SUBJECT: MEDICINAL CHEMISTRY
SUB.CODE: 18KP3CHELCH4

TOPIC : DRUG AND DRUG DESIGNS

UNIT-2
DRUG AND DRUG DESIGNS

PART 2.1

PHYSIOLOGICAL ASPECT OF DRUGS:

Orally administered drugs are passed through the gastrointestinal tract (GIT), which influences their next metabolism in the body. In the case of systemic administration, the drug is released from the dosage form, is dissolved and eventually absorbed. The residual amount is excreted in the faeces. The main factors influencing administered drugs are particularly pH, passage time, solubilizers or the oxido-reductive potential in different parts of the GIT. These factors are directly related to the release, absorption and stability of drugs. They can be used for simulation of the GIT environment in vitro and for the overall design of the dosage form in vivo. Because some literature data are not given in context and sometimes they are contradictory, this paper summarizes elementary values of the above-mentioned physiological parameters in the form of a review. Keywords: drug, digestion, absorption, pH, GIT, motility, digestive enzymes.

A physiological approach to drug kinetics describes the actual distribution and elimination of drugs. Anesthesiologists usually view and solve most problems in physiological terms. Therefore such an approach is one which simplifies learning drug kinetics and dynamics by using familiar concepts. An appreciation of the physiological basis of the currently used kinetic and dynamic models makes it easier to predict changes resulting from any disturbance of normal physiology. An appreciation of the physiological basis of drug distribution and elimination also shows some of the limitations of current pharmacokinetic models.

To investigate the variations in its physiological activity as well as to determine the nature of the habit formation produced by it. When the drug was given orally to animals such as cats and dogs, the effects appeared within three-quarters of an hour to one hour.

The physiological effect of some compounds is affected by circadian rhythm. For example, ethanol (alcohol) affects a person more in the evening than the day. 0.4 g/kg of ethanol had the same effect after 5 h of sleep as 0.8 g/kg produced after 8 h of sleep. Ethanol has less effect on daytime alertness/sleepiness for fully rested subjects than ethanol does for people with sleep deficits.

- Caffeine, a drug with primarily stimulating effects, has a metabolic half-life of 3–7 h; some factors influencing the half life are pregnancy (increases half life to as much as 18 h) and smoking (decreases half life). Caffeine has no day-to-day accumulations as it almost completely disappears from the body overnight.
- A pharmacological active dose is about 200 mg (about 3 mg/kg), depending upon the individual (body weight, body tolerance). reported increased sleep latency with doses as low as 75 .
- Although photic entrainment can be shown to produce subjective and physiological effects as a result of cortical stimulation, it is another issue entirely to conclude that it interacts with or produces endogenous rhythms. physiological effects that may result from VR use. To some extent the prevalence of these effects has been reduced with the increase in sophistication of the systems being used, but the issue of negative effects of using and viewing VR has not disappeared. It still appears that for a small percentage of the population, approximately 5%, these effects, particularly sickness, are experienced and are severe enough to prevent effective use of VR. Therefore the mediation of these effects, via system selection, environment design and training should be continued.

ORGANIC MEDICINAL SUBSTANCES OF NATURAL AND SYNTHETIC ORIGIN

Introduction:

Natural products continue to play an important role in the discovery and development of new pharmaceuticals, as clinically useful drugs, as starting materials to produce synthetic drugs, or as lead compounds from which a totally synthetic drug is designed. At the same time, synthetic compounds, unrelated to natural products, have played an increasingly progressive role in new drug discovery. Continuous improvements in synthetic methodology have provided practical access to a vast array of synthetic substances, most recently in the form of combinatorial synthesis. new drug substances since natural products often possess complex structural features not easily accessible by total synthesis. In this brief overview, some selected examples will be provided from the categories of natural, semisynthetic, and synthetic drugs.

NATURAL PRODUCT-RELATED DRUGS

Antibiotics and other anti-infectives:

Antibiotics are, by definition, natural products or derivatives of natural products. Since the discovery of penicillin, a large number of antibiotics have been isolated from scores of microorganisms, and several antibiotics make it to the clinic each year. The antibiotics are important, life-saving drugs. Major classes include â-lactams, tetracyclines, macrolides, and aminoglycosides. Additionally, explorations into the mechanisms by which both the clinically used antibiotics and those that are not used clinically exert their action have led to an understanding of the biology of the target pathogens that would not likely have been possible without these important biochemical probes. Further advances will surely be forthcoming with the application of more advanced molecular biology techniques. Among the most important antibiotics, both from a historical and a clinical utility perspective, are the â-lactams, which are predominated by the penicillins and cephalosporins.

PENICILLIN:

Among the most important antibiotics, both from a historical and a clinical utility perspective, are the â-lactams, which are predominated by the penicillins and cephalosporins. The naturally occurring penicillin first isolated from cultures of *Penicillium* in the middle of the last century were extraordinary discoveries, yet suffered certain shortcomings as therapeutic agents. While the â-lactam nucleus is required for the desired antimicrobial action, the early natural penicillins had a very narrow spectrum of activity, poor pharmacokinetics and chemical stability, and were easily destroyed by the action of penicillinase, which conferred resistance to bacterial strains capable of producing this enzyme. These shortcomings were overcome when it was discovered that 6-aminopenicillanic acid, the biosynthetic precursor to the natural penicillins, could be synthetically modified to introduce varying side chains (R) that determined the properties of the modified product. Presently, there are more than a dozen penicillin antibiotics in clinical use, but only two are produced without synthetic modification: penicillin G and penicillin V.

CEPHALOSPORINS:

Similarly, the first cephalosporin (cephalosporin C) lacked potency, spectrum, and other desirable Pharmaceutical properties. With the discovery of synthetic methodology to replace the side-chain of the naturally occurring cephalosporins with side-chains designed to confer more desirable properties, the door was opened to improve semisynthetic analogs. Currently, there are more than 25 cephalosporins in clinical use today, all of which are produced through semisynthesis or total synthesis. The discovery of new important anti-infectives is not limited to searching the microbial kingdom, but includes plant and animal sources as well. Artemisinin, a sesquiterpene with an unusual endoperoxide moiety, was isolated from the Chinese medicinal plant commonly known as Qinghaosu (*Artemisia annua*), an herbal remedy that had been used in China for centuries for the treatment of malaria. Subsequent efforts to develop artemisinin derivatives with more desirable pharmaceutical properties included many synthetic and semisynthetic studies, microbial transformations, biological evaluations, mechanism of action studies, and pharmacological studies of artemisinin and a number of related analogs.

Anticancer drugs:

Natural products have provided the most important successes in the chemotherapy of cancer. Most of the major anticancer drugs are unmodified natural products obtained from plants or microorganisms, and include such important anticancer drugs as bleomycin, doxorubicin, daunorubicin, vincristine, vinblastine, mitomycin, streptozocin, and paclitaxel (Taxol™). Ironotecan (a camptothecin derivative), and etoposide and tenoposide (podophyllotoxin derivatives) are examples of semisynthetic derivatives of natural products that are important anticancer drugs. Vincristine and vinblastine are complex, dimeric indole-indolines obtained from the rosey periwinkle (*Catharansus rosea*), and are among the most important therapies for the treatment of childhood leukemia, Hodgkin's disease, and metastatic testicular tumors. These unmodified natural products continue to be produced today by mass cultivation and processing of the plant material. Vinorelbine is a semisynthetic analog and has been reported to have decreased hematological toxicity.

1.Camptothecin, an alkaloid from the Chinese tree, *Camptotheca acuminata* Descne, was also discovered by Wall and Wani. Although showing promising antitumor activity, clinical studies were discontinued due to unpredictable side effects. Subsequent semisynthetic modifications led to the development of Ironotecan (Topotecin™, Campto™), a derivative of camptothecin that is now clinically available. The camptothecins act by inhibition of the topoisomerase I.

2. Podophyllin is a crude resin derived from *Podophyllum peltatum* and is used topically to treat condylamata acuminata (warts). Podophyllin contains, among other things, the lignan, podophyllotoxin, which is the chemical precursor to two important semisynthetic anticancer drugs, etoposide and tenoposide. These drugs inhibit topoisomerase II, a mechanism quite different from that of podophyllotoxin (spindle poison), thus illustrating that structural similarity alone is not always a reliable predictor of similar biological effect.

Cardiovascular drugs:

It was known as early as 1776 that extracts of *Digitalis* were effective in controlling heart disease. However, the active constituents, complex glycosides such as digoxin, digitoxin, and the lanatosides, were not isolated and structurally characterized until almost a century later. These compounds exert a powerful and selective positive inotropic action on the cardiac muscle, and are important drugs in the treatment of congestive heart failure. Perhaps due to the complexity of their structures, which include numerous chiral centers, the unmodified natural products continue to be used clinically, and also continue to be produced by mass cultivation and extraction of foxglove. In addition to the cardiac glycosides, a number of naturally occurring alkaloids are important drugs in the control of various cardiovascular conditions. For example, the alkaloid quinidine, from the bark of the *Cinchona* tree, is an important anti-arrhythmic drug.

