3rd Year Pharmacy
Inorganic Pharmaceutical Chemistry

Lecture 1
Atomic and Molecular Structure / Complexation

Basic Concepts

Electronic Structure of Atoms

Subatomic Particles and their properties

Atomic Orbitals

- Quantum numbers

- Representation of Atomic Orbitals

- Atomic Orbital filling applying Hund's rule and stability considerations e.g. Cr and Cu with z= 24 and 29 respectively

The Periodic Law

Electronegativity, definition and order

Electronic Structure of Molecules; δ, л, n, л*, δ*

Columbic attraction, electron –electron Repulsion and nuclear repulsion

Covalent; sharing of electron pairs

Ionic; electrostatic interaction

Orbital Hybridization- It involves mixing of atomic orbitals to provide a new set of degenerate orbitals having different spatial orientations and directional properties than the original atomic orbitals. Examples using Be, B and C including shapes and properties, p20.

sp, sp^2, sp^3, d^2sp^3. The effect of ligand strength and the magnetic properties of the complex in determining shape e.g. octahedral, tetrahedral or square planar.

Types of Bonding Interactions

Ionic, e.g. sodium and calcium chlorides

Covalent, e.g. hydrogen, chlorine, carbon, hydrocarbons, phosphorus, carbon dioxide and hydrogen cyanide.

Coordinate Covalent Bonding, e.g. in boron-trifluride etherate.

Q: What determines the nature of a bond?

Hydrogen Bonding

Hydrogen bonding is a weak secondary interaction usually intramolecular and also intermolecular. It explains some of the unusual properties of water such as its relatively high boiling point. It is also important in describing the structures of proteins and nucleic acids

To form a H-bond, there must exist a hydrogen atom attached directly to one of the three atoms F, O or Nitrogen. These atoms have high electronegativities.

Van der Waals Forces

Van der Waals forces are weak intermolecular forces to explain important phenomena including halogens and hydrocarbons as well as drug – receptor. These interactions depend on masses and distance between molecules.

Other types of Interactions

Polar interactions as well as induced dipole interactions are week forces. However, they are important in explaining some properties of compounds as well as drug – receptor interactions and the relative stability of some isomers. Apart of the extreme cases of pure covalent bonding of homonuclear diatomic molecules and pure ionic bonding between GI and GVII atoms, these is always varying degrees of ionic or covalent character described in terms of polarity. The later depends on;

1. polarisabilty, highest for cations of high q/r
2. polarising power, highest for anions of high q/r
3. dipole moment, difference in electronegativities.

Polarisation

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Coordination Compounds

Metallic cations, especially the transition metals are able to form stable compounds with additional anions or molecules with lone pair(s) of electrons, ligands, to form complexes. The maximum number of sites of the central metal

occupied is called the coordination number.The metal and its associated ligands is called the complex ion. The later with its counter ions is called the coordination compound. The stability of a complex depends on the metal ion and the basicity of the ligand, Lewis's concept. Ligands can be bidentate, tridentate, tertradentate, hexadentate or octadenate

Bonding in Complexes

The valence bond theory is used to obtain a quantitative picture of bonding in complexes. The theory uses the idea of hybridization of the central metal atomic orbitals. The orientation of the five d orbitals of the metal in a complex is made of two sets. The d_{x2-y2} and d_{z2} orbitals are oriented along the axes of the Cartesian coordinate system. The other three; d_{xy}, d_{yz} and d_{xz} are directed between the axes.

Octahedral Complexes, 1-3 electrons

For transition metals containing 1-3 electron in the d orital e.g Cr^{+3} complexing with six cyano, CN^- ions to form $Cr(CN)_6^{-3}$. Chromium (III) is a d3 ion; that is it contains 3 electrons in the in its 3d valance orbital. These electrons are unpaired and occupy the three off-axis d orbitals, thus leaving two d, one s and 3p orbitals empty for bonding with six cyano groups. If these six orbitals hybridize six equivalent orbitals are formed and will be occupied by the six lone pairs of electrons donated by the six cyano ligands.

Octahedral Complexes, 4-6 electrons

When four or more electrons in the outer d orbital, for example complexes formed with iron(III) which is a d^5 ion, the normal ground state arrangement of electrons use different orbitals for bonding .

