

# Hunner Lesion Obeys Michaelis-Menten Kinetics In Delaying The Elimination of Drugs

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**PITT'S HISTORIC IMPACT**  
**Life-Saving Drugs? Thank Maud Me...**

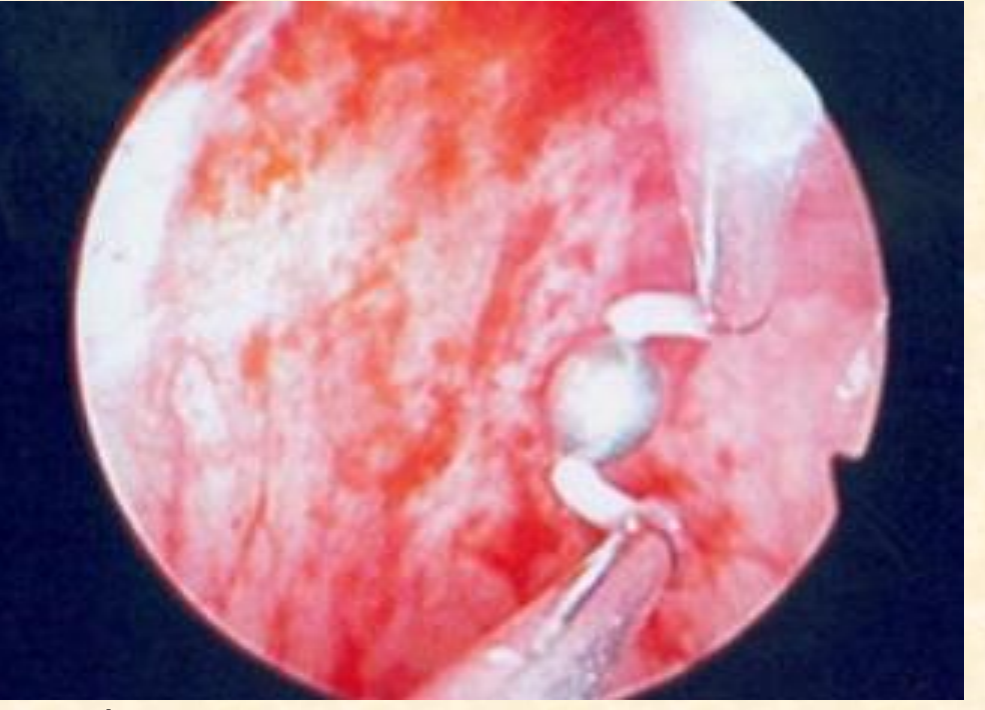
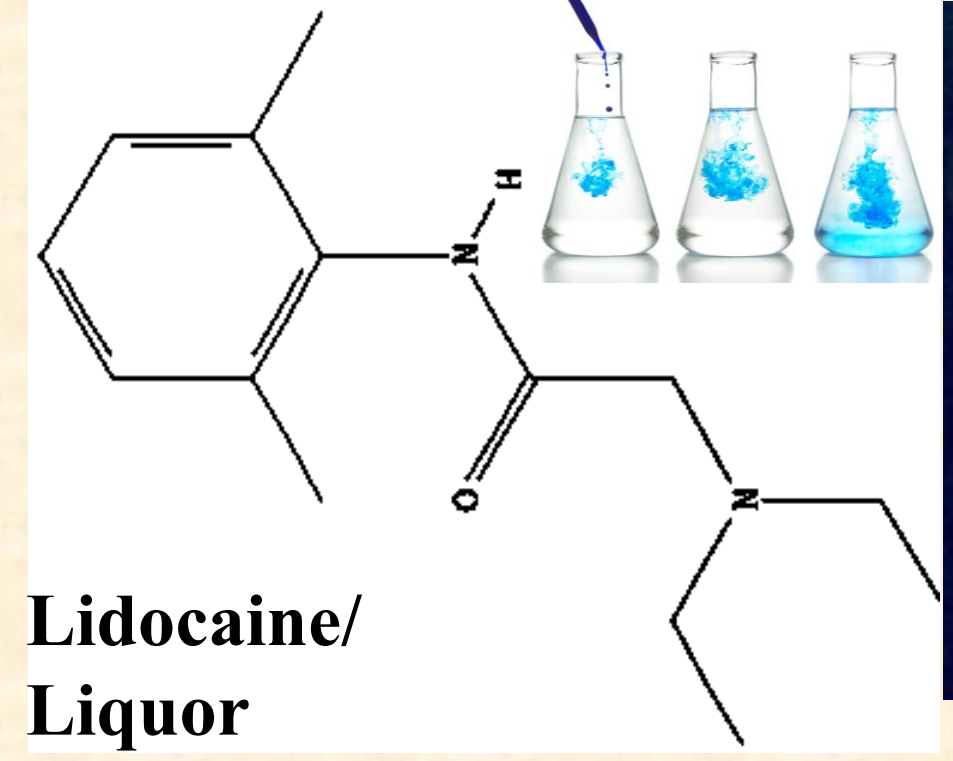
Maud Menten's research helped to lay the groundwork for modern drug therapy and biochemistry. Ignoring people who tried to talk her out of crossing the Atlantic by ship in 1912, not long after the Titanic sank, Menten traveled to Germany to work with biochemist Leonor Michaelis. The following year, she had developed the Michaelis-Menten equation, which provides a mathematical means for determining the rate of an enzyme reaction.

