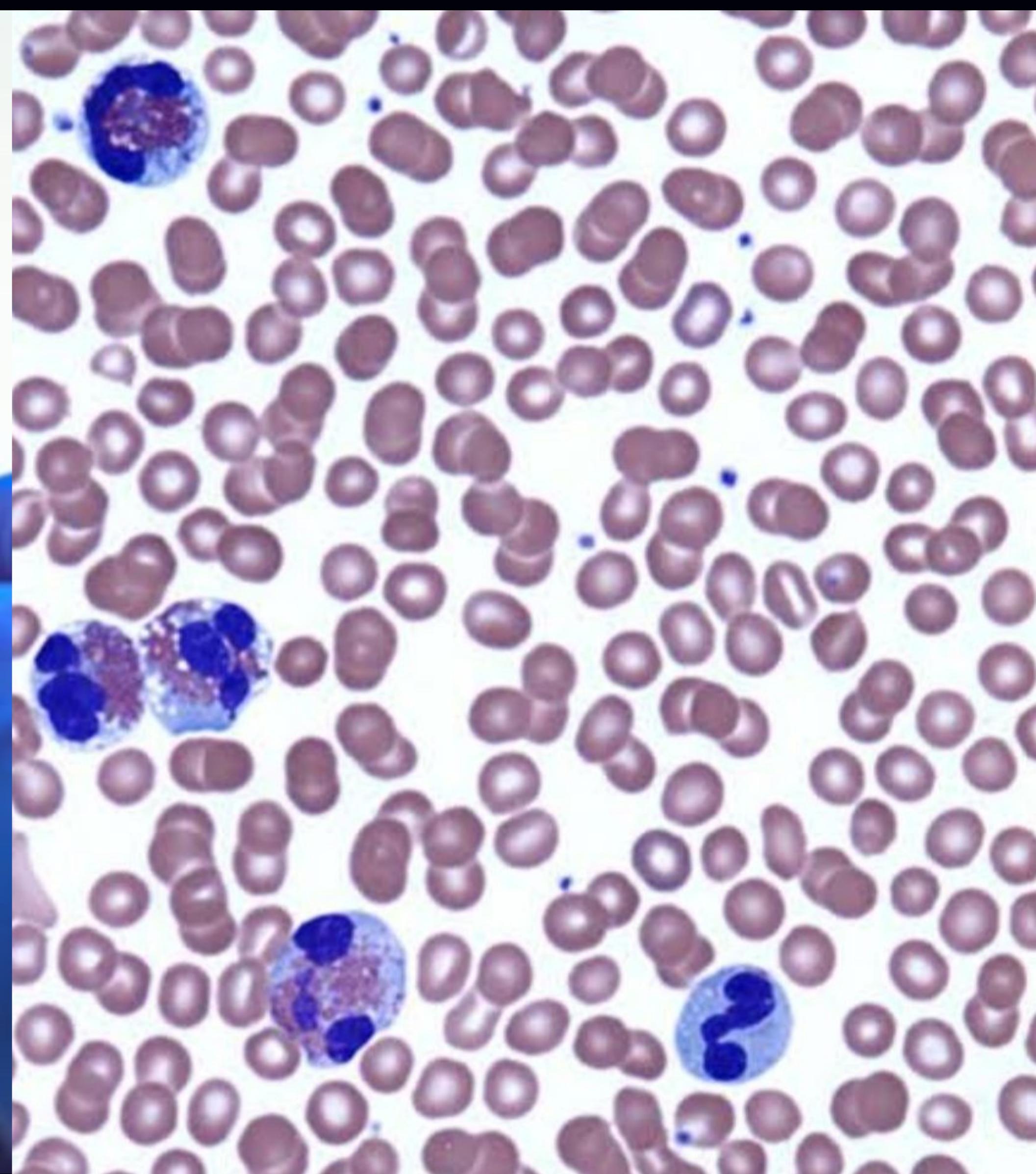


16#

GENERAL PATHOLOGY



Dr Najeeb's General Pathology lectures Notes

These notes explain General pathological conditions related to Human body which sir Najeeb explains in vedio lectures.

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Table of Content

Section:- 16

General Pathology

Topic Name	Slide/Page No
1-Neoplasias- (Nomenclature, Gene and Cancer)	06
2-Necrosis	38
3-Apoptosis	46
4-Inflammation (vascular events)	55
5-Mastering Edema	68
6-Circulatory Shock	77

PURPOSE

Purpose of writing this book;

- 1-You can use this book as revision notes for Dr Najeeb's lectures after taking dr Najeeb's vedio lectures.
- 2-If you don't have enough time to watch Dr Najeeb's lectures, then just read this book bcz this book is just a written form of Dr Najeeb's vedio lectures.
- 3-Most imp reason was to make such notes of dr Najeeb's lectures which become understandable by every Medical Student from any part of world.

NOTE

- > I apologies, If you find any mistake especially spelling mistakes while reading this book.
- > I hope you will love my work and don't forget to remember me in your precious prayers.
- >These notes are available on my Facebook group "free of cost" for all medical students. None of any other person have a right to sell these notes.

DEDICATION

I have made this book in honor of one of the best medical teacher in the world for his tremendous efforts in Medical education;

Sir Dr Syed Muhammad Najeeb

(www.drnajeeblectures.com)

eSource;

Dr Najeeb vedio lectures.

For Contact & Help;

For any kind of help or suggestions feel free to contact me on;

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NEOPLASIA (CANCER CELL)..

Q# Describe Molecular basis of Carcinogenesis OR
Molecular Changes occur in a cell that Convert normal
cell into Neoplastic??

Ans:-Cells which are going to Malignant, they proliferate
on its own (out of any regulatory mechanism or Control).
In Every Normal cell, there are 2 set of genes that
Regulate the growth of Cell.

1-One set of gene when Stimulated they produce
products and stimulate special DNA Replicatory Genes
and cell proliferate. This set of gene is called as PROTO-
ONCOGENES.

2-2nd set of gene when these genes are Stimulated they
inhibit the cellular growth by inhibiting DNA Replicatory
Gene. These set of genes are called as TUMOR
SUPPRESSOR GENES.

#If mutation Occur in Proto Oncogenes, proto-Oncogene
convert into Oncogenes.

In order to make tumor, Mutations that occur in Proto-
Oncogenes should be gain of function Mutation. So a
result cell become Self-sufficient in growth Signals. AND
#Loss Of Function mutation should Occur in tumor
Suppressor gene. So Cell show insensitivity to cellular
growth Inhibition signals.

3-Another set of gene which normally repair any
mutation in DNA which is Called as DNA Repair gene.
These genes should also be Mutant and DNA Repair
Genes should be Dysfunctional.

4- Cell also contain, Anti-Apoptotic gene and Pro-apoptotic gene. Cells in order to become Neoplastic, inside the Cell, Loss of function Mutation should Occur in Pro-apoptotic Genes WHILE Gain of Function Mutation should occur in Anti-Apoptotic gene.

So for normal cell to become Neoplastic, cell should be,

1-Self-sufficient in growth Signals.

2-Cell show insensitivity to cellular growth Inhibition signals.

3-DNA Repair Genes should be Dysfunctional.

4-Evasion of Apoptotic Mechanism should be Occur.

5-Limitless Replication Capacity :- Cancer Cells contain lot of Telomerases. Telomerases synthesize constantly ends of Chromosomes (Telomeres) as a result cells keep on Replicating its DNA and Proliferate Limitless.

6-Sustained Angiogenesis :- In Mutant cells, those genes are Stimulated that produce strong Angiogenic Factors. As result lot of blood vessels are produced and Infiltrate towards the Cancer Cells.

7-Malignant Cancer cells should invade the tissue and show metastasis :- Every well differentiated and mature cell live in special Microcirculation. Exp# Brain cells Live in df type of Microcirculation as Compare to Hepatocytes so normal cell can't live in microcirculation that are not belong to them so Normal cells Can't be Metastasized. But cancer cell act like a embryo cells and Can live and Proliferate in any Microcirculation. So cancer cells Can show the mechanism of Metastasis.

8- Cancer Cells should be able to escape the attack of Immunity.

Q# How Proto-oncogenes Normally Initiates cellular growth??

Ans:- Proto-Oncogenes are the Sets of genes that are present on df chromosomes within the Cell and are related with Cellular Growth. In Proto-Oncogenes, df Genes are present. So when cellular growth Starts,

1# 1st gene from Proto-Oncogenes Group, release Growth factor out of the cell into neighbouring Tissue.

2# 2nd gene release Growth factor receptor which appear on the Surface of cell. Most of the growth receptor factors are Tyrosine kinase Receptors. Growth factor has 2 Domains so they usually bind with 2 growth factor receptors Simultaneously. After binding of Growth factor with their receptors cells.

3# 3rd gene produce Signal transducer proteins. These protein bind with intracellular domain of growth Factor Receptor and activate another set of gene called as Responder Genes.

4# Responder gene produce Special Transcriptional factor Proteins that make RNA from Cyclins producing Gene Via Transcription. RNA then convert into Special Cyclins Proteins through Translation.

5# Cyclins bind with Cyclin-Dependent Kinase enzyme and activate it. Active cyclin-dependent kinase Phosphorylate RB (Retinoblastoma) Protein as a result RB protein leave the E2F gene.

E2F is a gene which normally initiates DNA replication and RB protein normally inhibit that gene. But when cell release growth factor and growth factor bind with its receptor then through intracellular mechanism (that have discussed above), Initiates E2F gene by Phosphorylating RB Proteins and cell enter into DNA replication phase or S phase of cell Cycle. So

All intracellular steps that eventually Stimulate E2F gene, which perform DNA replication Occur in G1 Phase.

Q# How normal cells convert into Neoplastic cell??

Ans:- There are many ways through which Gain of function Mutation can be seen,

1# Set of Proto-oncogenes Can undergo mutation as result of inherited defect, or due to Radiation or virus etc or their may be a Spontaneous mutation Occur which don't Repair. So as result, If any gene of proto-Oncogenes suppose 1st gene that produce growth factor become mutant and it produce abnormal growth factor which Over-stimulate the growth factor receptor as a result DNA replication become Fast.

2# Another Way by which Gain of function Mutation occur is Called as GENE AMPLIFICATION.

In gene Amplification, during Replication, there are more than 1 copies of Specific Genes are formed.

Suppose due to gene Amplification, 100 extra copies of growth factor Producing gene has been Formed. When this gene will be stimulated then this Amplified gene on Irritation will Produce 100 growth Factors which will overstimulate the growth factor receptors and DNA Replication will increase.

If too much Extra copies of gene is formed that chromosome Can't hold them then Extra copies fall into Nucleoplasm and Cytoplasm. These extra Copies are called as Extra Chromosomal Double Minutes of Gene.

#GAIN OF FUNCTION MUTATION is seen, when Gene is Translocated at new Place where it is Overstimulatd.

In B Lymphocytes, Translocation of of Anti-Apoptotic Bcl-2 gene from chromosomes No. 18 to 14 is seen, as a result of radiation etc.

As a result, Bcl-2 gene Reside near the Immunoglobulin Producing gene on chromosome no 14 and overexpress there, which result Cause Follicular Lymph Adenoma.

1# Out of 2 Alleles, Even if 1 allele get mutant, and other allele Remain normal then mutant Allele become dominant and Produce Abnormality. Such type of behaviour is shown by Mutant proto-Oncogenes.

2# But if out of 2 alleles, 1 allele gets mutant then, Mutant Allele Can't produce Mutation in the Presence of healthy allele so mutant Allele Show Recessiveness. Such type of behaviour is shown by Tumor suppressor gene. So in order to produce loss of function Mutation in tumor suppressor Gene, both Alleles should be Mutant.

3# Tumor suppressor gene Normally Release RB Proteins which inhibits E2F gene.

4# Normally tumor suppressor gene is regulated by P53 gene.

GENES THAT ARE INCLUDED IN PROTO-ONCOGENES :-

1# 1st group of gene include, Platelet derived growth Factor gene etc.

2# 2nd group of gene include, platelet derived growth factor Receptor etc.

IMPORTANT :-

3# In most Cancer cells, Mutations are present in Signal transducer genes as result mutant Signal transducer Proteins are produced. Abnormal signal transducer protein such as Ras Protein Overstimulate DNA replicator gene and as a result DNA over replicate and cell abnormally increased its number. Signal transducer Proteins include Ras Protein etc.

Ras Protein mutation is most common Signal Transducer protein that increases the DNA Replication.

Doctors now working on some drug that block the Ras-map Kinase pathway and inhibit it.

Most commonly Mutation can be Produce and present in intrinsic GTPase enzyme which normally convert GTP into GDP and control signal growth Signal mechanism.

Tumor suppressor gene also normally produce protein which Stimulate intrinsic GTPase Enzyme.

There is an another ABL tyrosine kinase protein normally Produce within the cells by ABL gene. ABL protein normally bind with cell membrane and stimulate cellular growth. But this protein is Normally inhibited by special protein which is produce by Tumor Suppressor Gene.

Mostly this protein get mutation as a result of Translocation Proecss.

#Actually ABL gene is present on chromosome 22. Due to Translocation ABL gene bind with bcr gene present on chromosome no. 9 and make a BCR-ABL hybrid gene complex. This complex produce mutant ABL tyrosine kinase Protein which can't be Inhibited by protein that normally produce by tumor Suppressor gene. So mutant ABL protein constantly stimulate cellular growth genes and Cells Overproliferate.

Designer drug such as Imatinib Mesylate drugs inhibit Mutant ABL Tyrosine Kinase Protein.

So gene that produce signals Transducer Proteins include Ras and ABL genes etc.

4# Gene that produce Transcriptional Factors mainly include FOS gene, Jun, Myb and Especially Myc gene. Myc gene mutation is very common in cancer cells.

5# 5th gene is Cyclin producing gene. This gene Produce Cyclin Protein that bind with CDK and stimulate DNA Replication.

6# 6th gene is a CDK producing gene. This gene Produce Cyclin dependent kinases.

TUMOR SUPPRESSOR GENES...

Q# How tumor suppressor genes normally work and how tumor suppressor gene behave when normal cell convert into Neoplastic cell??

Ans :- In normal cell cycle, RB gene act as molecular Breaks to stops cell cycle. But if cell get damage and start Overproliferation which is not control by RB gene then P53 gene come to an action and try to stop cell Cycle and Abnormal Proliferation.

#In normal non-proliferating cells, RB gene is expressing all the time.

1st Gene :- 1st gene that is present in tumor suppressor gene is RB gene. RB gene are non-proliferating gene and suppress the DNA replication by producing RB Proteins. RB Proteins bind with E2F and inhibit it.

RB protein are called so bcz these Proteins was 1st discovered in Retinoblastoma(RB) patients.

In Retinoblastoma, mutation is present in RB gene on chromosome Number 13. But imp point is that, Retinoblastoma occur only when both RB genes get Mutant means (Homozygous mutant RB genes are present).

Retinoblastoma Cases can be,

1-Sporadic Cases.

2-Familial Cases

1-Sporadic Cases:- 60% case of Retinoblastoma are Sporadic, Non- Familial or Non- Hereditary. These Person develop mutant RB Genes in any of Somatic cell due to Mutagenic environmental factors such as virus, chemicals, Radiations etc. These patients don't have mutant RB genes on Sex Chromosomes so these Persons don't pass the mutation to next generation.

Retinoblastoma occur in old age bcz these person were born with normal genetic material but with passage of time due to environmental factor both Alleles of RB genes get Mutant with passage of time and cell under go abnormal proliferation and has develop Retinoblastoma.

2-Hereditary :- 40% Cases are Familial or Hereditary. #Hereditary mutation run in Germ or sex Chromosomes and that mutation transfer from 1 generations to another.

These person develop Retinoblastomas in younger age bcz they acquire 1 mutant RB allele in inheritance. So any time if any mutagenic Factor hit the other RB allele and make 2nd RB gene also mutant then that cell of retina proliferate and make tumor which develop into Retinoblastoma.

IMPORTANT :-

Patients with Hereditary Retinoblastoma have also high risk of developing Osteosarcoma. Bcz in these patients, all cells have 1 RB allele mutant so 2nd RB allele in Osteocytes can get mutant and produce abnormal growth or Tumor.

KNUDSON HYPOTHESIS or TWO HIT Hypothesis tells that, Retinoblastoma develop only when both maternal and paternal alleles should be hit by loss of function Mutation.

This Hypothesis apply on all the Tumors which are Produce due to loss of function of tumor suppressor gene.

Q# How the loss of function Mutation develop??

Ans:- Loss of function Mutation can be seen by,

1-Interstitial Deletion of Particular gene from Chromosome occur. Exp, RB gene in patients with Retinoblastoma.

2- If Whole chromosome are Absent in a cell that contain particular both allele genes.

3- If point mutation is present in specific gene then it produce mutant Protein which is not Fully Functional.

IMPORTANT :-

All growth Factors that are produce by cell are Stimulatory in action Except Transforming growth factor(TGF- Beta) which is Inhibitory in action.

When cell release (TGF-beta) Growth Factor, then this growth factor bind with its receptor on neighbour cell and produce a special inhibitor protein CDK- Inhibitor protein. This protein inhibit CDK protein and block the cell cycle. So loss of function Mutation in any TGF-beta gene Can make the cell cycle abnormally very fast and able cell to Overproliferate.

HUMAN PAPILOMA virus develop cervical carcinoma. Papiloma virus enter into cervical cells and produce E7 protein. E7 protein block the RB Proteins and allow cell to Overproliferate.

Human Papilloma virus also produce E6 protein which bind with P53 and Neutralise P53.

2nd gene :- Most important tumor Supressor gene is P53 gene.

Ataxia Teleniectiva Mutant (A. T. M) gene is found mutant in disease Ataxia Conjectiva.

Q# What is the mechanism of working of P53 gene??

Ans:- P53 gene is called as Guardian of Human Genome Bcz this gene insure the safety of DNA from any mutation and repair damage part of DNA If It Present in DNA.

1# There are Proteins present in DNA that constantly read DNA and Sense any Demage to DNA. If DNA get demage due to some reason, DNA Demage or mutation sensor report mutation in DNA to P53 gene.

1-P53 gene is stimulated and it stimulate df sets of genes. One of gene produce CDK-inhibitors proteins which Inhibit the CDK protein and cell cycle stops.

2- 2ndly, P53 gene stimulate DNA Repair gene. DNA Repair gene Produce all the enzymes that are require for DNA Repair. Now

When Mutation sensor Proteins of DNA stops Stimulating P53 gene. Then P53 gene try to switch off. So for that,

1-P53 gene stimulate MDM-2 Genes which produce MDM-2 proteins. These Proteins catalyse the P53 and Inactivate it. As result of cell Cycle Starts.

Suppose when mutations occur in DNA demage Sensor enzyme or proof Reader Enzyme become Mutant and they over stimulate P53 gene. Due to Over stimulation, P53 irritated too much. So irritated P53 gene Plan to destroy the cell and Pushes cells to commit Suicide. For that, P53 gene stimulate 1 of the Pro-apoptotic gene. Pro- Apoptotic gene produce BAX. BAX destroy the Channel Stopper and allow Cytochrome c to come out of mitochondria into Cytoplasm.

Within Cytosol, Cytochrome C activate df Caspases which induce Apoptosis of a cell.

P53 is present on chromosome number 17.

CLINICAL IMPORTANCE:-

Most common mutant gene that is found in Cancer cells is mutant P53 gene.

Most common defect in Dominant Oncoproteins (produce by Oncogenes) is found in Ras Protein.

In DNA or cancer associated Genetic defect, most common defect occur in P53 gene which is actually loss of function Mutation in P53.

Initial Cause of any Hereditary gene defects include, Df Environmental Mutagenic Factors.

LE FRAWMANNE SYNDROME is a Condition in which people carry Inherited 1 mutant copy of P53 gene.

These people have 25 time more risk of developing Cancer by the age of 50 years as compare to normal One.

Q# Why Some Tumors Respond to chemotherapy, some tumors respond to Radiotherapy and some tumors don't respond at all??

Ans :- Those cancer cells that have functional P53 gene, these cancer Cells respond to chemotherapy and radioactive therapy very well bcz these techniques are used to irritate P53 gene in a cancer cell so that, P53 gene become irritated too much and turn cells toward Apoptosis.

Those tumour that contain both Copy of P53 mutant these cells show resistance, to chemotherapy or radioactive therapy.

APC-CATENIN PATHWAY OR SYSTEM :-

3rd Gene :- 3rd gene that is present in tumor suppressor gene set include APC gene. APC gene normally produce APC protein. APC protein bind with beta catenin and inhibit this protein. Normally Beta Catenin protein stimulate MYC (Protooncogenes) gene directly and as a result, myc gene produce Transcriptional Factors which Produce Cyclin and accelerate cell cycle.

HEREDITARY POLYPOSIS COLI:-

#In this syndrome, Mucosal Cells of colon proliferate abnormally due to loss of function Mutation in APC(Adenomatus Polyposis Coli) gene. If person has Heterogeneous mutant APC Alleles then by the age of 20, these People develop Thousand and thousands of adenoma in their Colon. And only treatment is Removal of Adenomatus colon from body. Bcz if colon is not remove then Adenomas with the passage of time Convert into Carcinoma.

There is an growth factor WNT. Normally When cell want to Proliferate, WNT bind with its receptor on Cell, it destroy the APC Protein and Release Beta Catenin Protein. Beta catenin stimulate cellular growth. WNT system increase cellular Growth.

4th Gene :- There ia an another tumor suppressor gene present which normally produce E-Cadherins proteins that Bind beta catenin with the cell membrane and don't allow it to work Normally. Such gene is called as E-Cadherins gene. In Gastric and Superficial Carcinomas, this gene become Mutant. Due to Loss of E-Cadherens gene, not only cells proliferate with that, Cells loss Adherence with each other and as a result abnormal tumor cells normally invade the tissue and become able to Metastasize.

About 70-80% patient who have Non-hereditary Colorectal Carcinomas, these patients have both mutant APC Genes.

Normally, Out of Total Production of Intracellular APC Proteins, About 50% of beta catenin is destroyed by APC protein WHILE 50% Beta catenin protein is held by E-Cadherins.

5th gene :-Neurofibromatosis 1 Gene(NF-1) is normally a tumor suppressor Gene. Normally it produces GTPase Activator Protein that Stimulates Intrinsic GTPase present on Ras protein so that GTPase immediately converts GTP into GDP and Inactivates Ras Protein. So stops the signal transducer Protein from Overstimulating cellular growth related Gene. But when this gene undergoes loss of function Mutation then NF-1 gene produces Abnormal GTPase Activator Proteins which are Non-functional so cells over proliferate and make 100s of Fibromas all over the Body. This gene is present on chromosome number 17.

6th gene :- Neurofibromatosis-2 is another tumor suppressor gene that normally produces Merlin protein.

FUNCTION OF MERLIN PROTEIN :- Merlin Protein from 1 side interacts with Transmembrane protein CD44 and from other Side this protein interacts with Actin and makes cytoskeleton and enables ICF of cells to interact with ECF and also allows one cell to interact with other Cell.

When NF-2 gene becomes Mutant, patients develop Schwannomas in vestibulocochlear nerve in both Ears.

7th gene :- VHL(Von Hippel Lindu) gene is another tumor suppressor gene. Normally this gene Produce special Portion Ubiquitin Ligase. This protein usually do Ligate activity bw HIF and Ubiquitin. Actually this protein takes HIF and give HIF to Ubiquitin so that it destroy HIF.

Q# Why HIF should be destroyed in the Cell??

Ans :- Normally when cells undergo Hypoxia, there is a gene present inside every Cell which is sensitive to Hypoxia and whenever cell experience Hypoxia, this gene is stimulated and it release HIF (Hypoxia induce factor). HIF stimulate df genes which eventually produce vascular Endothelial growth factor (VEGF) and Platelet derived growth Factors(PDGF). So that these growth factor make capillaries around the hypoxic cells and bring more oxygenated blood towards Hypoxic tissue, and when cells get out of Hypoxia then these growths factors are actively destroyed. Now

If due to any inherited defect, this VHL gene become Mutant and don't produce Ubiquitin Ligase then HIF remain in cell and can't be destroyed. So due to overwork of HIF Multiple vascular and Renal tumors are formed in body such as retinal Angiomas, Cerebral hemangioblastomas, Renal cell Carcinomas.

All these pathologies are collectively called as VON HIPPLE LINDU DISEASE.

1-Molecular break system for Ras Protein or signal transducer gene is NF-1 gene and its protein.

2-Molecular break for MYC gene is APC and E-Cadherens gene.

3-Molecular break for CDK Function are P21 protein which are Produce by P21 gene under the action of transforming growth Factor beta (TGF -beta).

Production of TGF-beta is initiated by set of genes. These genes include,

1-PATCHED,

2-KLF-6

3-TGF-BETA gene.

3-TGF-beta Receptor gene.

1# PATCHED gene stimulate TGF-beta gene and as a result TGF-beta is produced.

2# KLF-6 stimulate TGF- beta receptor gene that Produce receptor for TGF-beta growth factor

3# P21, P 27 and PTEN genes normally inhibit the action of cyclin-CDK Complex so all gene act as molecular break for CDK-Cyclin complex and inhibit cellular Growth.

WILINS TUMOR is the most common Renal Tumors in Children.

Wilins tumor is produced as result of loss of function Mutation in Wilins genes, so differentiation factors are not Produced. So Mesenchyme can't differentiate properly into epithelial cells. So Mesenchyme convert into abnormal epithelial cells and make abnormal bone, Cartilage Renal nephrons and produce Wilins Tumors.

There are 7 proto-Oncogenes and 16 are tumor suppressor gene are present in every cell.

ANTI-APOPTOTIC AND PRO-APOPTOTIC GENE :-

#Cell survival depends on balance regulations of Anti-Apoptotic and Pro- Apoptotic gene.

#If activity of Anti- Apoptotic gene increases in body. It decrease the life of cells and cells undergo Apoptosis.

If activity of Pro-apoptotic gene Increases in the body due to any mutation then cells don't die and survive for Long time.

Q# Difference bw Follicular and Non- Follicular Lymphoma produce by B Lymphocytes??

Ans:-1-B Lymphocytes cells which are present in lymph node and are well differentiated. These B cells normally live in group called as Follicle in lymph node. When these well differentiated B cells convert into Neoplastic cells and produce a Tumor then these cells make Follicular Lymphoma. WHILE

2-If B cells don't undergo well differentiation and are in early age and B cells become Neoplastic and these B cells make a tumors Inside Lymph Node which are poorly differentiated. Such type of B cells tumors are called as Non-Follicular Lymphoma.

3-Follicular Lymphoma is more dangerous Lymphoma then Non-Follicular Lymphoma. Bcz B cells of follicular Lymphoma are well differentiated and these Cells proliferate at faster rate as compare to Non-differentiated Neoplastic B Cell which make Aggressive Non- Follicular Diffuse Lymphoma.

4-Those B cells that make well differentiated Follicular Lymphoma. In these B cells, Anti-Apoptotic gene become Mutant.

So as result, these B cells over live and convert into well differentiated cells and slowly convert into Neoplastic with passage of time. BUT

5-Those cells that make Non-follicular lymphomas these B cells have mutation in MYC gene or signal transducer Protein producing gene. As a result, these cells live for normal life Span but these Cells due to presence of too much signal transducer Proteins Overproliferate rapidly and make tumor.

6-Non-follicular Lymphoma occur in B cell due to Translocation of MYC gene from chromosome number 8 to chromosome number 14. Due to abnormal Translocation Myc gene overexpress and cell Proliferate very much. WHILE

7-Follicular Lymphoma is cause by those B cells in which Bcl-2 (Anti-Apoptotic) gene is abnormally Translocated from chromosome No. 18 to chromosomes No. 14 as result Bcl-2 gene over express and cells live for long time.

BURKITT'S LYMPHOMA is an example of Non-Follicular Lymphoma.

8-Under Microscope Non-follicular Lymphoma seen as diffuse sheath of Neoplastic B cells in black colour. While some Macrophages are also seen in red colour which normally present there to Eat Neoplastic B cells.

9- Under Microscope, Neoplastic B Lymphocyte look well differentiated in Non-follicular Lymphoma.,

DNA REPAIR SYSTEM..

Every day in almost every cell there are 5 to 10 thousands damages Occur to DNA But all are Repaired by DNA Repair mechanism,

There are 3 DNA Repair mechanisms present in the body. These include

1- DNA Mismatch Repair System.

2- DNA Nucleotide Excision repair system.

3- Homologous recombination repair system.

Q#Df Environmental factor that produce mutation in DNA??

1# MISMATCH REPAIR SYSTEM :-

1- MSH-2 gene is 1 of the gene of DNA Mismatch Repair system.

When DNA Repair gene is mutant, person develop malignant tumors Exp # Colon Carcinomas especially Hereditary colon Carcinoma. Colon Carcinoma is of 2 types,

1-Hereditary Non-polyps Colon Carcinoma.

2-Familial Adenomatus Polyposis colon carcinoma.

1# Hereditary Non-polyps Colon Carcinoma patient develop Carcinomas in proximal Colon without developing Lot of Polyps.

These patients Receive 1 mutant gene such as mutant Mismatch Repair System (MSH-2) gene from their Parents. So any time due to environmental factor other allele related with MSH-2 gene also get defective. So DNA Repair system become Unstable and Abnormal DNA is Formed We called it DNA Instability Syndrome.

In these Female patients there is increase risk of Endometrial carcinoma and ovarian Carcinoma.

2-Familial Adenomatus Polyposis is an another type of Hereditary colon carcinoma in which person have 1 Hereditary mutant APC Genes. In such patients 100 of Polyps develop and out of 100 only 1 and 2 convert into Carcinoma if remain untreated for long time.

Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is an autosomal dominant genetic condition that is associated with a high risk of colon cancer as well as other cancers including endometrial cancer (second most common), ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin. The increased risk for these cancers is due to inherited mutations that impair DNA mismatch repair. It is a type of cancer syndrome. Because patients with Lynch Syndrome can have polyps, the term HNPCC has fallen out of favor.

#MICROSATELLITE in their position, number, type vary from person to person which help in a person to differentiate bw paternal as well as maternal chromosome in a person. Also use in the finger printing. Study of Microsatellite is also use to differentiate bw Cancer and Normal cell.

Replication Error Phenotype.

2# DNA NUCLEOTIDE EXCISION REPAIR SYSTEM:- Xeroderma Pigmentosa is disease which is Caused by defects in Nucleotide Excesion Repair. This system normally repair those DNA Mutations that are produce by UV light. So when UV light Fall on Cells, it damage the DNA with that, it also stimulate specific gene which produce UV specific Endonucleases.

FUNCTIONS of UV SPECIFIC ENDONUCLEASE ENZYME :-

- 1# UV specific Endonuclease recognise the Lesion.
- 2# Cut the damage part by Endonuclease activity.
- 3# Segment removal
- 4# Gap filling phase.
- 5# Ligase phase.

In Xeroderma Pigmentosa, gene that produce UV sensitive Endonuclease is mutant. So damage that is produced by UV is not repair at all, so mutation accumulate in the Cell. These Persons develop multiple Carcinomas. These persons have 1 to 2 thousands more ability to develop carcinoma as compare to normal person.

It is more common in white European people live near Equator such as in Australia, New Queen Island etc.

3# HOMOLOGOUS RECOMMENDATION REPAIR SYSTEM :- This system consists of those enzymes that repair the DNA only when both Alleles of same gene get damage due to action of Strong Radiation, Alkaline Agents. So for Repair of that gene, enzyme of this system find other Homologous chromosomes which is normal and make a Same normal template of damage gene from normal Homologous Chromosome and fit that DNA template in place for damage DNA.

Normally Homologous chromosomes are present Randomly in the Cell. Homologous chromosomes come near to each other and exactly lined opposite to each other only,

- 1- During Meiosis in Gametogenesis.
- 2- when Serious damage occur to DNA.

When Homologous Recombination Repair system become mutant. As a result, 3 diseases are produced. These diseases include,

1# Ataxia Teleniectasia.

Person develop cerebellar dysfunction, malignant Lymphocytes and immunodeficiency.

1 % of US population have Heterozygous mutant gene in their DNA for Ataxia Teleniectasia

2# Bloom syndrome.

Bloom syndrome is Very rare and person develop multiple Congenital anomalies and have risk of developing cancer.

3# Fanconi Anemia.

Ataxia Teleniectasia and Fanconi Anemia protein etc. sense the damage to double Strands of DNA.

Mutation in BRCA-1 and BRCA-2 gene is most commonly produce Breast cancer but also have little Chance to develop Ovarian Cancer.

If BRCA-1 gene is defective then breast cancer occur in Females and that is Familial breast Cancer.

If BRCA-2 gene get defective then, in this family, not only females develop Breast cancer but with that, Male of that family also develop Breast Cancer.

Telomerase enzymes are normally present in high concentration in Germ cells.

Diagram showing Genes that are involved in normal Cellular Growth...

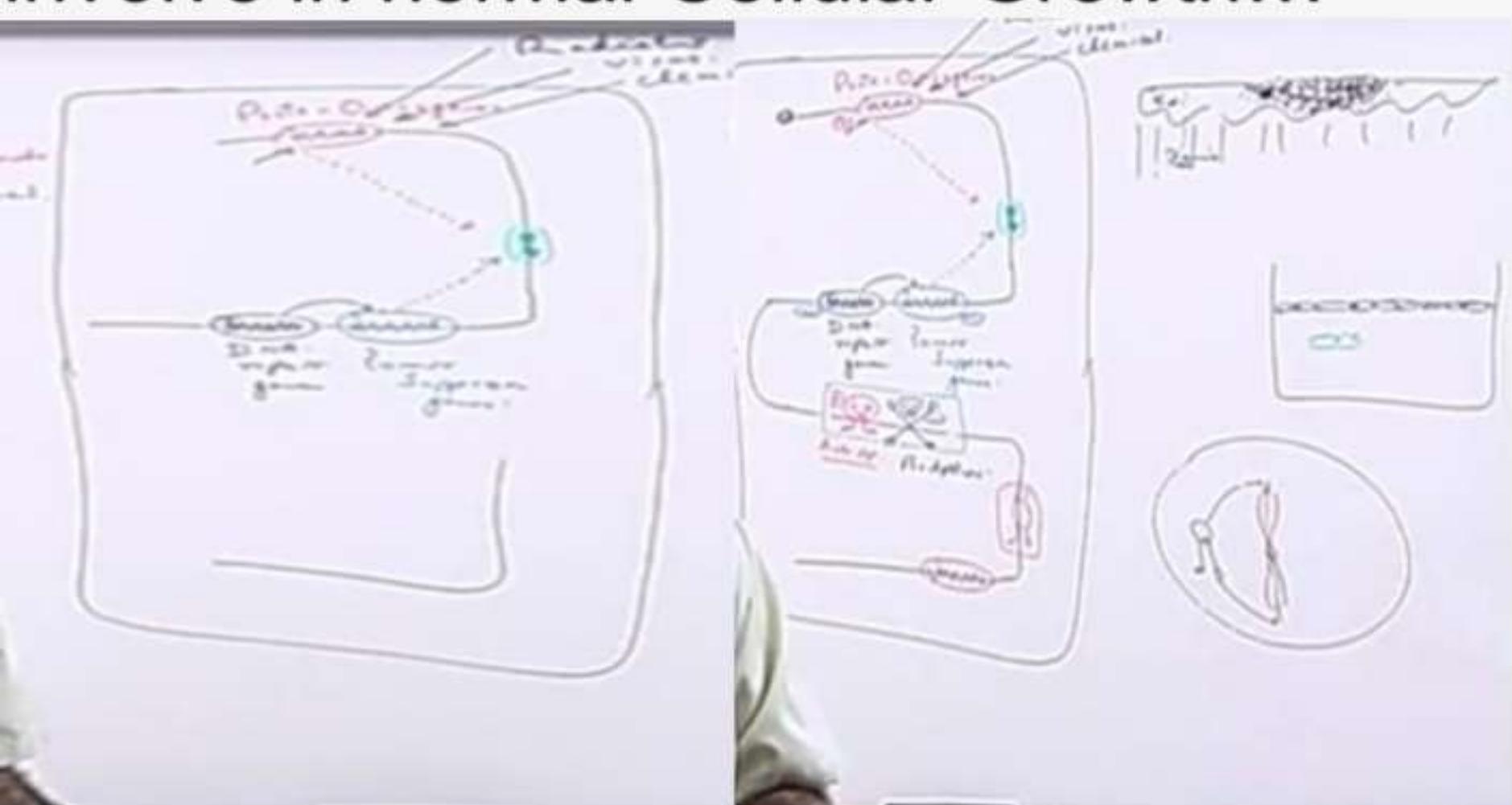


Diagram showing df features of Nacrotic cell or df points that are essential to convert normal cell into Neoplastic...

Df features that Convert normal cell into Neoplastic cells.

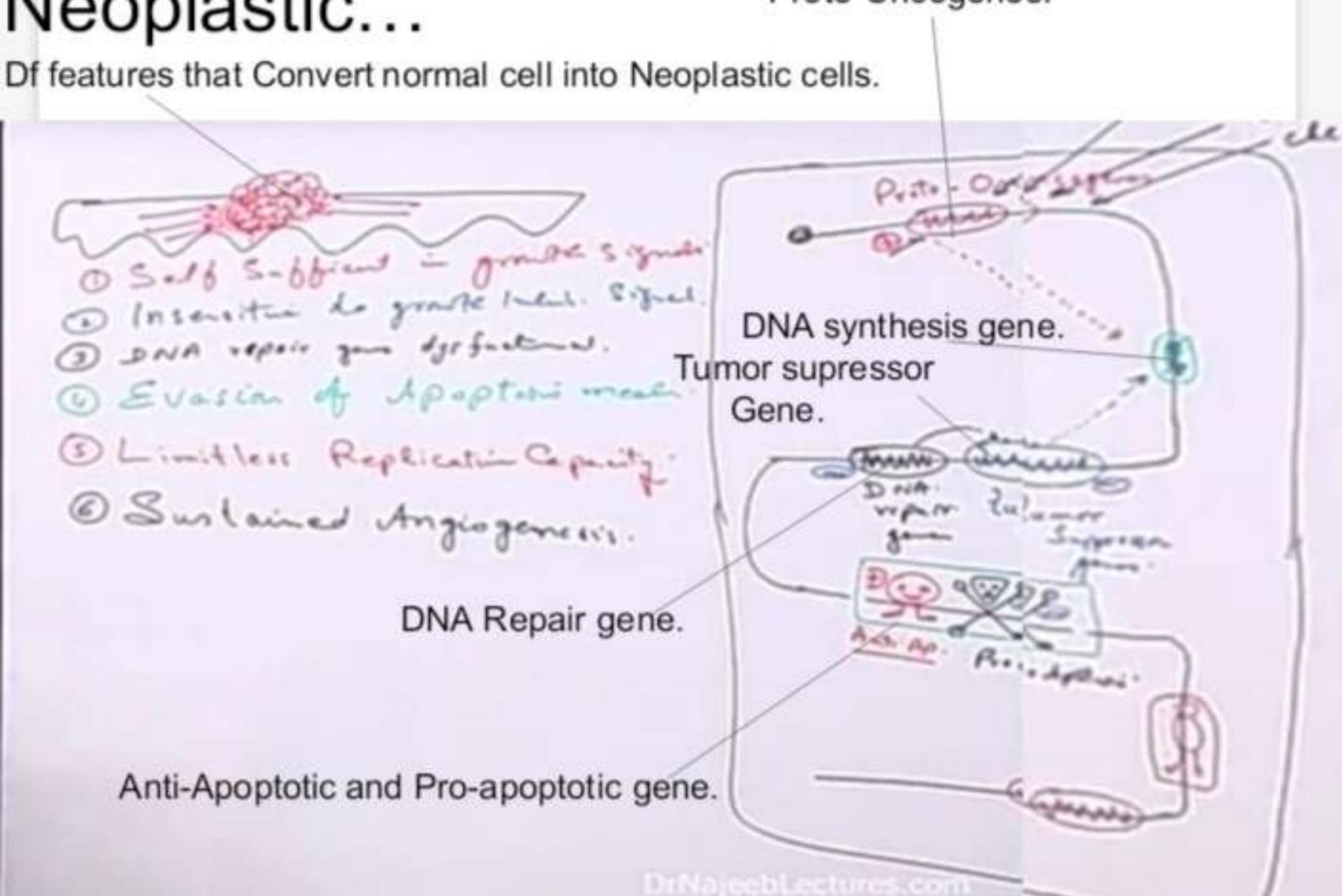


Diagram showing df Proto-Oncogenes that are involved in stimulation of E2F (Growth initiator) gene..