Central nervous system (CNS) drugs:

One of the oldest CNS drugs in use is *d-tubocurarine, a neuromuscular blocker derived from a plant* (curare) used as an arrow poison by South American Indians . Also, the opium alkaloids codeine and morphine are important analgesic drugs, and continue to be manufactured by processing opium exudate and extract. Delta-9-tetrahydrocannibinol (THC), the component of *Cannibas sativa responsible for* its CNS effects, is an important drug (Marinol) used to reduce nausea associated with cancer chemotherapy. Although prepared commercially using synthetic methodology, Marinol® is identical to natural THC. Physostigmine, a naturally occurring alkaloid, and its carbamate ester, neostigmine, are acetylcholinesterase inhibitors used for the treatment of myasthenia gravis and as antagonists to neuromuscular blockade by nondepolarizing blocking agents. Galanthamine, an alkaloid that occurs in the bulbs of daffodils, is also an acetylcholinesterase inhibitor and is currently in clinical trials as a possible therapy for cognitive impairment in Alzheimer’s disease.

Cholesterol-lowering agents:

The clinically useful cholesterol-lowering agents known as the “statins” were derived from natural products isolated from a fungus. These drugs inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase(HMG-CoA reductase), an enzyme critical in the biosynthesis of cholesterol. The first such agent, compactin, was initially reported as an antifungal agent. The development of the statins is a very good example of a natural productbased discovery of an important new drug class followed by optimization of properties yielding improved drugs. It illustrates the interconnection between a natural product and its semisynthetic andtotally synthetic analogs and the determining role of molecular structure, whether constructed by nature or humans, with respect to drug properties.

Immunomodulators:

The immunomodulators cyclosporin, originally isolated from the soil fungus *Trichoderma polysporum* and tacrolimus (FK-506), a secondary metabolite of *Streptomyces tsukabaensis*, are used to suppress immunological rejection of the transplanted organs. These unmodified natural products represent major breakthroughs for organ transplantation.

DRUGS OF SYNTHETIC ORIGIN

Anti-infectives:

The important antimalarial drugs primaquine, chloroquine, and mefloquine were all patterned after the alkaloid quinine, the active constituent of the "fever tree" *Cinchona succiruba*. The effort to design better antimalarial agents has also led to the discovery of other important anti-infectives, including a class of synthetic antibacterials that is among the most prescribed in clinical use today—the fluoroquinolones. The first of the quinolones to be used clinically, nalidixic acid, was synthesized as part of a large programy the Sterling Drug Company to synthesize new antimalarials based on the quinine nucleus. The1,8-naphthyridines were observed to be antibacterial, and in 1964, nalidixic acid became available for use in the United Kingdom for urinary tract infections. In particular, it was noted that analogs carrying a fluorine at position 6 showed broader and more potent antimicrobial activity, and the class of fluoroquinolones subsequently became one of the most studied structural classes of antimicrobials. Ciprofloxacin and norfloxacin are examples of currently available fluoroquinolone antibacterials that are used extensively in both community and hospital settings.

Anticancer drugs:

Included among the most important anticancer drugs in use today are tamoxifen and methotrexate, which are both synthetic drugs. Tamoxifen was derived from the diethylstilbesterol nucleus, which itself was patterned after estradiol. First reported for its contraceptive activity in rats, tamoxifen was later found to bind to human estrogen receptors, thus paving the way for its use in the treatment of breast cancer. Tamoxifen is now one of the most widely used and successful drugs in the treatment of breast cancer. Methotrexate is an antifolate, patterned after physiological folate, is one of the most widely used antineoplastic drugs available, and shows efficacy in the treatment of a variety of neoplasms.

Cardiovascular drugs:

An examination of the pharmacological activity of tetropide, a component of the venom of the pit viper (Bothrops jararaca), led to the discovery of the role of angiotensin-converting enzyme *(ACE*) in hypertension. Using a model system for the interaction of small peptides with the enzyme, captopril was designed as a specific, orally effective ACE inhibitor. Following the success of captopril for the control of hypertension, many additional ACE inhibitors, such as enalapril, were designed and synthesized. The ACE inhibitors now constitute one of the most important classes of cardiovascular drugs.

CNS drugs:

Totally synthetic drugs have been of the utmost importance in the CNS arena since the accidental discovery of the powerful analgetic properties of meperidine in 1937 and continuing through the synthesis of the currently widely used selective serotonin reuptake inhibitors as antidepressants. Along the way, the treatment of mental illness has been revolutionized through the discovery of CNS drugs such as the phenothiazines (chlorpromazine) and thebutyrophenones (haloperidol) for psychotic disorders,the tricyclic antidepressants (imipramine) for depression, and the benzothiadiazines (diazepam) for anxiety.Of the numerous synthetic CNS drugs that are now available in medicine, just two of the newer ones will be briefly discussed for illustrative purposes.

Olanzapine (Zyprexa®) is a recently introduced atypical antipsychotic agent with a high affinity for dopaminergic and serotonergic receptors, and it also has high anticholinergic activity. A key advantageover older agents is that it is less likely to produce extra pyramidal side effects and does not produce granulocytopenia.

Histamine antagonists and proton pump inhibitors:

H1 histamine receptor antagonists are used worldwide for the treatment of allergic rhinitis, conjunctivitis, and urticaria. Since the first clinically useful antihistamines were introduced in the 1940s, over 40 first-generation H1 receptor antagonists have been marketed. Adverse CNS effects and poor receptor specificity resulting in marked sedation and anticholinergic effects, have led to the development of second-generation H1 receptor antagonists largely devoid of these adverse effects. Loratidine and fexofenadine represent two of the more common second-generation agents prescribed. Other second-generation drugs of this class include acrivastine, astemizole, azelastine, cetirizine, ebastine, and mizolastine.

Cimetidine was constructed using histamine as the lead pharmacophore, and structural optimization was accomplished by modulation of physicochemical parameters including partition coefficients and ionization constants. Separation of agonist and antagonist properties initially led to the development of burimamide, metiamide, and finally cimetidine. Additional H2 receptor antagonists introduced later include ranitidine, famotidine, and nizatidine.

Part 2.2

Synthetic drug:

Synthetic drugs are created using man-made chemicals rather than natural. A designer drug is a structural or functional analog of a controlled substance that has been designed to mimic the pharmacological effects of the original drug, while avoiding classification as illegal and/or detection in standard drug tests.al ingredients.

Some of these drugs distort the senses and cause hallucinations or psychotic side effects as well. Some of the chemical messengers, or neurotransmitters, that the brain uses to send messages throughout the body are interfered with. For example, stimulant drugs like flakka or bath salts may increase norepinephrine levels and stimulate the central nervous system, raising heart rate, respiration, blood pressure, and body temperature, and decreasing a person's need to sleep and desire to eat while making the person energetic, excitable, and talkative. Spice may have the opposite effect, acting as a central nervous system depressant, slowing down these functions and leaving users mellow and euphoric.

- Synthetic drugs are unpredictable, however, and erratic behavior may be common as well. Suicide and self-harming behaviors, violence, aggression, and psychosis, and even heart attacks, seizures, and damage to internal organs, may be potential side effects of synthetic drug abuse, NIDA reports. The risk for overdose on a synthetic or designer drug is high as the chemicals used in their creation may be unknown and may have lethal interactions in a person's body and brain. Many of these potential side effects are short-term; however, with prolonged and regular use, the physical and chemical changes made to the brain and body may become more ingrained.

MODE OF ACTION IN THE BIOLOGICAL SYSTEM:

absorption :

most orally administered drug are absorbed in the upper intestine and they must pass through the intestine wall to reach the blood supply. If the drug has a low molecule weight less than 200 . It can squeeze through small gaps between the cells of the gut wall. Majority of drugs have molecular weight>200. they have to pass through the cells lining the gut wall. Since cells are bounded b cell membranes, such have to pass through cell membranes.

CELL MEMBRANE:

the cell membrane consists mainly of molecule called phospholipids in this thee is a polar head group containing an inied phosphate group and two non polar hydrocarbon chain.

DRUG ABSORPTION:

the drugs that are too hydrophilic cannot cross the cell membrane and the are to hydrophobic cannot dissolve in aqueous environment. Therefore, drugs and must have balance of hydrophilic and hydrophobic character. For that the necessary requirements are

i. Molecular weight les than 500
ii. Not more than five H-bonds donors
iii. Nor more than ten H-bonds acceptors
iv. Log p value less than +5

polar drugs which break these rules are not usually orally active and have too b administered by Injection have to pass through the cell membranes'. Such drugs must be hydrophobic enough to cross the cell membranes.

DISTRIBUTION:

once a drugs has been absorbed into blood, it is distributed to the various tissues and organs of the body.

DISTRIBUTION AROUND THE BLOOD SUPPLY:

the major artery carrying blood from the heart is called aorta. It divides into smaller and smaller arteries and finally become extremely narrow called capillaries. Only through these capillaries the drug molecules escape in order to reach the tissues and organs. Since the entire blood volume completes one circulation in one minute. The drug also travels throughout the body within a minute.

