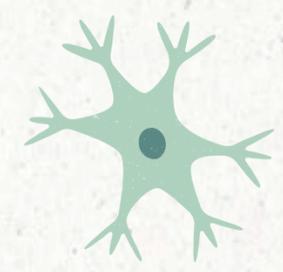


# VITAMIN - D SECOND STAGE

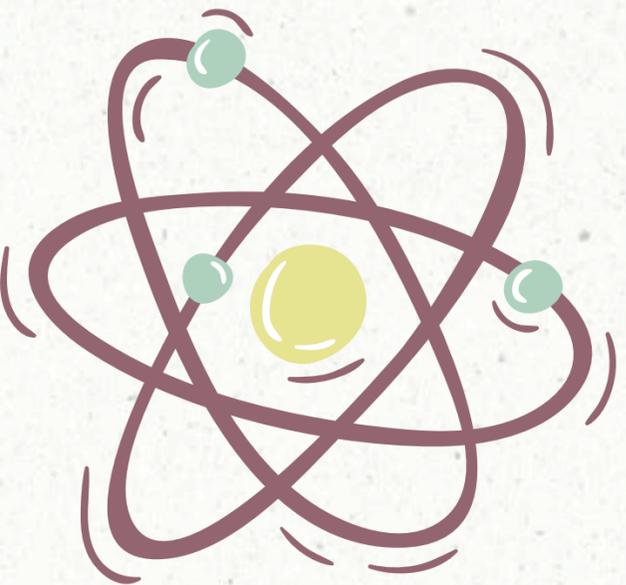
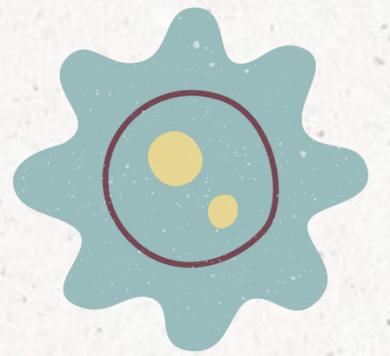
MEDICAL CHEMISTRY  
DR. RASHAD AL- TUUAMAH



## VITAMIN D

THE D VITAMINS ARE A GROUP OF STEROLS THAT HAVE A HORMONE-LIKE FUNCTION. THE ACTIVE MOLECULE, 1,25-DIHYDROXYCHOLECALCIFEROL ([1,25-DIOH-D3], OR CALCITRIOL), BINDS TO INTRACELLULAR RECEPTOR PROTEINS

THE 1,25-DICH-D3-RECEPTOR COMPLEX INTERACTS WITH RESPONSE ELEMENTS IN THE NUCLEAR DNA OF TARGET CELLS IN A MANNER SIMILAR TO THAT OF VITAMIN A (SEE FIG. 28.20) AND EITHER SELECTIVELY STIMULATES OR REPRESSES GENE TRANSCRIPTION. THE MOST PROMINENT ACTIONS OF CALCITRIOL ARE TO REGULATE THE SERUM LEVELS OF CALCIUM AND PHOSPHORUS.

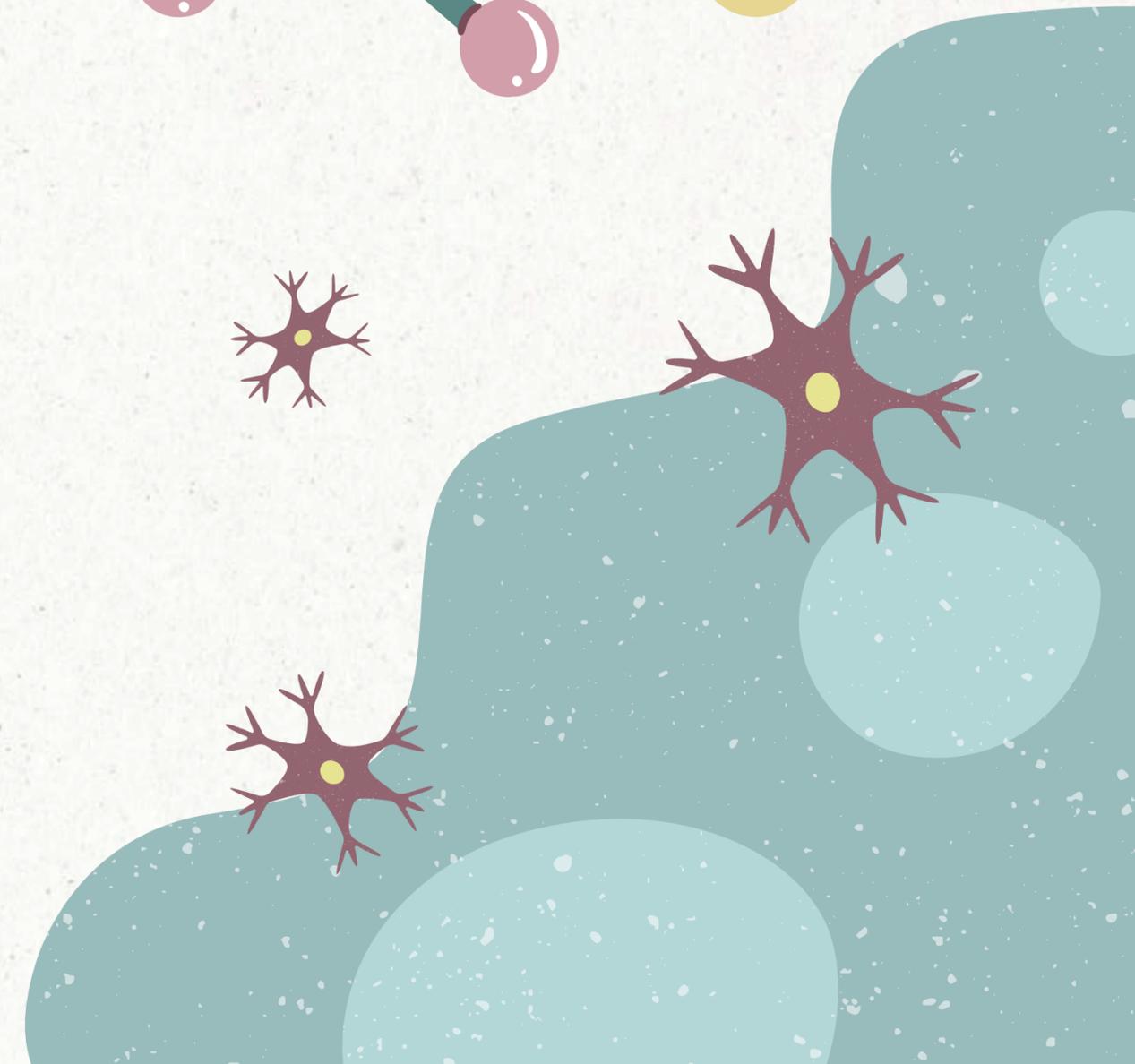
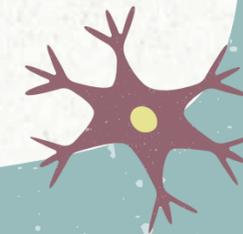
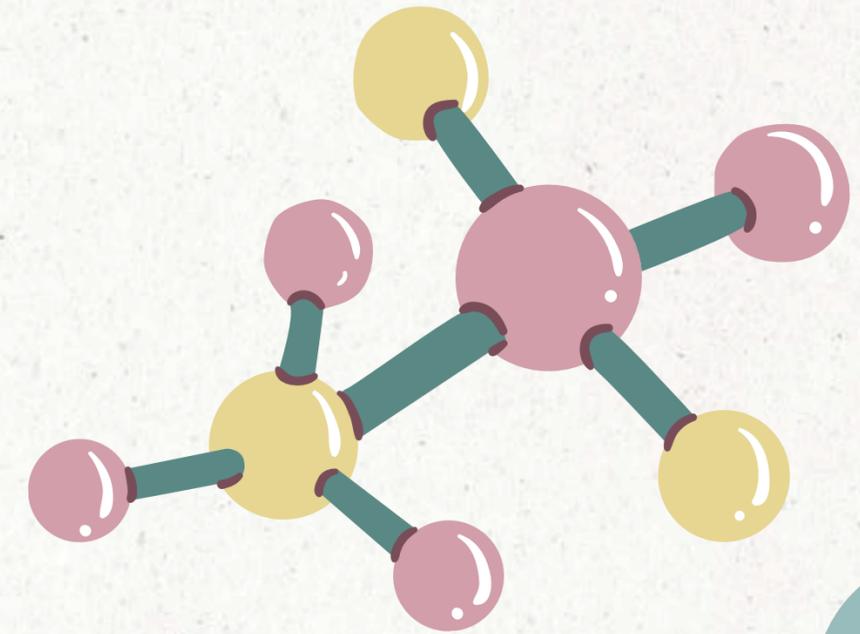
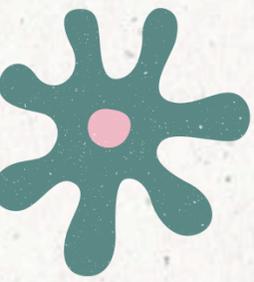
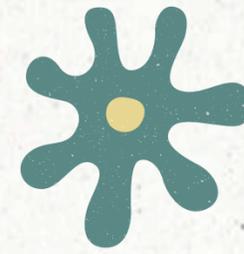


