Sheet Slides

Subject	Specialized Products Produced from Amino Acids
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Number of the lecture	33

Special Products of Amino Acids

Several compounds with biochemical and physiological importance can be produced by amino acids. In this section, we will go over some such compounds descriptively, and this section of the sheet is based on chapter 21 of Lippincott's textbook.

Yellow notes are extra information from the book

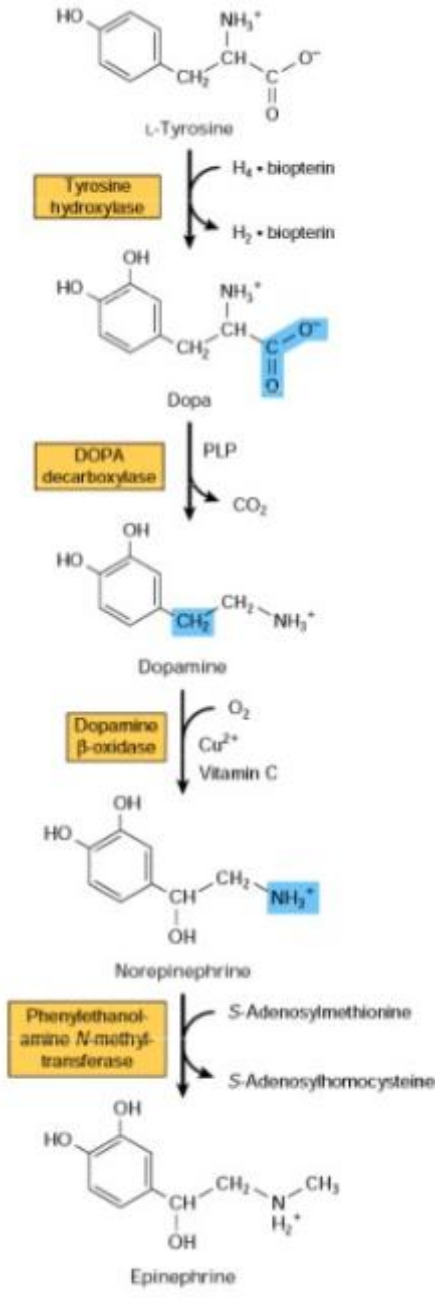
1. Tyrosine products:

Tyrosine can be metabolized to many important groups of compounds; such as:

A. Catecholamines:

Dopamine, norepinephrine, and epinephrine are biologically active (biogenic) amines that are collectively termed catecholamines.

Note: Catechol is a benzene ring with two OH groups on adjacent positions, having an extra amine group makes it catecholamines



Catecholamines are synthesized from tyrosine. Tyrosine is hydroxylated to 3,4-dihydroxyphenylalanine (DOPA) by a tetrahydrobiopterin (BH4)-requiring enzyme (tyrosine hydroxylase). It is the rate limiting step

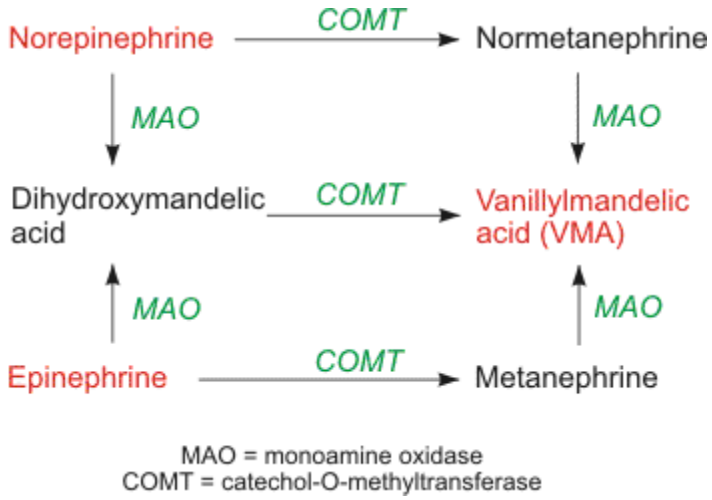
DOPA is decarboxylated to dopamine, which is a very important neurotransmitter, by a Pyridoxal phosphate (PLP)-requiring enzyme.

