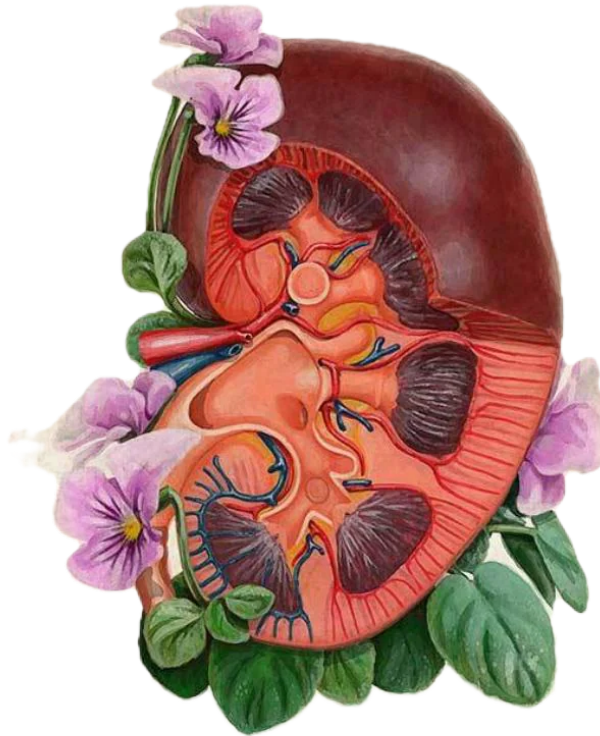




## **UGS Physiology Sheet #2**



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# Quantifying Kidney Functions

## Renal Plasma Flow

*Basic principle: amount extracted in the kidney is equal to amount received in urine.*

This is an application of the law of conservation of mass.

Let's say a substance (x) is completely eliminated upon passing: partially filtered, the rest is secreted, and none of it is reabsorbed. This means that none of it will return in the renal vein. The extraction or elimination **ratio** (ER) of this substance would be 1, as venous plasma concentration would be 0.

$$ER = \frac{\text{conc. artery} - \text{conc. vein}}{\text{conc. artery}} = \frac{[x] - 0}{[x]} = 1$$

- 1- How much (mass) of this substance enters the Kidney per minute?

The mass of a substance delivered to the kidneys per minute can be calculated by multiplying the Renal Plasma Flow (RPF, in mL/min) by the plasma concentration of that substance ( $P_x$ , in g/mL).

$$\text{Enters the Kidney: } RPF \times P_x = y \text{ g/min}$$

- 2- How much mass is excreted from the kidney per minute?

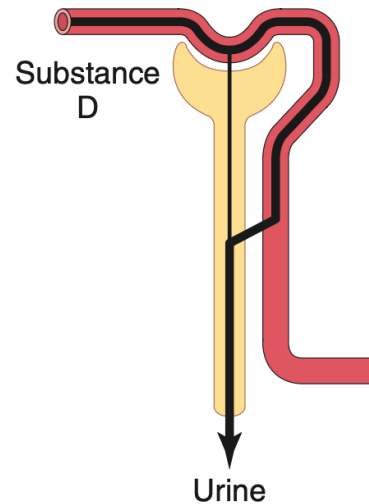
What is excreted from the kidney is equal to that received in urine. Urine flow ( $V$ ) and concentration of substance x in urine ( $U_x$ ) can be multiplied to determine the mass of this substance excreted in urine per minute.

$$\text{Excreted: } V \times U_x = y \text{ g/min}$$

If the substance is completely removed from the plasma as it passes through the kidneys (i.e., the extraction ratio,  $ER = 1$ ), then the amount **delivered** to the kidneys per minute is **equal** to the amount **excreted** in the urine ( $1 = 2$ ).

$$RPF \times P_x = V \times U_x$$

Since urine and plasma concentrations for a certain substance, along with urine flow are easily measurable, it's easy to calculate RPF. There is an exogenous substance called para-aminohippuric acid (PAH) that is very useful for this purpose, and it is considered to be a **RPF marker**.



