

IMMUNOSUPPRESSANTS

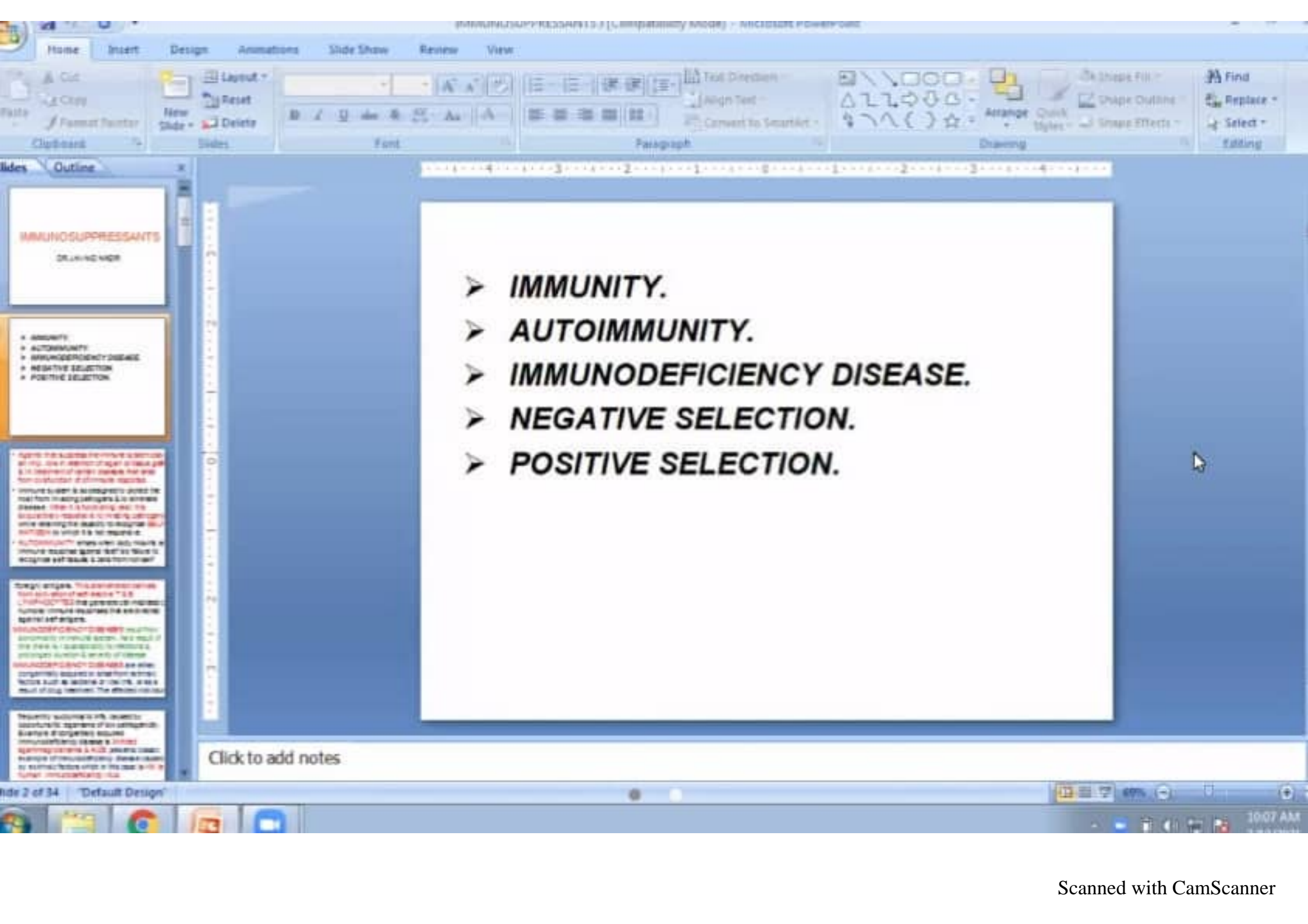
DR.JAVAID NAZIR

R

From Rabia Nadeem F18-103 Unknown to Everyone

F18-103

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- **IMMUNITY.**
- **AUTOIMMUNITY.**
- **IMMUNODEFICIENCY DISEASE.**
- **NEGATIVE SELECTION.**
- **POSITIVE SELECTION.**

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IMMUNOSUPPRESSANTS (Compatibility Mode) - Microsoft PowerPoint

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IMMUNOSUPPRESSANTS DRIVING FOR

- IMMUNITY
- AUTOIMMUNITY
- IMMUNODEFICIENCY DISEASE
- NEGATIVE SELECTION
- POSITIVE SELECTION

- Agents that suppress the immune system play an imp. role in retention of organ or tissue grafts & in treatment of certain diseases that arise from dysfunction of immune response.
- Immune system is so designed to protect the host from invading pathogens & to eliminate disease. When it is functioning best, it is exquisitely responsive to invading pathogens while retaining the capacity to recognize SELF ANTIGEN to which it is not responsive.
- **AUTOIMMUNITY** arises when body mounts an immune response against itself b/o failure to recognize self tissues & cells from non self

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IMMUNOSUPPRESSANTS

DRUGS AND

- IMMUNITY
- AUTOIMMUNITY
- IMMUNODEFICIENCY DISEASE
- NEGATIVE SELECTION
- POSITIVE SELECTION

Agents that suppress the immune system are called immunosuppressants. They are used to prevent rejection of organs and tissues in transplantation and to suppress the immune system in autoimmune diseases. They are also used to suppress the immune system in cancer treatment.