Norepinephrine is synthesized from dopamine by the enzyme dopamine β-hydroxylase (adds a hydroxyl group by the end of the reaction) , which needs copper and ascorbate (vitamin C) as cofactors. In the adrenal gland, norepinephrine is methylated to epinephrine. The methyl supplier is SAM.

Epinephrine and norepinephrine serve a major

function in the regulation of carbohydrates and lipids metabolism. They are also secreted in the fight-or-flight reactions.
Dopamine and norepinephrine are synthesized in the brain as neurotransmitters . Epinephrine and norepinephrine are synthesized in the adrenal medulla as hormones

The degradation of catecholamines is done by two enzymes; monoamine oxidase (MAO), and catechol-O-methyltransferase (COMT) using the methyl supplier SAM. The order of reactions is not important. The intermediates will be different but in any order, epinephrine and norepinephrine degradation ends with vanillylmandelic acid (VMA), and dopamine degradation ends with homovanillic acid. VMA is increased with pheochromocytomas, rare tumors of the adrenal gland characterized by excessive production of catecholamines.



*Note: please have a look at the figure to know the order of the intermediates in both ways because the Dr. mentioned them

Clinical application: *Parkinson's disease*

Parkinson's disease patients are characterized with symptoms like tremor, slow movement, impaired speech or muscle stiffness. In this disease, dopamine levels get reduced. DOPA (levodopa) therapy is used to treat Parkinson's disease rather than dopamine; since dopamine cannot pass the BBB but DOPA can.

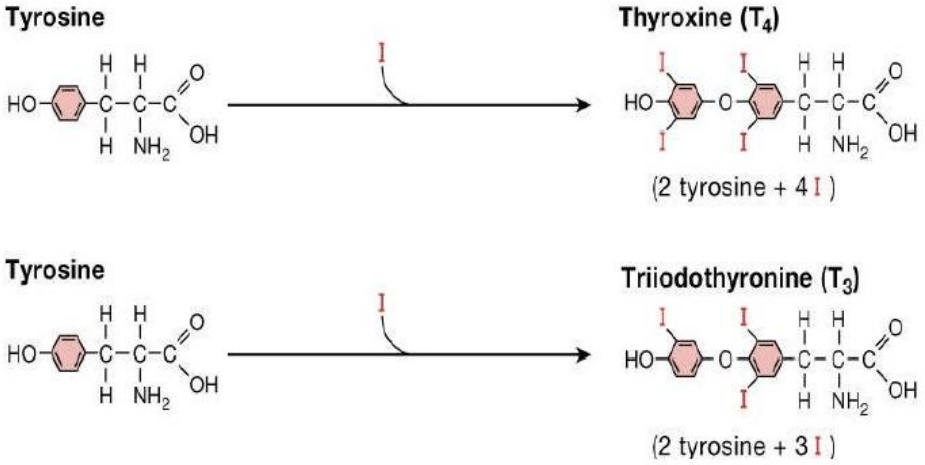
Pharmacologic application: MAO inhibitors

_MAO inhibitors would decrease the degradation thus increasing the level of epinephrine , norepinephrine , dopamine as well as serotonin . This would activate the sympathetic system and increase our happiness . The overall result will improve our mood and that’s why they can be used as antidepressants , but with side effects if misused .

B. Thyroxine

Thyroxine is the main hormone secreted into the bloodstream by the thyroid gland. It is the inactive form and most of it is converted to an active form by organs such as the liver and kidneys. Thyroxine is synthesized from tyrosine. Two tyrosine will be added to each other and modified with two iodine atoms per ring (4 atoms total) , then another modification will occur which removes another iodine atom to become the active T3