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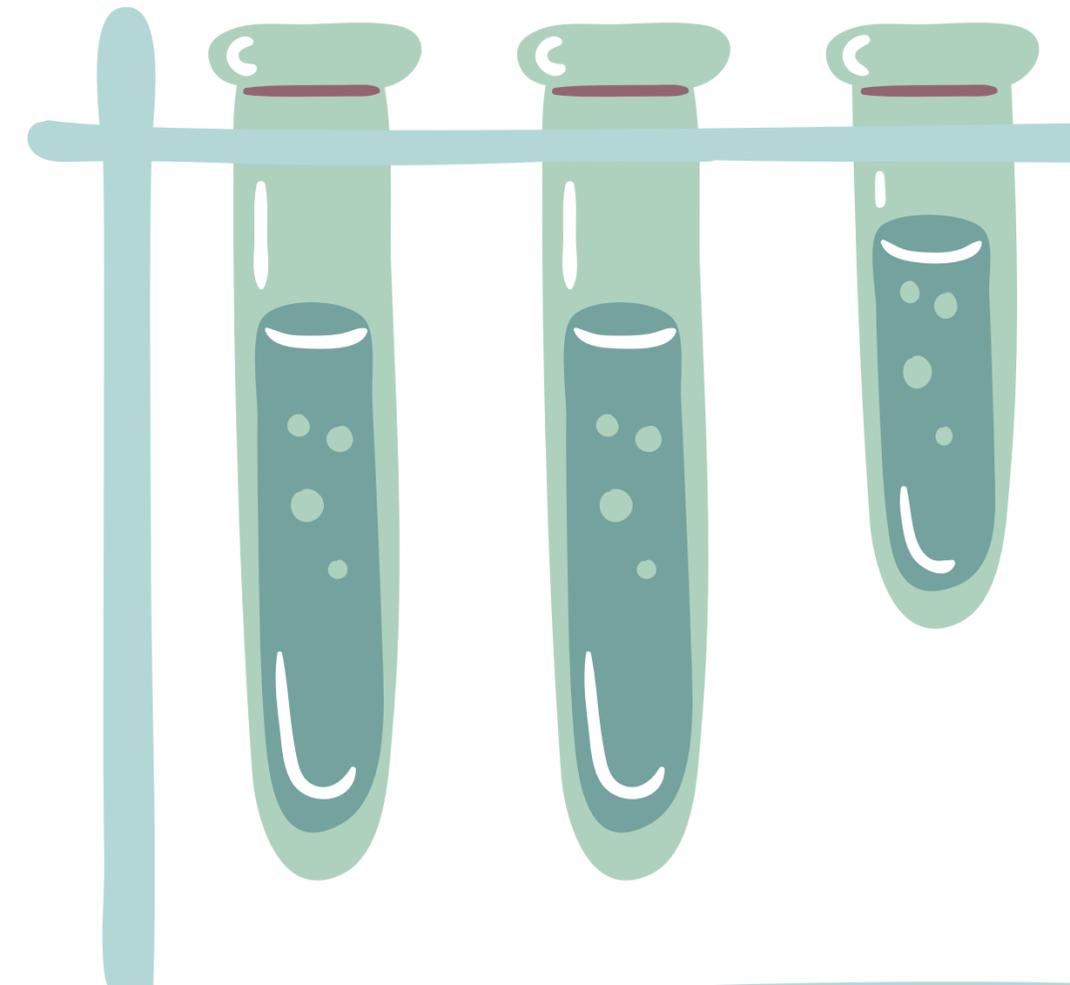
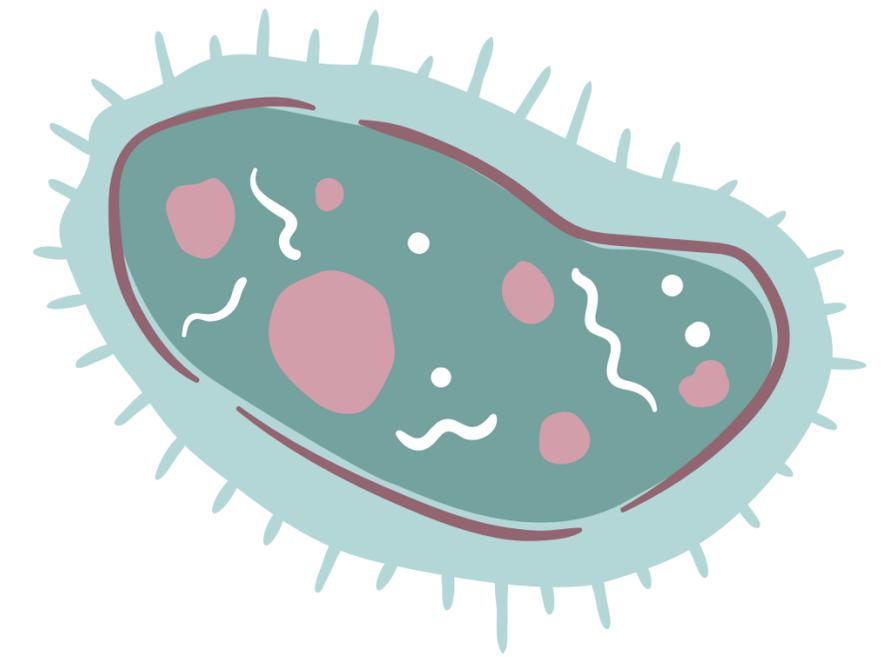
### ENDOGENOUS VITAMIN

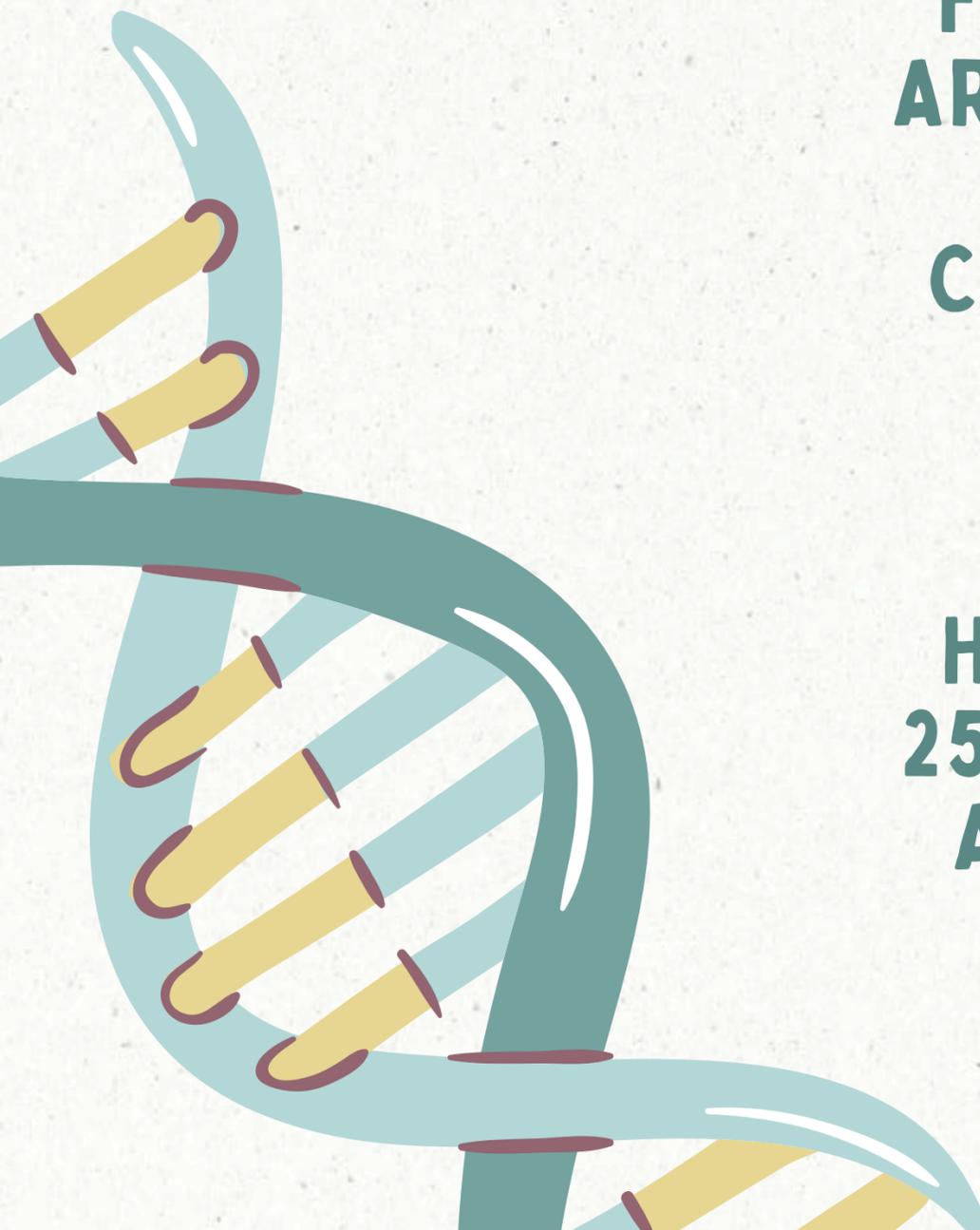
PRECURSOR: 7-DEHYDROCHOLESTEROL, AN INTERMEDIATE IN CHOLESTEROL SYNTHESIS, IS CONVERTED TO CHOLECALCIFEROL IN THE DERMIS AND EPIDERMIS OF HUMANS EXPOSED TO SUNLIGHT AND TRANSPORTED TO LIVER BOUND TO VITAMIN D-BINDING PROTEIN

DIET:  
ERGOCALCIFEROL (VITAMIN D2), FOUND IN PLANTS, AND CHOLECALCIFEROL (VITAMIN D3), FOUND IN ANIMAL TISSUES



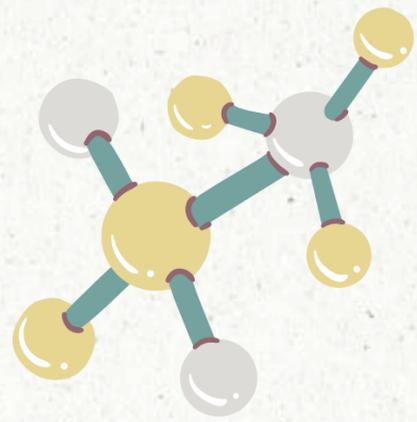
**THESE ARE SOURCES OF  
PREFORMED VITAMIN D  
ACTIVITY VITAMIN D2 AND  
VITAMIN D3 DIFFER  
CHEMICALLY ONLY IN THE  
PRESENCE OF AN  
ADDITIONAL DOUBLE-BOND  
AND METHYL GROUP IN THE  
PLANT STEROL DIETARY  
VITAMIN D IS PACKAGED INTO  
CHYLOMICRONS. (NOTE:  
PREFORMED VITAMIN D IS A  
DIETARY REQUIREMENT ONLY  
IN INDIVIDUALS WITH LIMITED  
EXPOSURE TO SUNLIGHT.)**



