⑤ HEMODYNAMIC DISORDERS, THROMBOLISM & SHOCK.

26 NOV 19

Tues.

THROMBO _ _ SIS.

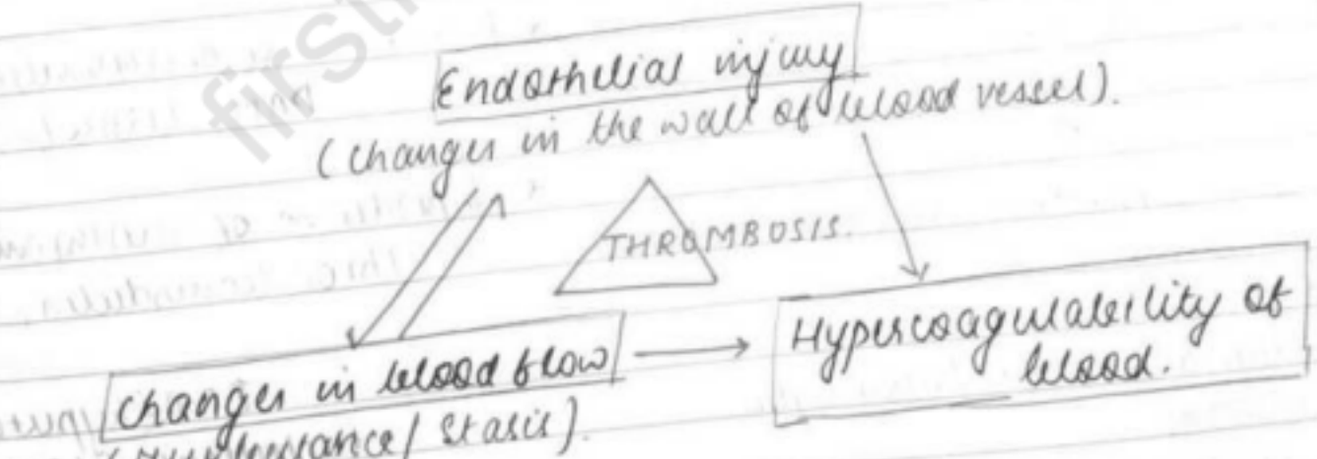
Def^n: Thrombogenesis is the process of form^n of solid mass in circulating blood from the constituents of flowing blood.

Thrombus: The solid mass formed is called thrombus.
↳ consists of an aggregate of coagulated blood, containing [fibrin
platelets
other entrapped cellular elements of the blood.

PATHOGENESIS OF Thrombosis:

ETIOLOGY.

VIRCHOW'S TRIAD: Three primary abnormalities which can lead to the form^n of thrombus constitute Virchows triad.



VIRCHOW'S TRIAD

ENDOTHELIAL INJURY

Physical endothelial injury

* imp for the format of thrombus in
  - Heart
  - Arterial circulation

Mechanism

Physical loss of endothelium
↓
exposes thrombogenic subendothelial ECM
↓
platelets adhere to the site of injury
↓
release prothrombotic tissue factor
* local depletion of antithrombotic factors - PGI₂

Cause

① Heart - chambers - endocardial injury due to (MI)
  - valves - small thrombus formed on valves - vegetations
② Arteries - ulcerated atherosclerotic plaques, vasculitis, traumatic / inflammatory vascular injury
③ Capillaries - vasculitis, DIC, acute inflammatory lesions

Endothelial dysfunction Activation

Def - altered state which induces endothelial cells, i.e.
- thrombogenic
- abnormally adhesive to inflammatory cells

Mech - disturbs the balance b/w
- prothrombotic
- antithrombotic

* ↑ production of prothrombotic factors - PAM, tissue factor, PAI (TNF, IL-1, cytokines)
* ↓ production of antithrombotic factors - thrombomodulin, PGI₂

Causes ① HTN (hypertension)
② Turbulent blood flow
③ Toxins
  - bacterial endotoxins
  - cigarette smoke
④ Radiation injury
⑤ Metabolic abnormalities
  - Homocysteinemia
  - hypercholesterolemia

Alterations in normal blood flow

Normal blood flow - laminar - platelets & other cellular elements of the blood are separated from endothelium by a slower moving layer of plasma.

* **Turbulence** - disturbed movement of blood
  - thrombus form
    - Heart
    - Arteries
* **Stasis** - major cause of venous thrombosis.

Mech ① promotes endothelial injury / dysfunct. & ↑ procoagulant activity
② brings platelets in contact with endo.
③ prevents cleansing of activated clotting factors.
④ prevents flowing in of ↓ - inhibitors

Causes

① Heart
  - acute (MI)
  - arterial fibrillation / arrythmias
② Arteries - ulcerated atheros. plaque
③ Veins - saphenous v. with varicosities, deep v.
④ Hyperviscosity of blood - polycythemia vera
⑤ RBC disorders - sickle cell anaemia.