In hexaaquoiron(III) which is a high spin complex, with similar magnetic moment as the free ion, hybridization of six orbitals (five 4d, one 4s, and three 4p) called <u>outer orbital hybridization</u>, sp^3d^2 instead of the usual sp^3d^2 hybridization. If the water molecules in hexaaquoiron(III) complex ion are replaced with cyano groups, the hexacyanoferrate (III) ion results which has lower magnetic moment, a low spin complex. This is a result of the high magnetic field of the cyano groups of sufficient strength to repel the electrons in the two d orbitals which directly oppose the approaching ligands. The electrons become paired with those in the other d orbitals. Pairing with the six orbitals of the ligands will result in a low spin octahedral complex.

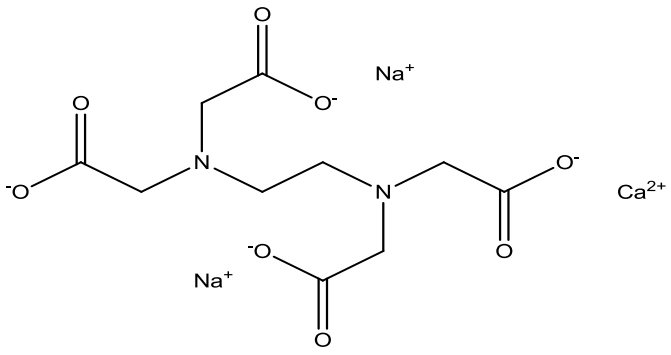
Complexes with 7-9 d electrons

Transition metal ions with seven, eight, or nine d electrons generally have coordination number of 4 which leads to either a square planar or a tetrahedral arrangement of the ligands.

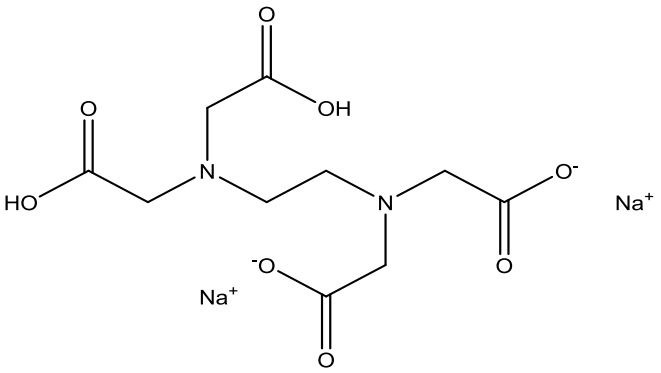
The strength of the ligand and the formation of high – and low spin complexes may be predicative of the type of hybridization and therefore the geometry of the complex. For example a d^8 ion complexing with a ligand having a relatively weak electrostatic field has no d orbitals available for bonding. However, the ligands can bond through the four sp^3 hybrid orbitals formed on the metal to give a tetrahedral complex. A strong ligand will force the metal into a low spin state and a square planar resulting from dsp^3 hybridization will be formed. The complex has one vacant d orbital.

Complexes and Chelating Agents

Chelating agents are important aspects of pharmacy, drug therapy. They have much efficacy in the treatment of heavy metal poisoning for elements such as leas, arsenic, mercury and iron. Chelating agents are important in treatment of metabolic disorders where metals such as iron and copper are accumulated in abnormal amounts in various tissues. Examples of important chelating agents include EDTA, BAL, penicillamine and deferoxamine.



calcium disodium edetate



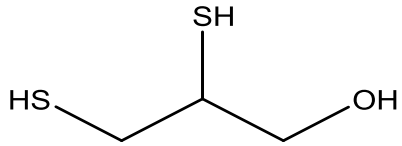
disodium edetate

<u>Disodium salt of EDTA</u> is a mixture of the dihydrate salt. It is a white crystalline granules or powder. It is odorless, slightly hygroscopic and has a faint saline taste. It is stable in air, soluble in water with pH between 6.5 and 8.0.