The equation is taught in every undergraduate biochemistry course (though textbooks often misquote Menten's name as "Henderson") and it's used exhaustively in most research laboratories. Without it, the development of most drugs over the last century would have been impossible.

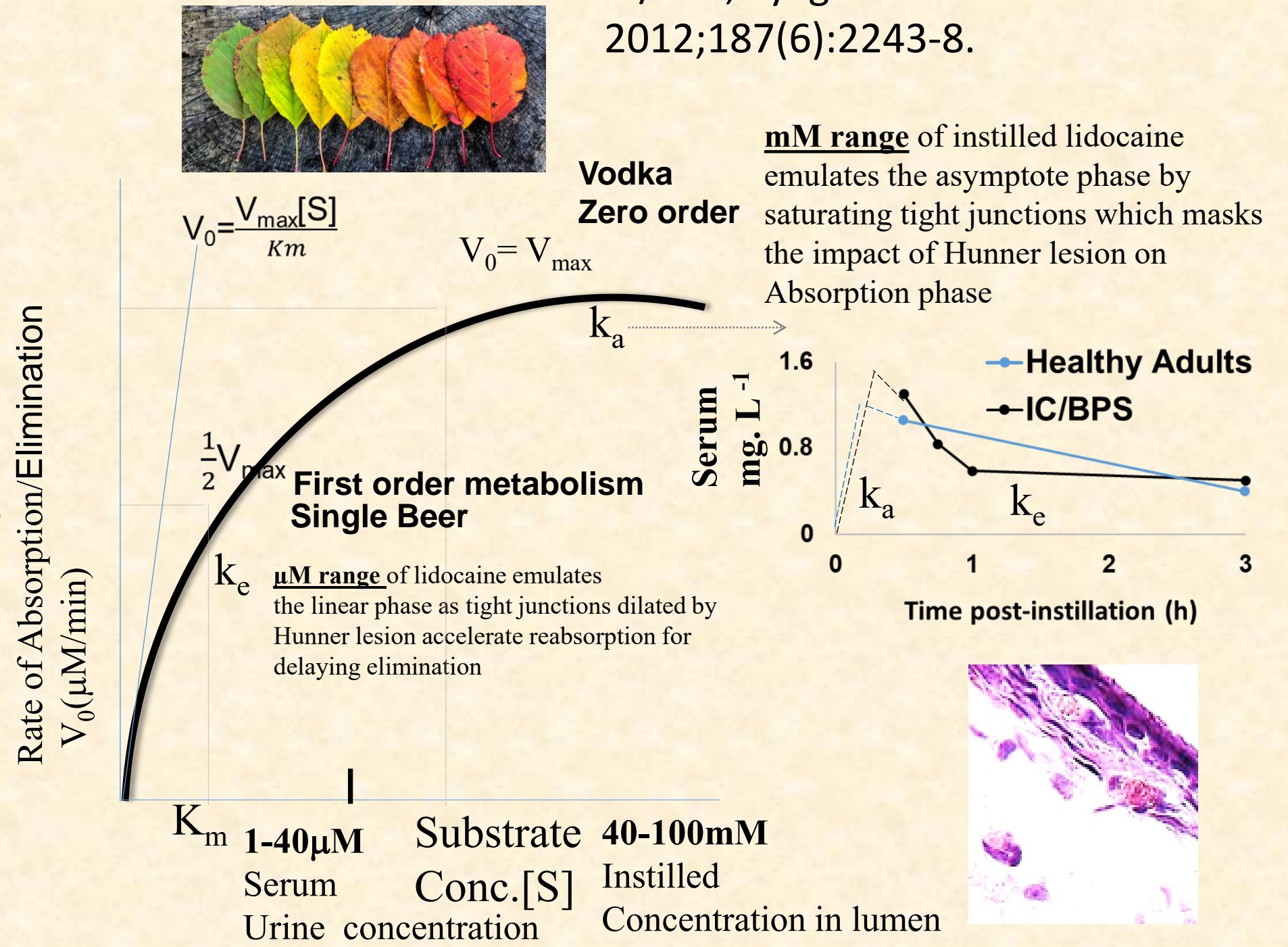