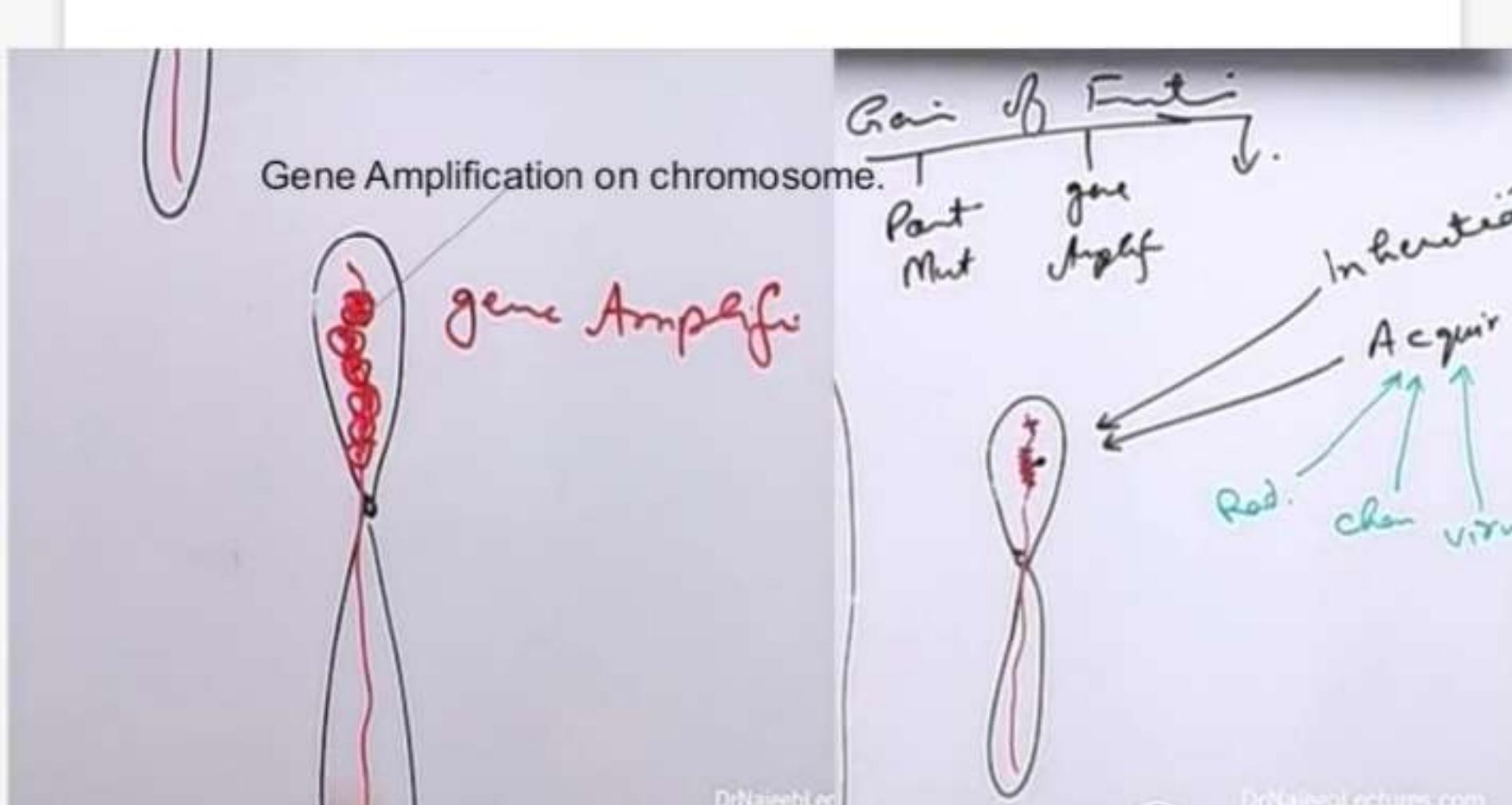
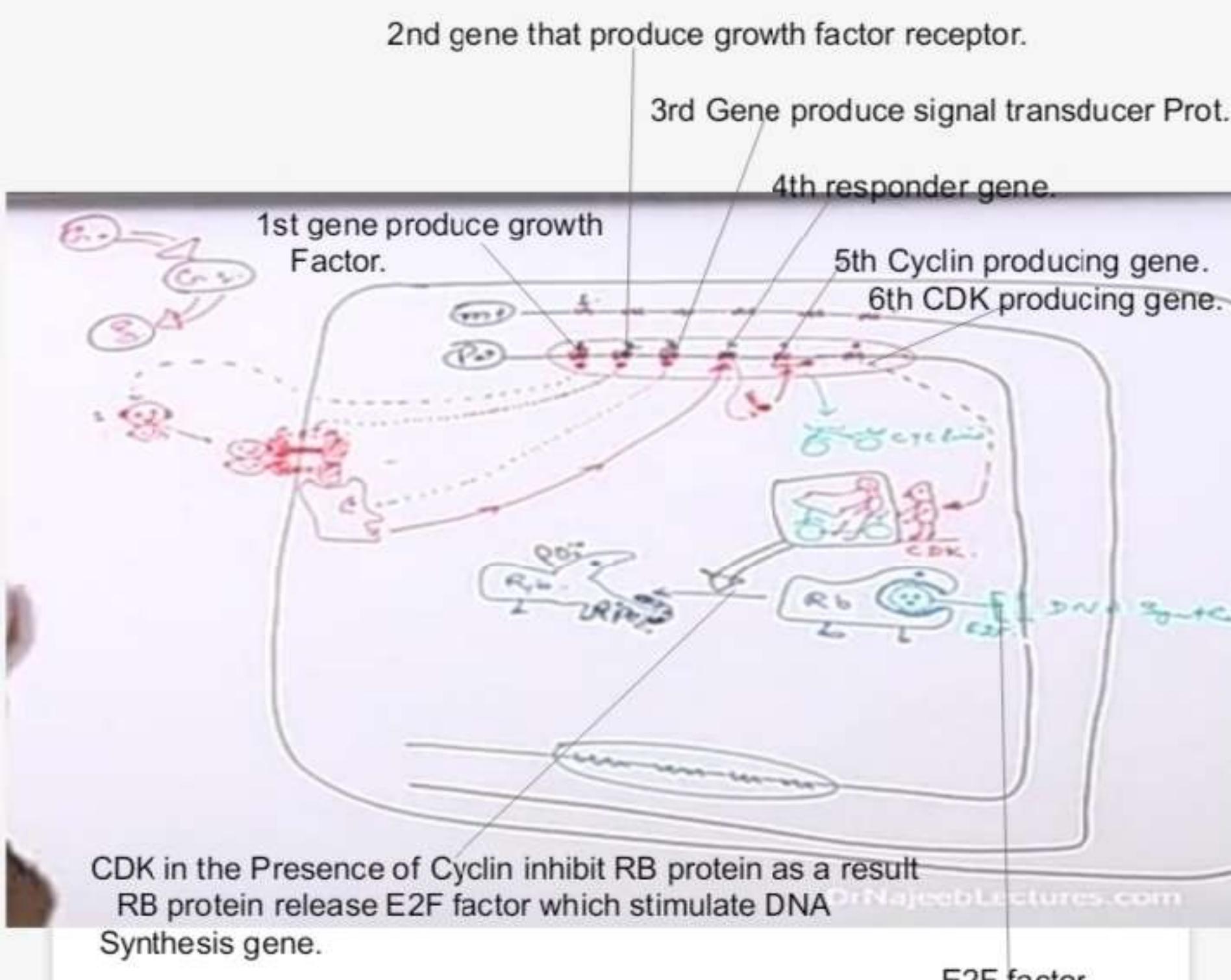
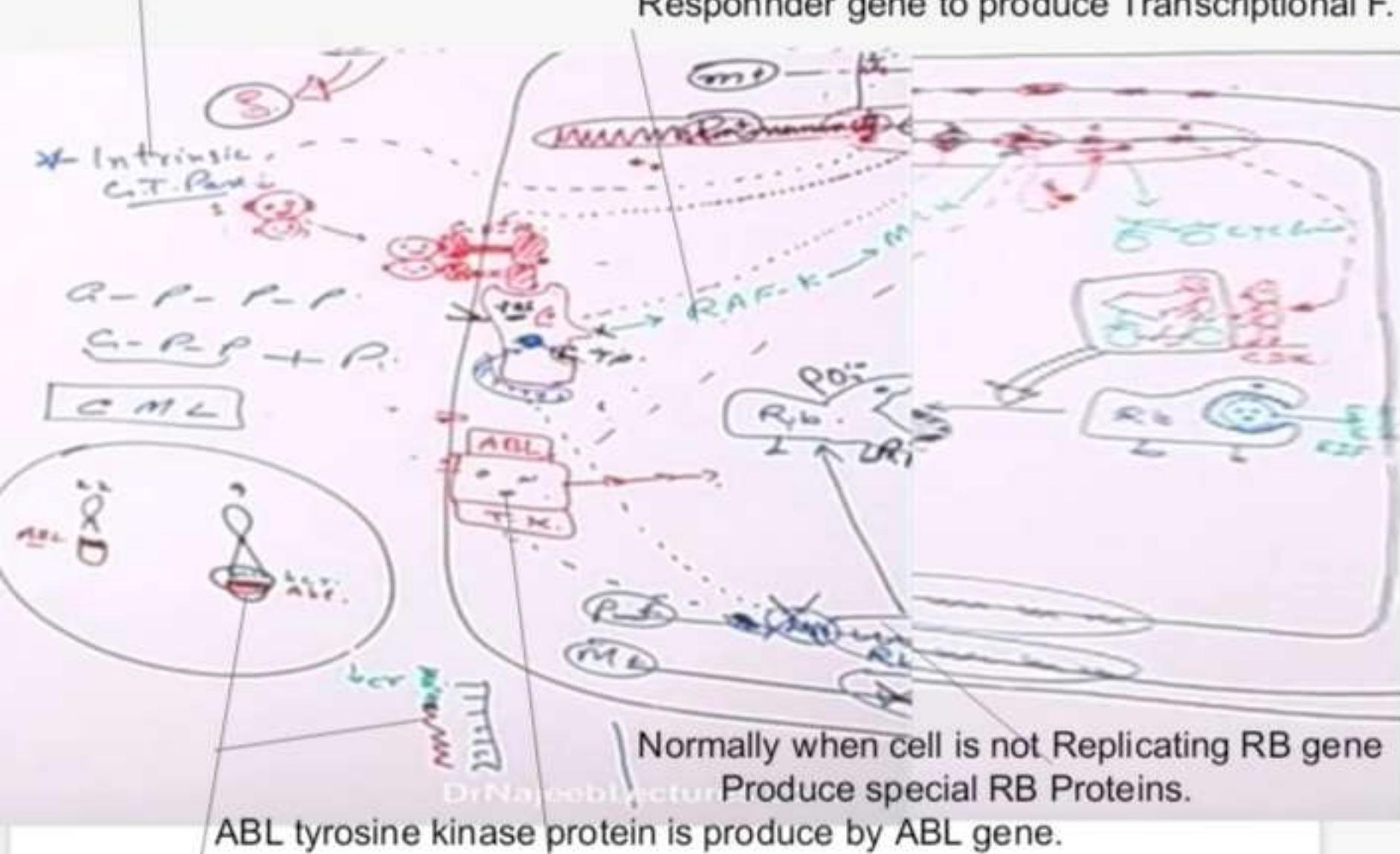


Diagram showing mechanism of action of ABL and RB protein...

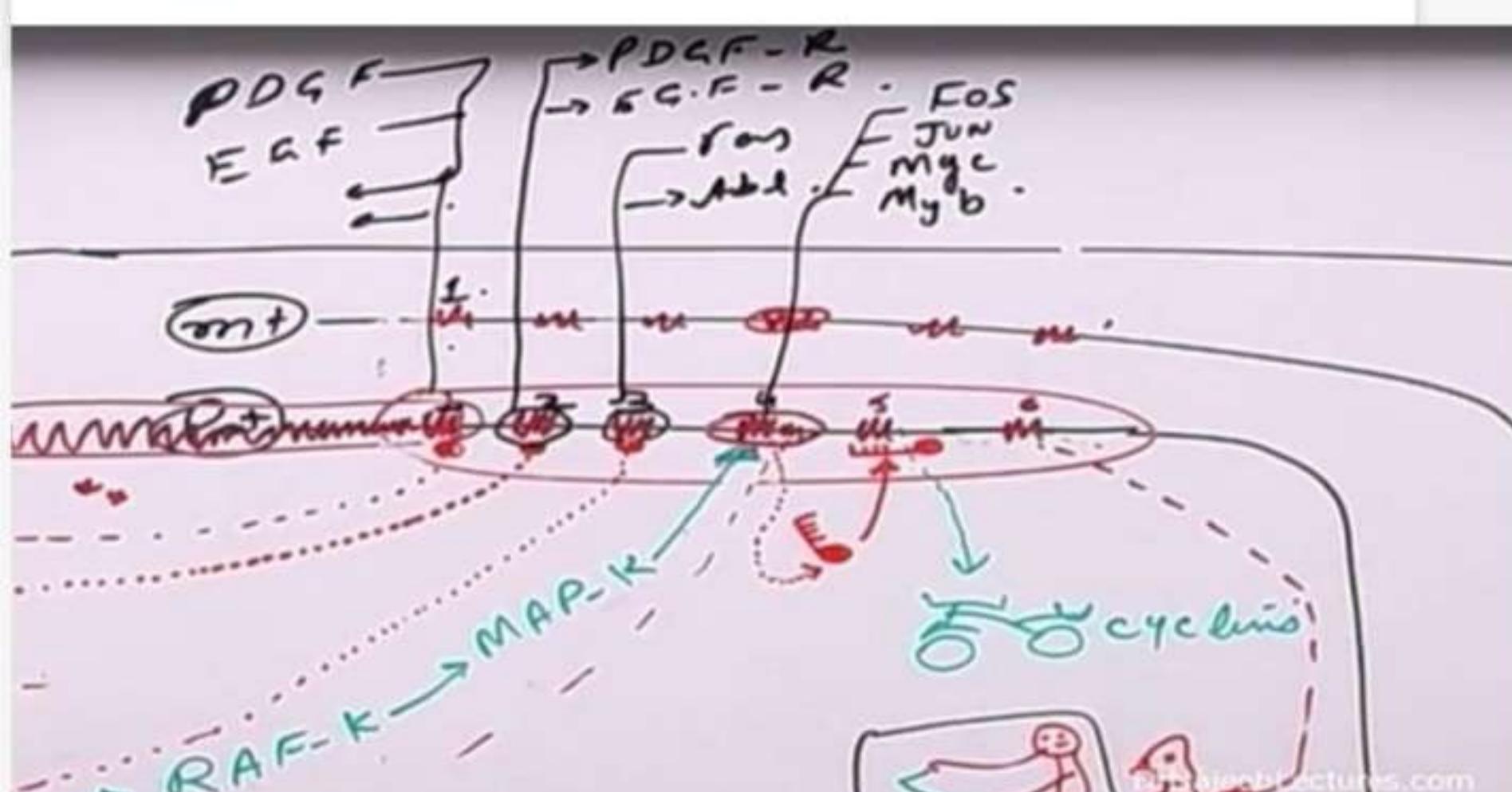
Intrinsic GTPase present on signal transducer Protein such as Ras Protein.

Ras Protein stimulate Raf kinase, Raf stimulate Map Kinase, MAP Stimulate Responnder gene to produce Transcriptional F.

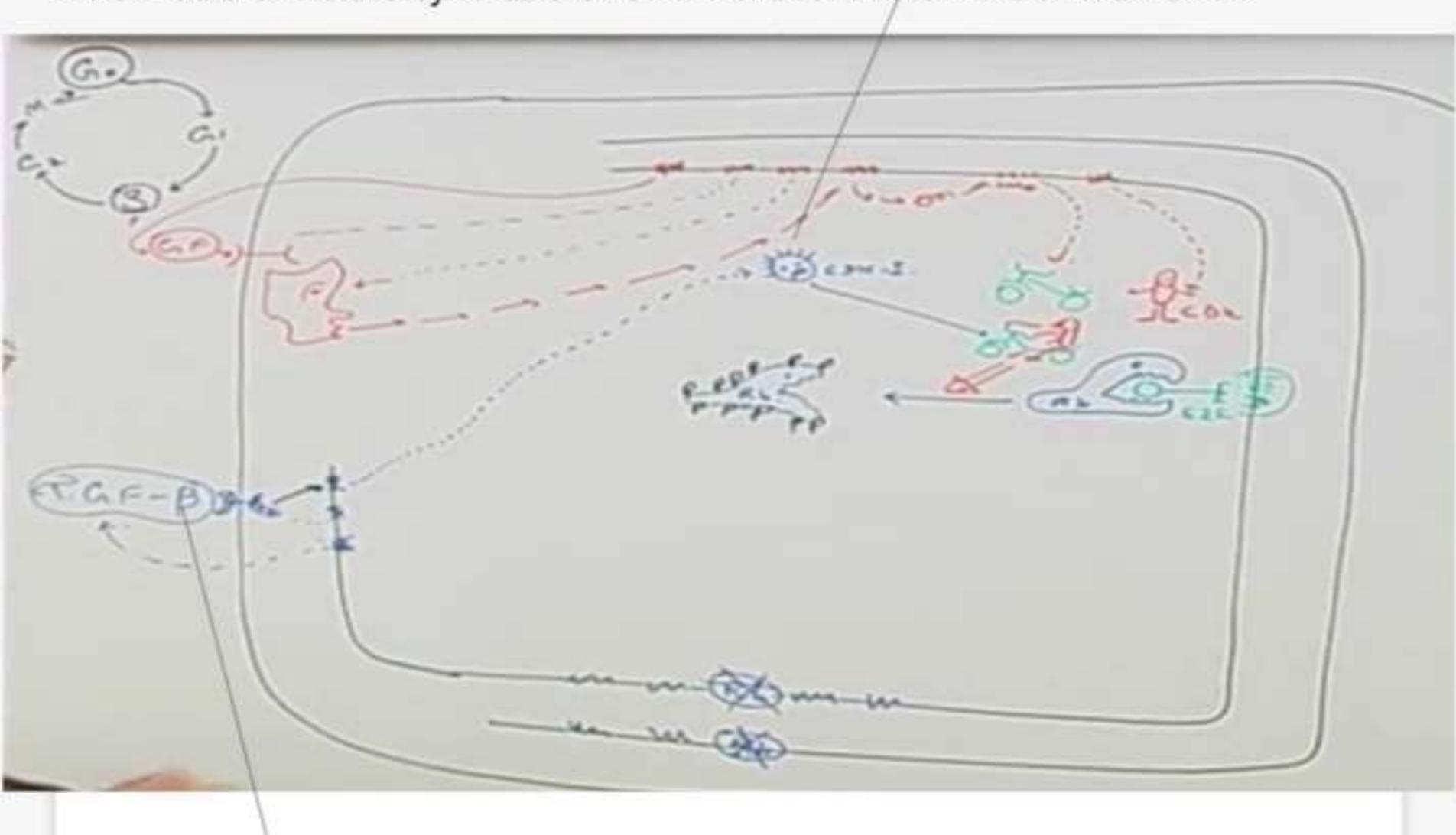


Abnormal Hybrid proteins are produced by ABL-BCR Hybrid gene complex as result of abnormal Translocation.

Diagram showing df Examples of Proto-Oncogenes...



2-TGF-beta stimulate synthesis of CDK inhibitor Protein that inhibit CDK.



1-TGF-beta bind with its receptor.

Diagram showing df types of mutation with that Classification of Retinoblastomas...

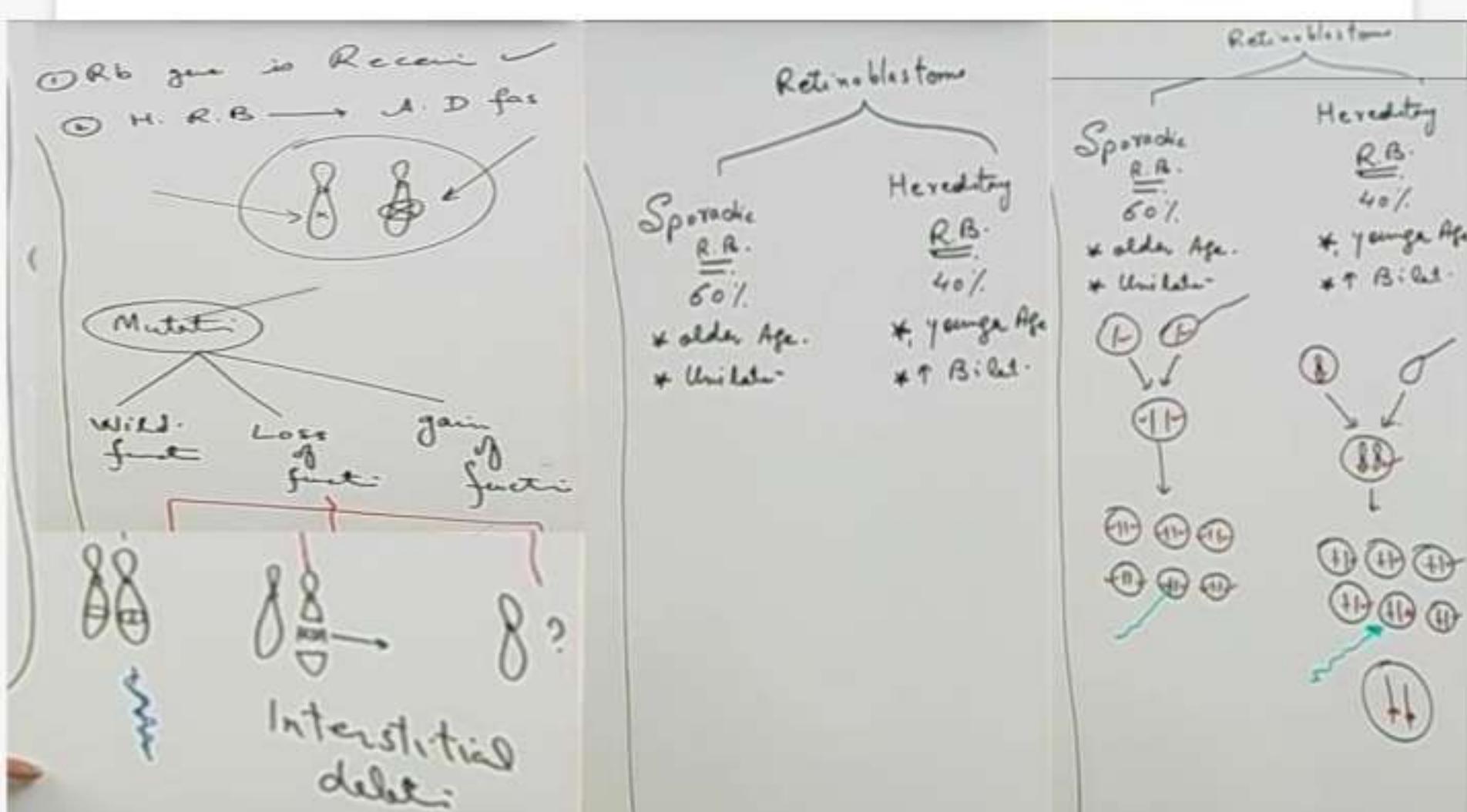


Diagram showing mechanism how P53 gene normally repair DNA damage

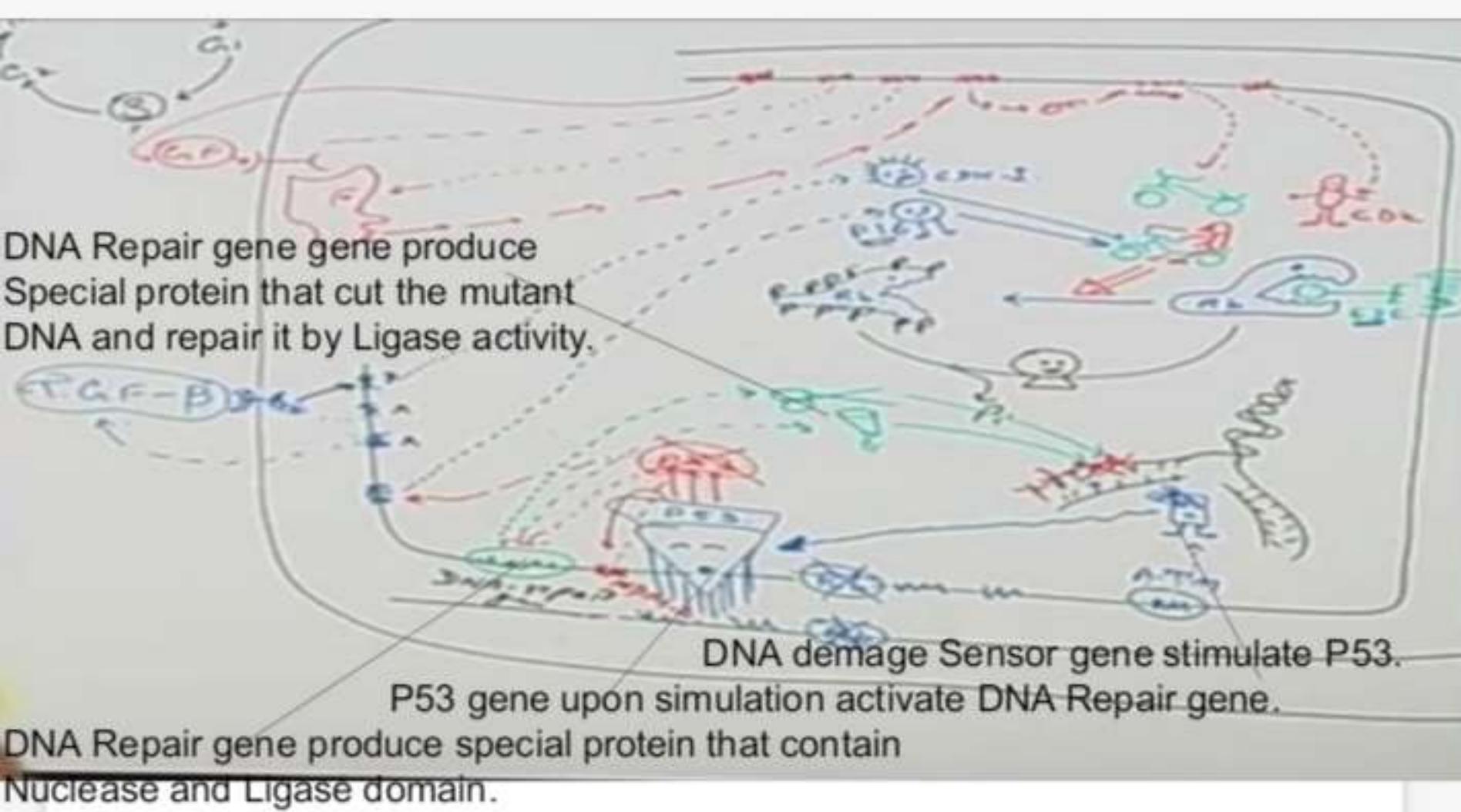


Diagram showing phenomenon of Apoptosis..

Normally Anti-Apoptotic and Pro-apoptotic gene produce Channel stoppers that block the Mitochondrial channels.

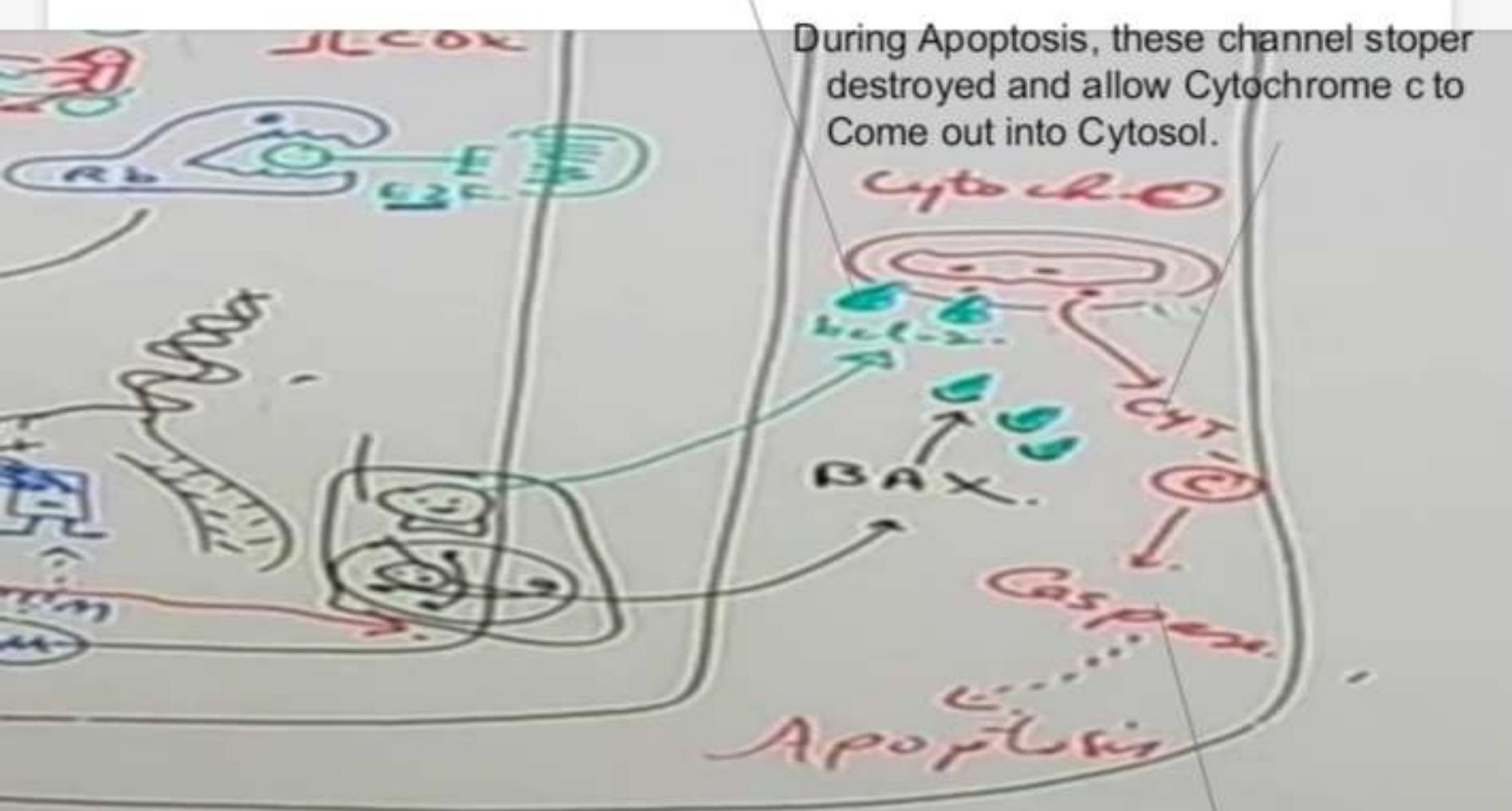
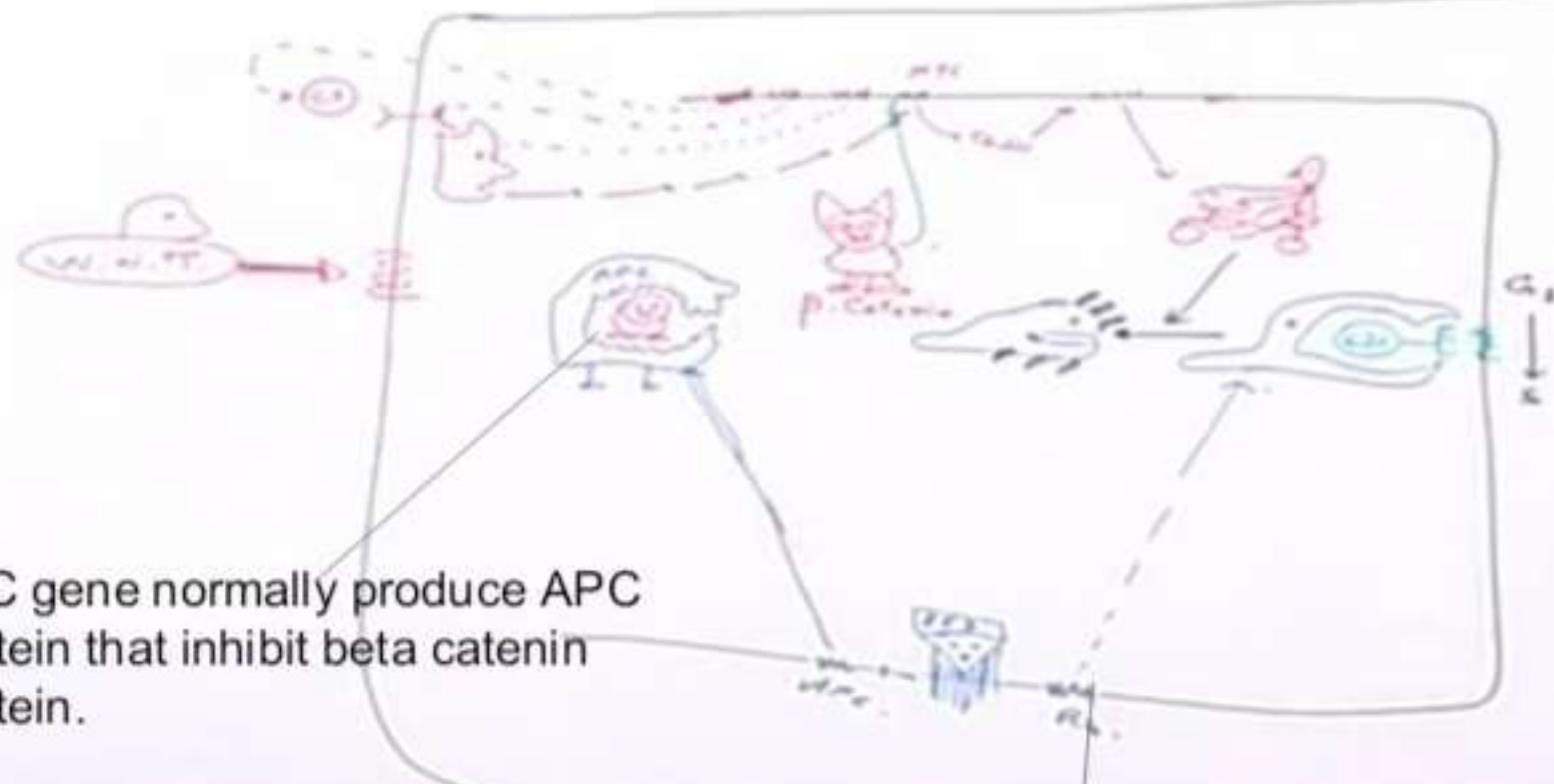
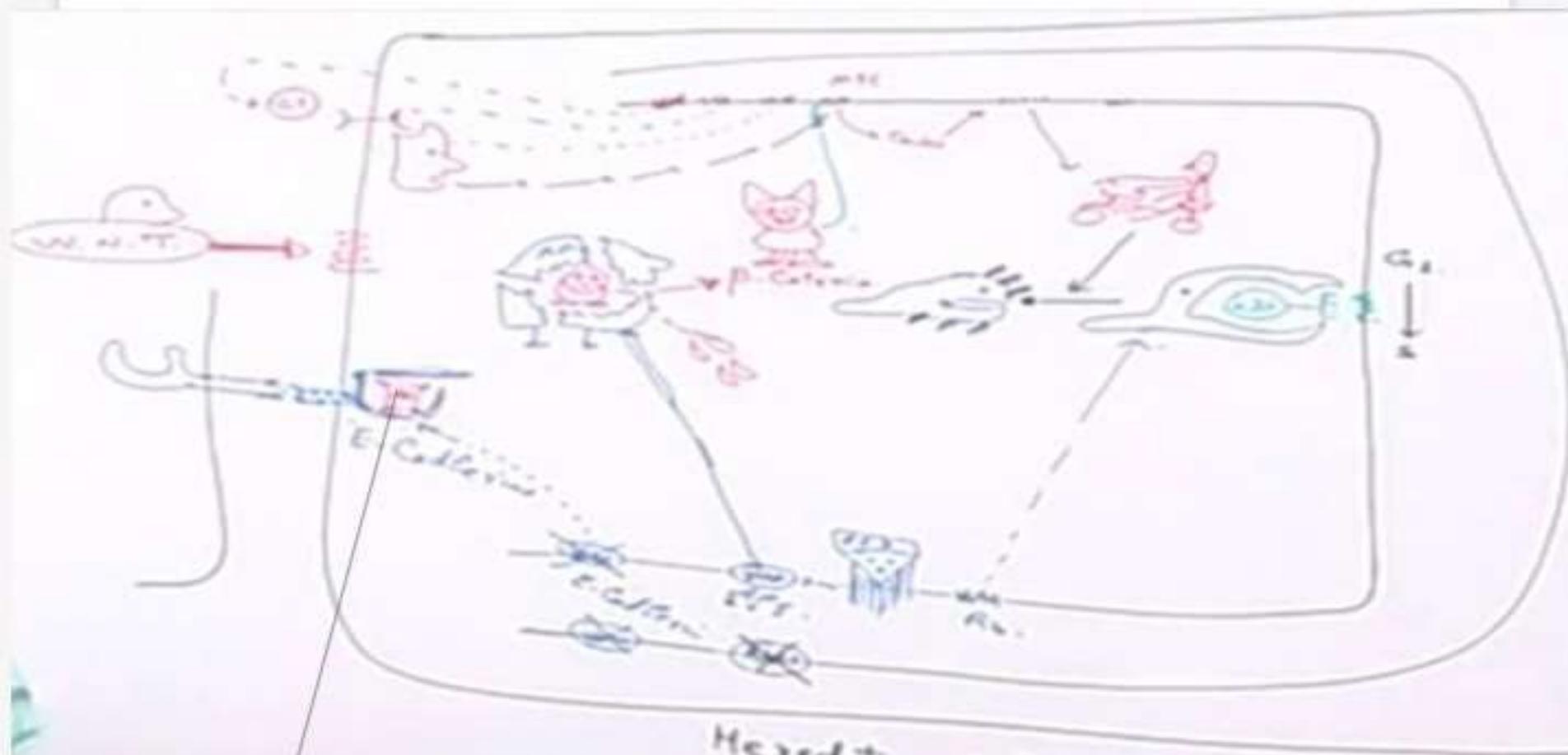


Diagram showing mechanism of action of APC and RB gene and E-Cadherins gene under command of P53 gene..

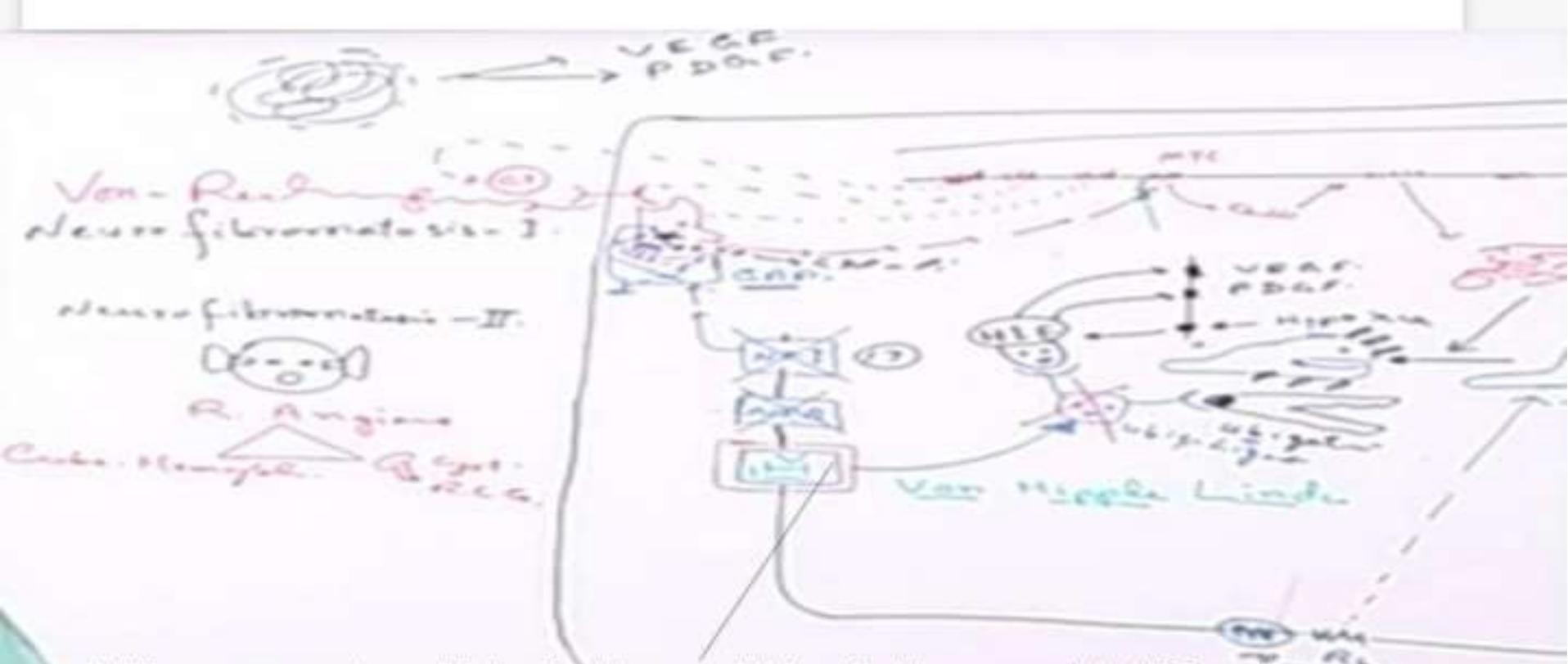
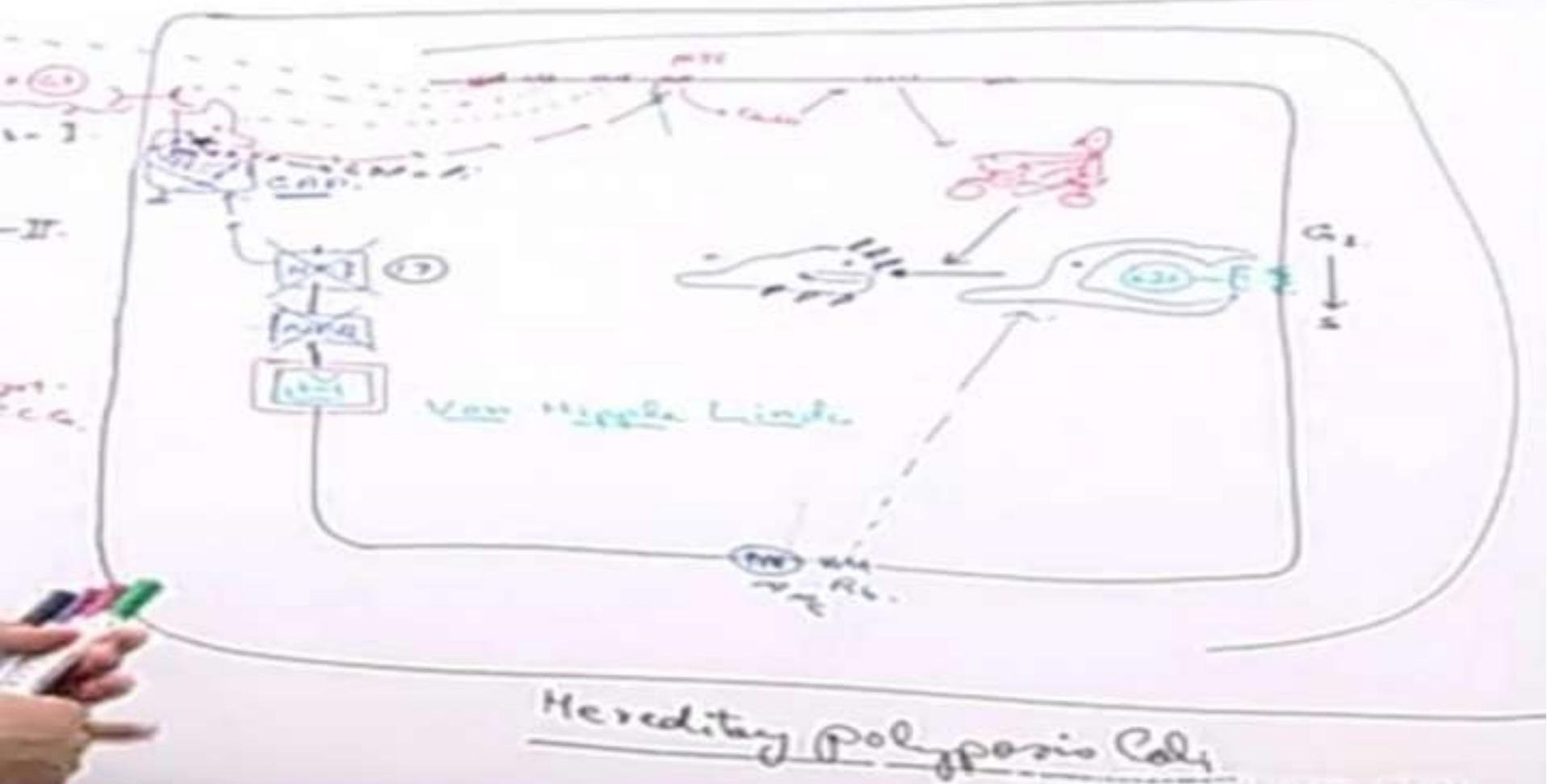


APC gene normally produce APC Protein that inhibit beta catenin Protein.