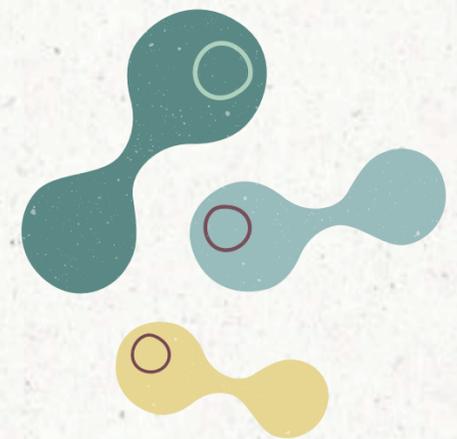


## **METABOLISM**

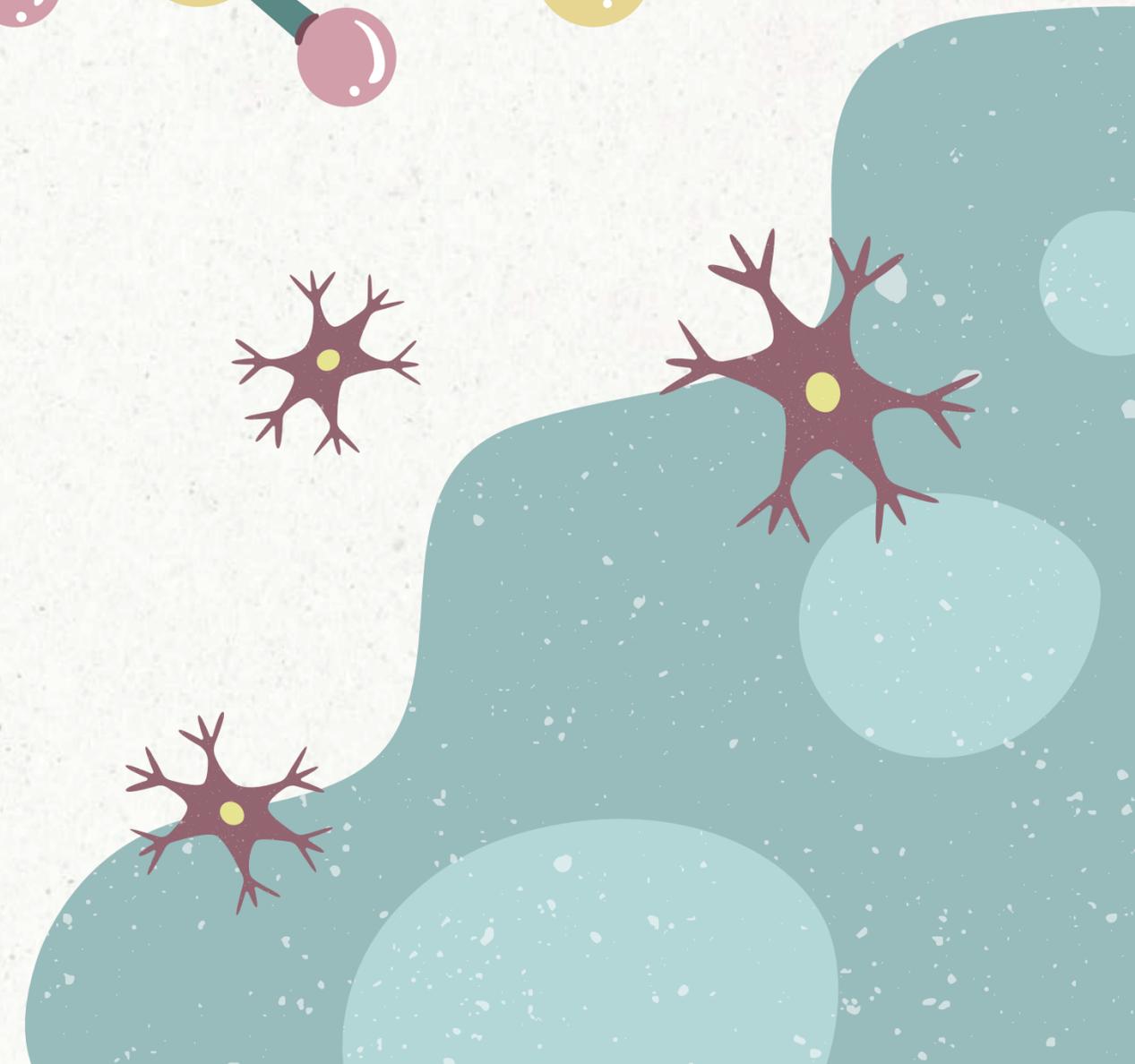
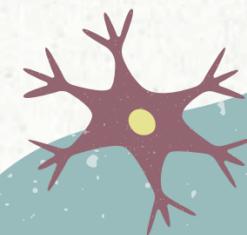
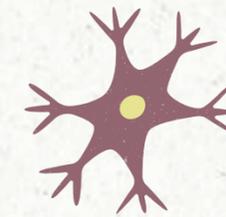
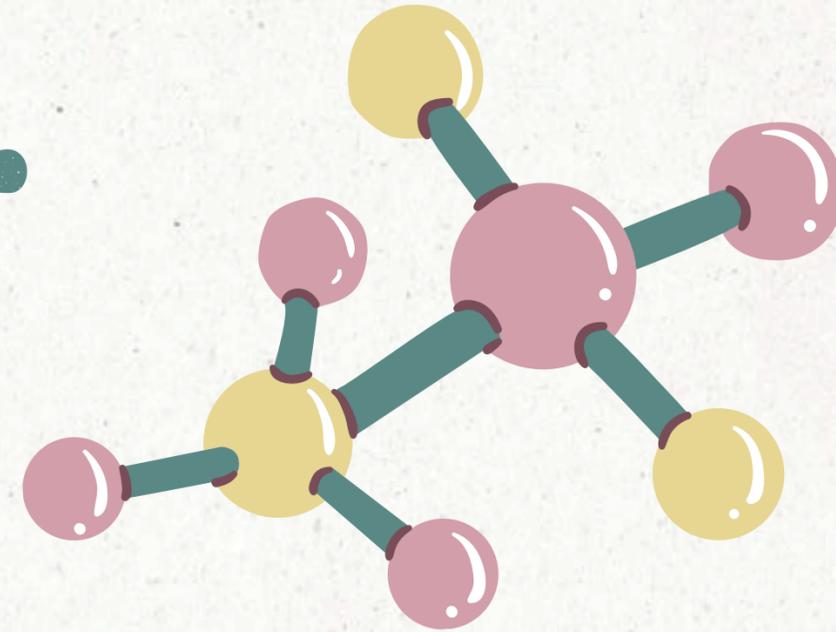
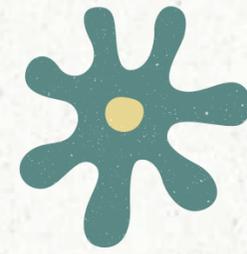
**1,25-DIHYDROXYCHOLECALCIFEROL  
FORMATION: VITAMINS D2 AND D3  
ARE NOT BIOLOGICALLY ACTIVE BUT  
ARE CONVERTED IN VIVO TO  
CALCITRIOL, THE ACTIVE FORM OF  
THE D VITAMIN, BY TWO  
SEQUENTIAL HYDROXYLATION  
REACTIONS THE FIRST  
HYDROXYLATION OCCURS AT THE  
25 POSITION AND IS CATALYZED BY  
A SPECIFIC 25-HYDROXYLASE IN  
THE LIVER.**



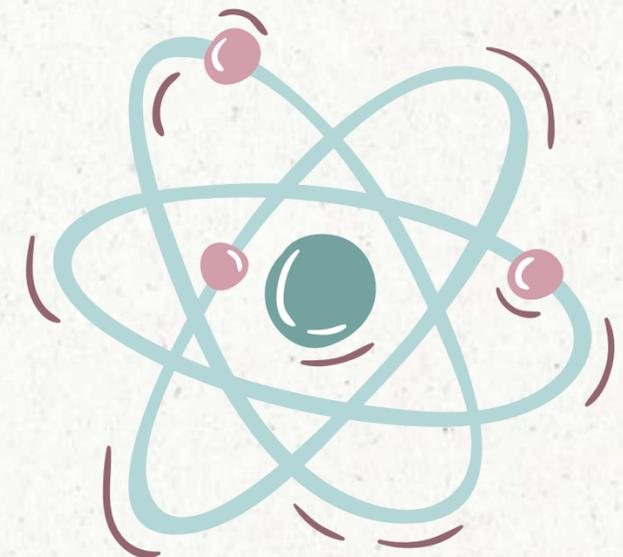
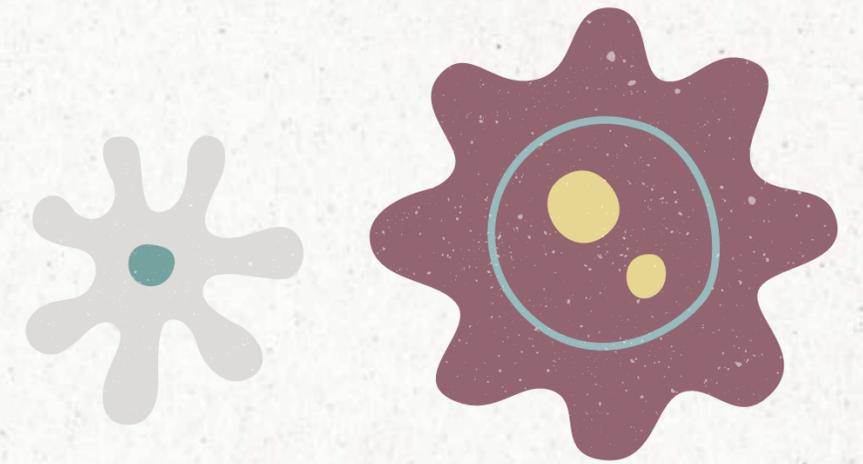
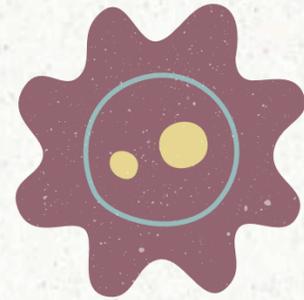
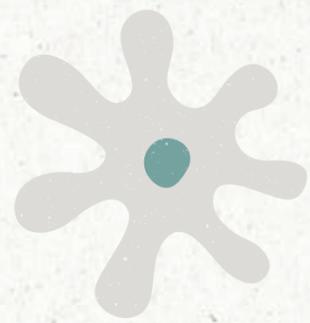
**THE PRODUCT OF THE REACTION, 25-HYDROXYCHOLECALCIFEROL ([25-OH-D<sub>3</sub>], CALCIDIOL), IS THE PREDOMINANT FORM OF VITAMIN D IN THE SERUM AND THE MAJOR STORAGE FORM. 25-OH-D<sub>3</sub> IS FURTHER HYDROXYLATED AT THE 1-POSITION BY 25-HYDROXYCHOLECALCIFEROL 1-HYDROXYLASE FOUND PRIMARILY IN THE KIDNEY, RESULTING IN THE FORMATION OF 1,25-DIOH-D<sub>3</sub> (CALCITRIOL).**



**(NOTE: BOTH HYDROXYLASES  
ARE CYTOCHROME P450  
PROTEINS.)  
HYDROXYLATION REGULATION:  
CALCITRIOL IS THE MOST  
POTENT VITAMIN D METABOLITE.  
ITS FORMATION IS TIGHTLY  
REGULATED BY THE LEVEL OF  
SERUM PHOSPHATE  
( $\text{PO}_4^{3-}$ ) AND CALCIUM  
IONS ( $\text{CA}^{2+}$ ).**