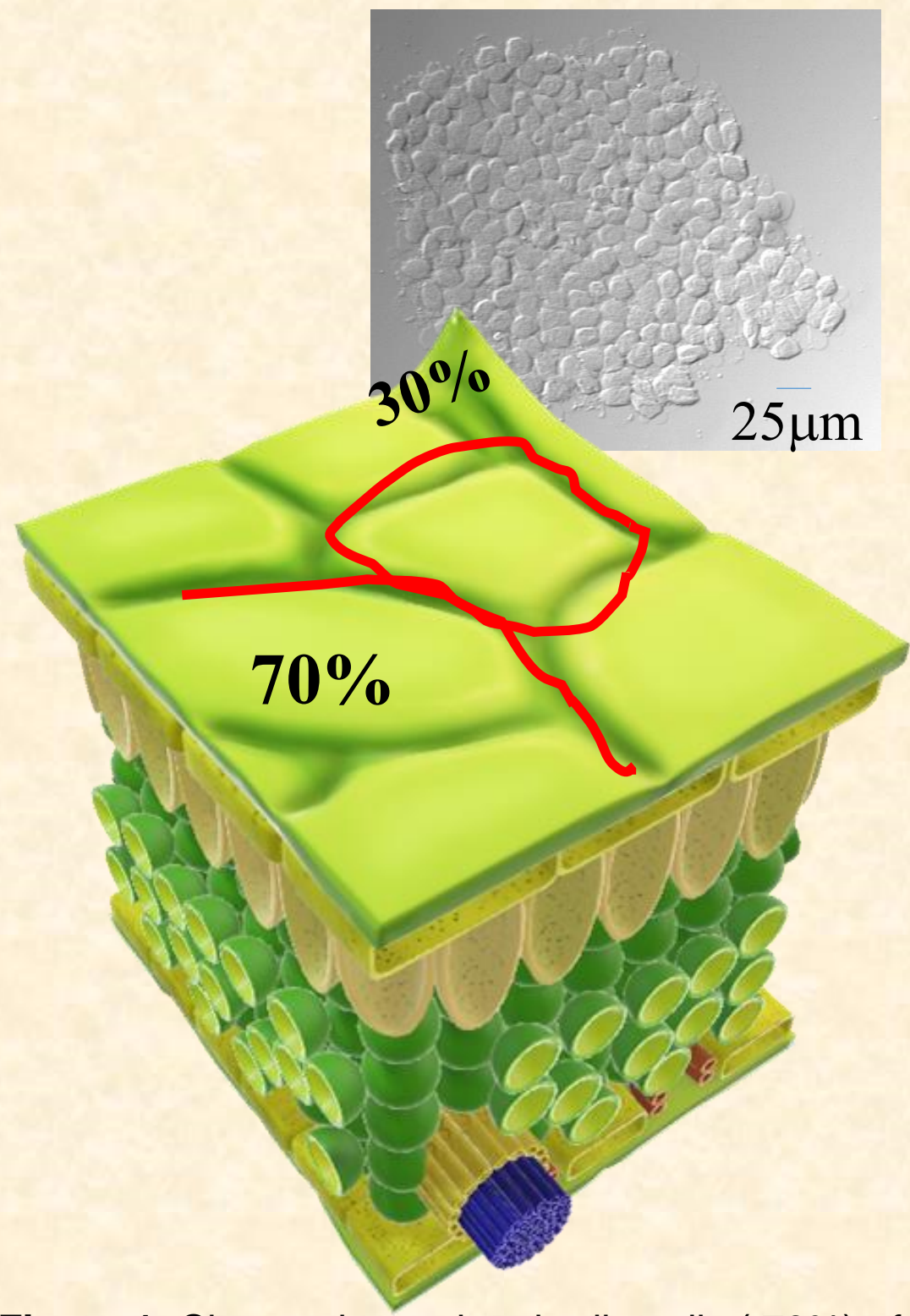
In 1916, Menten joined Pitt's Department of Pathology, where she became known for her 18-hour workdays—the delivered one-third of the department's lectures and attended every lab session—and as one of the University's most versatile scientists. She was also head of pathology at Children's Hospital of Pittsburgh.

