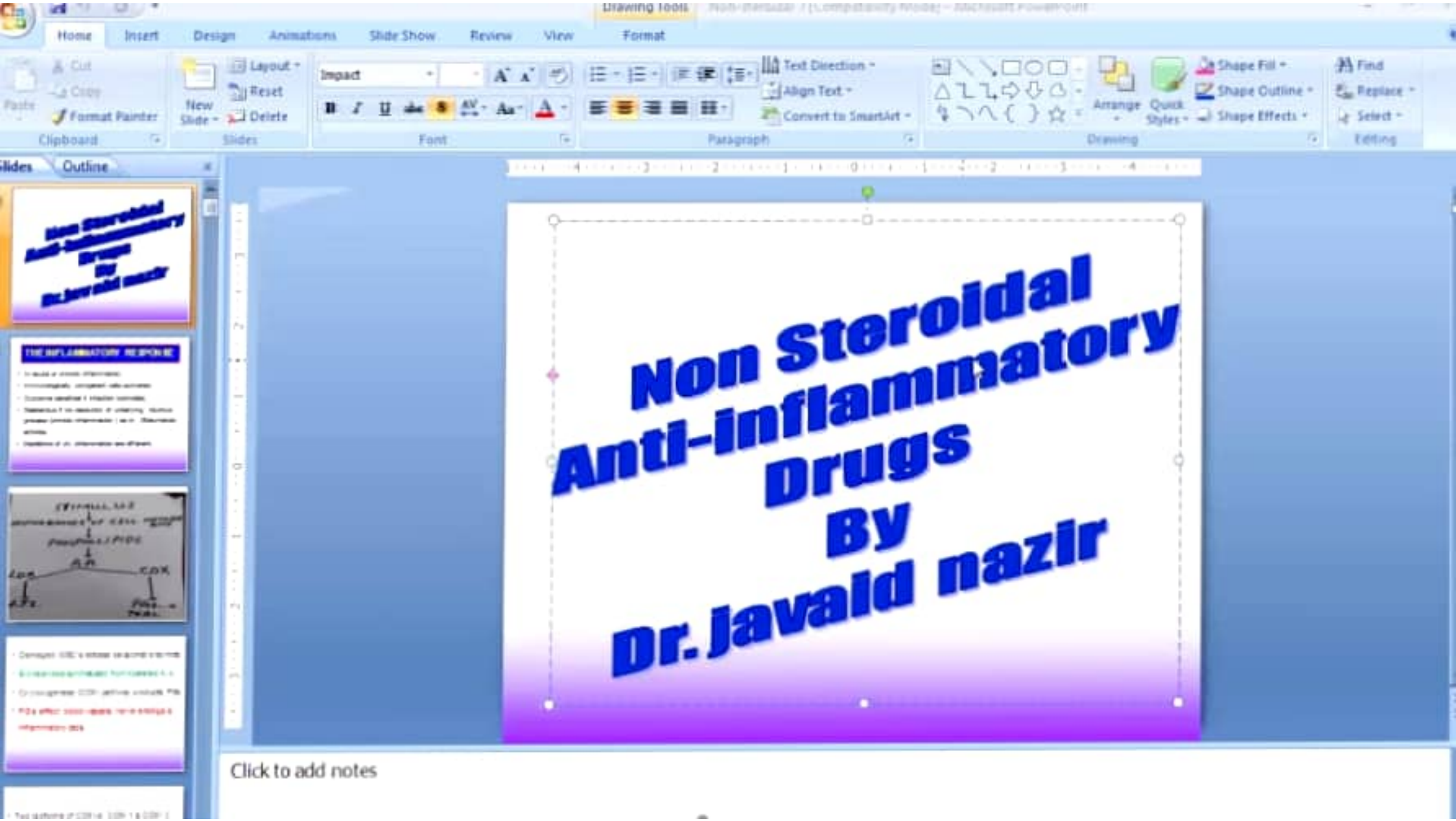

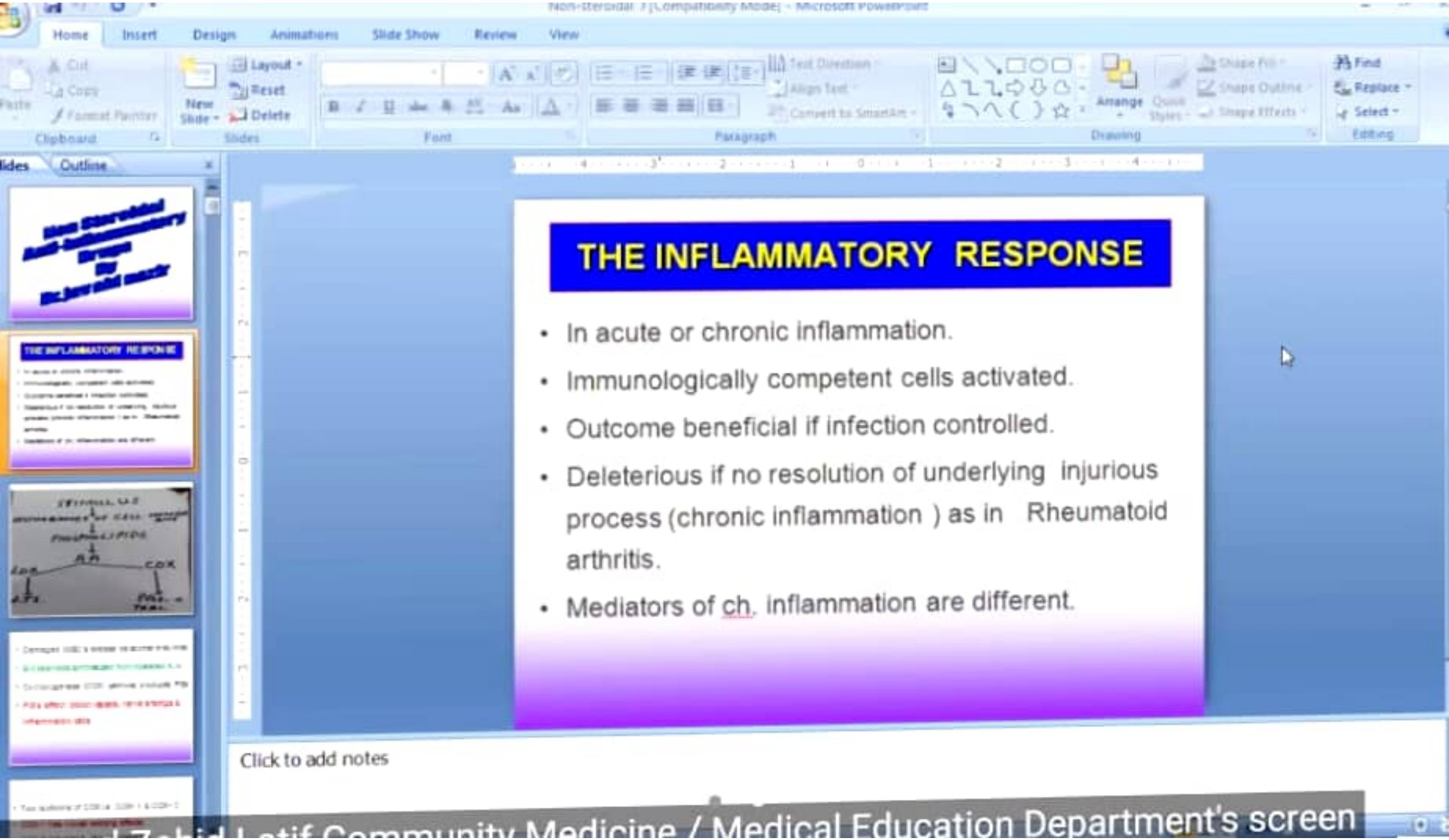


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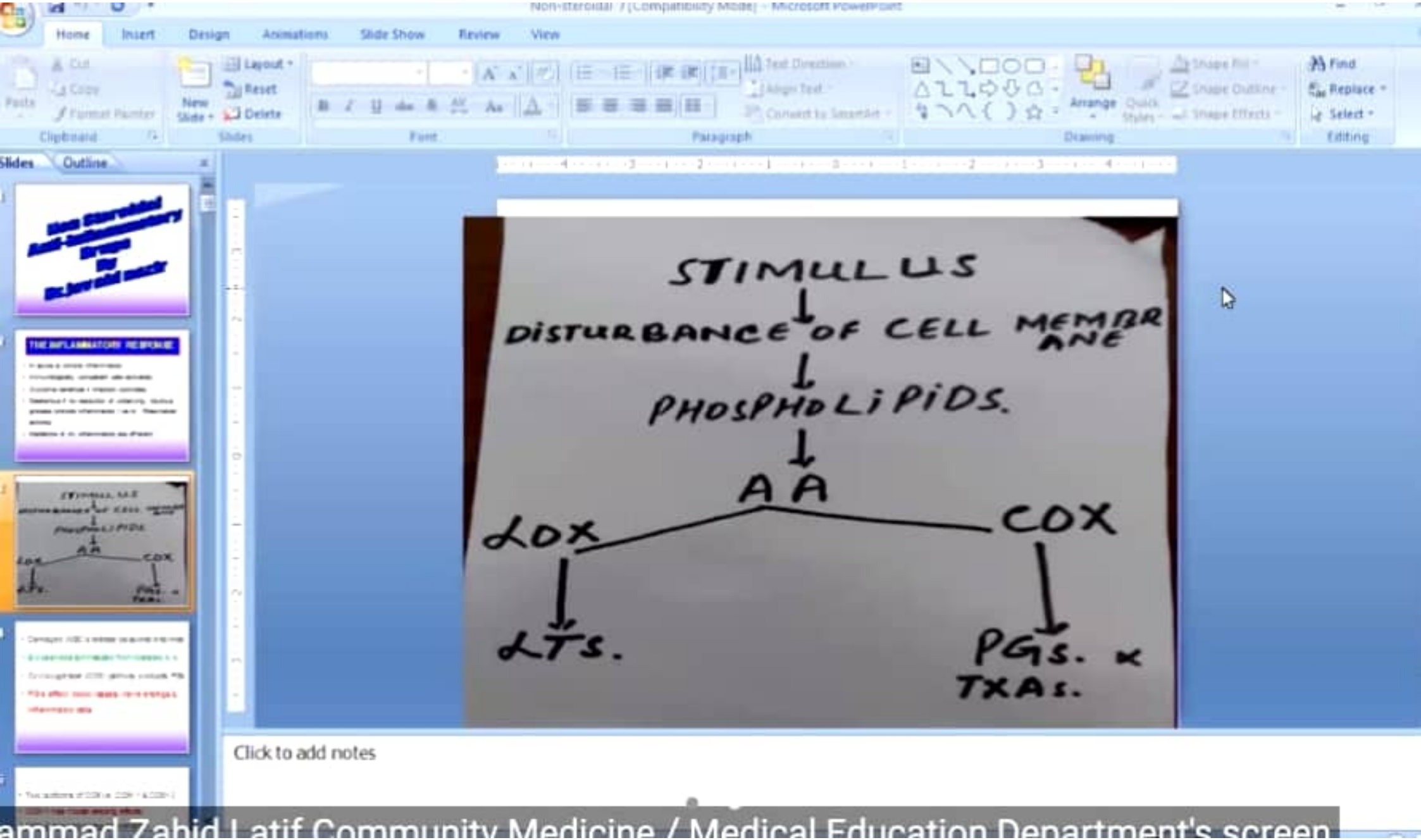