Hypercoagulability / THROMBOPHILIA

Def - systemic disorder ↑ed tendency for thromboembolism

Causes -
① 1° / Genetic cause
Deficiency of antithrombotic factor
- ↓ Protein C
- ↓ Protein S
- ↓ Antithrombin III

↑ed prothrombotic factor
① APC resistance
② ↑ Prothrombin (II)
③ ↑ Factor 9, 10, 11 (7, 8, 9, 11)
④ ↑ Von Willebrand factor
⑤ ↑ Fibrinogen (I)

② 2° / Acquired disorders
- Prolonged bed rest
- (MI) / atrial fibrillation
- Tissue injury - surgery
  - fracture
  - burn
- Cancer

MRUCCEL (PA)
Rub Rub Rub & PEA

	ARTERIAL THROMBUS	VENOUS THROMBUS
(M) ① Main cause	endothelial injury	Stasis
R ② Rate of blood flow	rapid	slow
U ③ Usual type of thrombus	Mural thrombus - attached to the wall of the blood vessel, projects into the lumen without complete occlusion of lumen → heart chambers & aortic lumen.	Occlusive thrombus - occludes the lumen of the blood vessel. → V / small / med. size A.
C ④ Common site	Aorta, coronary A, cerebral A, femoral a.	superficial v. - varicosities & deep v. of leg.
GROSS C ⑤ Color	gray-white	blue-red
C ⑥ composition	fragile meshworks - fibrin, platelets, RBCs & degenerating WBCs	more RBCs, relatively fewer platelets
L ⑦ Lines of Zahn	more prominent	less prominent
P ⑧ Propagation	Retrograde manner from the point of attachment of thrombus (i.e. towards the heart)	Antegrade manner from the point of attachment of thrombus towards the direction of blood flow (i.e. towards the heart)
⑨ Effects:	Ischemia (↓ blood supply) ⇓ infarction of the area supplied by A. conveying thrombus	Thromboembolism, edema, ulceration.
⑩	Aspirin —⊖→ a. thrombosis	Heparin, Warfarin }—⊖→ v. thrombosis

PHLEBOTHROMBOSIS / VENOUS THROMBOSIS

Def[n] - Thrombosis of veins — superficial veins of the leg / deep veins of leg

Phlebothrombosis

Superficial venous thrombi	Deep v. thrombus (DVT)
Site: Saphenous v. with varicosities	Largest in leg / above knee: ① popliteal vein, ② femoral vein, ③ iliac vein

Pathogenesis:

① Primary platelet thrombus: Damage to the endothelium, platelets adhere to the ...
⇓
Coralline Thrombus — fibrin & thrombin encourage further accumulation of platelets
⇓
alternate layers of platelets & fibrin with trapped blood vessels (LINES of ZAHN)
⇓
Occluding Thrombus — further growth of thrombus occludes the lumen of vein
⇓
Consecutive Thrombus — occluding thrombus stops blood flow
⇓
blood column beyond occluding thrombus forms consecutive clot

THROMBOPHLEBITIS

Def[n]: Inflammation of the wall of vein, cause damage to the endothelium, may lead to thrombus formation

- Thrombus formed is firmly attached, may embolize
- Arterial / venous thrombus may be formed

8. Comment:

THROMBUS

Def:- Thrombus is the solid mass that is formed in circulation, from the constituents of the flowing blood.

a) always formed in vivo, within the circulatory system.

b) Activation of platelets is mandatory.

∴ we can conclude that a thrombus differs from a clot.

CLOT

- Clot is solid mass that is formed from the conversion of soluble fibrinogen
  ↓
  insoluble polymerised fibrin.
- in ~~vo~~ vivo, as well as in vitro in test tube
- Activation of platelets is not essential.

Shock → ↓B.P → ↓C.O / ↓Systemic vascular resist / Total peripheral Resistance

TYPES OF SHOCK

progressive process ... tissue perfusion, followed by necrosis, potentially organ failure

* HYPOVOLEMIC SHOCK:

CAUSES/ETIOLOGY:

- Blood loss
  1. GIT bleed (peptic ulcer).
  2. Abdominal aortic Aneurysm (AAA)
  3. Trauma.
  4. post-partum hemorrhage (PPH)
  5. ectopic pregnancy.
  6. Hemoptysis (coughing of blood).

- Non blood fluid loss
  1. v. severe 3rd degree burn
  2. excess vomiting.
  3. diarrhea.
  4. bowel obstruction
  5. Acute pancreatitis.
     ↳ pancreatic protease ... other.
  6. Diabetes KetoAcidosis
     (↑ G) (hyperglycemia) ↑ urine output, ↑ water loss.

Q. How does the body compensate

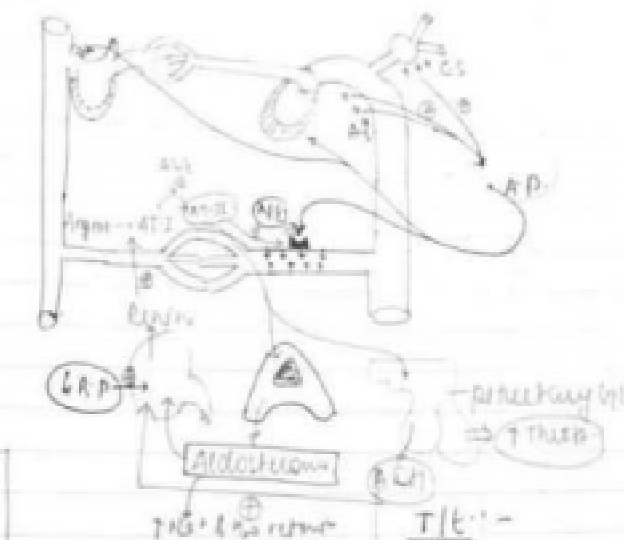
medullary centre ⇓ send A.P from medulla ⇓ goes to actual smooth m/c within Tunica media of blood vessel ⇓ release chemical like (NE) ⇓ cause the blood vessel to constrict (vasoconstriction) ⇓ ↑ total peripheral resistance ⇓ ↑ B.P.