This assumption is not entirely accurate, because about 10% of the blood entering the kidneys does not perfuse the nephrons or participate in filtration. Instead, it supplies other renal structures such as the capsule and pelvis. Therefore, the extraction ratio is closer to 0.9 rather than 1. The renal plasma flow calculated under the assumption of complete extraction is actually the effective renal plasma flow (*ERPF*), and the true renal plasma flow (*tRPF*) can be determined by correcting for the extraction ratio.

x = PAH:

$$ERPF = \frac{U_x \times V}{P_x} ; tRPF = \frac{ERPF}{ER}$$

Different substances can be used to measure different aspects of kidney function. **PAH** is used to estimate *renal plasma flow* because it is almost completely removed.

In contrast, **inulin** is used to measure *glomerular filtration rate* because it fulfills the 3 major criteria:

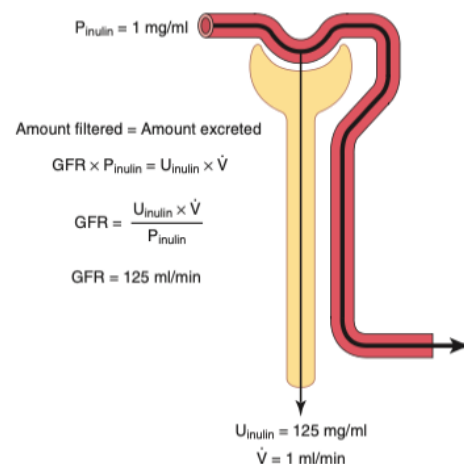
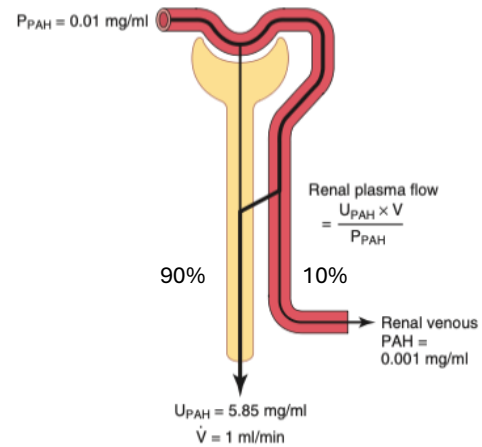
1. It is freely filtered at the glomerulus since its molecular weight is about 5000 (well below ~70,000).
2. It is not reabsorbed by the renal tubules.
3. It is not secreted by the renal tubules.

This means that the amount of Inulin excreted in the urine is exactly equal to the amount filtered at the glomerulus. Therefore, its clearance equals the Glomerular Filtration Rate (GFR), making it an ideal marker. However, inulin is mainly used in research because its measurement is technically difficult and impractical in clinical settings, so **Creatinine** is used instead. We will touch on inulin calculations later.

### Clearance

Renal clearance of a substance (CL / doctor used C) is the volume of plasma that is completely cleared of the substance by the kidneys per unit of time (**mL/min**). It is the most important renal physiology concept.

It does not represent a physical volume, but rather a “virtual” volume that reflects how efficiently the kidney removes a substance from the blood. A high clearance means the kidney is very effective at removing that substance, while a low clearance means it is not.



Think of it like this:

For blood volume passing through the kidney, how much of it got filtered or *cleared from the substance* and how much still has the substance, so basically like the ER but multiplied by RPF. One equation for clearance is:

$$CL = RPF \times ER$$

Clearance is the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit of time.

Clearance of a substance (x) can be calculated by its plasma and urine concentration (g/mL) along with urine flow (mL/min),

$$CL = \frac{U_x}{P_x} \times V$$

*PAH* clearance **equals ERPF** since all blood volume that undergoes filtration (and not kidney nourishment) is cleared of PAH. Their equations are the same as well.

*Inulin* clearance **equals GFR** because it is freely filtered and neither reabsorbed nor secreted; therefore, the volume of plasma filtered is equal to the volume cleared of inulin.

*Glucose* on the other hand has clearance that equals 0 mL/min normally, because it is completely conserved and not excreted through complete reabsorption.