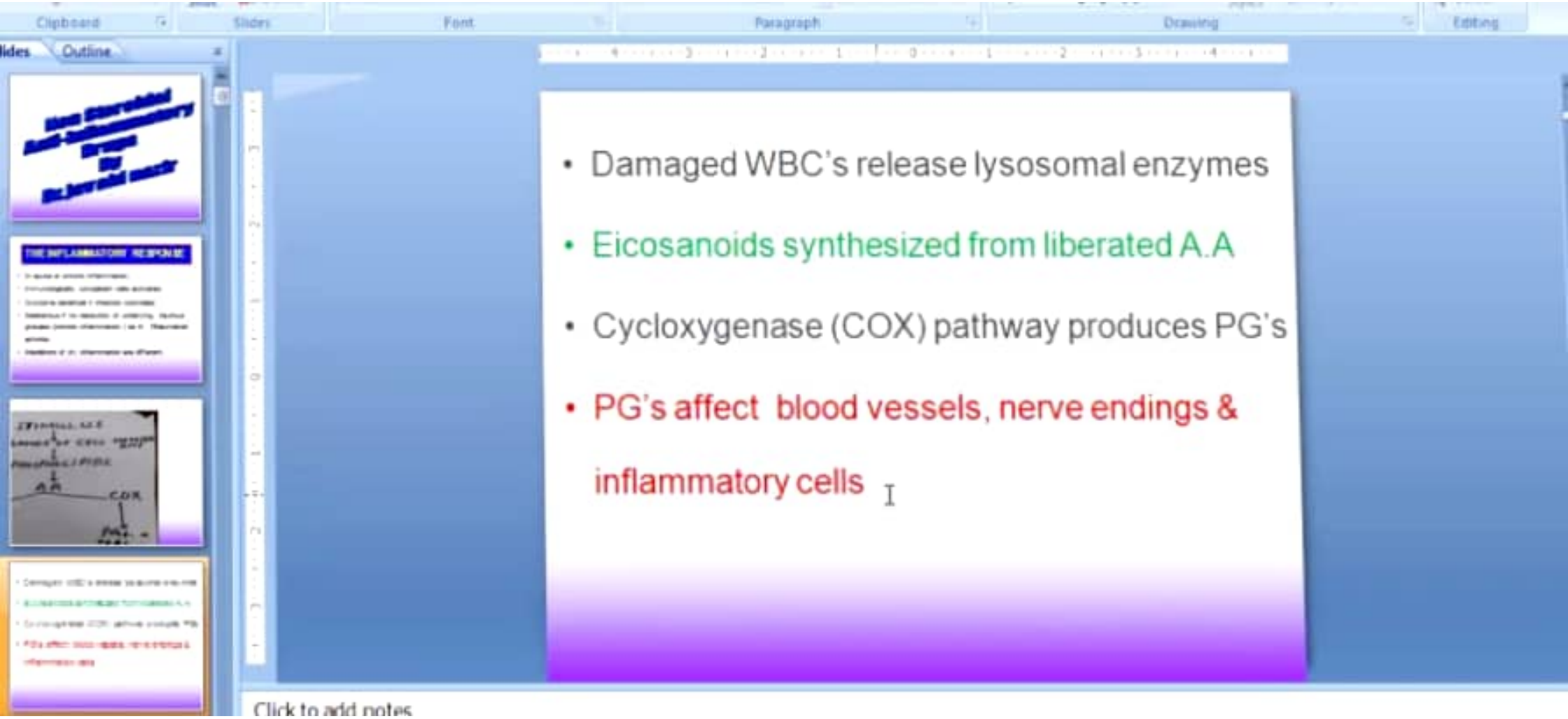
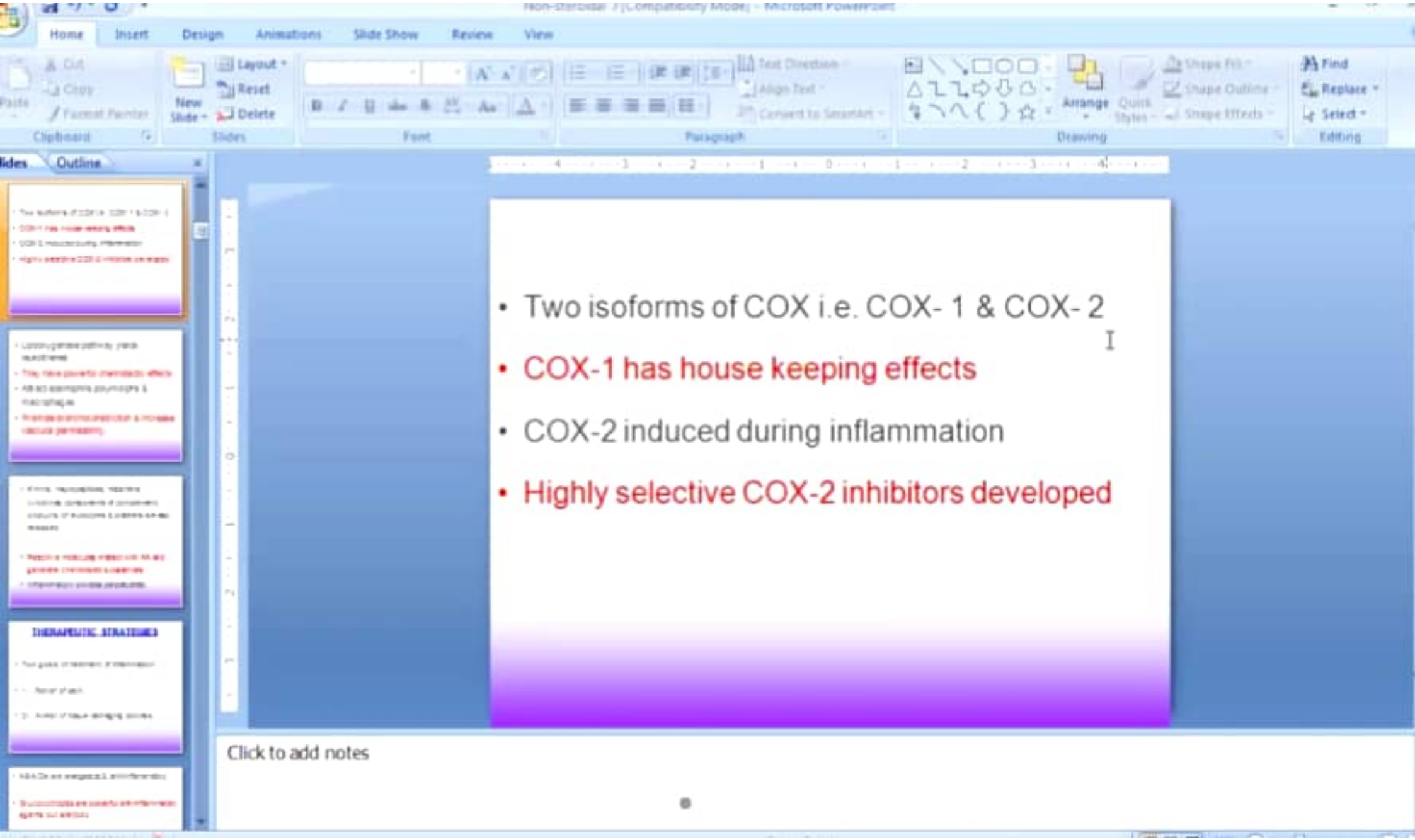
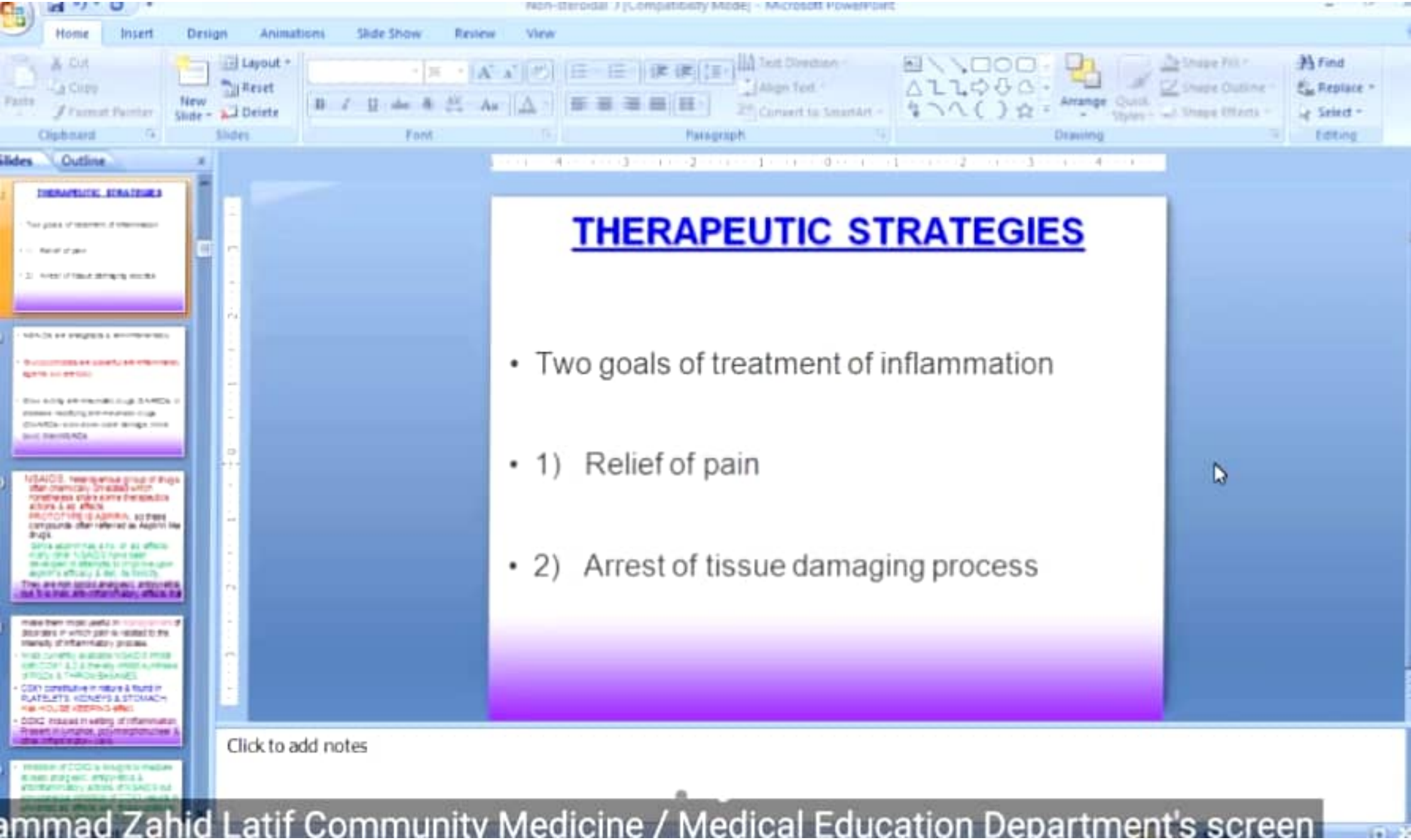
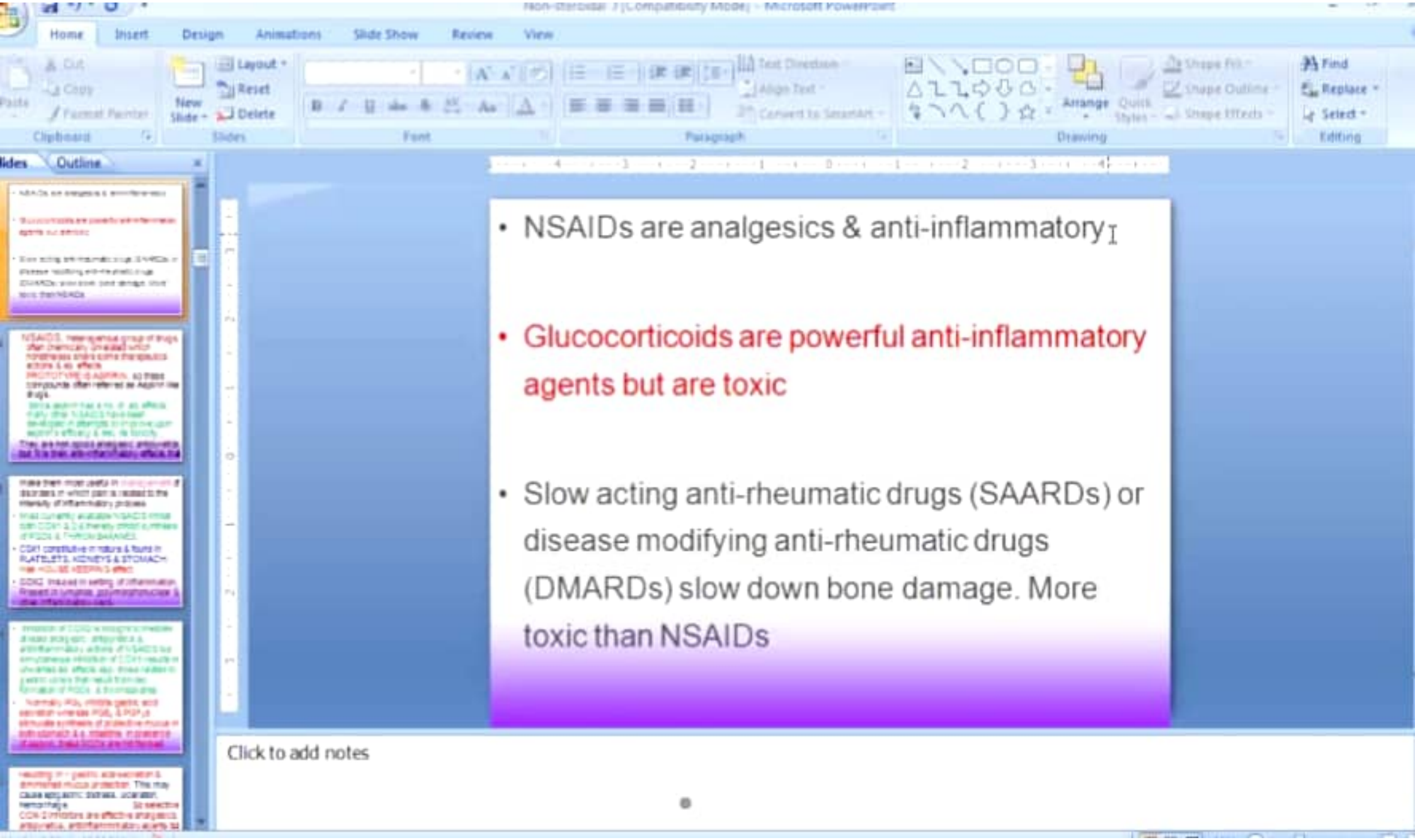
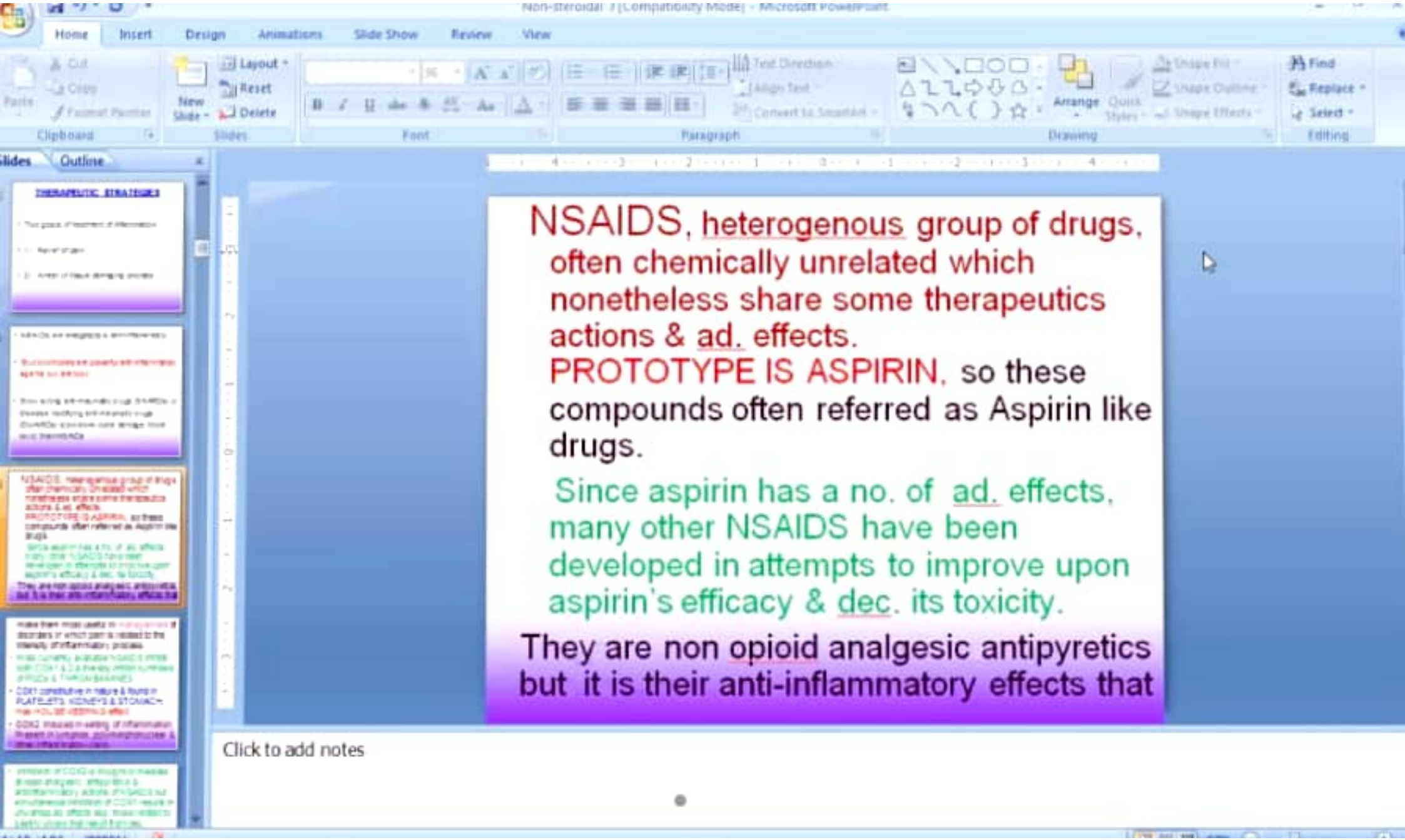