Loss of blood/plasma/fluid ⇓ blood vol ↓ (Hypovolemia) ⇓ Baroreceptor (aortic/carotid sinus) → goes to the heart ↑ try to ↑ H.R

• stroke vol dependent on — EDV ⊖ ESV

stroke vol = (EDV) − ESV

↓ enough blood vol.



• CLINICAL MANIFESTATIONS (↓ Blood vol)

1. ↓ C.O.
2. ↑ systemic vascular Resistance.
3. ↑ H.R. (Tachycardia).
4. In CBC — ↑ hematocrit – Hemoconcentration (non blood fluid loss); ↓ hematocrit (hemorrhage)
5. CYANOSIS.- bluish cast on lips, tongue, fingertips, face
   ↓ tissue perfusion
6. Hypoxia ⇒ ischemia ⇒ necrosis ⇓ multisystem organ failure

T/t:-

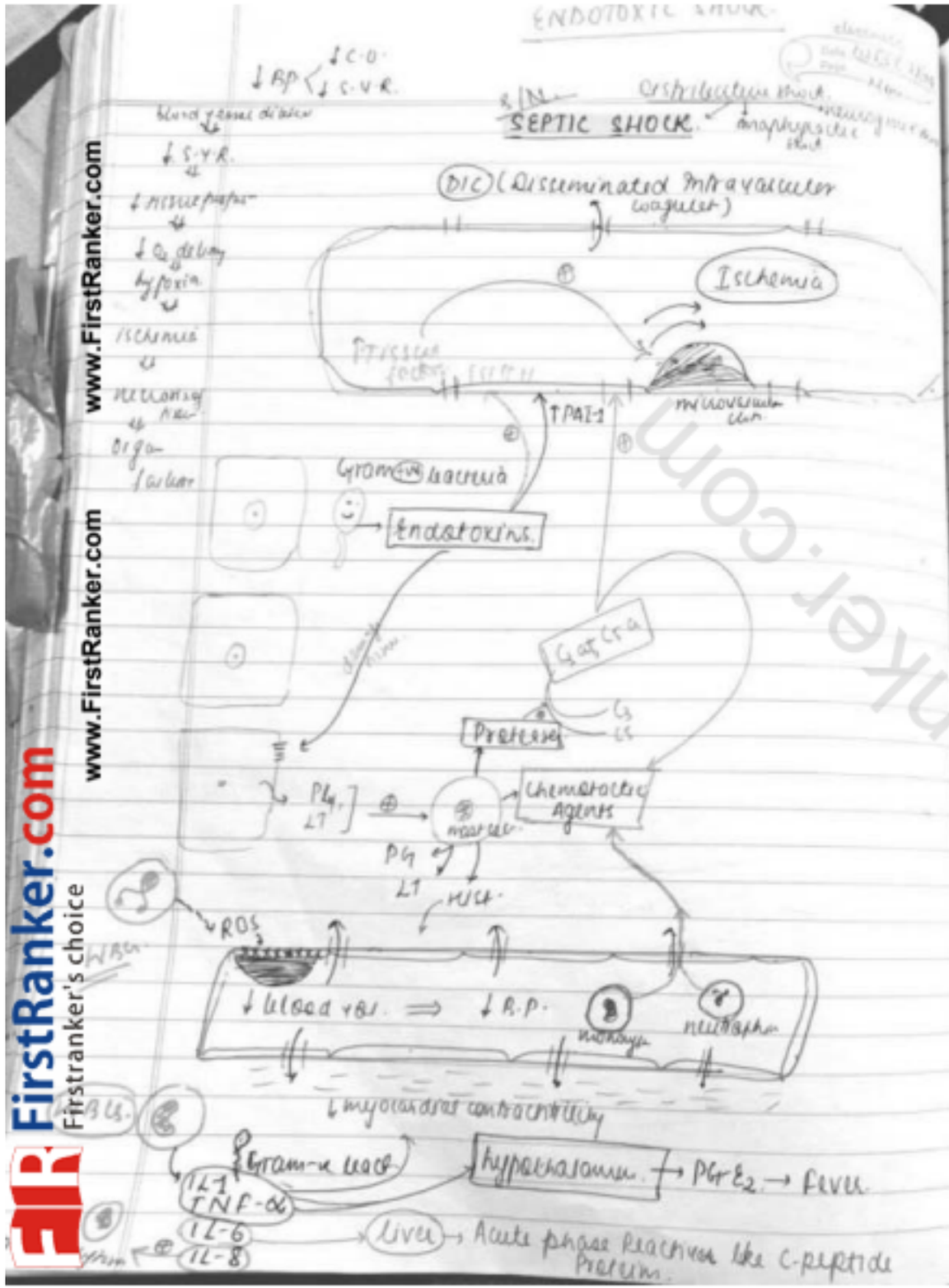
1. I.V. fluid infusion
   - crystalloids — Normal saline, Ringer lactate
   - Albumin, hetastarch
(11)