DISTRIBUTION TO TISSUES:

the walls of the blood capillaries are made up a thin, single layer of tightly packed cells. However there are pores between the cells . The drug will escape through these pores and they need not cross the membrane. Since the plasma proteins cannot escape through these pores. The drugs bound to plasma proteins cannot reach the targets organs.

BIOTRANSFORMATION:

The reactions undergone by a drug molecule inside the body is called drug metabolism or biotransformation. The products formed during these processes from the drug molecules are called metabolites which are more polar than the parent compounds. these reactions are catalyzed by metabolic enzymes which are present mostly in liver. during this biotransformation the drugs are either activated or deactivated.

Metabolic reactions are classified as phase I and II reactions.

Phase I or non synthetic reactions:

Phase I reactions consists of oxidation or hydrolysis or the combination of those two methods which alter the drug chemically.

Oxidation reactions:

Oxidation may involve the following

i) hydroxylation

ii) oxidative dealkylation

iii) oxidative deamination

Some highly polar drugs are absorbed from the digestive system through carrier proteins. These carrier proteins floating freely in the cell membrane transport highly polar amino acids ad nucleic acid bases for biosynthesis of proteins and nucleic acids.

EXCRETION:

Drug excretion is the removal of drugs from the body, either as a metabolite or unchanged drug. There are many different routes of excretion, including urine, bile, sweat, saliva, tears, milk, and stool. By far, the most important excretory organs are the kidney and liver.

Kidneys:

- The greatest proportion of drug excretion occurs through the kidneys.
- The liver makes most drugs and remedies water soluble for removal via the kidneys.
- One-fifth of the plasma reaching the kidney glomerulus is filtered through the pores in the glomerular cell membrane. The rest passes through the blood vessels around the renal tubules.
- Substances with a low molecular weight and not bound to plasma proteins can easily pass through the cell membranes into the tubules.
- Active secretion against a concentration gradient also takes place in the tubules.

Concentration of Drug or Remedy in Plasma:

Normally, a high concentration of unbound substance will ensure its removal if it is small and water soluble. Many drugs are bound to plasma proteins. How tightly they are bound then affects how easily they can be removed when they reach the kidneys. This can be controlled by pH or the amount of free substance in the plasma.

Liver:

A few drugs are actively secreted into the bile (e.g. carprofen). Some drugs undergo enterohepatic recycling, by which the drug is excreted into the bile (often as a glucuronide) and reabsorbed from the gut after deglucuronidation by gut microflora, which may be followed by renal or further biliary excretion. In the latter case continued resorption of the drug can greatly extend its duration of action.

Renal Excretion:

A main pathway for drug excretion from the body is through the kidney; this is the primary method of clearance for polar water-soluble chemicals. The kidney receives about 173 liters of water a day and returns approximately 171 liters back to the body.

Part 2.3

Drug design:

Drug design, also known as rational drug design, is the inventive process of finding new medications based on the knowledge of a biological target. Drug design defines the design of molecules that are complementary in shape and charge to the bimolecular target with which they interact and therefore will bind to it.

PRINCIPLE DRUG DESIGN:

medicinal chemistry is applied science that is food focused of new chemical entities and their optimization and development as useful molecules . In achieving this mandate the medicinal chemist must design and synthesize new molecules. Ascertain how they interact with biological macromolecules , elucidate the relationship between their structure and biological activities, determine their absorption and distribution thought the body and evaluate their transformation.

A drug molecule traverse three phases.

1. Pharmaceutical phase
2. Pharmacokinetic phase
3. Pharmacodynamic phase

1. Pharmaceutical phase:

   the pharmaceutical phase is the taken by the drug molecule from the point of administration until it is absorbed into the circulation of the body. A drug may be administered 1. orally 2. parenterally 3. topically drug is applied to the skin and is absorbed transdermally into the lungs.

2. Pharmacokinetic phase

   this phase covers the time duration from the point of the drugs absorption into the body until it reaches the microenvironment of the receptor site. The drug once absorbed into the blood stream is transported throughout the body and reaches every organ within 4 minutes. Hence only a very small fraction of the administered drug reaches the desired target organ. In addition to this statistical imbalance the drug molecule also endures a variety of additional assaults during pharmacokinetic phase. A drug molecule may be bound proteins.

3. Pharmacodynamic phase:

during this phase, the molecule binds to its receptor. The functional groups of the drug molecule interact with corresponding functional groups of the receptor macromolecules via a variety of interaction including ion-ion ion-dipole, dipole-dipole and hydrogen boding interaction.

CONCEPT OF LEAD COMPOUNDS AND LEAD MODIFICATION:

Lead compounds:

1.lead compound is one which as some properties considered therapeutically useful. It is not indented to be used as a clinical agent. It is the starting it does not matter whether the lead compounds is toxic or has desirable side effects.

2. Lead compounds are chemical compounds that show desired biological or pharmacological activity and may initiate the development of a new clinically relevant compound. Lead compounds are typically used as starting points in drug design to give new drug entities.

- **Biological Assays :**
- Preliminary pharmacokinetic behavior can be tested through a number of whole cell assays. Most commercially successful drugs are administered orally, meaning the drug must be able to enter the bloodstream by crossing membranes in the intestines. The most common membrane permeability assay is performed by monitoring the absorption and secretion of a compound by colon carcinoma cells (Caco-2). Diffusion across Caco-2 cell membranes is considered to be a valid model for molecular transport in the small intestines
- Drugs are mostly metabolized by liver enzymes, especially the cytochrome P-450 enzyme family. The ability for cytochrome P-450 enzymes to metabolize a hit is tested with liver microsomes. Liver microsomes consist primarily of endoplasmic reticulum that contains metabolic enzymes. Hits are individually incubated in the presence of the liver microsomes. Monitoring changes in concentrations provides a sense of the rate of metabolism of each hit. Liver microsomes are also used to determine whether the hit inhibits metabolic processes.

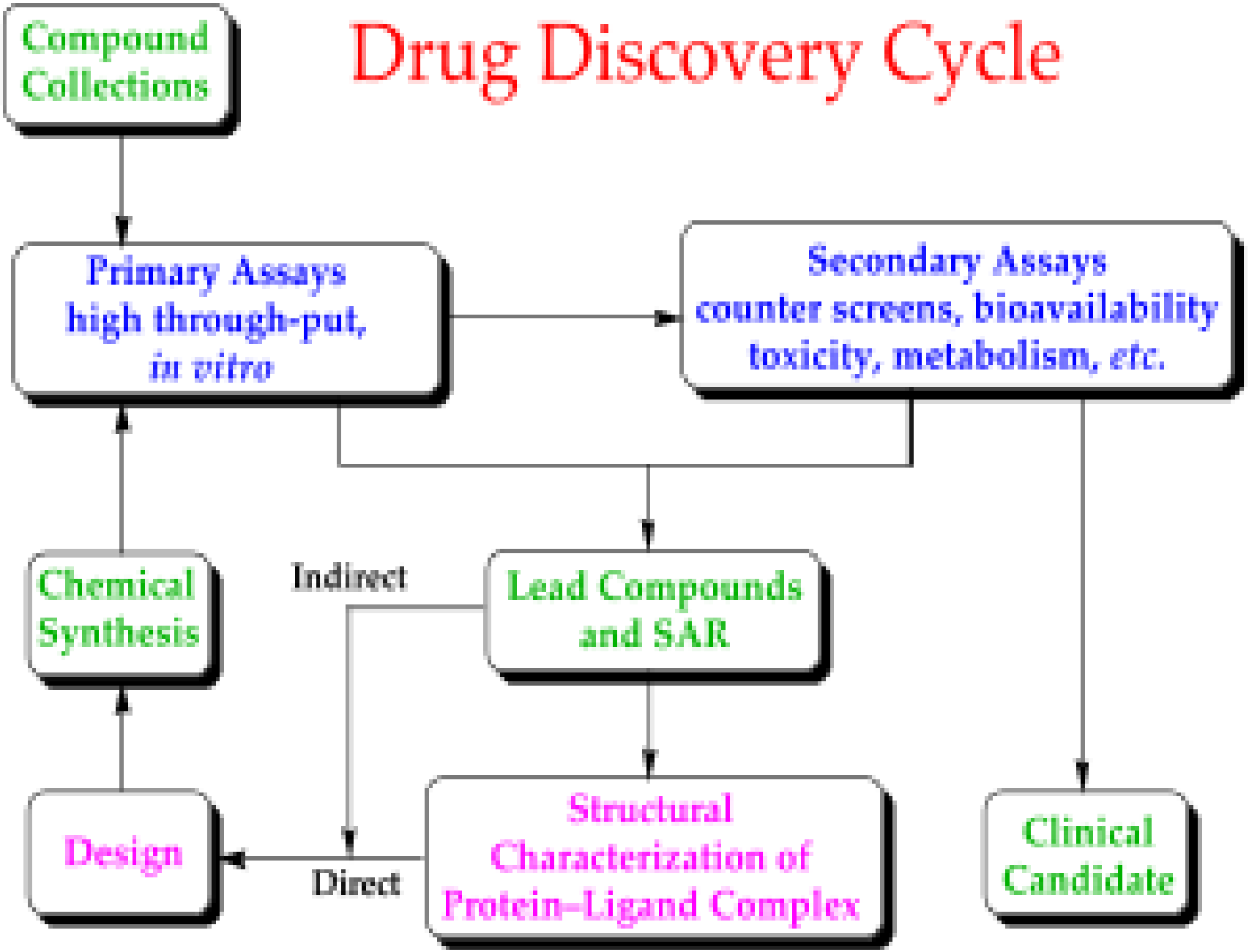
Traditional Library Screening

- The goal of screening of a library, in whole or in part, is to discover compounds with modest activity against a target. The active compounds discovered through a screen are called hits. The threshold for activity varies based on the target, but hit-level activity is typically 1 mM or lower. Targets are normally enzymes or receptors, so the term activity refers to an IC50 or EC50 value.