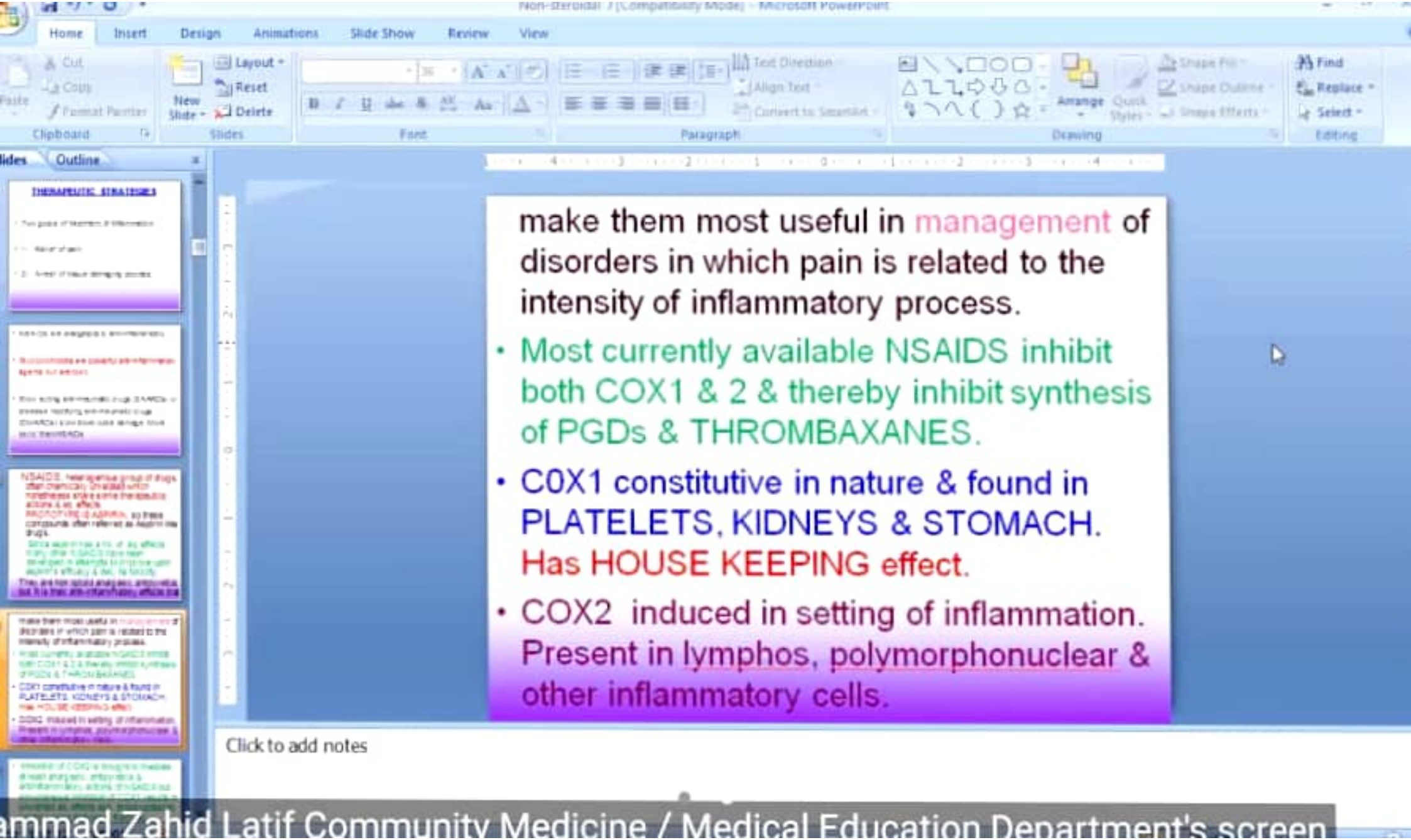


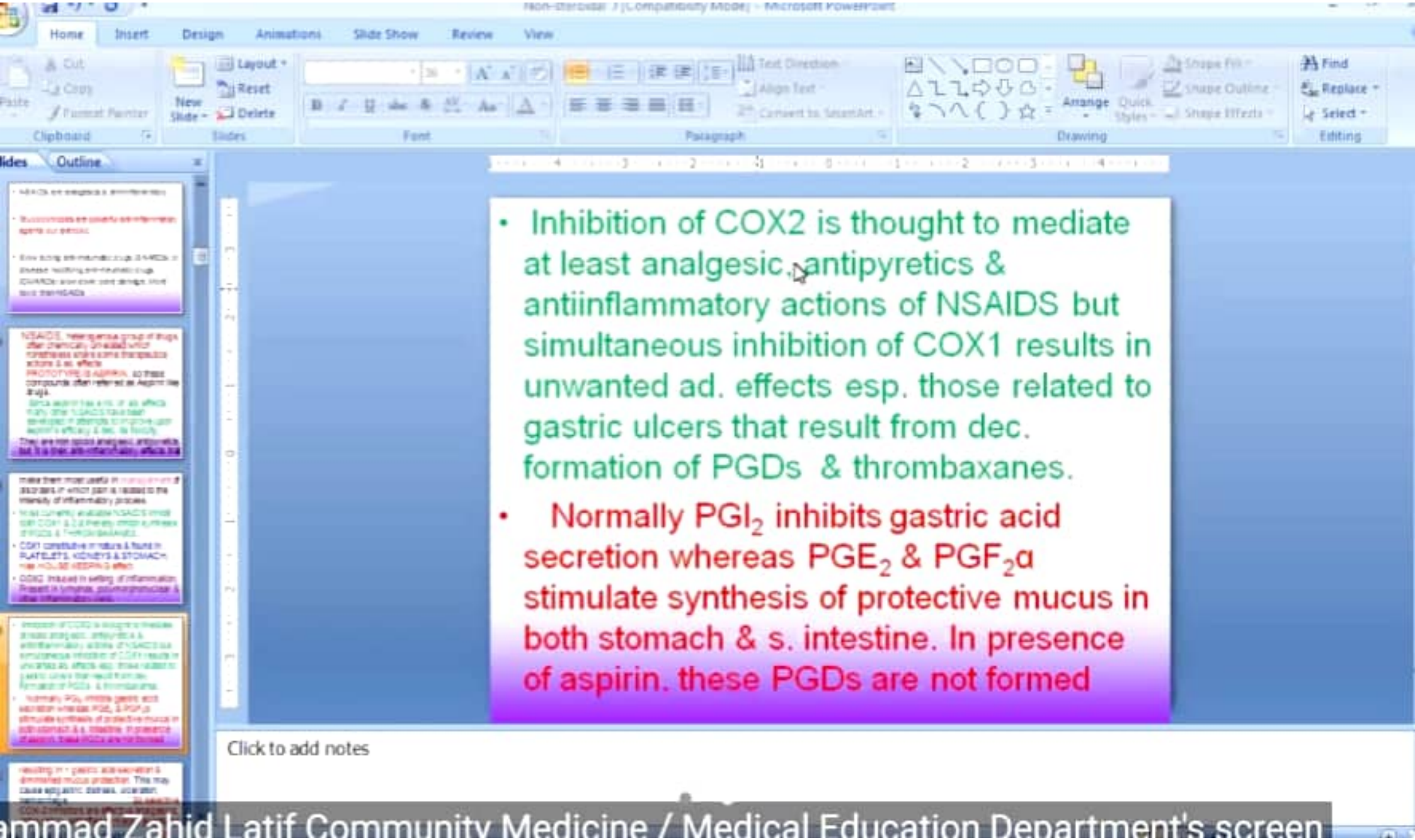


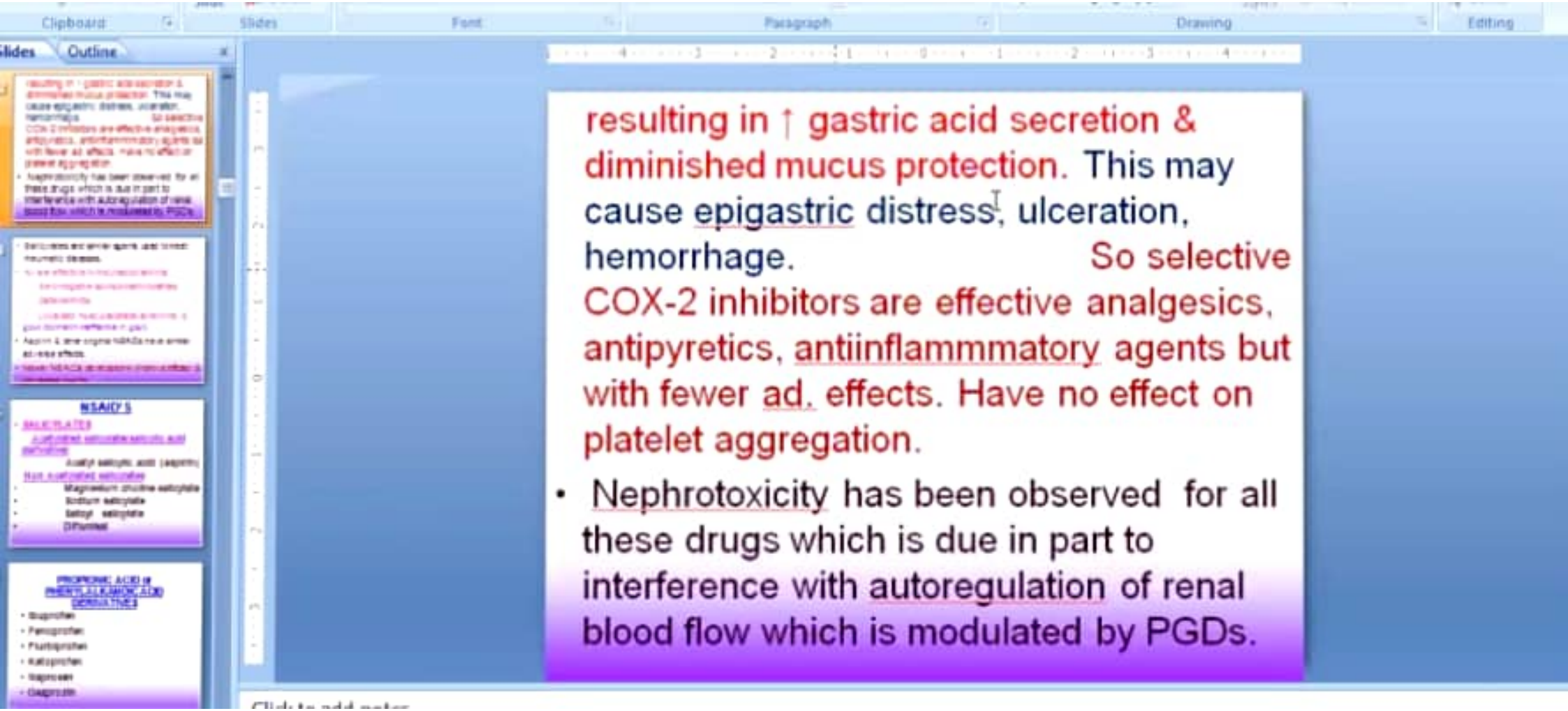


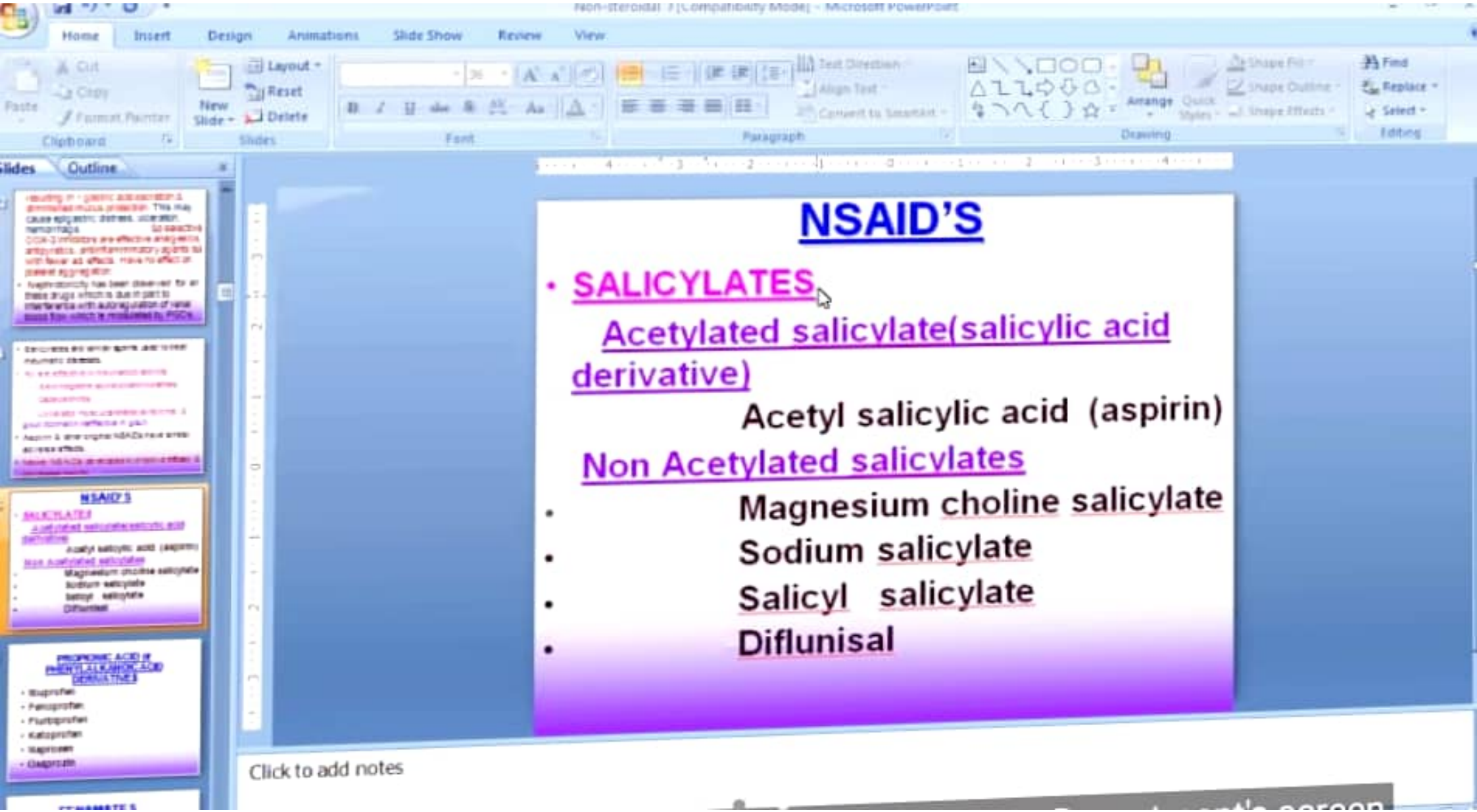


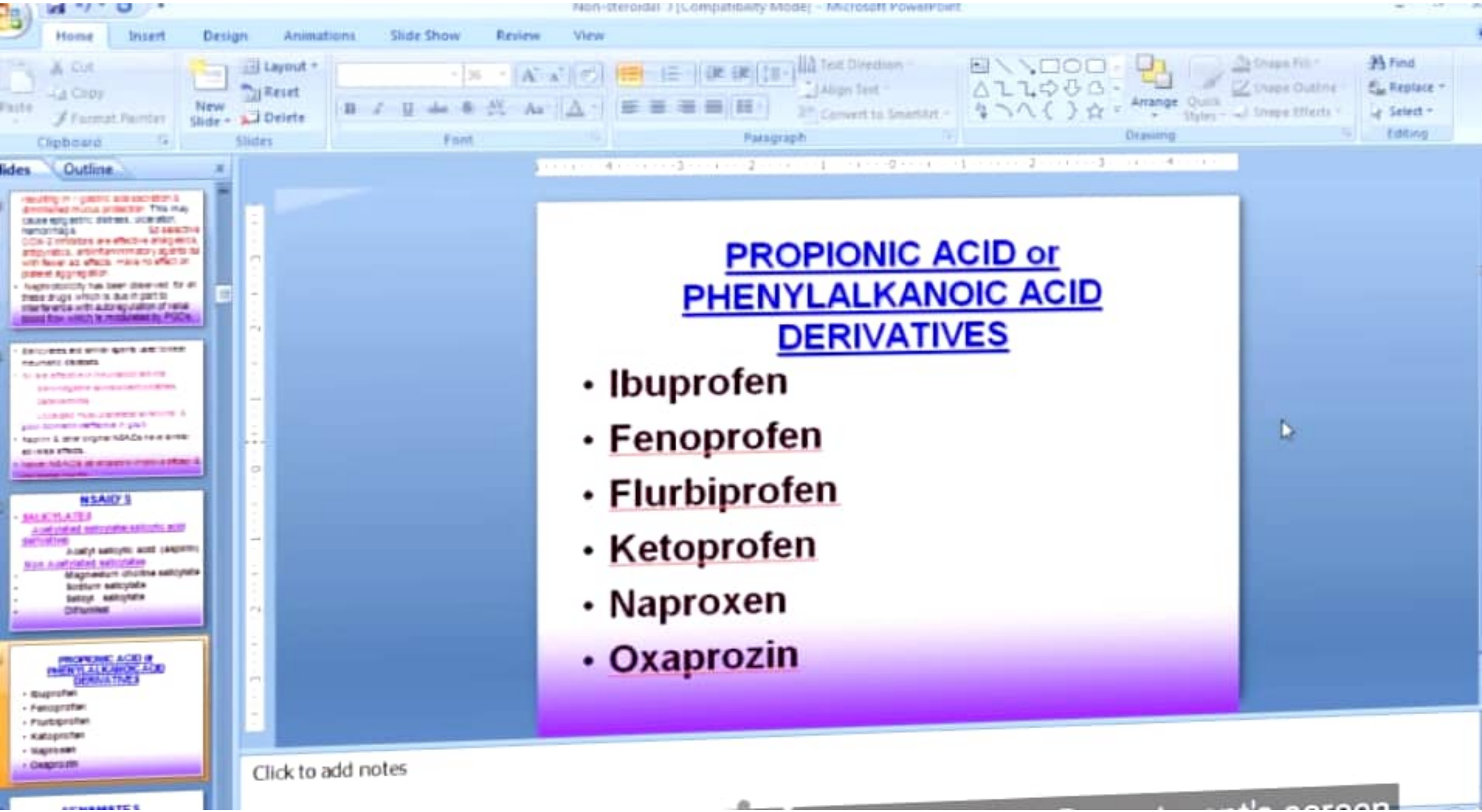