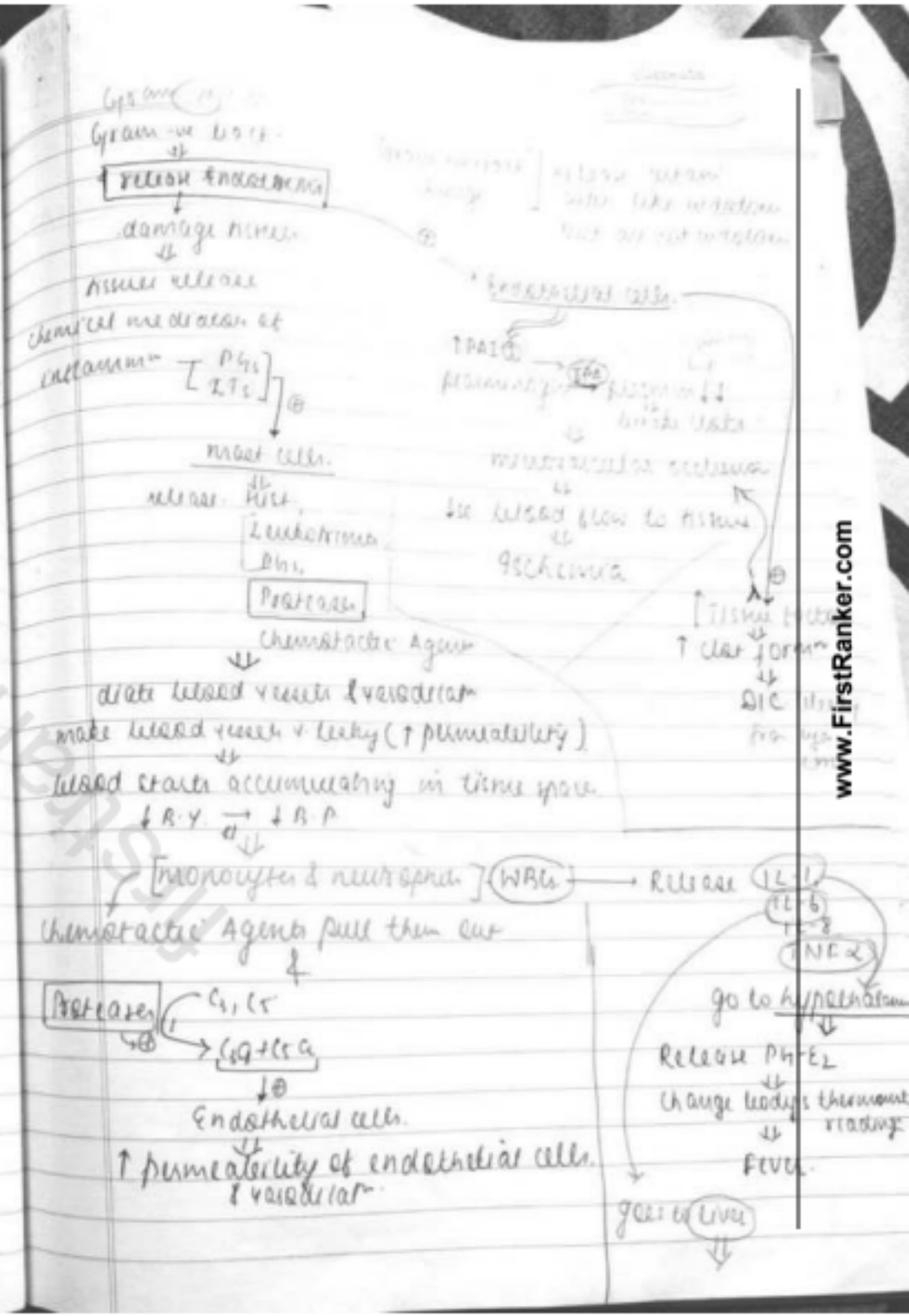
~~DISTRIBUTIVE SHOCK~~

Pathogenesis of circulatory shock:

① Hypovolemic shock. → [↓ Effective circulating blood vol. (Hypovolemia)
(blood loss, loss of plasma, loss of fluid.)
↓
↓ venous Return to heart
↓
Septic shock → [↓ C.O.
(Gram +ve Septicemia, Gram -ve Septicemia)
↓
↓ Blood flow (Vasodilation)
↓
cardiogenic shock → ↓ O_2 supply (Hypoxia)
(myocardial damage)
↓
Anoxia. — neuron
↓
inflammatory mediators
↓
SHOCK: — Organ failure
↓
death.

SEPTIC SHOCK





IL-1
TNF α] → ↓ myocardial contractility

↓ O2 supply

Liver
↓
produces Acute phase Reactive proteins
↓
indicator that there is lot of inflammation.

