

ECTS PhD Training Course, Oxford
2nd July 2009

Bone Metabolism and Calciotropic Hormones

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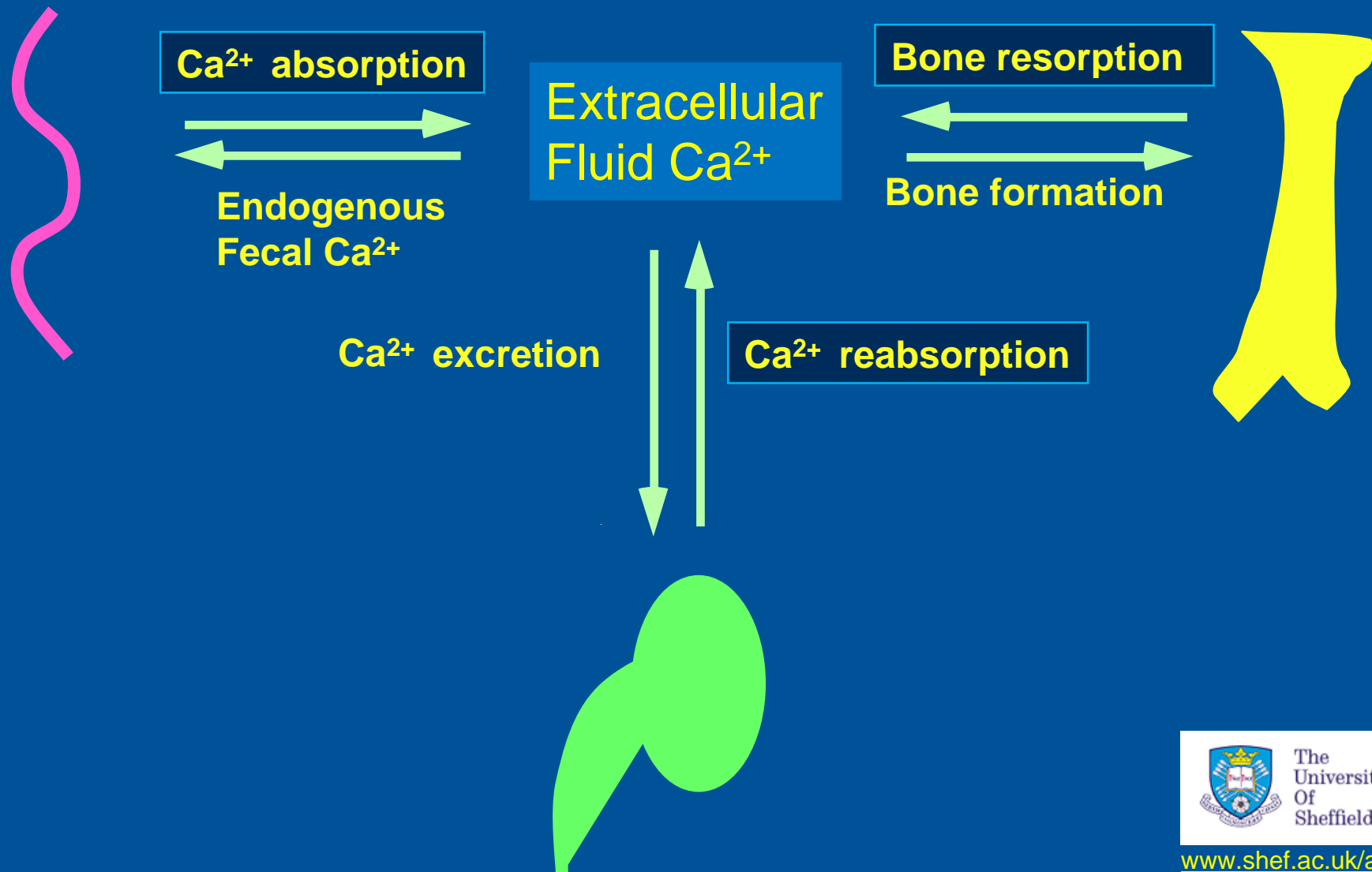


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Distribution of Calcium in the Body

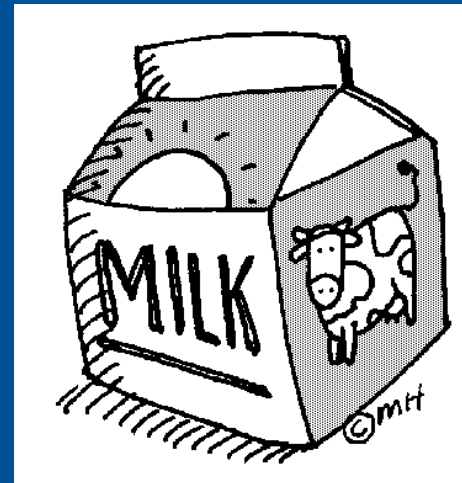
- **Skeleton is main reservoir**
 - 1200 g
- **Extracellular space has much smaller amount of calcium (only 1 g), but it is key for cell function**
 - Normal blood clotting
 - Muscle contractility
 - Nerve function

Calcium Kinetics



Dietary Calcium

- **Major sources**
 - Dairy products make up 2/3
 - Milk, yoghurt, cheese
- **Minor sources**
 - Vegetables, e.g. broccoli
 - Cereals, e.g. white bread
 - Oily fish, e.g. sardines



Calcium absorption

- **We absorb about 30% of dietary calcium**
 - Active absorption in duodenum and jejunum
 - Passive absorption in ileum and colon
- **We absorb a higher fraction of calcium when put on a low calcium diet**
 - This is mediated by $1,25\text{-(OH)}_2$ vitamin D, the active form of vitamin D
 - Most calcium is absorbed by active transport

Release of Calcium from Bone

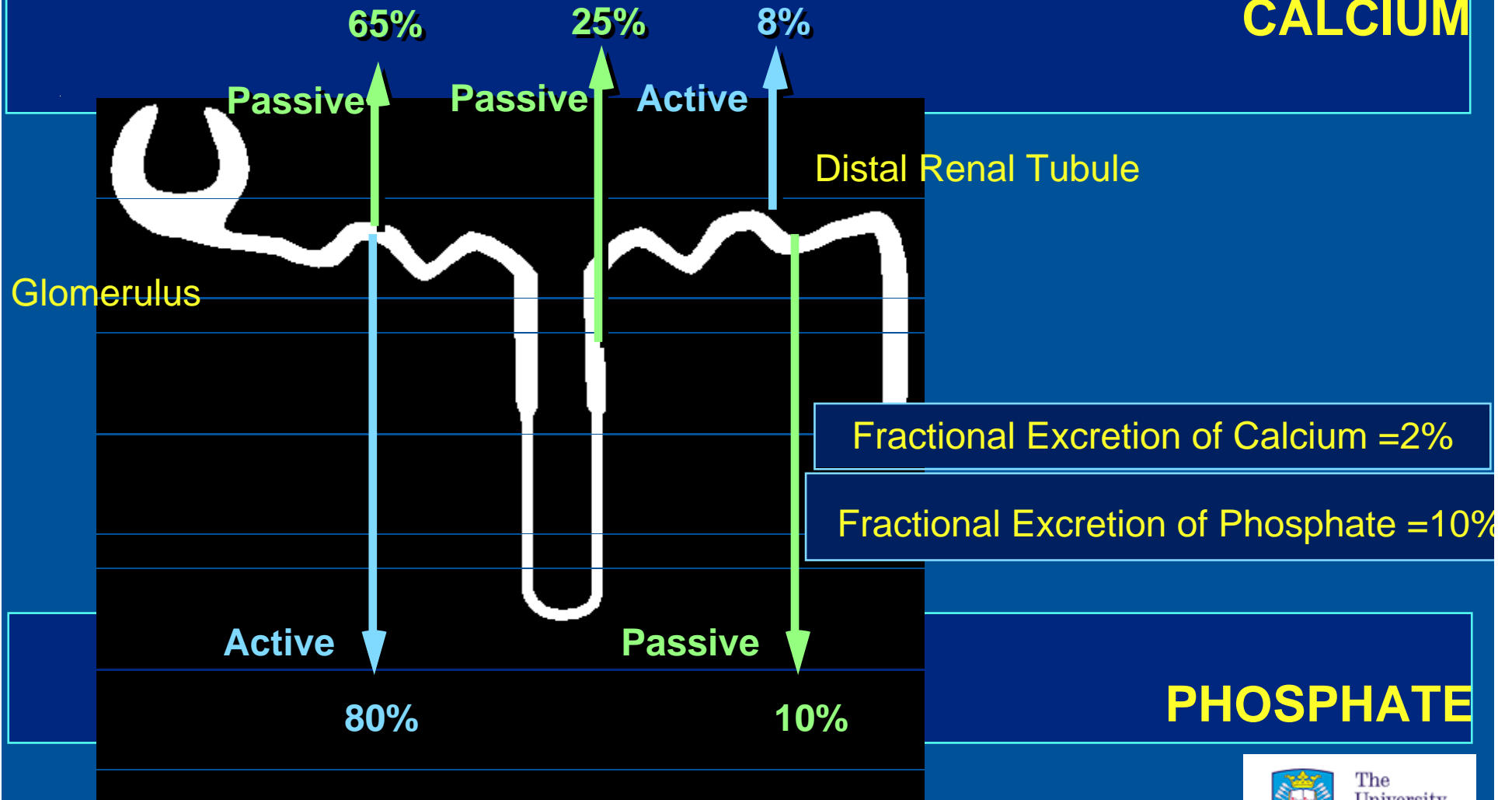
- **Calcium can be released rapidly from exchangeable calcium on the bone surface**
 - We don't know much about this mechanism
- **Calcium can be released more slowly by osteoclasts during bone resorption**