Development of a lead compound:

- A lead compound may arise from a variety of different sources. Lead compounds are found by characterizing natural products employing combinatorial chemistry or by molecular modeling as in rational drug design. Chemicals identified as hits through high-throughput screening may also become lead compounds. Once a lead compound is selected it must undergo lead optimization, which involves making the compound more "drug-like. This is where Lipinski's rule of five comes into play, sometimes also referred to as the "Pfizer rule" or simply as the "rule of five.] Other factors, such as the ease of scaling up the manufacturing of the chemical, must be taken into consideration.

Drug Discovery Cycle



- Drug design with the help of computers may be used at any of the following stages of drug discovery:
- hit identification using virtual screening (structure- or ligand-based design)
- hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)
- lead optimization of other pharmaceutical properties while maintaining affinity

Lead optimization phase:

- The objective of this drug discovery phase is to synthesize lead compounds, new analogs with improved potency, reduced off-target activities, and physiochemical/metabolic properties suggestive of reasonable *in vivo* pharmacokinetics. This optimization is accomplished through chemical modification of the hit structure, with modifications chosen by employing knowledge of the structure-activity relationship (SAR) as well as structure-based design if structural information about the target is available.
- Lead optimization is concerned with experimental testing and confirmation of the compound based on animal efficacy models and ADMET (*in vitro* and *in situ*) tools that may be followed by target identification and target validation.

drug development

- is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes preclinical research on microorganisms and animals, filing for regulatory status, such as via the United States Food and Drug Administration for an investigational new drug to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug
- **Pre-clinical** Many aspects of drug development focus on satisfying the regulatory requirements of drug licensing authorities. These generally constitute a number of tests designed to determine the major toxicities of a novel compound prior to first use in humans. It is a legal requirement that an assessment of major organ toxicity be performed (effects on the heart and lungs, brain, kidney, liver and digestive system), as well as effects on other parts of the body that might be affected by the drug (e.g., the skin if the new drug is to be delivered through the skin). Increasingly, these tests are made using *in vitro* methods (e.g., with

Clinical phase

- Phase I trials, usually in healthy volunteers, determine safety and dosing.
- Phase II trials are used to get an initial reading of efficacy and further explore safety in small numbers of patients having the disease targeted by the NCE.
- Phase III trials are large, pivotal trials to determine safety and efficacy in sufficiently large numbers of patients with the targeted disease. If safety and efficacy are adequately proved, clinical testing may stop at this step and the NCE advances to the new drug application (NDA) stage.
- Phase IV trials are post-approval trials that are sometimes a condition attached by the FDA, also called post-market surveillance studies
- If a compound emerges from these tests with an acceptable toxicity and safety profile, and the company can further show it has the desired effect in clinical trials, then the NCE portfolio of evidence can be submitted for marketing approval in the various countries where the manufacturer plans to sell it. In the United States, this process is called a "new drug application" or NDA.

Cost of drug development:

- In an analysis of the drug development costs for 98 companies over a decade, the average cost per drug developed and approved by a single-drug company was $350 million. But for companies that approved between eight and 13 drugs over 10 years, the cost per drug went as high as $5.5 billion, due mainly to geographic expansion for marketing and ongoing costs for Phase IV trials and continuous monitoring for safety.
- Alternatives to conventional drug development have the objective for universities, governments, and the pharmaceutical industry to collaborate and optimize resources.

Valuation:

- The nature of a drug development project is characterised by high attrition rates, large capital expenditures, and long timelines. This makes the valuation of such projects and companies a challenging task. Not all valuation methods can cope with these particularities. The most commonly used valuation methods are risk-adjusted net present value (rNPV), decision trees, real options, or comparables.
- The most important value drivers are the cost of capital or discount rate that is used, phase attributes such as duration, success rates, and costs, and the forecasted sales, including cost of goods and marketing and sales expenses. Less objective aspects like quality of the management or novelty of the technology should be reflected in the cash flows estimation.

Working with structure-activity relationships (SAR)

Working with SAR involves identifying if a structural activity relationship exists among a collection of molecules, and whether the details of one or more SAR can be uncovered. Most optimization projects try to improve drug potency, reduce the toxicity, increase the bioavailability, etc.

Currently, there are hundreds and thousands of chemical series, and it often becomes daunting to identify potential candidates. In such cases, using *in silico* methods to rapidly characterize SAR can help to efficiently capture and encode specific SAR. Computational methods, rather than providing a replacement, offer a guide to integrate and summarise large amounts of data.

However, caution needs to be exercised when interpreting SAR data. While computational methods do help to identify, explain, and predict structure-activity relationship, they are ultimately models – therefore, misuse of these methods can cause misleading interpretation of results.

Capturing SAR

1. There are mainly two methods that are used to capture and quantify SAR: statistical or data mining method and pharmacophore models. The choice of quantitative SAR methods can determine the detail to which a SAR can be explored.

2. Statistical QSARs that is based on two-dimensional descriptors often miss elements of stereochemistry that are based on the chirality of the molecule. Thus, QSARs that are based on three-dimensional approaches provide more information and can recognize ligand-receptor interactions in greater detail.

3. Various predictive models provide information regarding the new molecules and their SAR; however, all predictions are not necessarily reliable. Thus, one way to test the reliability is to probe the “domain of applicability” of a model. This parameter helps in understanding what are the exact conditions under which the predictions can be relied upon. Consequently, several methods have been developed to determine the domain of applicability of a model.

Part 2.4

Concept of drug receptors:

Receptors:

A receptor can be defined loosely as ‘a molecule that recognizes specifically a second small molecule whose binding brings about the regulation of a cellular process... in the unbound state a receptor is functionally silent’. This definition states that a receptor binds specifically a particular ligand (e.g. bombesin binds to bombesin receptors and not vanilloid receptors) but in reality selectivity is a more accurate definition as in some cases high concentrations of ligands will bind to multiple receptor types. The caveat that in the unbound state a receptor is silent holds true in most cases (particularly those encountered with current clinically useful drug-receptors) but an exception can be used to explain inverse agonism.

Receptors can be subdivided into four main classes: ligand-gated ion channels, tyrosine kinase-coupled, intracellular steroid and Gprotein-coupled (GPCR). Basic characteristics of these receptors along with some drugs that interact with each type.

DRUG–RECEPTOR INTERACTION:

- As noted above, drug receptor interaction can generally be defined as specific, dose-related and saturable. These characteristics of a drug at a receptor are described by KD and ED50 and can be obtained from ligand binding and dose–response curves.
- The equilibrium dissociation constant KD is loosely defined as the concentration of a radioligand that occupies half of a particular receptor population. The concentration used here is the in vitro concentration; clinically the mass (dose) of drug given to a patient is more commonly used (see below). KD is determined experimentally and is a measure of the affinity of a drug for a receptor. More simply, the strength of the ligand–receptor interaction. To determine KD, a fixed mass of membranes (with receptor) are incubated with increasing concentrations of a radioligand until saturation occurs. At saturation, Bmax is determined (maximum receptor number) and half of this is used to determine KD (Fig. 1). High affinity binding occurs at low drug concentrations; conversely, low affinity binding occurs at high drug concentration. If a ligand has affinity it does not necessarily mean that it will produce a response. For example, an antagonist that displays high affinity does not produce a response in its own right

Agonists and ED50:

An agonist is a drug that binds to a receptor and produces a functional response. Examples include morphine (m-opioid receptor) and clonidine (a2-adrenoceptor). The ability to produce a response is termed efficacy (or intrinsic activity); this varies with the type of response measured. This article will consider whole animal response as much as possible. The dose range over which a response is produced is termed potency. Potency of a particular agonist can be defined from the dose–response curve (Fig. 2) as the dose of drug that produces 50% of the maximum response (ED50); the maximum response itself is a crude measure of efficacy. It is important to remember that potency and efficacy are different concepts and cannot be interchanged. If an agonist has high efficacy, it does not necessarily mean that it will display high potency and vice versa. An agonist that produces the maximum response capable in that system is termed a full agonist and anything producing a lower response is a partial agonist.