And Menten wasn't just interested in science. She was also an accomplished clarinetist and linguist, and for years her original paintings hung uncredited in the halls of Pitt before finding their way into art exhibitions. Like Menten was less accomplished as a driver. Pedestrians learned to get out of her way as she lurched through Pittsburgh's Oakland and Shadyside neighborhoods in her Model T Ford. She never could remember which pedal to push when, so she would enthusiastically push them all.

Today, the University recognizes Menten with memorial lectures in her honor and a named chair.



IC/BPS; Tyagi et al J Urol. 2012;187(6):2243-8.



**Figure 2. Michaelis-Menten Kinetics-** The contrasting impact of Hunner lesion (IC/BPS) on the rate of absorption and elimination of lidocaine, fluorescein and salicylate conforms to Michaelis –Menten Kinetics. Restricted transcellular absorption leaves only the capacity limited, passive paracellular diffusion (across tight junctions) as the viable route for systemic uptake which is affirmed by a 3-fold rise in systemic uptake with tight junctions widened by prolonged dwell time of 120min from 10min (ref.5).

**Figure 1:** Since polygonal umbrella cells ( 70%) of luminal surface have restricted permeability, tight Junctions (30%) of luminal surface can be treated as paracellular ports of entry for lidocaine-capacity limited- amenable to Michaelis-Menten kinetics

## BACKGROUND

- We recently reviewed the pharmacokinetic basis for the use of instilled lidocaine as local anesthetic/ analgesic for TURB and intradetrusor inj<sup>1</sup>
- We were puzzled by the published lidocaine serum level plots in which the impact of Hunner lesion in interstitial cystitis/painful bladder pain syndrome (IC/BPS) patients<sup>2</sup> is much more easily discernible on elimination (downslope) than on the absorption (upslope) of instilled lidocaine
- The delayed elimination due to bladder reabsorption is not unique to lidocaine as orally ingested fluorescein<sup>3</sup> and instilled or injected salicylate<sup>4</sup> in animals also challenge the assumption of bladder as a non-returning (one-way traffic) compartment for drugs excreted into urine after **Absorption** → **Distribution** → **Metabolism** → **Excretion (ADME)**
- While Henderson Hasselbalch equation explains the accentuation of lidocaine anesthesia at 5min<sup>5</sup> following accelerated absorption but principle governing delayed elimination of lidocaine and other drugs is unclear
- Michaelis Menten Kinetics been previously used to elucidate the non-linear metabolism (M of ADME) of ethanol<sup>6</sup>, phenytoin, and paclitaxel
- Here, we distilled the published clinical evidence<sup>1-4</sup> to probe whether the apparent ceiling effect in intravesical absorption and First order reabsorption of lidocaine and fluorescein from urine by dilated tight junctions<sup>7</sup> of Hunner lesion(Fig.1) is amenable to Michaelis Menten Kinetics