Calcium Handling by the Kidney

- **The amount of calcium filtered by the glomerulus depends on**
 - The glomerular filtration rate
 - The ultrafiltrable calcium
 - Ionised
 - Complexed
- **98% of this filtered calcium is usually reabsorbed**
 - More is reabsorbed if the PTH level is high
 - Less is reabsorbed if the filtered sodium is high

Calcium and Phosphate Excretion Reabsorption by the Nephron

CALCIUM



PHOSPHATE

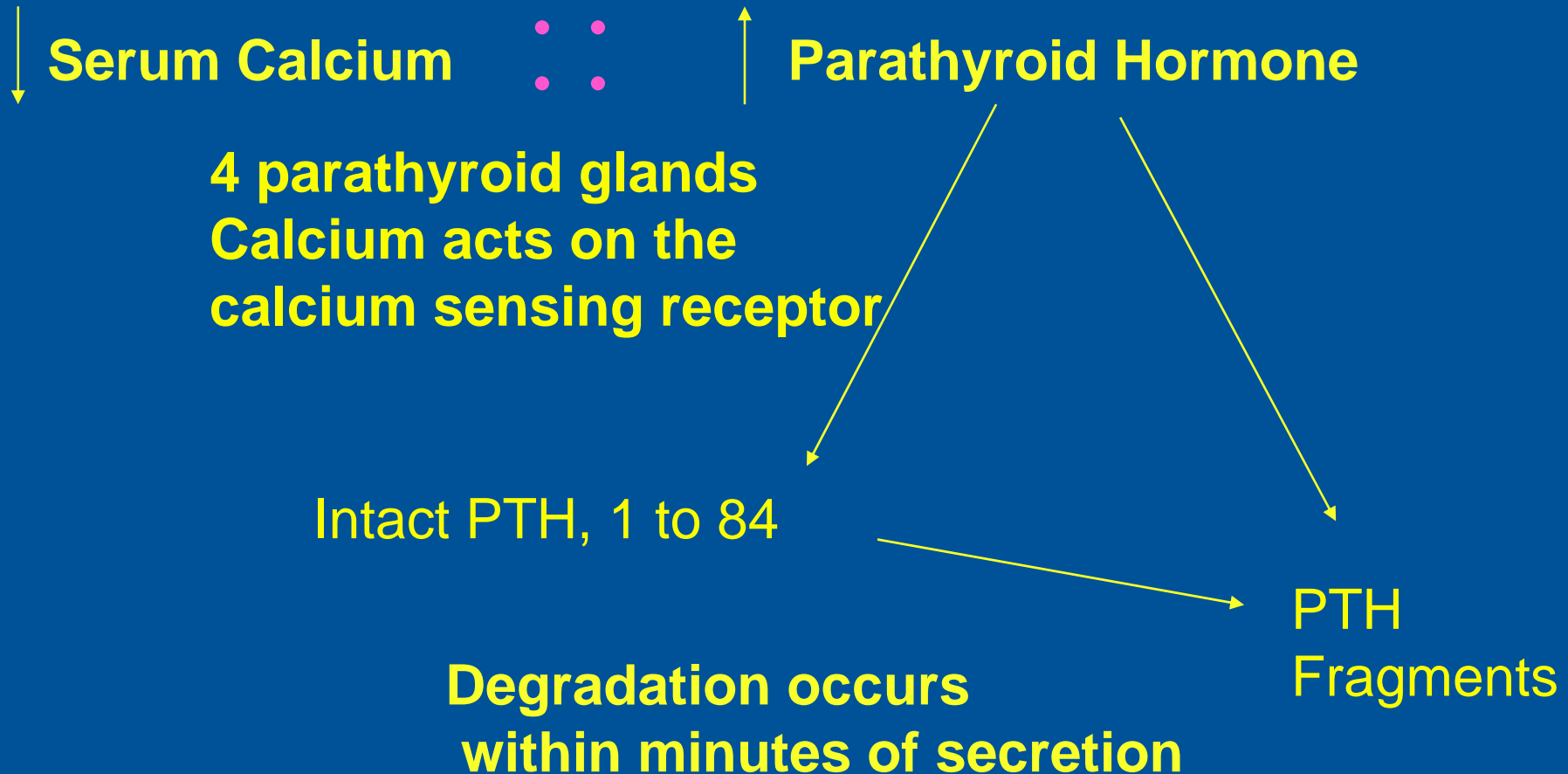
The Regulation of Serum Calcium



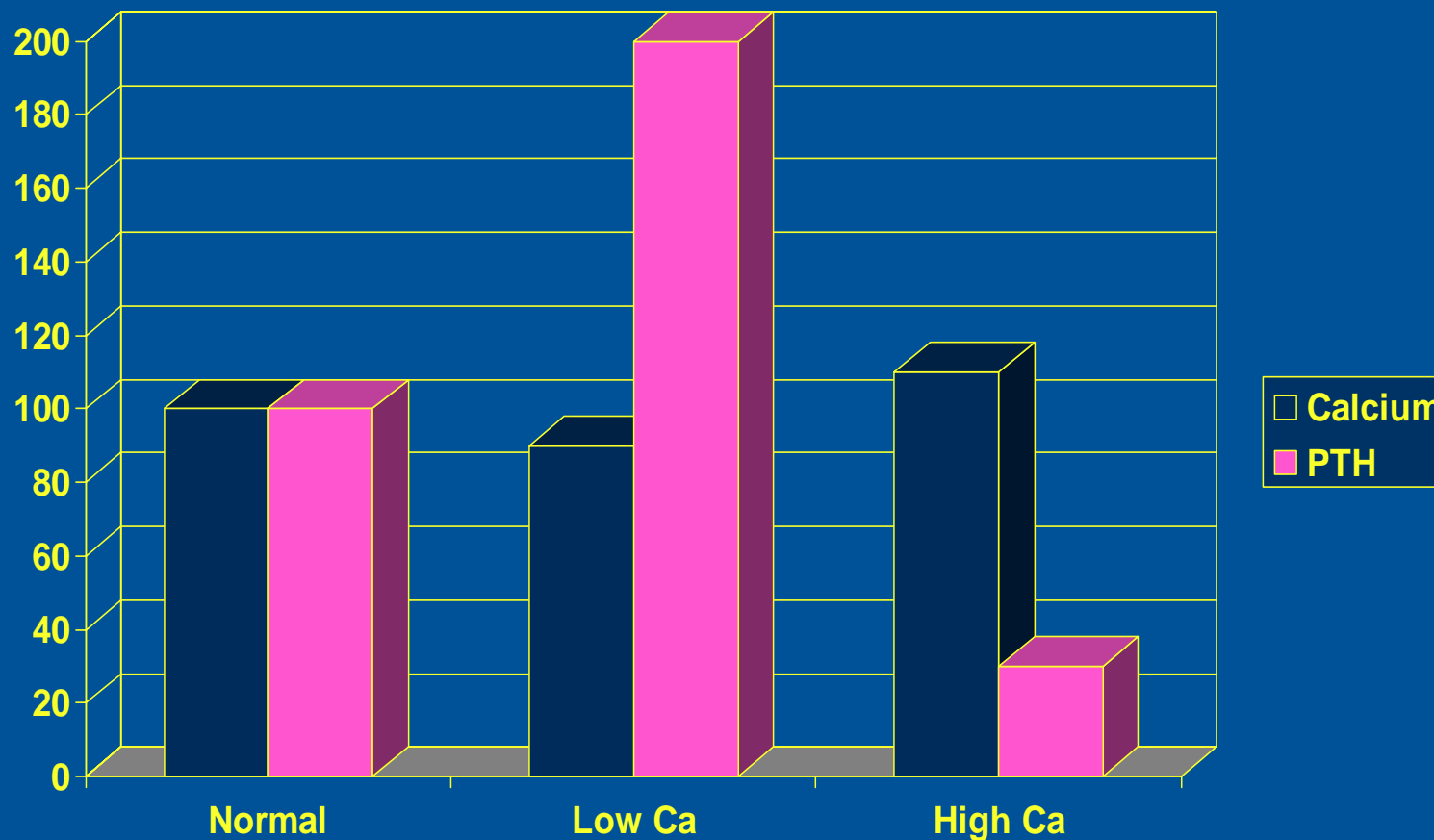
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Secretion of Parathyroid Hormone