RB gene normally produce RB protein.

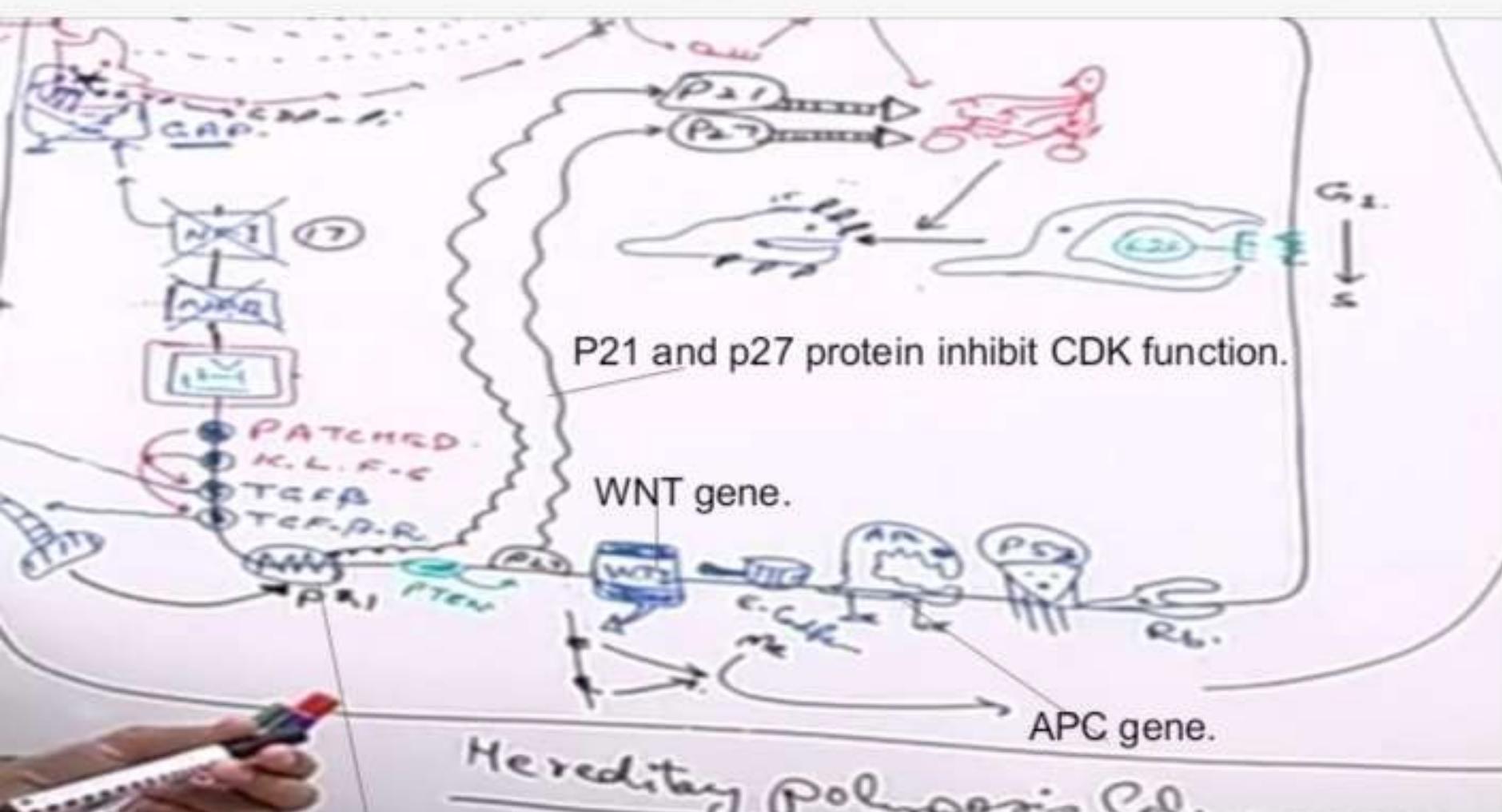


E-Cadherins gene produce E-Cadherins Proteins that attach with cell membrane Catch the Beta catenin.

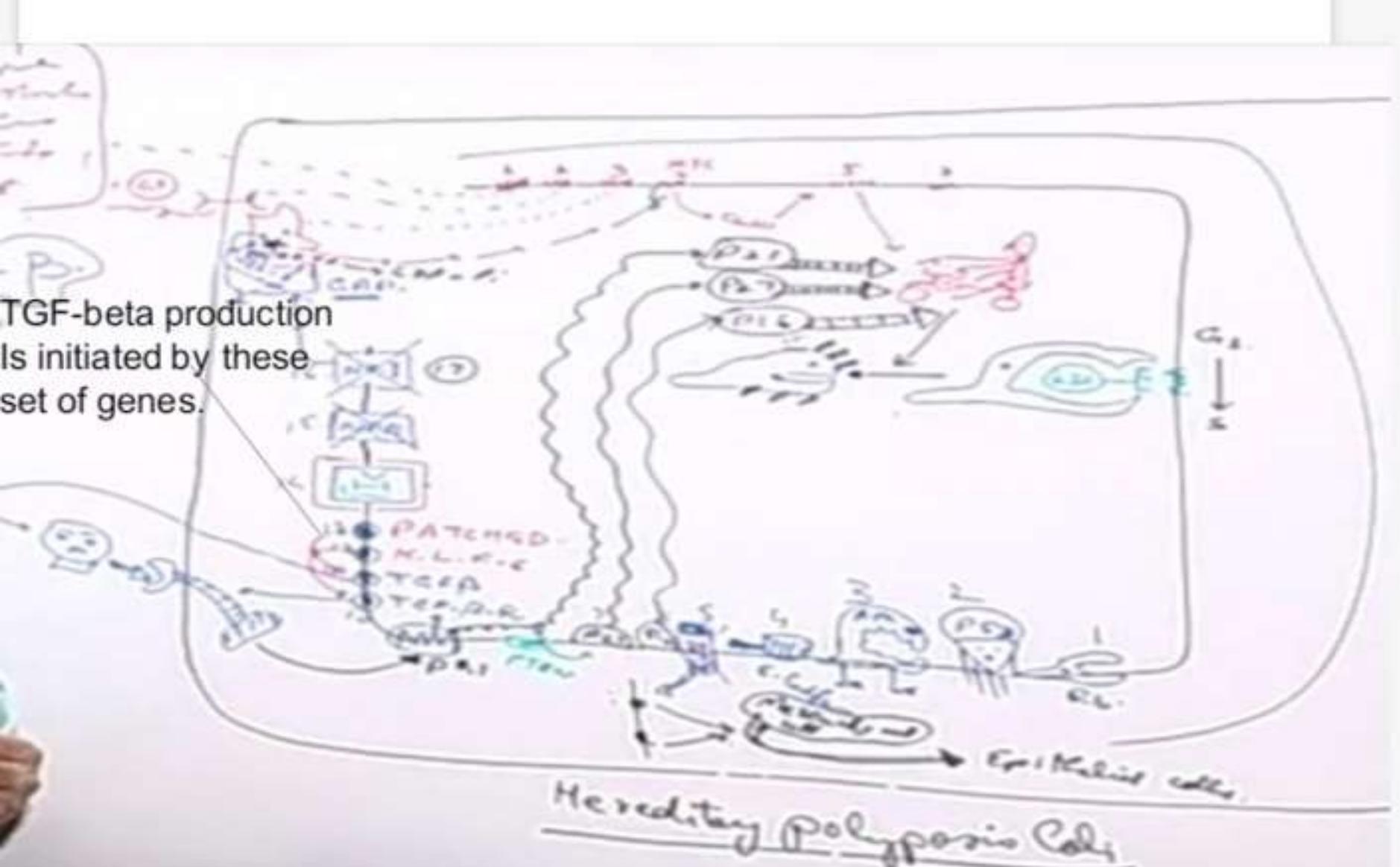


VHL gene produce Ubiquitin Ligase. Ubiquitin Ligase catch HIF and Give it to Ubiquitin so that Ubiquitin destroy HIF.

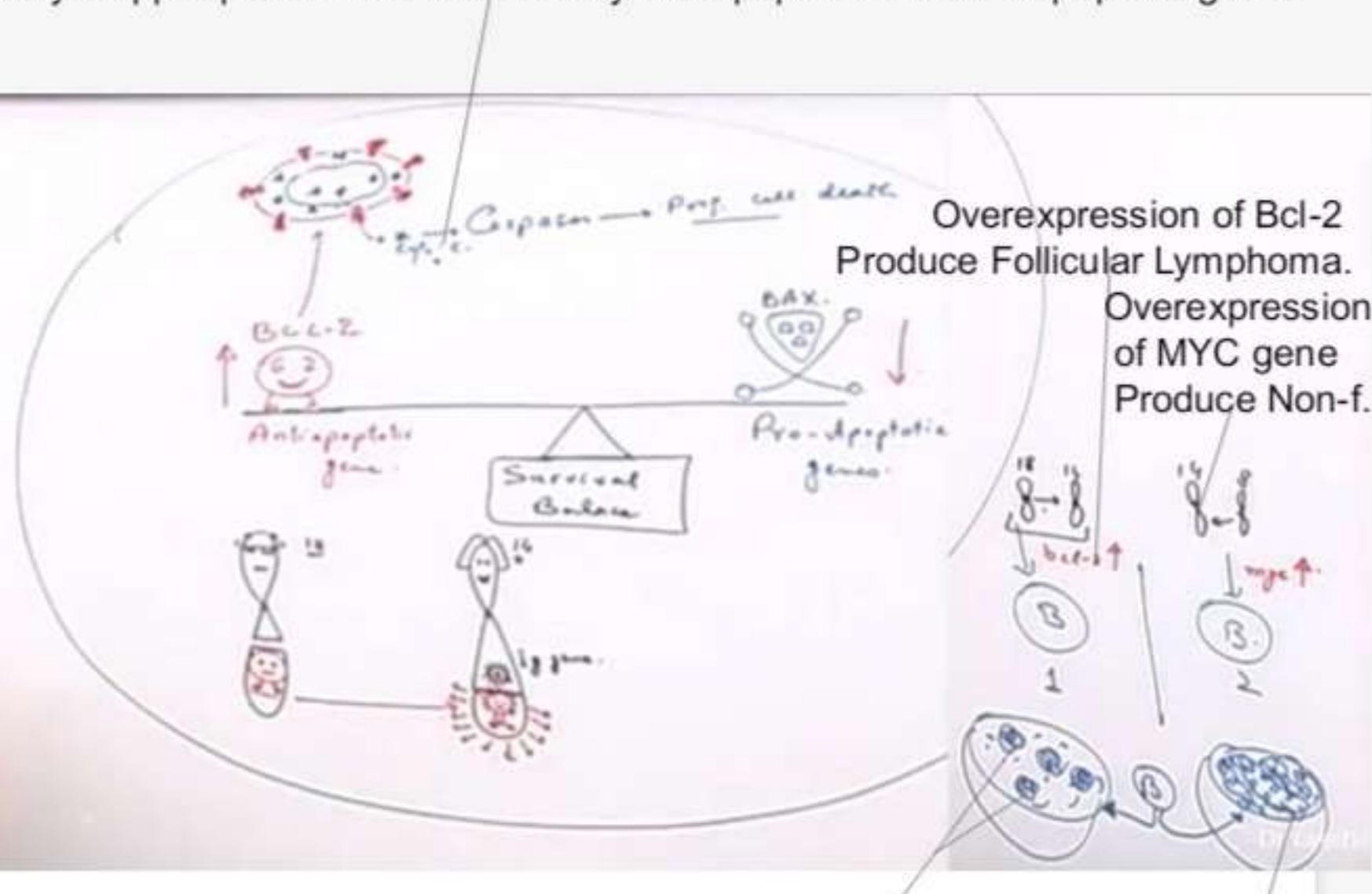
Heredity Polyposis



P21 and p27 gene produce P21 and p27 proteins.

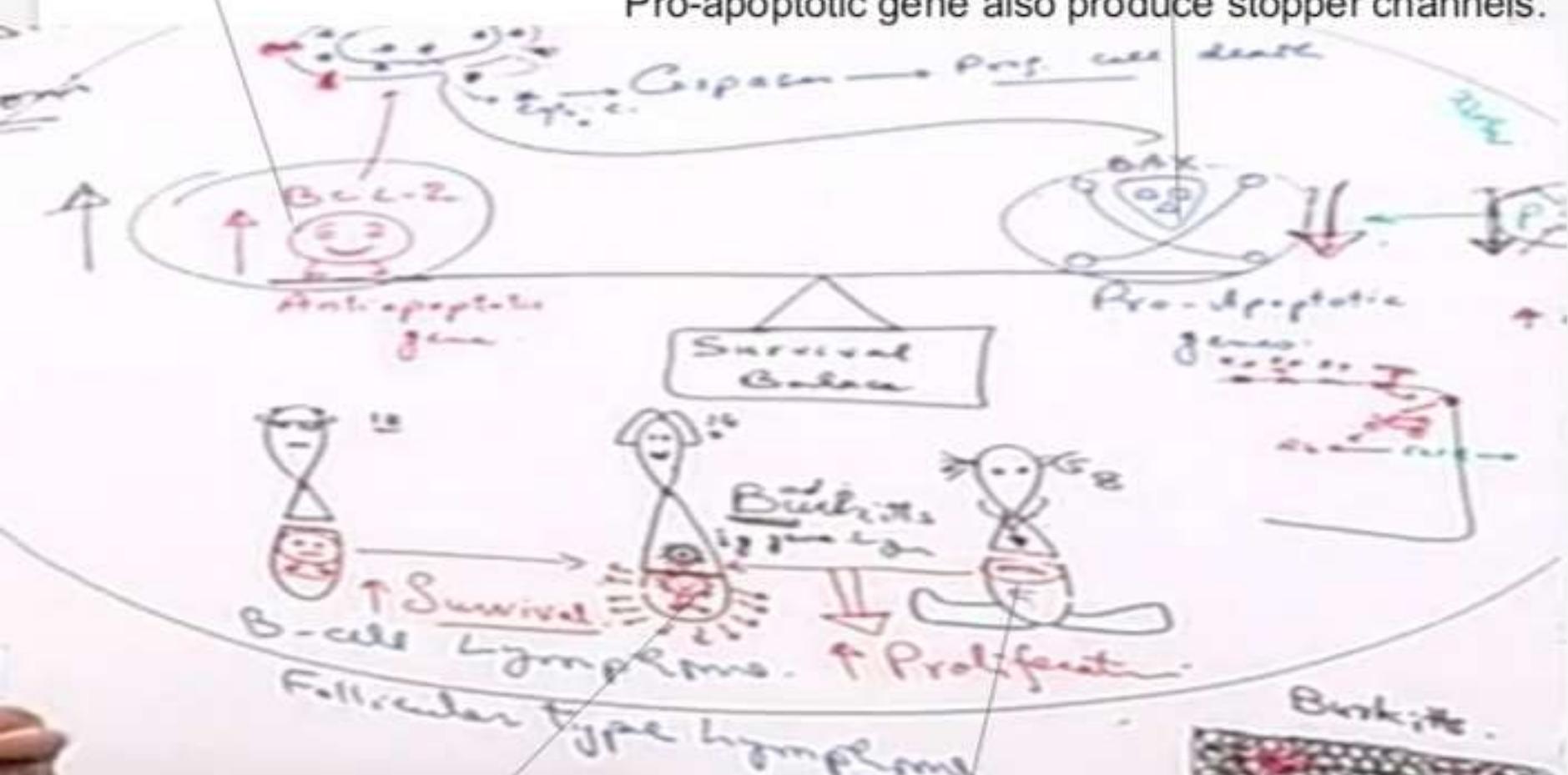


Normally stopper proteins are produced by Pro-apoptotic and Anti-apoptotic gene.



Stimulation of Anti-Apoptotic gene produce Stopper proteins.

Pro-apoptotic gene also produce stopper channels.



Genetic basis of Burkitt's Lymphoma.

Microscopic diagram of Burkitt's L.

MYC gene Overproliferate in Burkitt's Lymphoma.

Diagram showing different DNA Repair Mechanism...

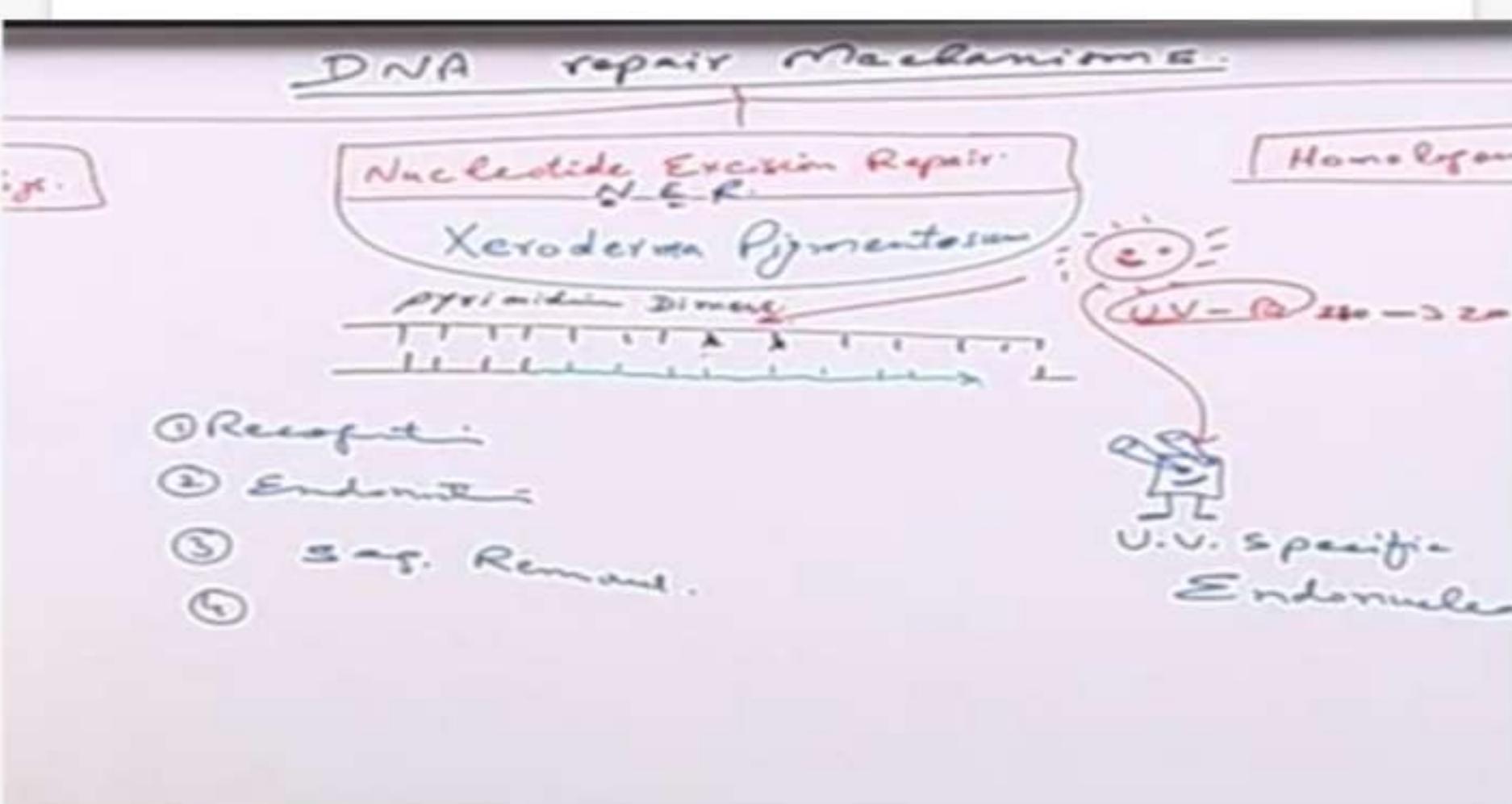
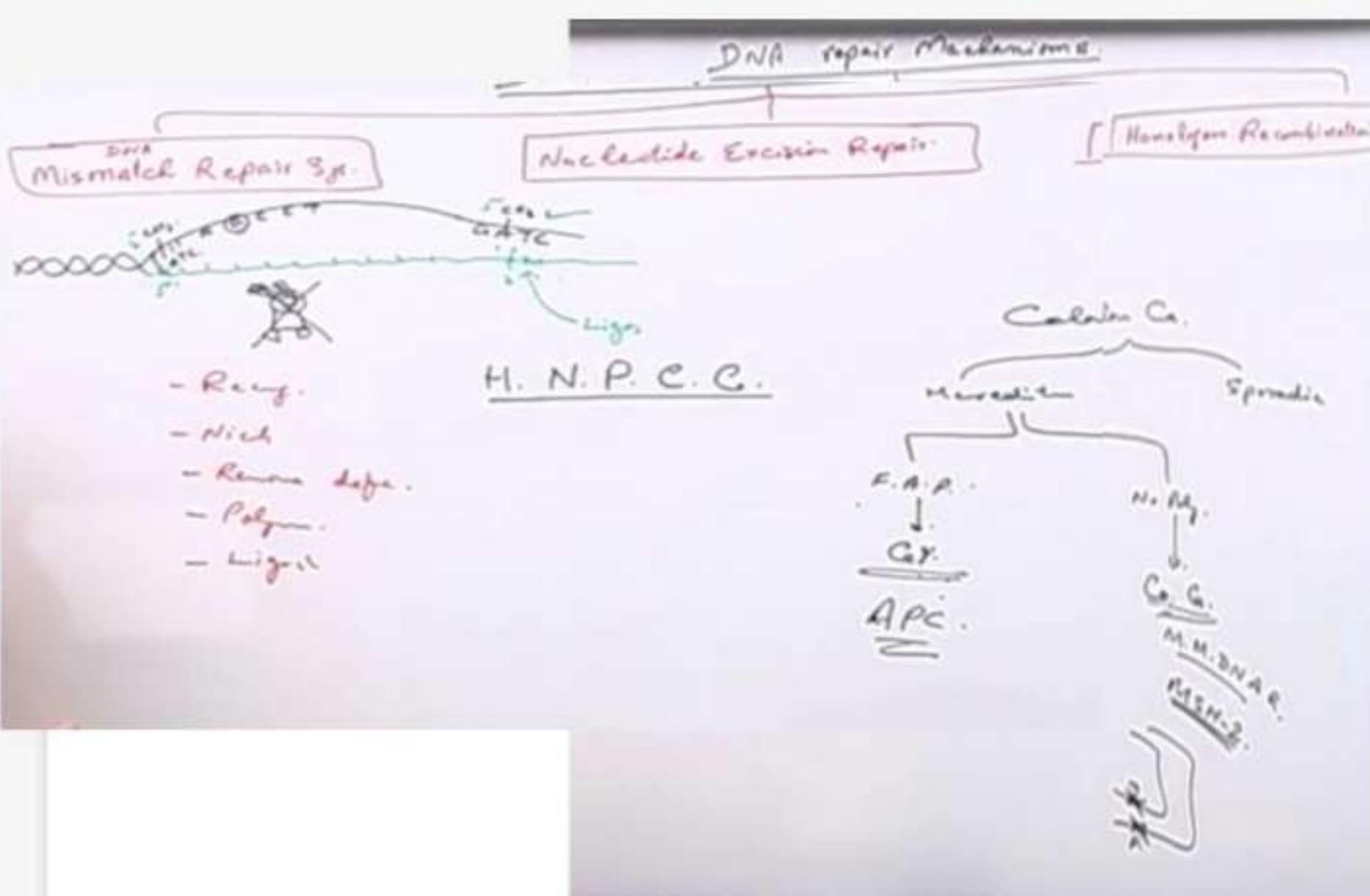
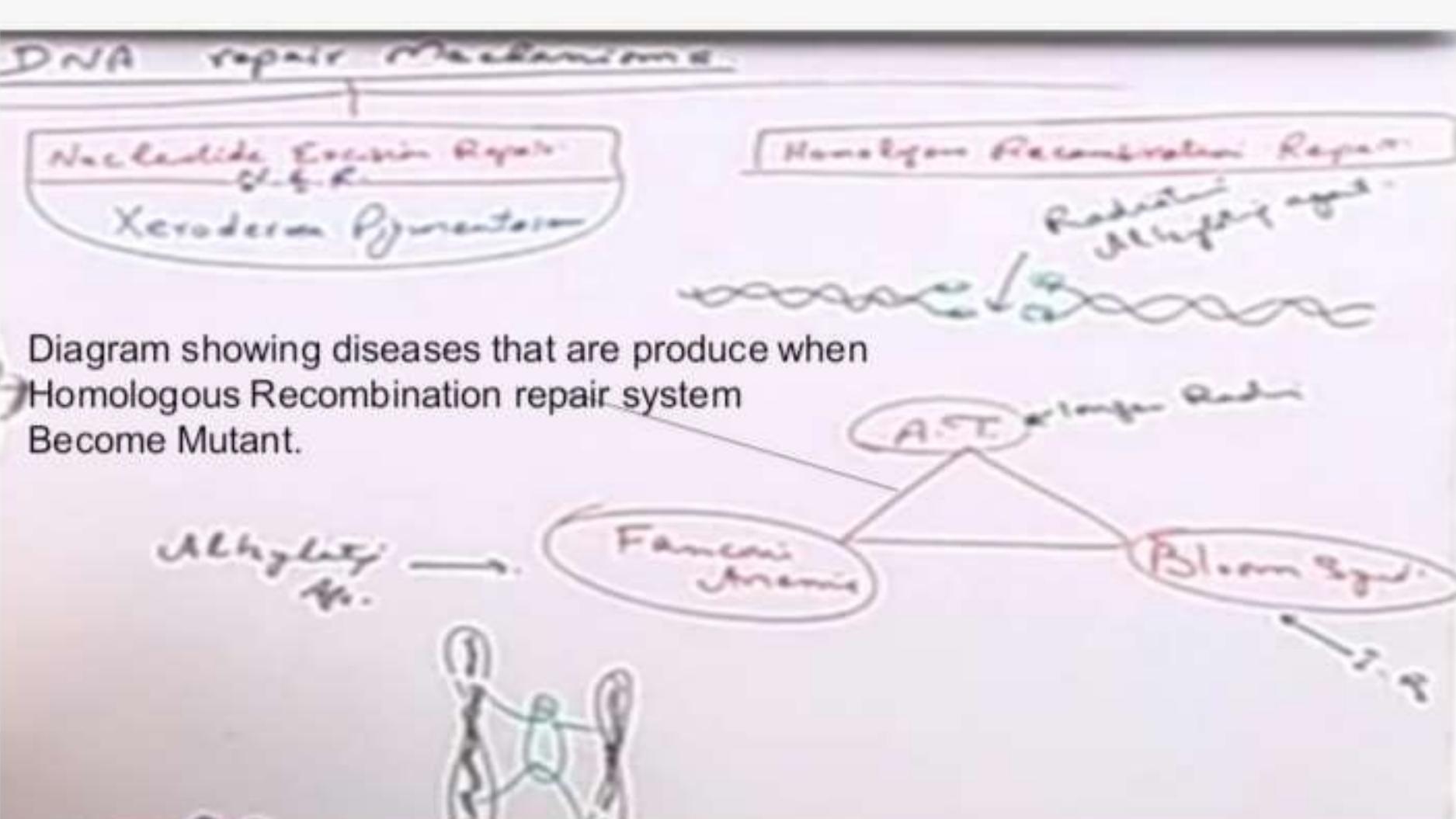
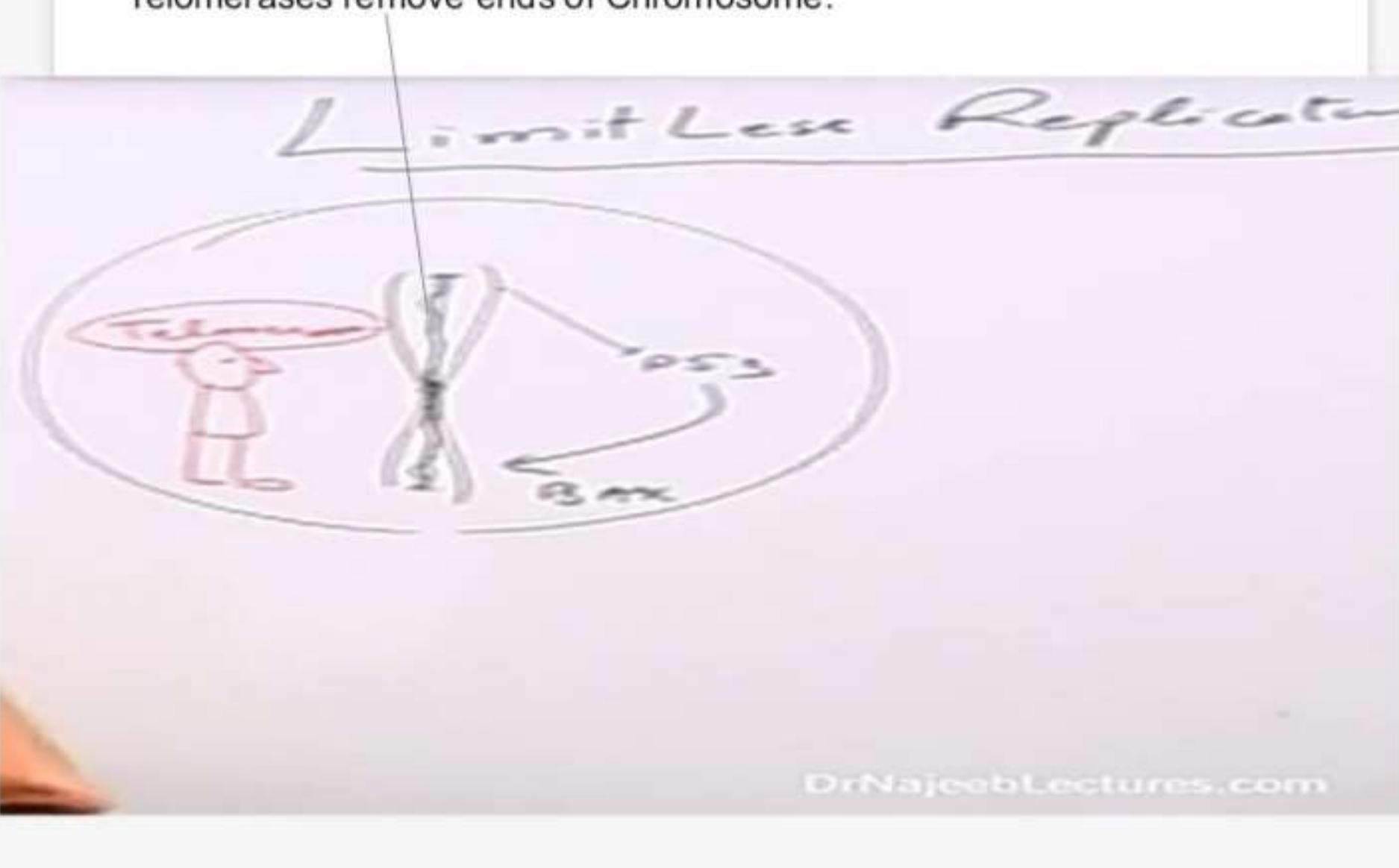


Diagram showing Homologous Recombination Repair system..



Telomerases remove ends of Chromosome.



NACROSIS...

Nacrosis is serious of morphological changes in a Leathley or Irriversibly Injured Cell. Nacrotic Cells can't convert back into normal cell.

Normally As result of of cell Injury, cell death occur either via Apoptosis or Nacrosis.

Q# What are the morphological Changes that Convert injured cells into Nacrotic cell??

Ans :- Morphological changes occur inside the injured cell due to,

1-Denaturatiin of Intracellular structural and functional protein.

2-Enzymatic Digestion of cells by its own enzymes such as Lysozymes etc (Auto-Lysis).

3-Nacrotic cells also attract Neutrophils, Pathogens such as Microbes and Bacteria etc.

These Pathogens and Neutrophils also release df Distructive Enzymes which Further digest the Leathley Injured cells and produce Further morphological Changes. This type of digestion of cell is called as HETEROLYSIS.

4-Hallmark of Nacrosis is that, Plasma membrane of Leathley Injured Cells become disrupted at df levels and allow ICF enzyme to move out of the cell and produce inflammation in surrounding tissue Cells.

5- Apoptosis usually occur in 1 cell or very small Cluster of Cell. WHILE

Nacrosis usually occur in large group of cell.

6- Unlike Nacrotic tissue, Inflammatory Process don't occur around Apoptotic cells.

7- Unlike Nacrotic Tissue, In Apoptotic cells, cell membrane don't Disrupt and don't release ICF enzymes into surrounding tissue and don't produce Inflammation.

Depending upon the Cause of Injury to cell, cell take lot of Hours to convert Itself into Nacrotic cell.

IMPORTANT point is that, Leathley injured cell undergo Nacrosis only when it is a part of living tissue not dead tissue.

Exp# Suppose Some part of Myocardium undergo Ischemia due to Atherosclerotic Lesions. As a result person die due to Tachycardia within 1 to 2 hours. Such person don't show any evidence of Nacrosis Bcz Ischemic cells can't Undergo Nacrosis as person die immediately and Bcz as we know for injured cell to be Nacrotic, cell require lot of hours. So in these Persons, you will see the evidence of atherosclerosis but don't find any Nacrotic cell.

IMPORTANT :-

Hallmark of Myocardial infarction is the high level of CK-MB and calcium binding Troponine in blood.

Both Proteins are present in Myocardium and release into blood when Myocardial cells undergo irreversible Injury.

1# CYTOPLASMIC CHANGE IN NACROTIC CELL:-

1-Denatured Protein bind Eosin more as Compare to Normally Folded Protein. So when cell under go Nacrosis it's protein get denatured and open up so these Proteins bind lot of Eosin and cytoplasm of the cell Become Eosinophilic and look Red. Moreover cell losses Ribosomes which normally Imparts Basophilic characteristics to Cell.

- 2-Cytoplasm of cell show Glassy Appearance due to Loss of Glycogen Granules.
- 3- Df cell Organelles undergo denaturation and Cytoplasm show Moth Eaten Appearance.
- # After Proteolysis of df Organelles, Phospholipid cell membrane of these organelles and df small pieces of Phospholipid membrane of cell Membrane of these Organelles deposit in cytoplasm. These clumps of phospholipids membrane are called MYELIN FIGURES.
- # Macrophages eats up myelin Figures. OR If Myelin figures remain in cytoplasm for long time then they attract Ca bcz Phospholipids are Negatively Charge so Myelin Figures undergo Dystrophic Calcification.
- # ULTRASTRUCTURAL CYTOPLASMIC CHANGES IN NACROTIC CELL :-
- # Plasma membrane of Nacrotic cells Ruptures.
- 1- Mitochondria of Nacrotic cell Swell up
- 2-Small multiple myelin Figures are seen under Electron Microscope.
- 3-Fluffy Amorphous material which show denatured Proteins.
- 2#NUCLEAR CHANGES OCCUR IN NACROTIC CELL:
- The Nuclear changes in necrosis and characteristics of this change are determined by the manner in which its DNA breaks down:
- 1# Karyolysis:- the chromatin of the nucleus fades due to the loss of the DNA by degradation. ...
- 2# Pyknosis:-the nucleus shrinks, and the chromatin condenses.
- 3# Karyorrehxis is the destructive fragmentation of the nucleus of a dying cell whereby its chromatin is distributed irregularly throughout the cytoplasm.

DF TYPES OF NACROSIS :-

1- COAGULATIVE NACROSIS:- Type of Necrosis in which structural and functional Proteins and Enzymes of Necrotic cell undergo degeneration simultaneously after injury. As a result, Injured cell don't Undergo Necrosis by Auto-Lysis Process. Rather when Leukocytes and Neutrophils reach the injured cell they release their enzyme which catalyse the denatured Proteins of injured cell and cells undergo Necrosis. This type of cell destruction is Called as Heterolysis.

Coagulative Necrosis can occur all tissues of the body except CNS.

Swear Hypoxia and Ischemia always produce Coagulative Necrosis in all tissues of the body except CNS. In CNS swear Hypoxia and ischemia produce Liquifactive Necrosis.

Localised area of tissue that undergo coagulative Necrosis is called as Infarction.

2- LIQUIFACTIVE NECROSIS

In Liquifactive necrosis, Structural Proteins die simultaneously But Functional Proteins and Enzymes remain Fully Functional. So in Liquifactive Necrosis cell Undergo,

1-Auto-Lysis and

2-Heterolysis.

Liquifactive necrosis Produce Pyogenic inflammation in all tissues of the except CNS bcz Liquifactive necrosis in CNS is produced due to Swear ischemia and Hypoxia.

Neutrophils reach the injured cell 1st as compare to Macrophage, bcz they are abundantly Present and are Faster as compare to Macrophages

Abscess is an example of Pyogenic Liquifactive Necrosis.

Diagram showing Necrosis and their Causes..

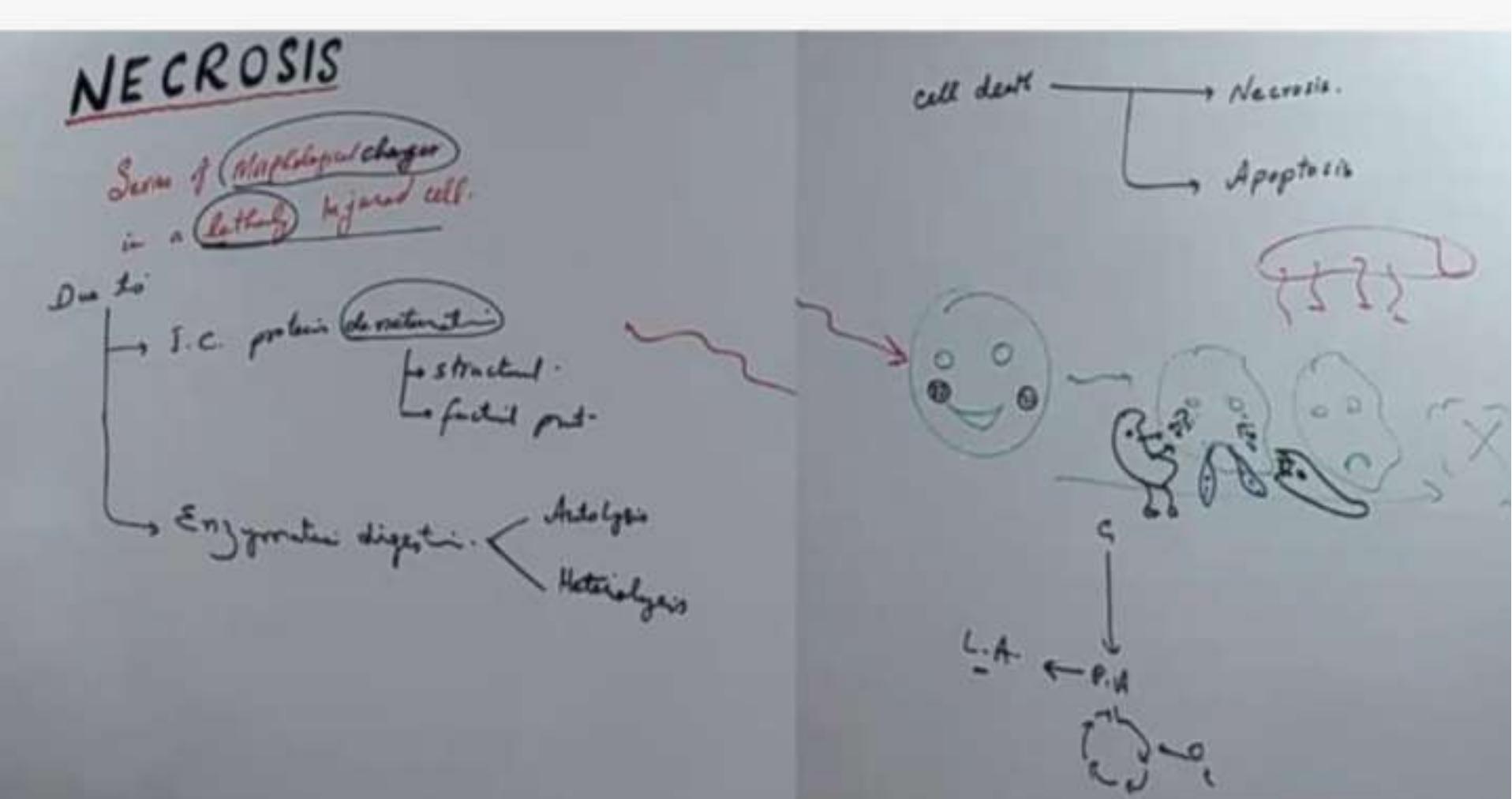


Diagram showing Causes of Necrosis.