IL-8 → other WBCs
↓
↑ phagocytic activity
&
↑ chemotaxis

WBC
└ release ROS
↓
damage endothelial cell.
↓
A/c - Virchow's triad.
↓
↑ Thromboses

- ↓ BP (hypotension)
- Fever
- ↑ incidence of
- DIC
- Ischemia

TX:

- I.V. antibiotics — broad spectrum Abs
- Crystalloids - I.V. fluid infusion.
-

DISEASES OF THE IMMUNE SYSTEM

Type I - HYPERSENSITIVITY

* Hypersensitivity Reactions are Ag specific

Ag (drug, pollen/food) → 1st exposure → sensitization of immune cells (Primes the immune system against that Ag).

↓

subsequent exposure → Primed immune cells towards "the Ag".

IN APPROPRIATE IMMUNE RESPONSE.

- Type I
- Type II
- Type III
- Type IV

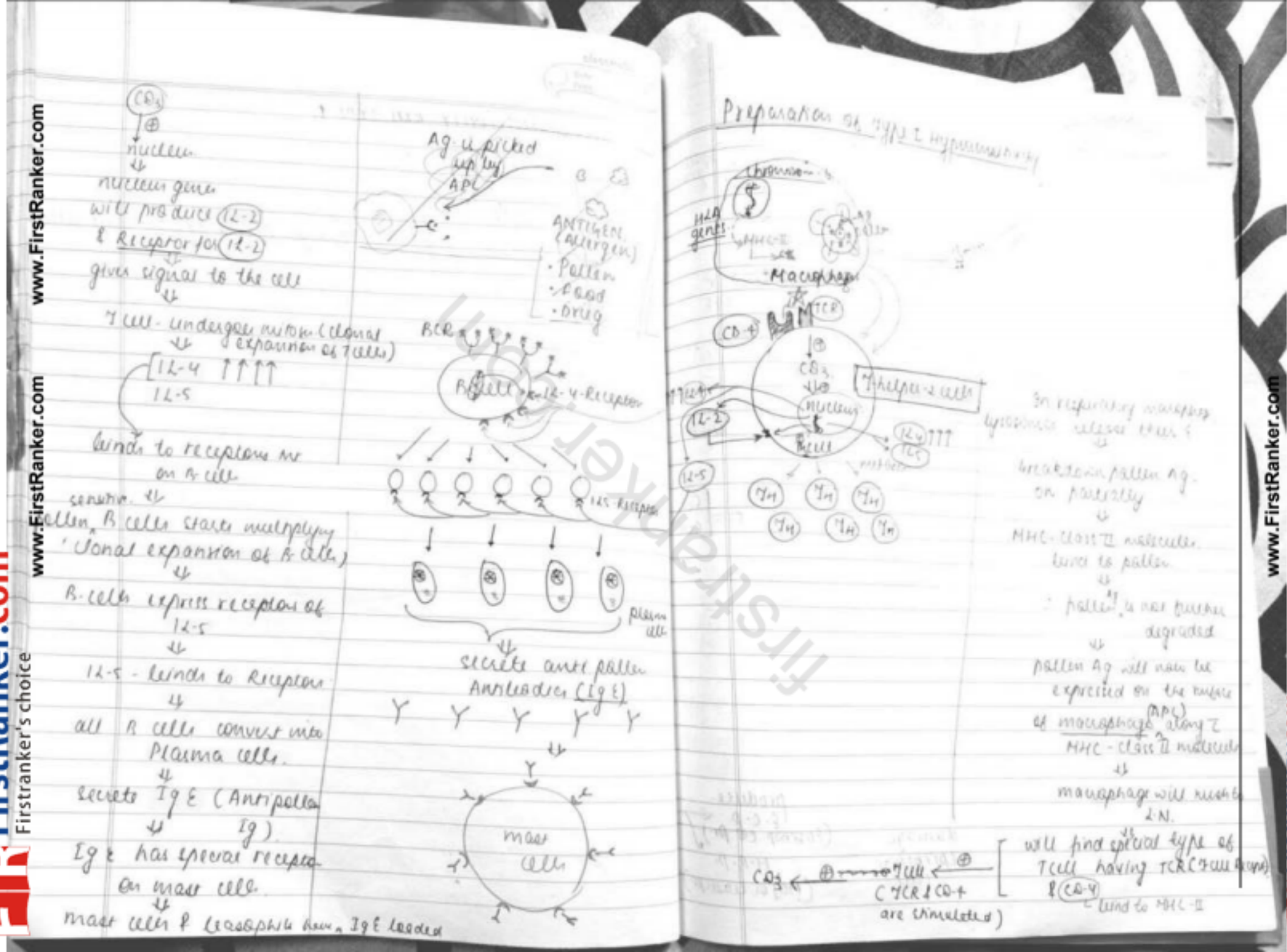
Ig./Ab. mediated

cell mediated

* HYPERSENSITIVITY Rxn TYPE I

- Immediate Reaction (Allergic Reaction)
  ↓
  occurs very fast

invalves recognition of Ag by primed IgE on mast cells.



Tues
10 Dec 2019

Type II - Hypersensitivity Reaction

- Immune mediated tissue damage.
- Immune complex ⇒ Inflammⁿ

* Free Ag — Exogenous — Bacterial, Fungal, Viral
  Endogenous — SLE

Ab (+) — IgG, IgM

* Ag + Ab ⇒ complement Activation + through inflammatory cells (neutrophils)
  (immune complex)

↓

INFLAMMATORY Rxn.