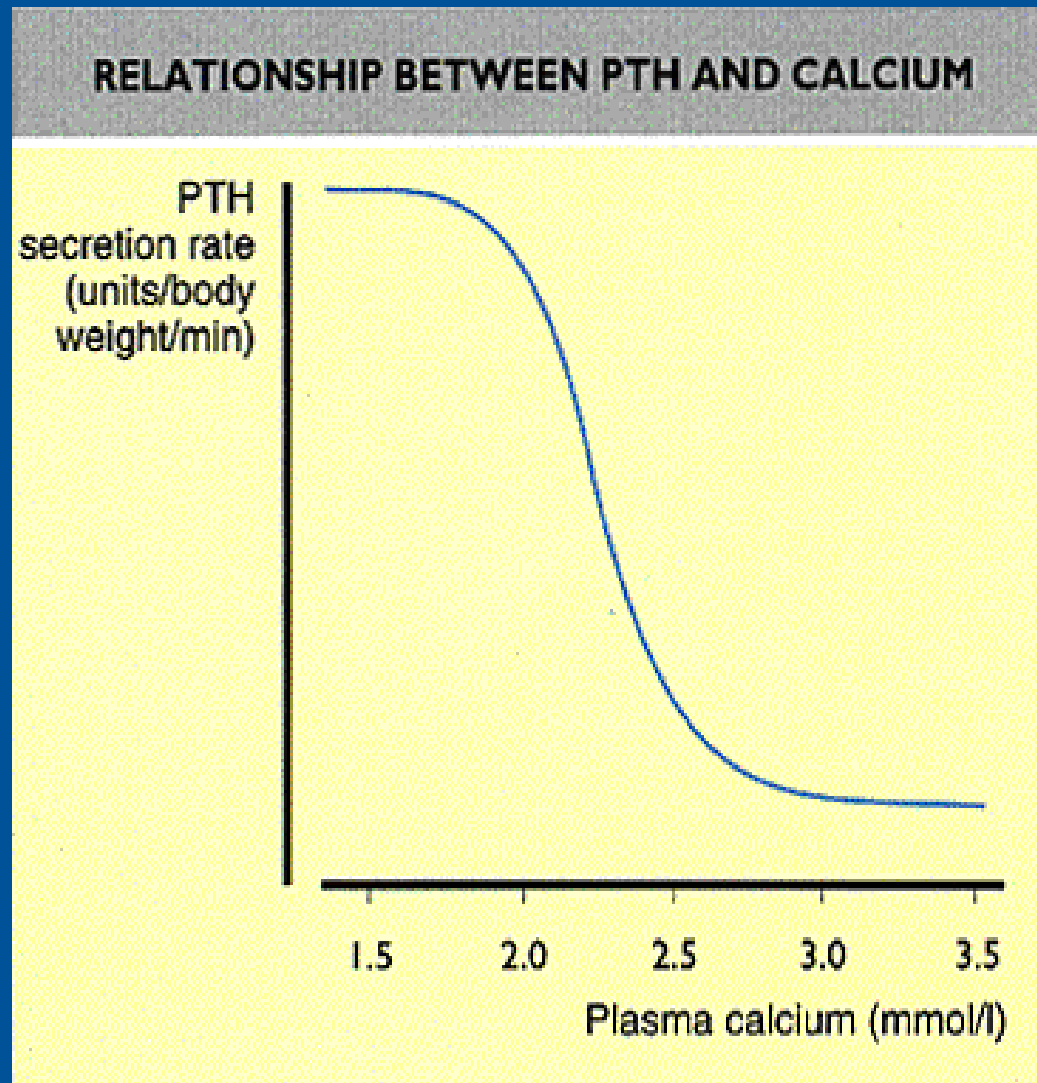
Relationship Between Serum Calcium and PTH



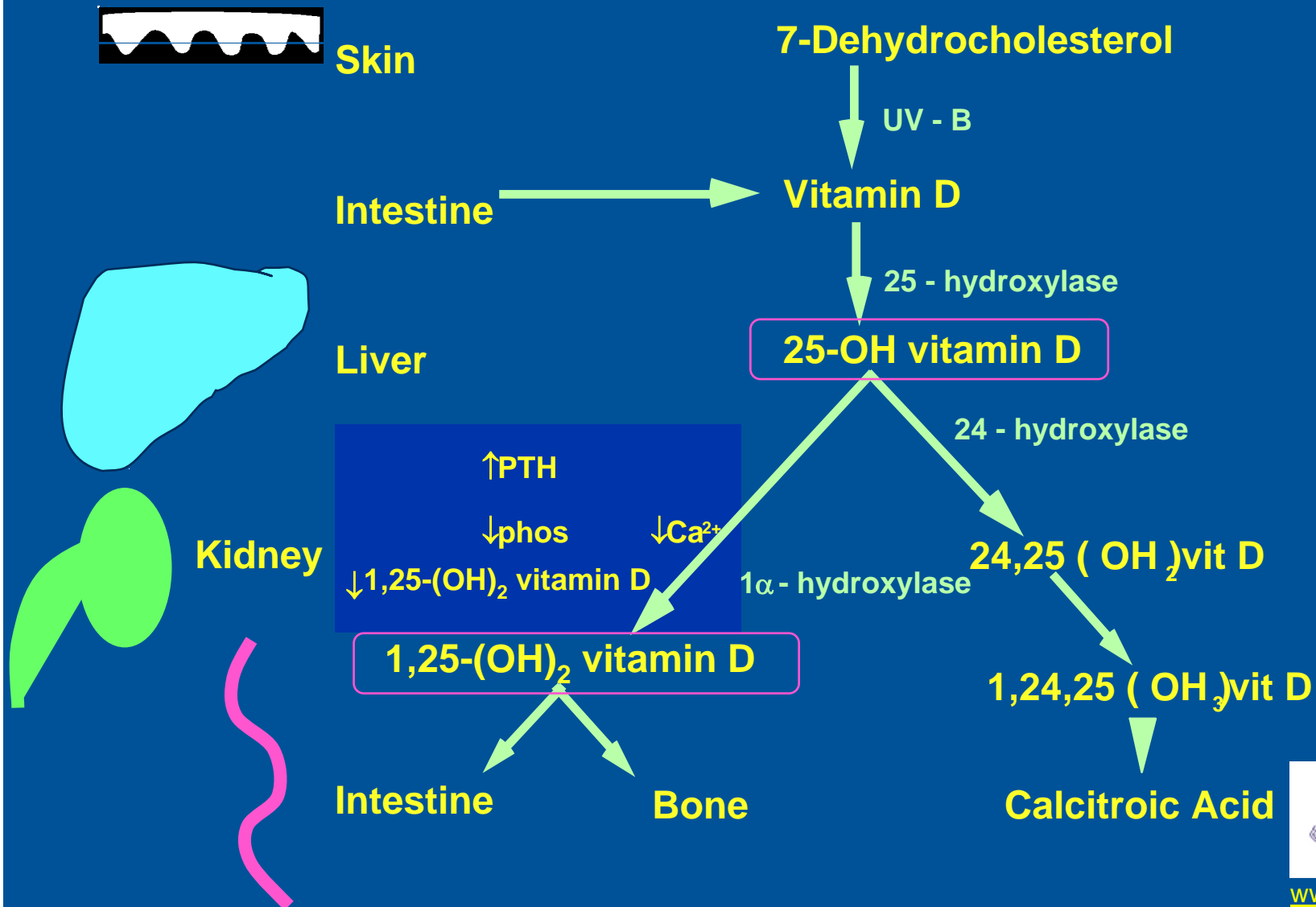
Note how small changes in serum calcium result in big changes in PTH