## METHODS

- Published clinical studies on IC/BPS and healthy controls<sup>1-2,5</sup> were analyzed to examine the impact of Hunner lesion on intravesical absorption and renal elimination of lidocaine, fluorescein<sup>3</sup> and salicylate<sup>4</sup>
- Whether the differential impact of Hunner lesion on absorption at instilled concentration and reabsorption at low urine concentration is amenable to Michaelis Menten Kinetics

## RESULTS

- The instillation of 2% alkalinized lidocaine in healthy controls and IC/BPS patients generated an overlap in the published C<sub>max</sub> range of 0.66 - 1.71 mg/L (7.2micromolar)<sup>2</sup> and 0.2 to 2.0 mg/L (8.5 micromolar), respectively at Tmax ~30min.
- The overlap is consistent with the comparable upslope<sup>1</sup> or absorption rate constant (k<sub>a</sub>) before C<sub>max</sub> in stark contrast to the significant differences in the downslope post C<sub>max</sub> between IC/BPS patients and healthy controls <sup>2</sup>
- Slower elimination rate constant (k<sub>e</sub>) of -0.082h<sup>-1</sup> in IC/BPS patients relative to -0.380 h<sup>-1</sup> for healthy volunteers alludes to the reabsorption of lidocaine in urine being accentuated by Hunner lesion
- Thus, application of the linear phase of Michaelis Menten Kinetics to urinary reabsorption is consistent with the demonstrated linearity between urine and mucosal concentration <sup>8</sup>

## INTERPRETATION

- Umbrella cells covering 70% of bladder luminal surface <sup>7</sup> are renowned for their transcellular impermeability, drugs like lidocaine are exclusively absorbed and reabsorbed like fluorescein across tight junctions, covering ~30% of luminal surface <sup>3</sup>(Fig.1),
- The limited number of tight junctions or ports of entry can be conceptualized as enzymes mediating lidocaine diffusion, and therefore the widening of tight junctions by distension<sup>9</sup> and inflammation<sup>4</sup> is bound to accelerate absorption/reabsorption(Fig.1)
- Thus, the variability in lidocaine reabsorption and the ceiling effect during absorption between controls and IC/BPS subjects manifest Michaelis-Menten kinetics of lidocaine if one considers that instilled concentration of 1-2% w/v lidocaine (45-85mM) achieves the maximum absorption<sup>10</sup> rate (k<sub>a</sub>) analogous to the maximum enzyme activity (beyond V<sub>max</sub>) depicted by the asymptote phase of Michaelis-Menten curve (Fig.2)
- The ceiling effect of V<sub>max</sub> at 45-85mM obscures any additional increase in k<sub>a</sub> rate from the widening of tight junctions by inflammation secondary to Hunner lesion which is easily discernible from flatter elimination slope of IC/BPS patients at lower urinary concentration in micromolar range

## CONCLUSIONS

- The differential impact of Hunner lesion on absorption (45-85mM) and elimination(<0.01mM) manifests compliance with the asymptote and linear phases of Michaelis-Menten kinetics, respectively.
- Higher concentration saturates tight junctions (entry ports on bladder luminal surface) to obscure any impact of tight junctions widened by inflammation secondary to Hunner lesion, which is discernible at lower urine concentration (<0.01mM)
- Thus, delayed clearance of lidocaine in IC/BPS patients relative to controls is amenable to Michaelis-Menten kinetics just as healthy adults are more likely to be inebriated with vodka (40% ethanol) than with single beer (5-10% ethanol)

## REFERENCES

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