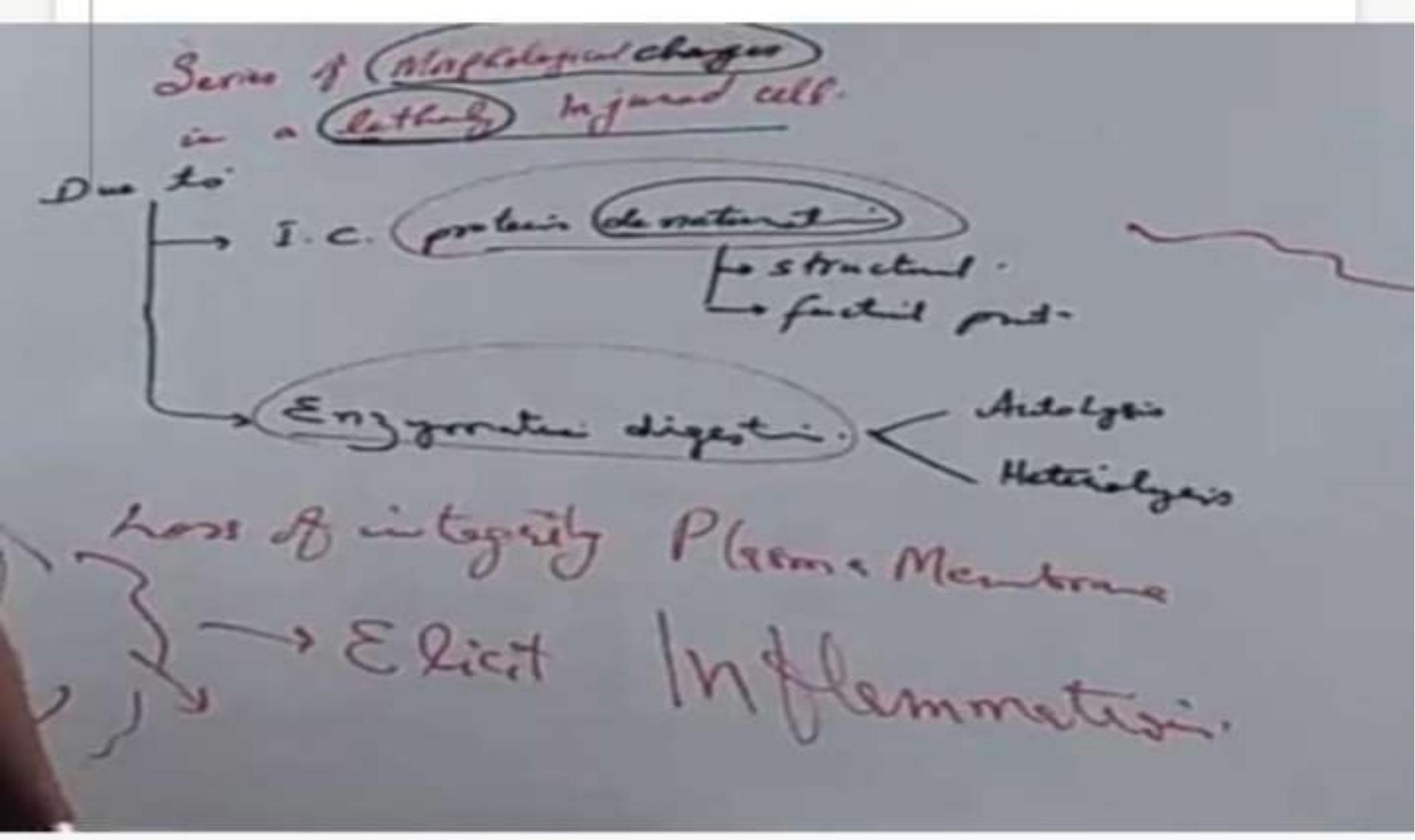


Diagram showing morphological changes that occur in Cytosol of Nacrotic cell...

Diagram showing Df morphological changes occur during Nacrotic cell.

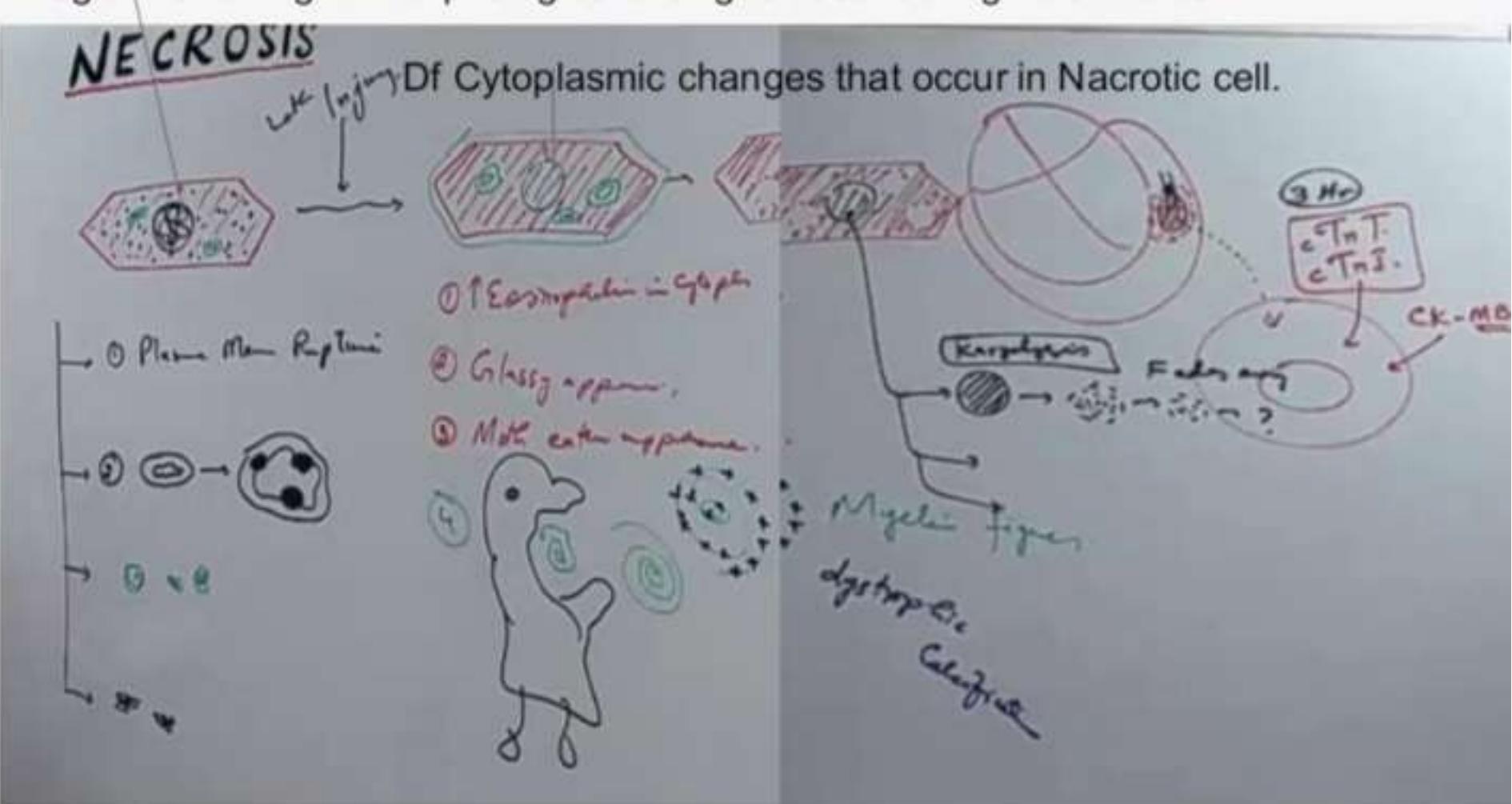


Diagram showing Nuclear changes that occur in Nacrotic cell...

Df Nuclear changes that occur in Nacrotic cell during Necrosis

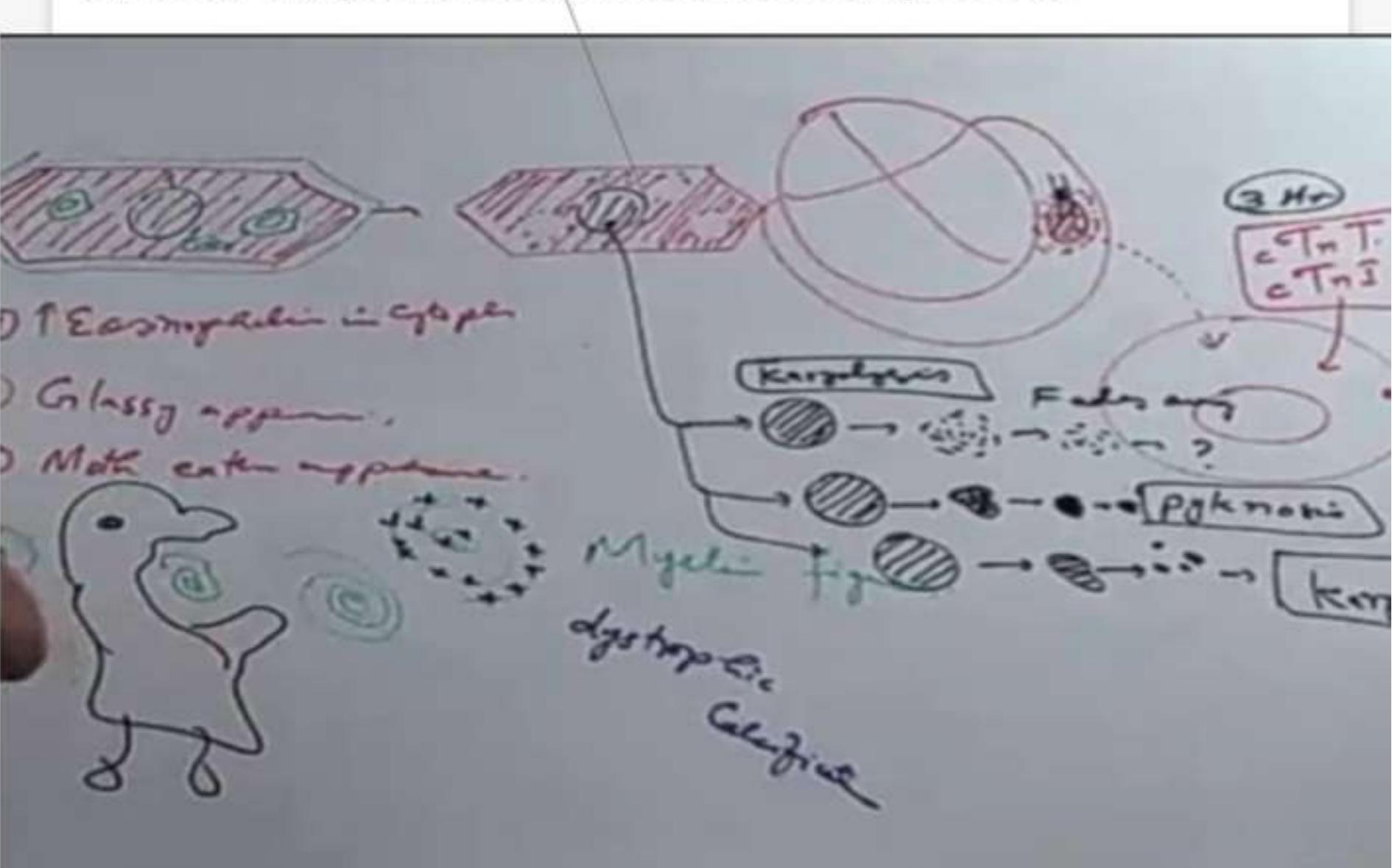


Diagram telling features of Coagulative Necrosis...

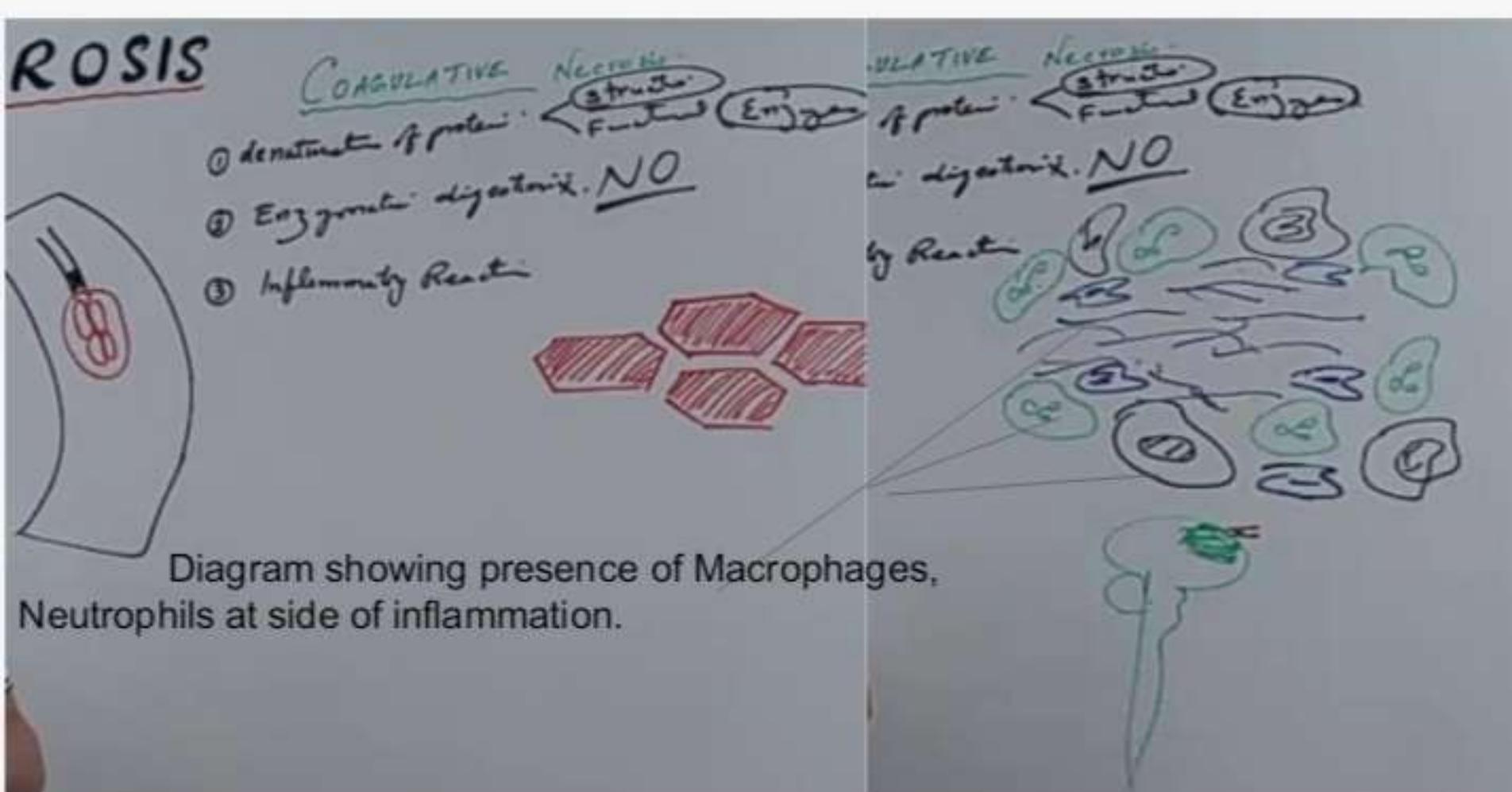


Diagram telling features of Liquefactive Necrosis..

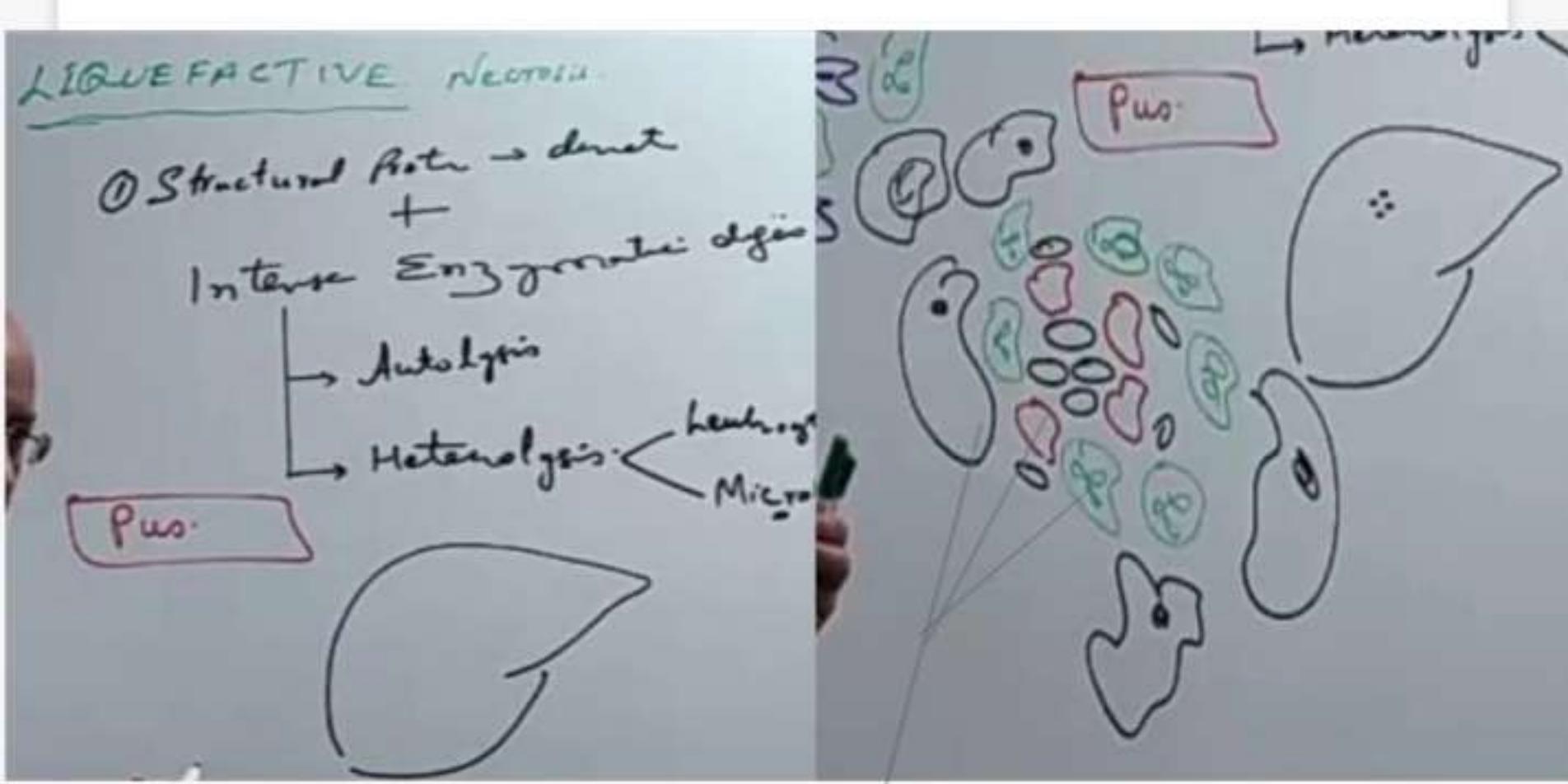
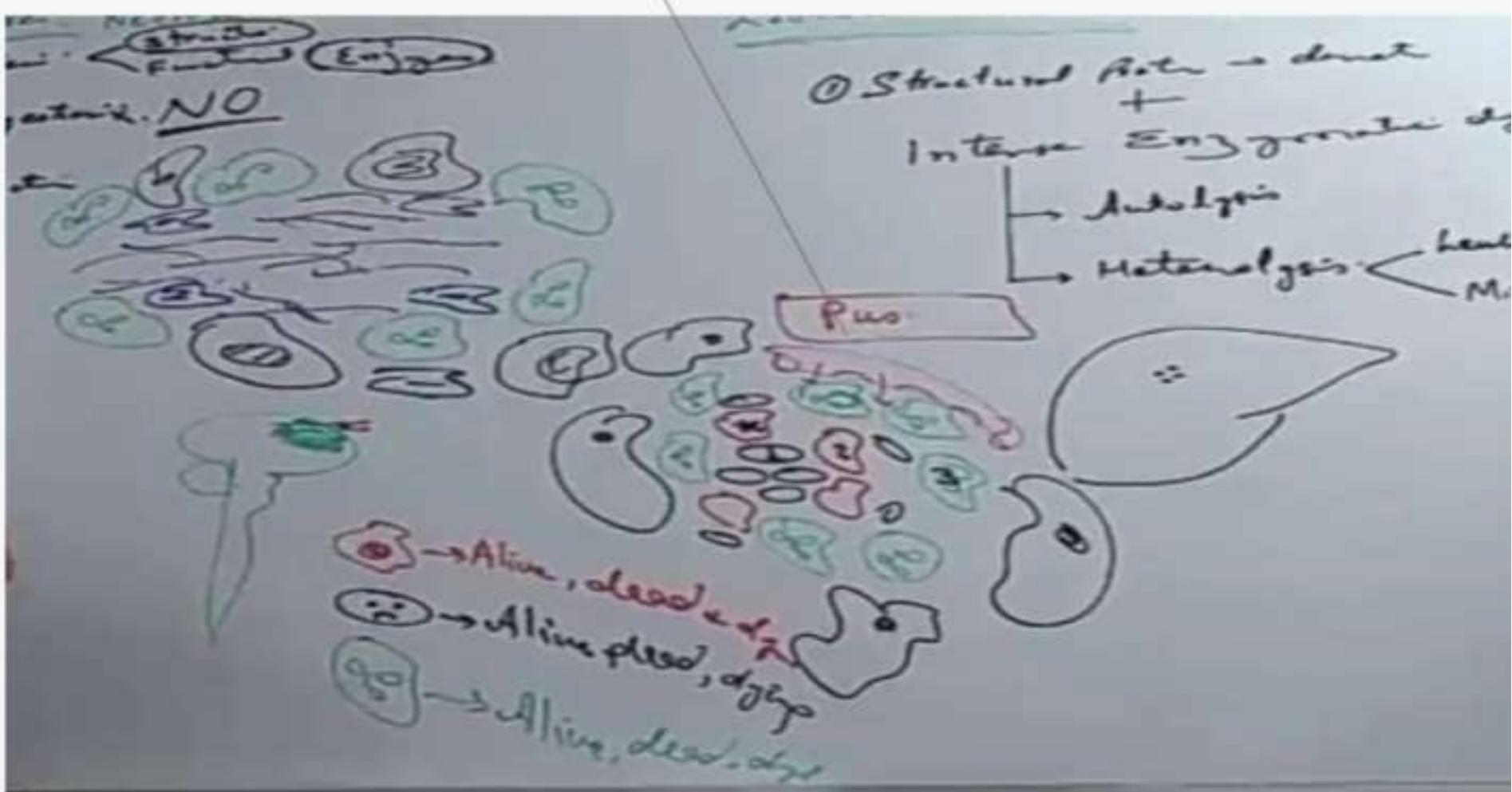


Diagram showing df contents of Pus such as Macrophages Neutrophils, dead bacteria etc

Diagram telling about df contents of Pus.



Intense Enzymatic de

→ Autolysis

→ Heterolysis ← Leuk M.

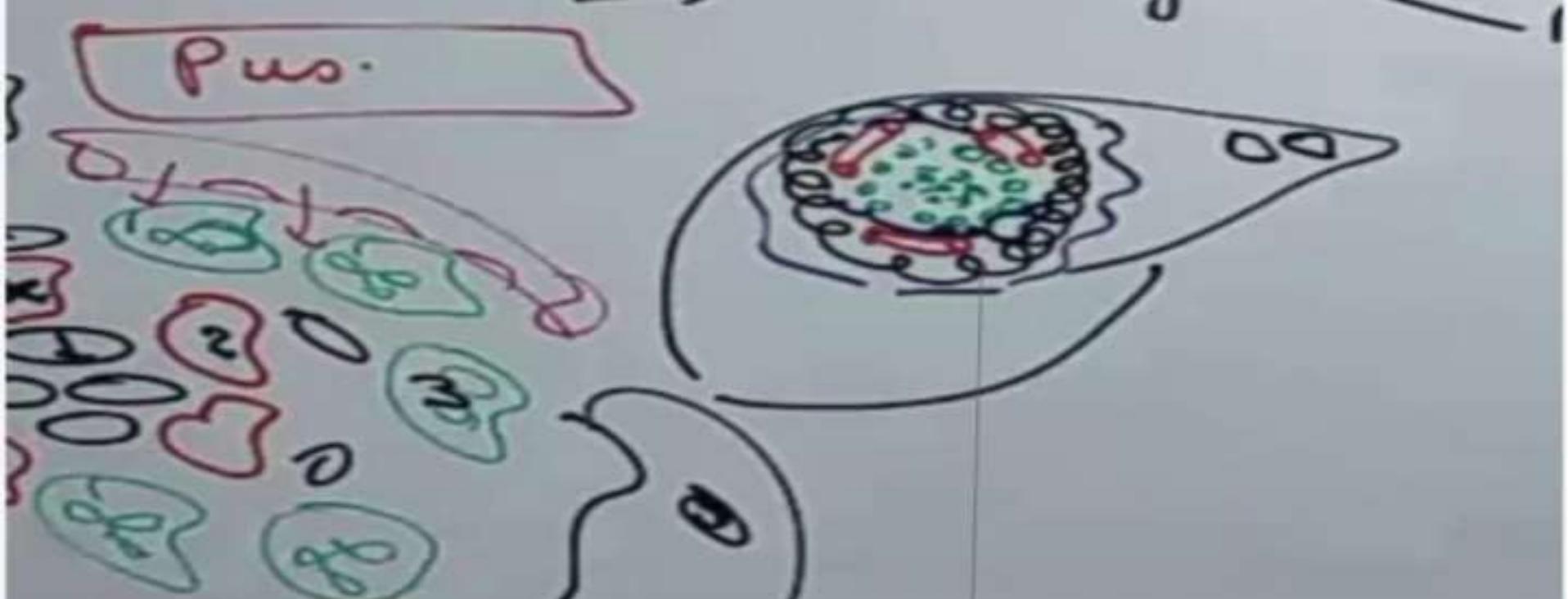


Diagram showing Necrotic cell of Liver.

APOPTOSIS

1# Necrosis always occur Pathologically While Apoptosis mostly occur Physiologically but sometimes also Occur Pathologically.

2# Necrosis is the murder of Cell WHILE Apoptosis is the suicide of Cell.

3# Necrotic cell Swell up While Apoptotic Cell get Shrinken.

4# In Necrosis, cell membrane of cell get injured as result intracellular enzyme leak out into surroundings healthy tissues. These Enzymes disrupt the surrounding tissues also and produce responses in form of Inflammation. But In Apoptosis, Intra-Cellular enzymes are pack into phospholipid membranes and make a small Pack. These small packs are called as Apoptotic Bodies. These Apoptotic bodies that contain intracellular content of Apoptotic cells are eaten up by Macrophages. So in Apoptosis, Intra-cellular enzymes don't freely enter into surrounding tissues and don't produce any damage to surrounding tissue so Inflammation is not produced in Apoptosis.

Q# Why cells undergo Apoptosis and what are its Importance?? With Example.

Ans:- Physiologically Apoptosis Occur,

1# During Embryogenesis many cells undergo Apoptosis.

2# Hormone dependent cells as result of withdrawal of their specific hormone these cells also undergo Apoptosis. Exp# Many Milk producing cells in female breast undergo Apoptosis when blood level of prolactin decreases during Non-breastfeeding Phase.

3# Normally, Apoptosis of Autoreactive T cells also occur in Thymus during Maturation of T cells.

4# Excess cells in Bone marrow Normally undergo Apoptosis.

IMPORTANT :-

1-Large component of Stools consist of, Necrotic cells of GIT Lining and Dead bacteria and Microbes of GIT. With that,

2-Stools also consist of Residues of food Substance.

EXAMPLES OF PATHOLOGICAL APOPTOSIS :-

1# When cell's genetic material undergo damage so severely as a result of radiation, virus etc that it Can't be Repaired then cells Stimulate Special Apoptotic genes such as P53 gene and force cell to Commit Suicide.

2# In Viral hepatitis/Hepatitis B, virus force Hepatocytes to commit Suicide is an example of Pathological Apoptosis.

Other Examples of Pathological Apoptosis.

Q# Molecular program in the Cell which are responsible for Apoptosis

Ans :- There are 2 molecular Pathways for Apoptosis.

1-Extrinsic pathway:-

As we know that, Cellular Death receptors are present on every cell. These death receptors include FAS or Tumor Necrotic Factor Receptor(TNF-R) etc.

Death induce molecule include FAS-Ligand etc.

EXTRINSIC PATHWAY are Initiated by interaction of Ligands and receptors on target Cell. Exp # FAS molecules interact with Fas receptor and in Initiates extrinsic pathway which is explain Below,

PATHWAY :-

1-When death induce molecules such as FAS ligands bind With death receptors on Cell. Special Intracellular adopter Proteins bind with intracellular domain of death receptors and become Active.

When 1 death molecules bind with its receptor other death receptors also migrate towards the Activated death Receptor. and make a group. So Polymerization of death receptors occur over the cell Membrane.

2-Death domain of Adopter Protein interact with Procaspsases and convert into Active Caspases. These are called as initiator Caspases such as Caspases-8.
3-Initiator Caspases Further Initiate Special Proteins called as **EXECUTIONAL CASPASES** such as Caspases-3,6,7.

4- Executional Caspases digest the Structural and Supportive Proteins of cell. Moreover, Executional Caspases Activate DNases.

5-Active DNases cut the DNA bw 2 DNA Nucleosomes. Such type of activity is called as Internucleosomal break down of DNA.

6-Now after destruction of genetic material and Proteins, cells membrane of Apoptotic cells bulges out at multiple points and make a Small membranal Packs that contain Destructive Protein and genetic materials. Such small Packs are called as **APOPTOTIC BODES**.

7-These Apoptotic bodies are Eaten by Macrophage

POINTS :-

1# Adopter Proteins are capable of simulating Very special Proteolytic Enzyme.

2# Normally when Caspases enzymes are present in Inactive Form. This enzyme is called as Pro- Enzyme or Procaspsases Enzymes. These are Cysteine containing Aspartate Specific Enzyme. Means these Proteolytic Enzymes Contain Cysteine Amino and Cut the protein by attacking on their aspartate Amino acid. These Enzymes as group are called as CASPASES. ("C" for Cysteine, "ASP" for Aspartate, "ASE" for Proteases).

CASPASES are the group of Proteolytic enzymes that Contain Cystine in their active site and cut target Amino acid chain at Aspartate.

In Apoptosis, Some CASPASES are Initiated at initial stage. These Enzymes are called as initiator CASPASES and some Caspases are Initiated during Late stages of Apoptosis. These Caspases are called as Executional CASPASES.

2-INSTRINSIC PATHWAY :-

Intrinsic pathway is regulated by Apoptotic gene. Apoptosis gene include,

- 1- Anti-Apoptotic genes such as Bcl-2, Bcl-x etc.
- 2- Pro-apoptotic Genes such as Bad, BAX, Bak etc.

Mitochondria contain Cytochrome C and AIF (Apoptosis Induce factors) If they enter into Cytoplasm they activate Apoptosis of Cell. NOW

1# Normally When growth Factor, Hormone or cell survival molecules bind with cells they constantly Stimulate the Anti-Apoptotic genes (Prolife gene) and Pro-apoptotic (Prodeath) Genes.

Anti-Apoptotic gene along with Pro-apoptotic gene make Homomeric or Heteromeric Proteins Dimers and fuse these Dimers on special channels of mitochondria and block these Channels so that mitochondrial toxic molecules such as AIF, Cytochrome C etc. don't enter into Cytoplasm.

2# But when growth factors and other Proteins are not stimulating cells. Then Anti-Apoptotic gene become off and don't make Dimers. As a result Pro-apoptotic gene make False protein Dimers which don't block the Mitochondrial channels Properly.

So as result, Cytochrome c enter into Cytoplasm and Stimulate initiator Caspases. While AIF enter into Cytoplasm and destroy Apoptosis inhibitory Proteins and lead cells towards Apoptosis.

Q# How T Cytotoxic cells Induce Apoptosis in injured Cell??

Ans:- MHC-2 is a protein which express on Cell only when virus is present and Proliferating inside cell.

TCR(T Cytotoxic receptors) are CD8 receptors of Cytotoxic T cells. Cytotoxic T cells bind with MHC-2 Proteins through TCR. After binding with MHC-2, Cytotoxic T cells activate Its Granzyme. Granzymes enter into viral infected cells and activate Executional Caspases which finally do Apoptosis of Cell.

After 20 minutes of Activation of P53 gene, P53 gene automatically Inactive itself if there is no Further mutation present in DNA.

Diagram showing df conditions when physiological Apoptosis occur in body.

Df types of cell death.



Diagram showing df causes that severely damage or injured the cells.

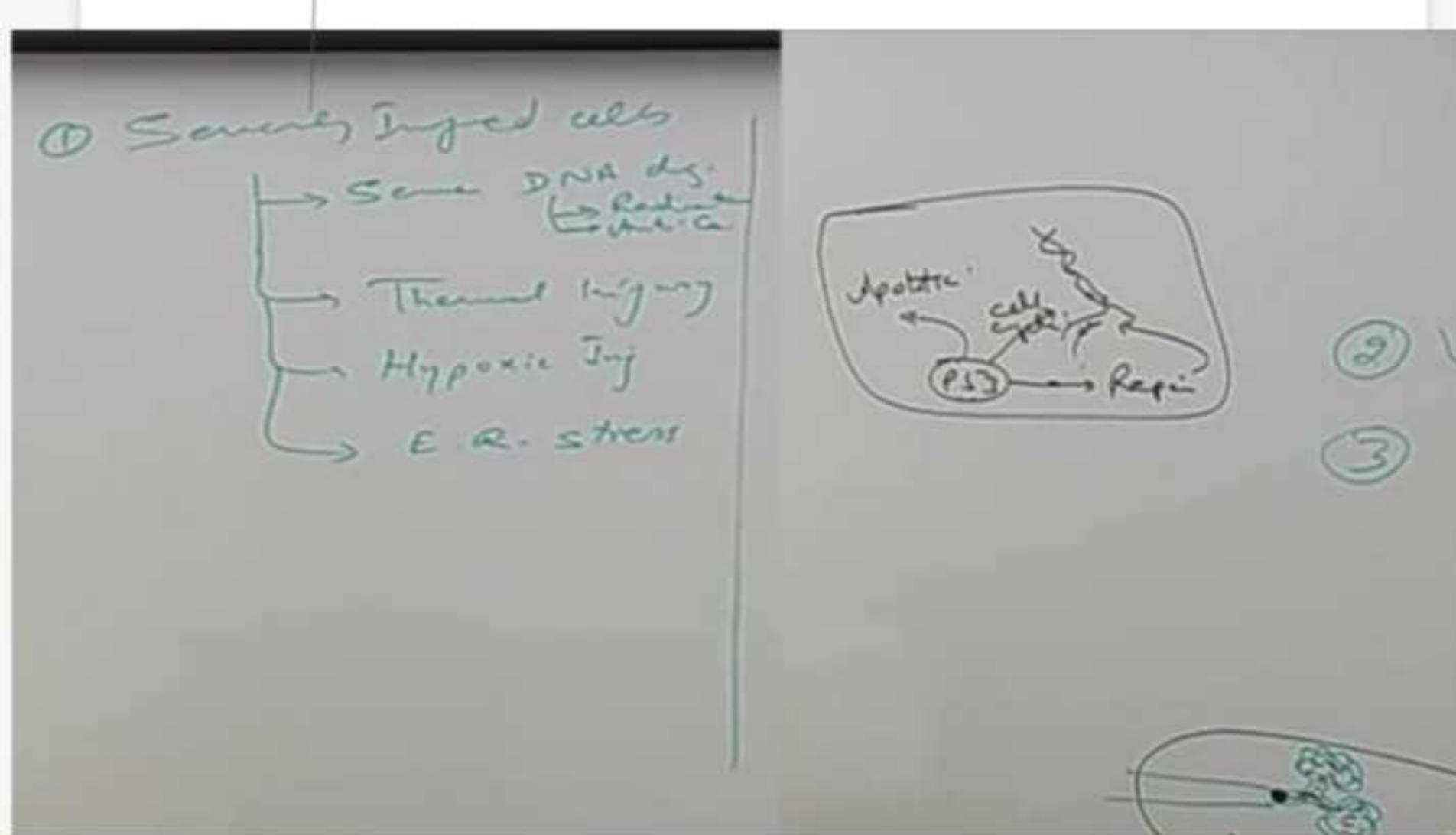
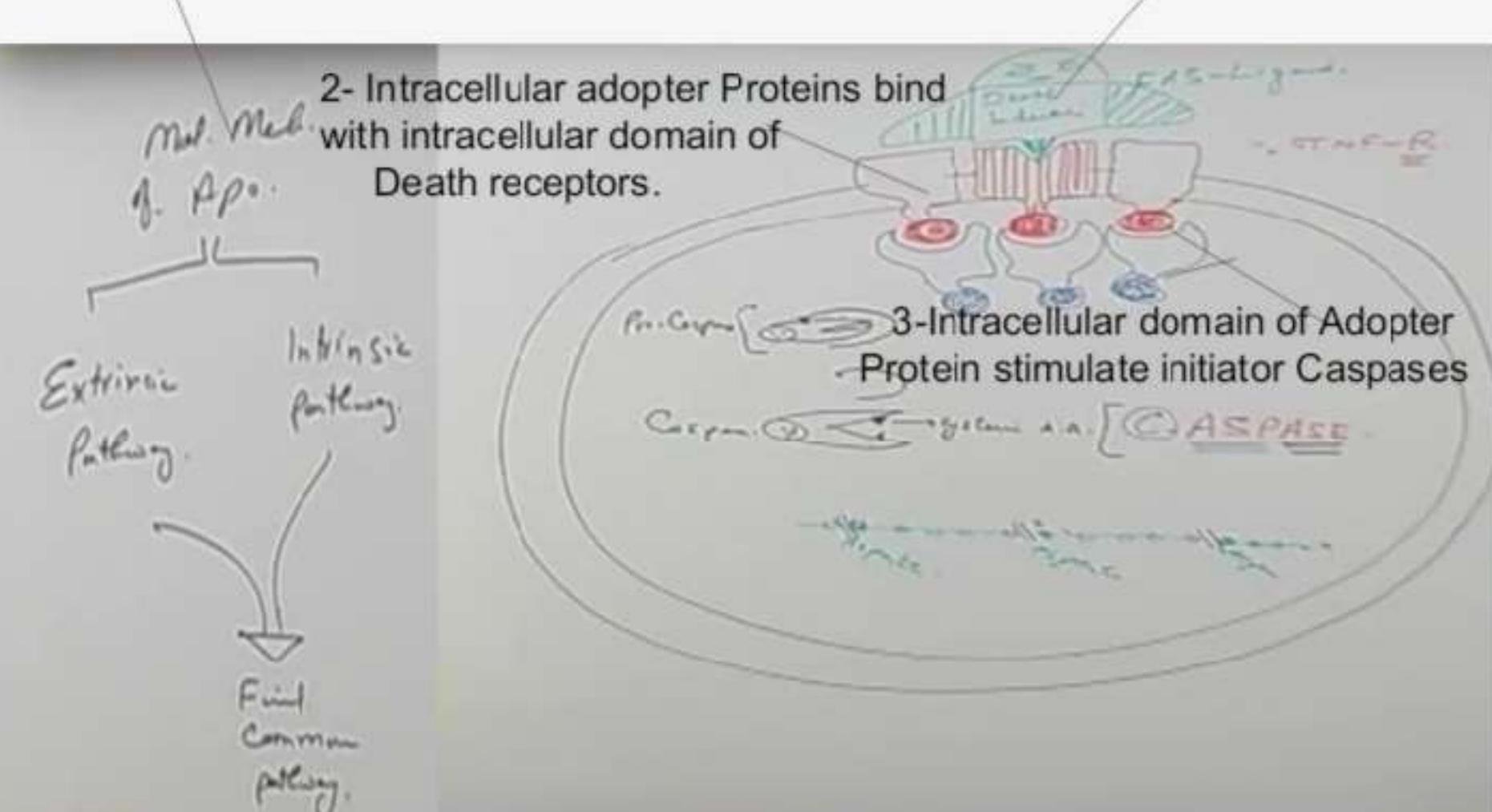


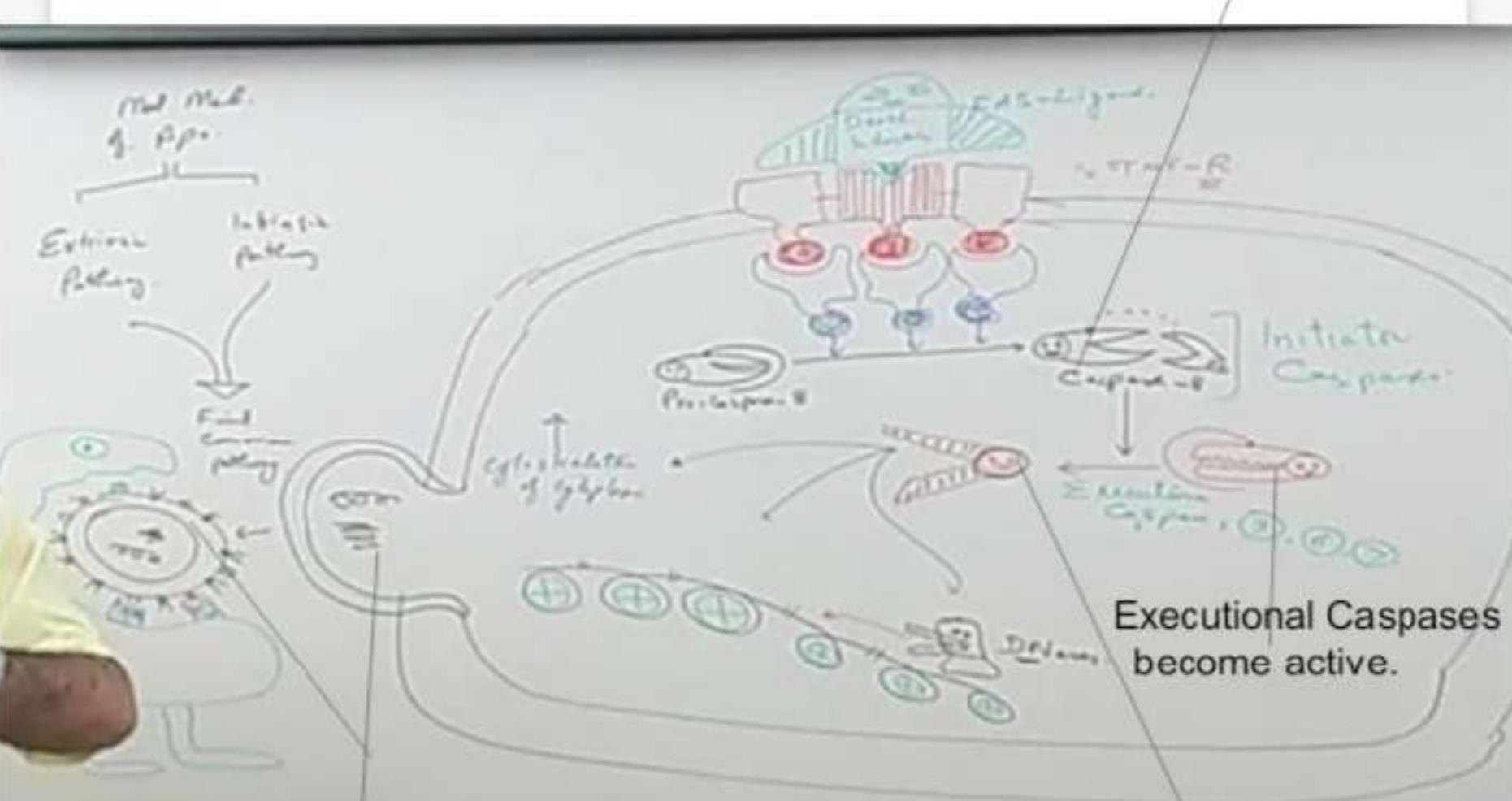
Diagram showing Molecular Intrinsic pathway or Mechanism of Apoptosis...