Nature of receptor–drug interactions:

Receptor occupancy model:

The receptor occupancy model, which describes agonist and competitive antagonists, was built on the work of Langley, Hill, and Clark. The occupancy model was the first model put forward by Clark to explain the activity of drugs at receptors and quantified the relationship between drug concentration and observed effect. It is based on mass-action kinetics and attempts to link the action of a drug to the proportion of receptors occupied by that drug at equilibrium. In particular, the magnitude of the response is directly proportional to the amount of drug bound, and the maximum response would be elicited once all receptors were occupied at equilibrium. He applied mathematical approaches used in enzyme kinetics systematically to the effects of chemicals on tissues. He showed that for many drugs, the relationship between drug concentration and biological effect corresponded to a hyperbolic curve, similar to that representing the adsorption of a gas onto a metal surface and fitted the Hill–Langmuir equation. Clark, together with Gaddum, was the first to introduce the log concentration–effect curve and described the now-familiar 'parallel shift' of the log concentration–effect curve produced by a competitive antagonist.

- **Competitive inhibition models:**
- The development of the classic theory of drug antagonism by Gaddum, Schild and Arunlakshana built on the work of Langley, Hilland Clark. Gaddum described a model for the competitive binding of two ligands to the same receptor in short communication to the Physiological Society in 1937. The description referred only to binding, it was not immediately useful for the analysis of experimental measurements of the effects of antagonists on the response to agonists. It was Heinz Otto Schild who made measurement of the equilibrium constant for the binding of an antagonist possible.

PHYSICO-CHEMICAL PARAMETERS:

- The **physico-chemical parameters** such as temperature, pH, electric conductivity, turbidity, alkalinity, dissolved oxygen, total dissolved solid, calcium, magnesium, sodium, chloride, phosphate, biological oxygen demand, nitrate and total hardness of water were analysed in the water samples.

EXPERIMENT:

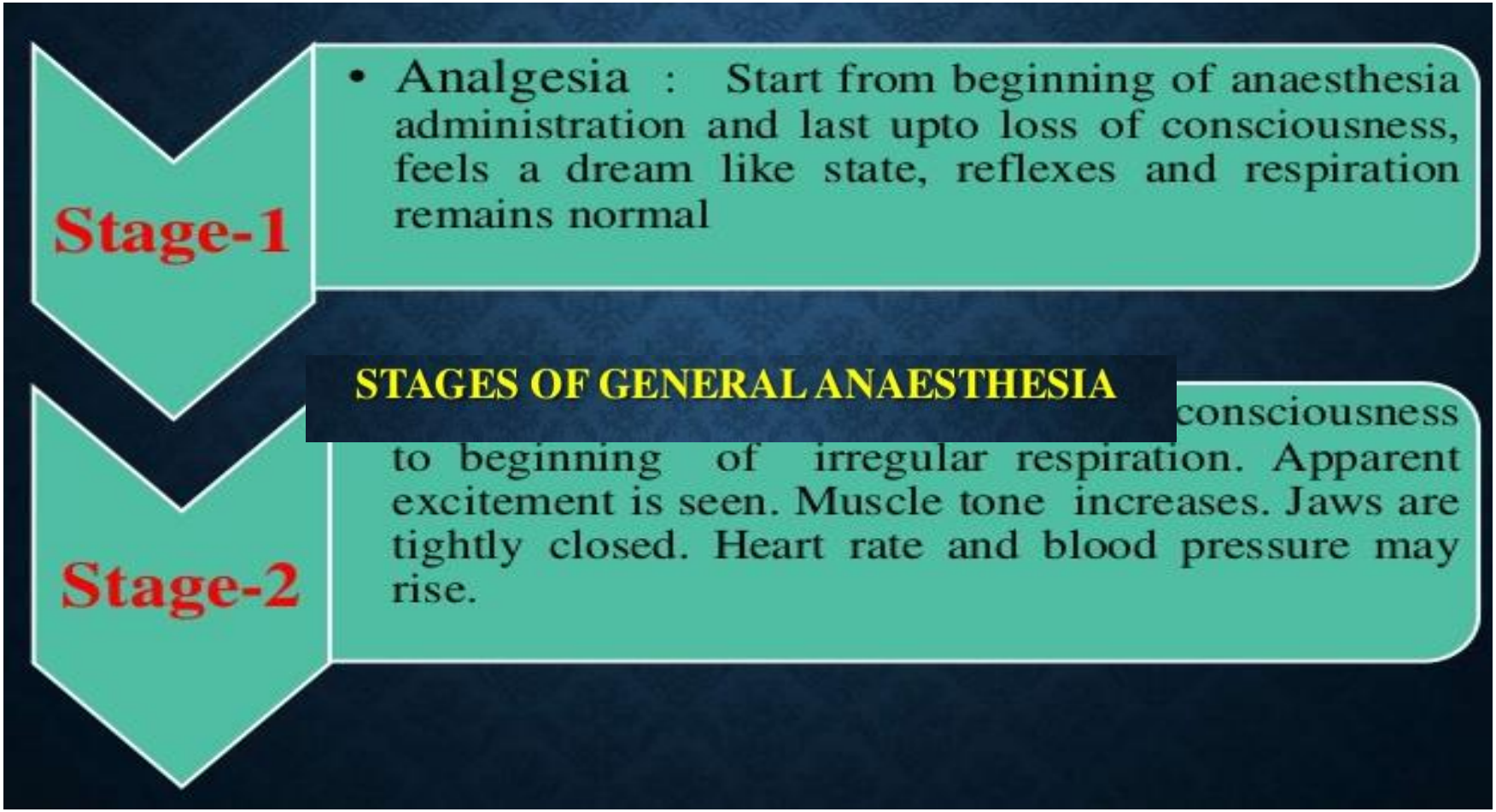
To study the physico-chemical properties of the lake water content, water samples were collected from the lake surface in a clean polythene container for the period of one year. Samples were collected using one litre container. The physical and chemical parameters were analyzed in the seasons of monsoon, winter and summer, respectively. Parameters including temperature, pH, electrical conductivity, turbidity, total dissolved solid, total alkalinity, total hardness, calcium, magnesium, dissolved oxygen, biochemical oxygen demand, chloride, sodium, nitrate and phosphate, were analyzed. We adopted standard guidelines of water sampling and physico-chemical parameters evaluation. Parameters such as temperature, pH, electrical conductivity, dissolved oxygen and turbidity, were directly evaluated in the study area whereas other parameters were analyzed in laboratory.

UNIT – V

- ANESTHETICS

- Definition : Anesthesia (an =without, aisthesis = sensation)
- The drugs which produce reversible loss of all sensations and consciousness
- Generally administered by an anaesthesiologist in order to induce or maintain general anaesthesia to facilitate surgery.