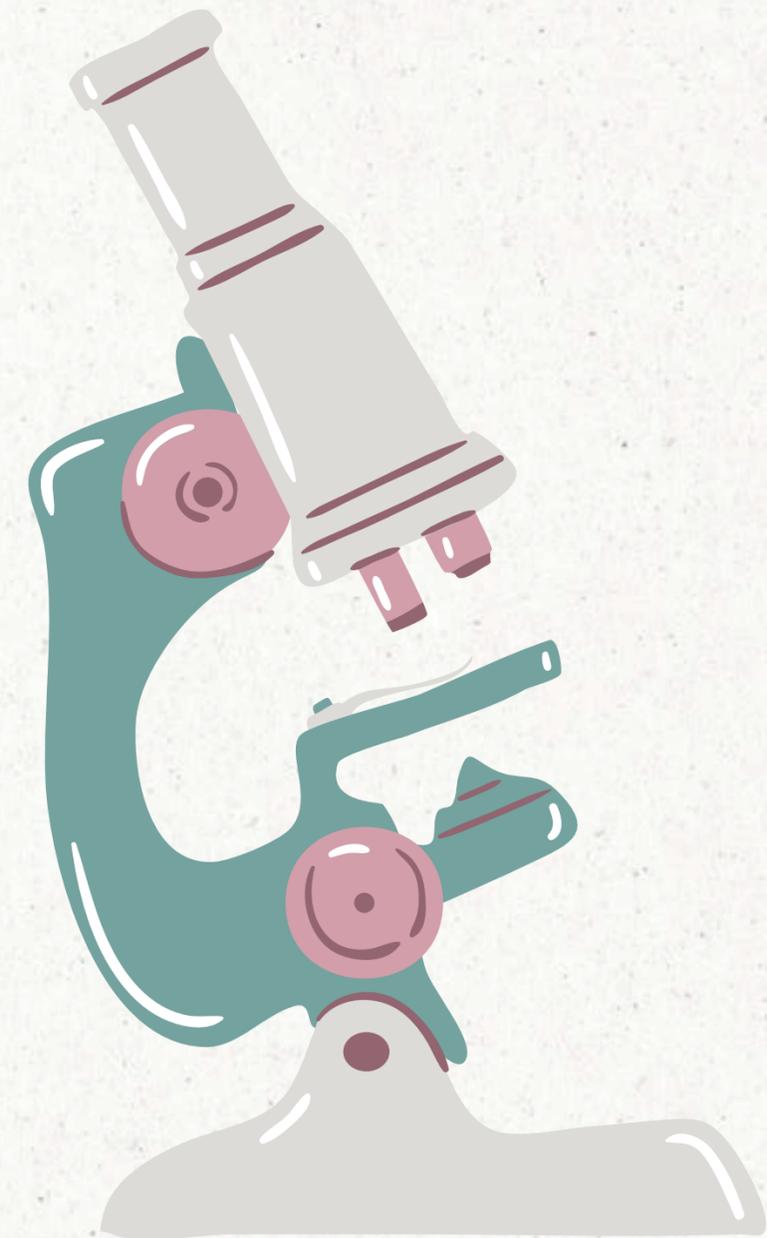


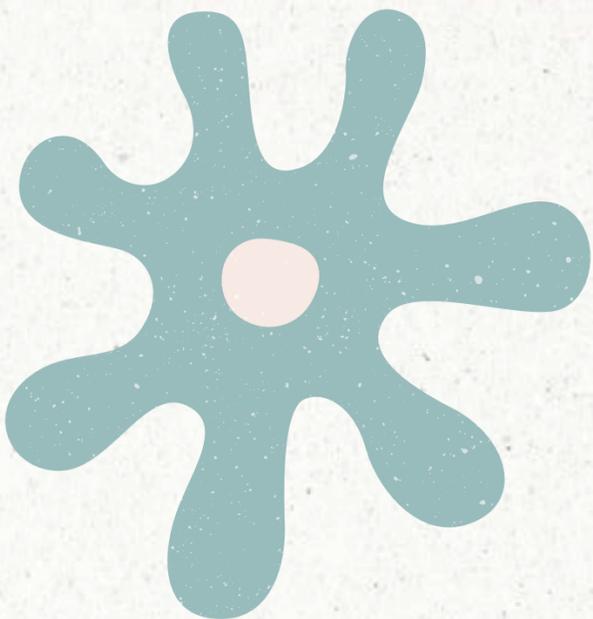
**25-HYDROXYCHOLECALCIFEROL 1-HYDROXYLASE ACTIVITY IS INCREASED DIRECTLY BY LOW SERUM  $PO_4^{3-}$  OR INDIRECTLY BY LOW SERUM  $CA^{2+}$ , WHICH TRIGGERS THE SECRETION OF PARATHYROID HORMONE (PTH) FROM THE CHIEF CELLS OF THE PARATHYROID GLAND. PTH UPREGULATES THE 1-HYDROXYLASE.**





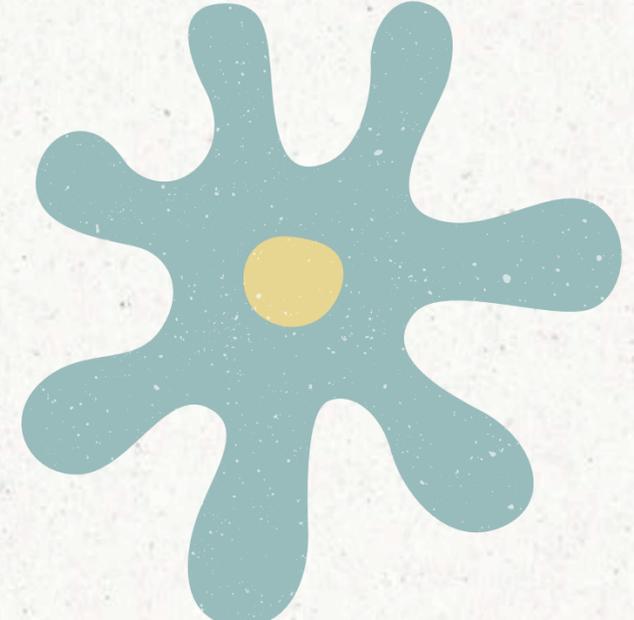
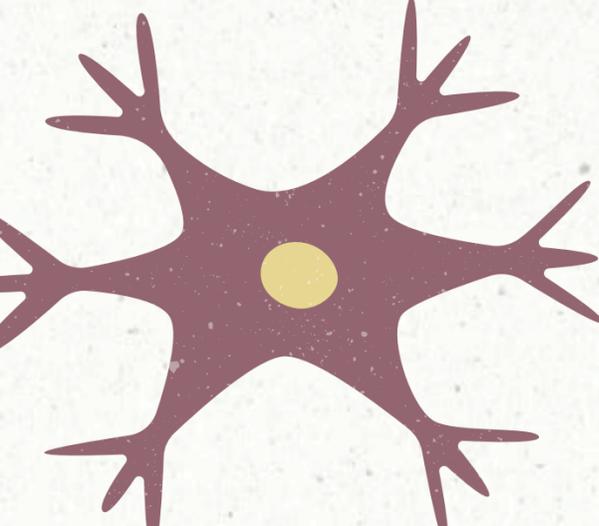
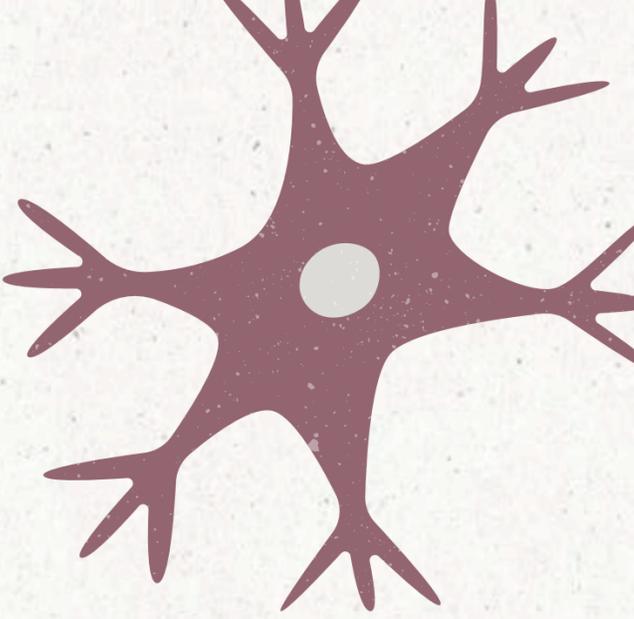
**THUS, HYPOCALCEMIA CAUSED BY INSUFFICIENT DIETARY  $Ca^{2+}$  RESULTS IN ELEVATED LEVELS OF SERUM 1,25-DIOH-D3. (NOTE: 1,25-DIOH-D3 INHIBITS EXPRESSION OF PTH, FORMING A NEGATIVE-FEEDBACK LOOP. IT ALSO INHIBITS ACTIVITY OF THE 1-HYDROXYLASE.)**





## FUNCTION :-

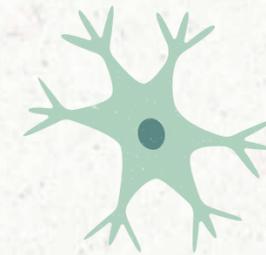
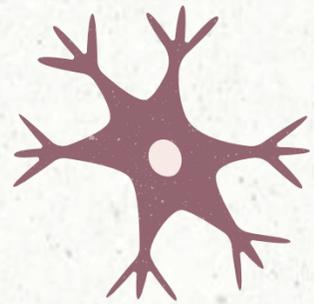
**THE OVERALL FUNCTION OF CALCITRIOL IS TO MAINTAIN ADEQUATE SERUM LEVELS OF  $Ca^{2+}$ . IT PERFORMS THIS FUNCTION BY (1) INCREASING UPTAKE OF  $Ca^{2+}$  BY THE INTESTINE, (2) MINIMIZING LOSS OF  $Ca^{2+}$  BY THE KIDNEY BY INCREASING REABSORPTION, AND (3) STIMULATING RESORPTION (DEMINERALIZATION) OF BONE WHEN BLOOD  $Ca^{2+}$**