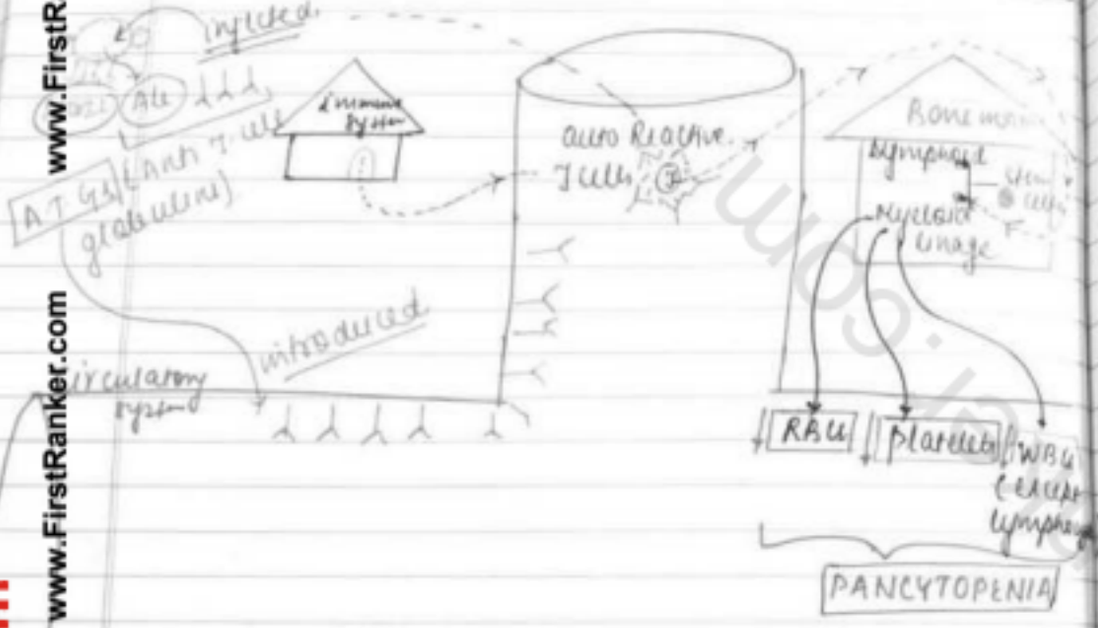
* ## Type III H.R.

↓

Generalized Rxn. (Serum sickness like Rxn)
↓
These days, it is due to drugs.

Localized Rxn. (Arthus Rxn.)

IMMUNE COMPLEX MEDIATED / T-III HYPERSENSITIVITY Rxn



Aplastic

autoreactive T cells

destroys

RBC ↓, WBC (other than lymphocytes) ↓, platelets ↓

Anemia Leukopenia Thrombocytopenia

PANCYTOPENIA

APLASTIC ANAEMIA

Bone marrow cells destroyed :. Hypocellular / hypoplastic

AMYLOIDOSIS

(1) Def^n^ - Amyloidosis is a disease due to abnormal folding/misfolding of protein

(2) In Amyloidosis
failure of control mech.
⇓
product of misfolded pr > degrade
⇓
accumulate outside the cell
⇓
unstable & self associated
⇓
deposited as fibrils in extracellular space.

PATHOGENESIS

(I) Production of abnormal of normal protein
↓
(1) Unknown (? carcinogen) (eg. Multiple myeloma)
↓ ⊕
(2) monoclonal proliferation of B lymphocytes
↓
Plasma cells
↓
↑↑ λ light chains of Ig
↓ incomplete breakdown
(3) Amyloid light (AL) chain pr.
→ AMYLOIDOSIS (1°)

(1) Chronic Inflammation (eg - Auto immune disease) (Ex - TB, Rheumatoid arthritis)
↓ ⊕
(2) Macrophage
↓
cytokines (IL-1, IL-6)
↓ ⊕
Liver
↓
(3) ↑ SAA protein
↓ incomplete breakdown by monocyte-derived E.
Amyloid Associated pr. (AA)
↓ (2°)
AMYLOIDOSIS

(II) Production of abnormal amt of mutant protein
Gene mutation (eg. mut in gene encoding TTR)
Familial Amyloidosis
↓
mutant TTR protein
⇓
prone to misfolding
⇓
Aggregation
↓ Resistant to proteolysis
ATTR protein
→ AMYLOIDOSIS

(i) Amyloid deposit ...
(iii) ...

PATHOLOGICAL EFFECTS

(1) Pressure on adjacent normal cells
⇓
Atrophy of cells

(2) Deposition in wall of blood vessel
- Narrowing of lumen ⇓ ischemic damage.
- ↑ permeability ⇓ proteins escape out.

PRIMARY AMYLOIDOSIS

1) **Incidence**: commonest form of generalized amyloidosis

2) **Disease associated**:- Multiple myeloma : commonest cause
5-15% develope this complication
· monoclonal gammopathy of uncertain significance (MGUS)
Ex-

3) **Pathogenesis**: immune mediated
monoclonal proliferation of B lymphocyte
↓
↑ synthesis of light chain Ig.