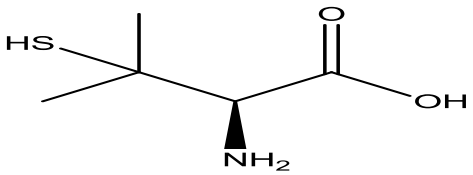
It is used in the treatment of heavy metal poisoning especially plumbsim and other metals but not for mercury arsenic or gold. An increase in the excretion of metal in the urine by 500ug/liter/24hr is an indication of poisoning. It induces hypocalcaemia states. Doses are IV or IM of 75mg/kg of body weight.

Preparation; a solution containing 200mg/ml for injection.

Disodium edetate is a white crystalline powder which is soluble in water and has pH of 4.0-6.0. It is used in treatment related to hypercalcemia including occlusive vascular disease and cardiac arrhythmias. It is not useful for dissolution of urinary calculi. Doses; IV injections of 50mg/kg of body weight. Preparation; 150mg/ml for injection.



2,3-bis(sulfanyl)propan-1-ol

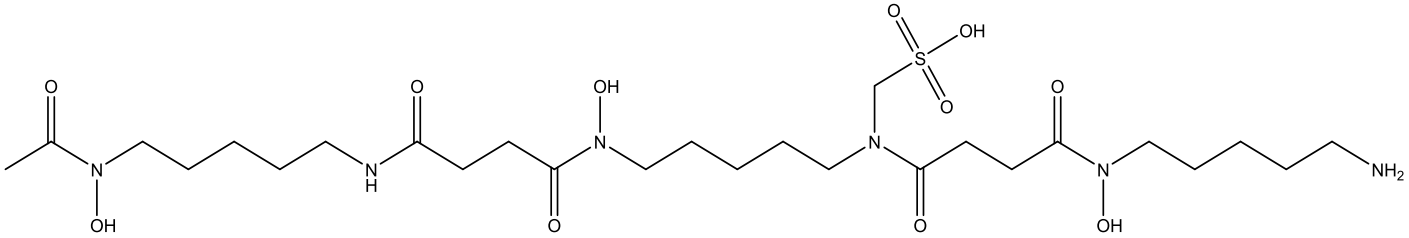


penicillamine

Dimercaprol (PAL) is a colorless of mercaptan-like odor. It competes with enzymes containing sulfhydryl groups (responsible for oxidation-reduction) for the metals causing poisoning. The mercatides formed are excreted in the urine. BAL is of value in the treatment of arsenic or gold poisoning and early mercury poisoning, within a few hours.
Dose: in severe arsenic or gold poisoning , 3.0mg/kg is given six times a day for two days, four times a day on the third day, then twice daily on the next ten days. For early mercury poisoning, 5.0mg/kg followed by 2.5mg/kg twice daily for ten days. Preparations: IM imgectio of 100mg/ml in peanut oil.

Pencillamine is a white crystalline powder having characteristic odor. It is freely soluble in water with pH of 4.5-5.5. Pencillamine is used for treatment of poisoning of many metal including lead, iron, mercury and gold. Pencillamine is is used for treatment of hepatolentecular degeneration (degeneration of the brain associated with increased levels of copper and Wilson's disease which is associated with elevated levels of copper in tissues including; eye, liver, brain and kidney. Pencillamine is used in the treatment of gold dermatitis.
Pencillamine is used in the treatment of cystinurea, the presence of crystals of cystine in urea.
Dose: 250mg capsules given four times a day. Preparations: Cuprimine capsules containing 250mg of penicillaime for oral administration.
The effectiveness of pencillamine as compared to is attributed ;
1. its ability to resist metabolic inactivation by aa oxidase since it doesn't have a hydrogen on the beta carbon atom.

2. its sulfhydryl group ability to convert Cu^{+2} to Cu^{+}, with the formation of a tetrahedral rather than a square planar complex which has less affinity in competition with the tissue proteins containing –SH groups of oxidative value.



N-[5-[[4-[5-[acetyl(hydroxy)amino]pentylamino]-4-oxobutanoyl]-hydroxyamino]pentyl]-N'-(5-aminopentyl)-N'-hydroxybutanediamide;methanesulfonic acid

Deferoxamine is for acute iron deficiency.
It forms an octahedral complex with Fe^{+3}. It has no affinity to divalent ions including Fe^{+2}. Deferoxamine is not soluble in the gastrointestinal tract so oral administration is not effective. It is produced by streptomyces as as a ferric Fe(III)complex. After chemical removal of the iron, the chelating agent is purified as the methyl sulphonate salt. Dose: IV or IM injections of 1.0g followed by 0.5g every 4-12 hours. Preparations: Desferal ampules containing 500mg of the lyophilized powder for injection.