Immunosuppressants are used to suppress the immune system. They are used to prevent rejection of organs and tissues in transplantation and to suppress the immune system in autoimmune diseases. They are also used to suppress the immune system in cancer treatment.

Autoimmunity arises when self-reactive immune response against self-antigens results in chronic self-damage & loss of function.

Foreign antigens: The presence of self-antigens is not sufficient to initiate T & B lymphocyte response. The presence of self-antigens is not sufficient to initiate T & B lymphocyte response. The presence of self-antigens is not sufficient to initiate T & B lymphocyte response.

Immunodeficiency diseases are either congenitally acquired or arise from extrinsic factors such as bacterial or viral infections, or as a result of drug treatment. The affected individual

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(foreign) antigens. This phenomenon derives from activation of self reactive T & B LYMPHOCYTES that generate cell mediated or humoral immune responses that are directed against self antigens.

IMMUNODEFICIENCY DISEASES result from abnormality in immune system. As a result of this there is ↑ susceptibility to infections & prolonged duration & severity of disease.

IMMUNODEFICIENCY DISEASES are either congenitally acquired or arise from extrinsic factors such as bacterial or viral infs. or as a result of drug treatment. The affected individual

Microsoft PowerPoint 2010 interface showing a slide with text about T cell selection. The ribbon includes Home, Insert, Design, Animations, Slide Show, Review, and View. The ribbon tabs are Clipboard, Slides, Font, Paragraph, Drawing, and Editing. The slide content is as follows:

-IVE SELECTION T cells develop & learn to recognize self & non-self in thymus. T cells that bind with high affinity to self antigens in thymus undergo apoptosis (**-IVE SELECTION**) while those T cells that are capable of recognizing foreign antigens are retained & expanded for export to periphery (lymph nodes, spleen & peripheral blood). **This is +IVE SELECTION.**

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Outline:

- IVE SELECTION T cells develop & learn to recognize self & non-self in thymus. T cells that bind with high affinity to self antigens in thymus undergo apoptosis (-IVE SELECTION) while those T cells that are capable of recognizing foreign antigens are retained & expanded for export to periphery (lymph nodes, spleen & peripheral blood). This is +IVE SELECTION.
- IMMUNOSUPPRESSION
 - Immune reactions in man may be actively mediated (B cell) or T cell mediated
 - Regulation of T cells is essential - avoids excessive self damage
 - Suppression of a damaging immune response is employed in allergy & autoimmune disease & in failure to reject grafts to prevent rejection.
- FACTORS OF IMMUNOSUPPRESSION
 - Suppressed immune response involving suppressor T cells (CD8+) or Treg cells.
 - CD4+ regulatory T cells (Treg) suppress other T cells. Deletion of Treg cells occurs from thymic selection (CD4+ regulatory T cells).
- FACTORS OF IMMUNOSUPPRESSIVE DRUGS
 - Immune response is long term use of drugs is **IMMUNOSUPPRESSIVE** drugs. Use of **IMMUNOSUPPRESSIVE** drugs is essential in organ & bone marrow transplantation.
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- T cell in thymus & spleen
- T cell in thymus & spleen



Notes Outline

- THE SELECTION T... (faded text)
- IMMUNOSUPPRESSION
 - Immune response... (faded text)
 - Rejection of... (faded text)
 - Suppression of a... (faded text)
- HAZARDS OF IMMUNOSUPPRESSION
 - Suppressed immune... (faded text)
 - ... (faded text)
- HAZARDS OF IMMUNOSUPPRESSIVE DRUGS
 - ... (faded text)
 - ... (faded text)
 - ... (faded text)
- ... (faded text)
- ... (faded text)

IMMUNOSUPPRESSION

- Immune responses in man may be antibody mediated (B cell) or T cell mediated.
- Rejection of grafts & delayed allergic reactions are cell mediated.
- Suppression of a damaging immune response is employed in allergic & autoimmune diseases & in tissue or organ grafting to prevent rejection.

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- HAZARDS OF IMMUNOSUPPRESSION
- HAZARDS OF IMMUNOSUPPRESSIVE DRUGS
- INDICATIONS
- IMMUNOSUPPRESSIVE AGENTS

HAZARDS OF IMMUNOSUPPRESSION

- **Impaired** immune responses render the subject more liable to **BACTERIAL OR VIRAL** infs.
- **CARCINOGENICTY** is also hazard generally after **4-7 yrs of therapy**. Cancers most likely to occur are those thought to have **VIRAL** origin(**LEUKEMIAS & LYMPHOMAS**).

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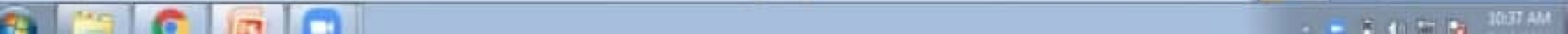
Outline

- THE SELECTION of immunosuppressive drugs
- IMMUNOSUPPRESSION
 - Immune response: in man may be actively mediated (T cell) or T cell mediated
 - Regulation of immune response: immune response are cell mediated
 - Suppression of a damaging immune response is employed in allergic & autoimmune diseases. It is also used in organ grafting to prevent rejection.
- HAZARDS OF IMMUNOSUPPRESSION
 - Impaired immune response increases susceptibility to bacterial, viral, fungal, etc.
 - Chronic toxicity: may lead to renal, hepatic, etc. damage
- HAZARDS OF IMMUNOSUPPRESSIVE DRUGS
 - Include those of long term use of drugs eg CORTICOSTEROID therapy, then of CYTOTOXICS (bone marrow depression, infertility & teratogenesis).
 - When cytotoxics are used, there is an additional risk of MUTAGENICITY which may induce cancer.
 - While hazards are relatively acceptable for treating grave life endangering diseases in elderly, they give more cause of concern when agents are used in younger pts. with less
- IMMUNOSUPPRESSANTS (Compatibility Mode)

HAZARDS OF IMMUNOSUPPRESSIVE DRUGS

- Include those of long term use of drugs eg **CORTICOSTEROID** therapy, then of **CYTOTOXICS**(bone marrow depression, infertility & teratogenesis).
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Clipboard Slides Outline Font Paragraph Drawing Editing

serious diseases e.g. Rh. Arthritis, Ulcerative colitis.

