCY

Liver is the site of synthesis of all clotting factors except factorVIII,vWF.

Hepatic failure will result in coagulopathy.

Asso with platelet dysfunction.

Tt is by giving vitk,FFP,cryoprecipitate and platelets.

ACQUIRED DISORDERS

HYPOTHERMIA

HYPOTHERMIA

Usually seen in a lengthy open surgery on the abdomen or thorax.

The coagulopathy is because of defect in platelet function,fibrinolytic activity,coagulation cascade enzyme.

Intraoperatively all efforts should be made to keep the temp normal by warming fluids,heated ventilation and warm environment.

ACQUIRED DISORDERS

MASSIVE TRANSFUSION

MASSIVE TRANSFUSION

Defined as more than 10 units of transfused blood or replacement of the pts total blood volume within 24 hrs.

Pts have thrombocytopenia,low fibrinogen and prolonged PT.

These changes result from low temperature of blood,increased citrate level,increased k level,low pH,decreased ca level.

Tt is by infusion of FFP,PLATELETS.

POST-OP THROMBOSIS

WHY?

1. NO MUSCLE CONTRACTION

2. FIBRINOGEN , PLATELET,vWF, FACTOR VIII

3. DECREASED ANTITHROMBIN III

4. SEPSIS

5. DAMAGE TO VEINS

POST-OP THROMBOSIS

PREVENTION:

Intermittent compression or electrical stimulation

Aspirin, dextran, di-pyridamole

Low dose heparin, low molecular weight heparin

Early mobilization

Hydration

T E D stockings

Surgery in patients on anticoagulants

DRUG	BLEEDING RISK	ELECTIVE SURGERY	EMERGENCY SURGERY
1 .HEPARIN	Low / Moderate	Discontinue high dose Give low dose heparin	Same as elective
	High risk	Discontinue 6 – 12 hrs before surgery	Discontinue Give Protamine sulphate
2. L M W H --	Discontinue 12 – 24 hrs before surgery especially in high risk		group

Surgery in patients on anticoagulants

DRUG	BLEEDING RISK	ELECTIVE SURGERY	EMERGENCY SURGERY
3. Warfarin	LOW	Adjust dose to I N R < 2.5	Discontinue warfarin
	MODERATE "		Discontinue warfarin FFP to decrease INR to < 2.5.
	HIGH	Discontinue & allow P T to normalize. Substitute with heparin .	Discontinue warfarin FFP , Vit K to normalize PT.

Surgery in patients on anticoagulants

Aspirin:

Discontinue 1 week before surgery.

Platelet transfusion

DDAVP

} In emergency surgery

Fibrinolytics:

Wait for half life

- 6 min for TPA
- 23 min for Streptokinase
- 16 min for Urokinase

EACA: Only in emergency.

Weigh benefit Vs risk

CONCLUSION

The more exotic these approaches become, the more one is compelled to emphasize that gentle handling, precise dissection and accurately applied haemostasis constitute much the art of surgery.

Injecting, burning, stuffing, and scorching wounds is not likely to lead to a higher plateau of accomplishment.

John A Collins , M.D