Lecture 2
Body Major Electrolytes
Positive and Negative Ions

The Body Compartments

The electrolyte concentration will vary with a compartment. The three body fluid compartments are;

1. Intracellular fluid (45-50%) of body weight.
2. Extracellular fluid, made of two parts;

A) Interstitial fluid (12-15%) of body weight.
B) Vascular fluid or plasma (4-5%) of body weight.

The three compartments are separated from each other by permeable membranes. The later allows the passage of water and some inorganic as well as organic substances.

Ion/Chemical	Plasma	Interstitial Fluid	Intracellular Fluid

Sodium	142	145	10
Potassium	4	4	160
Calcium	5	3	--
Magnisium	3	2	35
Total	**154**	**154**	**205**
Chloride	103	115	2
Bicarbonate	27	30	8
Phosphate	2	2	140
Sulphates	1	1	--
Organic Acids	5	5	--
Protiens	16	1	55
Total	154	154	205

Units of Concentration

Electrolyte concentrations are expressed by units of mEq/l or w/w %.

Eq.wt ÷ mEq/l = mg/l

Eq./mole ÷ Mol. wt = Eq.wt

Ex.Calculate the amount of salt necessary to make a solution that contains 153mEq/l each of Na or chloride ions and state w/w %

Sodium

Sodium is the principal cation in extracellular fluid. Its responsible for maintaining osmotic pressure and hydration.

Its absorbed from daily diet by the intestinal tract.

Excess sodium is excreted by the kidneys, approximately 80-85% of sodium is reabsorbed. A complex hormone system may be involved in the reabsorption of sodium. Renin, angiotension I and II and aldosterone –produced by the adrenal cortex-which regulates the absorption of sodium in renal tubules.

Hyponatremia

Conditions causing hyponatremia (low sodium serum level) include:

1. Extreme urine loss such as seen in diabetes insipidus which caused by deficient insulin secretion by the beta cells of the islets of Langerans in the pancreas.
2. Metabolic acidosis, in which sodium is excreted.
3. Addison's disease with decreased excretion of the ADH, aldesterrone .
4. Diarrhea and vomiting
5. Kidney damage

Hypernateria

Hypernateria may be caused by:
1. Cushing's syndrome with increased in ADH, aldesterone production,
2. Severe dehydration,
3. Certain types of brain injury,
4. Excess treatment with sodium salts.