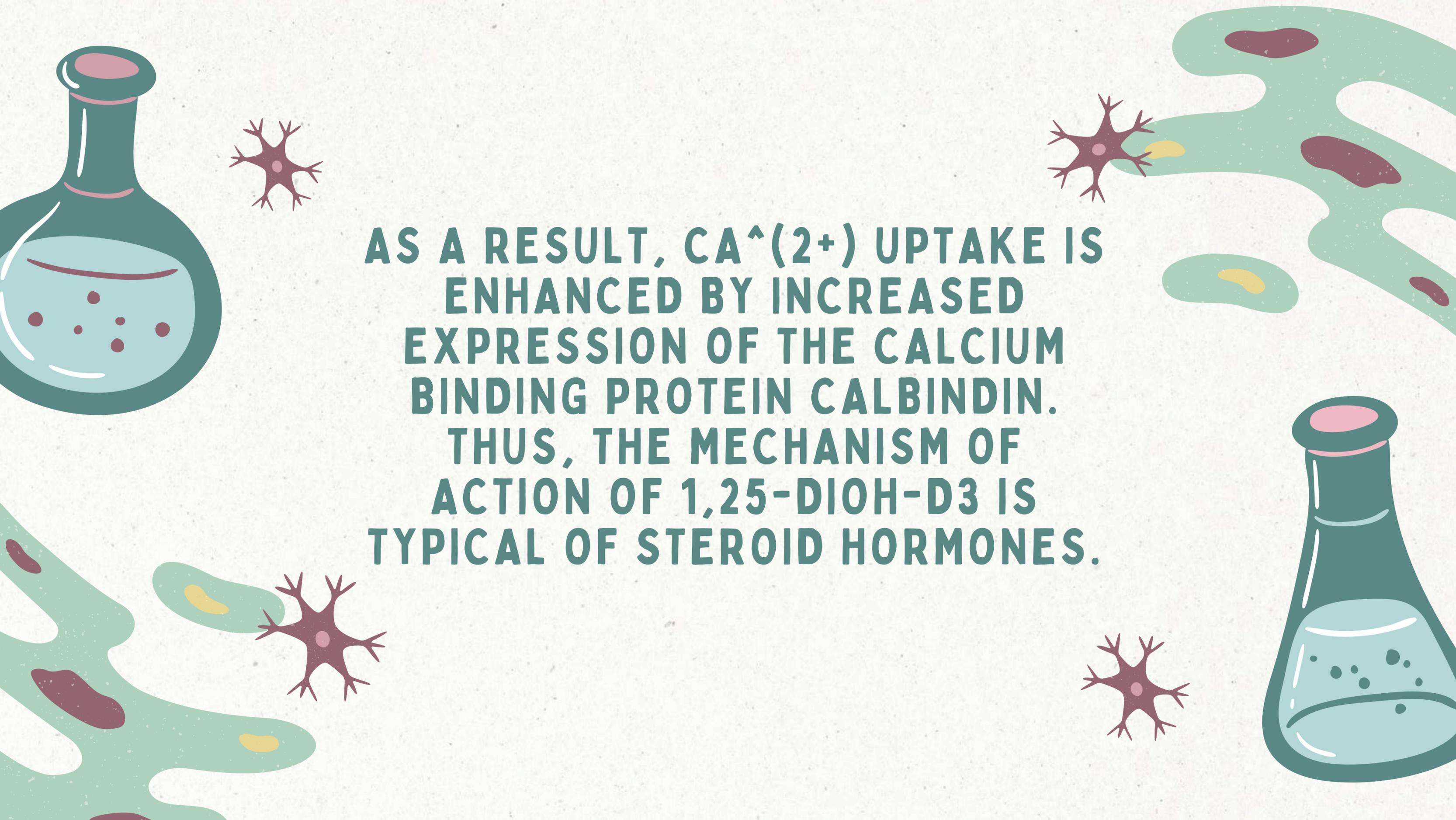




## EFFECT ON THE INTESTINE :

**CALCITRIOL STIMULATES INTESTINAL ABSORPTION OF  $Ca^{2+}$  BY FIRST ENTERING THE INTESTINAL CELL AND BINDING TO A CYTOSOLIC RECEPTOR. THE 1,25-DIOH-D3-RECEPTOR COMPLEX THEN MOVES TO THE NUCLEUS WHERE IT SELECTIVELY INTERACTS WITH RESPONSE ELEMENTS ON THE DNA.**

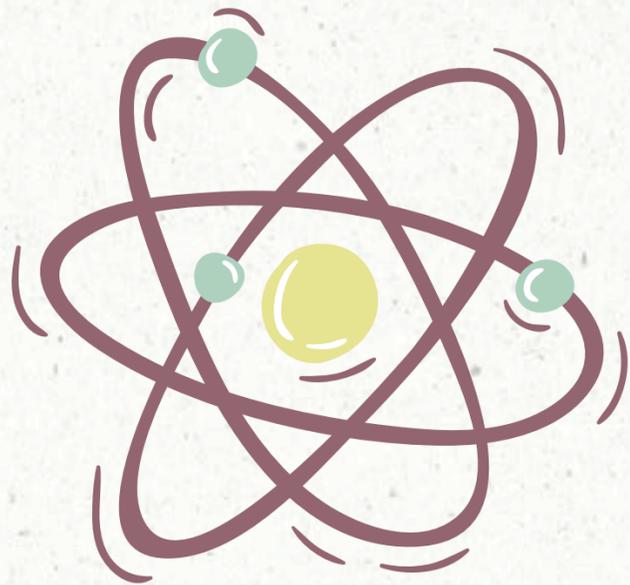
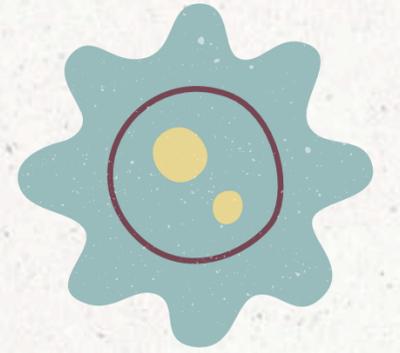




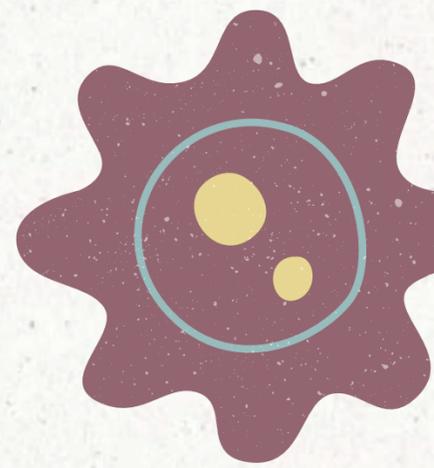
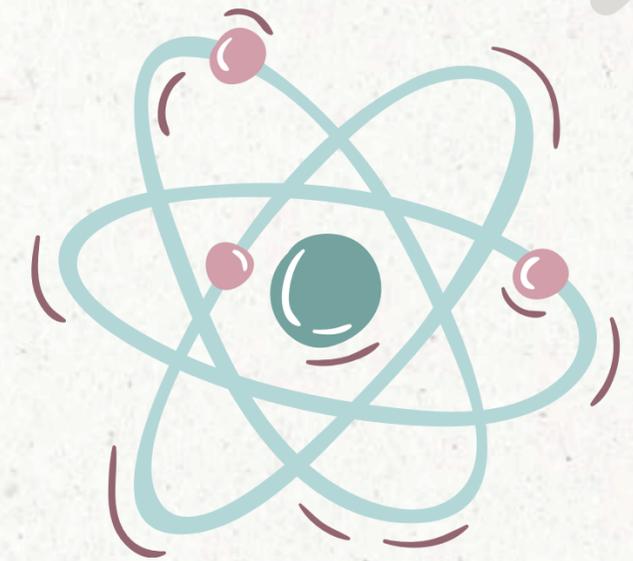
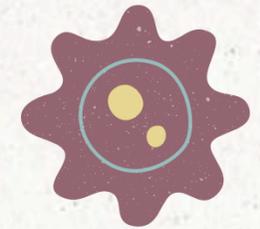
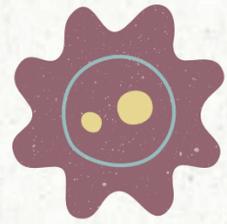
**AS A RESULT,  $Ca^{2+}$  UPTAKE IS ENHANCED BY INCREASED EXPRESSION OF THE CALCIUM BINDING PROTEIN CALBINDIN. THUS, THE MECHANISM OF ACTION OF 1,25-DIOH-D3 IS TYPICAL OF STEROID HORMONES.**

## EFFECT ON BONE:

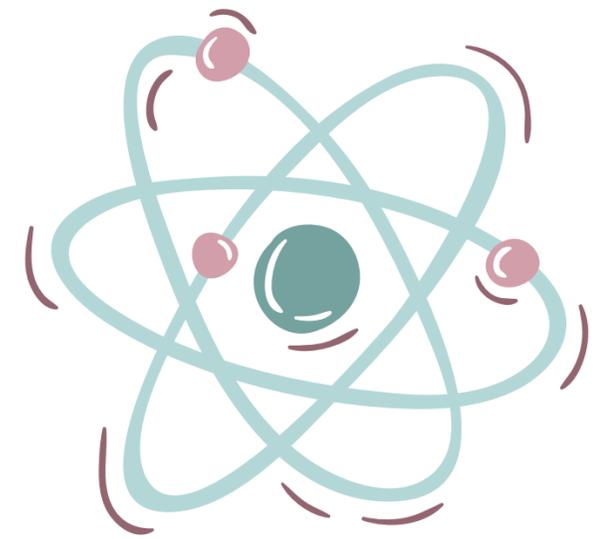
BONE IS COMPOSED OF COLLAGEN AND CRYSTALS OF  $\text{Ca}_5(\text{PO}_4)_3\text{OH}$  (HYDROXYAPATITE). WHEN BLOOD  $\text{Ca}^{2+}$  IS LOW, 1,25-DIOH-D3 STIMULATES BONE RESORPTION BY A PROCESS THAT IS ENHANCED BY PTH. THE RESULT IS AN INCREASE IN SERUM  $\text{Ca}^{2+}$ . THEREFORE .



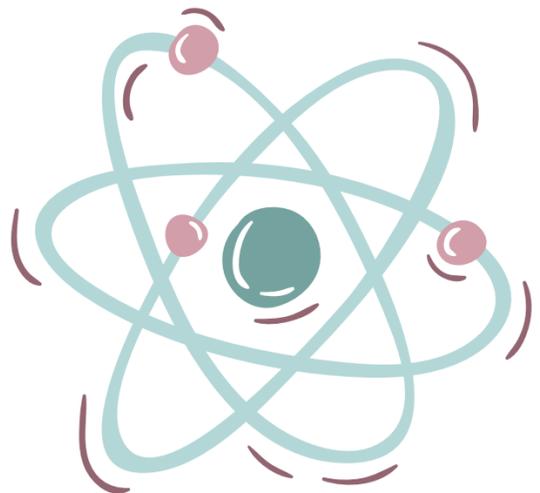
**, BONE IS AN IMPORTANT RESERVOIR OF  $Ca^{2+}$  THAT CAN BE MOBILIZED TO MAINTAIN SERUM LEVELS. (NOTE: PTH AND CALCITRIOL ALSO WORK TOGETHER TO PREVENT RENAL LOSS OF  $Ca^{2+}$ .)**

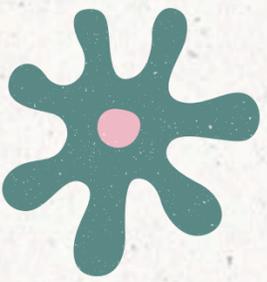
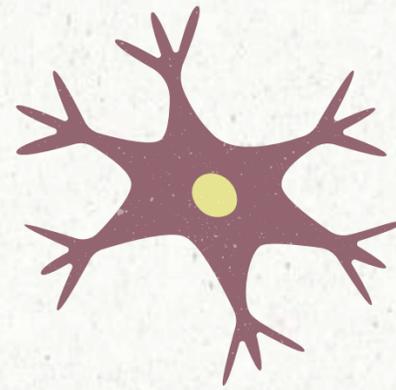
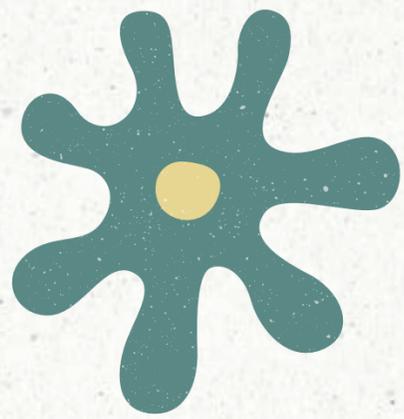