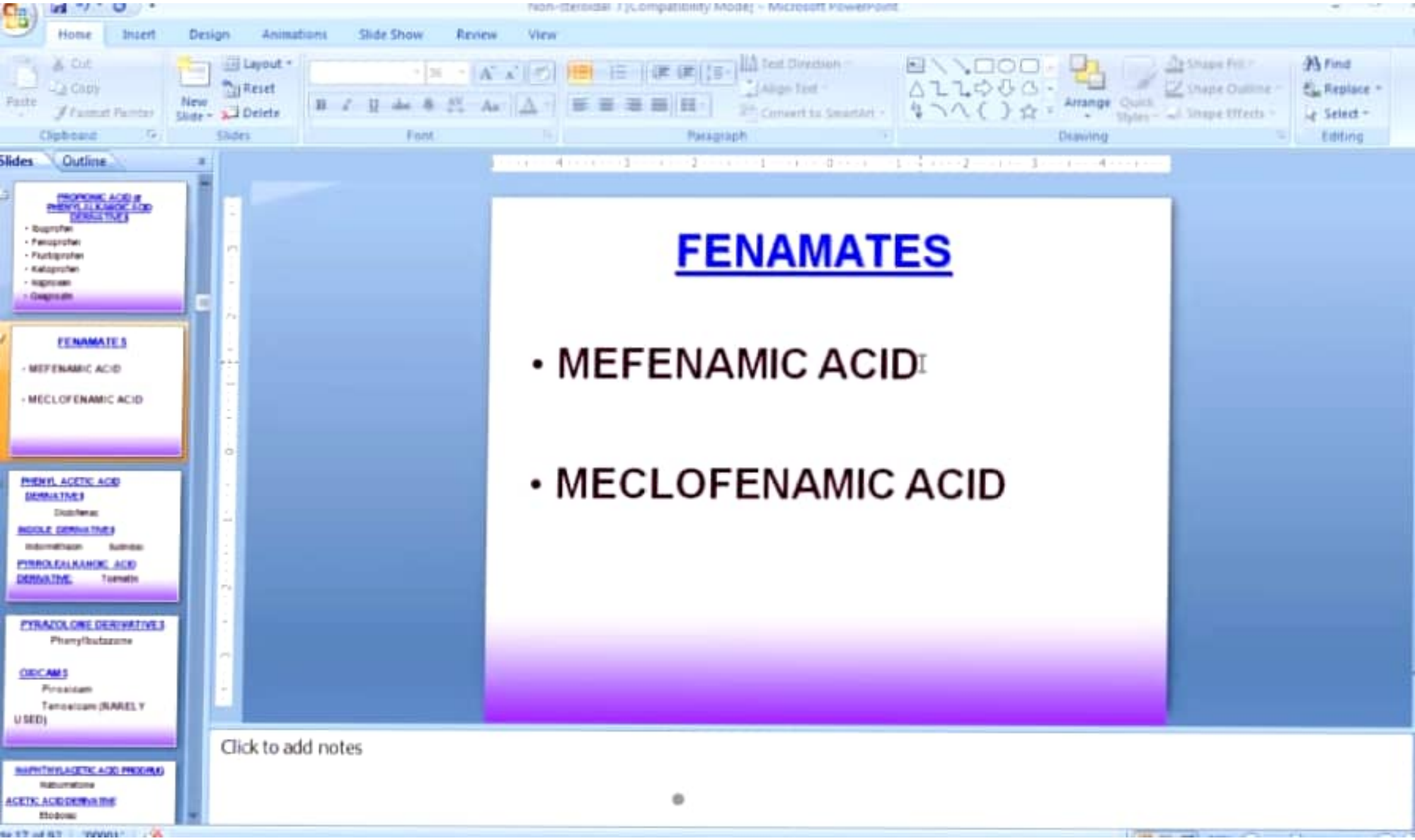


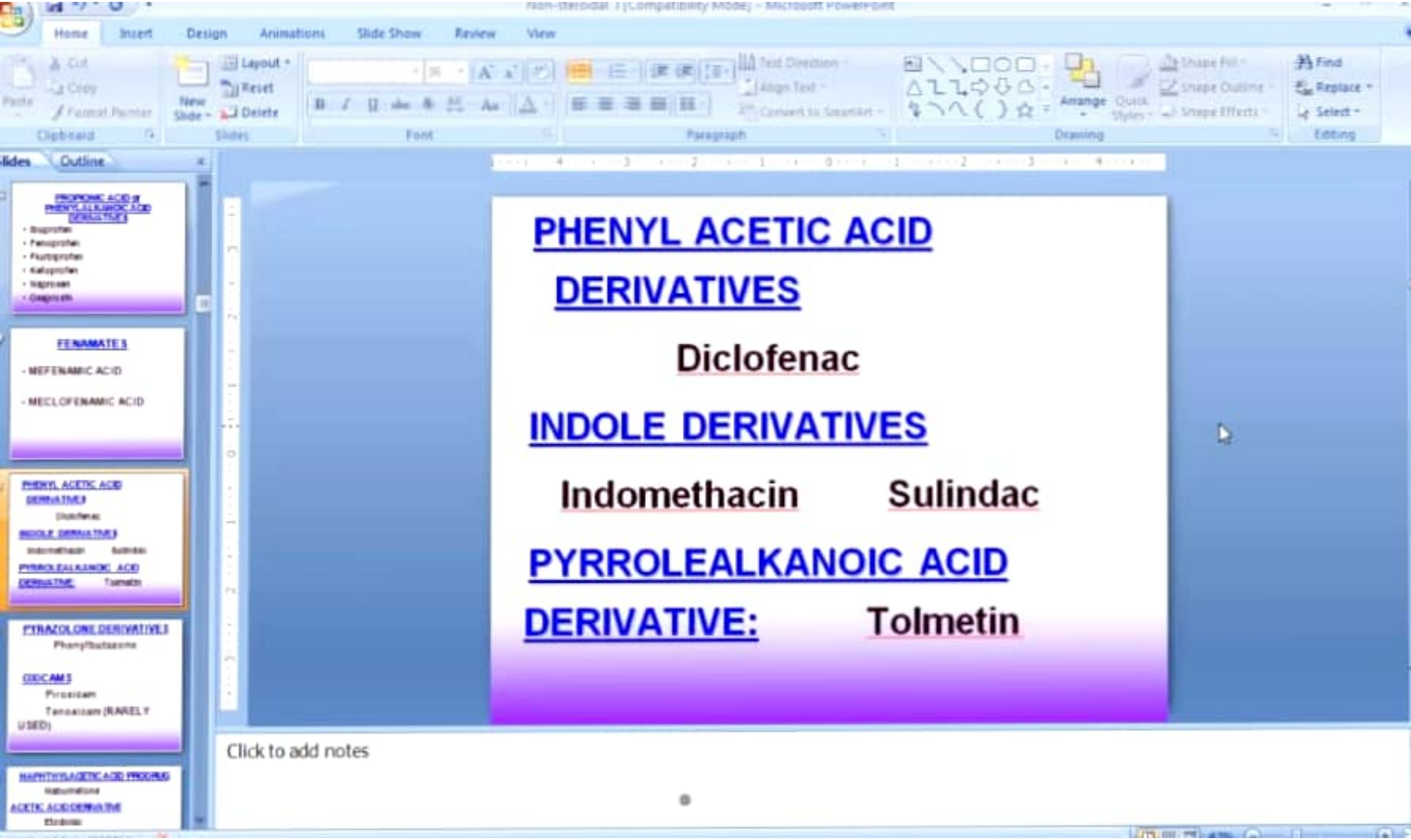












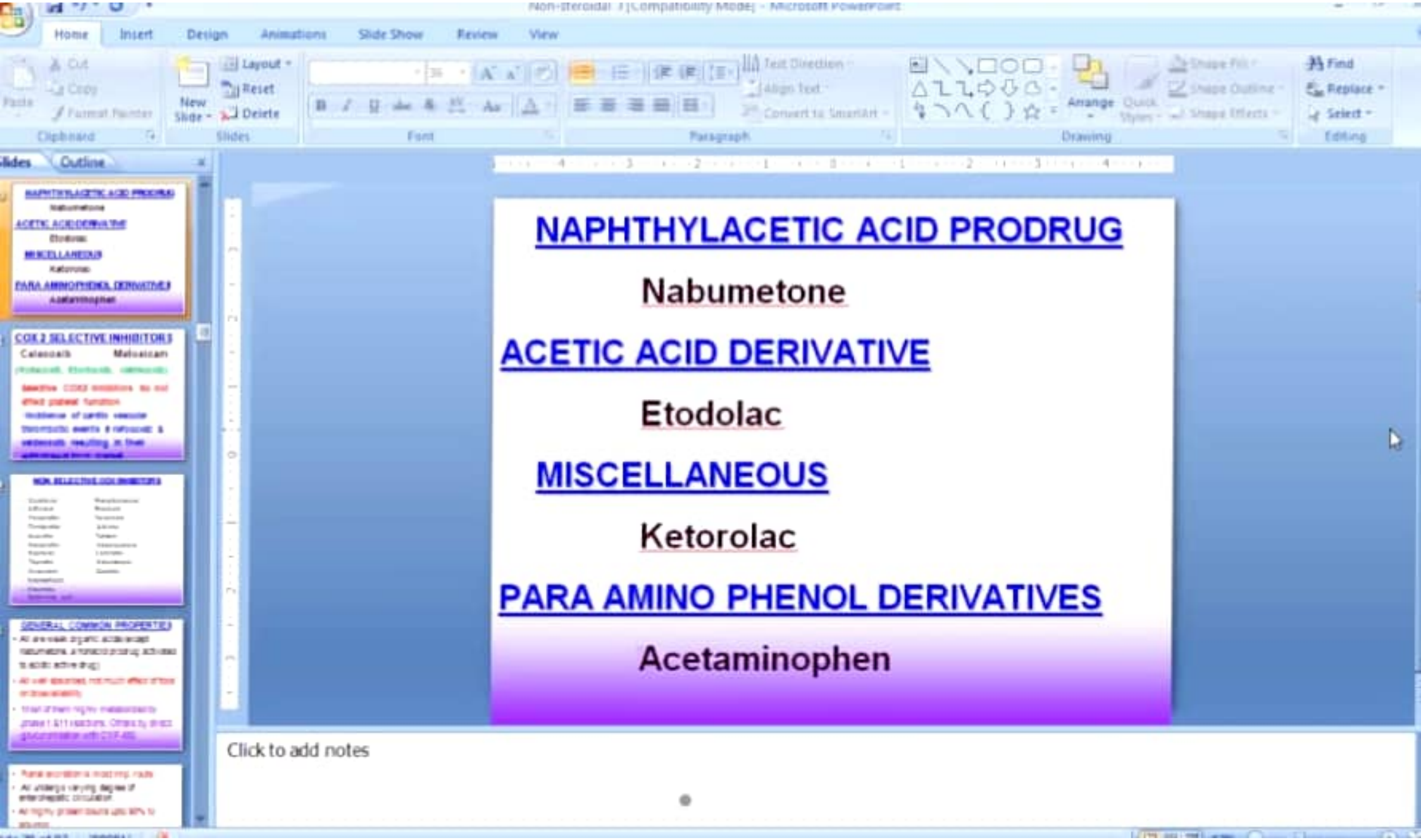
## PYRAZOLONE DERIVATIVES

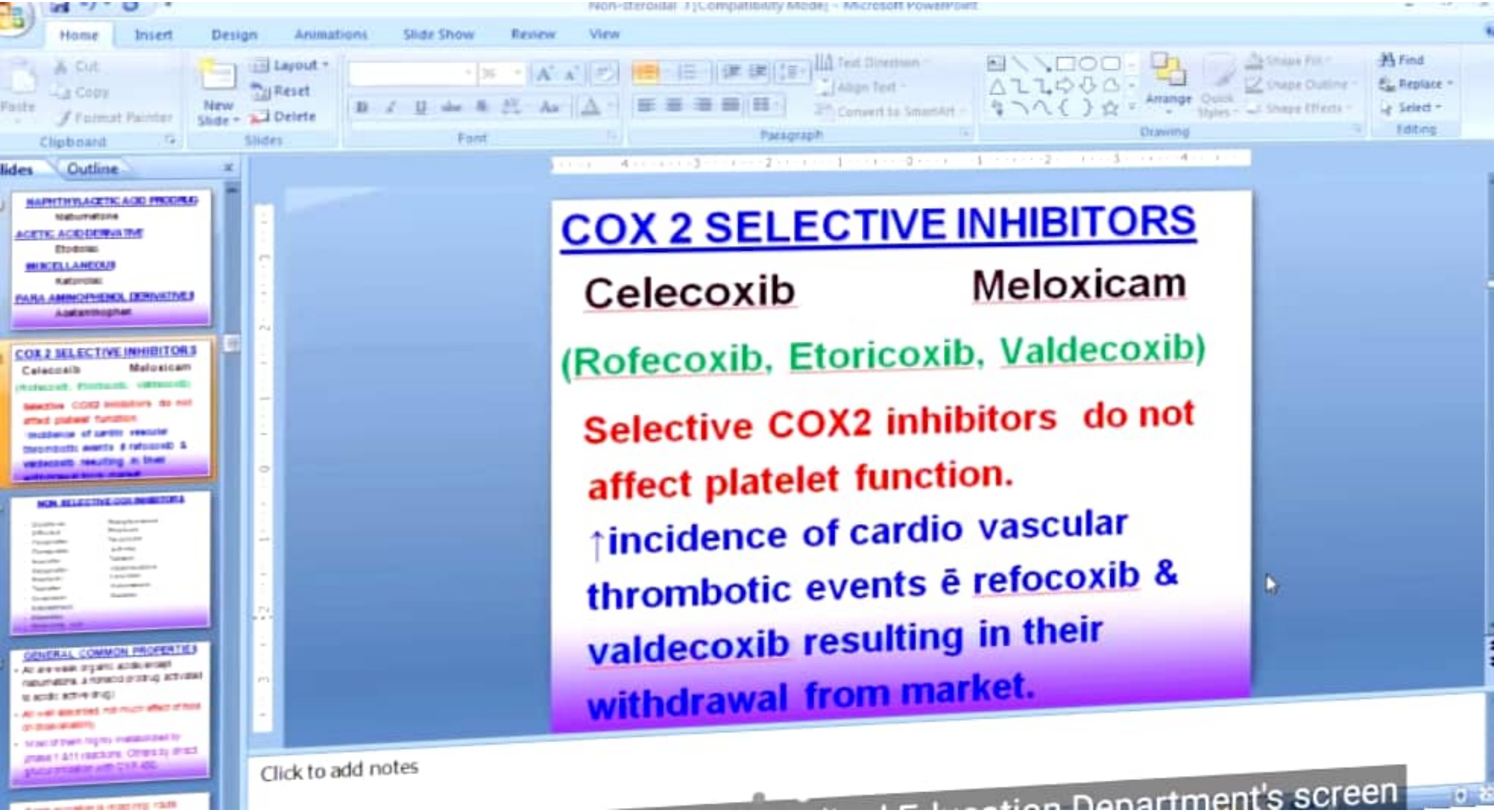