- Treat all infs. early & vigorously.
- Use human γ globins to protect if there is exposure to viral infs. eg MEASLES & VARICELA.
- (Mutagen is a physical or chemical agent that changes the genetic material usually DNA of an organism & thus inc. the frequency of mutation.)

INDICATIONS
Subcutaneous or intramuscular
Prevention of measles, mumps, rubella, and chickenpox (varicella) in children and adults
Prevention of measles, mumps, and rubella (MMR) in children and adults
Prevention of measles, mumps, and rubella (MMR) in children and adults
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IMMUNOSUPPRESSIVE AGENTS
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CONTRAINDICATIONS
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ADVERSE EFFECTS
Prevention of measles, mumps, and rubella (MMR) in children and adults
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PHARMACOLOGY
Prevention of measles, mumps, and rubella (MMR) in children and adults
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Microsoft PowerPoint 2010 interface showing a slide with immunology notes.

Interferons: Proteins grouped into 3 families
IFN α , IFN β , & IFN γ .
 , Both IFN α & IFN β -- type 1 IFN are acid stable
 & act on same receptors on targets cells

IFN γ --- type 2 IFN acid labile & acts on separate
 receptors on targets cells.

Anti TNF α agents e.g. Etanercept.

Other Cytotoxic agents: Cyclophosphamide,
 Methotrexate, Leflunomide, Cytarabine,
 Vincristine.

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PHARMACOLOGY (Compatibility Mode) - MICROSOFT POWERPOINT

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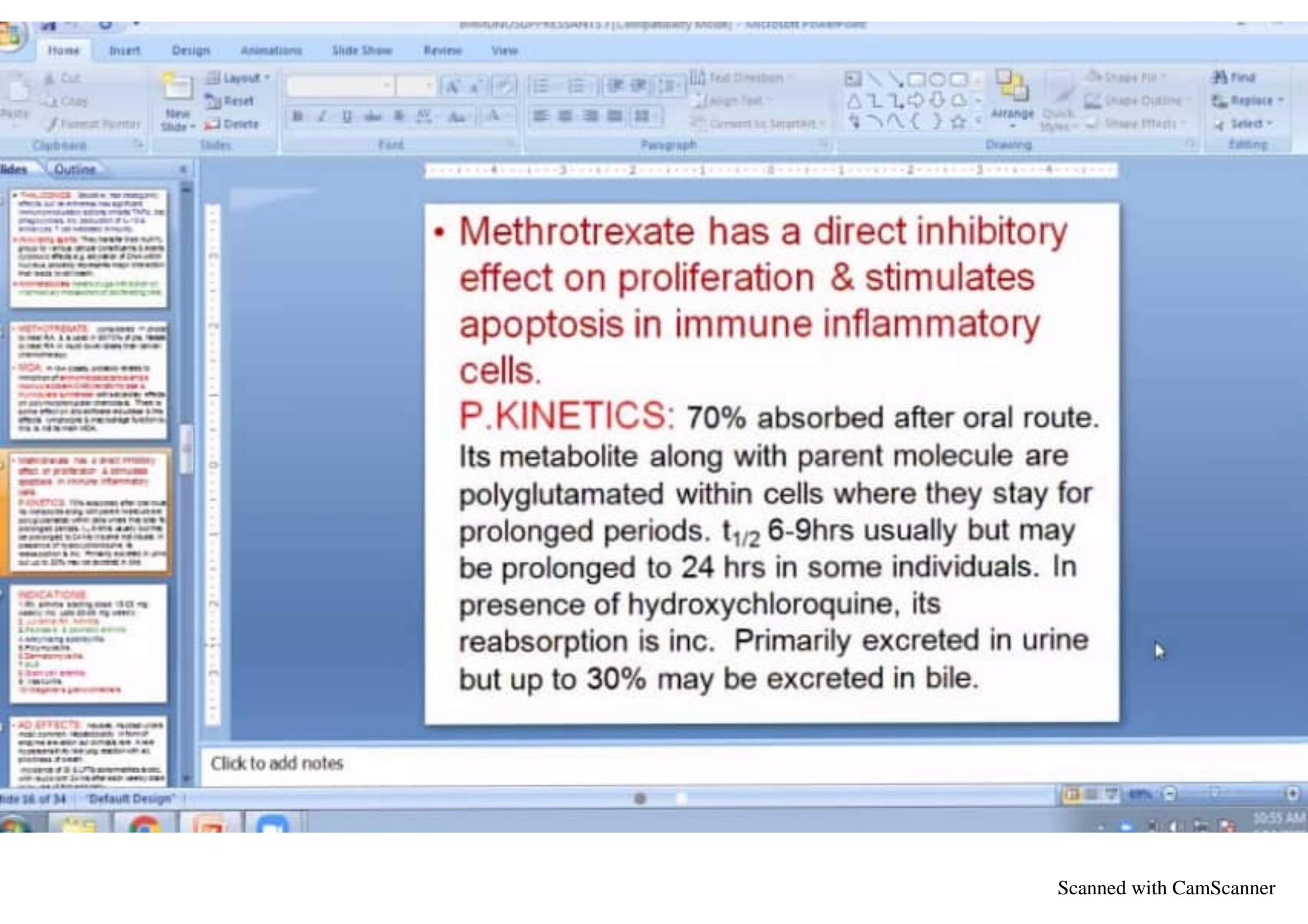
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Notes Outline