**DISTRIBUTION AND REQUIREMENT VITAMIN D OCCURS NATURALLY IN FATTY FISH, LIVER, AND EGG YOLK. MILK, UNLESS IT IS ARTIFICIALLY FORTIFIED, IS NOT A GOOD SOURCE. THE RDA FOR INDIVIDUALS OF AGES 1 TO 70 YEARS IS 15 MG/DAY AND 20 MG/DAY IF OVER AGE 70 YEARS. EXPERTS DISAGREE**

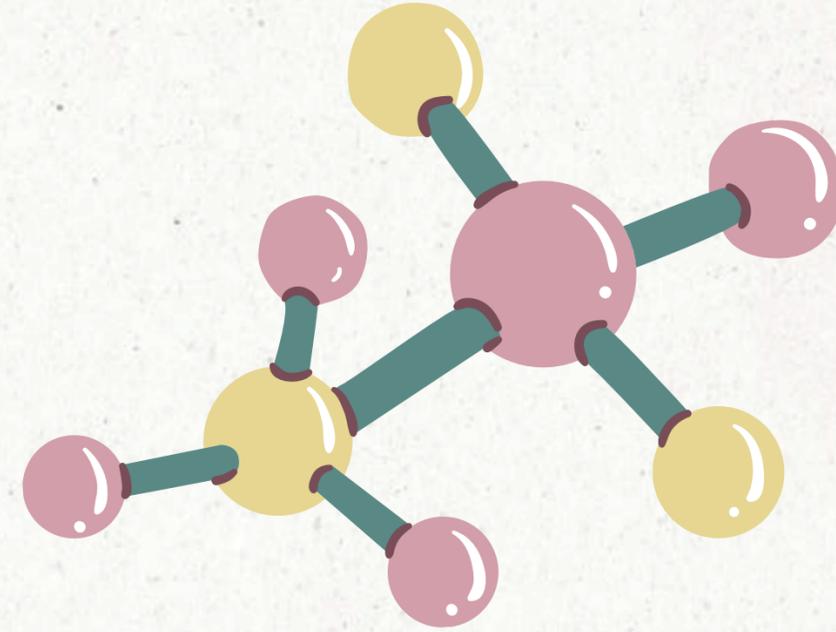


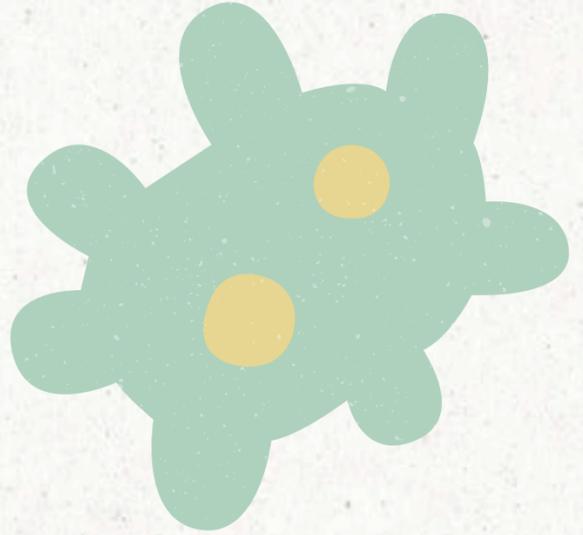
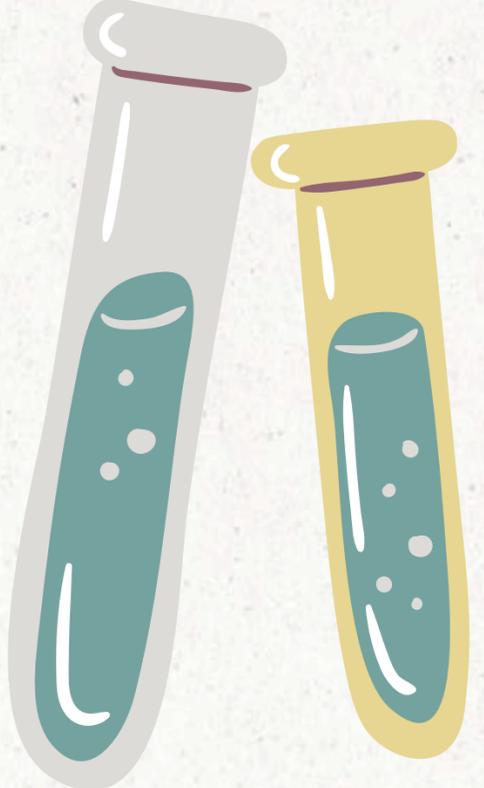
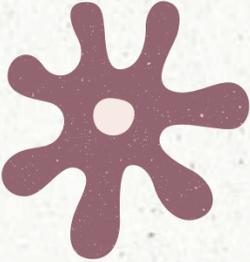
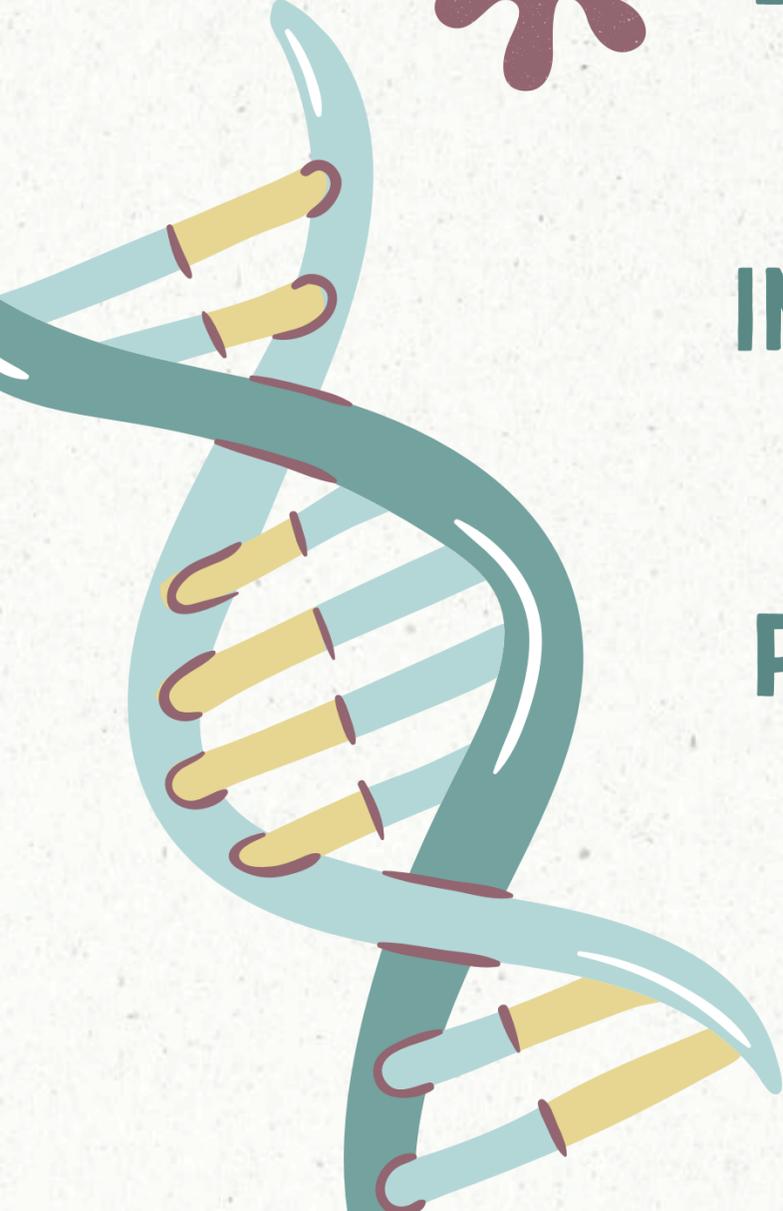
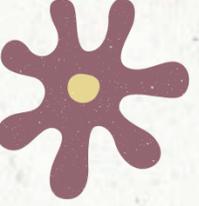
**HOWEVER, ON THE OPTIMAL LEVEL OF VITAMIN D NEEDED TO MAINTAIN HEALTH (NOTE: 1 MG VITAMIN D = 40 INTERNATIONAL UNITS [IU].) BECAUSE BREAST MILK IS A POOR SOURCE OF VITAMIN D, SUPPLEMENTATION IS RECOMMENDED FOR BREASTFED BABIES.**





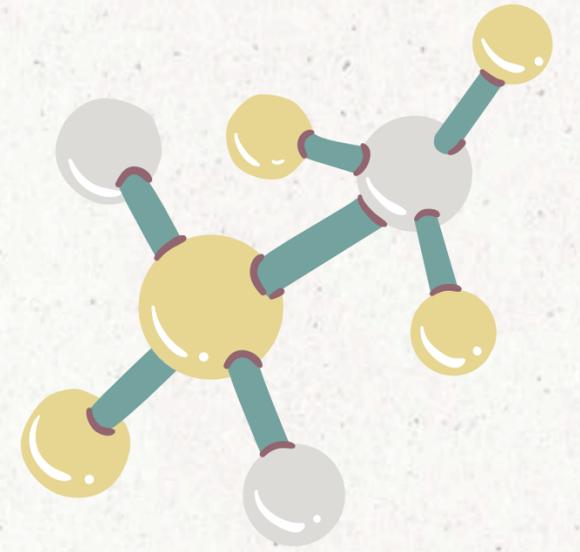
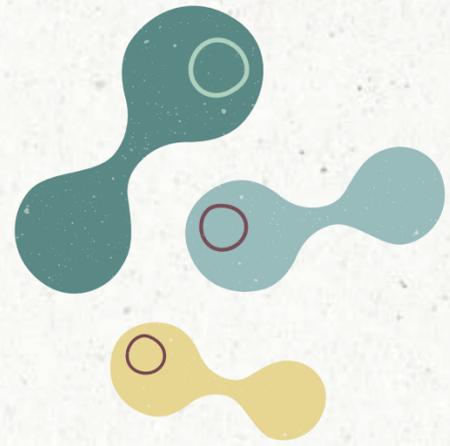
**NUTRITIONAL DEFICIENCY CAUSES DEMINERALIZATION OF BONE, RESULTING IN RICKETS IN CHILDREN AND OSTEOMALACIA IN ADULTS. RICKETS IS CHARACTERIZED BY THE CONTINUED FORMATION OF THE COLLAGEN MATRIX OF BONE, BUT INCOMPLETE MINERALIZATION RESULTS IN SOFT, PLIABLE BONES.**