Molecular mechanisms of Apoptosis.

1-Fas molecule bind with Fas receptor(death recep)



4- Initiator Caspases Further stimulate Executional Caspases.



6-Cytosolic metabolites are pack into the

Apoptotic bodies and Come out of cell.

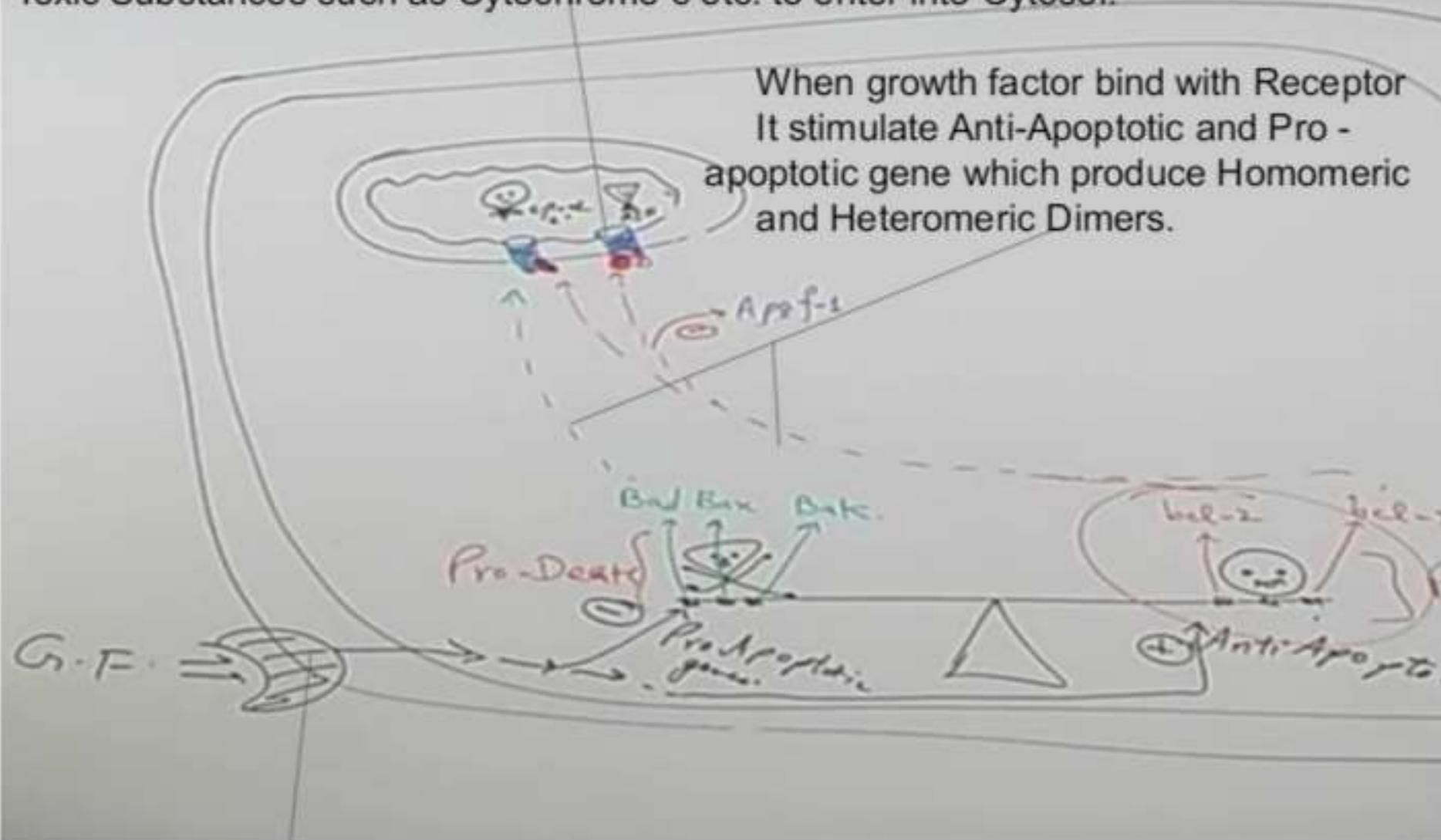
Macrophages digest these Apoptotic bodies.

5- Executional Caspases stimulate df

Cytosolic enzyme especially DNAase.

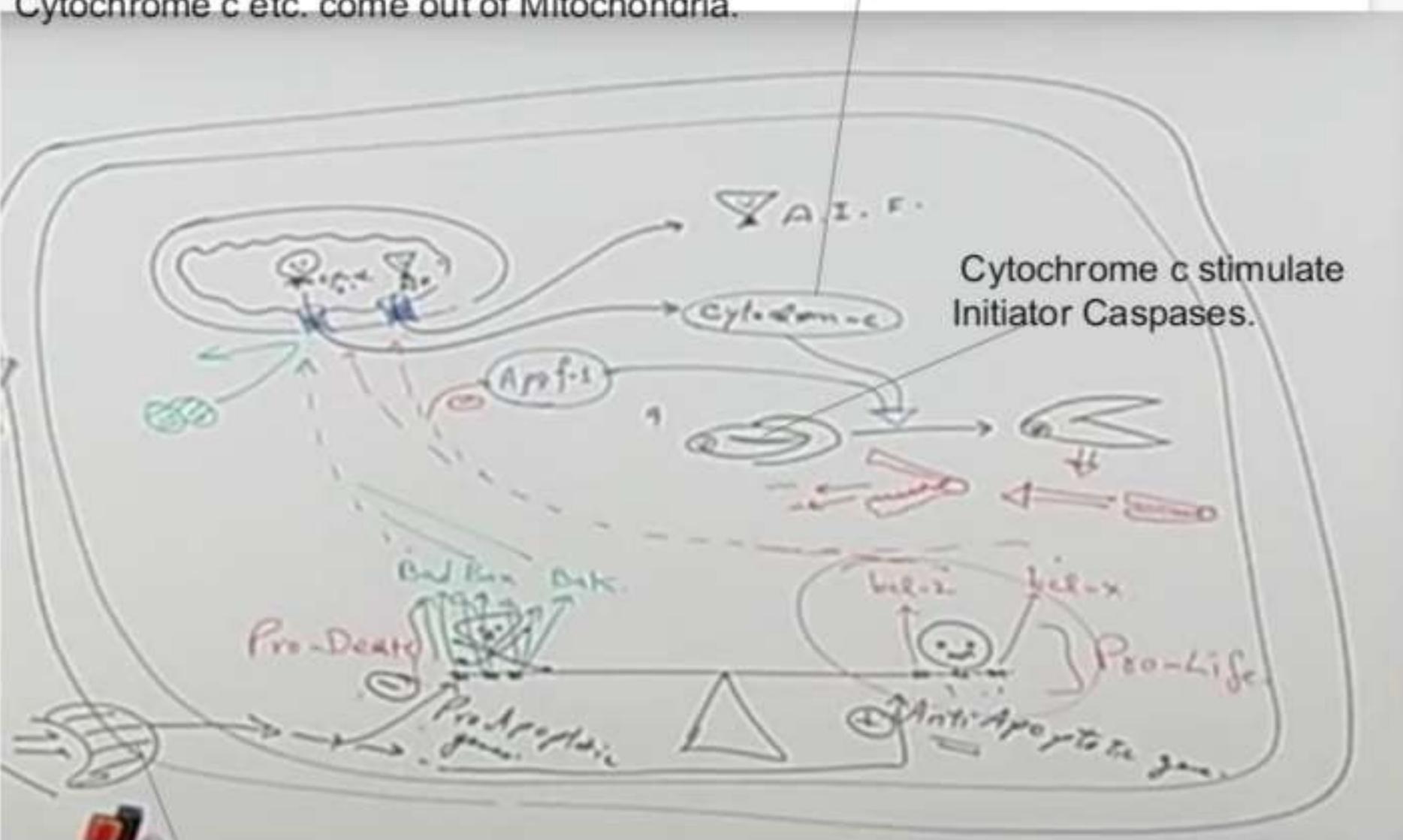
Diagram showing genetic mechanism Initiates intrinsic pathway of Apoptosis...

Normally Homo or Heteromeric block the Mitochondrial channels and don't allow Toxic Substances such as Cytochrome c etc. to enter into Cytosol.



Growth factor bind with Receptor.

When growth factor don't bind with Receptor, Anti-Apoptotic gene is not Stimulated as result false Dimers are form. As a result mitochondrial toxic Substances such as Cytochrome c etc. come out of Mitochondria.



Growth factor receptor.

Diagram showing How Cytotoxic T cells Induce mechanism of Apoptosis...

Cytotoxic T cells bind with MHC-2 Proteins present on cell membrane of Apoptotic cells and activate its intracellular Granzyme.

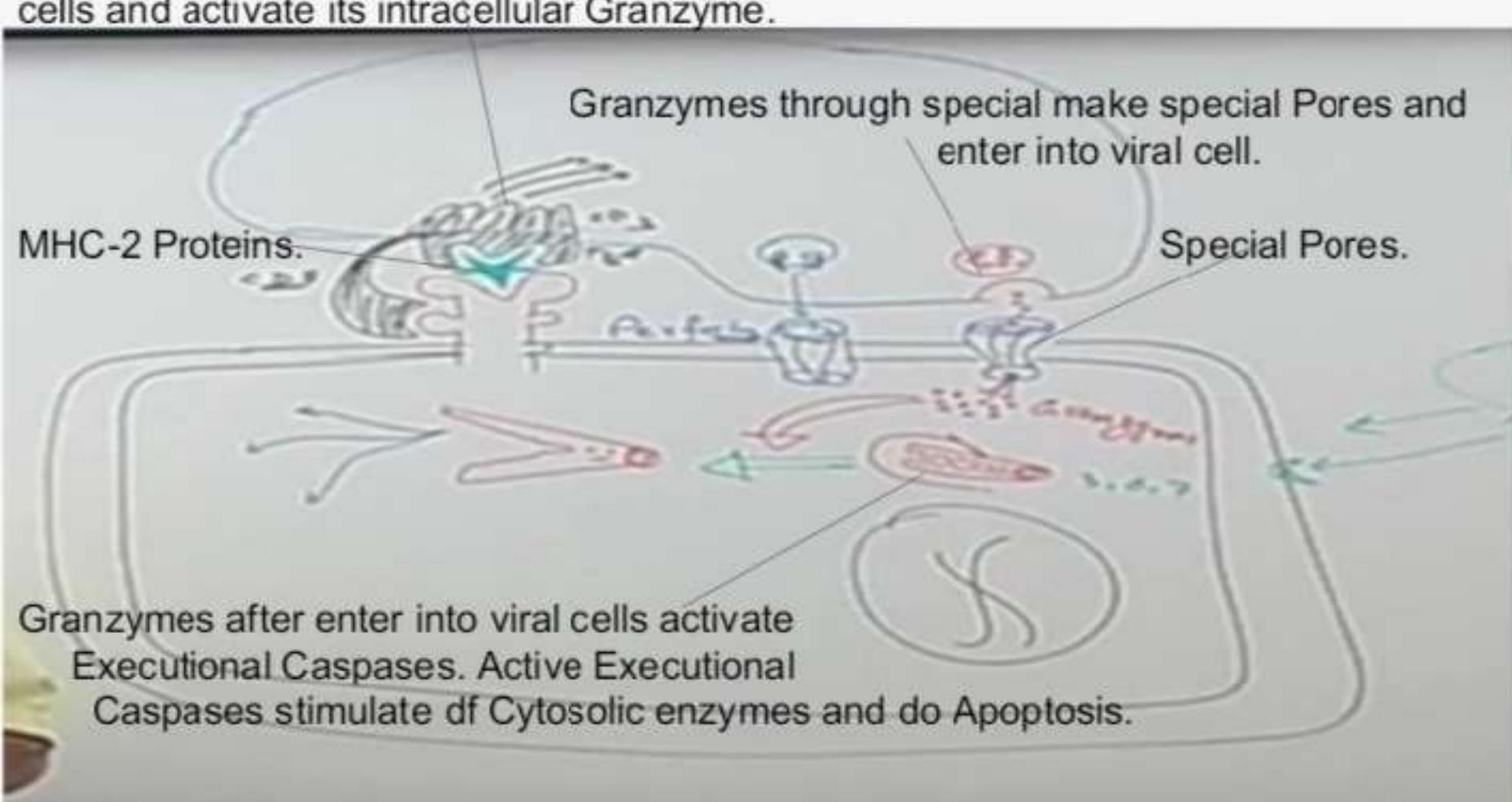
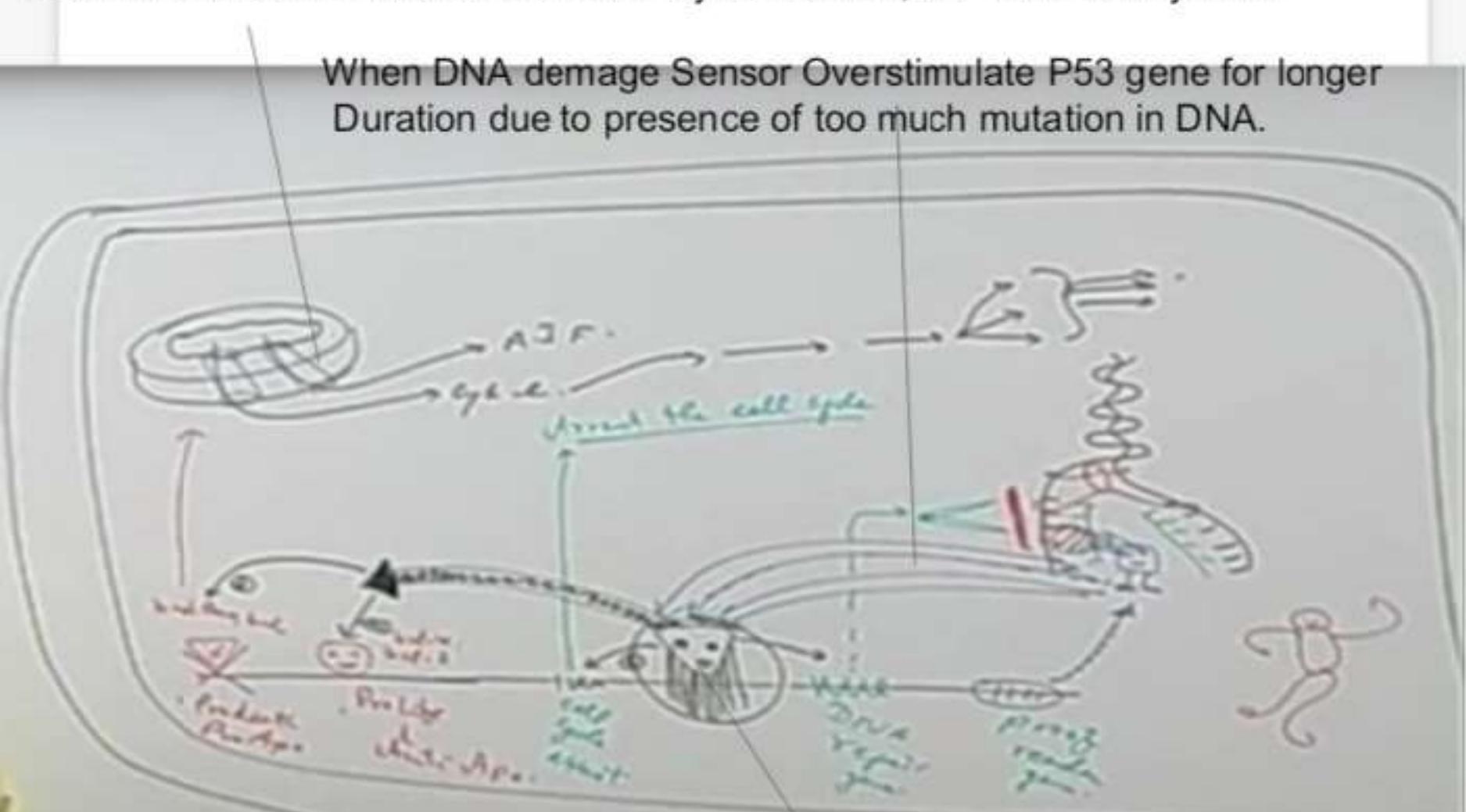


Diagram showing Role of P53 in Apoptosis

Mitochondrial toxic molecules such as Cytochrome c, AIF leak into Cytosol.



Irritated P53 gene stimulate Pro-apoptotic gene and inhibit Anti-Apoptotic gene. Due to Inhibition of Anti-Apoptotic gene, Abnormal Dimers are formed which can't block the Mitochondrial channels. So as result, Mitochondrial toxin such as Cytochrome c enter into Cytosol and Initiates Apoptosis.

INFLAMMATION (Vascular Events)..

Inflammation is a response of Vascular connective tissue towards injury regardless of what is the Cause of Injury. If tissue is Vascularise and that tissue get injured, inflammation must occur their.

Inflammation occur all over the body Tissues including CNS.

Q# What is the purpose of inflammation at side of every injury??

TYPES OF INFLAMMATION :-

There are 2 main types of inflammation,

1-Acute inflammation. 2-Chronic Inflammation.

PARENCHYMAL CELLS refer to the main functional cells of Every Tissue.

Exp # In CNS, neurons are Parenchymal cells, in Liver, Hepatocytes are parenchylam cells etc.

STROMAL CELLS refers to Supportive cells of every Tissue such as resident Mast cells, Lymphocytes, Macrophages etc. Present in every tissue.

When every tissue is injured, injured Stromal cells and Parenchymal cells of every tissues release df enzymes and molecules such as cytokines, PGs, NO, PGs etc. These chemical Substances initiates df steps of inflammation. chemicals Substances which are release by injured cells and some chemical Substance of blood are collectively called as inflammatory chemical Mediators.

In acute inflammation, 2 type of changes occur, 1-Vascular changes. 2-Cellular Events which are mainly WBCs events.

1# VASCULAR EVENTS :-

1-injured Endothelial cells and other connective tissue cells such as Mast cell Macrophages release Histamine, PGs, NO which bind with Smooth muscle Cells of surrounding arterioles and dilates arterioles. Due to Arteriolodilation, Blood flow to the injured area increases which increase Hydrostatic pressure in injured cells capillaries. So lot of Fluid from vessels enter into injured area and injured tissue Inflamed.

Moreover due to increase blood pressure flow, injured tissue become Red and Hot.

EXCUDATION is a Process in which excessive protein rich fluid from vascular compartment enter into interstitium of Injured Cell due to increase Hydrostatic pressure, decrease Osmotic pressure and due to increase permeability of Vascular Endothelial Cells.

Exudate has specific gravity which is more than 1.020 bcz Exudate is a fluid rich in Proteins and WBCs.

If permeability of vessels remain normal and there is no cellular injury is present BUT,

TRANSUDATION :- Due to any Reason if Hydrostatic pressure in Microcirculation increases and osmotic pressure Decreases then lot of Fluid which is low in protein, cross vascular Compartment and enter into Intertitium without any injury. This process is called as TRANSUDATION and fluid which cross the vascular compartment is called as Transudate.

Transudate has less specific gravity as compare to Exudate.

Edema can be Cause due to Exudation OR Transudation.

2- During initial Phase of inflammation, Bradykine by plasma Proteins, Histamine by Mast Cells, Leukotrine by injured Cells bind with Endothelial cells of Vessels and Shrinken the Endothelial cell of Micro- Circulation. Due to Shrinkage of Endothelial cells lot of Fluid from vascular compartment enter into interstitium for very short duration bcz half life of Histamine, Bradykinin etc are very short so endothelial cells remain Contract for very short time. This process is called as Immediate Transient Response.

DF MECHANISMS THAT INCREASES Endothelial cells Permeability.

1st mechanism :- Cellular contraction followed by Retraction :-

Q# What is the df bw Retraction and Contraction of Vascular Endothelial cells??

Ans:- 1# **CELLULAR RETRACTION** is a Partial shrinking of Endothelial cells in response to action of Cytokines. Cytokines are produce after some Hours of injury. It produce delayed or chronic Inflammation.

2# **CELLULAR CONTRACTION** is a full Shirking of a Vascular Endothelial cell. It is produce by Bradykinin, Histamine which is release at initial phase of Inflammation and produce acute Inflammation.

Phospholipase A2 is present in cell membrane of every Cell. When cells under go Injury, this enzyme get activated and start breaking lipid of cell membrane into Arechdonic acid. Arechdonic acid is convert into PGs and Leukotrienes.

Increase permeability is seen in Venules more as compare to arteriolar side at Microcirculation. Bcz Endothelial cells of Venules contain lot of Receptors for chemicals Mediators such as Histamine, Bradykinin which produce Vasodilation.

2nd mechanism :- Delayed Prolonged endothelial Gaps are produced due to direct compression on arterioles, Capillaries and Venules of injured Area.

Some times, very Delayed but Prolonged increase in Vascular Permeability occur long and long times after the injury, which Cause chronic Inflammation. This happens due to Delayed release of cytokines in the body such as in case of Sun burn etc.

3rd mechanism :- Leukocytes mediated endothelial cells injury are seen in pulmonary Capillaries and Glomerular Capillaries. Neutrophils increase the permeability of pulmonary and Glomerular Capillaries.

4th mechanism :- Formation of Vesicular- Vacuoles Organelles in Endothelial Cells increase Permeability of the Endothelial cells in acute inflammation.

5th Mechanism :- Newly Formed vessels (Neovascularisation) which are formed at the site of injury during healing process are not fully mature and endothelial gaps are present bw these endothelial cells so fluid from new vessels also leaks into interstitium in Acute inflammation.

These are the mechanism which increase endothelial cells permeability during Acute Inflammation

2# CELLULAR EVENTS :- It include different actions or events performed by WBCs such as Neutrophils, Macrophages etc. at the site of injured and inflammed area in order to remove Cause of Injury.

In Linear blood flow, Axial or Central blood flow consist of large WBCs, then RBCs then platelets, then outer most plasma zone.

1-Due to Exudation as a result of Vasodilation, blood become thick and Viscous.

2-Microcirculation show Stasis process and Hemoconcentration process.

3-When blood will become Viscous then RBCs clumps with each other and become larger than WBCs and Come in center of blood and Push the WBCs from center of vessels out into Intertitium. This process is called as Margination Process.

Weibel Palade Bodies such as Selectins etc. are Sticky or adhesive molecules express on endothelial cells when Histamine, TBX, Leukotrienes etc. Bind with Endothelial cells of Microcirculation. Sialyted Sugar are the sticky molecules which are present on Extension of Neutrophils.

4-Endothelial adhesion molecules stick with Sialyted sugar of WBCs and as a result interaction Bw endothelial cells and WBCs.

Interleukin-1 and TNF are release by Mast Cells after 1 to 2 hours of injury These substance also bind with Endothelial and stimulate endothelial cells. WHILE Mast cells Release Histamines, Leukotrienes immediately after the injury in order to Stimulate Vascular endothelial CELLS.

5-After Endothelium- WBCs interaction, WBCs Roll over the Endothelial cells lining of Vessels. This process is called as Rolling of WBCs.

6-After Rolling, some Macrophages produce Hemokines which make PCAM and VCAM on endothelial cells and activate integrins molecules of WBCs. Integrins of WBCs stick with PCAM, VCAM and stick WBCs very tightly with them. This process is called as Pigmentation Process. As a result of this, WBCs keep on sticking with Vascular Endothelial cells.

Emigration, Diapedesis or Extravasation is a process in which, WBCs shift from Vascular compartment into the Intertitium. WBCs which was sticked with vascular endothelial cells now shift from vascular compartment into Intertitium.

In Diapedesis, endothelial cells and WBCs express Same molecules (Homophilic) molecules. So due to presence of Homophilic molecules on both cells, endothelial cells push the WBCs away and push them through endothelial gaps into interstitium. But after crossing the gap WBCs get stuck in Basement Membrane. Now cytokines stimulate WBCs to release destructive enzymes. These Enzymes cut the basement membrane and enter into injured Cellular Areas.

Injured cells, Mast cells, Macrophages etc produce df Chemicals or Chemotactic that attract the WBCs towards the injured cells area. So WBCs follow the Chemotactic Agents and reach injured cells area. This process is called as Chemotaxis.

Importance of CD44 receptors in Chemotaxis.

Enlist df Chemotactic Agents??

WBCs reach injured Cellular area and start process of Phagocytosis there.

CLINICAL POINTS :-

Sometimes, Due to Genetic mutation WBCs don't contain Sialyted sugar so they can't stick vascular Endothelial cells and don't show rolling Process and bounce back. This situation is called as LAD-2.

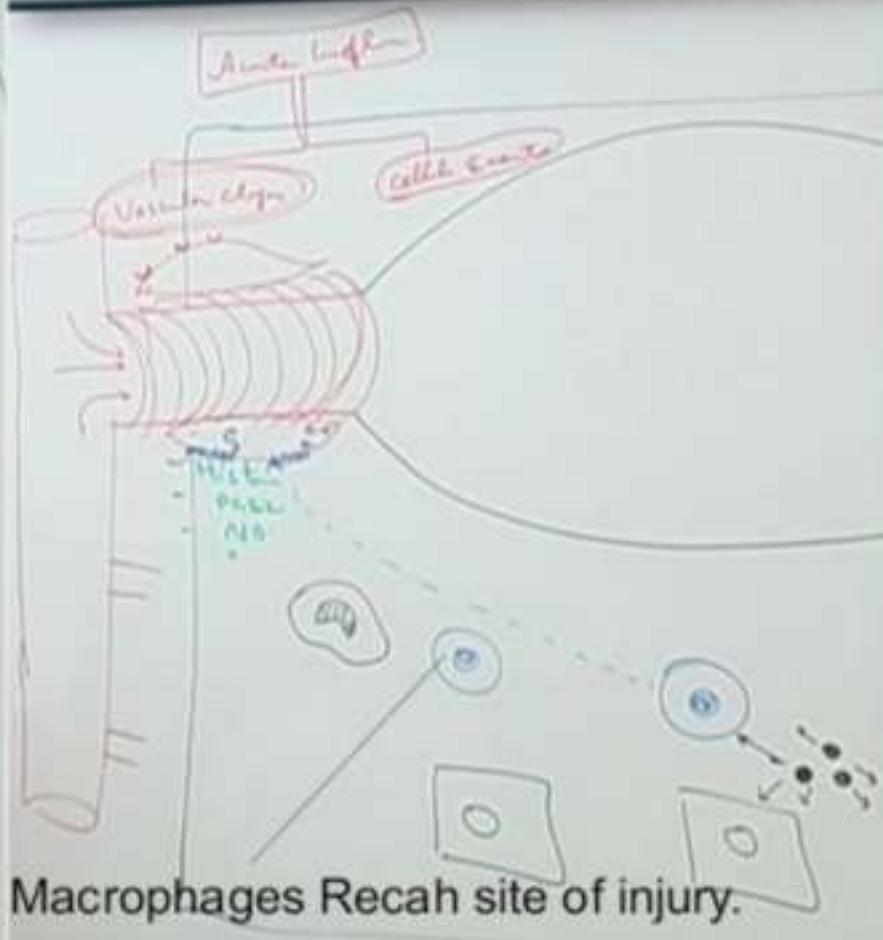
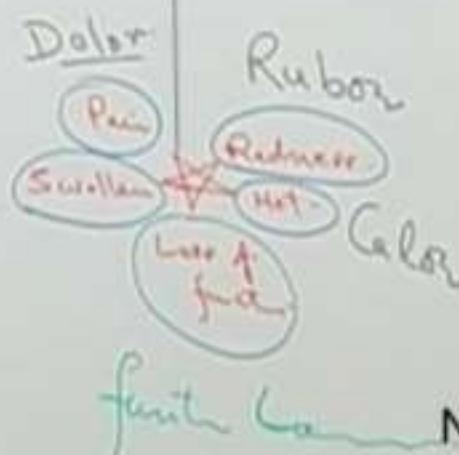
Why Patients Who have high Catecholamines, Cortisol and lithium level in blood. When we take blood sample of these patients, Neutrophils levels in blood also record as Elevated Neutrophils level??

Ans :- Reason is that, normally small portion of WBCs always present in attachment with vascular Endothelial Cells. But when blood level of Catecholamines, Cortisol or lithium become high it suppress vascular endothelial not to express their adhesion molecules so that Neutrophils can't stick with Endothelial cells. So as result Neutrophils get deattach from vascular endothelial and enter into circulation. and when we take blood sample from that person we find that, Neutrophils level in blood sample is High. But actually Neutrophils production remains Normal and don't increase.

Opposite to that,

High level of Endotoxins in blood, stimulate vascular endothelial cells to show lot of adhesion molecules. As a result lot of Neutrophils bind with Endothelial cells and blood Neutrophils level Decreases.

Diagram showing Classical Features of Inflammation.



Neutrophils and Macrophages reach site of injury.

Diagram showing vascular events for inflammation that occur just after the injury...

Initially smooth muscle cells of arterioles produce df Vasodilator Substances.

Due to Vasodilation in case of Injury Hydrostatic pressure remain Elevated throughout exchange.

Normally Hydrostatic pressure Incre.
During intial phase of Capillary Exchange and then decr.

Capillary endothelial Cell also release df Substances.

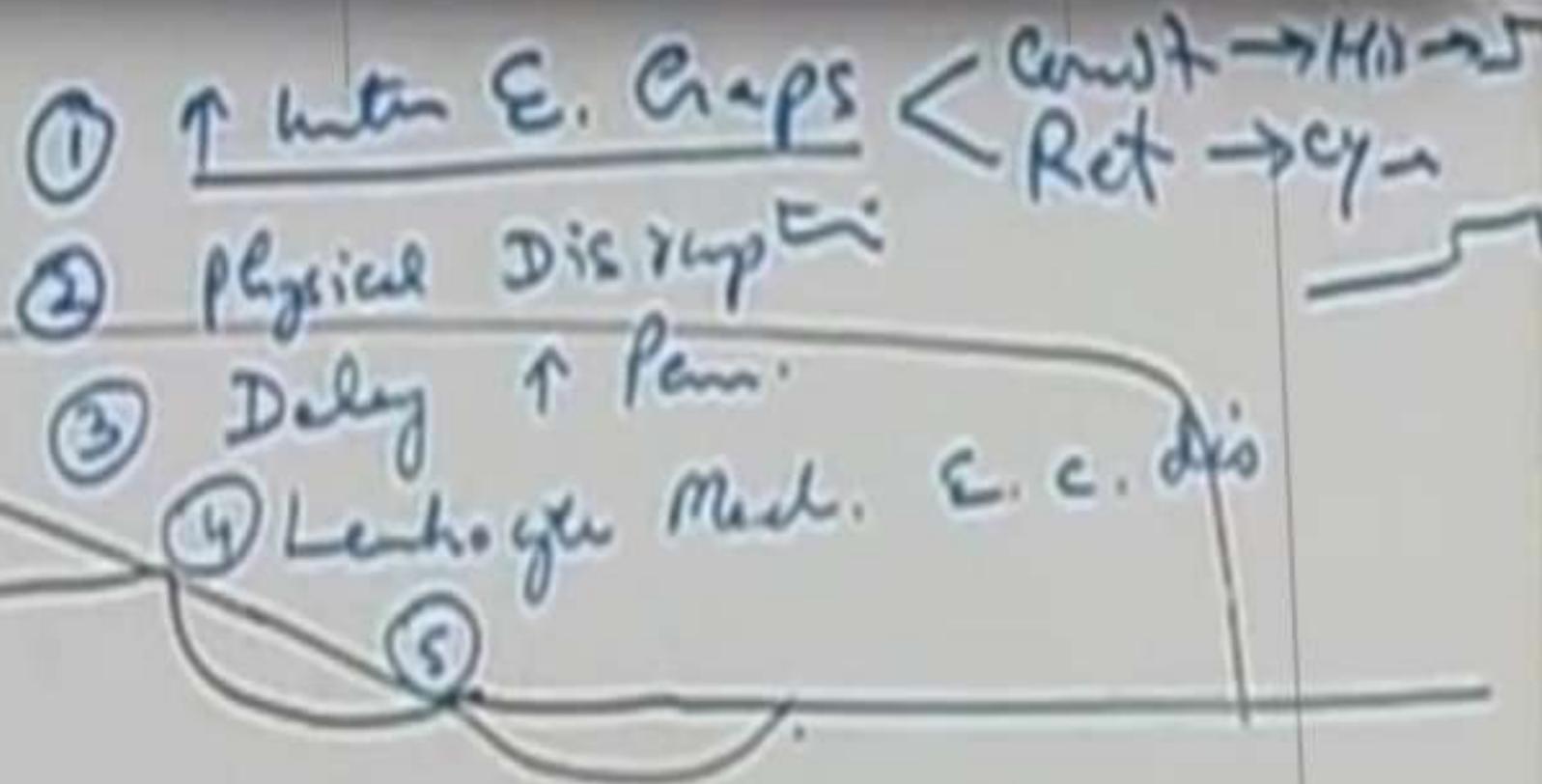
Normally, Oncotic Pressure Decrease during initial phase of Capillary Exchange then slowly it increase at Late phase.

Due to Vasodilation in case of injury, Hydrostatic pressure Elevates

Too much as result Hydrostatic pressure overcome oncotic pressure throughout phases of Capillary exchange.

Diagram showing initial vascular changes that occur during acute inflammation.

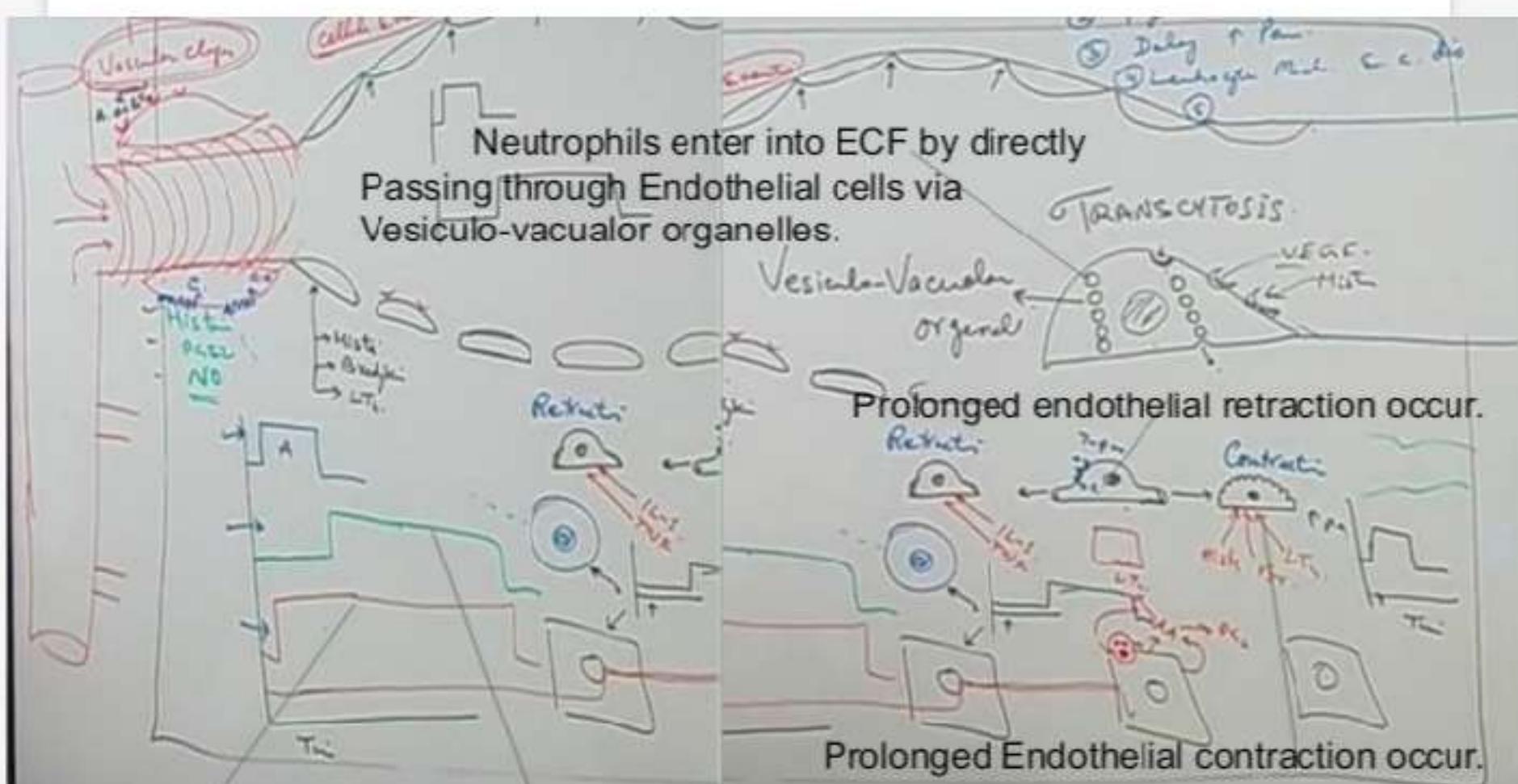
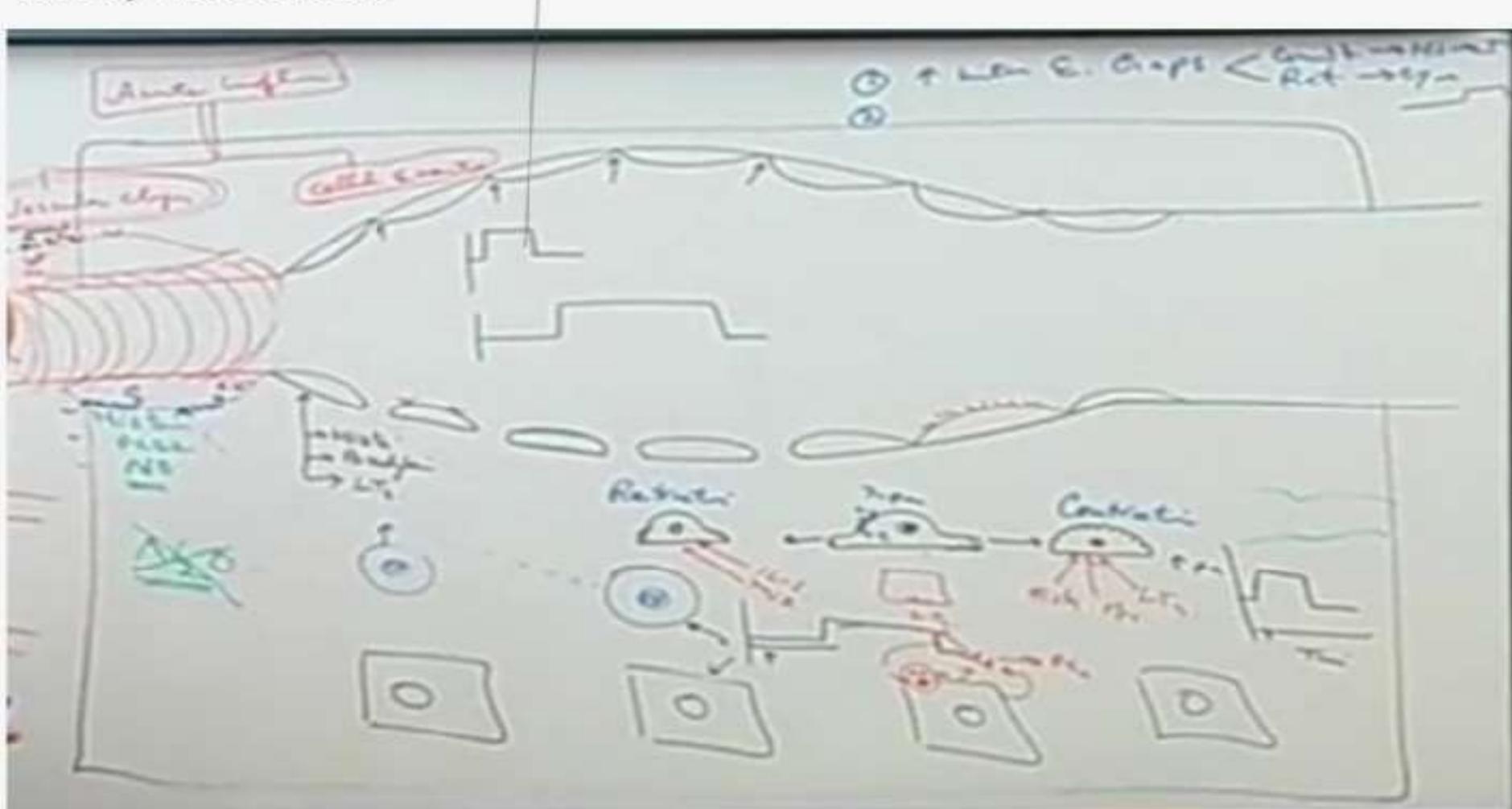
Histamine produces endothelial contraction.