4) **Chemical nature of Amyloid**- AL (amyloid light chain pr)

5) **Organ development**- (involv.) tongue, skin, heart, GIT, kidney — skin, tongue, GIT, heart, kidney

6) **Additional investigat for diagnosis**: – pre of M-band in electrophoresis
– Bence-Jones pr.

7) **Prognosis**:-

SECONDARY AMYLOIDOSIS

i) second common cause of generalized amyloidosis

ii) chronic infection disorders - TB, Rheumatoid arthritis, bronchiectasis, ...

iii) chronic inflam- → macrophages → IL-1, IL-6, TNF-α → Liver → ↑ synthesis of SAA → (incomp. breakdown) → AA pr

iv) Amyloid associated (AA) pr

5) Kidney commonly involved
Adrenal gland, thyroid.

6) – ↑CRP
– ↑ blood level of other acute phase reactants (AP)

Genetic disorders

X-LINKED PATTERN of Inheritance:

- Almost all Mendelian disorders are X-linked.
- ♂ - mutation in Y gene are usually infertile.
  ∴ there is no Y linked inheritance.
- Expression of X-linked disorder - diff in ♂ & ♀

♀	♂
- clinical expression of X-linked disorder depends on whether it is dominant / recessive.	X-linked disorder is always expressed in ♂, even with one copy, irrespective of whether it is dominant / recessive.

- ♀ - rarely affected by X-linked recessive disorder
  └ affected by X-linked dominant disorder.

X-Linked Recessive disorder

Ex - Hemophilia A & B, G-6PD def, chronic granulomatous disease, etc.

① Location of mutant gene - X chromosome, no ♂ → ♂ transmission

② Required no of defective genes - ♂ - single copy of mutant gene
♀ - double copy of mutant gene is required.

③ Sex Affected - ♂ - more commonly affected
♀ - rarely affected in X-linked recessive disorder

④ Pattern of inheritance -
transmitted by heterozygous carrier (♀)

⑤ Risk of transmission to children / offspring
Affected ♂ ┬ all daughters are carriers
└ transmit the disease to none of his sons
~~Affected~~ carrier ♀ - transmits the disease to 50% sons
50% daughters are carriers.

X-Linked Dominant disorder - v rare.

Ex - Vit D Resistant Rickets

(i) X-chromosome, no ♂ to ♂ transmission

(ii) both ♂ & ♀ - single copy of mutant gene can produce the disease.

(iii) ♀ - more commonly affected
often lethal in ♂

(iv) no carrier state

(v) Affected ♂ - transmits the disease to all of his daughters
none of his sons.
Affected ♀ - transmits the disease to 50% sons &
50% daughters.

KARYOTYPING.

① - The chromosomal constitution of an cell / an individual is k/a karyotype.

- Normal human karyotype — 22 pairs Autosomes + 1 pair sex chromosomes
- Normal karyotype for ♂ — 46, XY
  ♀ — 46, XX

- Study of the ch pattern of chromosomes in a given sample of cells is k/a KARYOTYPING
  ⇓
  includes both [no. of chromosomes, appearance (phenotype) of complete set of chromosomes

- karyotyping requires the cells to be in a state of cell division & arresting it in metaphase stage of cell cycle.

⇒ **SOURCES OF CHROMOSOMES:**
To produce karyotype, it is necessary to obtain cells which are capable of [growth, cell division

cells are obtained from:
Culture / Directly

- fibroblasts
① - cells obtained from amniocentesis (amniotic fluid)
③ - peripheral blood smear - lymphocytes

- bone marrow
② - chorionic villi } biopsy sample

① - **STAINING** - There are various staining methods using specific dyes, to ... individual ... Most commonly used - Giemsa stain.

② - **CLASSIFICATION OF CHROMOSOMES IN KARYOTYPING**

- There are various classification systems to study the ch / morphology of chromosomes.

Denver system of classificⁿ
- Chromosomes are grouped from A → G
A/c to their [length & position of centromere

Paris System of classificⁿ
- universally accepted
- chromosomes are classified a/c to various banding pattern

③ - **CHROMOSOMAL BANDING:**
Banding is the method to study the ch of chromosome.
⇒ chromosomes are stained by using special stain
eg. Giemsa
⇓
binds to specific bands of chromosome.
⇓
shows characteristic banding pattern
eg. alternate light & dark bands which helps them to id them.

- TECHNIQUES:

(i) G-banding: most commonly used staining technique. Produces alternate light & dark stained bands.

(ii) Q-banding: stained by Quinacrine-fluorescent stain

(iii) R-banding: reverse of G-banding.

iv) C-banding: stains the centromere.

v) T-banding: stains the telomeric ends of chromosome.

vi) High Resolution banding: used to increase sensitivity

(6)- KARYOTYPE ANALYSIS:

expressed in std. short hand format in the following order. Ex- XP21.2 / 5 III

(i) Total no. of chromosomes ✓

(ii) sex chromosome constitution. ✓

iii) Description of abnormalities in ascending numerical order.
long arm → 'p' (petite)
short arm → q (que)
Each arm is divided into 2 or 3 regions.
Each region is divided into bands & sub-bands.

iv) Structural changes in chromosomes.