### **Filtered Load**

Another important concept is the filtered load (FL), which refers to how much of a substance is filtered into the nephron each minute (g/min). This depends on the Glomerular Filtration Rate (GFR) (mL/min) and the concentration of the substance in the plasma ( $P_x$ ) (g/mL), since the concentration of the substance in the filtrate is equal to its concentration in the plasma (for a freely filtered substance). After filtration, the substance may be reabsorbed back into the blood or secreted into the tubule; processes which don't affect the FL.

$$FL = GFR \times P_x$$

Example for potassium:

$$GFR = 125 \text{ mL/min} = 180 \text{ L/Day}, P_x = 4 \text{ mEq/L}$$

$$FL = 180 \times 4 = 720 \text{ mEq/day}$$

Example for sodium:

If GFR is 125 mL/min ( $\approx 180$  L/day) and plasma sodium concentration is 140 mEq/L, then the filtered load is:

$$FL = 180 \times 140 = 25,200 \text{ mEq/day.}$$

In a steady state, intake equals excretion. Since we ingest only about 155 mEq/day, we only excrete 155 mEq/day, and the rest is reabsorbed:

$$\text{Reabsorption} = 25,200 - 155 = 25,045 \text{ mEq/day.}$$

Thus, approximately 99.4% of the filtered sodium is reabsorbed.

Since the amount of a substance provided for excretion per minute equals the amount entering the urine per minute. For inulin, since it is only filtered (not reabsorbed or secreted), the amount filtered at the glomerulus equals the amount excreted in the urine.

$$\text{Filtered load} = \text{Excretion rate}$$

$$FL = GFR \times P_{\text{inulin}} = V \times U_{\text{inulin}}$$

$$GFR = \frac{U_{\text{inulin}}}{P_{\text{inulin}}} \times V$$

Since  $GFR = CL_{\text{inulin}}$ , we can also use the CL equation to arrive to this formula.

RPF, GFR, and CL are related. Since CL of a substance is the easiest to measure, we use special substances and measure their CL to estimate GFR or RPF, as reflected in their equation (Inulin clearance = GFR; PAH clearance = RPF).

**In-lecture MCQ:** The maximum possible clearance rate of a substance that is completely cleared from the plasma by the kidneys would be equal to

1. glomerular filtration rate
2. the filtered load of the substance
3. urine excretion rate of the substance
- 4. renal plasma flow**
5. renal blood flow

### ***Estimating GFR clinically***

We know that in a clinical setting, measuring GFR is essential for assessing kidney function. **Inulin** is the gold standard for GFR measurement, but it is an exogenous substance, so its clinical value is limited. Instead, we rely on **creatinine**, an endogenous substance that is both convenient and reasonably reliable.

Creatinine is freely filtered and not reabsorbed, but about 10% is secreted by the renal tubules, meaning it does not perfectly meet the 3 criteria of an ideal GFR marker. This secretion increases the amount of creatinine appearing in the urine, which on its own would overestimate GFR. On the other hand, approximately 10% of plasma creatinine is protein-bound and therefore not filtered. However, laboratory measurements report total plasma creatinine, slightly *overestimating* the plasma concentration that is actually filterable, which on its own would *underestimate* GFR. When we calculate GFR, these two opposing effects mostly cancel each other out. As a result, the final estimate of GFR is fairly accurate in most clinical situations. Remember the equation.

Why does creatinine still work?

Because:

- Secretion → pushes GFR up
- Protein binding → pushes GFR down

These two effects roughly cancel each other

Measuring urine flow rate (V) requires 24-hour urine collection, which is impractical because it is time-consuming and prone to significant errors if any urine is missed. In contrast, estimated GFR (eGFR) requires only a plasma creatinine measurement and does not depend on urine flow or urine creatinine concentration. It is calculated using established equations that incorporate variables such as age, sex, and sometimes body size.

There is no need to memorize these equations, but it is important to understand the factors they depend on. Sex is included because females generally have lower muscle mass and therefore produce less creatinine (about 85% compared to males). Age is also important, as GFR declines with aging at approximately 1% per year after the age of 40.

### **GFR clinical use**

GFR is used clinically to classify the severity of renal impairment by comparing the lab value with what should be normal:

- 1- GFR is 50 – 100% of normal: there is a **reduction in renal reserve**. At this stage, plasma urea and creatinine levels may still remain within the normal range because the kidneys can compensate despite nephron loss.
- 2- GFR is 20–50% of normal: there is **renal insufficiency**. A key feature at this stage is *isosthenuria*, where urine osmolarity becomes approximately equal to plasma osmolarity (~300 mOsm/kg) regardless of water intake or salt consumption because the kidney loses its ability to concentrate or dilute urine in this disease. As the kidneys cannot concentrate urine effectively, another symptom is polyuria. Additional complications include *azotemia* (elevated urea and creatinine), *anemia* (due to reduced erythropoietin production), and *hypertension*.
- 3- GFR of 5–20% of normal: there is **advanced renal failure**. At this stage, oliguria or anuria may develop. Patients can be managed by reducing the workload on the kidneys, for example by limiting sodium intake (e.g., from about 4 g to 1 g per day) and reducing protein intake to decrease urea production.
- 4- GFR is < 5% of normal: The patient has **end-stage renal disease (ESRD)**. Kidney function is no longer sufficient to sustain life, and life-long dialysis or kidney transplantation is required.