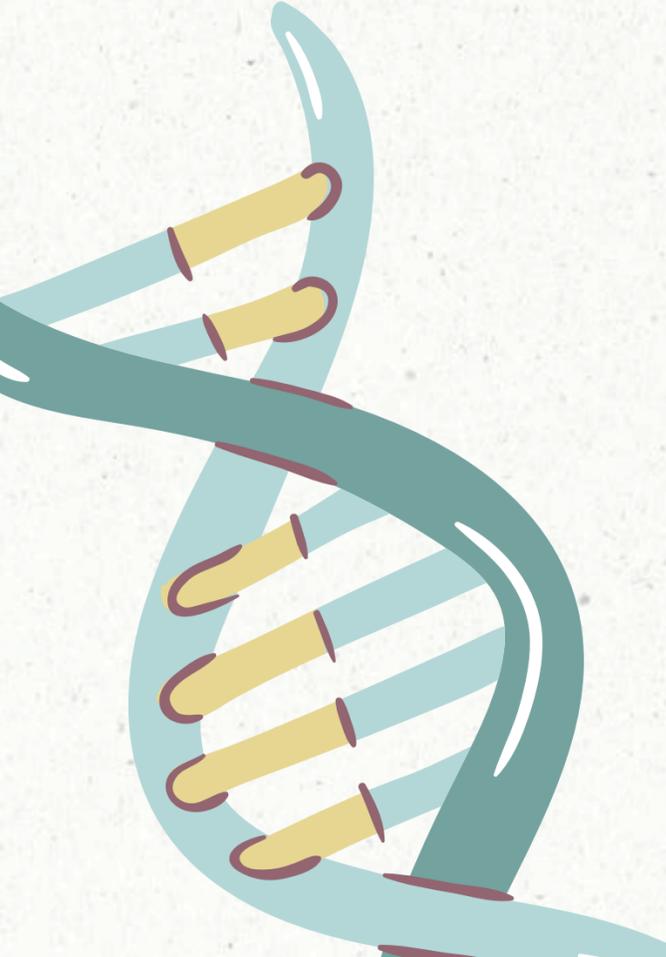




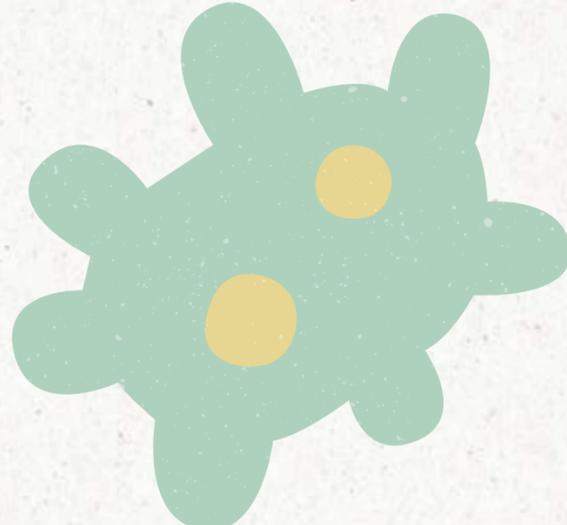
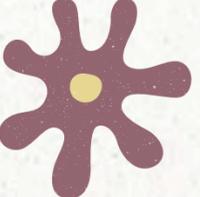
**IN OSTEOMALACIA,  
DEMINERALIZATION OF PRE-EXISTING  
BONES INCREASES THEIR  
SUSCEPTIBILITY TO FRACTURE.  
INSUFFICIENT EXPOSURE TO DAYLIGHT  
AND/OR DEFICIENCIES IN VITAMIN D  
CONSUMPTION OCCURS  
PREDOMINANTLY IN INFANTS AND THE  
ELDERLY.**

**VITAMIN D DEFICIENCY IS MORE COMMON IN THE NORTHERN LATITUDES, BECAUSE LESS VITAMIN D SYNTHESIS OCCURS IN THE SKIN AS A RESULT OF REDUCED EXPOSURE TO ULTRAVIOLET LIGHT. (NOTE: LOSS-OF-FUNCTION MUTATIONS IN THE VITAMIN D RECEPTOR RESULT IN HEREDITARY VITAMIN D-DEFICIENT RICKETS.)**

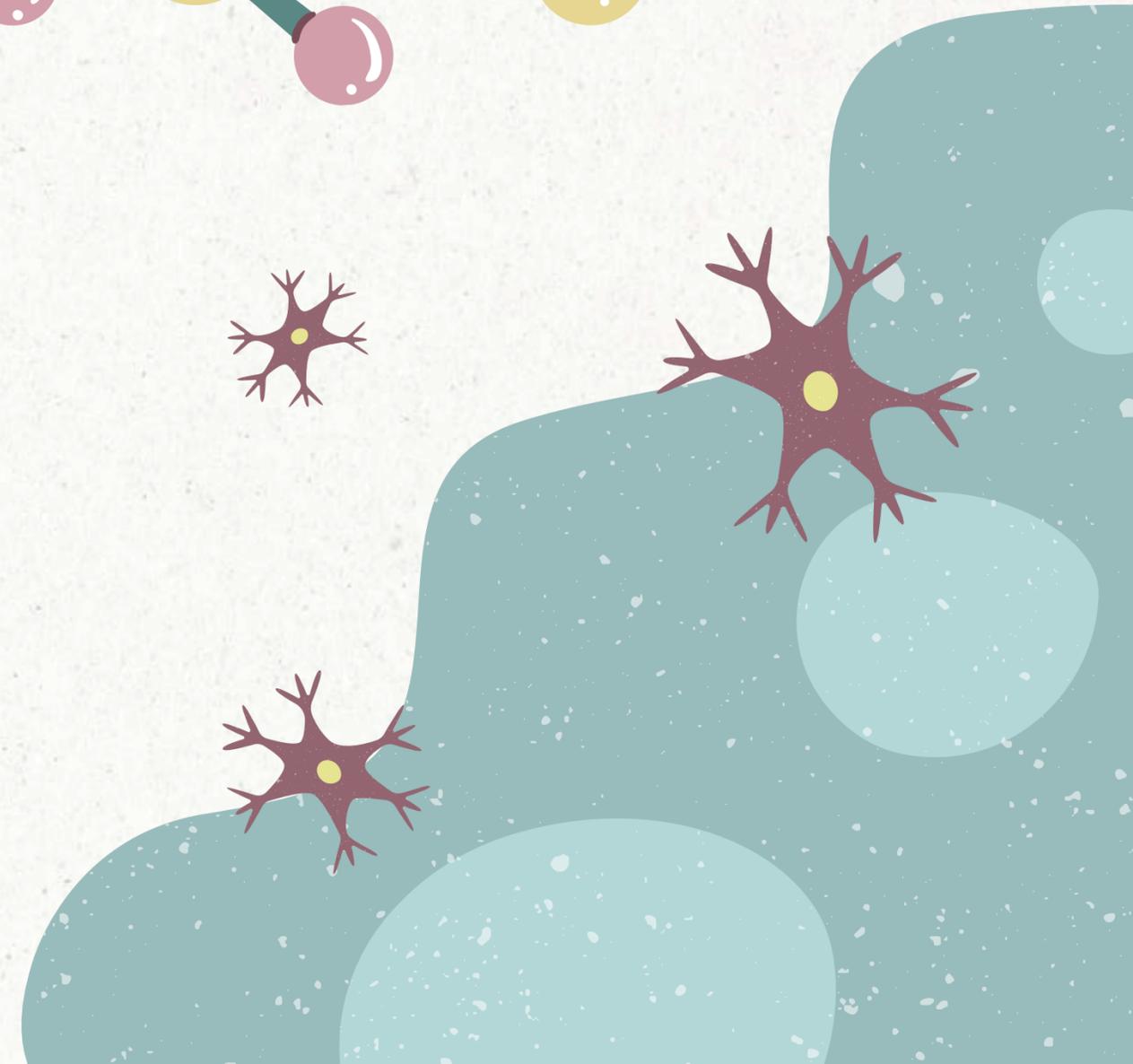
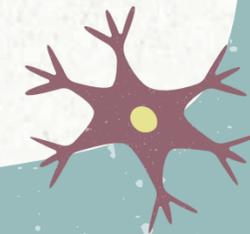
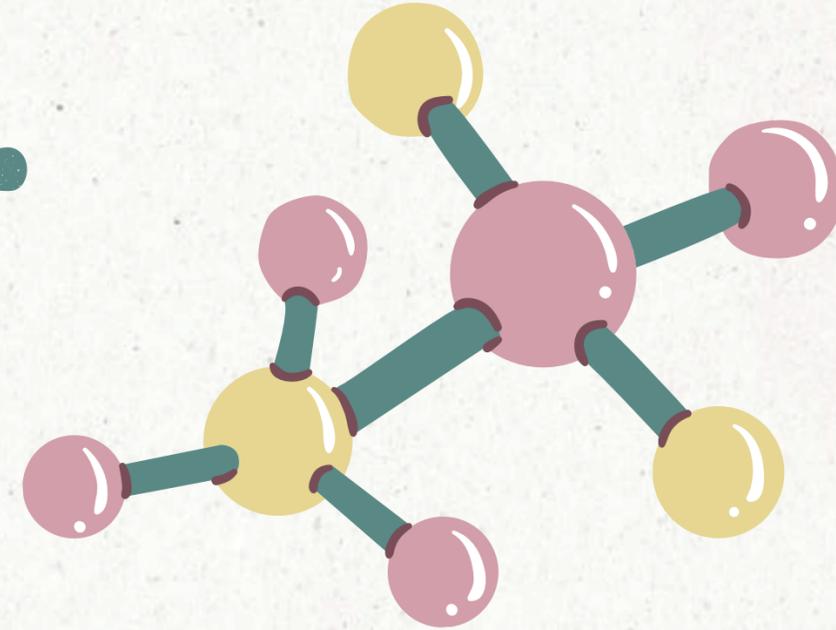
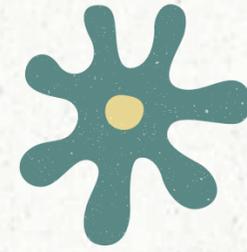




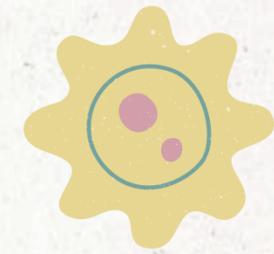
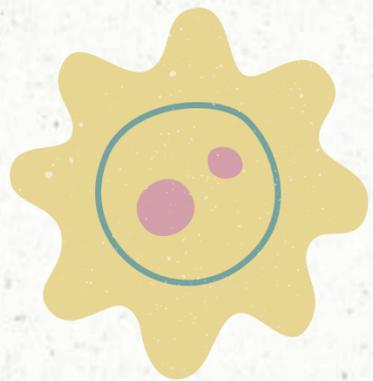
**RENAL OSTEODYSTROPHY: CHRONIC  
KIDNEY DISEASE CAUSES  
DECREASED ABILITY TO FORM  
ACTIVE  
VITAMIN D AS WELL AS INCREASED  
RETENTION OF  $\text{PO}_4^{(3-)}$ ,  
RESULTING IN HYPERPHOSPHATEMIA  
AND HYPOCALCEMIA. THE LOW  
BLOOD  $\text{CA}^{(2+)}$  CAUSES A RISE IN  
PTH AND ASSOCIATED BONE  
DEMINERALIZATION WITH RELEASE  
OF  $\text{CA}^{(2+)}$  AND  $\text{PO}_4^{(3-)}$ .**