Phenylbutazone

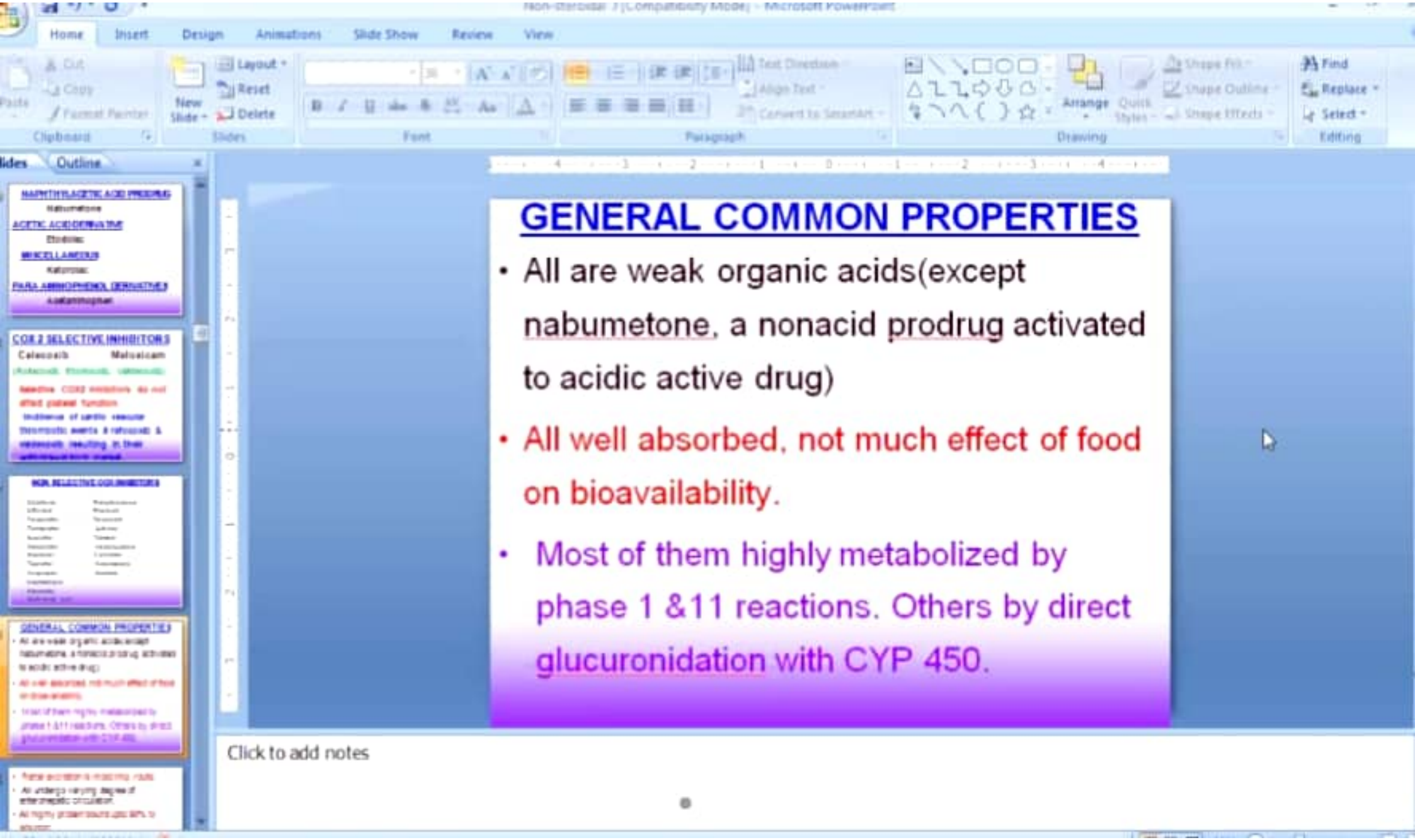
## OXICAMS

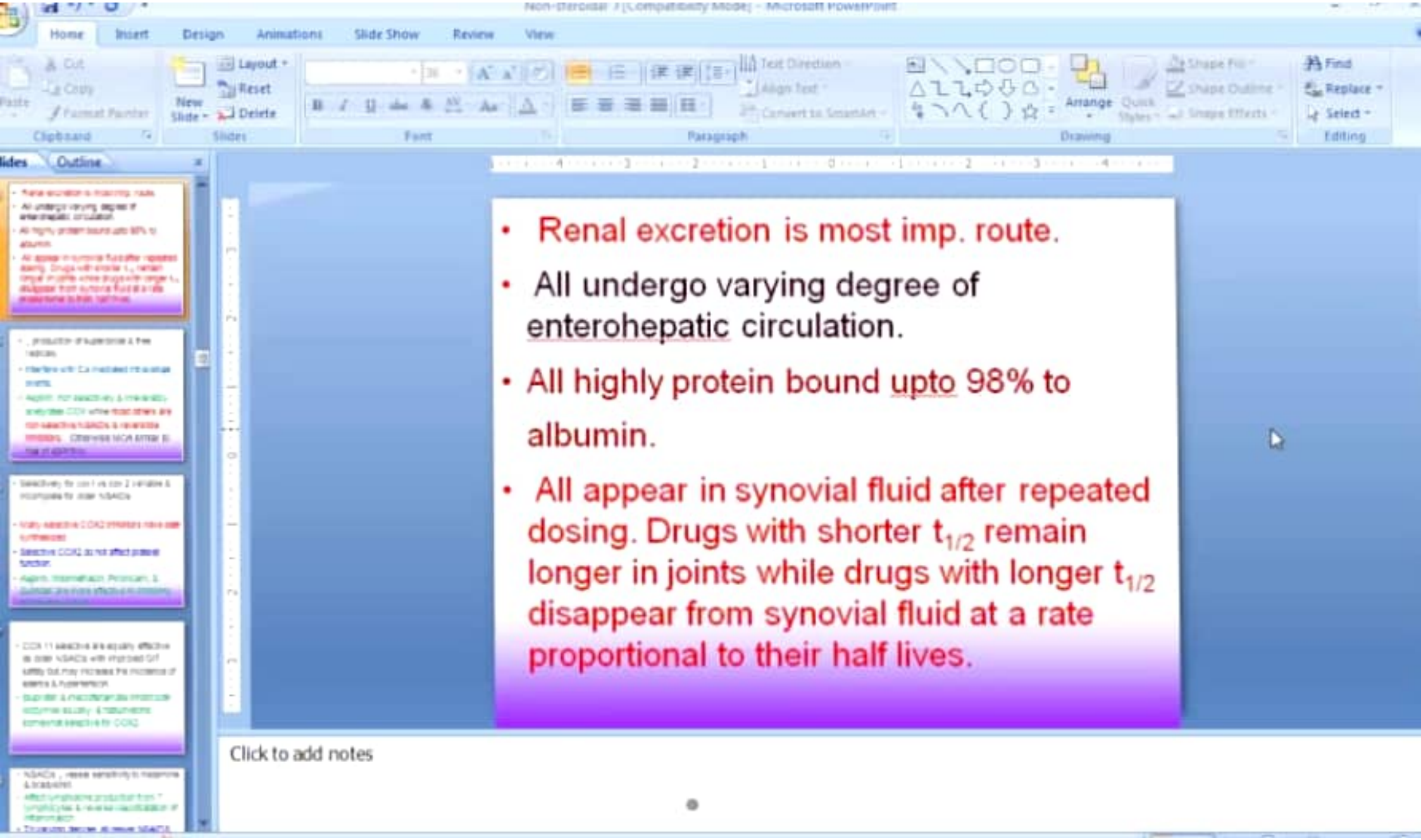
Piroxicam

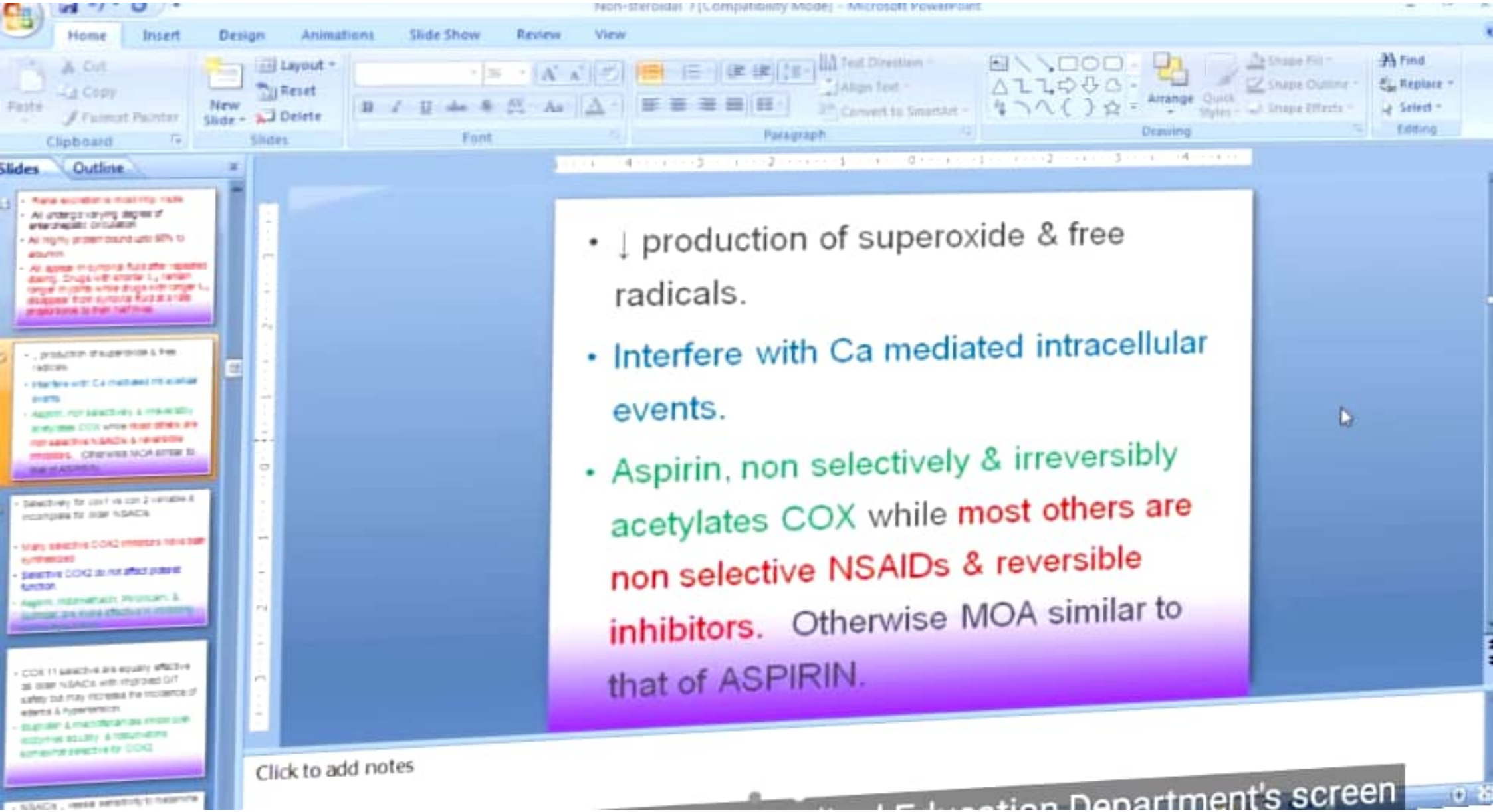
Tenoxicam (RARELY USED)