# Renal Handling of Different Substances

## **Water compartments**

The human body consists of 3 fluid compartments which are 60% of the total human weight, so a 70 kg human has: 42 L of total body fluid, 28 L intracellular and 14 L extracellular. Extracellular fluid is divided into 11 L interstitial fluid and 3 L plasma.

These 3 water compartments have many differences, but they share the same osmolarity, because water moves freely between them. An increase in the osmolarity in one compartment, will pull water from other compartments until they all reach equilibrium and osmolarity equalizes.

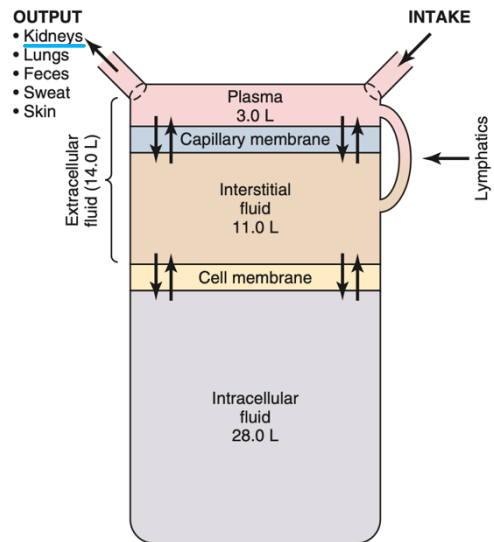
Blood plasma (3L) is the fluid compartment that is cleared by the kidney. Filtration in the glomeruli is the first step in renal clearance, and since the GFR is 180 L / day, plasma is filtered around 60 times daily.

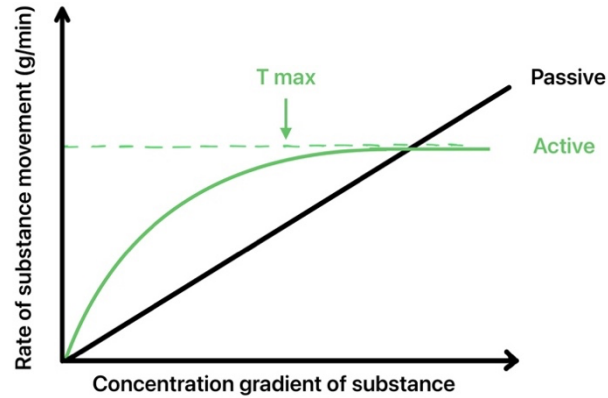
## **Saturation of transporter**

A large part of renal function revolves around substance transport across cell membranes, which can be divided according to whether protein transporters are involved or not into 2 main types:

**Passive transport** happens across the membrane directly and doesn't require any protein to facilitate movement; examples are diffusion, osmosis, or bulk flow due to high pressure (such as in the glomerulus). **Active transport** on the other hand requires carrier proteins with examples such as facilitated diffusion, primary or secondary active transport.

This distinction matters because active transport proteins saturate after a certain substance concentration is reached and rate of substance movement (tubular secretion or absorption for example) approaches a maximum where the rate plateaus and reaches  $T_{max}$ . In contrast, Passive transport or bulk flow (glomerular filtration) do not show saturation and the movement rate keeps increasing as long as substance concentration increases.