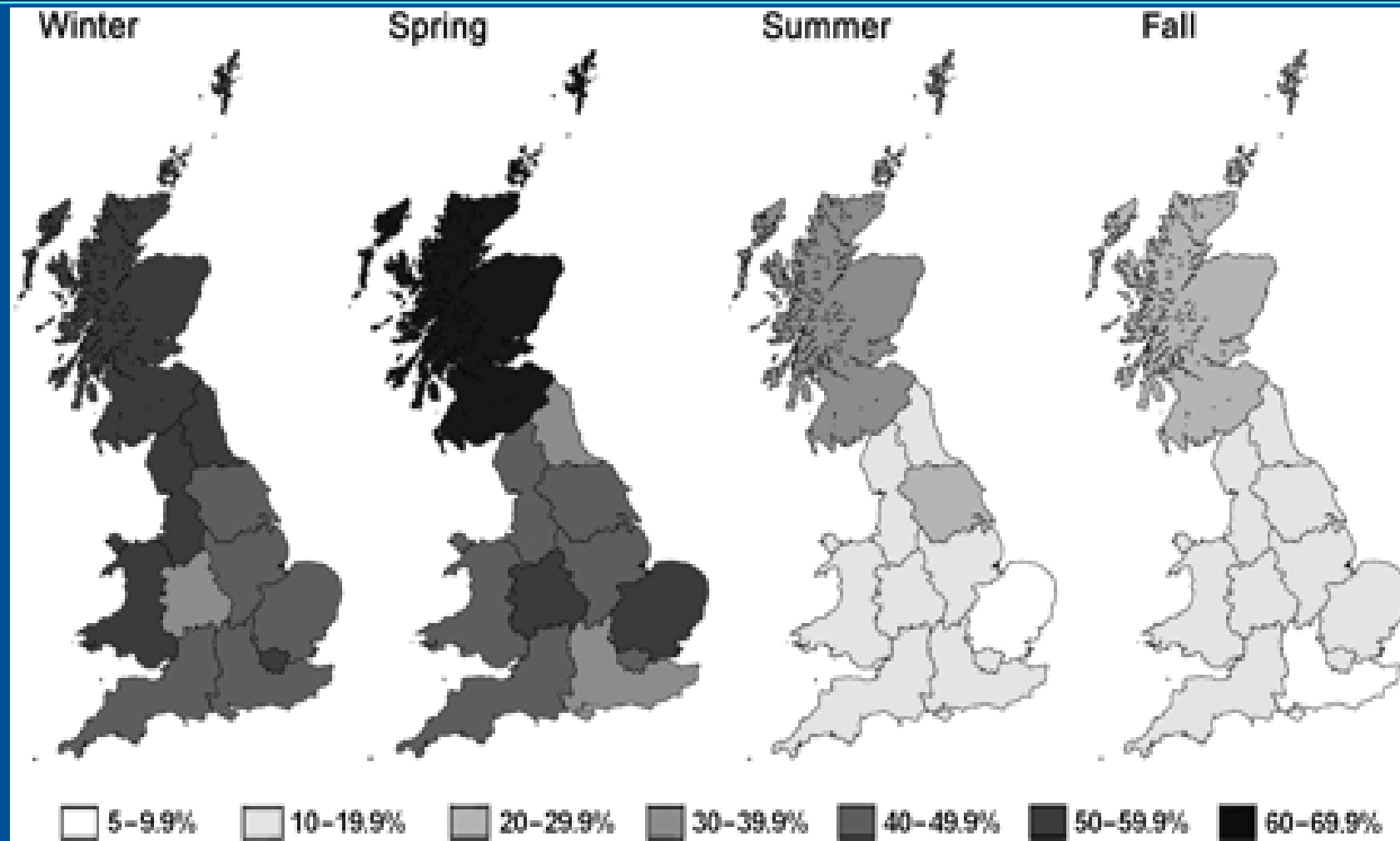
Relationship Between Serum Calcium and PTH - 2



VITAMIN D Biosynthesis



Seasonal and geographical variation in the prevalence of hypovitaminosis D (25-hydroxyvitamin D <40 nmol/L) in Great Britain

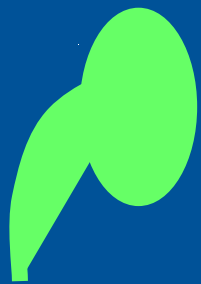


Hypponen E and Power C. Am J Clin Nutr. 2007;85(3):860-8

Calcitonin

- **Hormone produced by C cells in the thyroid**
- **Its secretion is stimulated by an increase in serum calcium**
- **Its effect is to lower bone resorption**
- **The importance in man is uncertain**
 - It is much more important in animals living in a high calcium environment, e.g. fish