- IMMUNOSUPPRESSIVE AGENTS**
 - Corticosteroids** - Suppresses Immune Response
 - Anti-TNF** - Inhibits TNF
 - Anti-IL-6** - Inhibits IL-6
 - Anti-CD20** - Inhibits CD20
 - Anti-CD40L** - Inhibits CD40L
 - Anti-CCR5** - Inhibits CCR5
 - Anti-CCR4** - Inhibits CCR4
 - Anti-CCR2** - Inhibits CCR2
 - Anti-CCR1** - Inhibits CCR1
 - Anti-CCR3** - Inhibits CCR3
 - Anti-CCR6** - Inhibits CCR6
 - Anti-CCR7** - Inhibits CCR7
 - Anti-CCR8** - Inhibits CCR8
 - Anti-CCR9** - Inhibits CCR9
 - Anti-CCR10** - Inhibits CCR10
- METHOTREXATE** - Considered 1st choice to treat RA. & is used in 50-70% of pts. Needed to treat RA in much lower doses than cancer chemotherapy.
- MOA**: In low doses, probably relates to inhibition of **aminoimidazolecarboxamide ribonucleotide(AICAR)transformylase & thymidylate synthetase** with secondary effects on polymorphonuclear chemotaxis. There is some effect on dihydrofolate reductase & this affects lymphocyte & macrophage function but this is not its main MOA.

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• Methotrexate has a direct inhibitory effect on proliferation & stimulates apoptosis in immune inflammatory cells.

P.KINETICS: 70% absorbed after oral route. Its metabolite along with parent molecule are polyglutamated within cells where they stay for prolonged periods. $t_{1/2}$ 6-9hrs usually but may be prolonged to 24 hrs in some individuals. In presence of hydroxychloroquine, its reabsorption is inc. Primarily excreted in urine but up to 30% may be excreted in bile.

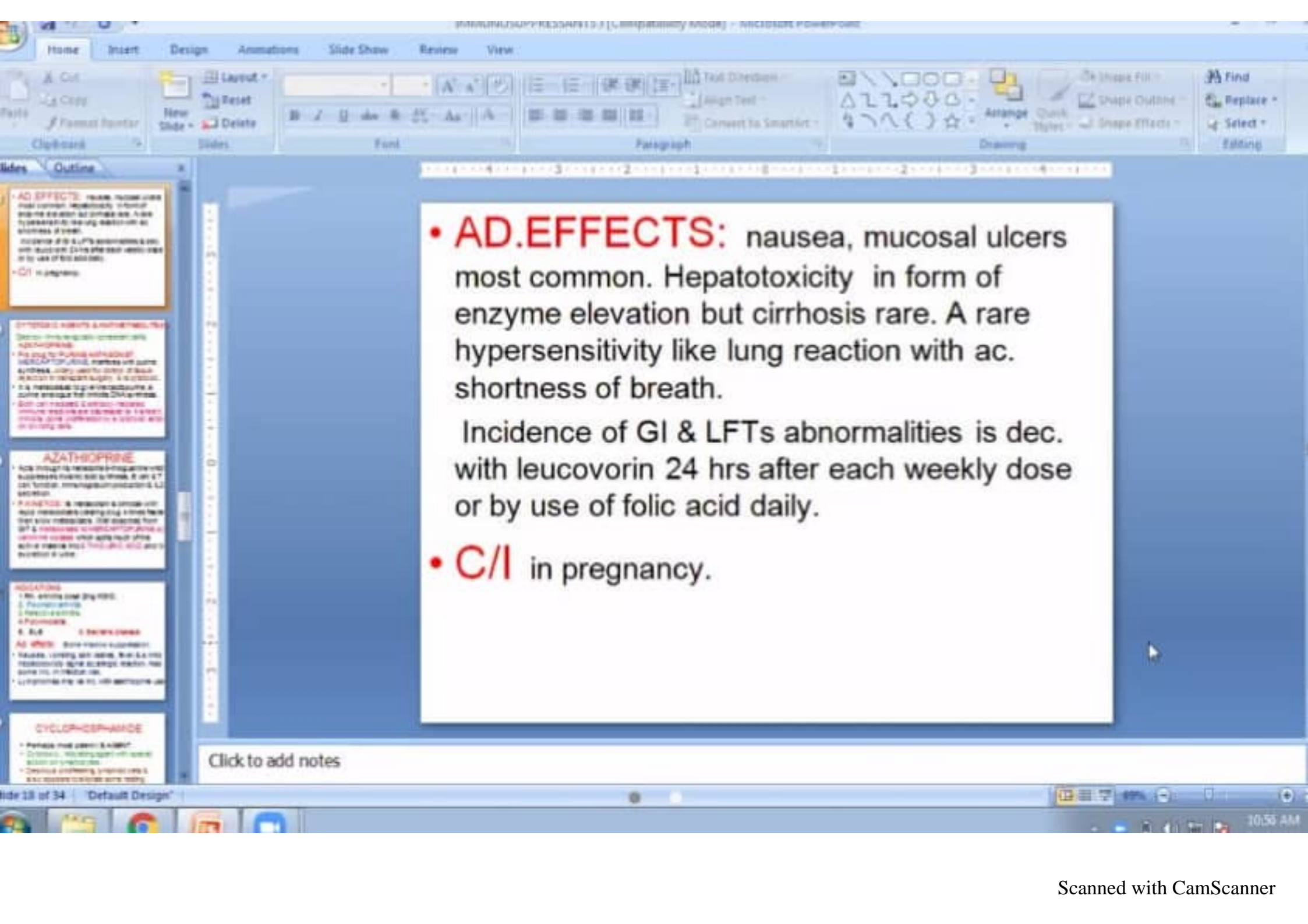
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Microsoft PowerPoint 2010 interface showing a slide titled "INDICATIONS:" with a list of 10 conditions. The ribbon includes Home, Insert, Design, Animations, Slide Show, Review, and View. The left sidebar shows the Outline pane with various notes.