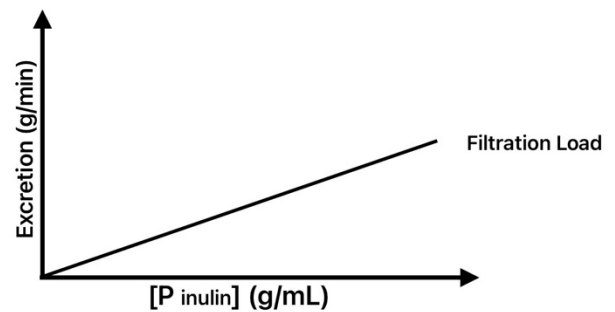
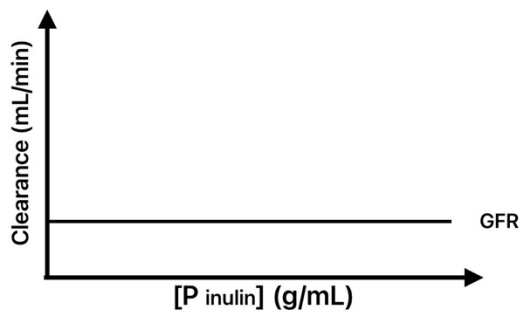




### Renal handling of different substances

#### A) Inulin

We already took that inulin is a GFR marker, meaning its clearance depends only on GFR. Since GFR is mostly constant (and is 20% of the RPF), the clearance rate of inulin remains constant regardless of the concentration of inulin in the plasma (left graph). This is because clearance represents the volume of plasma cleared of the substance regardless of how much the plasma originally had. Also remember that if  $GFR = CL_{inulin}$ , and GFR is constant then  $CL_{inulin}$  must be constant as well. Conversely, the amount (grams) excreted of inulin / min equals its FL, and the FL of any substance depends on both the GFR and  $P_x$ , so inulin excretion rate increases proportionally as  $P_{inulin}$  increases (right graph).



Since GFR is 125 mL/min and urine flow rate ( $V$ ) is 1 mL/min, inulin becomes concentrated about 125 times in the urine compared to plasma.

#### B) PAH

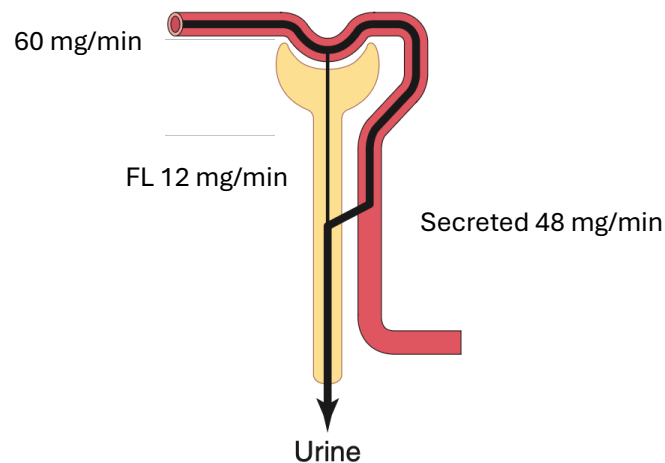
PAH is used as a marker of renal plasma flow (RPF) because it is almost completely cleared from plasma in a single pass through the kidneys (about 20% is filtered and ~80% is secreted).

If the plasma PAH concentration is 0.1 mg/mL and RPF is 600 mL/min, then the amount of PAH delivered to the kidneys is:

$$600 \times 0.1 = 60 \text{ mg/min}$$

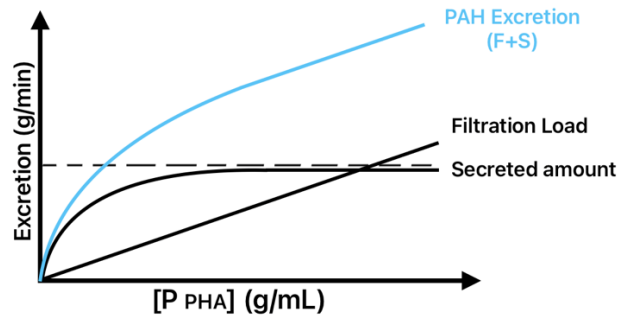
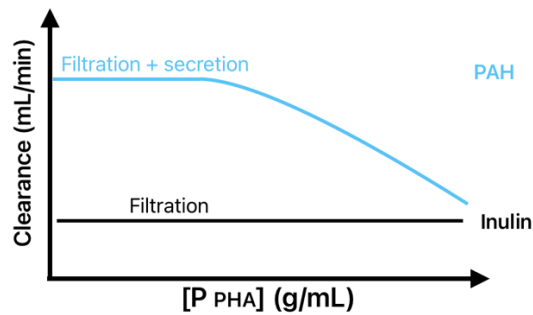
Approximately 20% of this (12 mg/min) is removed by filtration, while the remaining ~80% (48 mg/min) is removed by tubular secretion.