(7)- USES OF KARYOTYPING:

(i) Diagnosis - of genetic disorders

ii) To detect the cause of repeated multiple abortions.

iii) Prognosis - in certain cancers
Ex- Philadelphia chromosome in chronic myeloid leukemia

GAUCHER'S DISEASE

- most common lysosomal storage disorder, due to mutation in the gene which codes for glucocerebrosidase (cleaves glucose from ceramide)
- autosomal recessive mode of transmission

mutation in the gene which codes for Glucocerebrosidase

↓

deficiency of the enzyme glucocerebrosidase

↓

accumulation of glucocerebroside mainly in lysosomes of macrophages

- PATHOLOGICAL changes are due to

(i) ↑ accumulation of Glucocerebroside

(ii) activation of macrophages

↓

secrete cytokines - IL1, IL-6, TNF.

Gaucher's cell.

CLINICAL SUBTYPES

Type I: CHRONIC NON-Neuronopathic form:	Type II: Acute neuronopathic form.	Type III
• most common type (99%)	• presents acute cerebral pattern.	
• Glucocerebrosidase activity only in mononuclear phagocytes throughout the body, mainly — spleen, skeletal system	• Absent complete or almost complete glucocerebrosidase activity in the tissues ↓ progressive involvement of CNS & brain ↓ death at an early stage	
• does not involve the brain		

cytogenetic disorders — Down's syndrome; Klinefelter's syndrome; Turner's syndrome

DOWN'S SYNDROME

- is described by Dr Langdon Down.
- cytogenetic disorder, affecting the autosomes
- most common chromosomal disorder
- leading cause of mental retardation.
- due to trisomy of chromosome 21.
  - ∴ total of 47 chromosomes, instead of 46
- Parents are normal, with normal karyotype.

• ETIOLOGY & PATHOGENESIS:

i) Maternal Age: > 45 yrs mother (old age mother)
ii) Exposure of [illegible] radiation, alcohol, caffeine, etc

• MECHANISM OF TRISOMY OF CHROMOSOME 21:

① copies of chromosome 21 occurs due to :-
i) Non disjunction of chromosomes at the time of gametogenesis
ii) Robertsonian translocation.
iii) Mosaicism

• CLINICAL FEATURES:

- Down's syndrome usually apparent at the time of birth by looking at infants characteristic cranio-facial appearance
- confirmed by cytogenetic analysis.

• CHARACTERISTIC FEATURES

i) Mental status: [illegible]
ii) Craniofacial Appearance: [illegible]
  - Enlarged & [illegible]
  - Large tongue (macroglossia) [illegible]
iii) Abundant neck skin
iv) Heart: (congenital anomalies)
  - AV & septal defect.
  - Patent ductus arteriosus & Fallot's tetralogy
v) Skeleton: short stature
  - Broad palm with characteristic palm crease (simian crease)
vi) Reproductive system: ♂ - sterile (arrest of spermatogenesis)
vii) Immune system: susceptible to infection (weak immune system)
viii) Endocrine system: Antithyroid Ab may lead to hypothyroidism.
ix) Acute myeloid leukemia.
x) wide gap b/w 1st & 2nd toe.

KLINEFELTER'S SYNDROME

- cytogenetic disorder, affecting sex chromosome.
- trisomy of sex chromosome
  - 2 ≤ X-chromosome
  - 1 ≤ Y-chromosome
- reduced spermatogenesis and infertility

PATHOGENESIS:

- patients of Klinefelter's syndrome have extra copy of X-chromosome (47, XXY)
- Results from non-disjunction of chromosomes at the time of gametogenesis in either of the parents.
- Minority of them are mosaic.

CLINICAL FEATURES:

- usually diagnosed after puberty & hypogonadism is a consistent finding.

(i) Tall & thin.
(ii) Not mentally retarded but avg. I.Q. ↓
(iii) remarkably ↑ LH & FSH
(iv) ↑ pitch voice
(v) Gynaecomastia; ↑se incidence of breast cancer
(vi) ~~the~~ ~~incr~~ ♀ pattern of pubic hair
(vii) Testicular atrophy
↓ Testosterone
↓ spermatogenesis → Azoospermia & Infertility
(viii) Long legs
(ix) Rare body
(x) ↑se incidence of Type II Diabetes

TURNER'S SYNDROME

- cytogenetic disorder involving sex chromosomes
- complete / partial monosomy of X-chromosome
- most common sex chromosome abnormality in ♀

KARYOTYPE ABNORMALITIES:

i) Missing of an entire X-chromosome results in karyotype 45, XO
ii) Structural changes in X-chromosome :
   - due to isochromosome of long arm
   - translocation,
   - deletion
iii) Mosaicism.

CLINICAL FEATURES –

not diagnosed before puberty,
diagnosed after puberty, due to :
failure to develop normal secondary sexual characters.

i) Short stature (<5ft ht.)
ii) low posterior hairline,
webbed neck.
iii) broad chest,
wide carrying ∠ of arm,
widely spaced nipples,
poor breast development.

iv) congenital heart ... [illegible]
bicuspid ... [illegible]
v) ... [illegible]
vi) little pubic hair
infantile genitalia
thick ... [illegible]
primary amenorrhea
infertility

vi) Autothyroid Ab may lead to hypothyroidism
vii) Barr body ... [illegible]