INDICATIONS:

1. Rh. arthritis starting dose 15-25 mg weekly inc. upto 30-35 mg weekly.
2. Juvenile Rh. Arthritis.
3. Psoriasis & psoriatic arthritis.
4. Ankylosing spondylitis.
5. Polymyositis.
6. Dermatomyositis.
7. SLE
8. Giant cell arteritis.
9. Vasculitis.
10. Wegener's granulomatosis.

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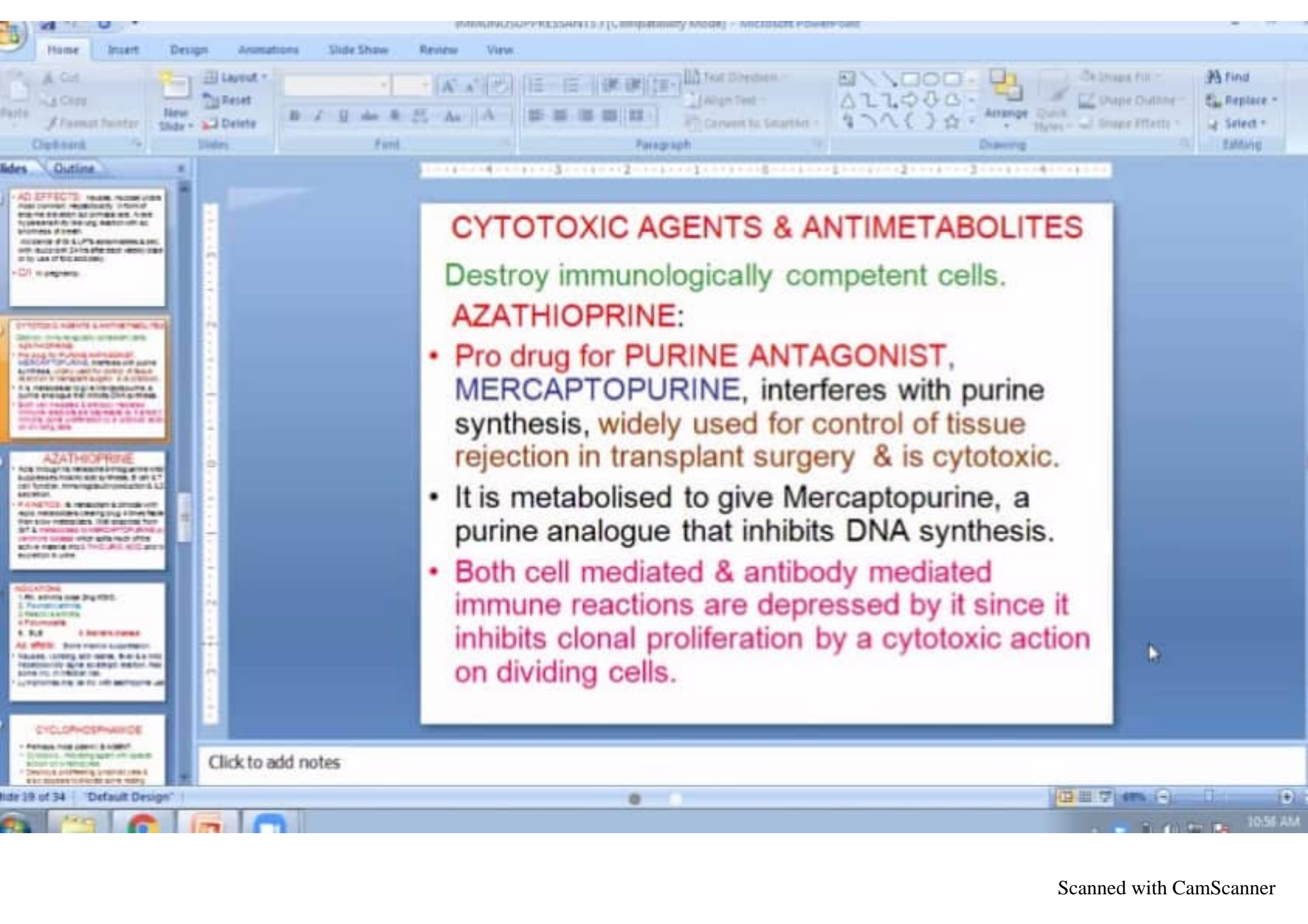


- **AD.EFFECTS:** nausea, mucosal ulcers most common. Hepatotoxicity in form of enzyme elevation but cirrhosis rare. A rare hypersensitivity like lung reaction with ac. shortness of breath.

Incidence of GI & LFTs abnormalities is dec. with leucovorin 24 hrs after each weekly dose or by use of folic acid daily.

- **C/I** in pregnancy.

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CYTOTOXIC AGENTS & ANTIMETABOLITES

Destroy immunologically competent cells.