The filtered portion behaves like inulin (freely filtered, no transport limit), so it does not show a transport maximum. In contrast, the secreted portion depends on carrier-mediated transport and therefore exhibits a transport maximum ( $T_m$ ), meaning secretion plateaus at high plasma concentrations.



As PAH concentration increase, the FL keeps increasing proportionally while the secretion rate plateaus and reaches  $T_m$ . Beyond this point, the contribution of secretion to the total excretion rate becomes progressively less. As a result, the excretion rate becomes increasingly dominated by filtration alone, and the excretion rate and FL begin to converge. This convergence effect is best seen with a CL graph. Clearance rate begins as a horizontal line (585 mL/min) but as secretion plateaus the clearance rate falls steadily and converges with inulin's clearance.

This gives us a very important criterion to use PAH as a RPF marker: **its plasma concentration must be kept below the saturation level of the secretory transporters**. This is typically achieved by administering it at around 80 mg/min; otherwise, if saturation occurs, RPF will be **underestimated**.



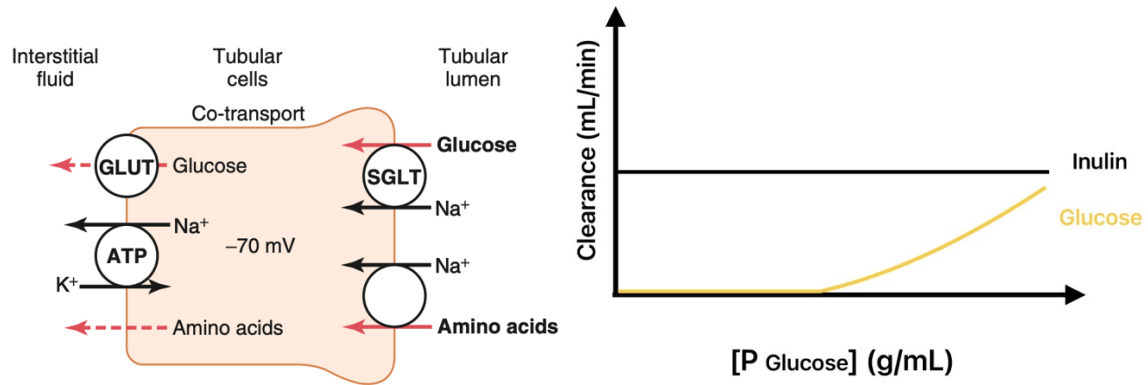
### C) Glucose

We know that glucose shouldn't be excreted in urine under normal conditions, but since it's only 180 MW, it's freely filtered and so it must be reabsorbed.

Glucose is reabsorbed in the PCT via secondary active transport along with sodium. Sodium is going down its concentration gradient from 140 in the tubule to 14 in the proximal tubular cell, through a sodium-glucose cotransporter (SGLT) on its apical border. These cells have a brush border and a lot of mitochondria due to being very active.

Sodium is then pumped out of the cell into the surrounding blood across the basolateral membrane via the  $\text{Na}^+/\text{K}^+$ -ATPase pump, which uses ATP to move sodium against its concentration gradient. This active transport maintains the low intracellular sodium concentration that drives glucose reabsorption. Around 90% of the ATP consumed by the kidney is used by the  $\text{Na}^+/\text{K}^+$ -ATPase pump, which means that most of kidney function is related to sodium homeostasis, and that's why patients with damaged kidneys are recommended a low salt diet to decrease stress on their kidneys, as stated earlier.

Glucose reabsorption in the proximal convoluted tubule is limited by a transport maximum ( $T_m$ ), since the SGLT carriers can become saturated. Under normal conditions P glucose is 70-110 mg/dL, and the filtered load of glucose is fully reabsorbed, so there is no glycosuria. In diabetes mellitus however, the plasma glucose rises significantly and increases tubular glucose concentration beyond  $T_m$ . Once the carriers are saturated, any additional glucose cannot be reabsorbed and appears in the urine. At this point, glucose clearance increases from zero because excretion begins. At very high concentrations, glucose clearance increases further and converges with inulin.



In short, substances modified in the tubule behave as unhandled substances at very high concentrations due to saturation of transporters, with their clearance either increasing or decreasing to converge with inulins' (GFR).