Parathyroid Hormone Actions



Ca²⁺ reabsorption

Phosphate Reabsorption

1 α - hydroxylation of 25-OH vitamin D



Bone Remodelling

Bone Resorption > Bone Formation

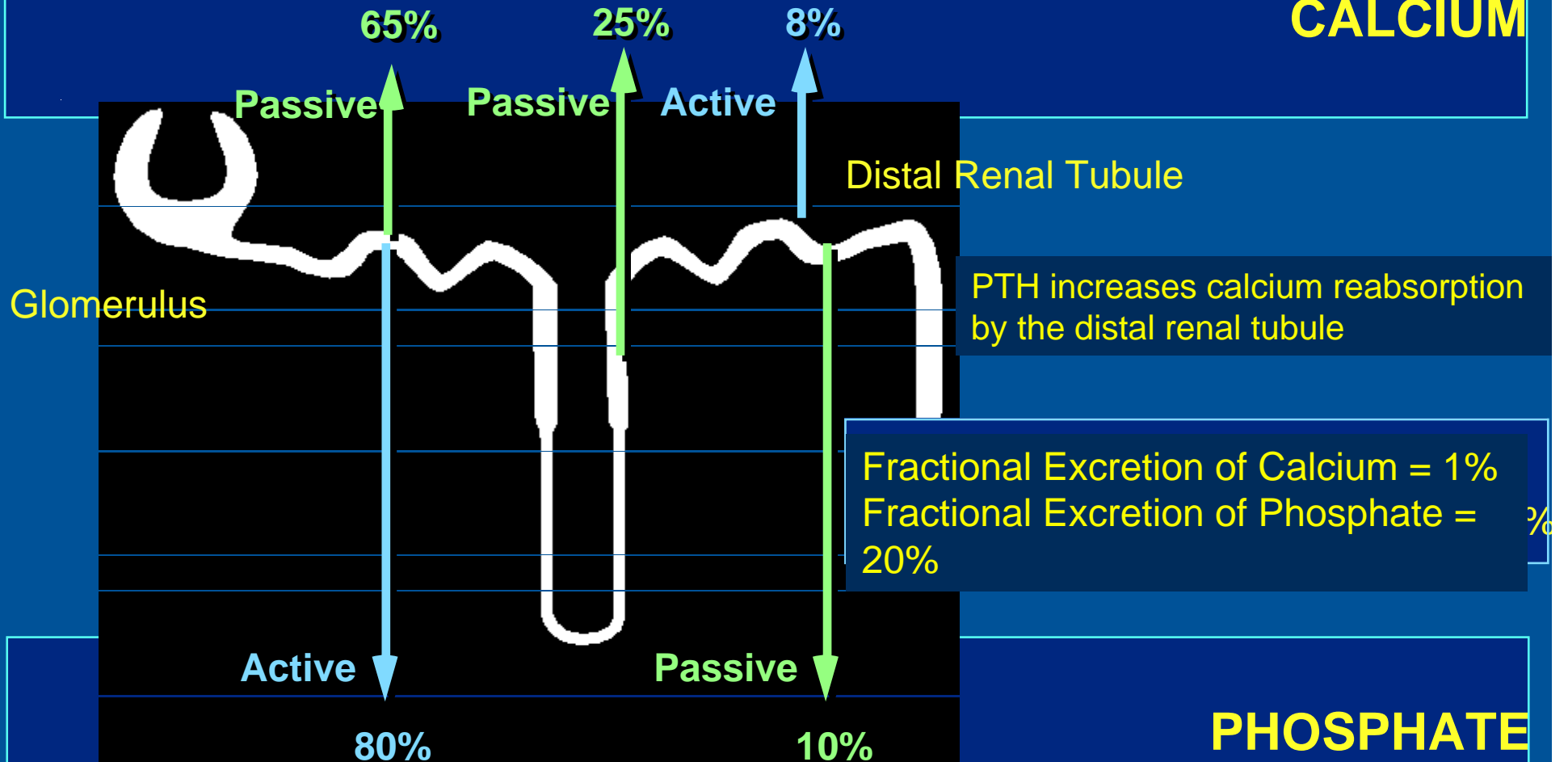


No direct effect

Ca²⁺ absorption because of increased 1,25-(OH)₂ vitamin D

Calcium and Phosphate Excretion Regulation by PTH

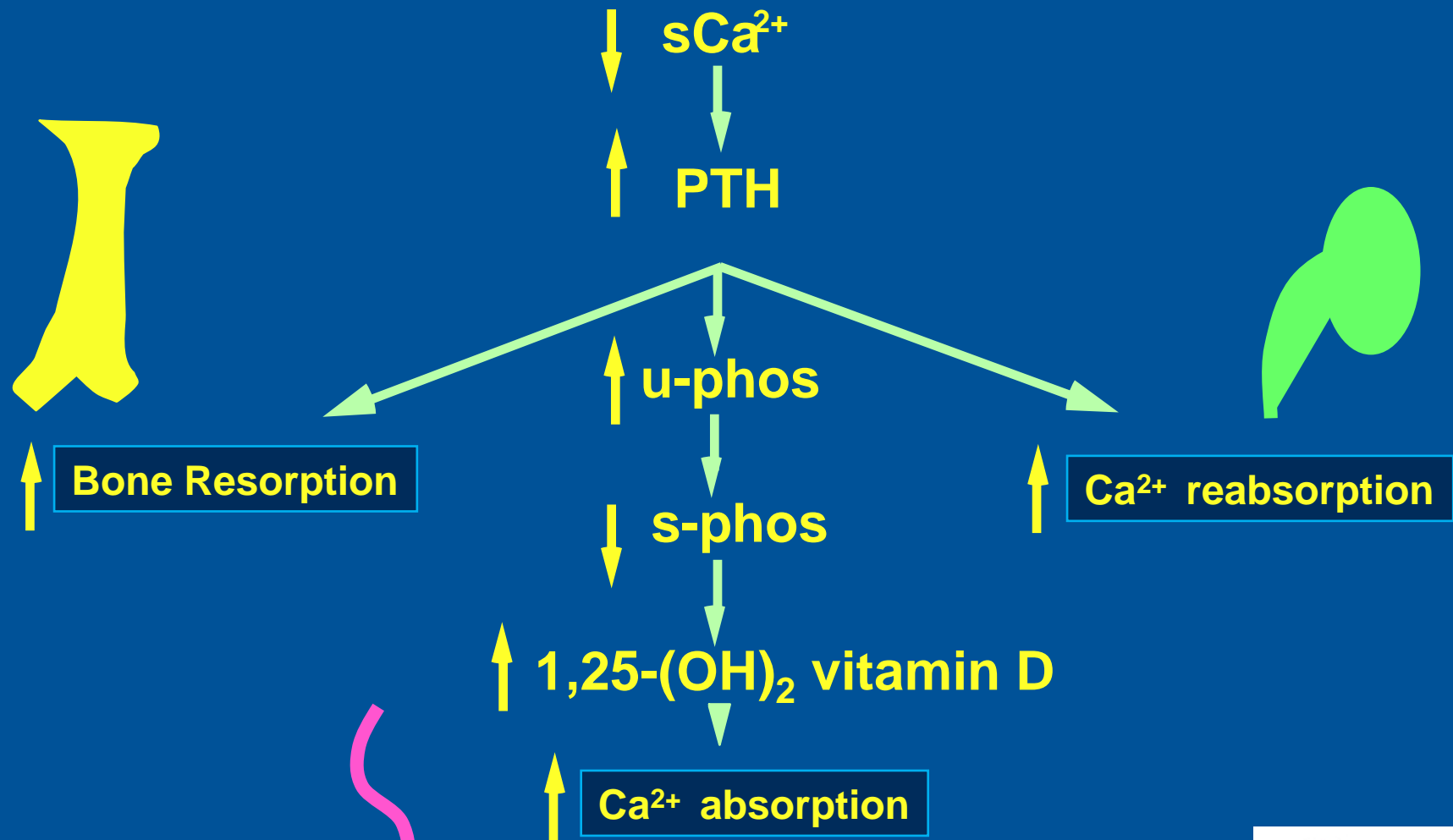
CALCIUM



PHOSPHATE

PTH decreases phosphate reabsorption by the proximal renal tubule

Summary of Calcium Homeostasis Response to a Decrease in Serum Calcium



Example of Adaptation Response to a Low Diet Calcium

- **Low dietary calcium means,**
- **Less calcium is absorbed,**
- **This results in lower serum ionised calcium,**
- **This results in higher PTH,**
- **This results in fast and slow actions**
 - Fast action, increased flux of calcium from bone and decreased excretion of calcium from kidney
 - Slow action, increased bone resorption, and increased fractional absorption by the intestine
- **This returns serum ionised calcium to normal**

Disorders of Calcium Homeostasis

Definition of Hypocalcaemia and Hypercalcaemia

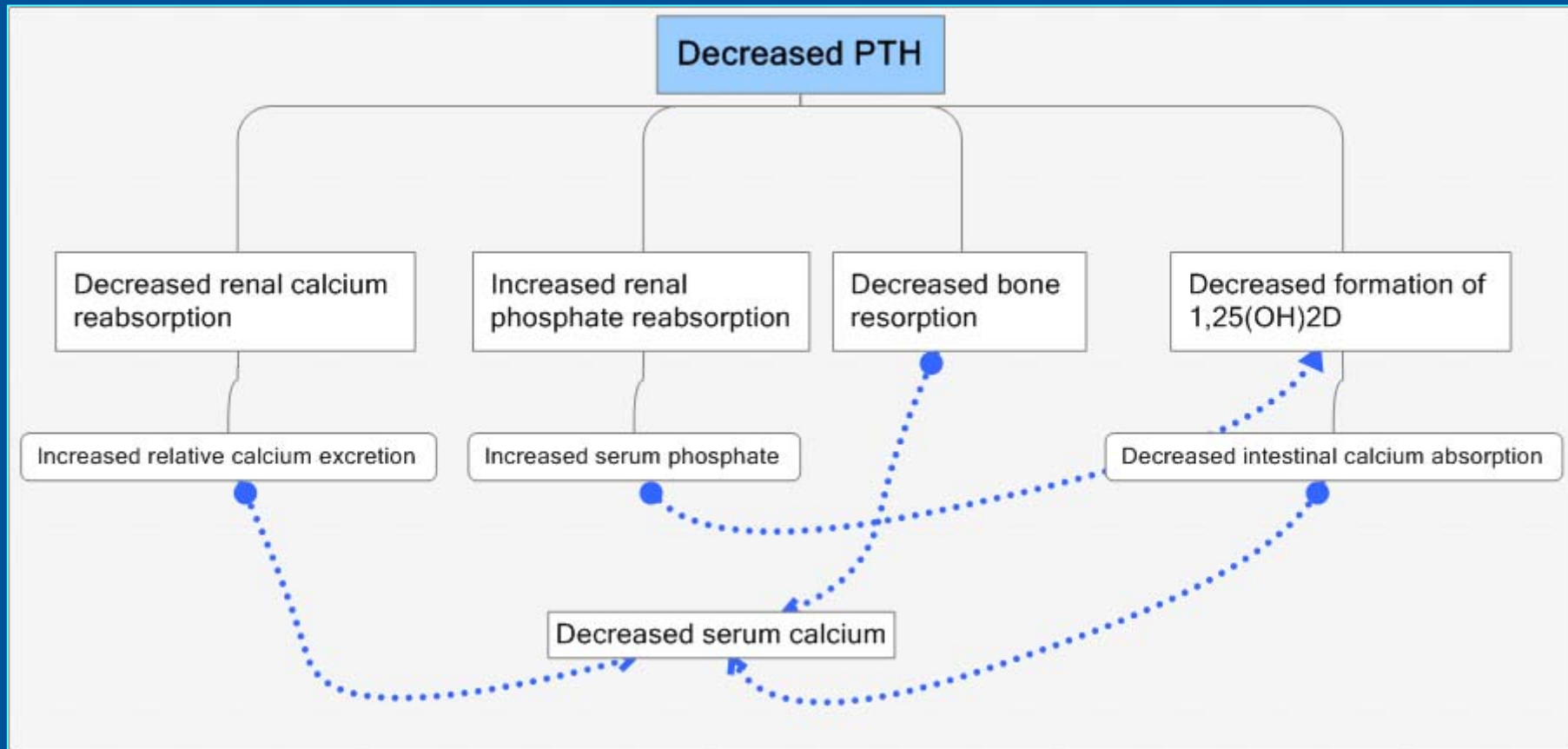
- **Hypocalcaemia**

- The serum calcium is below the reference range
- Watch out for false results
 - Low serum albumin

- **Hypercalcaemia**

- The serum calcium is above the reference range
- Watch out for false results
 - Leave on the tourniquet for too long

Causes of Hypocalcaemia Hypoparathyroidism



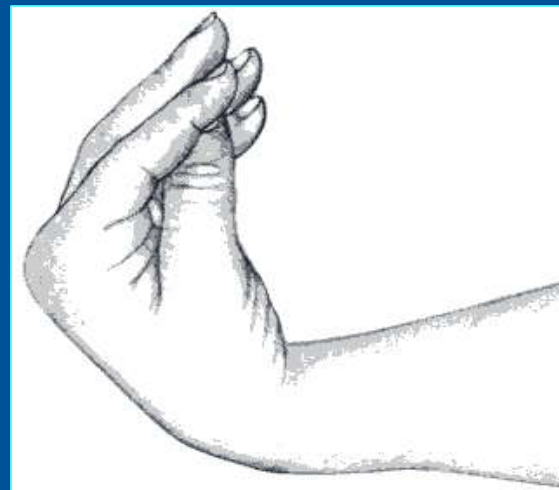
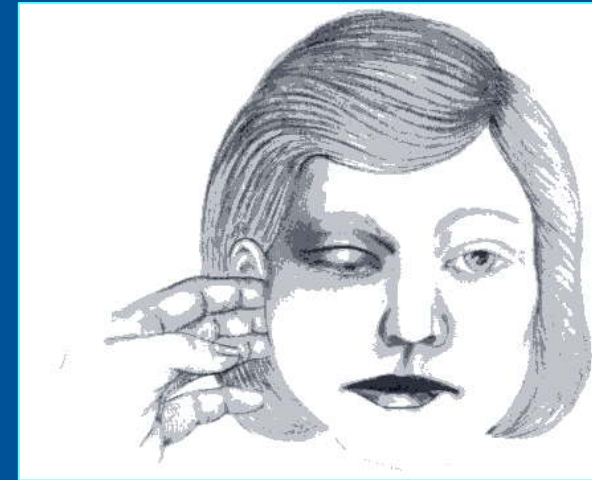
Note – the mineralisation is normal as the calcium-phosphate product is normal –
The serum calcium may be low, but the serum phosphate is high
Note – the most common cause of decreased PTH is surgical damage to
the parathyroids, although the condition can be idiopathic or genetic