AZATHIOPRINE:

- Pro drug for PURINE ANTAGONIST, MERCAPTOPURINE, interferes with purine synthesis, widely used for control of tissue rejection in transplant surgery & is cytotoxic.
- It is metabolised to give Mercaptopurine, a purine analogue that inhibits DNA synthesis.
- Both cell mediated & antibody mediated immune reactions are depressed by it since it inhibits clonal proliferation by a cytotoxic action on dividing cells.

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Microsoft PowerPoint 2010 interface showing a slide titled "INDICATIONS:" with a list of conditions and "Ad. effects: Bone marrow suppression." The slide content is as follows:

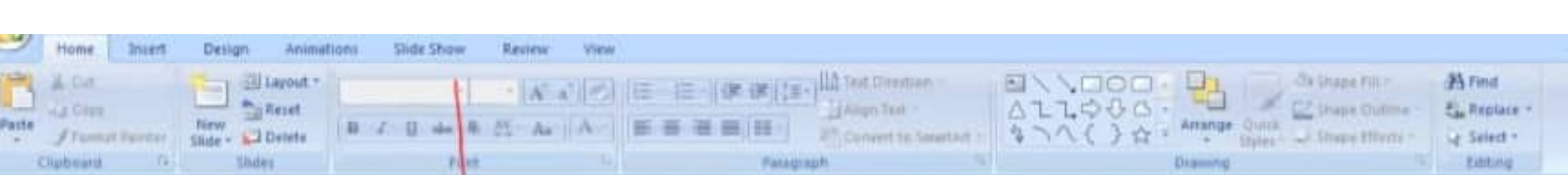
INDICATIONS:

1. Rh. arthritis dose 2mg/KG/D.
2. Psoriatic arthritis.
3. Reactive arthritis.
4. Polymyositis.
5. SLE
6. Bechet's disease.

Ad. effects: Bone marrow suppression.

- Nausea, vomiting, skin rashes, fever & a mild hepatotoxicity signal ac. allergic reaction. Also some inc. in infection risk.
- Lymphomas may be inc. with azathioprine use.

The slide is part of a presentation with a sidebar on the left containing notes for other drugs: AD EFFECTS, CYCLOPHOSPHAMIDE, AZATHIOPRINE, and CYCLOPHOSPHAMIDE.



CYCLOPHOSPHAMIDE

- Perhaps most potent I.S.AGENT.
- Cytotoxic. Alkylating agent with special action on lymphocytes.
- Destroys proliferating lymphoid cells & also appears to alkylate some resting cells.
- Decreases antibody mediated & cell mediated immune reactions.
- In small doses very effective against autoimmune disorders.

CYCLOPHOSPHAMIDE

Most active metabolite of cyclophosphamide. It suppresses T cell & B cell levels by 20-40%. T cell & B cell counts return to normal within 4-6 weeks.

AD EFFECTS: Nausea, vomiting, bone marrow depression & leukopenia & neutropenia. No effect on platelets & hemoglobin. May cause hair loss & skin rash.

Also to suppress immune response. Hematologic counts are low & do not recover.

with absolute neutrophil count below 1500/mm³.

INDICATIONS:

1. Malignancy
2. SLE
3. Rheumatoid
4. Organ's transplant.

CYCLOSPORINE

Fungal poison with potent immunosuppressive effect on cell proliferation.

MOA: Thought regulation of gene transcription in control of T & B lymphocyte production & secondary antibody maturation. It's an inhibitor of T cell response. T cell response & antibody are reduced.

EFFECTS: Neutrophil count & lymphocyte count. Bone density. Thrombocytopenia. Also effects on B cells. Neutrophils in 7-8 days. Lymphocytes in 10-14 days.

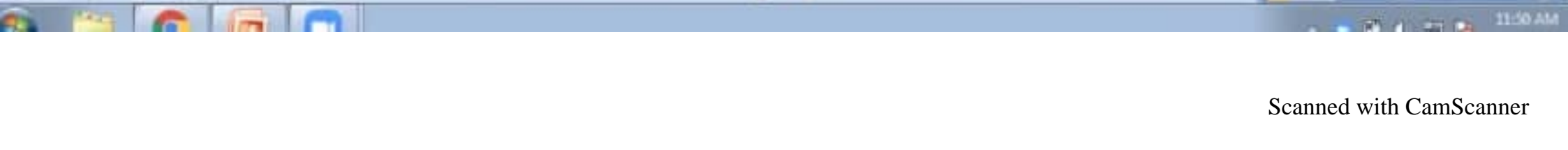
INDICATIONS:

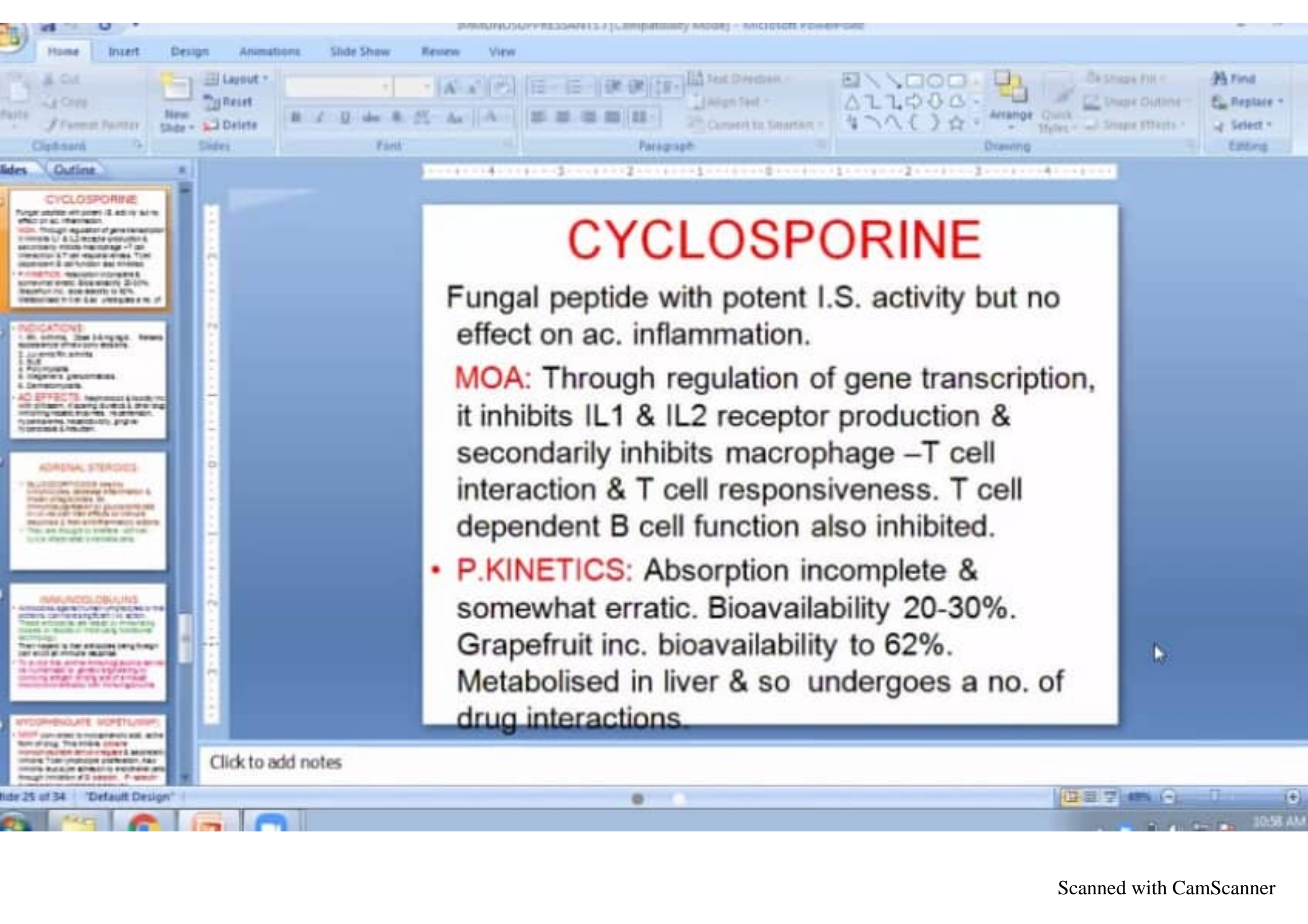
1. Malignancy. Organ transplant. Heart transplantation after organ donation.
2. Psoriasis & alopecia.
3. SLE.
4. Psoriasis.
5. Organ's transplant.
6. Dermatomyositis.

CYCLOPHOSPHAMIDE

- Perhaps most potent I.S.AGENT.
- Cytotoxic . Alkylating agent with special action on lymphocytes
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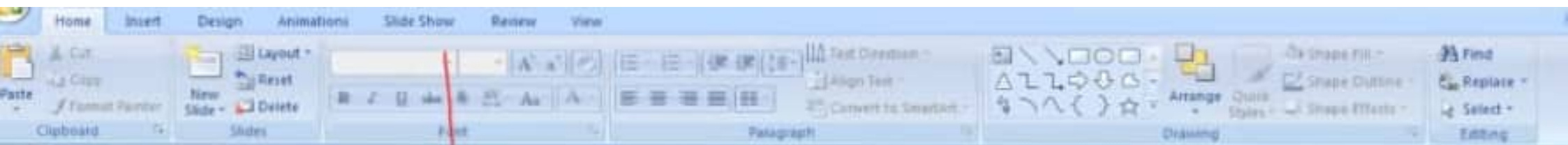
CYCLOSPORINE

Fungal peptide with potent I.S. activity but no effect on ac. inflammation.

MOA: Through regulation of gene transcription, it inhibits IL1 & IL2 receptor production & secondarily inhibits macrophage -T cell interaction & T cell responsiveness. T cell dependent B cell function also inhibited.

- **P.KINETICS:** Absorption incomplete & somewhat erratic. Bioavailability 20-30%. Grapefruit inc. bioavailability to 62%. Metabolised in liver & so undergoes a no. of drug interactions.

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Slides Outline

- INDICATIONS
- AD EFFECTS
- ADRENAL STEROIDS
- IMMUNOSUPPRESSANTS
- MYCOPHENOLATE MOFETIL (MMF)

MYCOPHENOLATE MOFETIL (MMF)

- MMF** converted to mycophenolic acid, active form of drug. This inhibits **cytosine monophosphate dehydronegase** & secondarily inhibits T cell lymphocyte proliferation. Also inhibits leucocyte adhesion to endothelial cells through inhibition of **E-selectin, P-selectin & intercellular adhesion molecule 1**.

USED for TM of renal disease due to SLE. Also in vasculitis & wegener's granulomatosis. Occasionally used for TM of Rh. ar. at a dosage of 2g/d.