Cytokines produces Endothelial Retractions.

Diagram showing vascular events in Chronic inflammation...

During acute inflammation, Vasodilation occur for short periods, endothelial gaps are formed for very short duration.



Oncotic pressure remain low for longer time

In chronic inflammation, Vasodilation occur for longer period as a result, Hydrostatic pressure Elevates for longer time and lot of fluid from circulation enter into ECF.

Diagram showing df Events occur during acute inflammation.

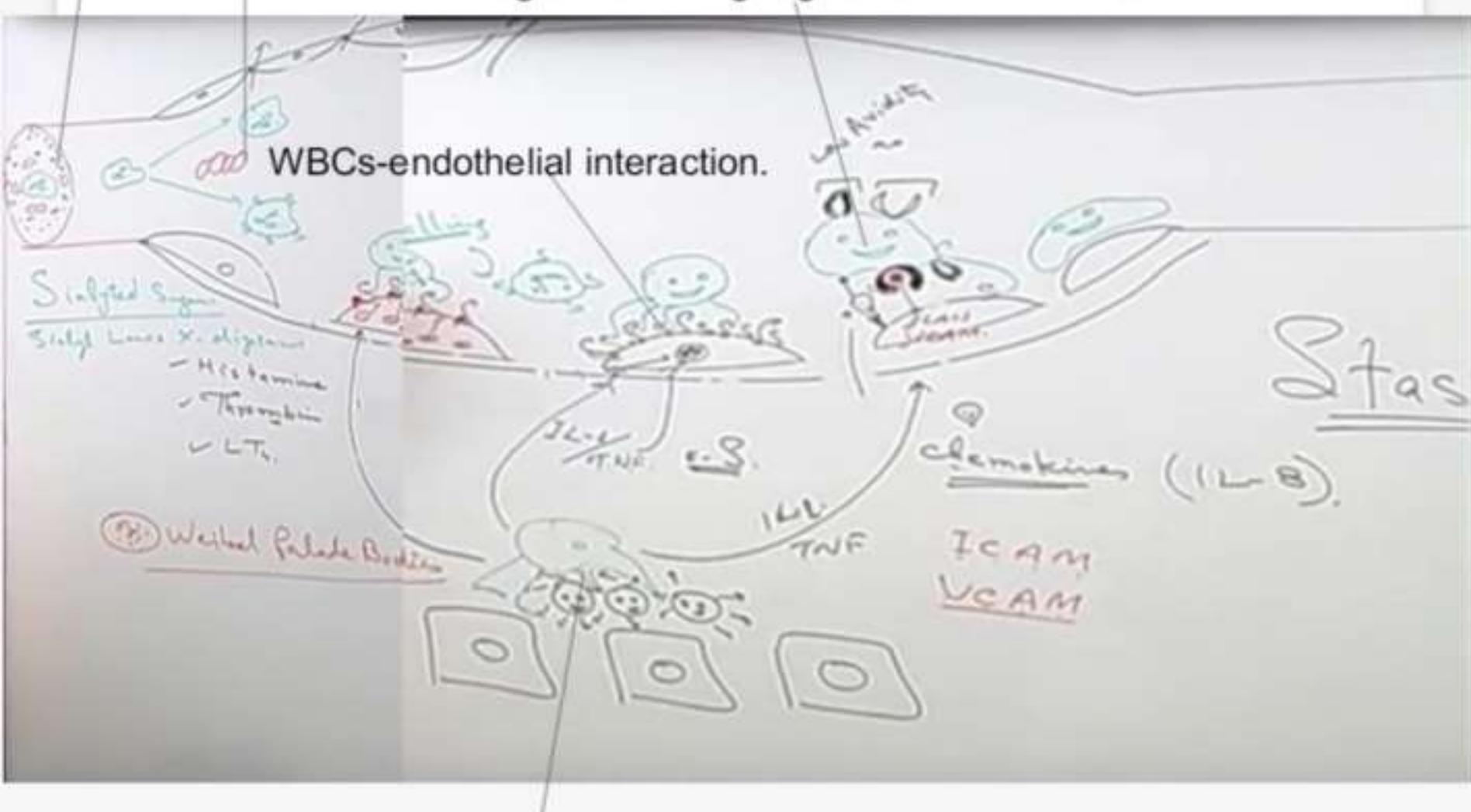


Diagram showing df cellular events occur in acute and chronic inflammation

Normally In Linear blood flow, WBCs are present in center, then RBCs then platelets and outer margins of vessels are occupied by plasma.

Due to stasis during inflammation, when blood become Viscous, RBCs clump and make Bigger mass then WBCs kicks WBCs from central axis.

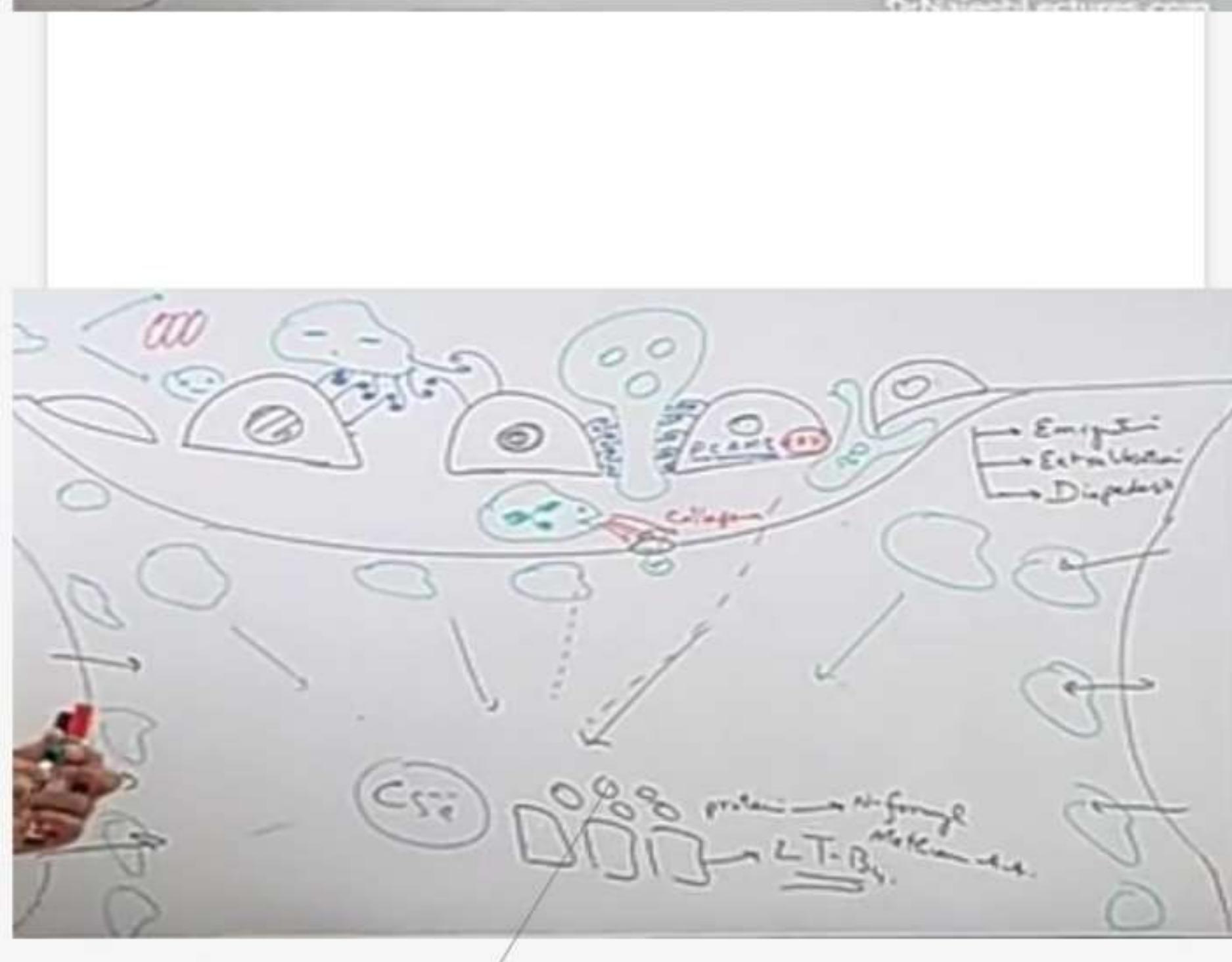
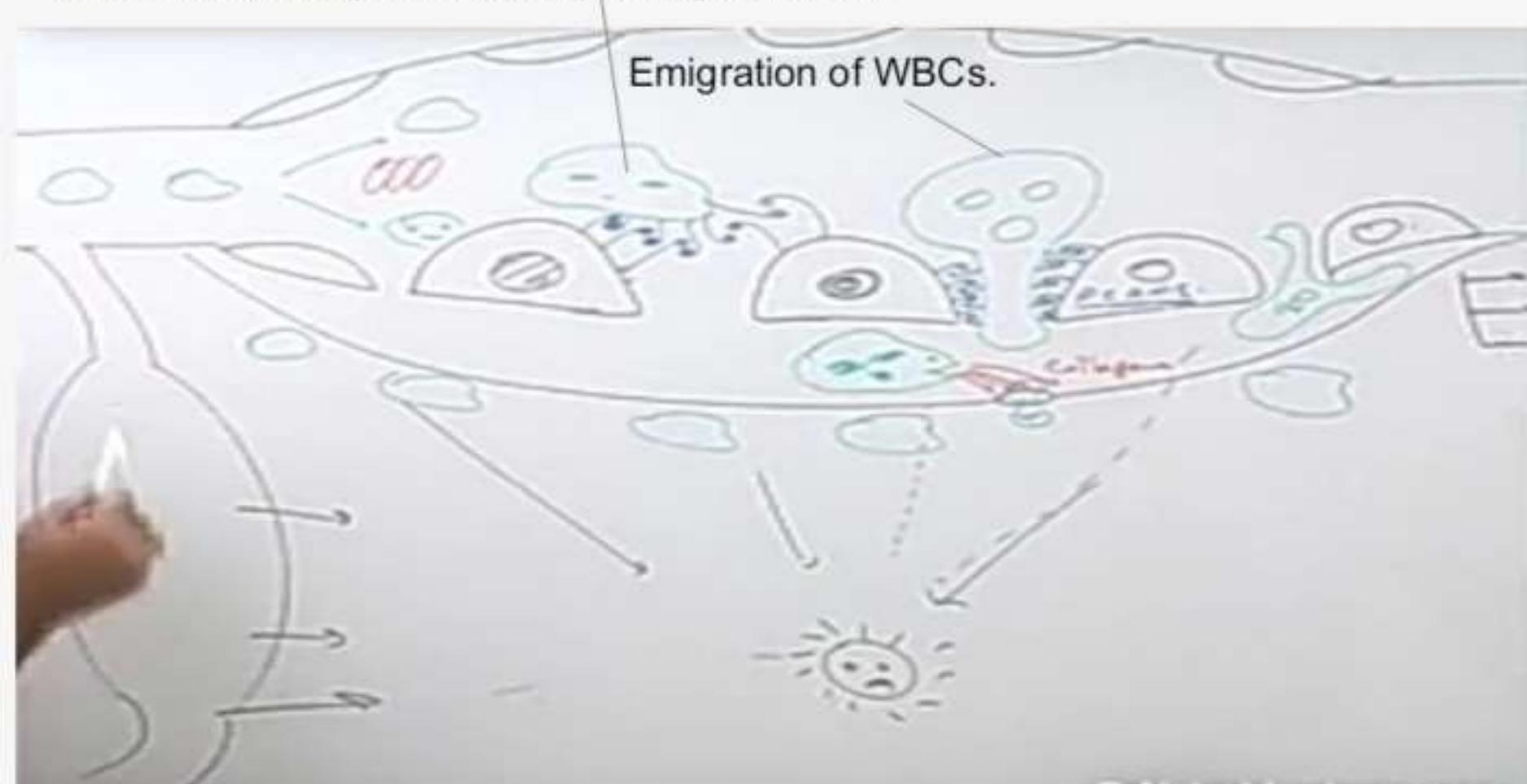
Diagram showing Pigmentation of WBCs.



Macrophages produce Hemokines that make ICAM, VCAM over endothelial cells.

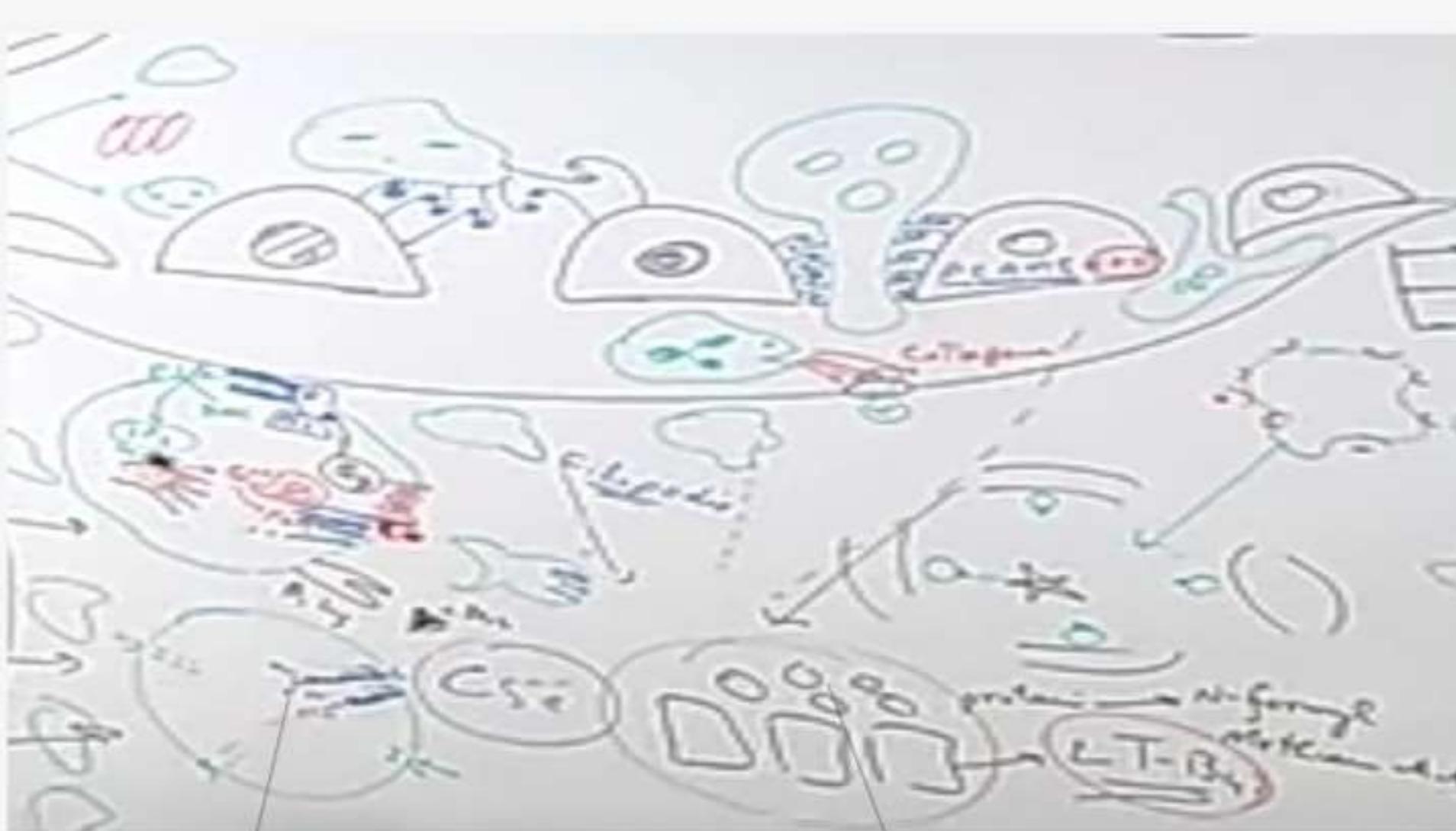
Diagram showing cellular events such as migration of Neutrophils at infection site...

Diagram showing rolling of WBCs.



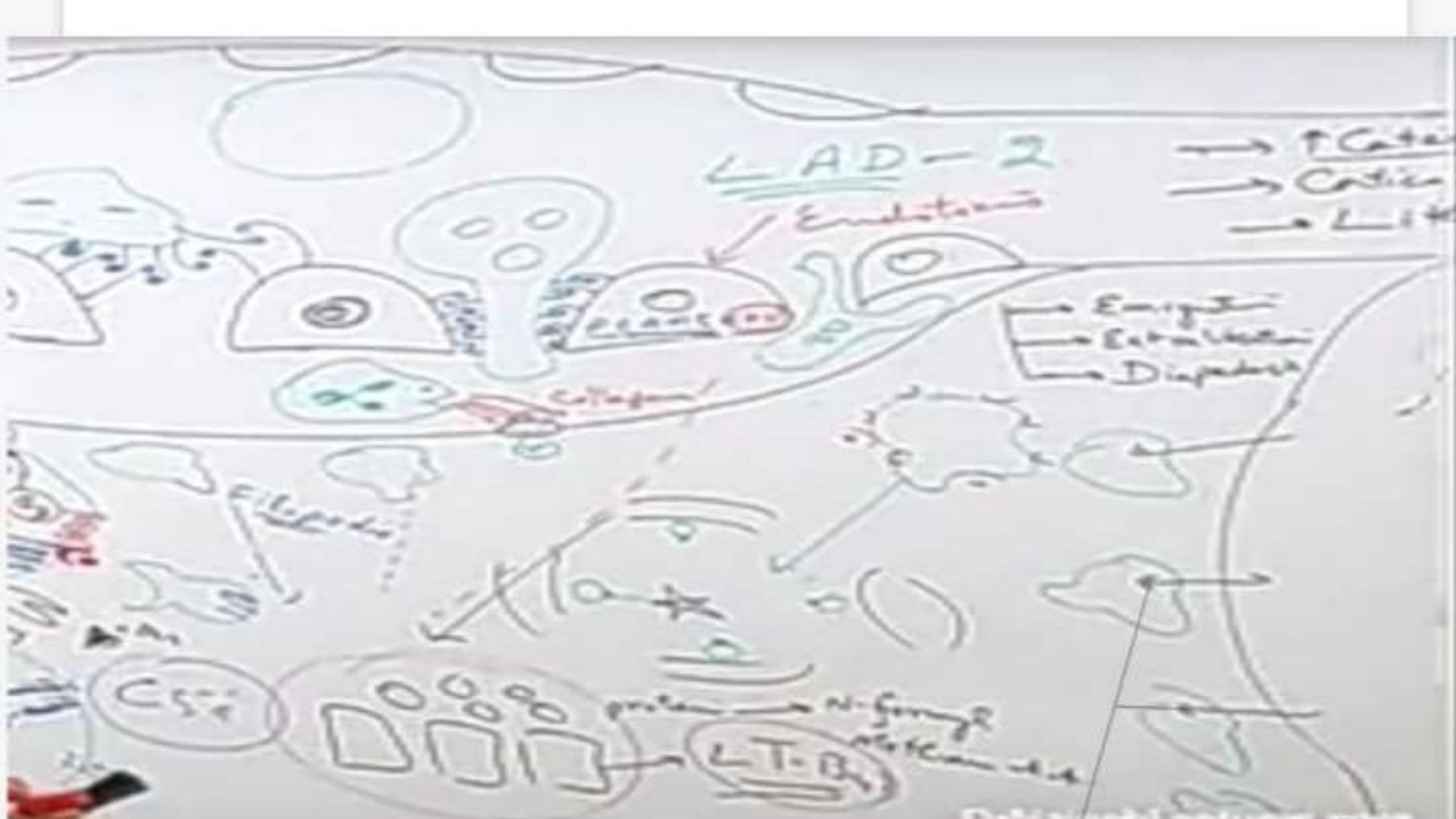
Neutrophils and Macrophages Recruit site of injury.

Diagram showing migration of Macrophages and Phagocytosis proc..



Dead and dying bacterial cell, WBCs and Macrophages.

Macrophages engulfing
and Destroying Bacterial cells.



Neutrophils from all sides reaches the site of injury immediately..

MASTERING EDEMA...

#Accumulation of Excessive fluid in the body tissue which are extravascular tissue, it may be an intracellular (inside the Cell) or Extracellular (outside the cell in interstitium) fluid Accumulation.

Edema is generally divide into 2 Types,

1-Intracellular Edema (Edema inside the Cell).

2-Extracellular Edema(Fluid Accumulation in interstitium (Non-circulating ECF)) and fluid Accumulation in Serous Body cavities such as pleural, peritoneal cavities etc. BUT Generally word Edema in medical literature is used for Extracellular Edema, not for intracellular Edema.

#Normally water make 60% of body weight. Out of 60%, $\frac{1}{3}$ is present in extracellular fluid and $\frac{2}{3}$ is present intra cellular fluid(ICF). Out of $\frac{1}{3}$ of water which is present in ECF, $\frac{1}{3}$ of water is present intravascularly and $\frac{2}{3}$ is present in interstitium(Non-circulating ECF).

Suppose if a person is 72 kg, total amount of water in his Body is 42 Liter (60%). Out of 42 Liter, 28 Liter of water is present in ICF. 14 Liter are making ECF. Out of 14 liters, 10 or 10.5 Liter is making interstitium (Non Circulating ECF) and remaining 3.5 Liters are present intravascularly.

Accumulation of Excessive Fluid in Pericardium is called as PERICARDIAL EFFUSION or HYDRO PERICARDIUM.

If Pericardial effusion don't allow Ventricle to relax and don't allow ventricles to filled Properly, Then we called Pericardial Effusion as PERICARDIAL TYPONADE.

Accumulation of Excessive fluid in pleural cavity is called as Pleural effusion or HYDRO THORAX, AND Accumulation of Fluid in Peritoneal cavity is called as

peritoneal Effusion or Hydro peritonium or ASCITES (most Commonly).

#A good doctor should detect the Ascites when there is a Half Liter Fluid get Accumulated in Peritoneal cavity.

If the blood volume all over the body Increases we call it as HYPER-VOLUMIC condition. But if an Excessive blood voulme is present only in Specific Tissue we call it as HYPEREMIA or CONGUSTION or we say that Tissue is Hyperemic. In this Condition tissue look reddish, called it as ERYTHEMA or tissue is ERYTHMIC.

Q#What is the difference bw tissue congestion and tissue Hyperemia?

Ans:-increases in fluid Concentration in microcirculation due to increase blood flow to tissues is called as Hyperemia and If fluid concentration increases in microcirculation due to decrease in outflow of blood from microcirculation is called as Congustion, Such as due to presence of Thrombus in vein blood don't drain well into vein and retain in microcirculation.

Vascular Engorgment is a term which is used when Vessels become Hyperemic and Congustion also Simultaneously. We say there is tissue Engorgment due to vascular Engorgment.

CAUSES OF INTRACELLULAR EDEMA :-

Intracellular Edema occur when cells become Hyperosmolar.

Cell become Hyperosmolar when Na-k ATPase don't work properly Due to any cause or if Cell Membrane got damage due to any Cause. Or if ECF become Hypo Osmolar.

Normal Na concentration in blood is 135-145 miliequi/Liter. It is same in blood as well as in ECF.

CAUSES OF EXTRACELLULAR EDEMA :-

Extracellular Edema is mainly occur due to disturbance or rearrangement of Starling Forces. Out of that, one of the major cause is

1-increase in Hydrostatic pressure.

2-Decrease in Oncotic pressure in case of Hypoproteinemia.

In both conditions Excessive fluid enter into ECF and don't drain well by Venous system. This kind of Edema is usually pitting Edema. But

3-If Starling forces are Normal but lymphatic Drainage system is blocked then, Proteins which enter into ECF from blood will not drain back, and as a result proteins will accumulate in ECF and will Generate the osmotic pressure, so more water will enter into ECF and present around these Proteins Tightly. This type of Edema don't produce any kind of pit, so it's called as Non-pitting Edema.

Normal concentration of Total plasma proteins in plasma is 6-8gm/dl(100ml) or 60-80gm/Liter. Both are the same Values. dl=deci Liter.

#Albumin is the Plasma protein which is present in High concentration in plasma and its the main determinant of oncotic Pressure.

Generalised Edema(Edema all over the body) is also called as ANASARCA.

#**DEPENDENT EDEMA** is a type of Generalised Edema which move or Distributed in df parts of the body under the action of Gravitational Force. Suppose if a patient is standing than Edema will shift to legs and legs will be more Edematus, or if a person is sitting than edema will shift towards the sacral Region. In this type of Edema, Intertitial fluid move freely in intertium bcz of the absence of glycoproteins (which are normally present in

intertitium having brush piles which holds and absorb the water present in interstitium to move freely). Or If large amount of Fluid enter into interstitium although the glycoproteins are normally present, Excessive fluid make glycoprotein free area, and water move towards the part of the body under high gravitational Force.

4-Increase Permeability such as in case of Inflammation, Membrane become permeable which also cause Edema.

5-Salt and water retention can also Cause Edema.

Q#Why increase In blood pressure normally dont cause Edema?

Ans :-Normally, when blood pressure increase, Hydrostatic pressure don't increase at microcirculation level in order to cause Edema Bcz there are special Sphincters present at the end of each Arterioles. These smooth muscle sphincter are called as Pre-capillary sphincter. When blood pressure goes up, these sphincter constrict and become Tight and don't allow more Pressure to pass through them, so that Hydrostatic Pressure in capillaries don't increase and don't cause Edema. But when B.p decrease these Sphincters relax and allow blood to pass through them. # But there is no post Capillary dphi present on Venous side and if these Sphincters are Present, They are very weak. So whenever pressure inside Venous system increases such as in right Ventricular Failure or Pulmonary edema or in Congestive Heart Failure Etc. Hydrostatic pressure in microcirculation Increases which cause Edema bcz there is no Tight Sphincter present in veinules.

Q# Who tell Pre-capillary sphincter to constrict and Relax with fluctuations in B.P?

Ans:- Actually, Sphincters work on Myogenic reflex or Mechanism. In Myogenic reflex when B.P increases and reach the sphincter, it stretch the sphincter, Due to that smooth muscles cells also stretch and Ca channel which are present over smooth muscle cell also stretch as a result Calcium move in and cause muscle Contraction.

CAUSES OF INCREASE HYDROSTATIC PRESSURE:-

Little rise in Hydrostatic pressure at microcirculation level don't cause Edema, if lymphatic Drainage system working well, bcz if there is Minor increase in fluid in interstitium, and Lymphatics are working well it drain the extra fluid and Edema don't Develop.

Hydrostatic pressure can be increase by
1-Arteriodilation which may be cause by Heat or Neuro humoral dysfunction. Hyderilazine is a drug which is a strong Precapillary relaxant and can cause localiized Edema as a side effect.

2- Thrombus formation in Vein such as In deep Venous Thrombosis, Hydrostatic pressure increases and cause local Edema.

Congestive Cardiac Failure cause generalise Edema.

Diagram showing Distribution of water in a Formation of df Fluid Compartment of Body...

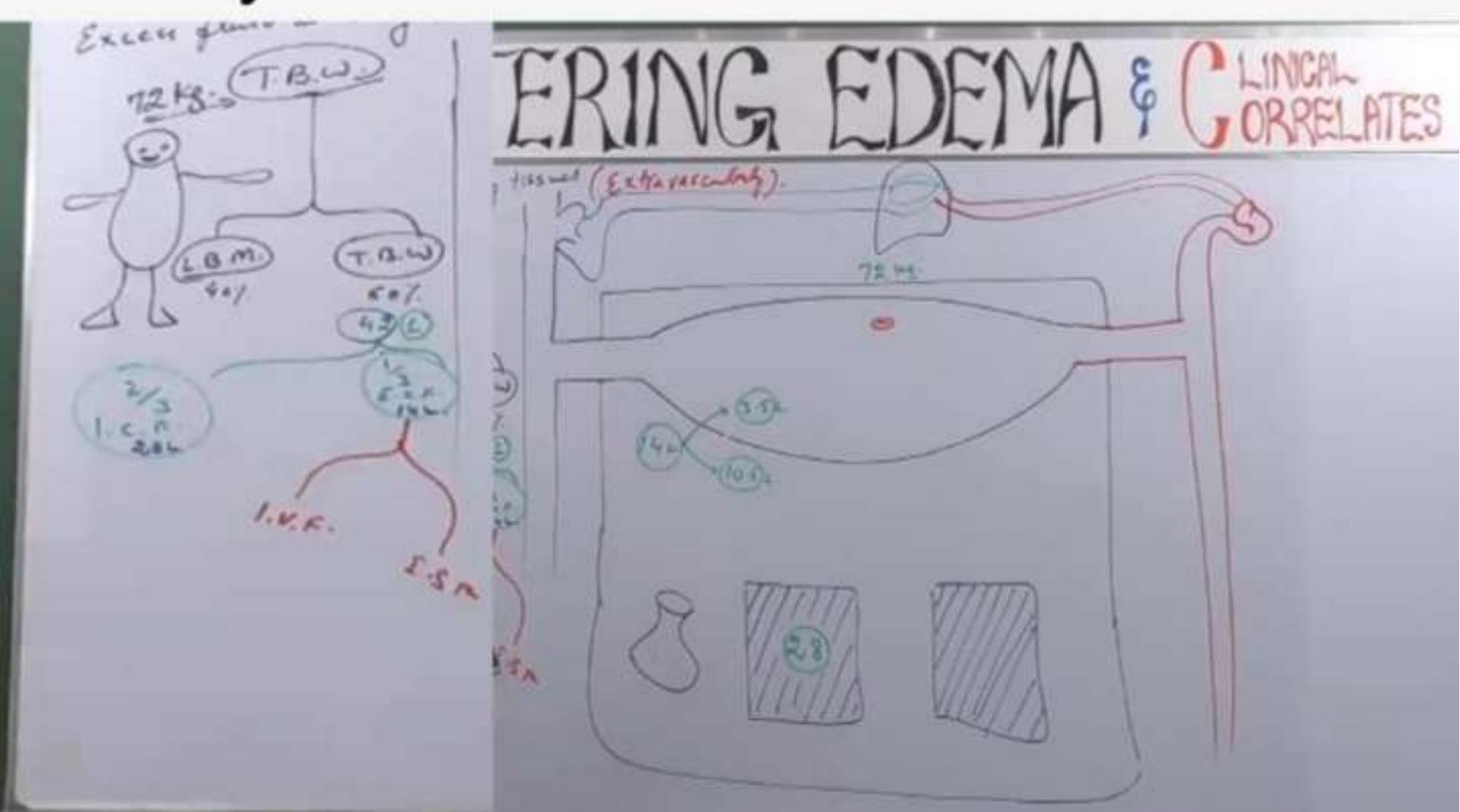


Diagram showing df types of Edema..

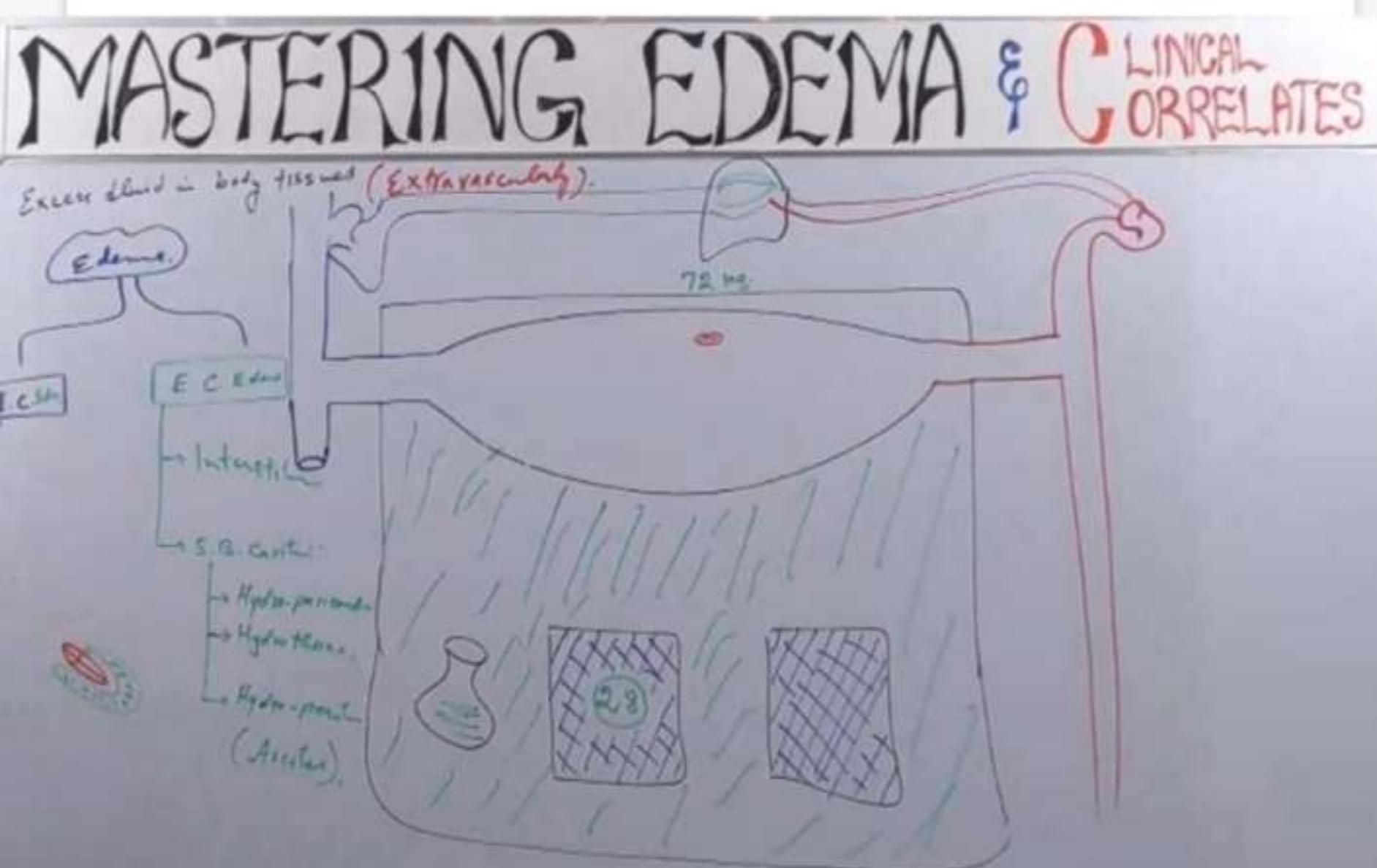
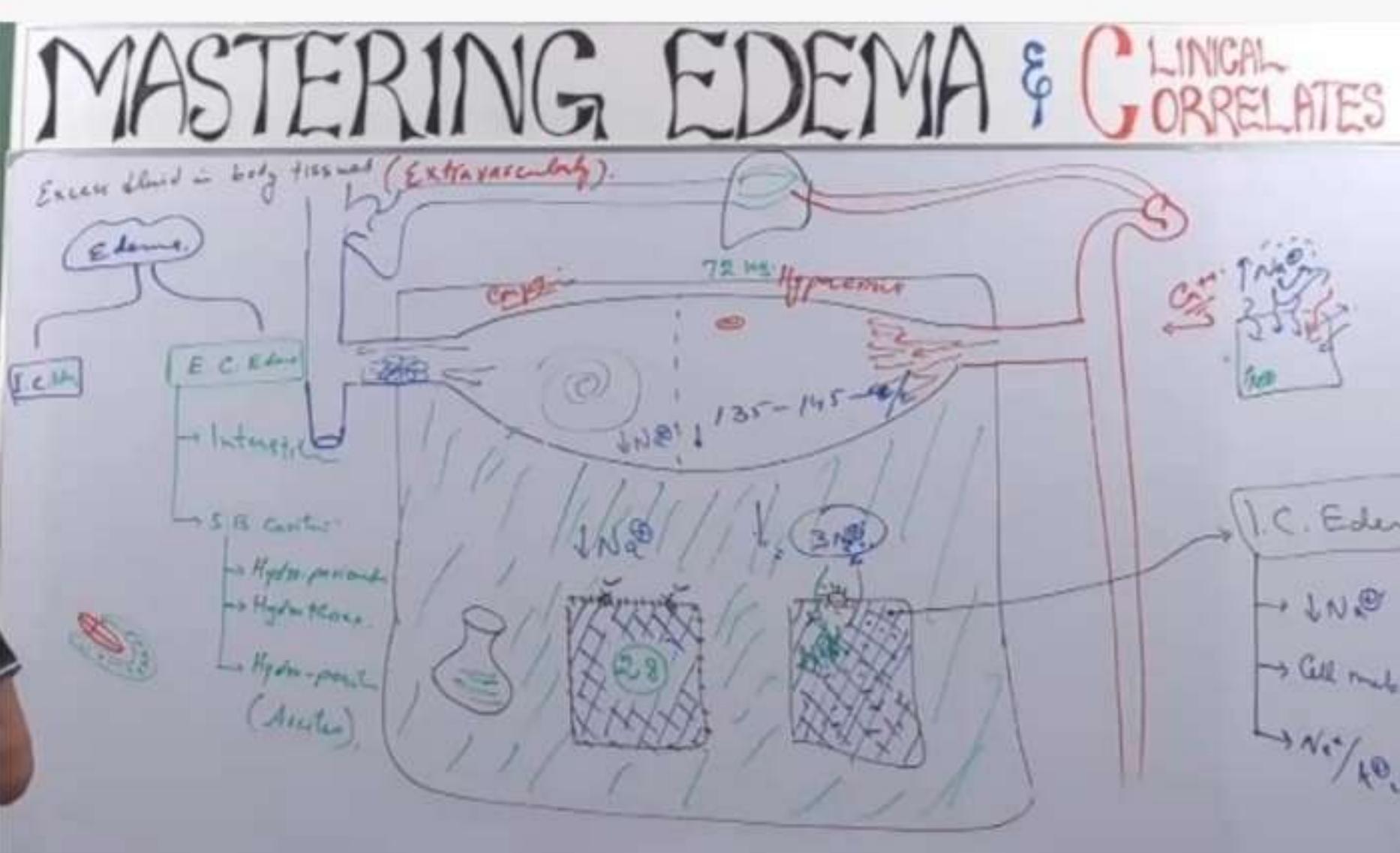
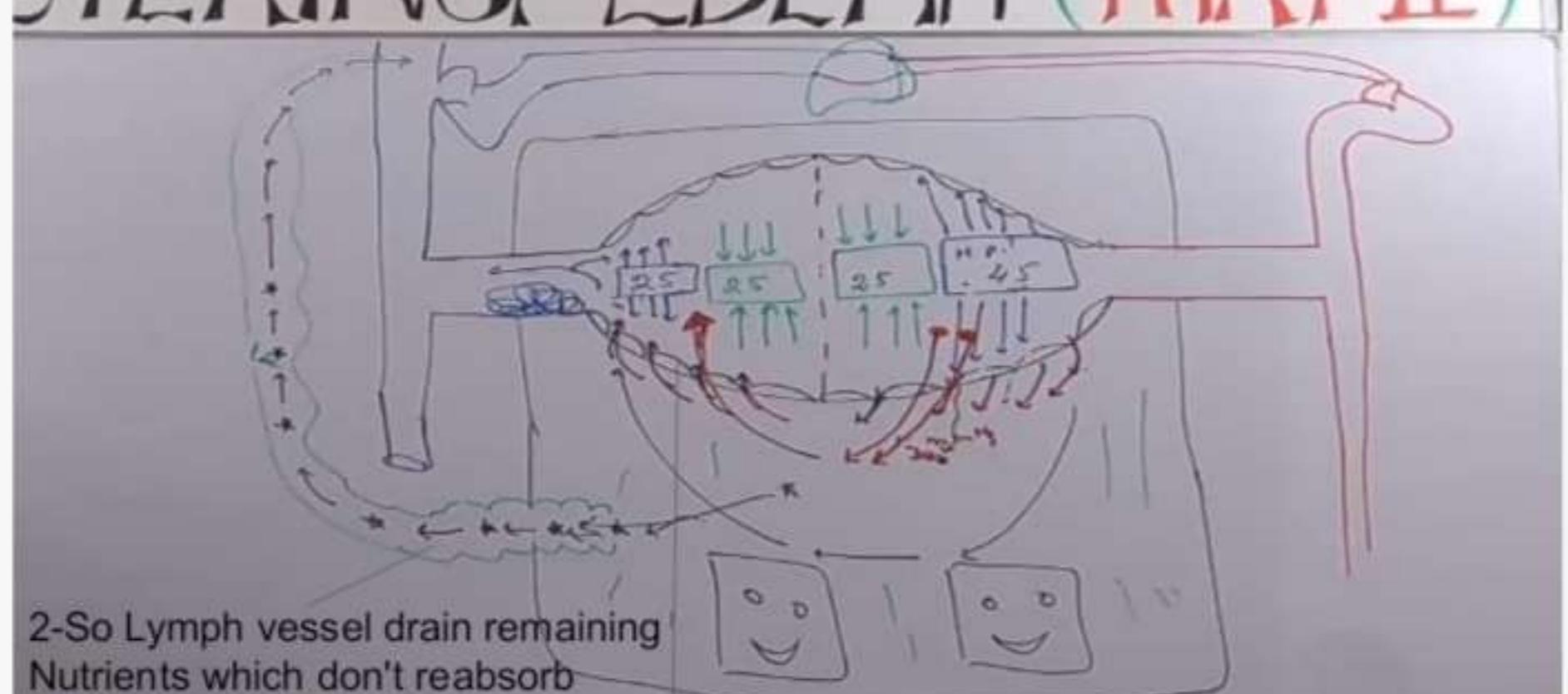


Diagram showing df types causes of Intracellular Edema, and also telling about Congustion and Hyperemia..