Consequences of Hypocalcaemia

- **Muscle spasm**
 - Hands and feet
 - Larynx
 - Premature labour
- **Epilepsy**
- **Basal ganglion calcification**
- **Cataracts**
- **ECG abnormalities**
 - Long QT interval

Chvostek's Sign
Tap over the facial nerve
Look for spasm of facial muscles

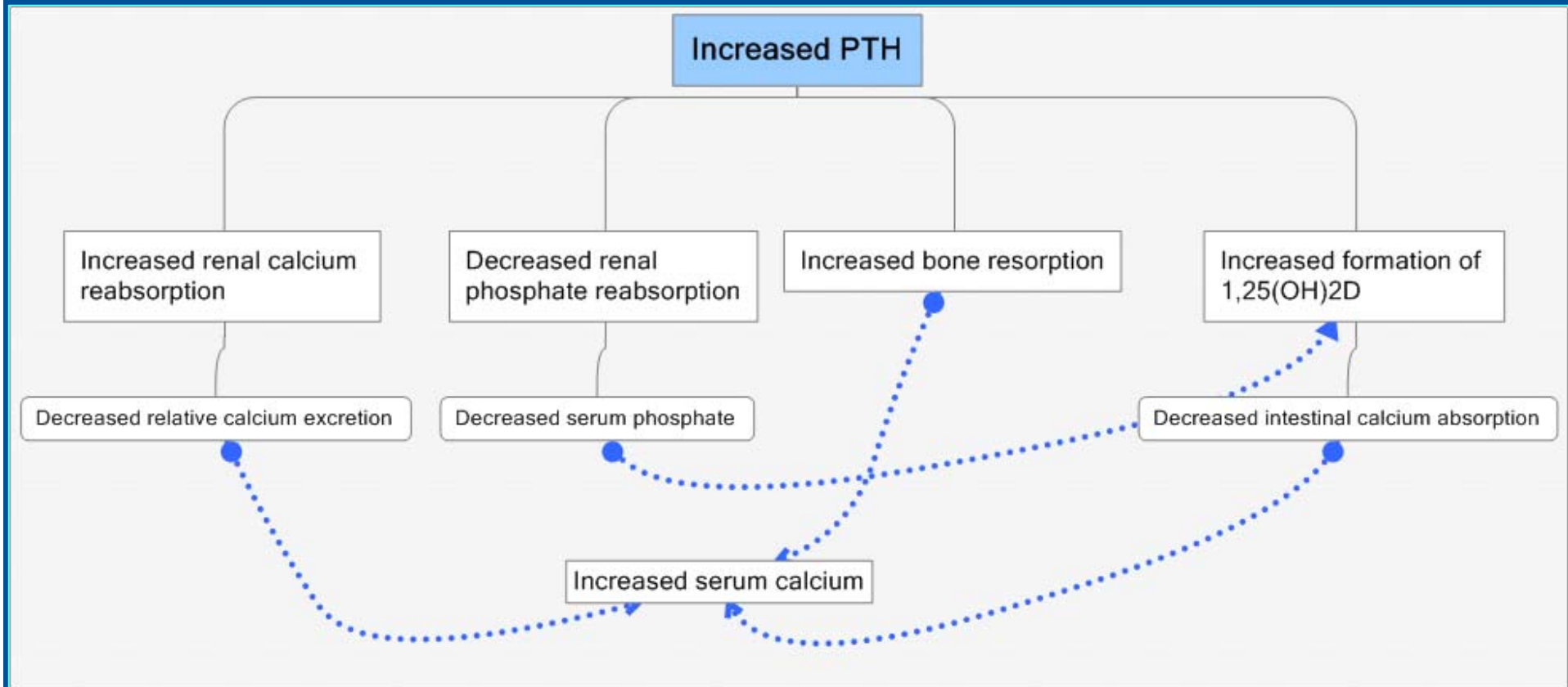


Trousseau's Sign
Inflate the blood pressure cuff
to 20 mm Hg above systolic
for 5 minutes

Causes of Hypercalcaemia

- **Primary hyperparathyroidism**
 - Usually a single adenoma
 - May be familial, when it is hyperplasia of several glands
 - Common condition in postmenopausal women
 - Commonest cause in outpatients or GP setting
- **Hypercalcaemia of malignancy**
 - The diagnosis of cancer is usually obvious
 - Commonest cause in inpatient setting
- **Lots of other causes, but less common**

Primary Hyperparathyroidism



Note – the calcium excretion (or urinary calcium) may be low for a given level of serum calcium, but it is still often increased above normal and so the risk of kidney stones is increased

Consequences of Primary Hyperparathyroidism

‘Bones, stones, groans and abdominal moans..’

- **Bone disease**
 - Osteitis fibrosa cystica
 - Osteoporosis
- **Kidney**
 - Stones
 - Nephrogenic diabetes insipidus
 - Is common in a mild form causing thirst and polyuria
- **Fatigue; confusional state due to dehydration**
- **Abdominal pain**
 - Constipation (due to dehydration)
 - Acute pancreatitis

Note – these are all consequences of hypercalcaemia, except for the bone disease which is specific to primary hyperparathyroidism

Primary Hyperparathyroidism

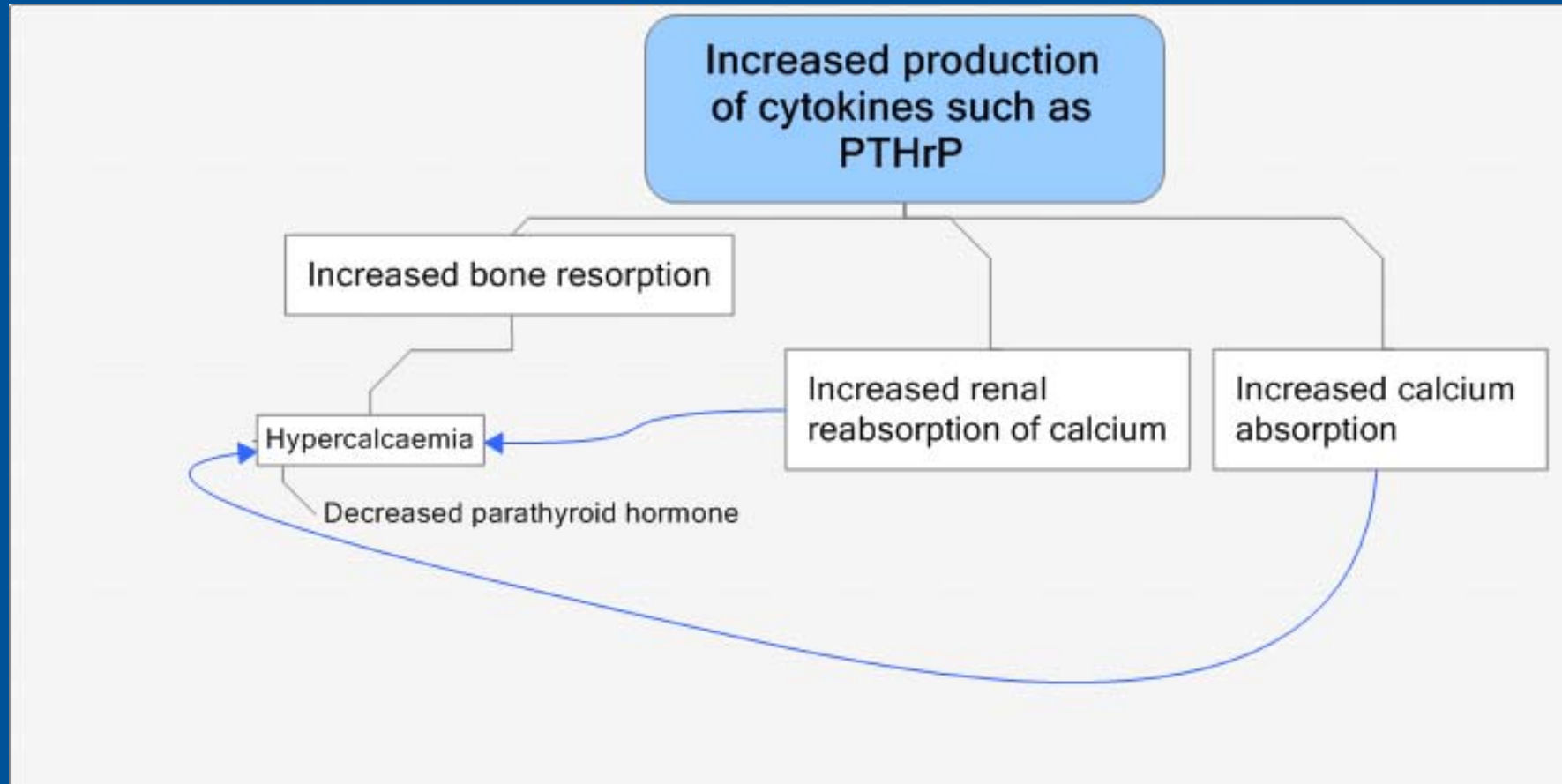


The arrows show sub-periosteal erosions of the phalanges



The skull shows cysts
'Osteitis fibrosa cystica'