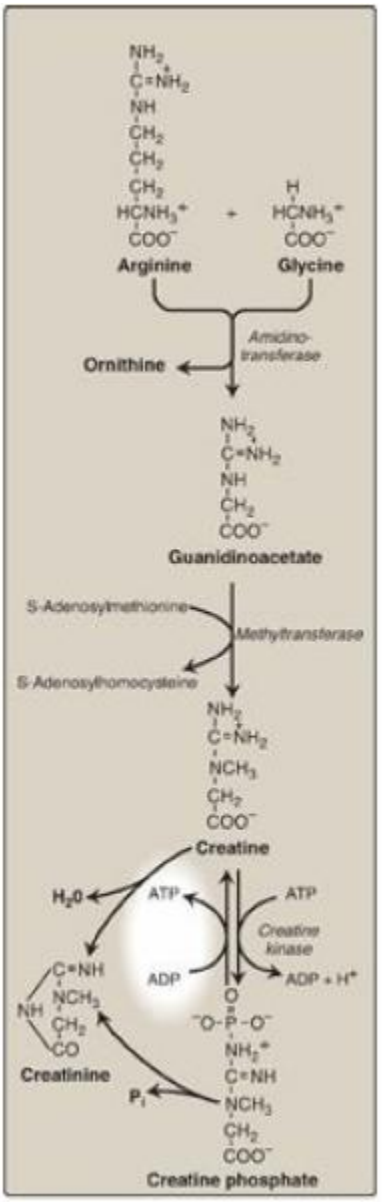
Thyroxine is responsible for regulating the metabolism of the whole body , that's why hypothyroxine patients are fat and lazy because there are no metabolism and no energy as well as bradycardia . on the other hand , hyperthyroid people do not



gain weight no matter how much they eat . They are so hyper which might lead to lack of sleeping as well as tachycardia . 12% of Jordanian have problems with the thyroid but mostly hypothyroxine

2. Creatine phosphate

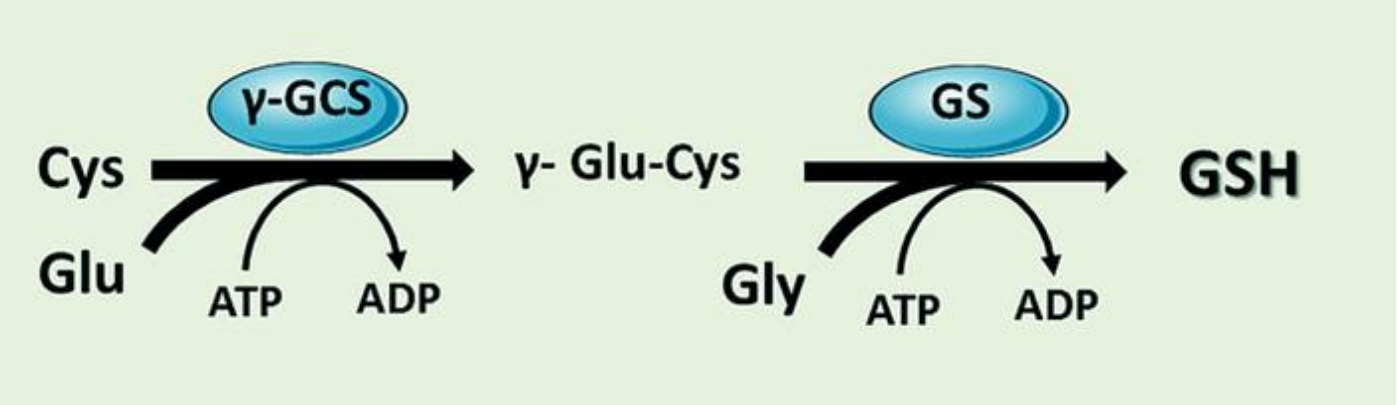
Creatine phosphate is an important energy reservoir for skeletal and heart muscles. Creatine is synthesized from arginine and glysine. Guanidine group(carbon +2 nitrogens) of arginine is transferred to glycine by amidino trasferase ; resulting with gunidionoacetate and ornithine. So, ornithine is obtained from this pathway and the arginase enzyme. Gunidionoacetate is methylated to form creatine with SAM being the methyl supplier. Creatine levels are directly proportional to the muscle mass.



Creatine is reversibly phosphorylated in the presence of ATP by creatine kinase (CK), to produce creatine phosphate. Creatine phosphate is an important rapid-energy reservoir for energy supply in cases of muscle outburst activity. But this reservoir does not last for long time. Creatine is cyclized to creatinine by dehydration , which is excreted in the urine.

Clinical application: *CK levels*

The presence of creatine kinase (MB isozyme) in the plasma is indicative of heart damage and is used in the diagnosis of myocardial infarction. This test is important for MI diagnosis. In addition to this isozyme, skeletal muscle isozyme also has a clinical significance for the diagnosis of skeletal muscle damage.