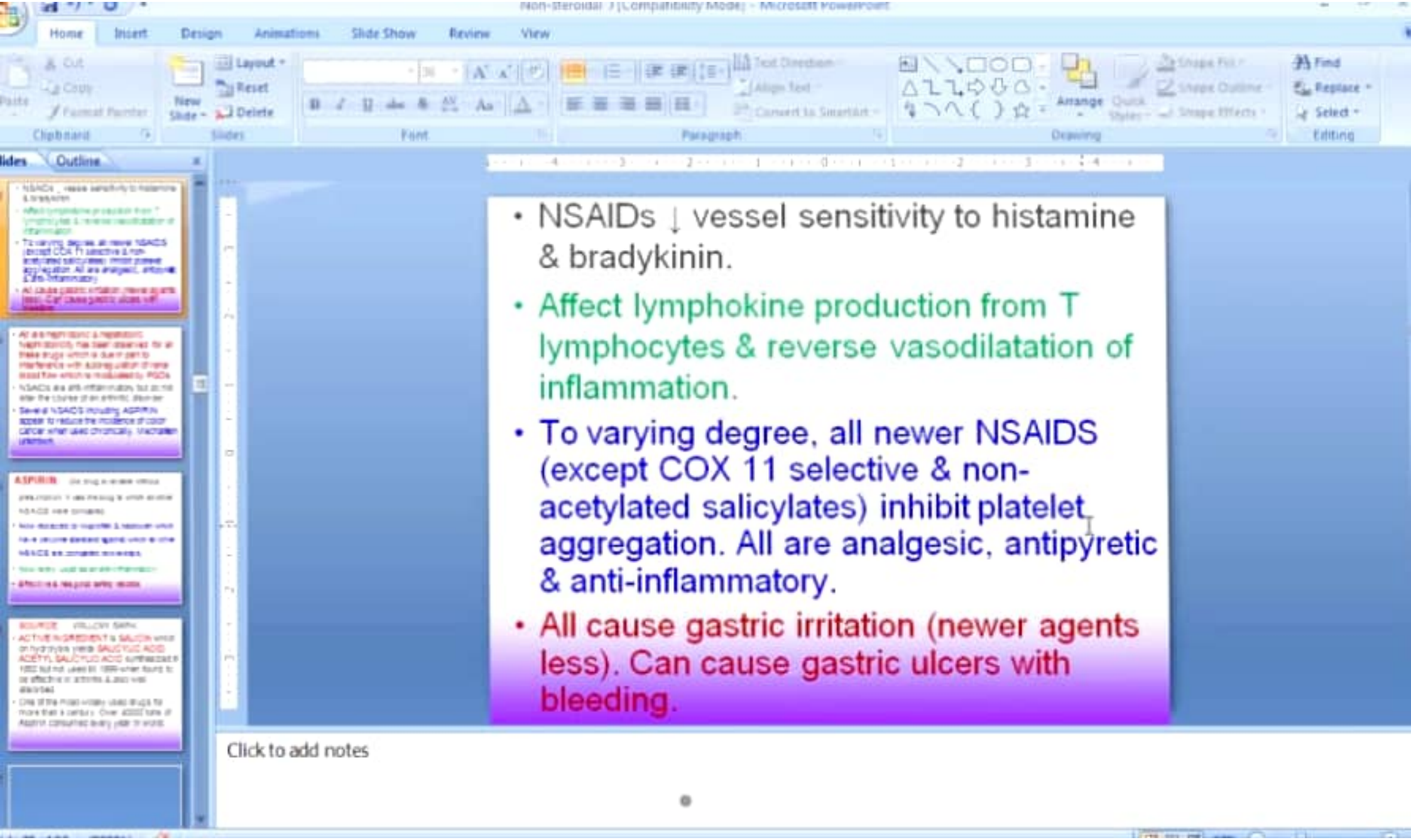


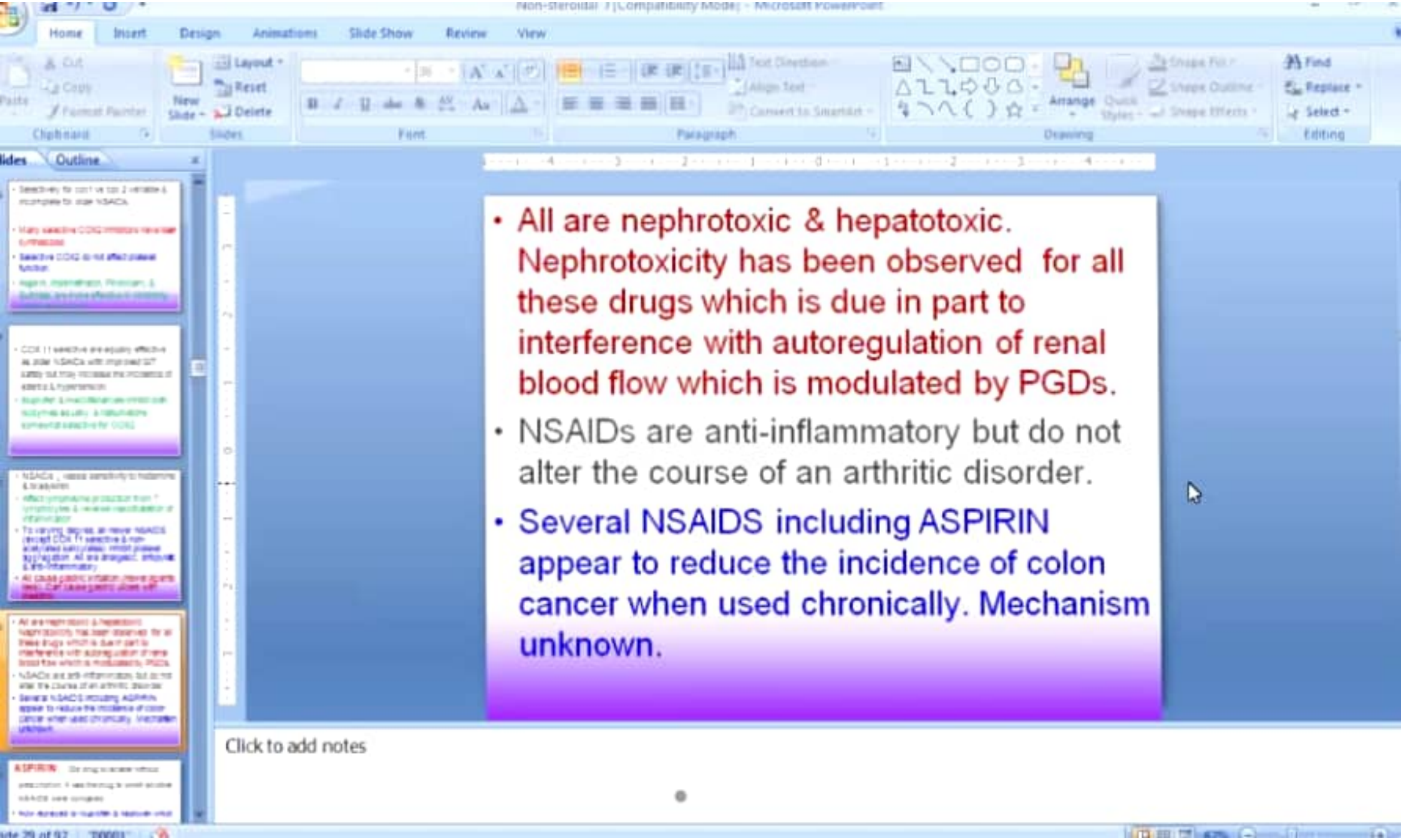


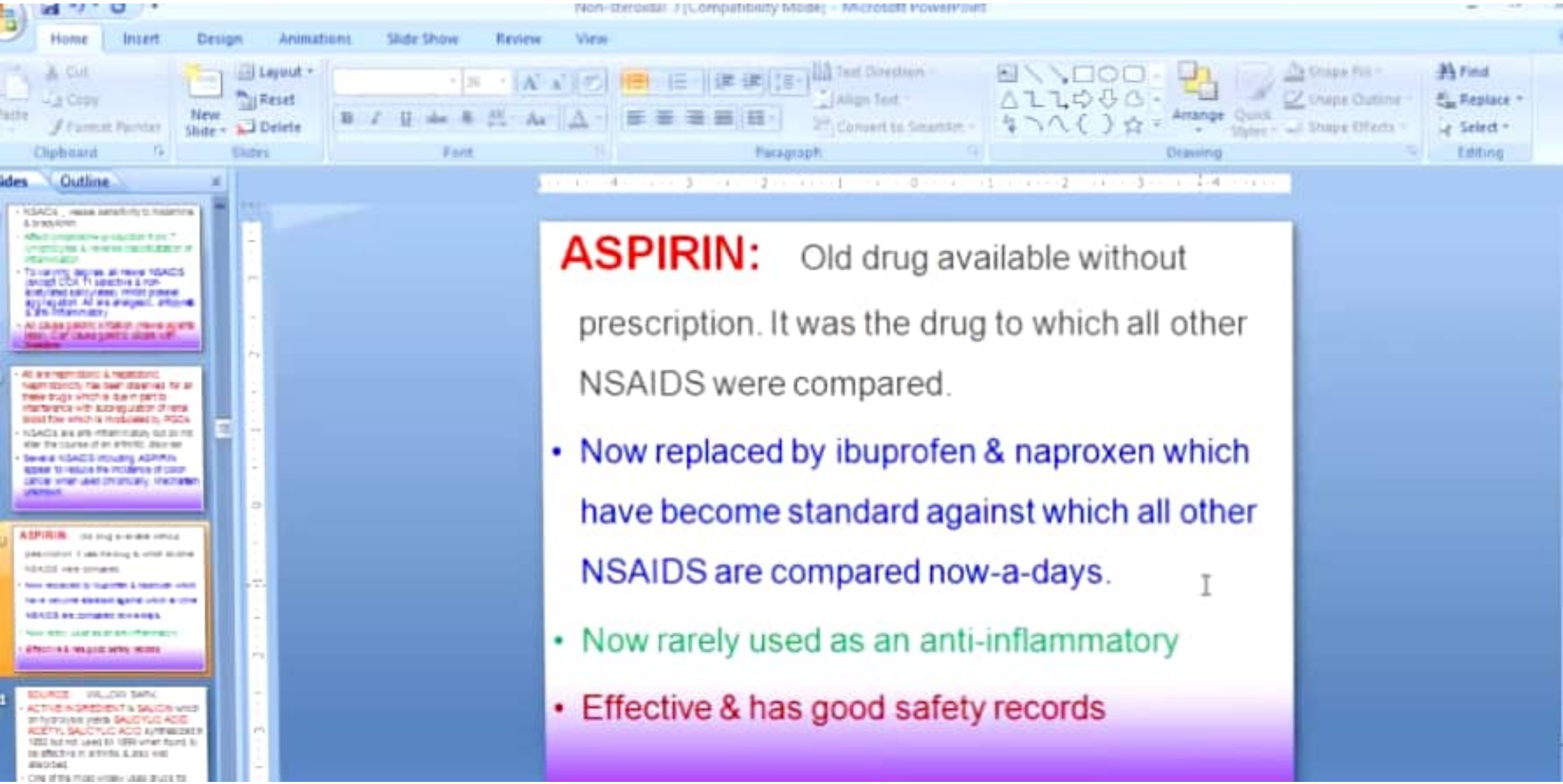


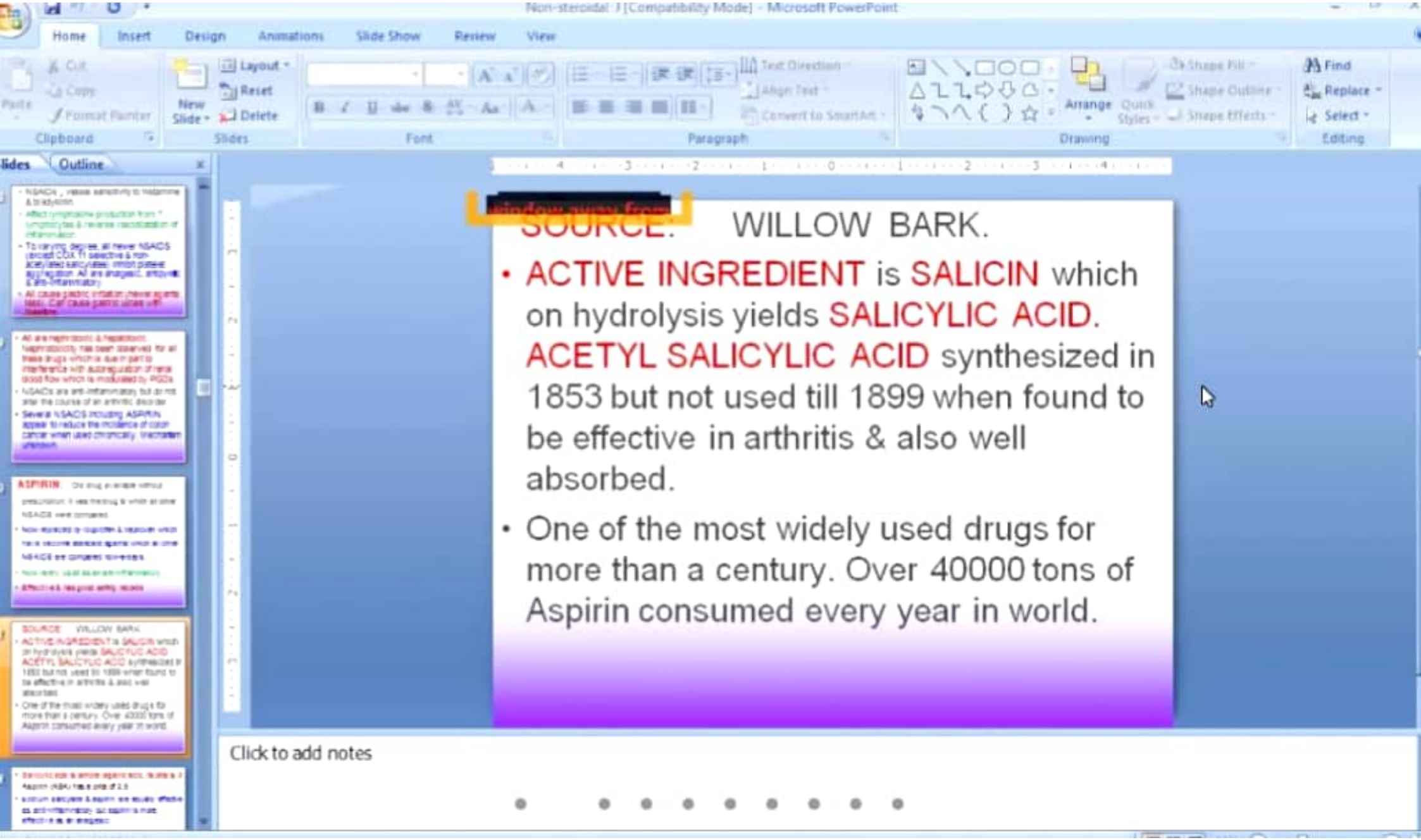


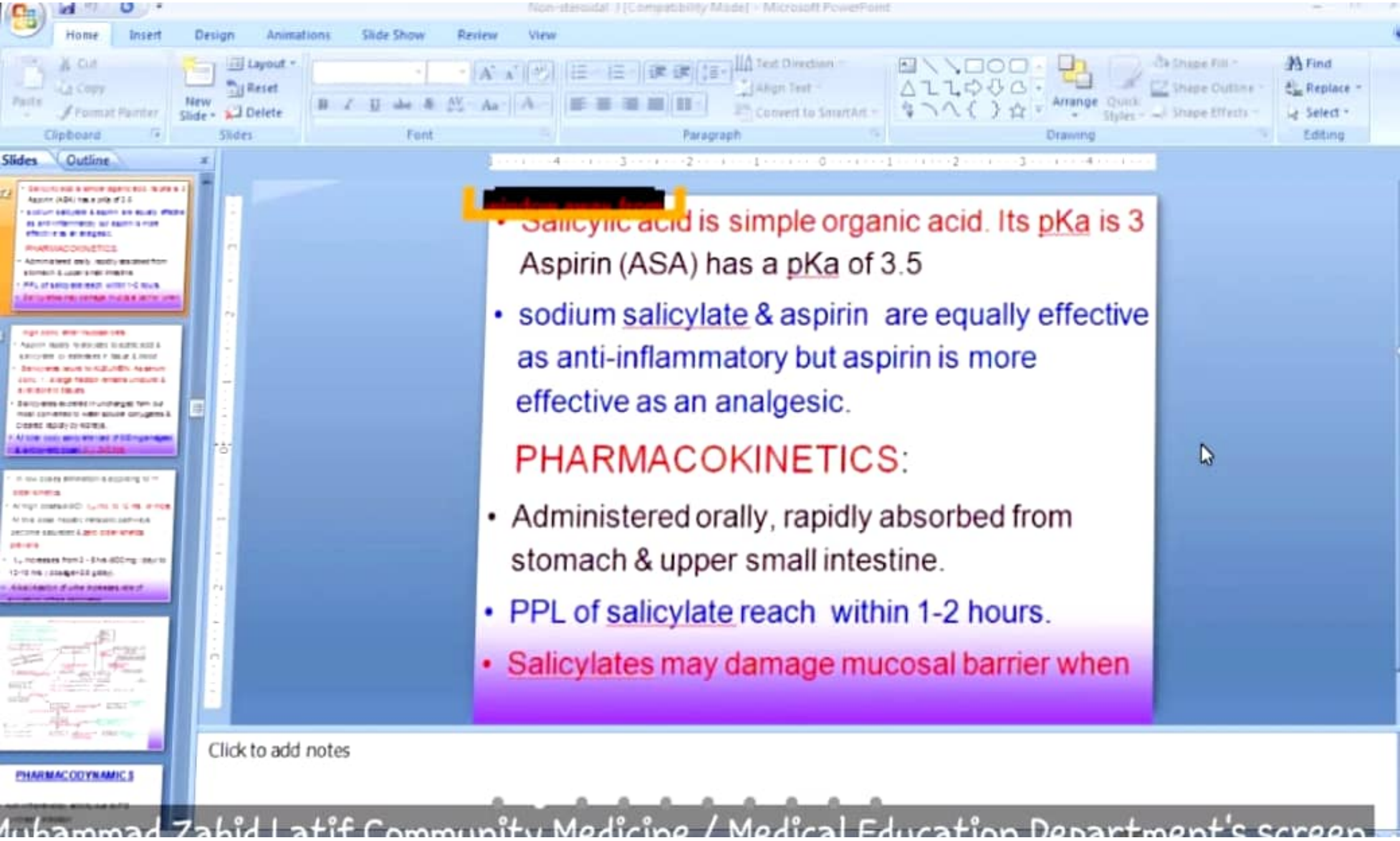












high conc. enter mucosal cells.

- Aspirin rapidly hydrolyzed to acetic acid & salicylate by esterases in tissue & blood.
- Salicylates bound to ALBUMEN. As serum conc. ↑, a large fraction remains unbound & available to tissues.
- Salicylates excreted in unchanged form but most converted to water soluble conjugates & cleared rapidly by kidneys.
- At total body salicylate load of 600mg(analgesic & antipyretic dose), $t_{1/2}$ 3-5 hrs.

Click to add notes

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- In low doses elimination is according to 1st order kinetics.
- At high doses(4G/D) $t_{1/2}$ inc. to 12 hrs. or more. At this dose, hepatic metabolic pathways become saturated & zero order kinetics prevails.
- $t_{1/2}$ increases from 3 - 5 hrs (600 mg / day) to 12-16 hrs ( dosage>3.6 g/day).
- Alkalinization of urine increases rate of excretion of free salicylates.