STAGES OF GENERAL ANAESTHESIA



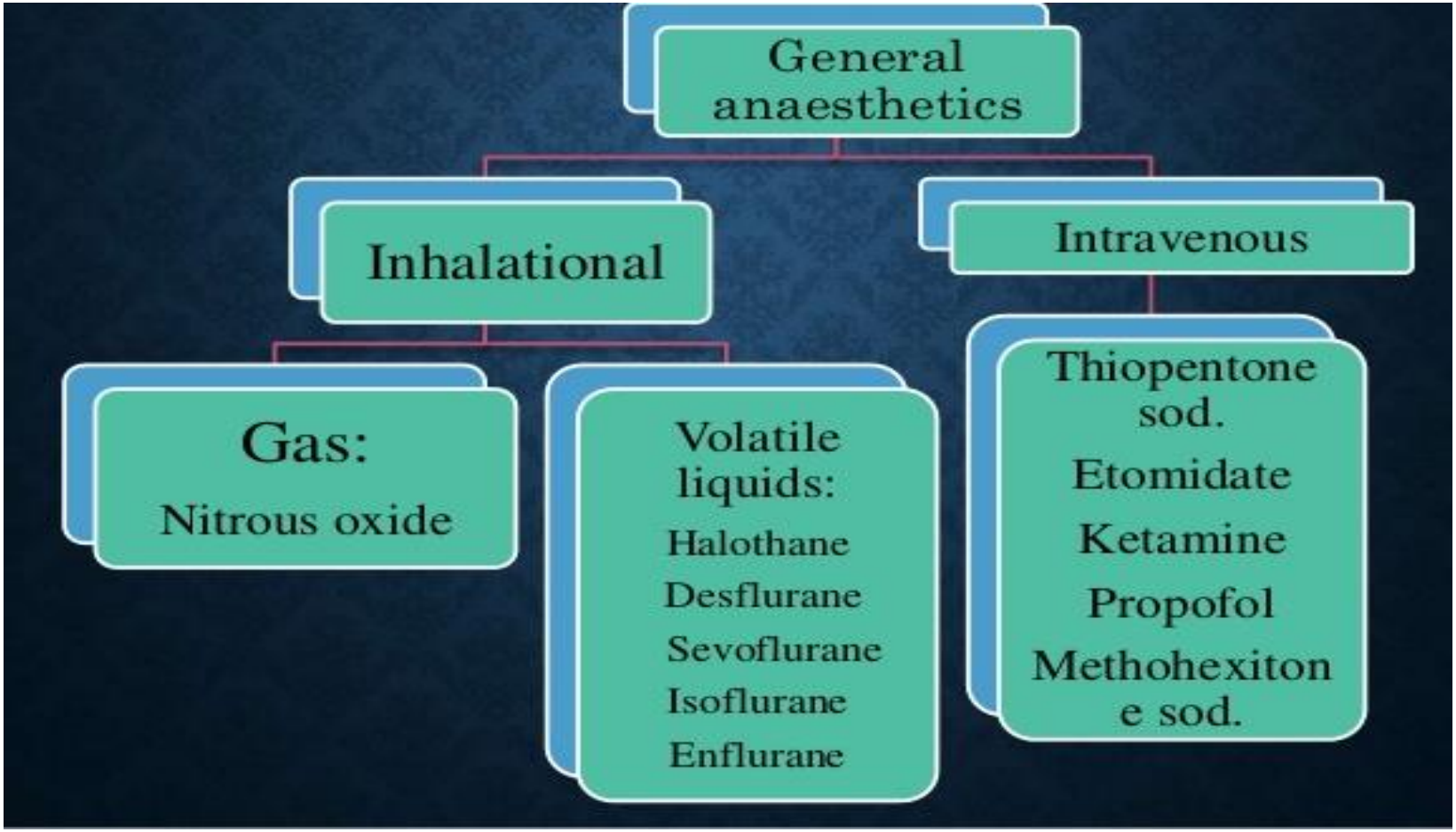
Stage-3

- Surgical anaesthesia : Extends from onset of irregular respiration to cessation of spontaneous breathing. This has been divided into 4 planes
- Plane1:This plane ends when eyes become fixed
- Plane 2: Loss of corneal and laryngeal reflexes
- Plane 3:Pupil start dilating and light reflexe
- Plane 4: Dilated pupil, decrease muscle tone ,BP falls

Stage-4

- Medullary paralysis : Respiratory and vasomotor control ceases

CLASSIFICATION



NITROUS OXIDE

- Colourless, odourless gas at room temperature.
- Very insoluble in blood and other tissues (quick recove
- Rapid induction of anaesthesia and rapid emergence following discontinuation of administration.
- Completely eliminated by the lungs.
- It is weak anaesthetic and powerful analgesic.
- The mac value is 105%.
- Causes megaloblastic anaemia.
- Used as adjunct to supplement other inhalationals.

HOLATHANE

- Volatile liquid at room temperature.
- Light sensitive
- High fat solubility => slow induction & recovery
- Eliminated unchange via lungs
- Commonly used in children, where preoperative placement of an iv catheter can be difficult
- It is marketed in amber bottles with thymol added as a preservative
- Metabolised in liver by Cyt-P450

SEVOFLURANE

- Pleasant smell , non irritant and bronchodilation makes it agent of choice for paediatric anaesthesia.
- 2nd agent of choice for
  - Neuro anaesthesia.
  - Cardiac anaesthesia .
  - Asthmatics.

- Sevoflurane reacts with soda lime used in anaesthetic circuit to form "compound A" which acts as renal toxin (nephrotoxic).
- Agents that should not be given with soda lime.

1) Trielene.(trichloro ethylene)

2) Sevoflurane.

3) Desflurane

ANTISEPTICS & DISINFECTANTS

ANTISEPTICS

- These are chemical substances

  which inhibit the growth or kill micro-organisms on living surfaces such as skin & mucous membrane.

DISINFECTANTS

- Destruction or inhibition of growth of all pathogenic organisms (bacteria, viruses, fungii) on non living surfaces
- If spores are also killed process is Sterlization

PROPERTIES OF GOOD ANTISEPTICS/DISINFECTANTS

1. Cidal
2. Non staining & good odour
3. Active against all pathogens
4. Active in presence of pus, blood & exudates
5. Rapid acting
6. Non irritating to tissues / non corrosive
7. Non absorbable
8. Non sensitizing/

Mechanisms of action of antiseptic and disinfectants

- Oxidation of bacterial protoplasm
  - Potassium permagnate, H_2O_2, Halogens
- Co-agulation (denaturation) of bacterial proteins & disrupt cell membrane
  - Phenols, chlorhexidine, alcohols, aldehydes
- Detergent like action ↑ permeability of bacterial cell membrane
  - Cetrimide, soaps

CLASSIFICATION

- Phenol derivatives:
  - phenol, cresol, hexachlorophene, chlorohexylenol (dettol)
- Oxidizing agents:
  - Hydrogen peroxide.
- Halogens:
  - Iodine, chlorine, chlorophores.
- Biguanides:
  - Chlorhexidine.
- Quaternary ammonium:
  - Cetrimide.

- Alcohols:
  - Ethanol, isopropanol
- Aldehyde:
  - Formaldehyde
- Acids:
  - Acetic acid, boric acid
- Metallic salt:
  - Mercuric compounds , silver & zinc salts
- Dyes:
  - Gentian violet, acriflavine

ANTIBIOTIC

"Antibiotic" is from antibiosis, meaning against life.

Substances derived from a microorganism or produced synthetically (Sulfonamides & Quinolones) to kill or suppress the growth of other microorganisms.

CLASSIFICATION

Antibiotics are classified by several ways:

- On the basis of mechanism of action
- On the basis of spectrum of activity
- On the basis of mode of action

MECHANISM OF ACTION OF

1. Inhibition of cell wall synthesis:

- Penicillins, Cephalosporins, Bacitracin & Vancomycin

2. Inhibition of functions of cellular membrane:

- Polymyxins

3. Inhibition of protein synthesis:

- Chloramphenicol, Macrolides & Clindamycin
- Tetracyclines & Aminoglycosides

4. Inhibition of nucleic acid synthesis:

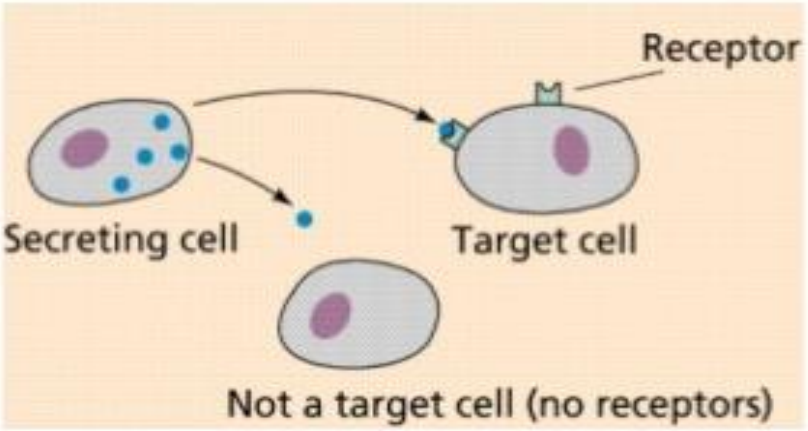
- Quinolones
- Rifampin

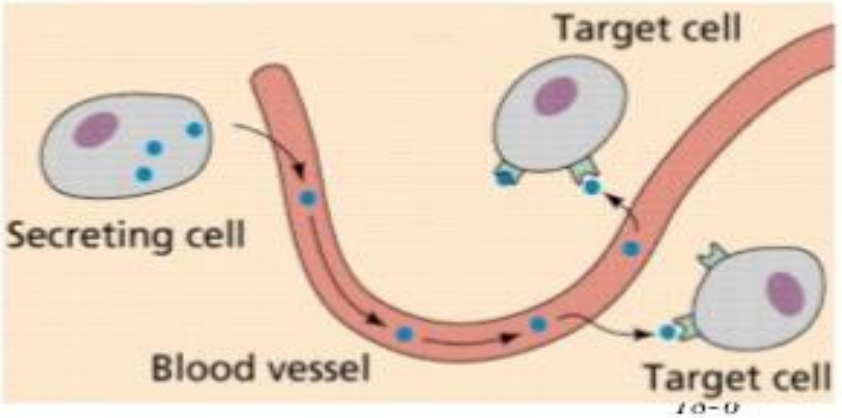
5. Inhibition of folic acid synthesis:

- Sulfonamides & trimethoprim

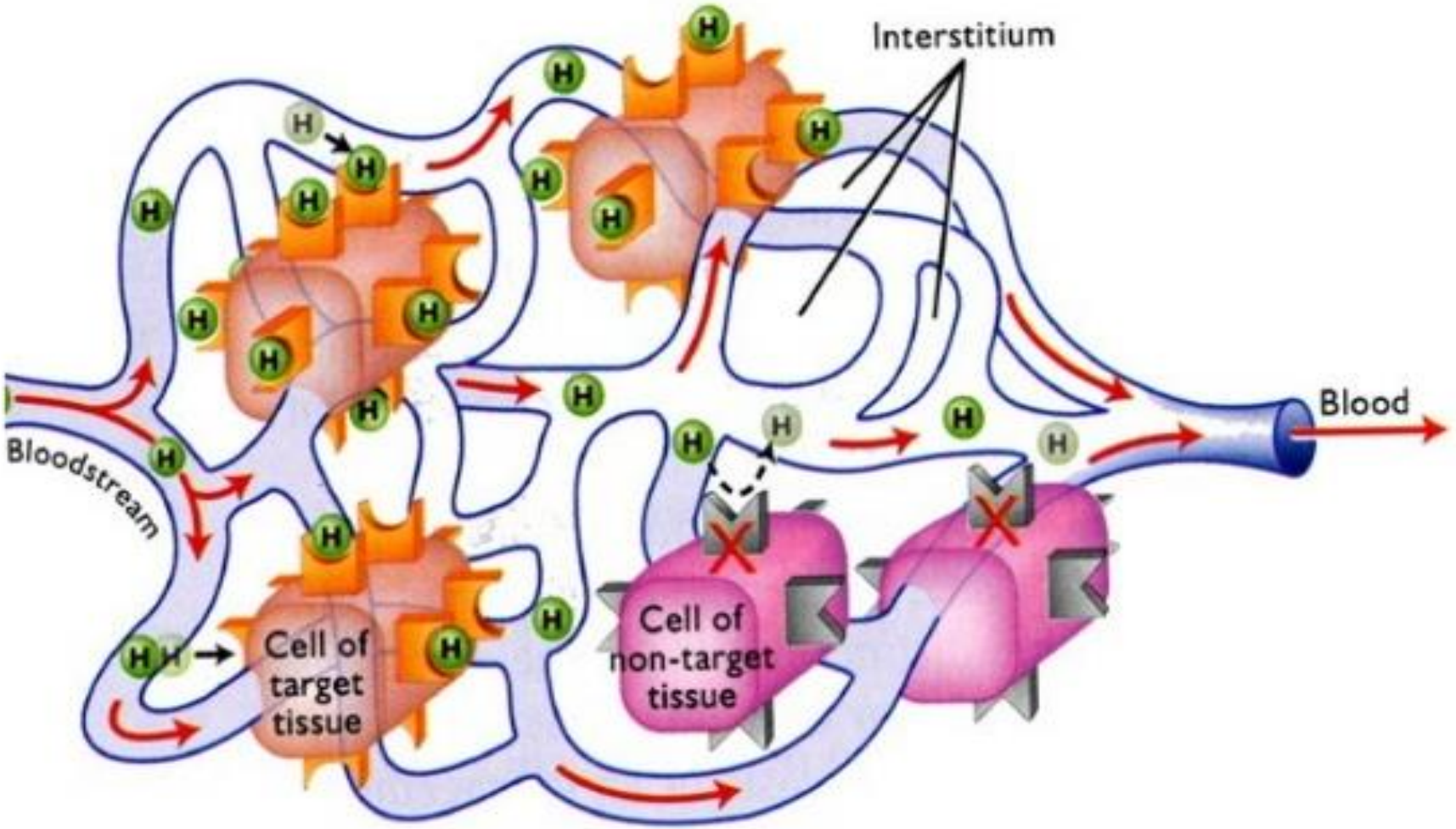
HORMONES

- The endocrine system is a collection of glands that secrete chemical messages we call hormones.
- These signals are passed through the blood to arrive at a target organ, which has cells possessing the appropriate receptor.

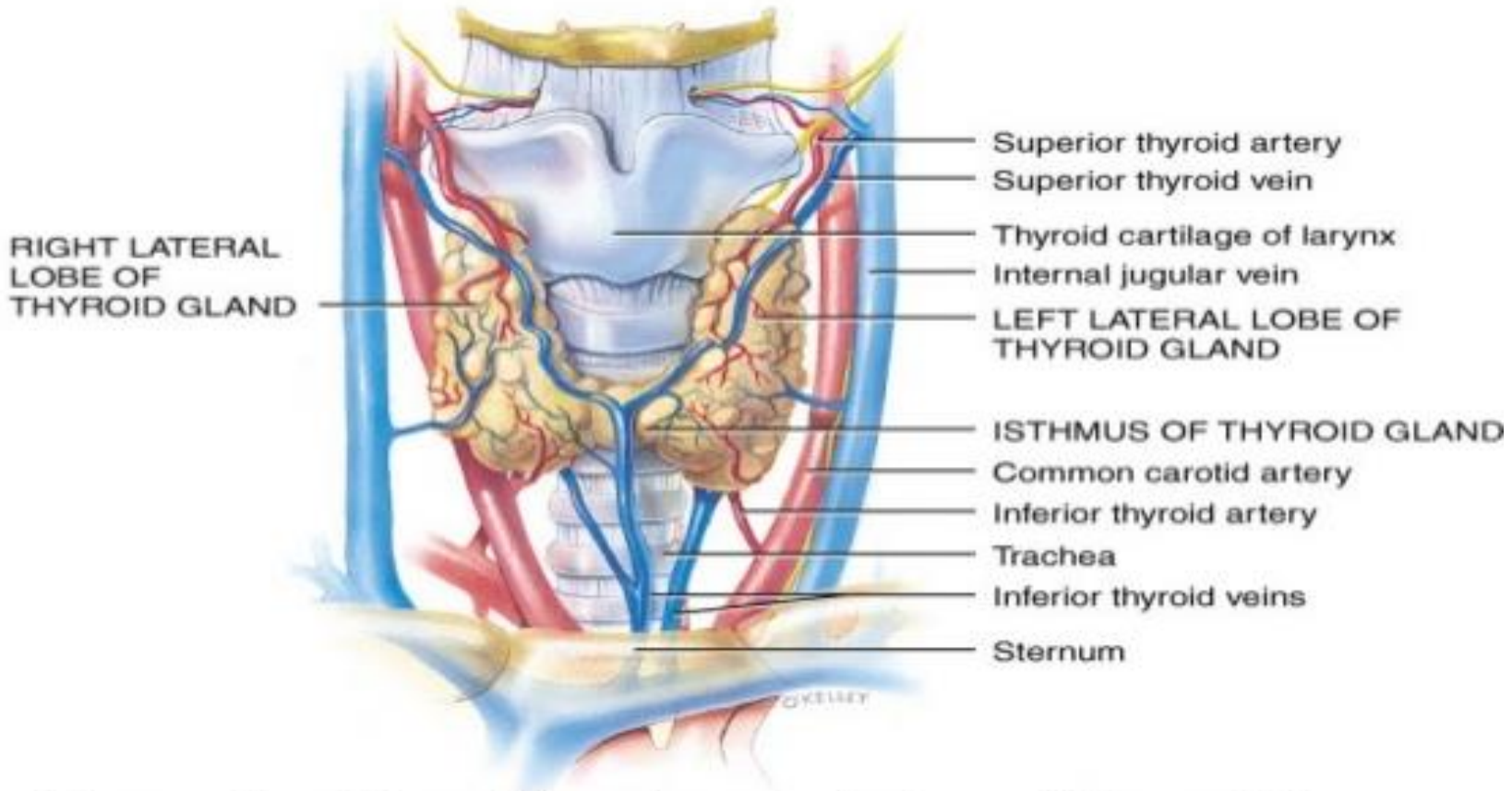




Mechanism of Hormone Action

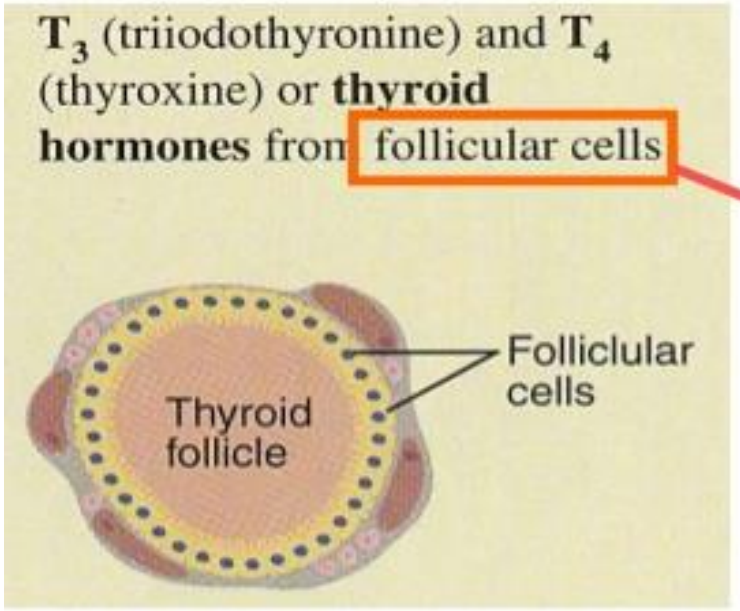


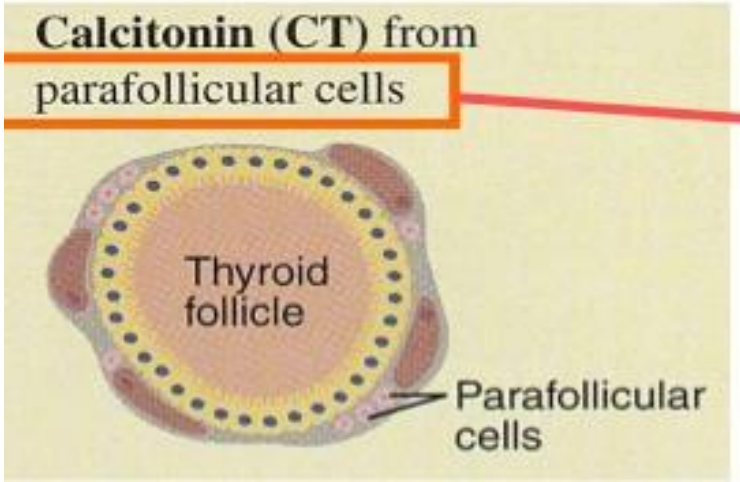
Thyroid Gland



- On each side of trachea is lobe of thyroid
- Weighs 1 oz & has rich blood supply