Clinical application: *creatinine excretion*

Any rise in blood creatinine is a sensitive indicator of kidney malfunction, because creatinine normally is rapidly removed from the blood and excreted. A typical adult male excretes about 1–2 g of creatinine per day. The disadvantage of this test that it is a late indicator

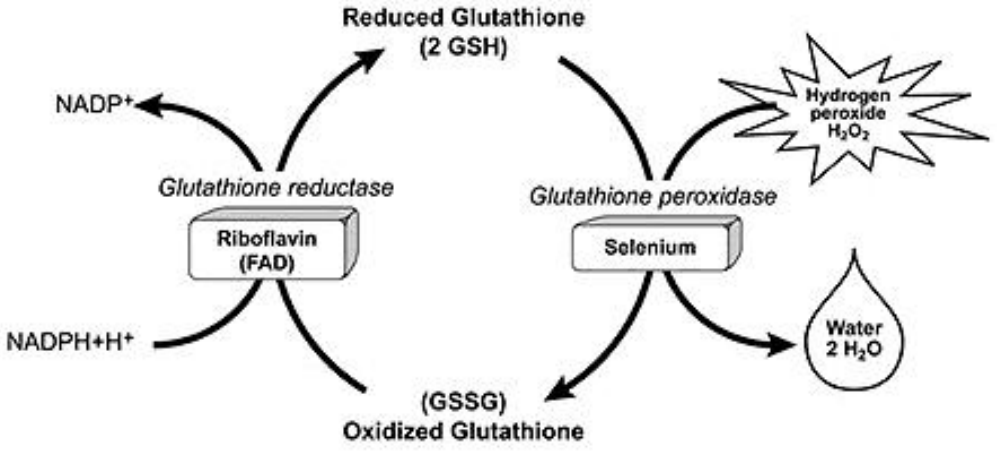
Another thing is , when muscle mass decreases for any reason (for example , from paralysis or muscular dystrophy) , the creatinine content of the urine falls

3. Glutathione "slides only"

Many articles indicate about the importance of antioxidants for our health, and the benefits of the foods which are rich with antioxidants. There are many antioxidants which we ingest with healthy diets; such as: vitamin C, E and β-carotene. Flavonoids (polyphenols), which are present in skin of many fruits like apple, strawberry, blueberry and grapes, are also important dietary antioxidants.

Our body makes many antioxidants; such as uric acid, bilirubin and glutathione (GSH). The body enzymatic system that protects us from ROS is composed from catalase, superoxide dismutase and GSH peroxidase.

GSH is a major antioxidant in our cells. It is a tripeptide (γ-glu-cys-gly), and it is synthesized by 2 reactions; 1: the conjugation of cysteine with the γ carboxylic group of glutamate (ATP-requiring); 2: the conjugation of glycine with cysteine (ATP-requiring). Its –SH group acts as a scavenger for ROS. GSH antioxidant system works in the following manner: 2 molecules of GSH are needed to be oxidized by GSH peroxidase; providing a reducing power "antioxidant power"; the oxidized form of glutathione (GSSG) has got to be reduced to 2 GSH molecules to maintain the protection against ROS, a function done by GSH reductase. GSH peroxidase requires Selenium, and GSH reductase requires NADPH as a reducing power