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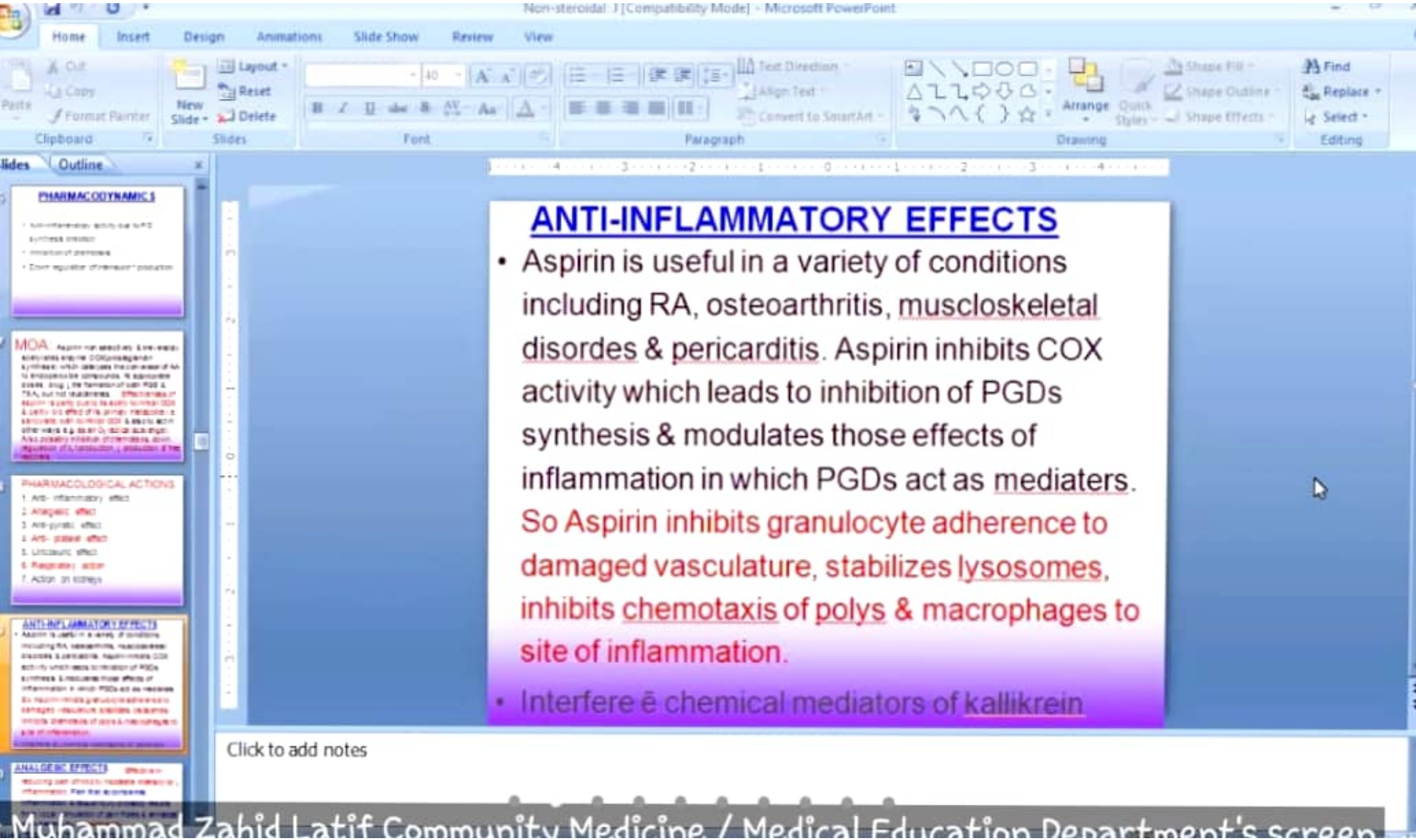
# PHARMACODYNAMICS

- Anti-inflammatory activity due to PG synthesis inhibition
- Inhibition of chemicals
- Down regulator of interleukin production

**MOA:** Aspirin non selectively & irreversibly acetylates enzyme COX(prostaglandin synthase) which catalyzes the conversion of AA to endoperoxide compounds. At appropriate doses, drug ↓ the formation of both PGS & $TXA_2$ but not leukotrienes. Effectiveness of aspirin is partly due to its ability to inhibit COX & partly b/o effect of its primary metabolite i.e salicylate, both to inhibit COX & also to act in other ways e.g. as an $O_2$ radical scavenger. Also possibly inhibition of chemotaxis, down regulation of IL1production, ↓ production of free radicals.

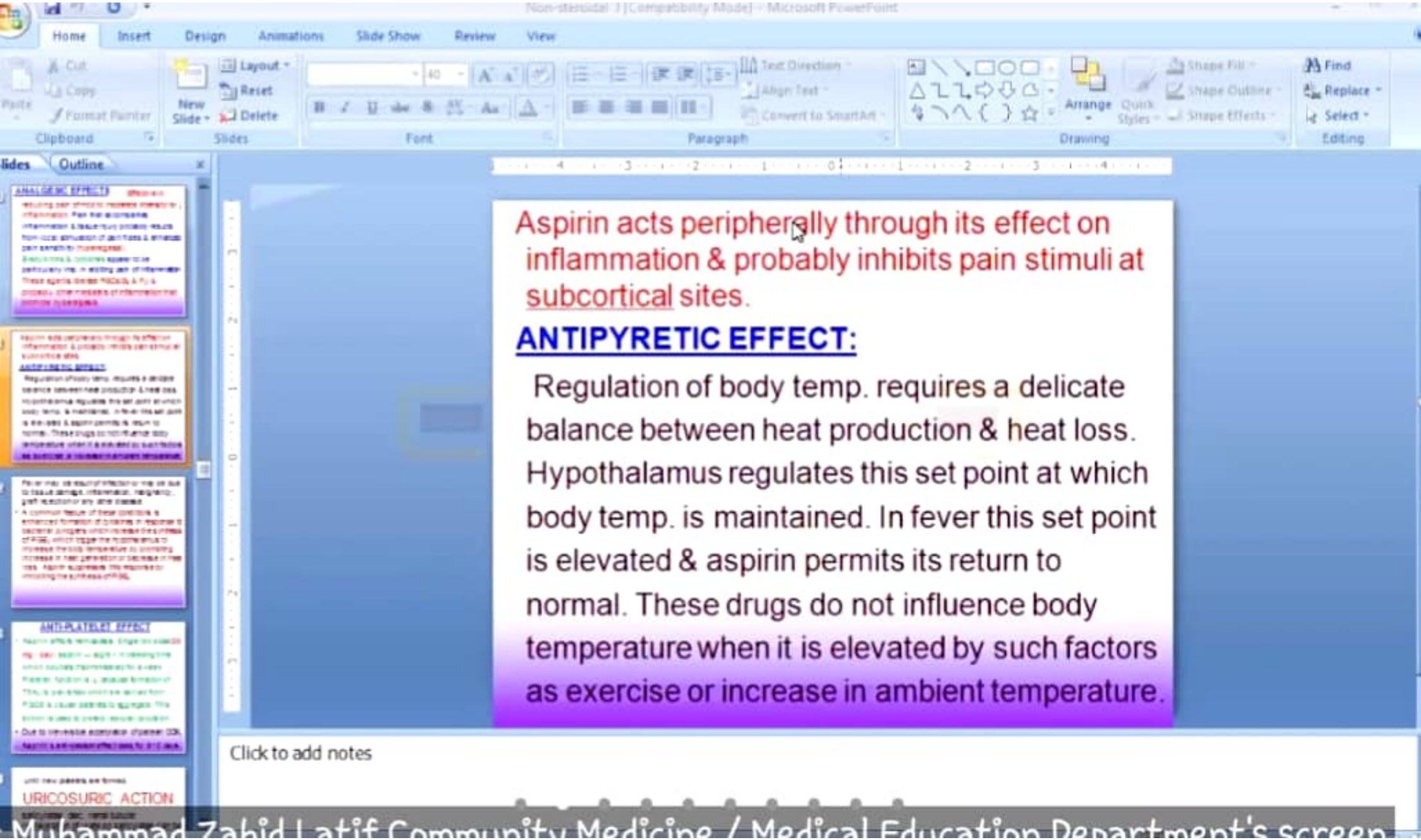
# PHARMACOLOGICAL ACTIONS

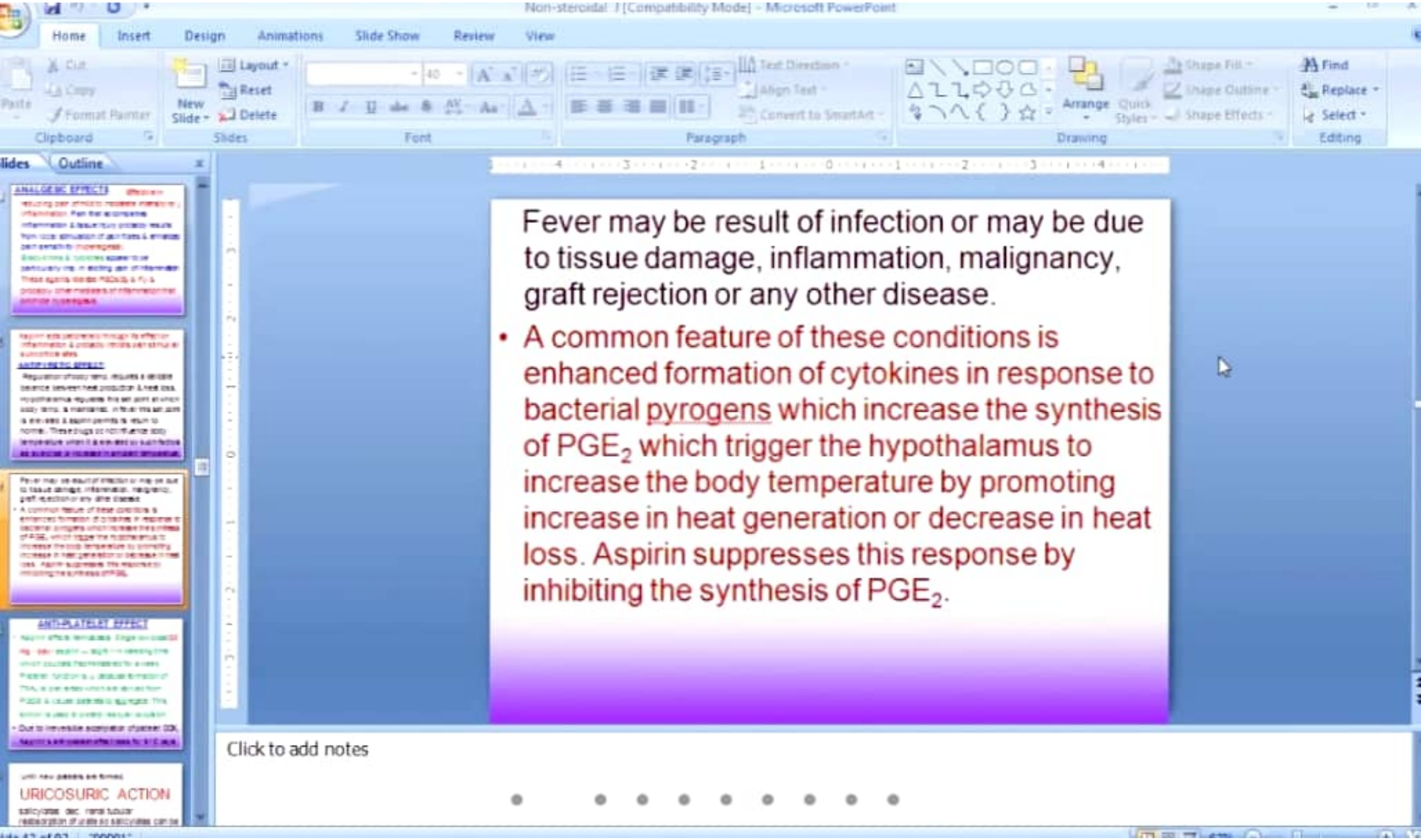
1. Anti- inflammatory effect
2. Analgesic effect
3. Anti-pyretic effect
4. Anti- platelet effect
5. Uricosuric effect
6. Respiratory action
7. Action on kidneys

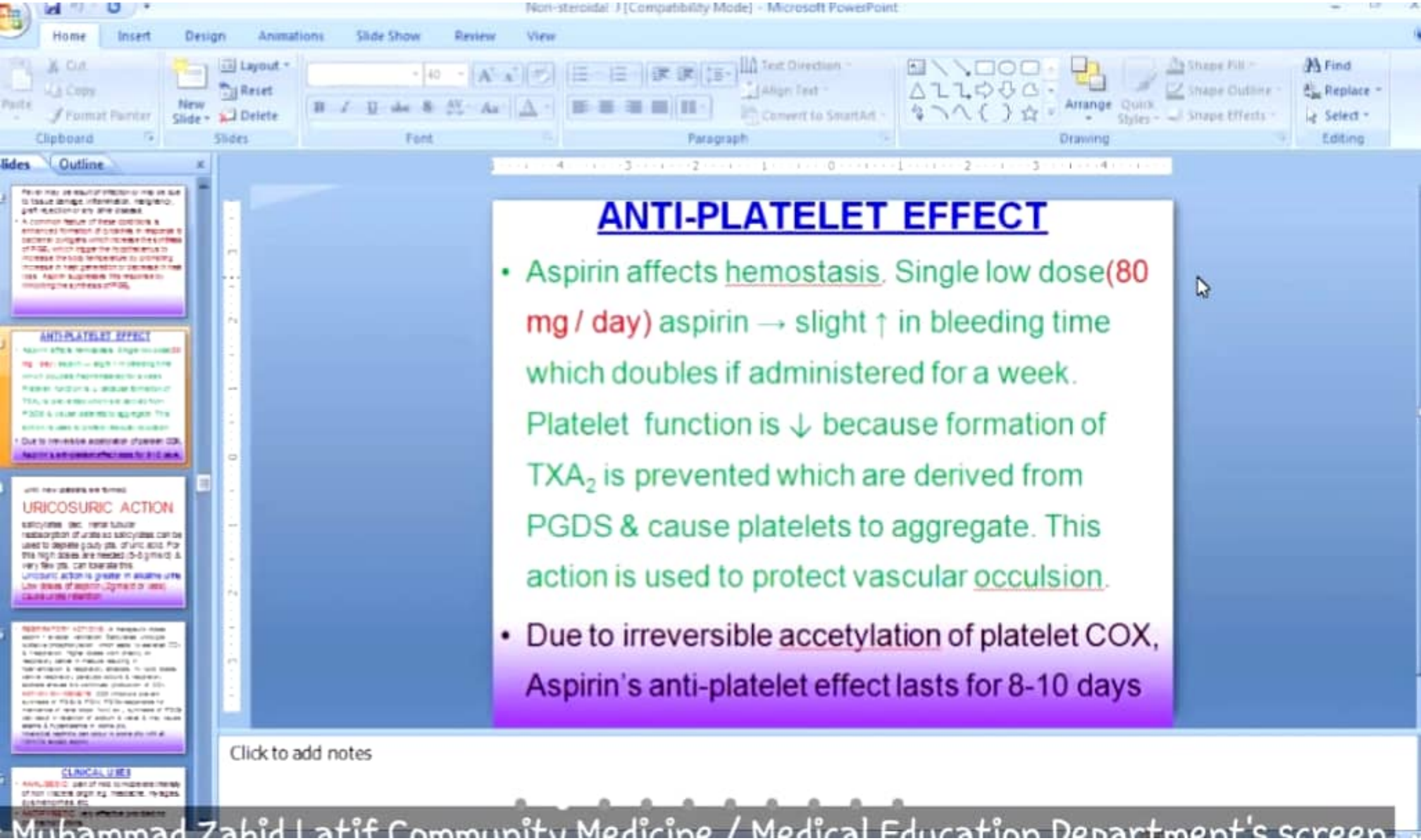


**ANALGESIC EFFECTS**: Effective in reducing pain of mild to moderate intensity by ↓ inflammation. Pain that accompanies inflammation & tissue injury probably results from local stimulation of pain fibres & enhanced pain sensitivity (hyperalgesia).

Bradykinins & cytokines appear to be particularly imp. in eliciting pain of inflammation. These agents liberate PGDs($E_2$ & $F_2$) & probably other mediaters of inflammation that promote hyperalgesia.