Hypercalcaemia of Malignancy



Tumours produce a variety of factors that can stimulate bone resorption, such as parathyroid hormone related protein (PTHrP)
PTHrP has a similar structure to PTH and works in the same way as PTH (it binds to the PTH receptor) but it is not measured by the PTH assay

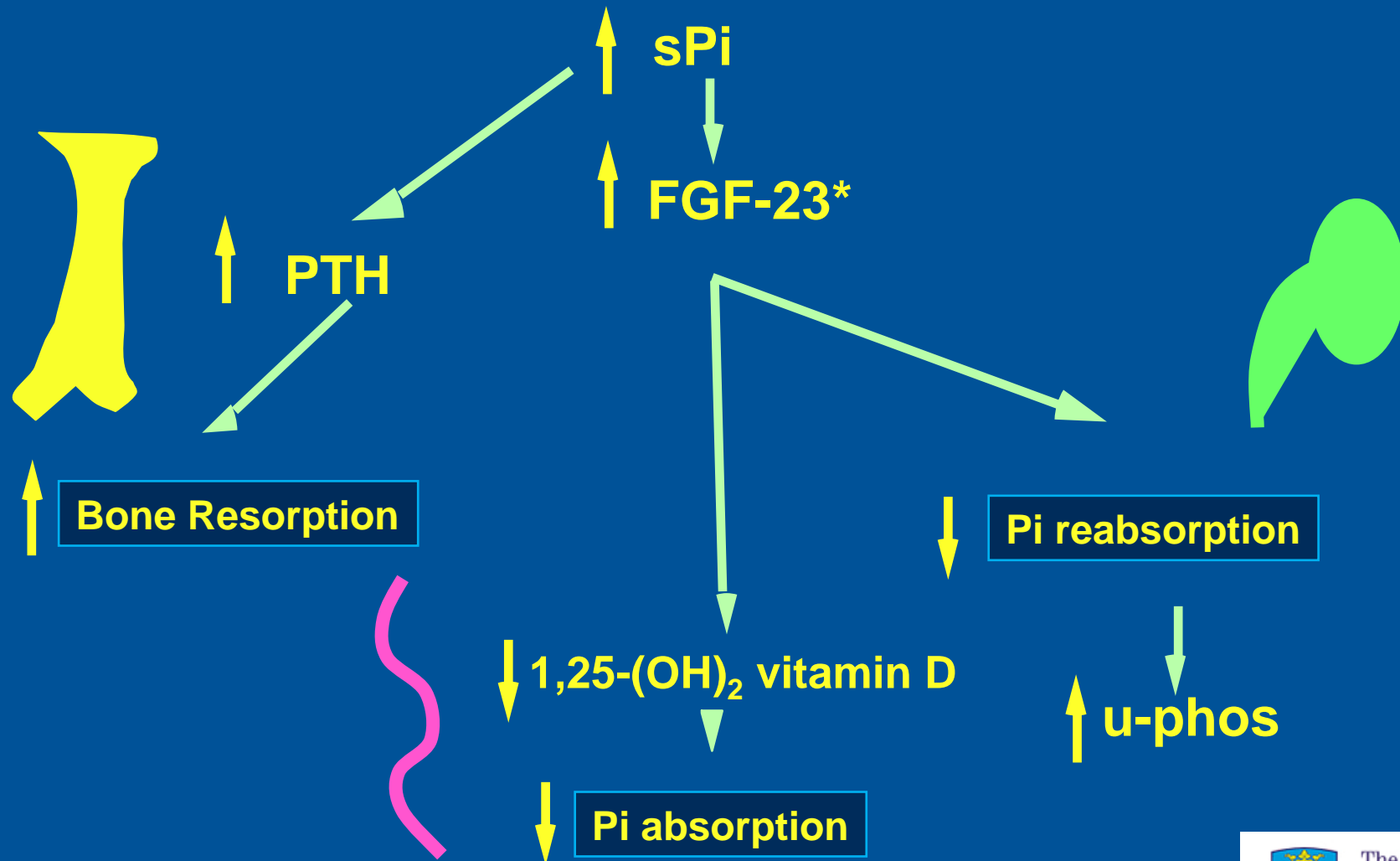
Phosphate Homeostasis



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Summary of Phosphate Homeostasis Response to an Increase in Serum Phosphate



* FGF-23, fibroblast growth factor 23

Disorders of Phosphate Homeostasis



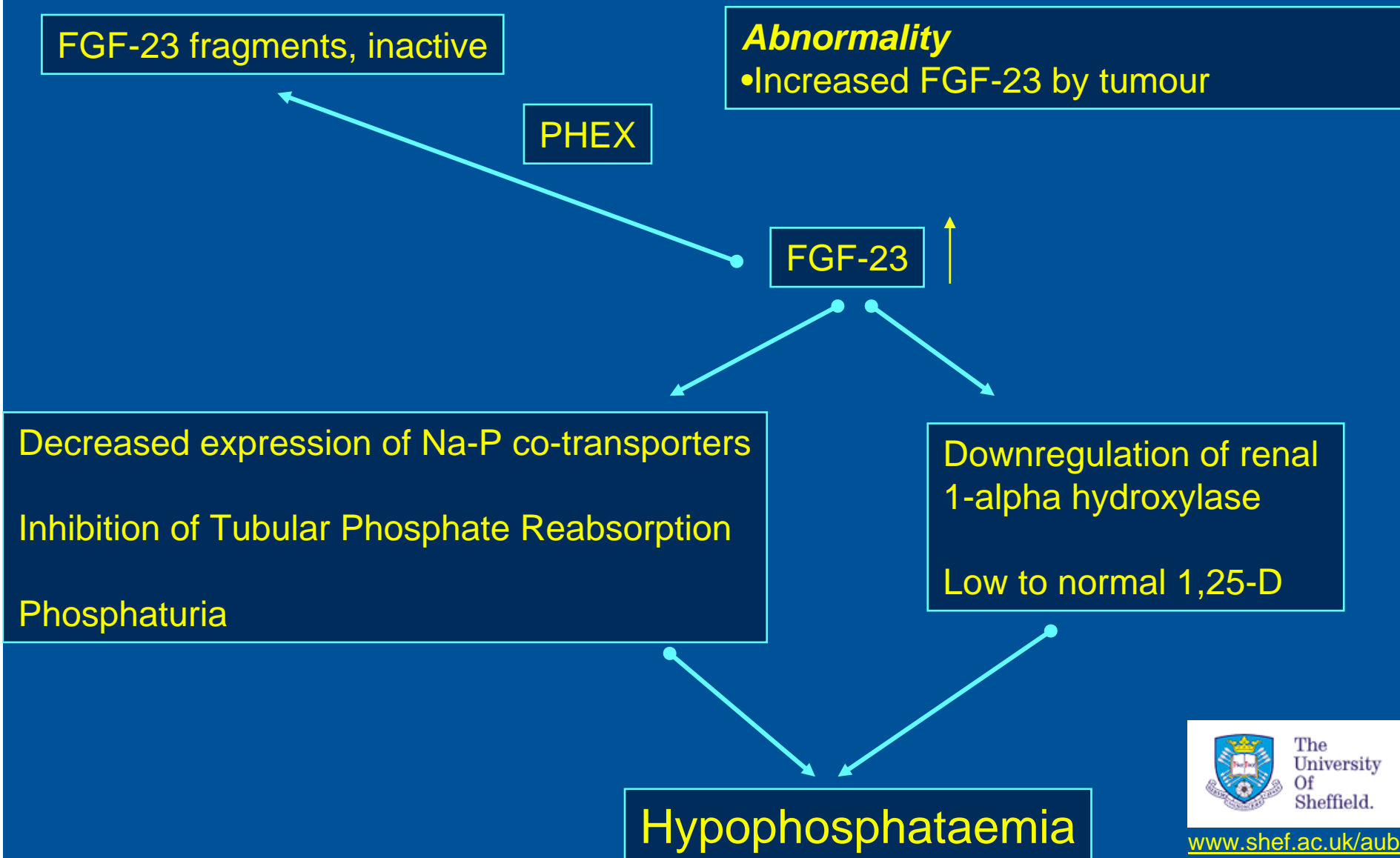
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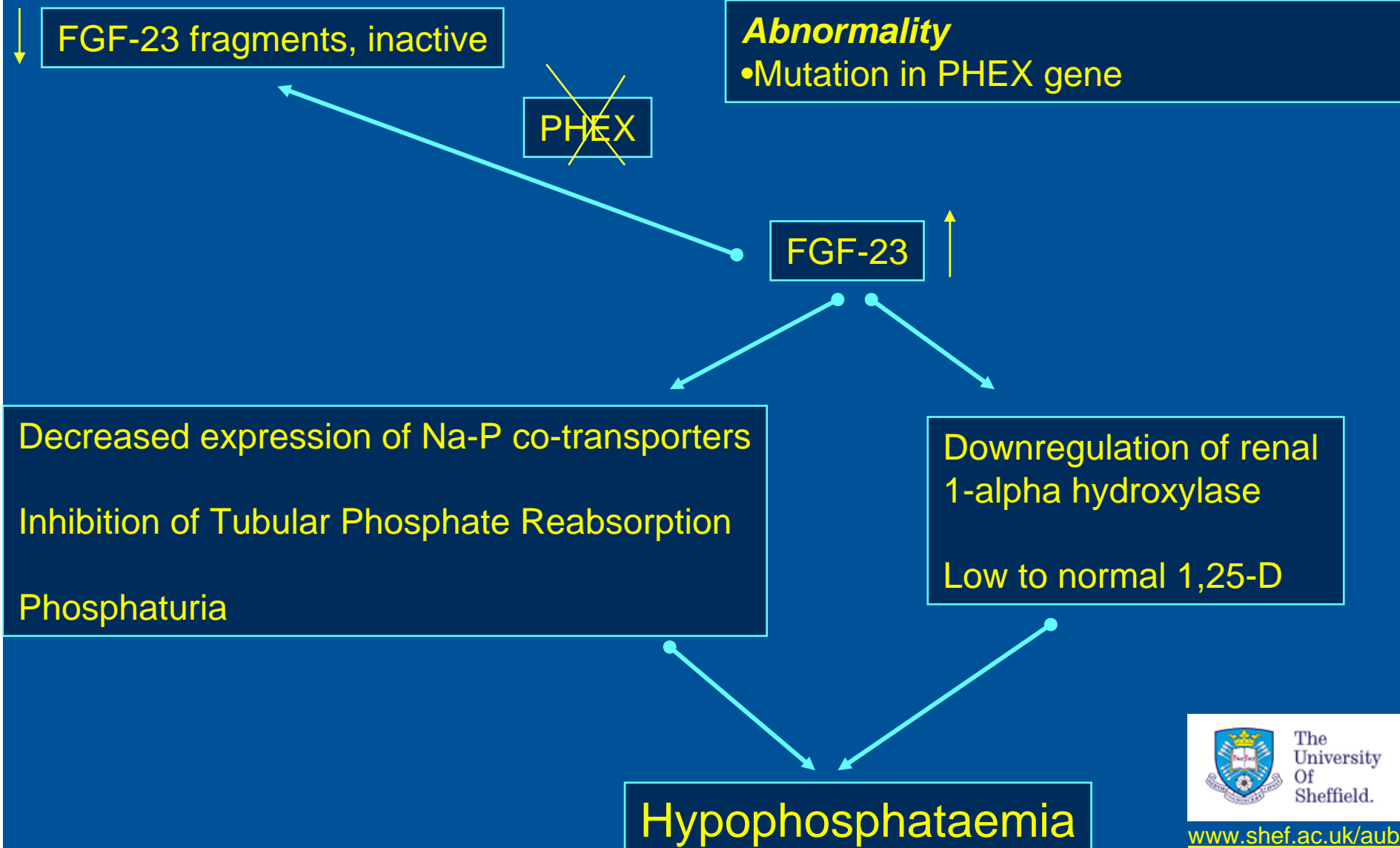
Causes of Hypophosphataemia