Actions of Thyroid Hormones

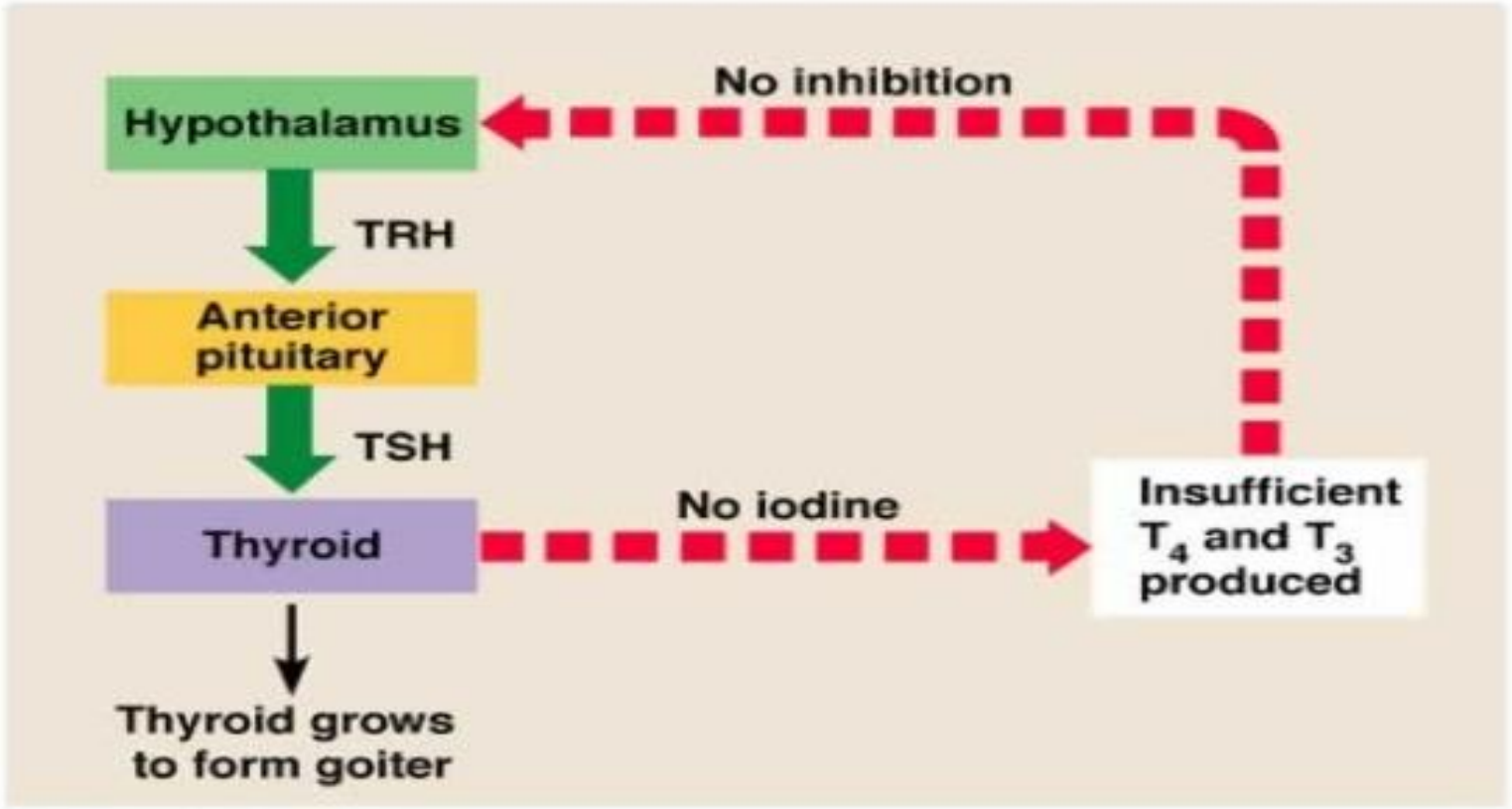




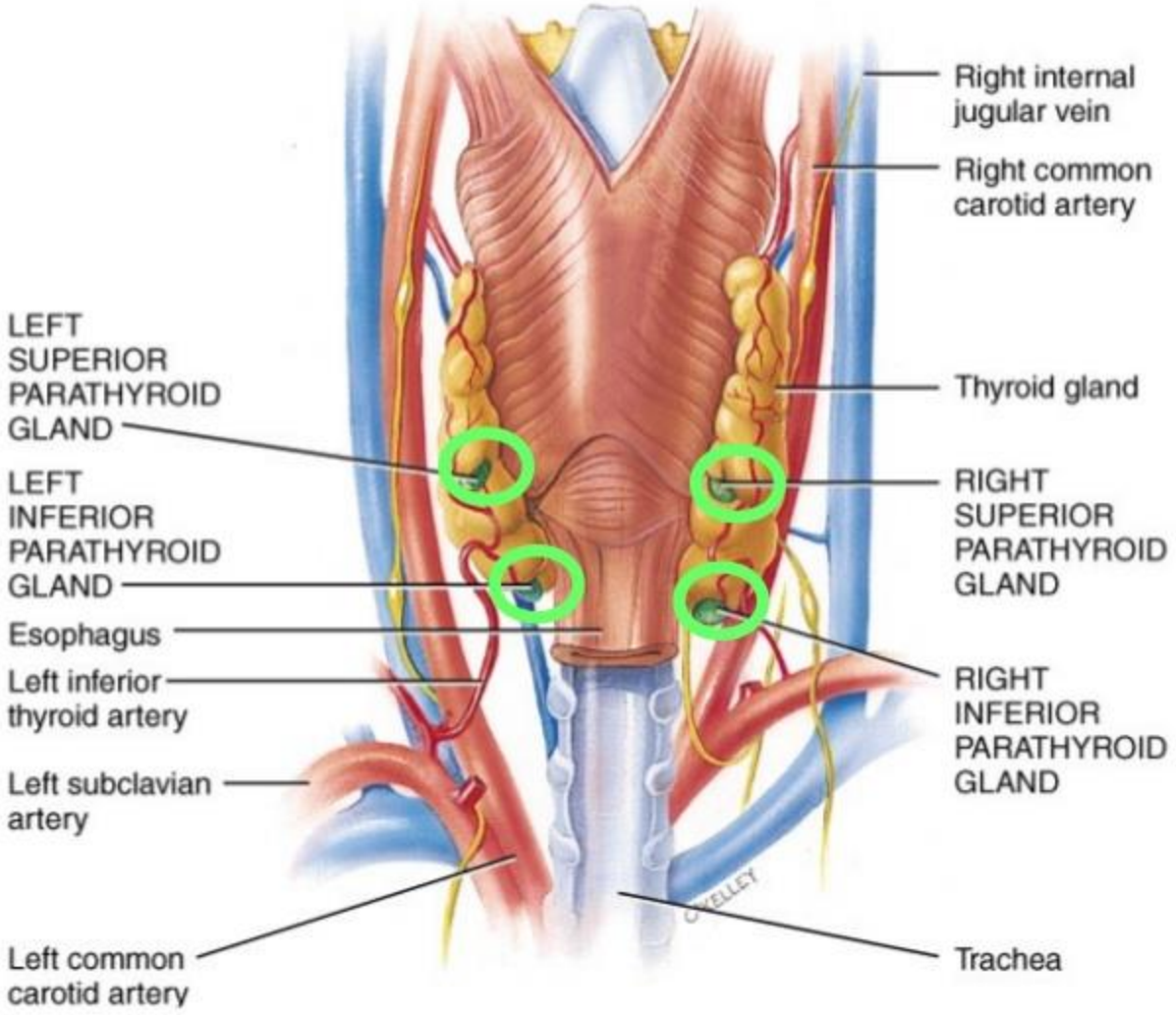
- T3 & T4 = thyroid hormones responsible for our metabolic rate, synthesis of protein, breakdown of fats, use of glucose for ATP production
- Calcitonin = responsible for building of bone & stops reabsorption of bone (lower blood levels of Calcium)

Mechanism

- ***Goiters*** A thyroid goiter is a dramatic



Parathyroid Glands



- 4 pea-sized glands found on back of thyroid gland

Parathyroid Hormone

- Raise blood calcium levels
  - increase activity of osteoclasts
  - increases reabsorption of Ca^{+2} by kidney
  - promote formation of calcitriol (vitamin D3) by kidney which increases absorption of Ca^{+2} and Mg^{+2} by intestinal tract

THANK YOU