STERLING EDEMA (PART-II)



1- Pathologically, if Venous pressure Increases due to thrombus etc. Hydrostatic pressure at Venous Capillary side may increase, which Decreases rate of Nutrients reabsorption.

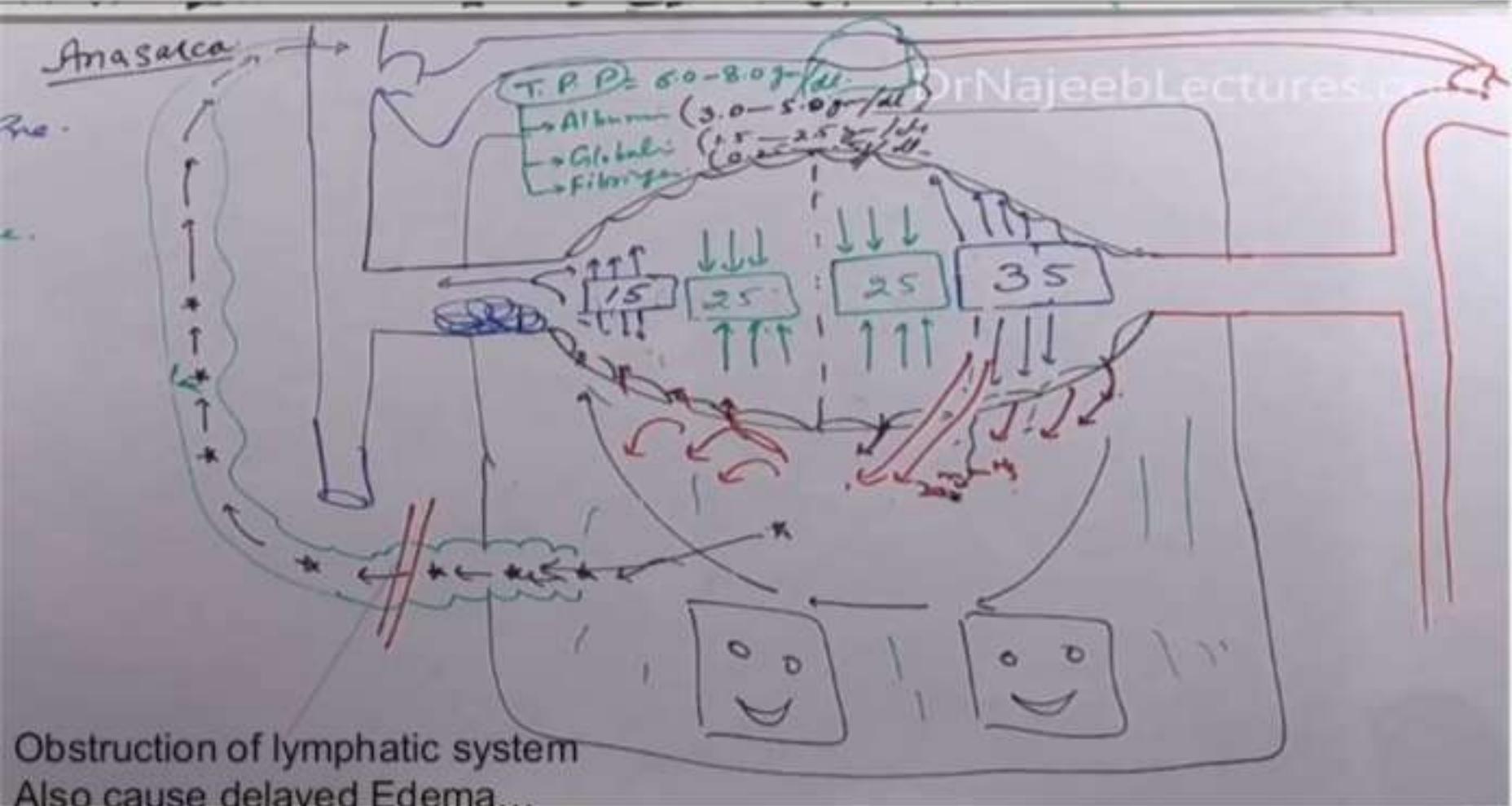
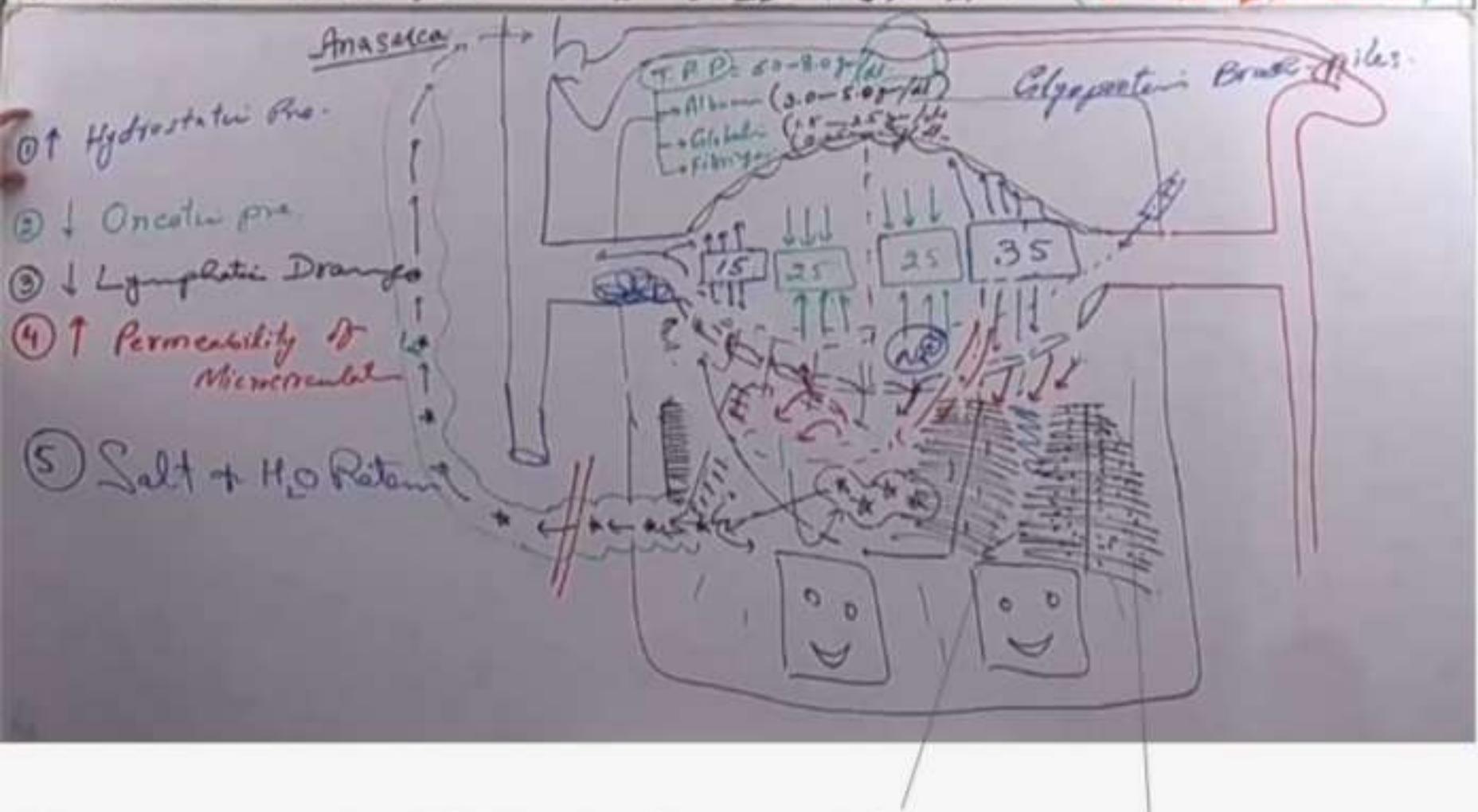


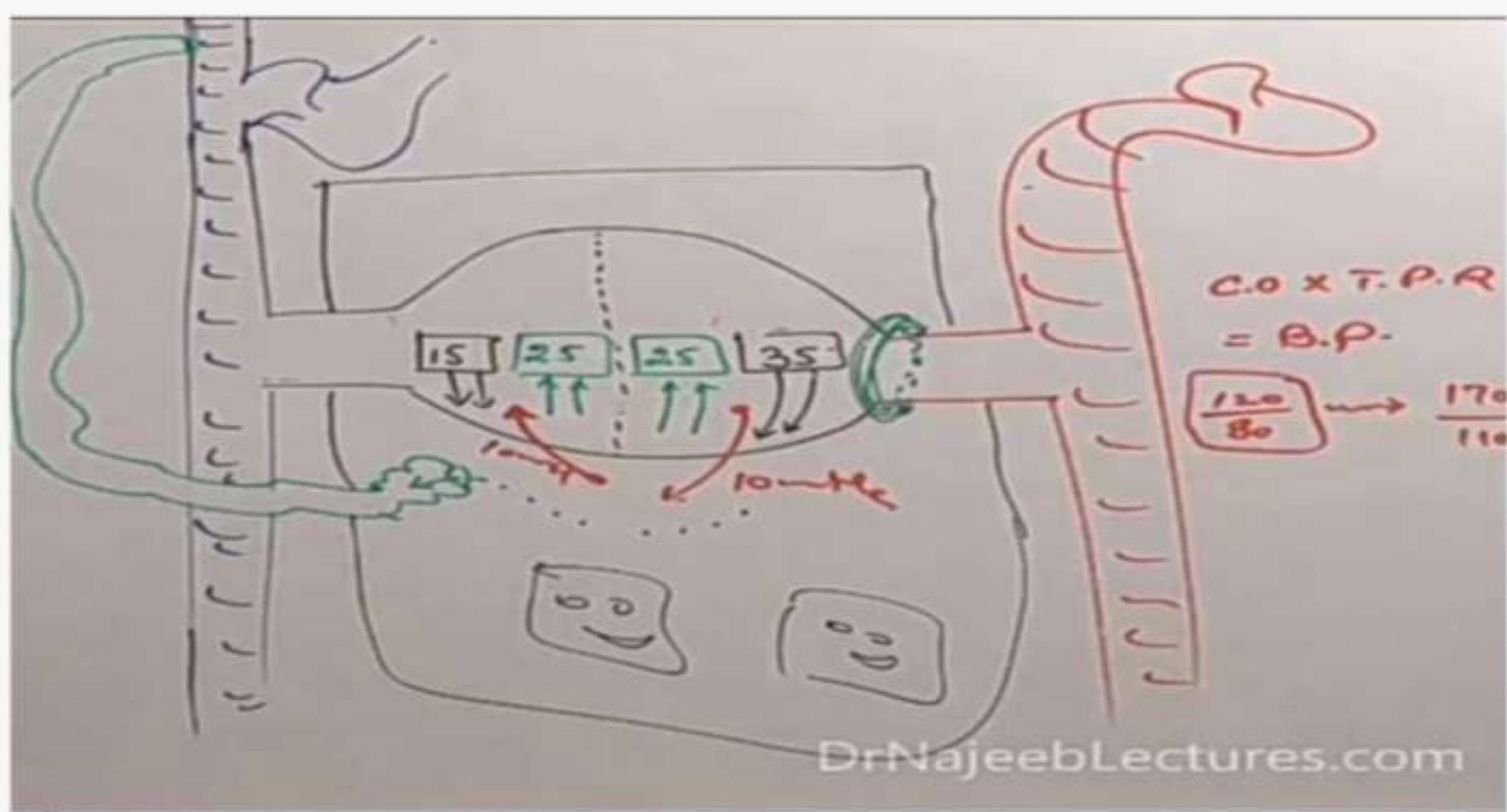
Diagram showing df causes of ECF Edema...

MASTERING EDEMA (PART-II)

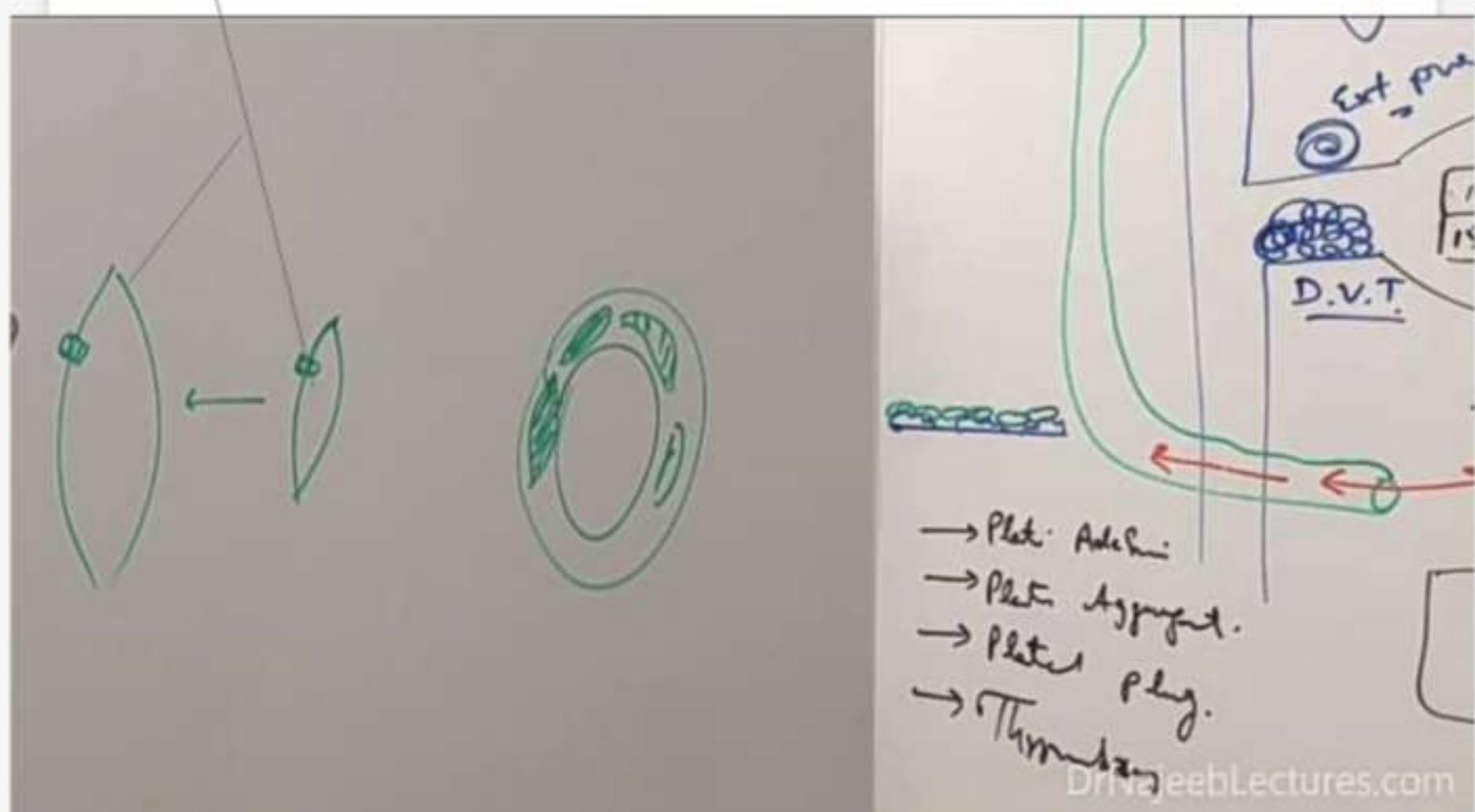


When water enter into ECF it make Glycoprotein free area, water Through free area reach Nutrients, water reach cells..

Glycoproteins Brush Piles in ECF



When smooth muscle Expands, Calcium Channels which are present over smooth muscle cell become open, as a result Ca move in, and Cause Contraction.



SHOCK

SHOCK is a Clinico-pathological Condition in which there is cardiovascular failure or collapse resulting into so poor Peripheral Arterial Perfusion that Tissues are not receiving the minimum amount of Nutrients and oxygen for their Metabolism. So Failure of CVS Leads to Generalised Hypoperfusion in the Body.

DF TYPES OF SHOCKS include,

1-Hypovolumic shock,

2-Cardiogenic shock.

3-Distributive Shock produce due to pathological vasodilation in df Areas of Body.

Anaphylactic Shock, Neurogenic shock, Septal shock, Acute adrenal Failure produce Shock etc. are the Exp. of distributive Shock.

Neurogenic shock produce due to Loss of Sympathetic tone in blood vessels as a result blood vessels Dilates and produce Shock. Exp# If patient take lot of Sympatholytic drugs, or take Vasomotor Depressant, ganglion Blockers, drugs which block the release of Epinephrine or drugs which block receptors of Epinephrine on smooth muscle cells of blood vessels. As a result blood vessels loose their Tone and Vessels Dilates and Eventually produce Shock.

4-Obstructive Shock.

1-CAUSES OF HYPO-VOLUMIC SHOCK :-

Causes include External or Internal Causes. (Given in diagram).

IMP# Production of Fecal matter Around 200 ml every day is Normal. More than 250ml is considered as diarrhea.

2# CAUSES OF CARDIOGENIC SHOCK :- Given In diagram.

3# CAUSES OF DISTRIBUTIVE SHOCK :- (in diagram)

CAUSES OF OBSTRUCTIVE SHOCK :- (in diagram)

IMPORTANT :-

SYNCOPE is define as Transient loss of consciousness due to Generalised Hypoxia to the Cerebral Cortex.

Its a Vasovagal situation that in some Patients suddenly due to fear, due to Prolonged Standing, heavy Cough they develop Swear parasympathetic as well as Vagal activity. Vagal activity slow down the heart and Parasympathetic activity dilates the blood Vessels so due to low Cardiac output and vasodilation, CVS Can't maintain the blood supply to cerebral cortex and as a result Transient loss of unconsciousness occur.

STAGES OF SHOCK :-

1# Non-Progressive (Compensated) stage.

2# Progressive (Reversible) Stage.

3# Refractory shock or Irreversible Stage of Shock.

1# Non-Progressive Stage :- This is the initial stage of Circulatory Shock in which Compensatory mechanism of body Stimulated and they try to stablise the CVS. If these Compensatory mechanism fails then shock enter into 2nd Progressive stage. These Compensatory mechanisms include,

1-Increase the activity of Vasomotor center as a result of decrease blood pressure. So Vasomotor center lead to activation of Sympathetic nervous System. Most of the body blood vessels constrict mainataine blood supply to heart and Brain. Moreover, due to stimulation of Adrenal medulla and Sympathetic nervous system, Arteries as well as Veins constrict and push blood towards heart and maintain Cardiac Output.

Sympathetic activity perform Arteriolo constriction increase TPR and maintain Diastolic Pressure. Venoconstriction increase Venous return to the Heart and increase the Systolic volume. While Epinephrine from Adrenal medulla reach heart and increase Heart rate.

2-RENIN-ANGIOTENSIN mechanism is the 2nd Compensatory mechanism that initiate as result of Low Perfusion to kidney.

3- ADH is release into blood.

4-Central Ischemic Response also Initiates.

5- Reverse stress relaxation of Circulatory System also come into action.

6- Intertitial Fluid try to shift from intertitium into vessels. So during Compensatory stage Shock Person,

1-Have Cold Extremities due to peripheral Vasoconstriction.

2-Rapid Pulse.

3-Patients look Anxious, Fear.

4-Gray colour Face.

Q# How Circulatory Shock Jump from stage 1 to Stage 2 Shock??

Ans :- If tissue remain Hypoxic for longer time that, Compensatory Mechanism Can't Compensate the Loss so, Hypoxic tissues switch to Anaerobic Glycolysis and produce lot of Lactic acid and release in Blood.

IMP#Lactic acid act as vaso Dilator and Depressor of Heart. So when

1# Lot of Lactic acid produce in blood It fight against Vasoconstrictor Compensatory mechanism and Overwhelm the Compensatory mechanism. So blood Vessels Dilates with that, Heart activity also get Depressed. So blood due to excessive vasodilation pools into peripheral area of the body and over that, heart activity is Depress so heart rate decreases with that, stroke volume decrease.

2# Vasomotor center also get Fail.

3# Due to increase Conc. Of Lactic acid, Carbonic acid in blood endothelial cells of Vessels get damage and produce lot of Nitric Oxide. Nitric oxide also dilates the blood Vessels.

4# blood pressure goes down.

5# Epithelial cells of blood Vessels get Shrinken and Fluid enter into interstitium from vessels.

6# Tubular Necrosis may Even Starts in stage 2.

IMP# Upto to the 2nd Stage If Proper treatment is done. Shock can be Recover.

2# In Irreversible Stage of shock:- Hypoxic cells Start dying by Apoptosis and in this Stage body show Resistance to treatment.

In irreversible Stage,

1-Na and Ca enter into Cell and K move out of the cell.

2- Intracellular protons level increases.

3- Decrease ATP level in Hypoxic cells destroy the Lysosome as a result Lysozymal Enzymes release inside the Cell and Rapidly Destroy df Organelles of the cells. Moreover ATP which is present inside the Cell is convert into ADP, then into AMP. AMP is further degrade to produce Adenosine. Adenosine is released into blood which convert into Uric acid and as a result adenosine can't renter into Cell.

Now at this stage, In Management If you increase the oxygenated blood flow to the Hypoxic cell then Hypoxic cell will not show any response Bcz due to Absence of Adenosine inside the Cell, AMP, ADP can't be converted into ATP. So tissue will die and eventually Person will die.

COMPLICATIONS PRODUCE IN IRRIVERISIBLE STAGE :-

1-Patients who died due to Circulatory Shock and you take adopsy of the patient then You will find, Some dead CNS neurons.

Myocardial infarction due to Prolonged ischemia.

2-Hepatocytes will under go fatty change or will be Nacrotic.

3- In kidney PCT become Nacrotic.

4-Adrenal cortex cells will get demage(Imp).

5-Micro infarction in GIT also seen.

SEPTIC SHOCK :-

In Septic shock patients, you will find that in the lungs, microcirculation will heavily damage and cells will become Adematus.

2 hundreds thousands patient in ICU due to septic Shock in USA. Septic shock is the most common cause of death in ICU Patients.

Presence of bacteria in blood is called as **BACTERAEMIA**. It occur very Commonly. But these Bacterias are normally destroyed by immune system of the body.

If Bacteria enter into blood and start multiplying and demaging df tissues of the body then it is called as **SEPTICEMIA**.

ENDOTOXIMIA is a condition in which, Endotoxin level in blood Increases. Endotoxins are Special Lipopoly - Saccharides present in gram Negative bacteria. When gram negative bacteria Die, they release Endotoxins in blood which produce Endotoxinemia.

DF BW GRAM POSITIVE AND GRAM NEGATIVE BACTERIA :-

1- Every GRAM NEGATIVE bacteria is made up of inner lipid layer, middle thin peptidoglycans layer and outer thin lipid layer also.

- # Every gram negative bacteria Contain specific Endotoxin (lipopoly Saccharides chain) that differentiates every Endotoxins from each other.
 - # Endotoxins are the toxins which are the integral component of Bacterial structures. Endotoxins are release only when Bacteria Dies.
 - # 70% of septic shock occur due to Endotoxins release.
 - # Due to Septic shock df organs of the body become Hypo Perfused so Multi organ of the body under go ischemia and eventually multiple organ failure are Seen.
 - # In laboratory investigations, These patients have Neutrophilia,
50% of Patients with septic shock develop thrombocytopenia.
3% of these patient develop Coagulation Abnormalities.
 - # Take at least 3 blood sample from septic shock patients and send it to laboratory.
- 2- GRAM POSITIVE bacteria and Fungi don't Contains Endotoxins.
- # Gram positive bacteria is made up of Inner lipid layer, Thick layer of peptidoglycans.
 - # Some Gram positive bacteria and fungi also contain some endotoxin like substance that can also produce septic shock.
 - # Super antigens Can activate lot of Macrophages and other T cells at one time.

DIFFERENCE BW ENDOTOXINS AND EXOTOXINS:-

1# EXOTOXINS are release by living bacteria and these are release from gram negative as well as gram positive bacteria also. These are not the integral part of Gram Positive or Negative bacteria.

2# Moreover, mechanism of all Endotoxins are Same especially lipid A Endotoxins. But Mechanism of action of Every Exotoxin is df from each other. Every Exotoxins are Specific in their action they act on Specific target tissues and every Exotoxin Produce df disease.

1# ENDOTOXINS are lipid in nature While Endotoxins are Proteins in Nature.

2# Endotoxins remain stable at high temperature while Exotoxins denatured at high temperature.

3# Endotoxins usually don't induce Antibodies. Means body immune system don't make Antibodies against the Endotoxins WHILE Immune system make antibodies against Exotoxins if introduce in the body.

PYOEMIA is a condition in which, Pus from some areas of Body enter directly into blood.

EMPYEMA is a Localise collection of Pus in the epithelial Lined areas such as gallbladder Empyema etc.

ABSCESS is a simply collection of Pus.

Q# How Endotoxins work and produce Septic shock Especially ???

Ans:- 1-When Gram negative bacteria release Lipopoly-Saccharides(Endotoxins) into blood. These Endotoxins bind with Lipopoly Saccharides binding Proteins and reach the target Cells such as endothelial cells or Macrophages.

2-On the target cell, Endotoxins bind with special type of CD14 Receptors of target Cells and stimulate the genetic material of these cells to produce and release Cytokines into the blood.

3-When these cells release lot of cytokines into blood then blood level of cytokines Elevates which directly damage df tissues of the body especially Myocardium and produce septic shock. So Endotoxins produce Septic shock by increasing the production of lot of Cytokines. Moreover,

4-Endotoxins also irritates target Cells to release lot of Nitric oxides. So as result, nitric oxide dilates blood vessels too much and produce distributive Shock also.

IMPORTANT :-

#Every patient with septic shock don't develop Fever. Out of 100 patients of Septic shock, 5% patient remain Normothermic. 15% patients become Hypothermic. While 80% patients develop Fever. Reason is that, many Endotoxins also effect the Hypothalamus so temperature changes are seen. But every patient of septic shock have warm hands and feet due to excess Vasodilation.

IMPORTANT :-

ADVANTAGES OF LOW CYTOKINES LEVEL :-

1# Cytokines in low concentration in blood is good for the body. Low cytokines activate WBCs such as Neutrophils and Macrophages to Phagocytose dead gram - ve bacteria at area, where Localised inflammation has Started. So enhance the immune system. Moreover, Low cytokines also Shrinken endothelial cells of local Vessels which are present around the injured area. so lot of Fluid drag platelets and WBCs towards the inflammation site. WHILE

DISADVANTAGES OF MODERATE OR HIGH LEVEL OF CYTOKINES IN BODY :-

2# Cytokines in moderate or high Conc. are dangerous for the body.

1-Moderate concentration of Cytokine stimulate Hepatocytes to produce Special Proteins called as Acute phase proteins or Reactants. These are the group of Proteins. Some of these Proteins also play role in rising ESR. Some of these Proteins are C reactive Proteins. Conc. of C reactive protein in blood is diagnostically used to check level of inflammation in body.

2- Moderate Cytokines blood level also stimulate bone marrow and release lot of Neutrophils into blood develop Neutrophilia.

3- Moderate Cytokines level such as interleukin - 1 and TNF disturb the Hypothalamus and Hypothalamus produce PGE2. PGE2 act on special Hypothalamic related with thermostates and induce fever.

4- HIGH LEVEL of cytokines damage endothelial cells lining the blood Vessels and also Shrinken endothelial cells and produce severe Vasodilation at df tissues over the body which lead to distributive Shock.

5-High cytokines also damage the Endothelial cells of pulmonary circulation. As a result of this, Macrophages and Neutrophils stuck at pulmonary vessels and start Phagocytosis process and damage pulmonary system and produce ARDS(Acute respiratory distress syndrome).

6-High level of Cytokines are cardiac Depressant.

Q# What are the Df types of Cytokines?,

Diagram showing Diagrammatic view of df types of Shocks...

In Cardiogenic shock, heart Fail to Pump.

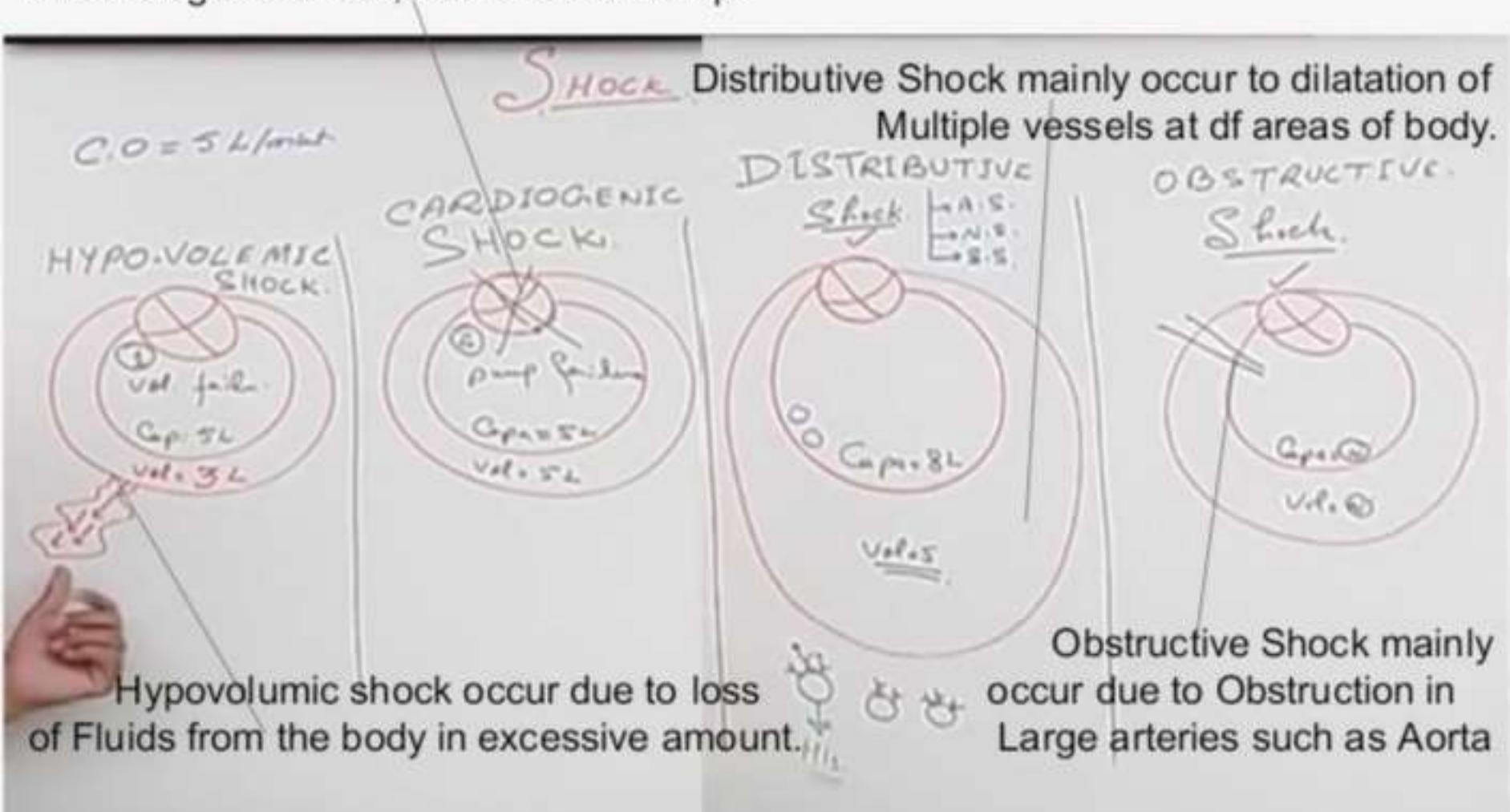


Diagram showing df causes of Hypovolumic shock...

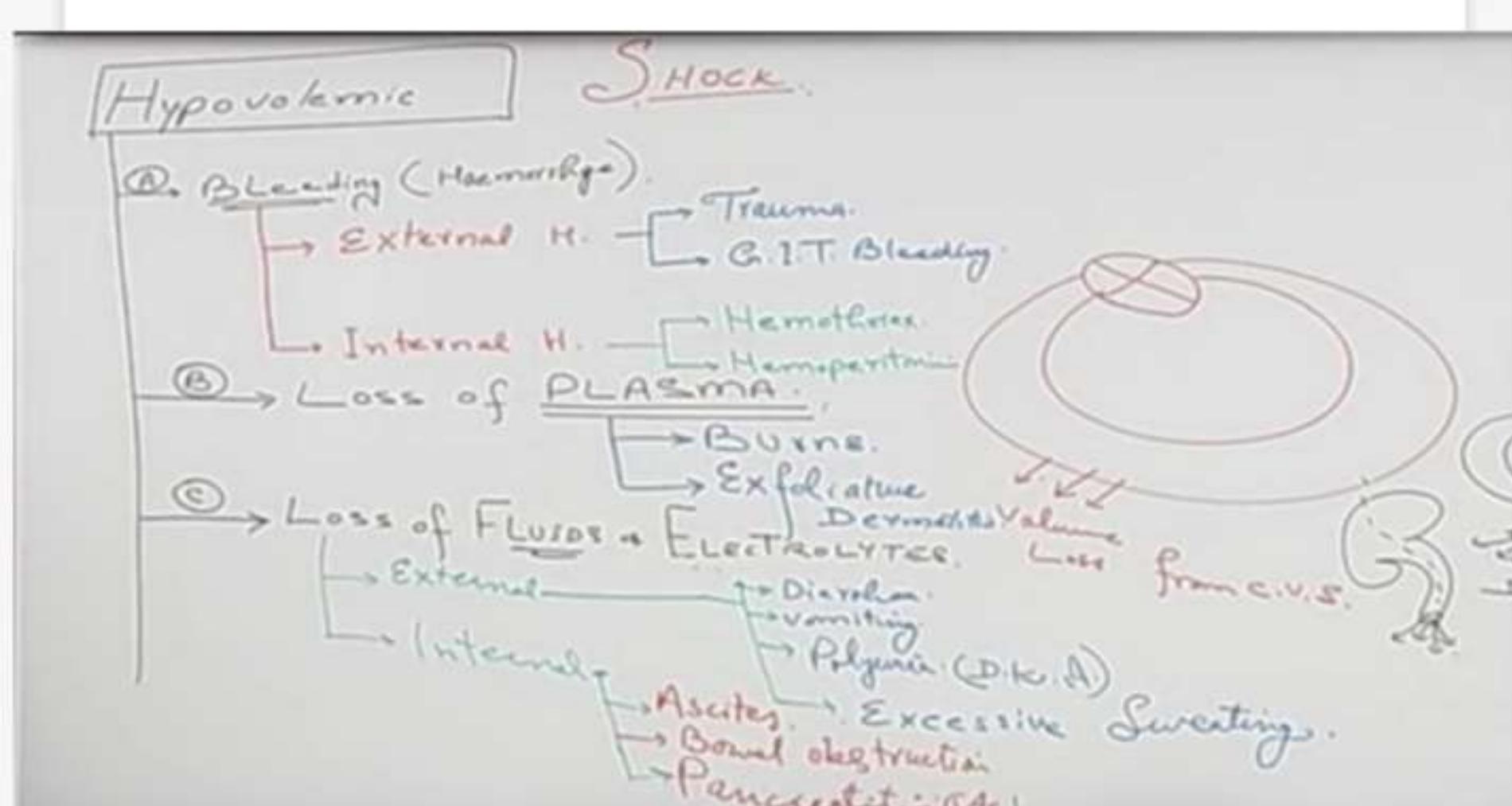


Diagram showing How You Can calculate cardiac output and Related terms...

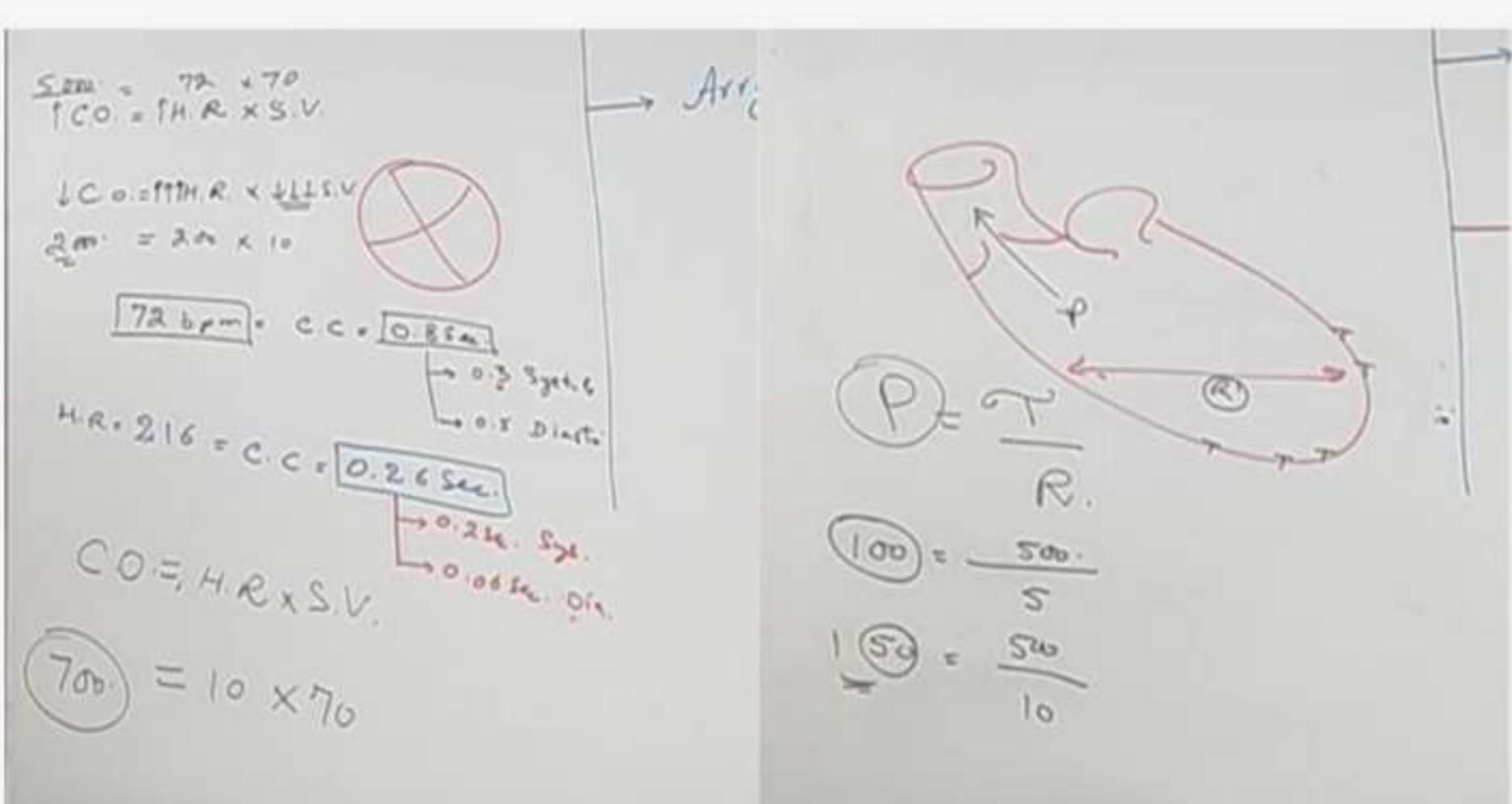
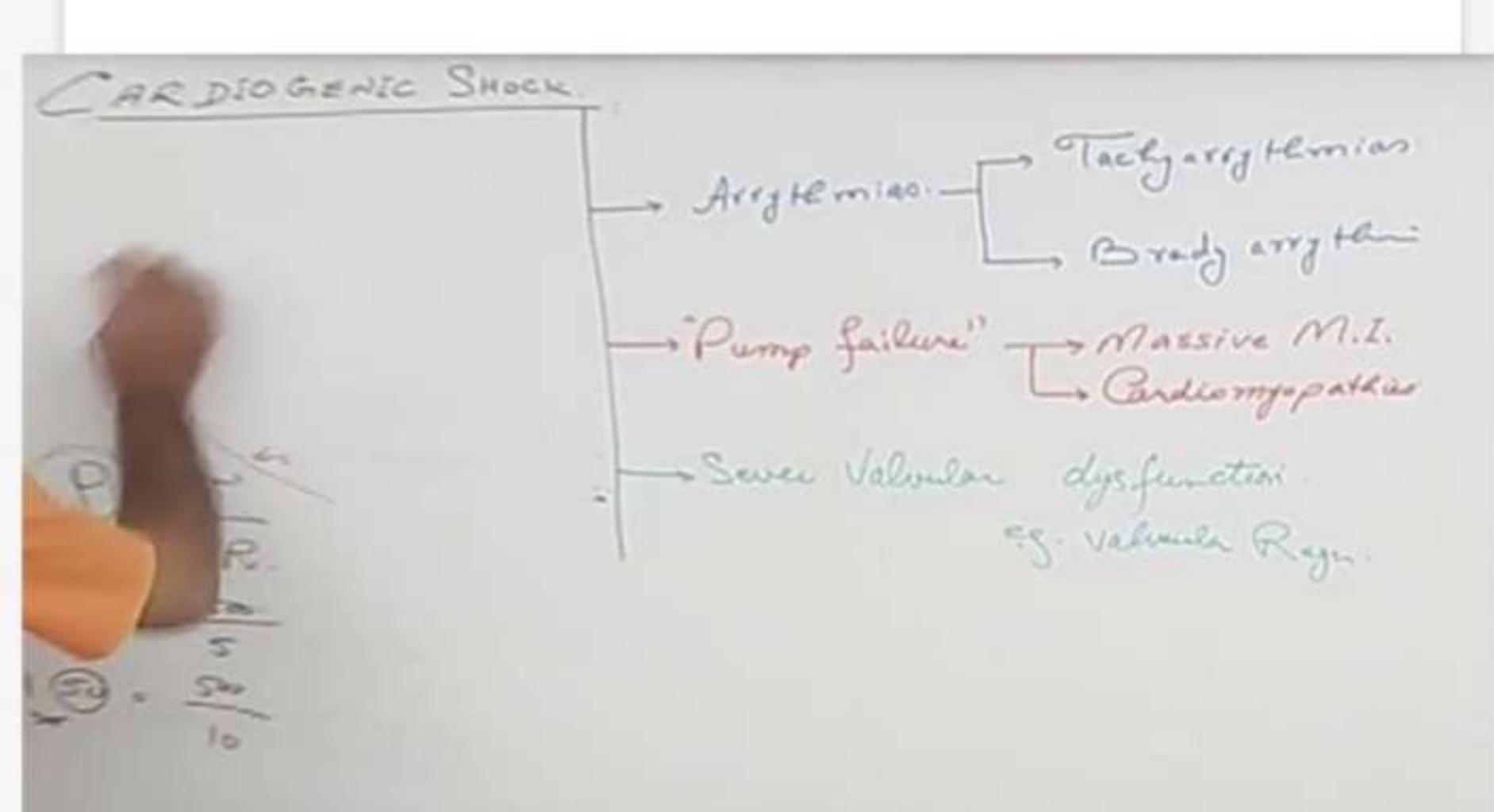


Diagram showing df causes of Cardiogenic shock..