- **Too little phosphate intake**
 - Diet
 - Phosphate binders (aluminium hydroxide)
- **Shift of phosphate into cells**
 - Intravenous glucose and insulin
- **Renal phosphate leak**
 - Tumor-induced
 - X-linked
 - Others

Pathogenesis of Tumour-Induced Osteomalacia



Pathogenesis of X-Linked Hypophosphataemic Rickets



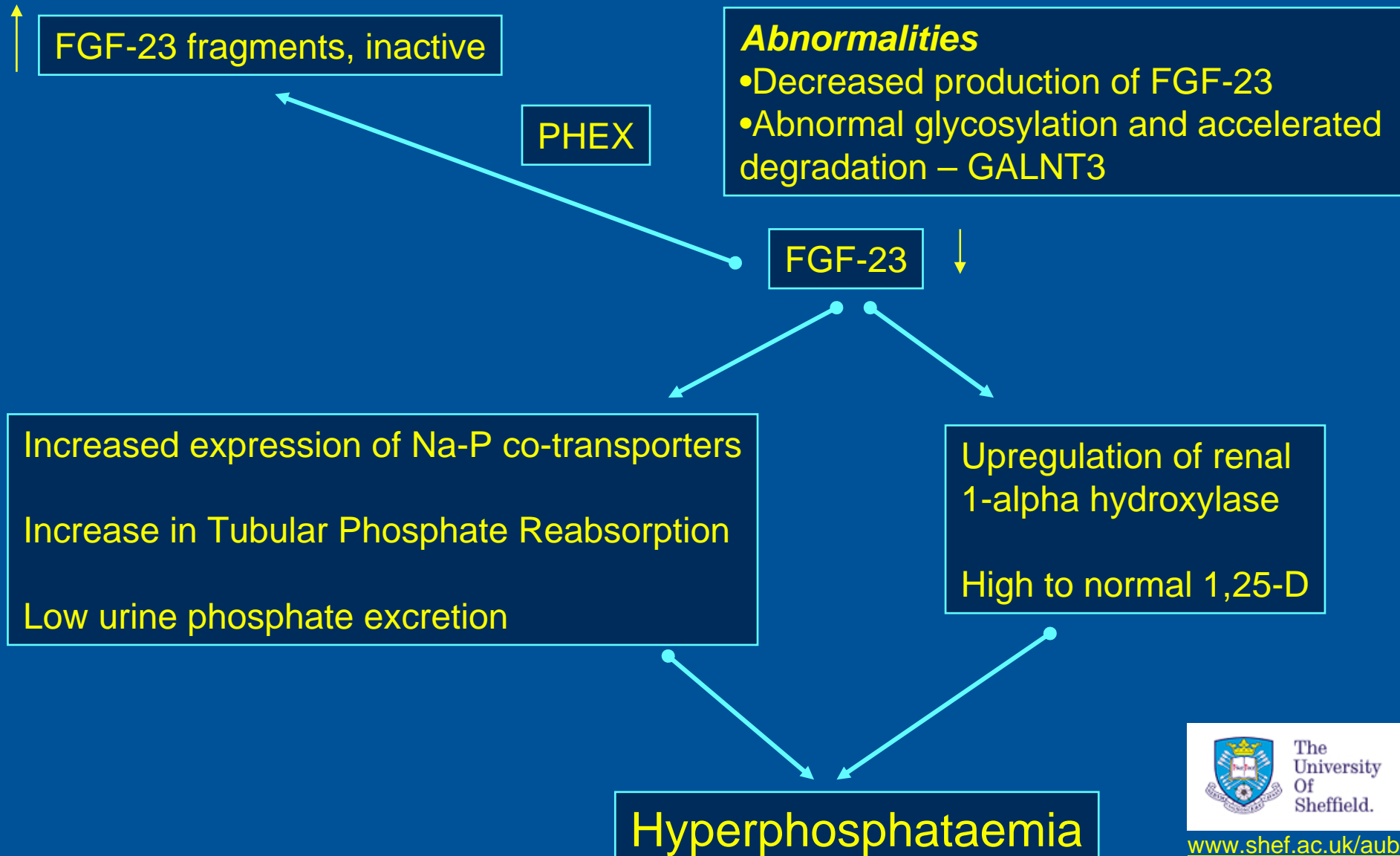
Clinical Features of Hypophosphataemia

- **Rickets and osteomalacia**
 - Without any symptoms of hypocalcaemia
- **The likely cause of the impaired mineralisation is the low serum calcium-phosphate product**
- **The biochemical changes**
 - Low serum phosphate
 - High alkaline phosphatase
 - Normal serum calcium and PTH

Causes of High Serum Phosphate

- **Chronic renal failure – decreased phosphate excretion**
- **Hypoparathyroidism – decreased PTH levels**
- **Tumoral Calcinosis – low FGF-23**
- **Increased catabolism, e.g. diabetic ketoacidosis**

Pathogenesis of Tumoral Calcinosis



Clinical Features of Hyperphosphataemia

- **Tumoral calcinosis**
 - Calcific deposits around shoulder and pelvis
 - The calcium-phosphate product is high
 - High levels of
 - Serum phosphate
 - 1,25-D

Calcific Deposits around Right Hip



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Thanks for your attention



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