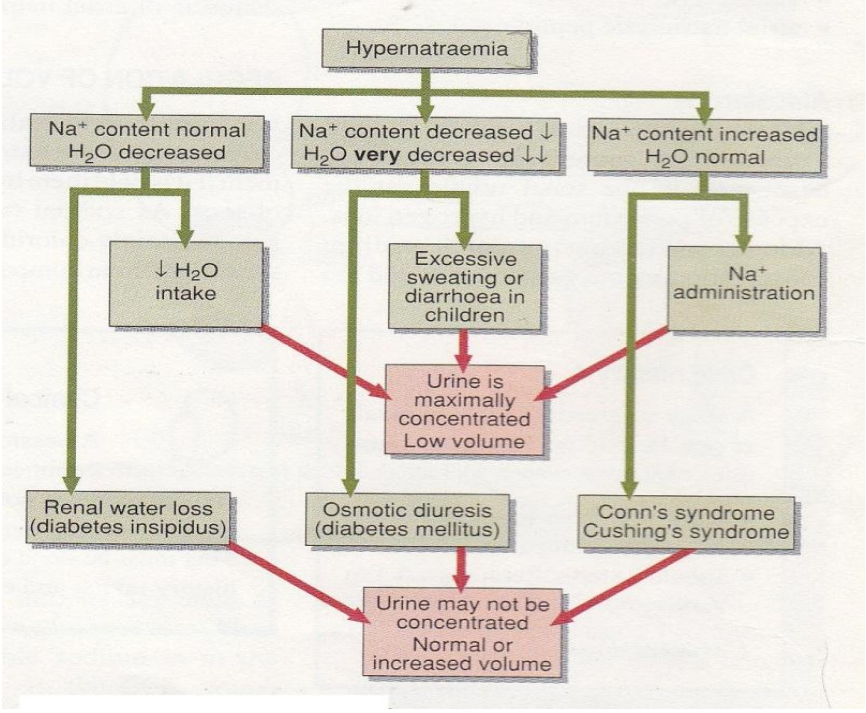
Sodium level and Hypertension

Sometimes the body is unable to eliminate sodium and the concentration starts to increase, water is retained in the tissues to maintain osmotic balance. Edema results and the patient can take a puffy appearance with swelling, particularly of the lower extremities. The buildup of fluids puts an added burden on the heart which may be aggravated if the heart is also diseased. Treatment includes low salt diets, diuretics, cardiotonic drugs or combination of each.

Sodium Control and Replacement

Sodium – free salt substitutes can be used to enhance the flavor of food. A wide variety of these are now available in the market such as Neucartasal and Co-Salt mixtures.

Sodium Chloride: Oral 1 gram three times a day or IV 1 liter of a 0.9% solution. Fructose and sodium chloride injections; 10% fructose and 0.9% NaCl. It is nutrient and electrolyte replenisher.



POTASSIUM

Potassium is the major intracellular cation present in concentrations approximately 23 times higher than the concentration of potassium in the extracellular fluid. The small fraction 2% of total body potassium which is in the extracellular fluid is distributed proportionately between the interstitial and the plasma. The concentration in serum is around 4.5mmol/l. The concentration content is maintained by an active transport mechanism. During transmission of a nerve impulse, potassium leaves the cell and sodium enters the cell, sodium-potassium pump.

Potassium in the diet is rapidly absorbed and the excess potassium is rapidly excreted by the kidneys. Potassium salts have been used for their diuretic action because of the efficient excretion of potassium by the kidneys, since a certain volume of urine will be excreted in order to keep the potassium salt in solution. Whole body counts of potassium can be found by measuring levels of potassium - 40.

<u>Hypopotassemia</u>

Hypopotassemia can be serious to the patient. It causes changes ECG and in myocardial function, flaccid and feeble muscles and low blood pressure. The main causes of hypopotassemia are;

1. Vomiting and Diarrhea
3. Burns
4. Hemorrhage

5. Diabetic coma
6. IV infusion of solution lacking in potassium
7. Overuse of thiazide diuretics
8. Alkalosis, movement of potassium into cells as protons move out of the cell into the proton deficient extracellular fluid.

Hyperpotassemia

Hyperpotassemia is less common and occurs during certain types of kidney damage. If the kidney is functioning properly the body can eliminate excess potassium readily. In certain acidotic conditions, interference with the sodium and potassium proton exchange can result in potassium retention. Potassium may be released from some damaged cells leading to increases serum potassium.

Potassium Replacement

1. Potassium chloride, irritant to gastrointestinal tract.
2. Potassium Gluconate, less irritating than the chloride.

Potassium Level and the Heart

The heart is sensitive to potassium concentrations.
In hypopotassemia there are alterations in the ECG (fattened T wave) and distict hitological alterations in the myocardium.
Hyperpotassimea also results in changes in the ECG (peaked T wave) and causes the heart muscles to become flaccid with possible cessation of heart beat (potassium unrest). It is thought that potassium may replace calcium in the cardiac muscle since a decrease in calcium will produce a similar pattern in heart muscle and may explain why calcium glutamate is effective in hyperpotassimia conditions.

CALCIUM

About 99% of body potassium is found in bones and the remaining is in ECF. Calcium is absorbed by the upper part of the intestinal track where the contents are still acidic. At neutral or alkaline media calcium is precipitated as the dibasic phosphate $CaHPO_4$, carbonate, oxalate and sulfate salts and as insoluble calcium soaps. The fatty acid portion of the soaps comes from lipase – catalysed hydrolysis of dietary triglycerides.