CARDIOGENIC SHOCK



In septic shock, interventricular Septum undergo infarction and as a result blood move From Left to Right Side and Can't pump properly into Aorta.

In septic shock due to MI, blood may enter into Pericardial space and Block the heart movement.

In Cardiogenic shock, heart Valves Become Dysfunctional.



Cardiogenic shock also occur due to MI.

Diagram showing mechanism of development of Neurogenic Shock...

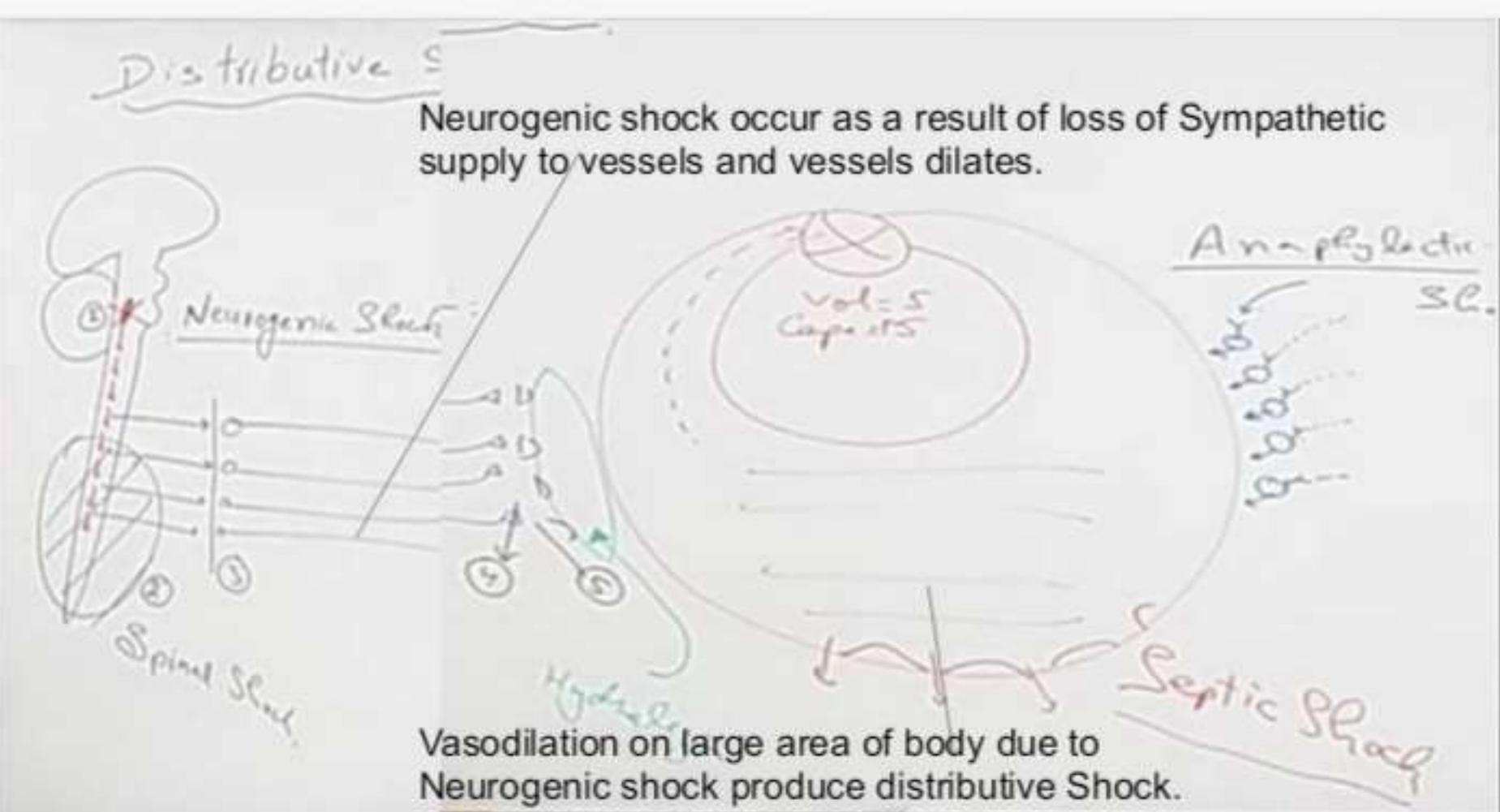


Diagram showing df Causes of obstructive Shock...

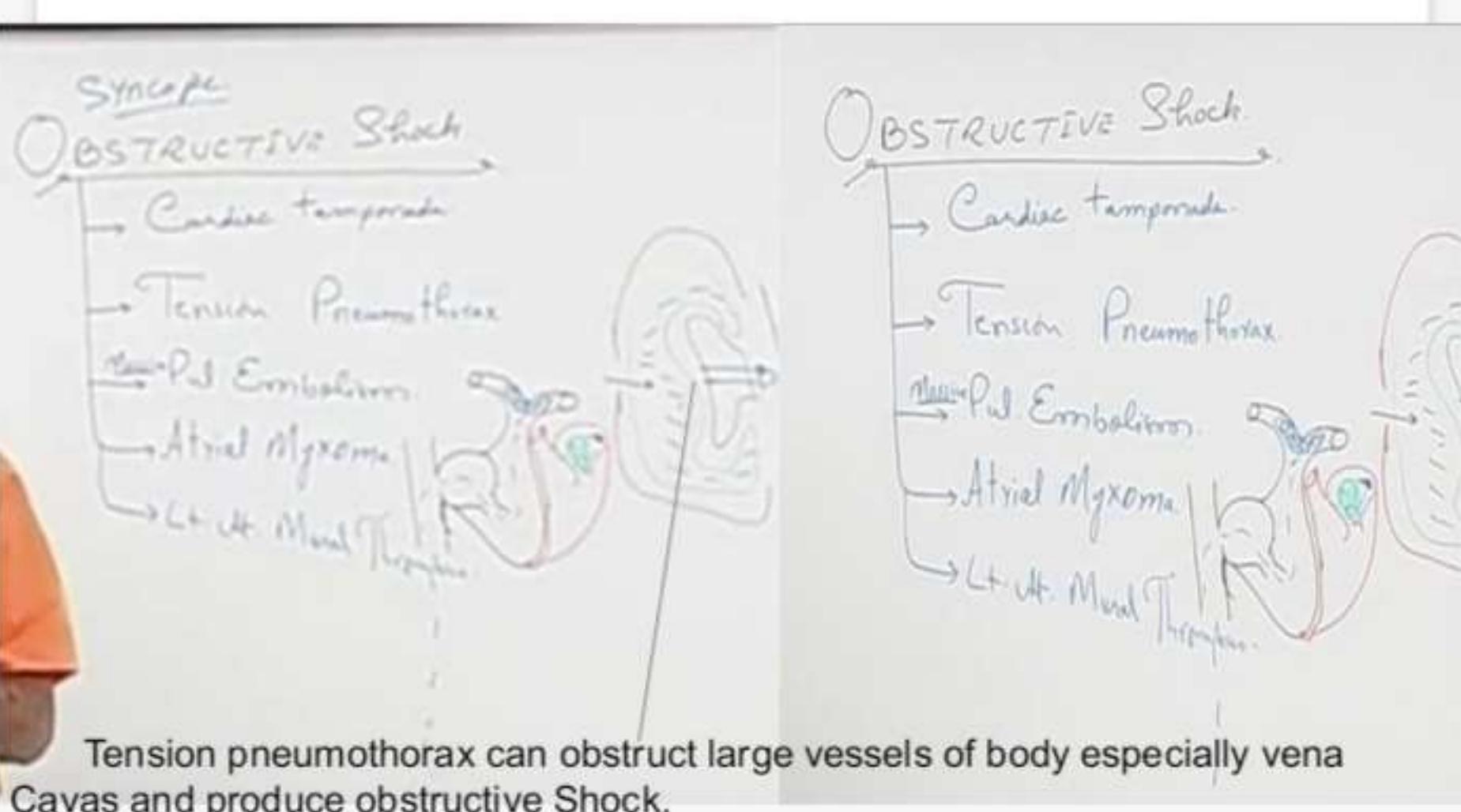
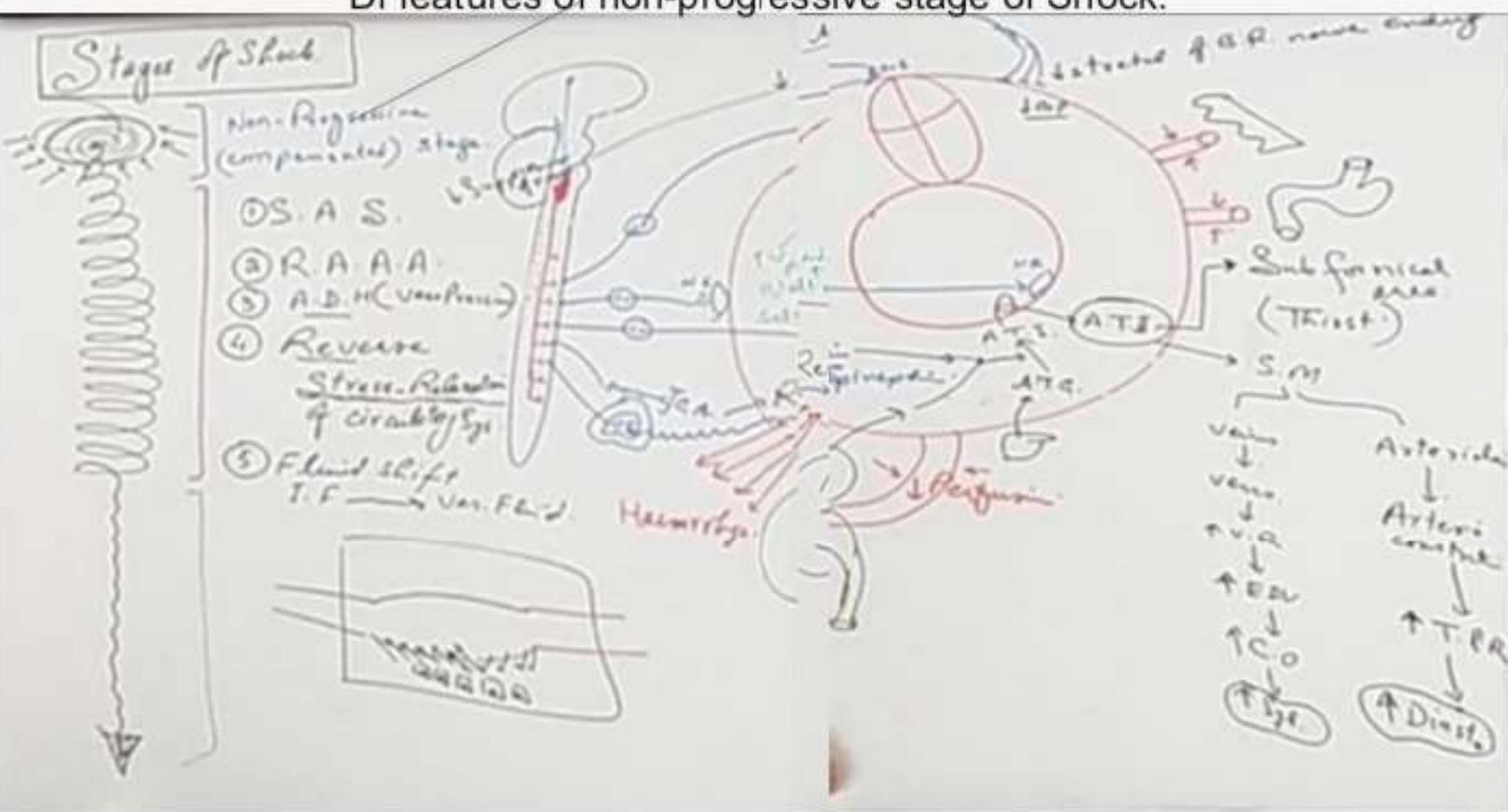


Diagram showing df stages of shock
and also Telling about Features of Non
Progressive shocks...

Df features of non-progressive stage of Shock.



Df stages of the shock.

Due to Pericardial effusion, heart get Shrinken and due to Pericardial compression which is Characterise by Elevated JVP.

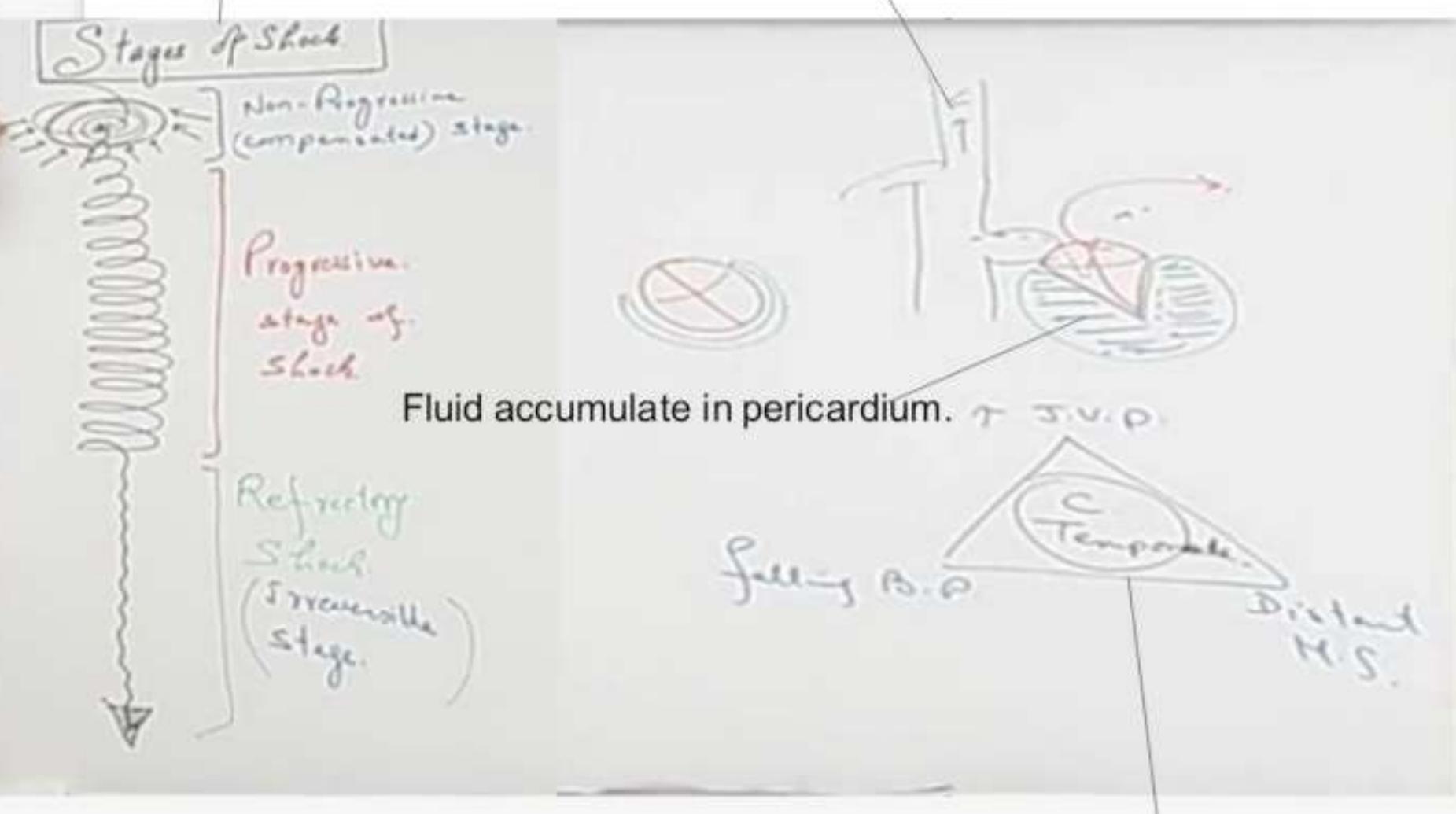


Diagram showing Clinical features of cardiac Tamponade

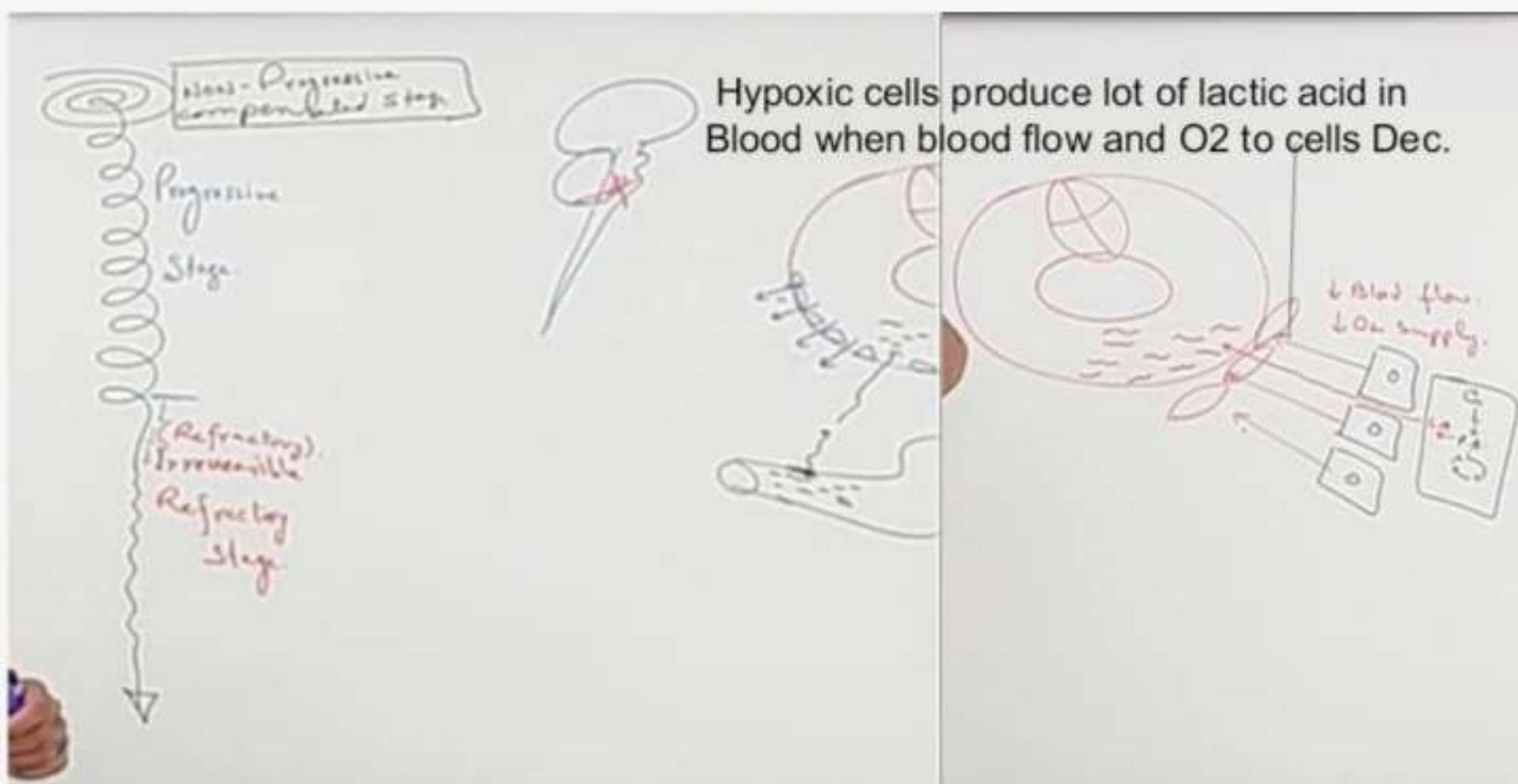
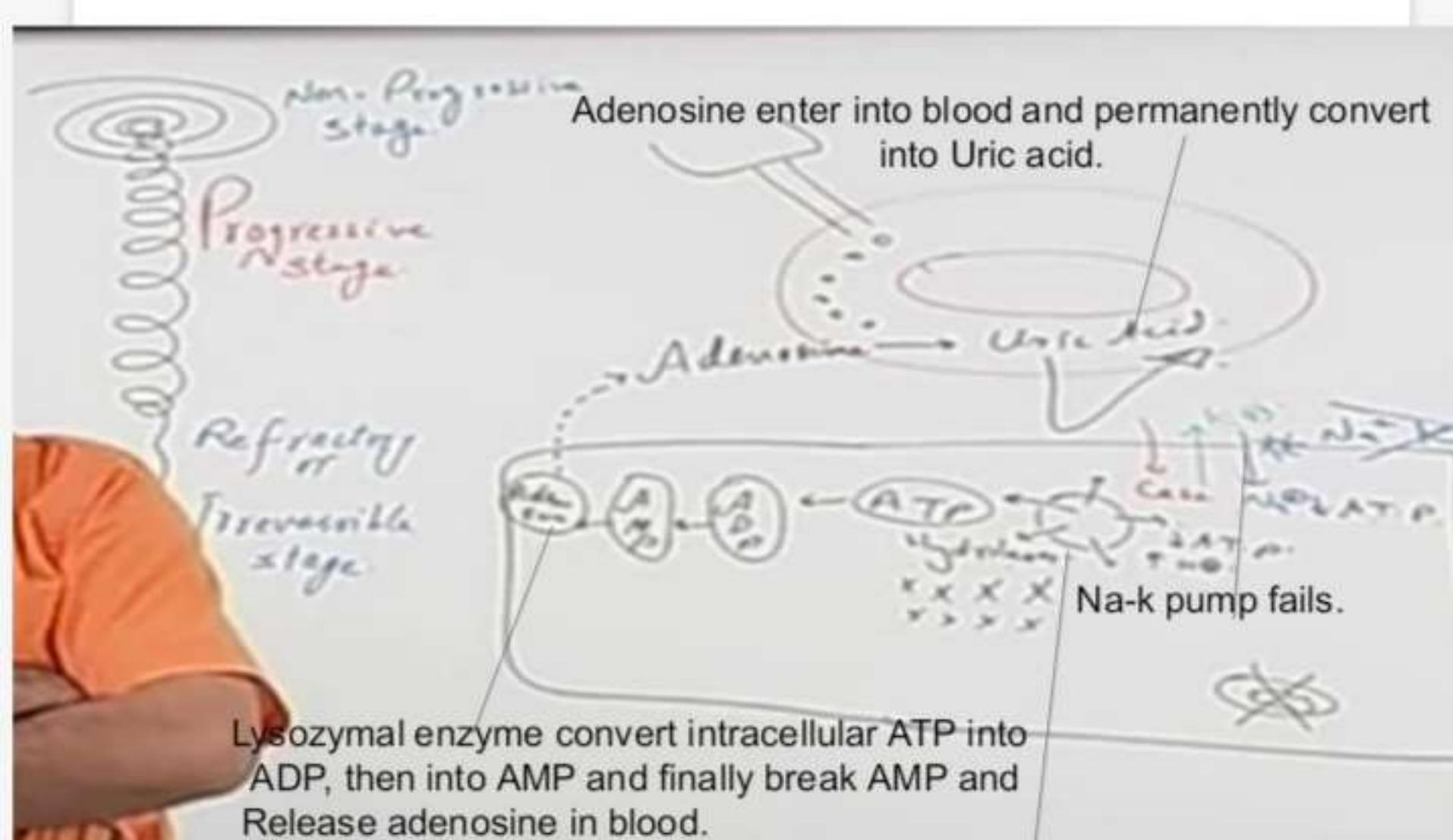


Diagram showing df changes that occur during irreversible stage of Shock...



When tissue become Hypoxic then Lysosomes get destroyed due to Hypoxia as a result, lot of Lysozymal enzyme destroy df Organelles of the body.

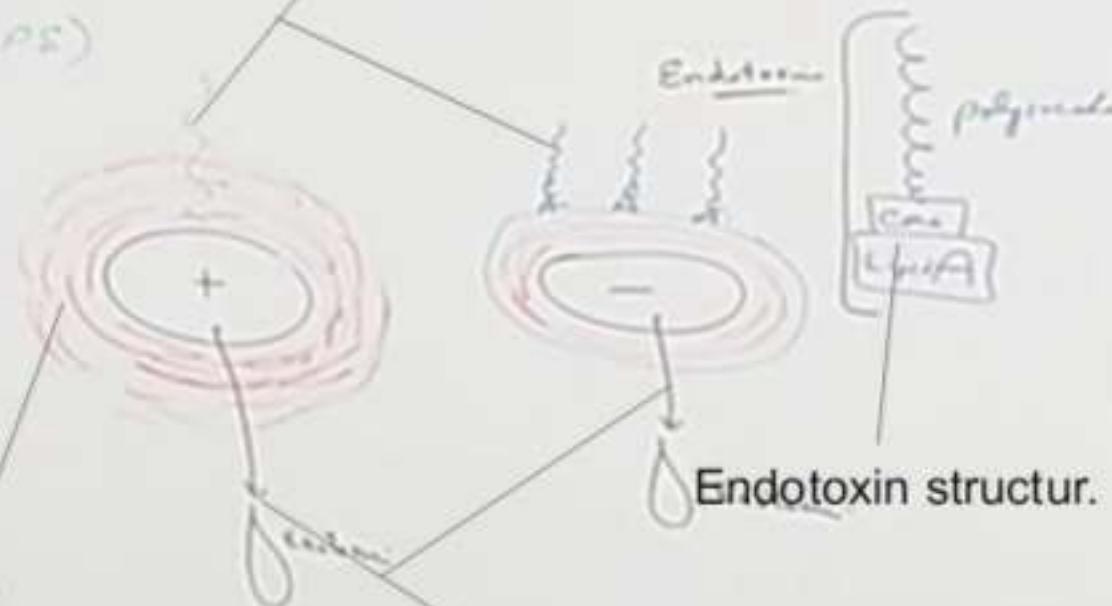
Diagram showing gram positive and negative bacteria and df Imp. Terms...

Septic Shock

- C.
① Bacteremia.
② Septicemia
③ Endotoxemia (LPS)
④ Pyrexia
⑤ Empyema.
⑥ Alkalosis.



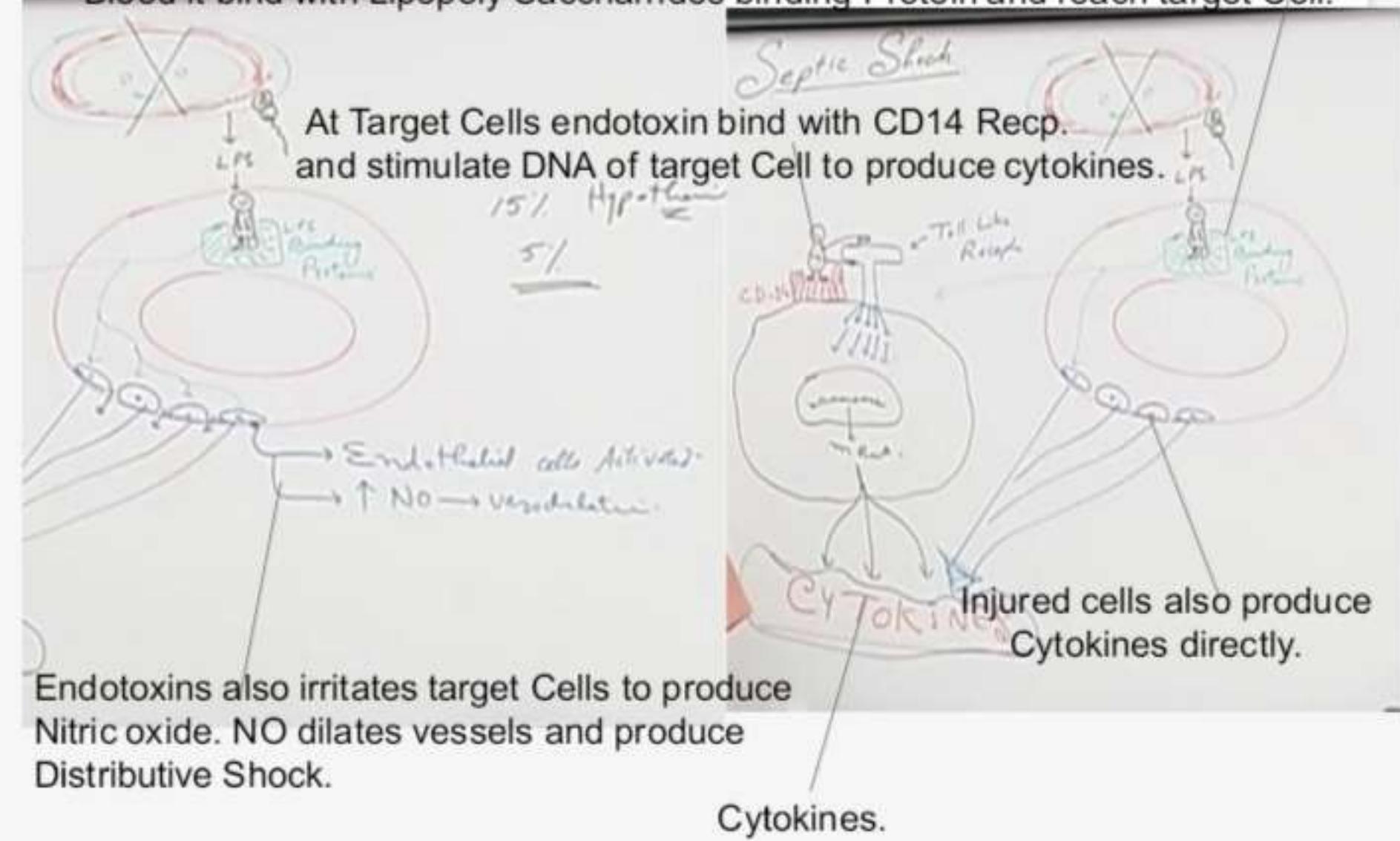
Gram negative bacteria produce Endotoxins in Large amount as compare to gram +ve bacteria



Gram +ve bacteria mainly release Exotoxins while Body of Gram Positive bacteria. Gram - ve produce Exotoxins in low amount.

Diagram showing mechanism of action of Endotoxins in body...

When gram negative bacteria release Endotoxins (Lipopoly Saccharides) into Blood it bind with Lipopoly Saccharides binding Protein and reach target Cell.



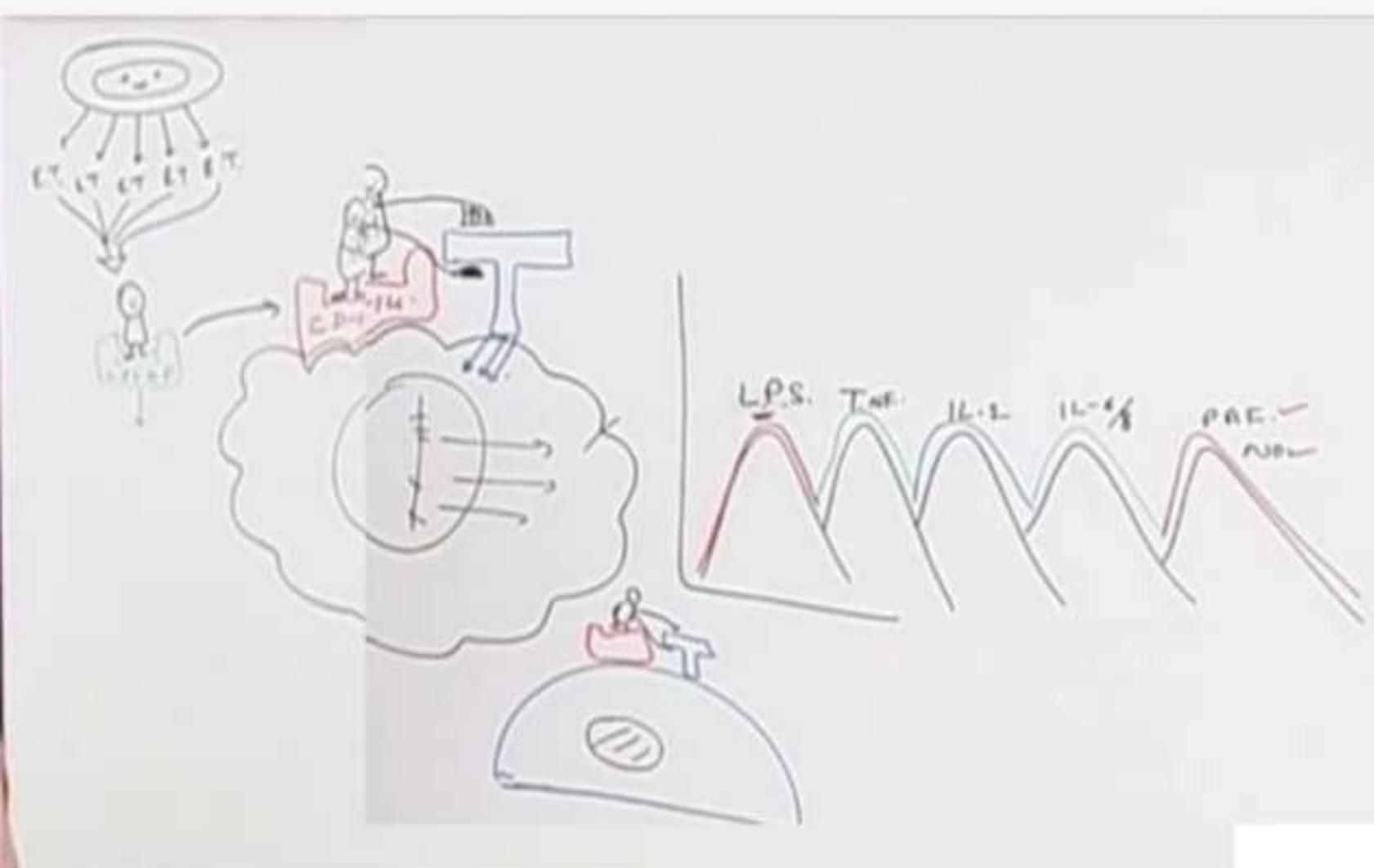
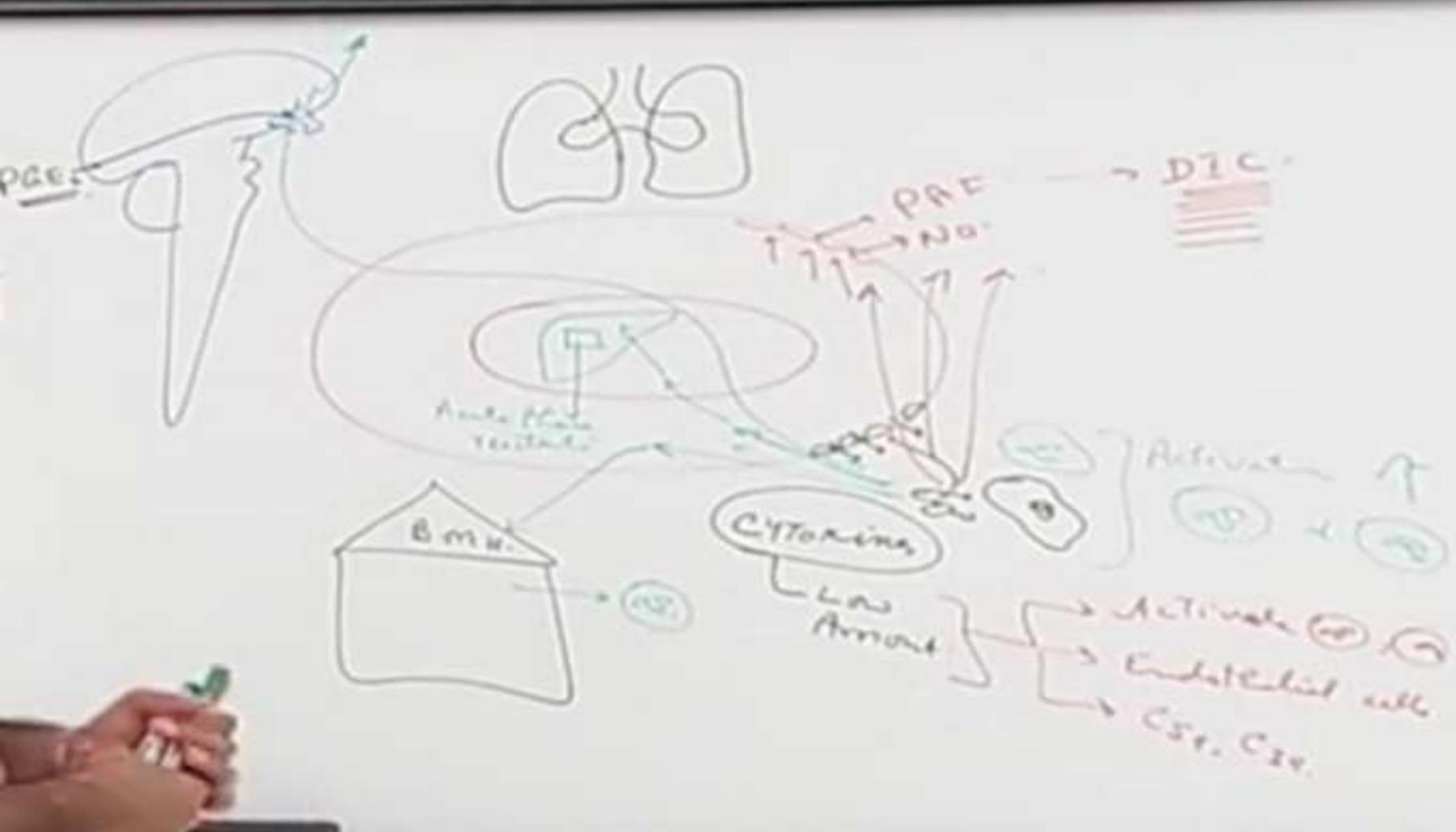


Diagram showing cellular events occur during acute inflammation...



INDEX

General Pathology

- Proto-Oncogenes 06
Tumor suppressor Gene 06
Gene amplification 09
Gain of function Mutation 09
Tumor suppressor Gene 12
TWO HIT Hypothesis 13
Human papilloma 14
Li fraumeni syndrome 16
Hereditary polyposis Coli 17
VON Hippel LINDAU Disease 19
Wilms tumor 20
Anti-Apoptotic Gene 21
Pro-Apoptotic Gene 21
DNA repair system 23
Necrosis, Heterolysis 38
Myelin figures, karyolysis 40
Karyorrhexis, pyknosis 40
Necrosis types 41
Apoptosis 46
Extrinsic apoptotic pathway 47
Intrinsic apoptotic pathway 49
Inflammation, Parenchyma cells 55
Stroma cells 55
Exudation, Transudation 56
Cellular retraction 57
cellular Contraction 57
Margination process 59
Pericardial effusion 68
Pericardial Temponade 68
hydrothorax 68
Hypervolemia, Erythema 69
Hypermedia 69
Non-pitting Edema, Dependent Edema 70
Anasarca 70
Shock types 77
Syncope 78
Shock stages 78
Septic shock, Bacteremia 82
septicemia, Endotoxemia 82
Gram negative bacteria 82
Gram positive bacteria 83
Exotoxins, Endotoxins, Pyaemia 84
Empyema, Abscess 84