**SUPPLEMENTATION MUST  
BE ACCOMPANIED BY  
 $\text{PO}_4^{3-}$  REDUCTION  
THERAPY TO PREVENT  
FURTHER BONE LOSS AND  
PRECIPITATION OF  
CALCIUM PHOSPHATE  
CRYSTALS.**



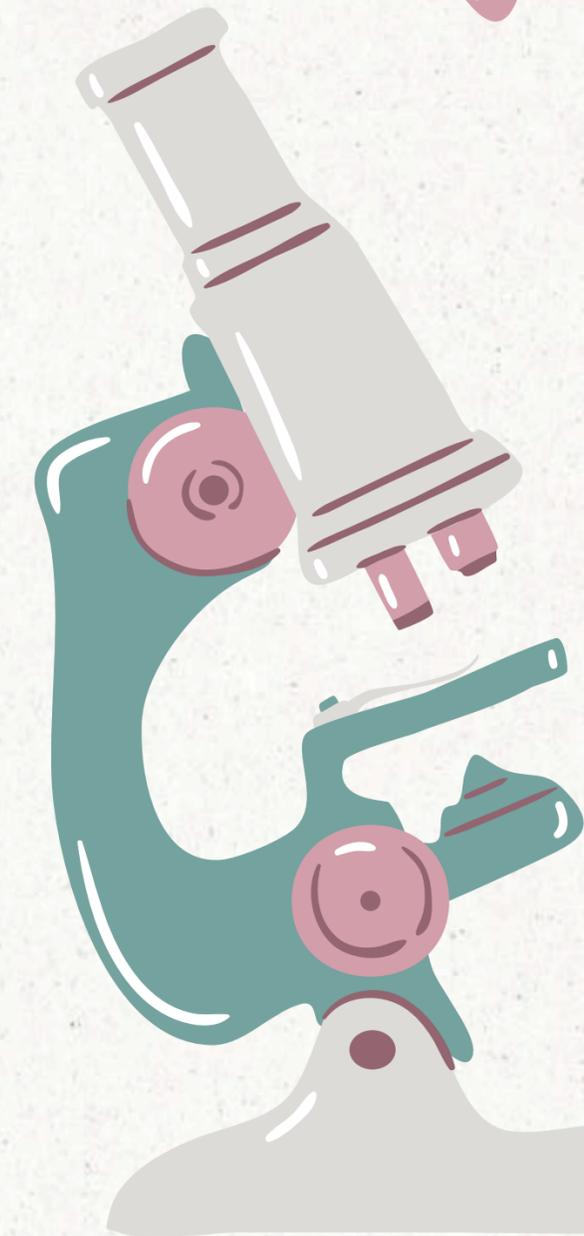
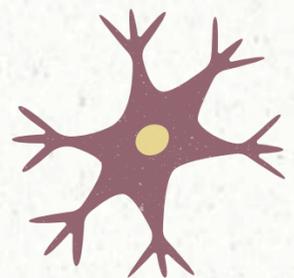
**HYPOPARATHYROIDISM:  
LACK OF PTH CAUSES  
HYPOCALCEMIA AND  
HYPERPHOSPHATEMIA.  
(NOTE: PTH INCREASES  
PHOSPHATE EXCRETION.)  
PATIENTS MAY BE TREATED  
WITH VITAMIN D AND  
CALCIUM  
SUPPLEMENTATION.**



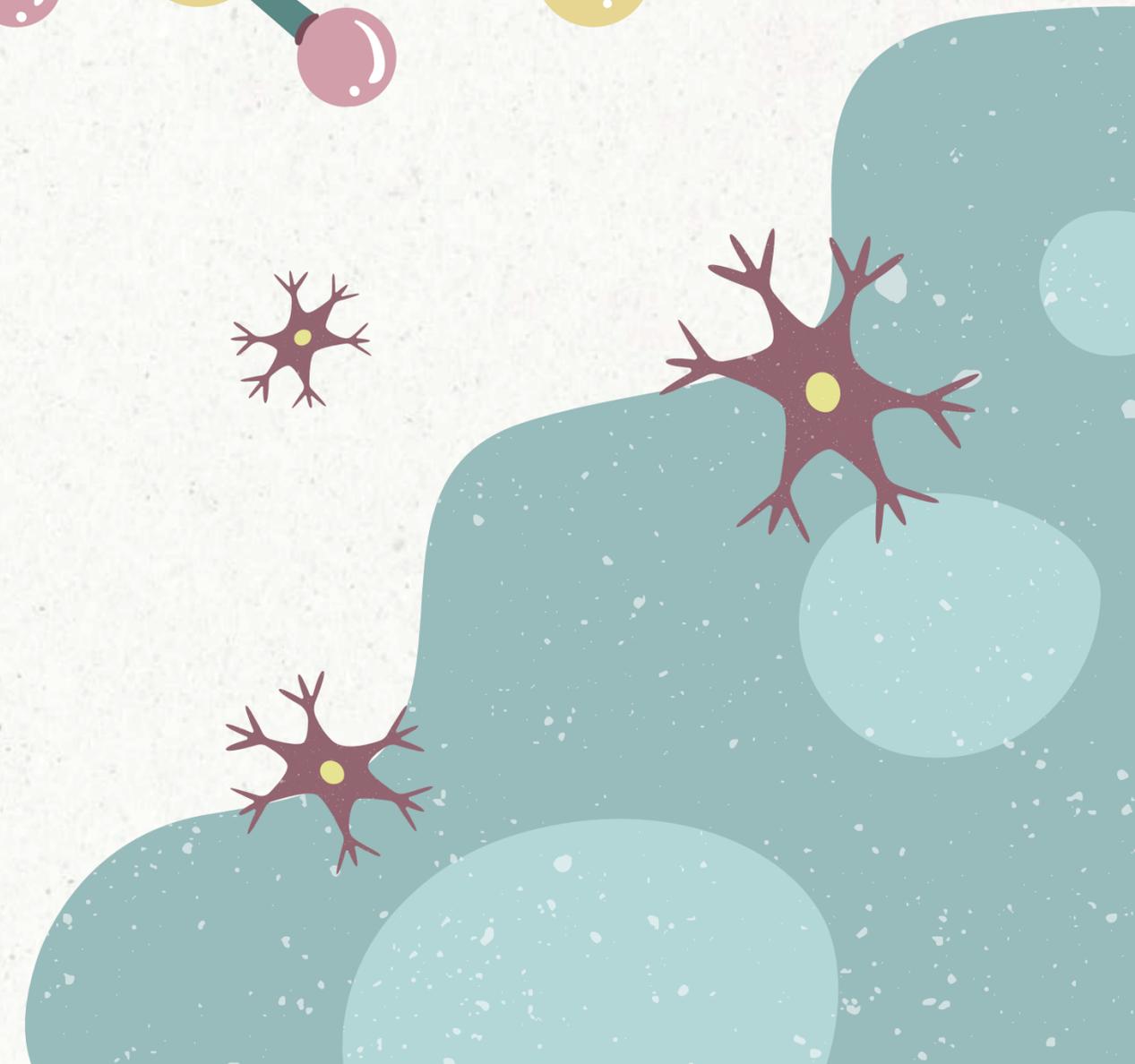
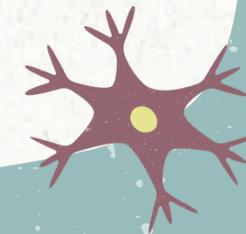
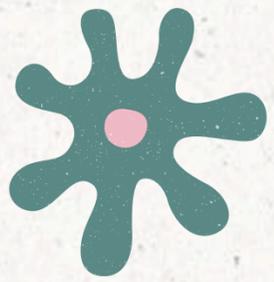
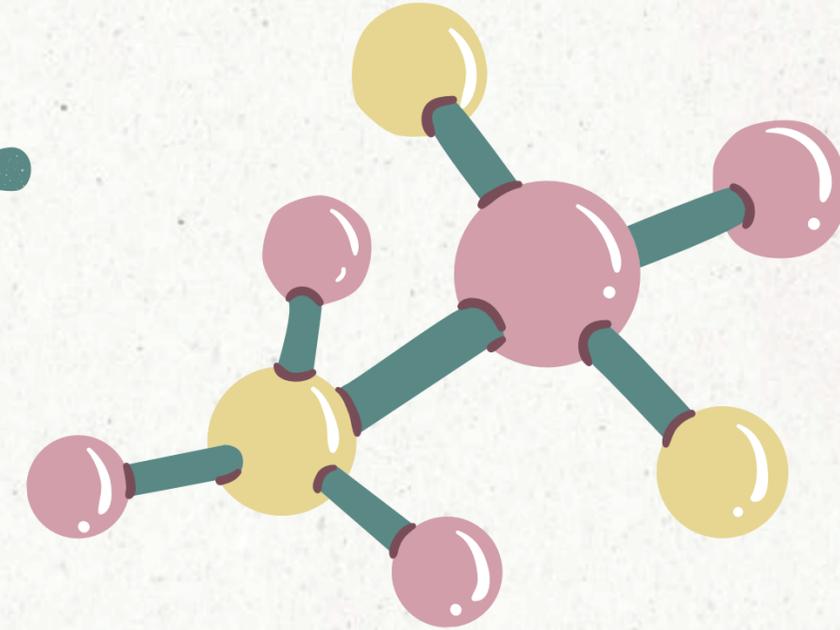
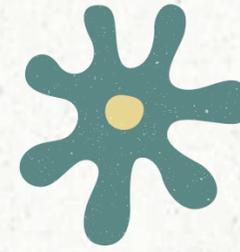
# TOXICITY

LIKE ALL FAT-SOLUBLE VITAMINS, VITAMIN D CAN BE STORED IN THE BODY AND IS ONLY SLOWLY METABOLIZED. HIGH DOSES (100,000 IU FOR WEEKS OR MONTHS) CAN CAUSE LOSS OF APPETITE, NAUSEA, THIRST, AND WEAKNESS.

ENHANCED  $Ca^{2+}$  ABSORPTION AND BONE RESORPTION RESULT IN HYPERCALCEMIA, WHICH CAN LEAD TO DEPOSITION OF CALCIUM SALTS IN SOFT TISSUE (METASTATIC CALCIFICATION).



**THE UL IS 100 MG/DAY (4,000 IU/DAY) FOR INDIVIDUALS AGES 9 YEARS OR OLDER, WITH A LOWER LEVEL FOR THOSE UNDER AGE 9 YEARS. (NOTE: TOXICITY IS ONLY SEEN WITH USE OF SUPPLEMENTS. EXCESS VITAMIN D PRODUCED IN THE SKIN IS CONVERTED TO INACTIVE FORMS.)**





**THANK YOU!  
FOR YOUR  
ATTENTION**