Calcium Absorption

Calcium absorption across the intestinal walls is controlled by the parathyroid hormone, PTH, and a metabolite of vitamin D3. The activated metabolite, 1,25-dihydroxycholecalciferol, may function as a gene activator causing the synthesis of calcium binding protein which transfer the calcium ions across the intestinal walls. Epileptic children on anticonvulsant may have low calcium levels. Phosphates concentration affects the intestinal absorption and serum calcium level. Increased serum phosphorus level will lower serum calcium. The administration of phosphorus salts has been used with some success in the treatment of hypercalcemia..

Lactose and Calcium

There is also evidence that lactose plays a role in calcium absorption with lactose-deficient patients having a higher incidence of osteoporosis.

Blood Ca ions Level and the PTH

Blood calcium levels control the secretary activity ◌the parathyroid gland: decreased blood calcium increases parathyroid secretion and vice versa. Removal of the this gland will lead to muscle tetany as a result of severe drop in calcium levels and the rise in phosphate levels. PTH controls both calcium and phosphate levels by acting on the kidneys and the bone. Administration of PTH raises the blood calcium and decreases the blood phosphate. The hormone calcitonin also affects calcium absorption. Its action on bone is to inhibit calcium resorption. In the kidneys calcitonin increase the urinary excretion of phosphate by an indirect effect. Because calcitonin produces hypocalcemia, PTH is released causing urinary phosphate excretion.

99% of the body calcium is found in bone, as hydroxyapatite. The remaining ionic calcium is involved in the neurohormonal functions., blood clotting, muscle contraction and other biochemical processes.

Calcium is necessary for the release of acetylcholine from nerve endings. Muscles become flaccid when calcium is removed or displaced. Heart muscles are affected when potassium displaces calcium in hyperpotassemia.

Another main role of calcium in body is in blood clotting. This can be avoided when citrate is added to complex calcium hence preventing clot formation in the collected blood.

Treatment is urgent if the serum calcium is greater than 3.5 mmol/l. IV saline is administered to restore the glomular filteration rate and promote diuresis. Steroids, calcitonin and IV phosphate have been used to lower calcium

concentration. Biophosphate and aminohydroxyprpoylidene have been proved to be the best in lowering serum calcium. Surgical removal of a parathyroid adenoma usually provides a complete cure. Immediately after successful surgery transient hypocalcaemia may have to be treated with vitamin metabolites.

Symptoms of hypercalcaemia fatigue, muscle weakness, constipation, anorexia and cardiac irregularities. If the conditions persists calcium sal ts may deposit in kidneys and blood vessels. Methods of reducing intestinal calcium absorption include;
1. Precipitation of calcium as insoluble calcium sulfate pr phosphate salts.
2. Complexation with EDTA.
3. Using cellulose phosphate.

Causes of Hypercalcemia
Hypercalcemia is found in;
1. Hyperparathyroidism
2. Hypervitaminosis D, e.g.in treatment of hypoparathyroidism or renal disease.
3. Bone neoplastic disease
4. Diuretic therapy, the hypercalcamea is usually mild.
5. Immobilisation: especially in young people or patients with Paget's disease.
6. Milk alkali syndrome: the combination of increased calcium intake together with bicarbonate, as in a patient self medicating with proprietary antacid.

Hypocalcemia can be caused by;
1. Hypoparathyroidism
2. Vitamin D deficiency
3. Osteoblastric metastasis.
4. Cushing's syndrome (hyperactive adrenal cortex)
5. Acute pancreatitis
6. Acute hyperphosphatemia.

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Calcium Control
When a person is fasting or sleeping reabsorption of bone takes place in order to maintain blood calcium levels.
In osteoporosis, the bones become weaker and more fragile with broken hips is commonly seen in elderly with this disease.
Page's disease is another problem associated with calcium metabolism. This may be treated using phosphate salts and or calcitonin.
Calcium Replacement:
1. Calcium chloride contains 0.033% $CaCl_2$.$2H_2O$
2. Calcium gluconate

Magnesium
After potassium, magnesium is the second most prevalent cation in ICF and the fourth most abundant cation in the body. About 50% of magnesium is in bones. It is also essential in protein synthesis and for the functioning of neuromuscular system. Electrical properties of cell membranes are affected by any reduction in extracellular magnesium concentration. Some 300 enzyme systems are magnesium dependant.
Magnesium influences the secretion of PTH by the parathyroid glands. It affects glycolysis, oxidative metabolism and transmembrane transport of potassium and calcium.