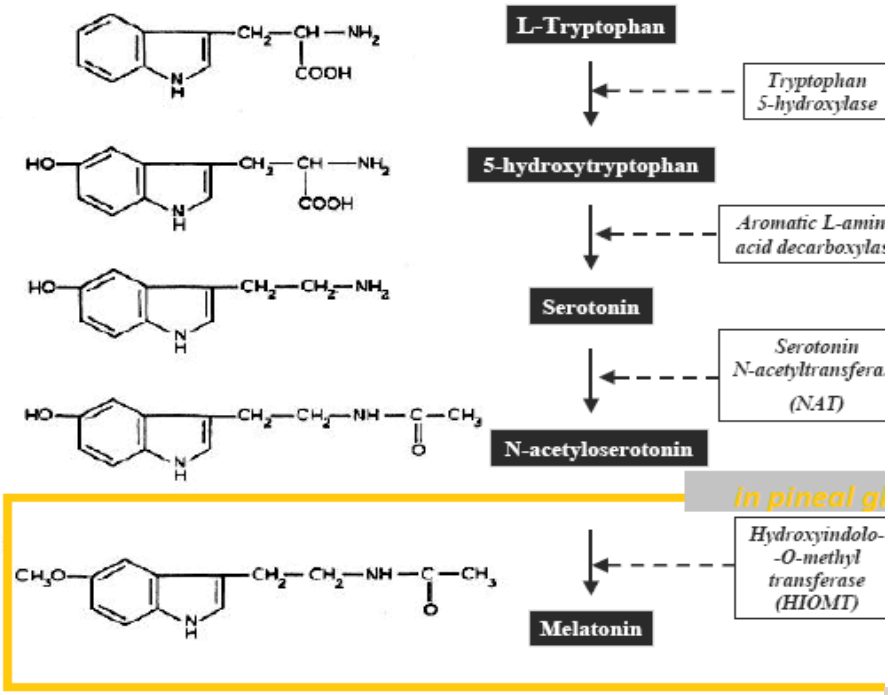


Functions of GSH are numerous; it does not only work as an antioxidant as mentioned, but also serves many biochemical functions. GSH is used to conjugate drugs, so they can be more soluble and so they can be excreted. Moreover, GSH helps to transport amino acids across cell membrane. It also helps to rearrange the disulfide bridges in proteins, by reducing them and remodeling them.

Another example is GABA (gamma-amino-butyric acid) which is a modification of glutamate .It acts as an inhibitory neurotransmitter

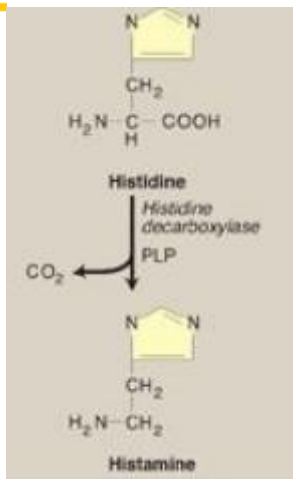
4. Serotonin and Melatonin

Serotonin (also called 5-hydroxytryptamine) is an important factor, which is present in the GI tract, in the CNS as a neurotransmitter, and is secreted by the platelets. Serotonin has multiple physiologic roles including pain perception, regulation of sleep, appetite, temperature, blood pressure, cognitive functions, and mood (causes a feeling of well-being).



Serotonin is synthesized from tryptophan by a two-step pathway: a tetrahydrobiopterin-requiring hydroxylation reaction, followed by a PLP-requiring decarboxylation. In pineal gland, serotonin is converted to melatonin. Melatonin is produced when exposed to darkness by acetylation of the amine group followed by methylation of the hydroxyl group, and helps to regulate the sleep cycle. To degrade serotonin, It is oxidized by MAO enzyme.

Selective serotonin reuptake inhibitors (SSRIs) act as antidepressants as well



*Note: Check the figure above and have a look at the name of the enzymes (the doctor didn't mention them in the record)

Tryptophan also helps in the synthesis of nicotine amide , a component of NADH and NADPH .

Finally , tryptophan by the bacteria of the GI tract is used to synthesize indole ring (a benzene ring fused with a 5 member ring)

5. Histamine

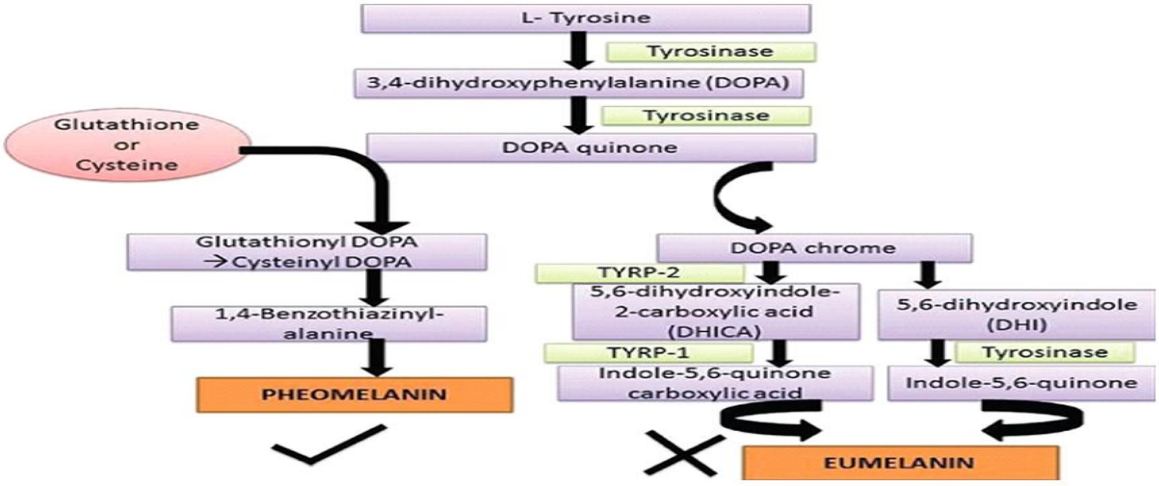
Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions and gastric acid secretion. It is secreted by the granular mast cell. Histamine is synthesized from histidine by decarboxylation reaction, which requires PLP as a cofactor.