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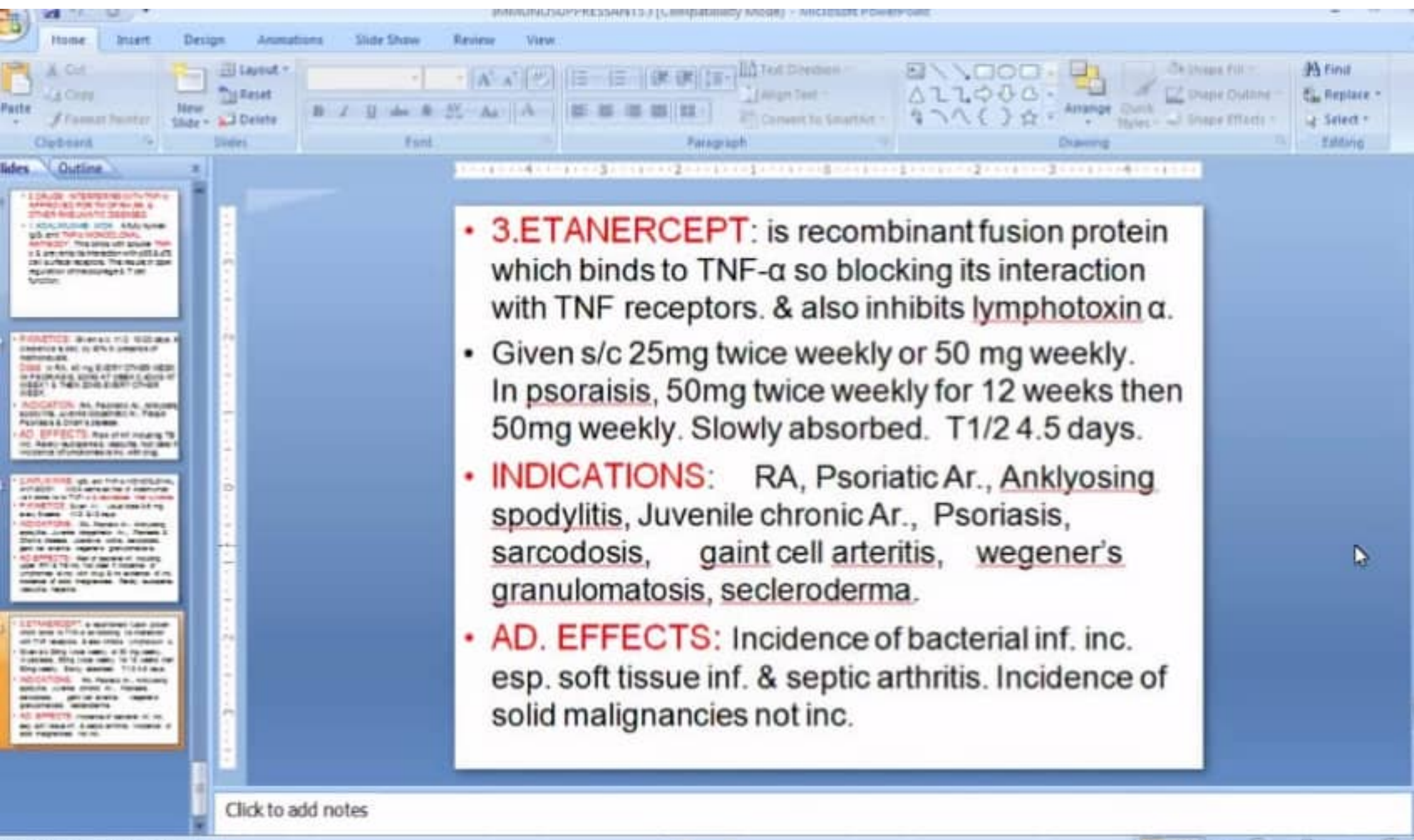
Slides Outline

- 3 DRUGS INTERFERING WITH TNF- α APPROVED FOR TM OF RH.AR. & OTHER RHEUMATIC DISEASES.
- 1. ADALIMUMAB: MOA: A fully human IgG₁ anti TNF- α MONOCLONAL ANTIBODY. This binds with soluble TNF- α & prevents its interaction with p55 & p75 cell surface receptors. This results in down regulation of macrophage & T cell function.
- 2. INFlixIMAB: MOA: A fully human IgG₁ anti TNF- α MONOCLONAL ANTIBODY. This binds with soluble TNF- α & prevents its interaction with p55 & p75 cell surface receptors. This results in down regulation of macrophage & T cell function.
- 3. ETNERCEPT: MOA: A fully human IgG₁ anti TNF- α MONOCLONAL ANTIBODY. This binds with soluble TNF- α & prevents its interaction with p55 & p75 cell surface receptors. This results in down regulation of macrophage & T cell function.

• 3 DRUGS INTERFERING WITH TNF- α APPROVED FOR TM OF RH.AR. & OTHER RHEUMATIC DISEASES.

• 1. ADALIMUMAB: MOA: A fully human IgG₁ anti TNF- α MONOCLONAL ANTIBODY. This binds with soluble TNF- α & prevents its interaction with p55 & p75 cell surface receptors. This results in down regulation of macrophage & T cell function.

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- **3. ETANERCEPT:** is recombinant fusion protein which binds to TNF- α so blocking its interaction with TNF receptors. & also inhibits lymphotoxin α .
- Given s/c 25mg twice weekly or 50 mg weekly. In psoriasis, 50mg twice weekly for 12 weeks then 50mg weekly. Slowly absorbed. T1/2 4.5 days.
- **INDICATIONS:** RA, Psoriatic Ar., Ankylosing spondylitis, Juvenile chronic Ar., Psoriasis, sarcoidosis, giant cell arteritis, wegener's granulomatosis, scleroderma.
- **AD. EFFECTS:** Incidence of bacterial inf. inc. esp. soft tissue inf. & septic arthritis. Incidence of solid malignancies not inc.

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