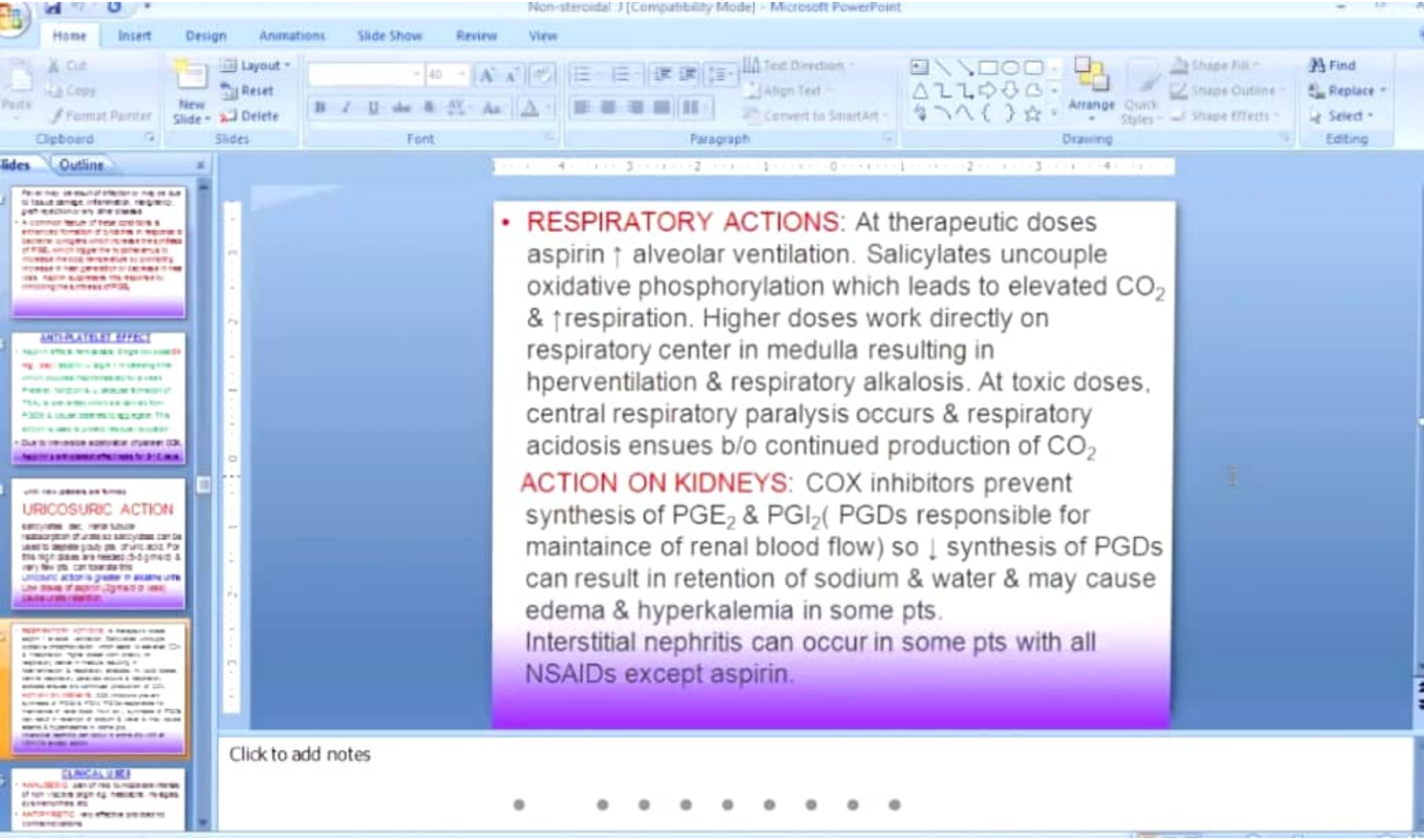
until new platelets are formed.

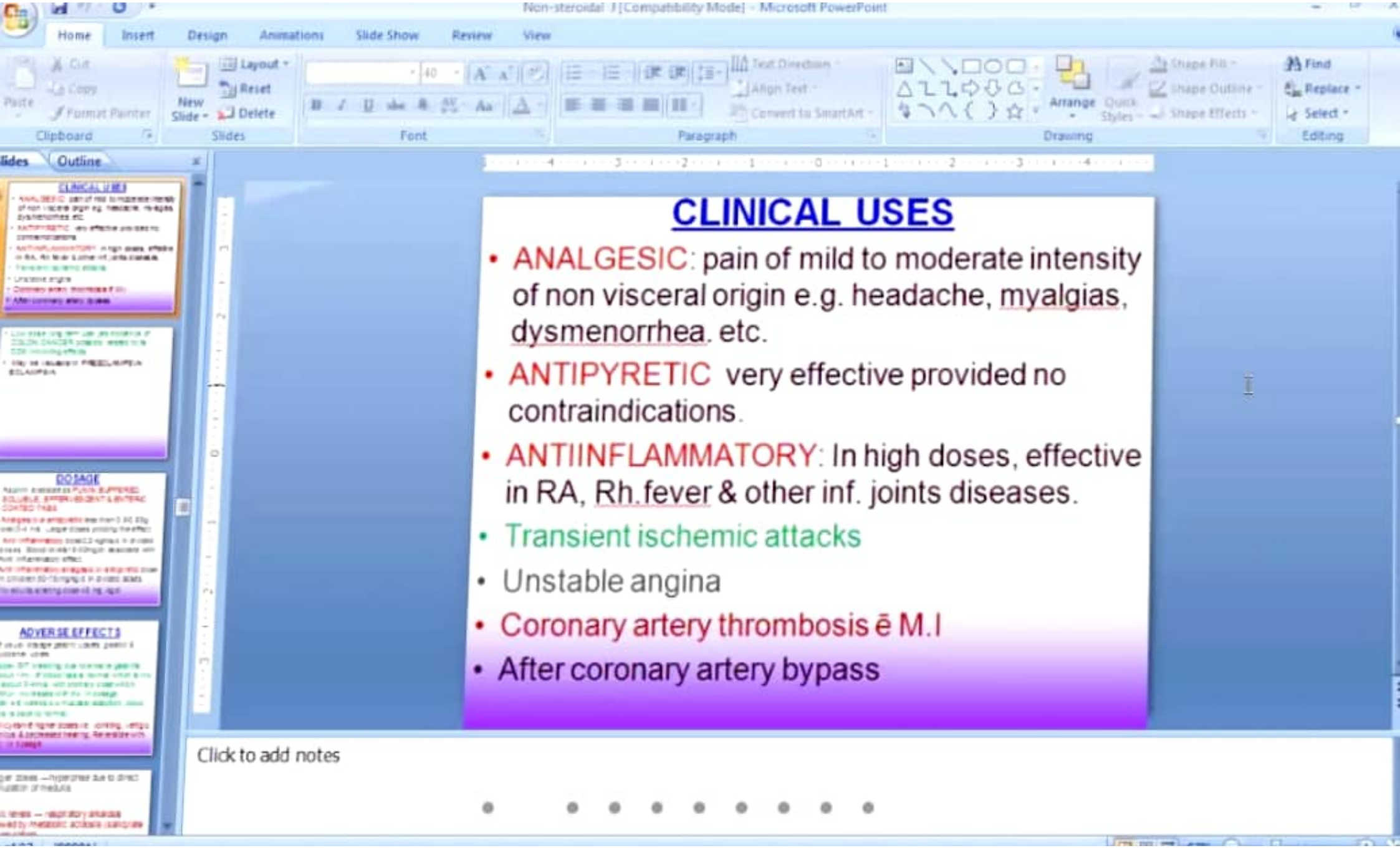
# URICOSURIC ACTION

salicylates dec. renal tubular reabsorption of urate so salicylates can be used to deplete gouty pts. of uric acid. For this high doses are needed (5-8 gms/d) & very few pts. can tolerate this.

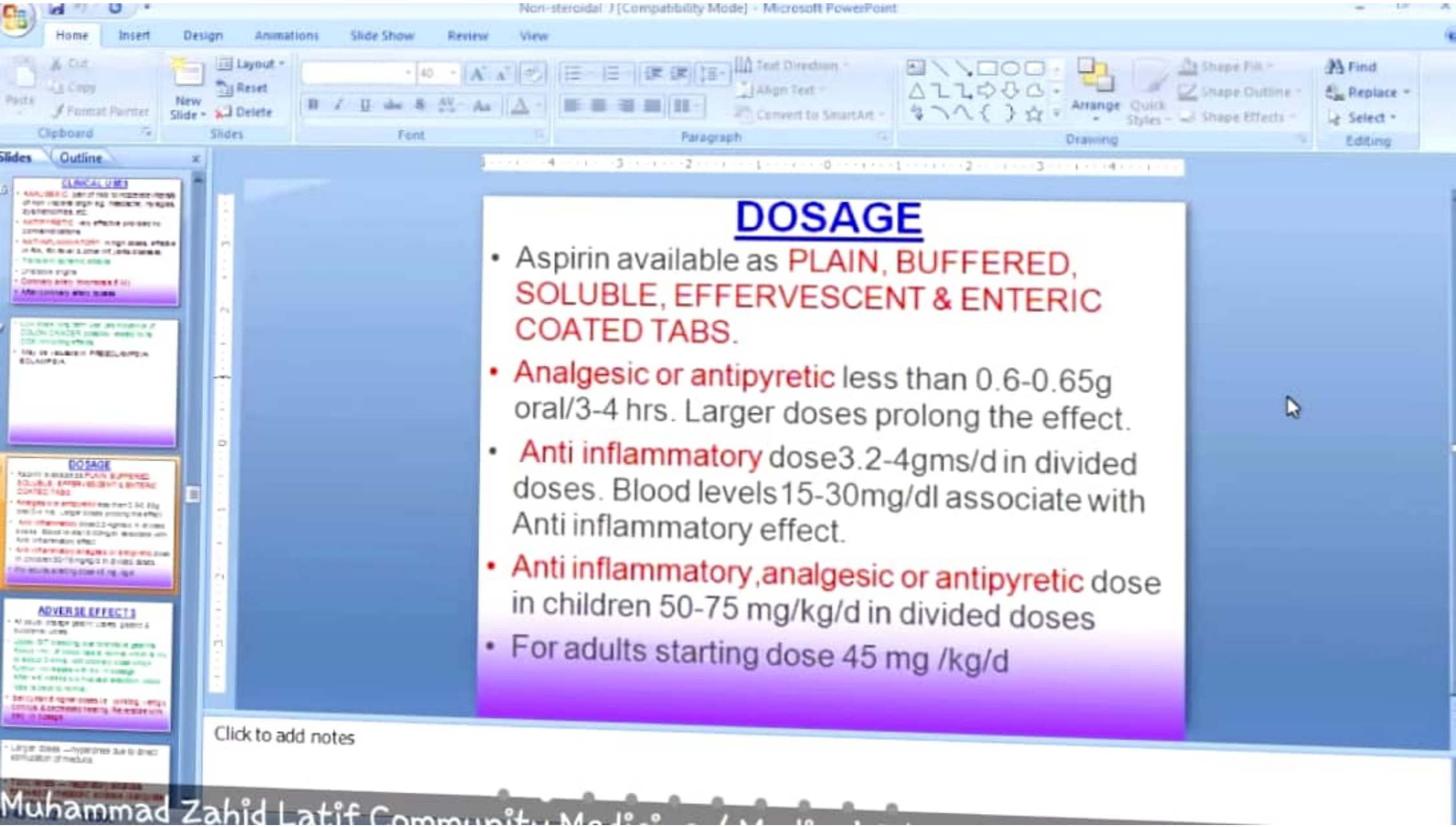
Uricouric action is greater in alkaline urine.

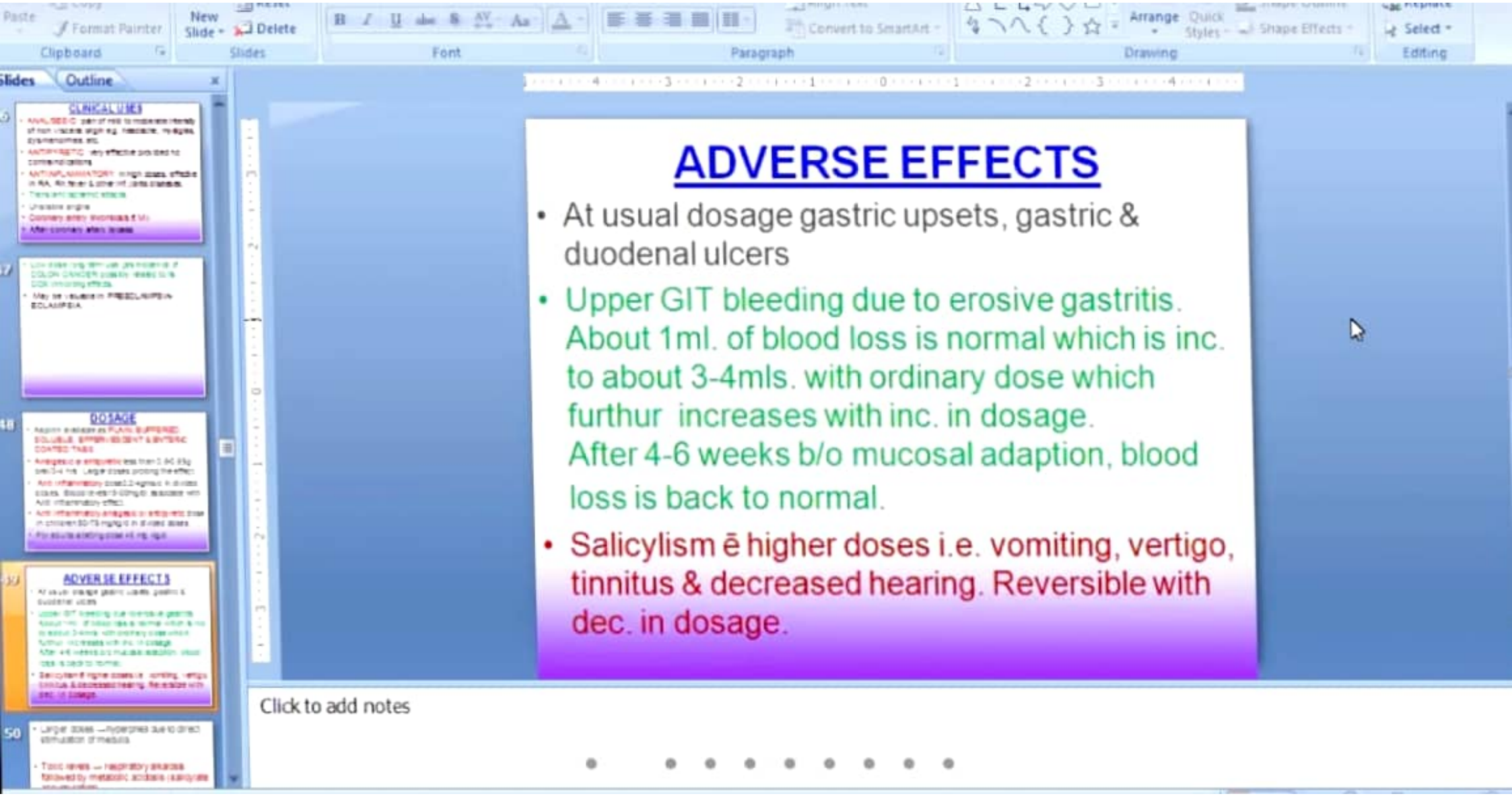
Low doses of aspirin (2gms/d or less) cause urate retention.





- Low dose long term use lessens incidence of COLON CANCER possibly related to its COX inhibiting effects
- May be valuable in PREECLAMPSIA ECLAMPSIA





Larger doses → hyperpnea due to direct stimulation of medulla.

Toxic levels → respiratory alkalosis followed by metabolic acidosis (salicylate accumulation)

Respiratory depression, cardio toxicity & glucose intolerance can occur at toxic doses.