6.Melanin

A pigment in several tissues particularly in the hair , skin and the eyes . It's synthesized from tyrosine by copper containing tyrosinase in melanocytes of the epidermis . it functions to protect the underlying cells from the harmful effects of sunlight .

A defect in the enzyme used results is oculocutaneous albinism its Inheritance modes: AR (primary mode), AD, or X-linked.

There are two types of melanin , eumelanin which is responsible for the black/brown color . people with more eumelanin have darker skin and hair color . the other type is pheomelanin which is responsible for the red/orange color of the hair .Sunlight stimulates the melanosomes to translocate to the surface of the skin to become darker (tanned)



Some side notes of different amino acids

1-methylation of lysine helps in the synthesis of carnitine (for fats metabolism)

2-Serine is used in the synthesis of some phospholipids (phosphotidylserine for example) . It also can be changed to ethanolamine and choline

3-orthinine is used in a multistep reaction to synthesize spermine which gives the odor of semen

Nucleotide Metabolism

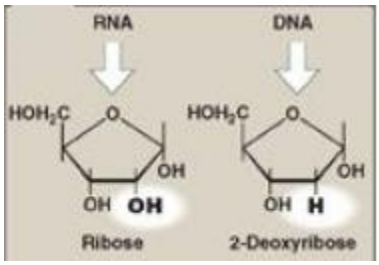
Chapter 22

In the next lectures, we will study the synthesis and the degradations of nucleotides, and the disorders associated with that. In this lecture, we discuss an introduction to this chapter.

Introduction

The importance of nucleotides lies in that they are: the main components of nucleic acids (DNA and RNA); the energy currency of the cell; activators of many molecules (ex. UDP-glucose; CDP-choline); parts of cofactors (including coA, NADH, NADPH, $FADH_2$); regulatory molecules (ex. cAMP; cGMP).

- Sources of nucleotides



1- De novo synthesis: building the nucleotides from zero.
2- Salvage pathway: one single reaction that builds the nucleotides from parts of pre-existing nucleotides. These parts can result from nucleic acids degradation. This pathway provides a way to use nucleotides parts instead of excreting them, and this pathway is very important for the brain.
3- Diet: this is a very minor source; since dietary nucleotides are metabolized in the mucosal cells, and very a very little proportion can escape to the blood.

General features and information:

- Nucleotides vs. Nucleosides:
  Nucleoside = nitrogenous base + pentose
  Nucleotide = nitrogenous base + pentose + phosphate = nucleoside phosphate

- Solubility: because the pentose is polar, and the phosphate is charged, the nitrogenous base is less soluble than the nucleoside, which is less soluble than the nucleotide.

- Purines and pyrimidines:

	Purines	**Pyrimidines**
Structure	Two fused rings; 5-mem. And 6-mem.	One 6-mem. ring
Examples	Adenine; guanine; hypoxanthine	Thymine; cytosine; uracil (in RNA)
Linkage with the pentose	B-N-glycosidic [1-- 9]	B-N-glycosidic

- Di- and tri-phosphonucleosides amounts in the cell are more than that of monophosphonucleosides. ATP is the most common. Also, ribose nucleotides are more common than hydroxyribose nucleotides.

- Nucleotides can be quantitatively measured in nucleic acids by routine measures of 280nm absorption; especially purines nucleotides.

DO NOT FORGET TO REVISE YOUR DOCTOR'S SLIDES.

Smile in the mirror. Do that every morning and you'll start to see a big difference in your life.