<u>Causes of hypomagnesia include:</u>
Malnutrition Dietary restriction
Chronic alcoholism
Faulty absorption or utilization
Gastrointestinal diseases
Osmotic diuresis such as occurs in diabetes mellitus.
Medications, for example treatment with immunosuppressant drug cyclosporine.
Parathyroid hormone imbalances.
The repeated demonstration of a magnesium concentration of less than 0.7 mmol/l in a serum specimen is evidence of marked intracellular depletion and of clinical condition which may benefit from magnesium therapy.
Normal subjects retain 90% of IV test material compared to 40% in patients with hypomagnesia.

Symptoms of hypomagnesia include:
Personality changes after depletion of 3-4 months.
Failure to gain weight properly. Cardiac disturbances.

Magnesium ion has a definite pharmacological action which resembles that produced by chloroform. This depressant action affects the cellular portion of the neuron and the neuromuscular junction. An excess of magnesium decreases the amount of the neuro transmitter substance, acetylcholine. Calcium ions relieve the block produced by magnesium ions and restore output of acetylcholine from nerve endings. The alkalinity of the gastrointestinal tract reduces the absorption of magnesium which normally takes place at the upper part of the intestinal tract, the duodenum.
Magnesium supplements in oral diets is complicated by the fact they often cause diarrhea. A variety of oral, intramuscular and intravenous regimes have been proposed. In any case must be taken in case of impaired kidney function to avoid toxicity.

Magnesium Replacement:
Magnesium Sulphate, when injected used as CNS depressant, 4 grams in 10% solution. Magnesium sulphate; Oral dose 1-10 grams daily.

Negative Electrolytes

Chloride

It's the major extracellular anion and is responsible for maintaining osmotic pressure, proper hydration and normal cation - anion balance in the plasma and interstitial fluid compartments. Chloride ions are absorbed from food in the intestinal tract and is removed from blood by glomerular filtration and possibly reabsorbed by the kidney's tubules. The chloride ions, as such, has no particular pharmacological activity.

Hyporchloremia
Hypochloremia can be caused by;
Salt – losing nephritis (inflammation of the kidney).

Metabolic acidosis as in diabetes mellitus and renal failure, leading either to excessive production or diminished excretion of acids leading to the replacement of chloride by acetoacetate and phosphate.
Prolonged vomiting with loss of chloride as gastric hydrochloric acid.

Hyperchloremia can be caused by;
Dehydration decreased renal blood flow found with congestive heart failure, severe renal damage
excessive chloride intake.

PHOSPHATE

Phosphate is abundant in the body and is an important ICF and ECF anion. Much of the phosphate in the body is attached to lipid and proteins. Most of the body phosphate is in bone. Phosphate changes accompany calcium deposition or reabsorption by bone. Control of ECF phosphate is achieved by the kidney, where tubular reabsorption I reduced by PTH. The phosphate which is not reabsorbed in the renal tuble acts as an important urinary buffer.
Most phosphate salts of pharmaceutical concern and are phosphate esters. Their biochemical interest are derived from phosphoric acid, commonly written as H_3PO_4 but more accurately represented as $PO(OH)_3$. This acid is also known as orthophosphoric acid. Other important phosphate forms are metaphosphoric acid and pyrophosphoric acid.
The common phosphate salts of pharmaceutical importance are sodium dihydrogen phosphate, sodium monohydrogen phosphate and sodium phosphate. In ECF the total concentration of both monohydrogen phosphate and dihydrogen phosphate is maintained in the limits 0.8-1.4 mmol/l. This phosphate must be distinguished from organically bound phosphate such as in ATP.
The main phosphate ion in intracellular fluid compartment is HPO_4^{-2}

Its main role can be summerised a follows:
1. ATP is the potential chemical energy storage which contains the phosphoric acid anhydride linkage.
2. The phosphate is important in the buffer system HPO_4^{-2}/ $H_2PO_4^-$
3. The sugars hexoses are metabolized as phosphate esters.
4. Phosphorous is essential for the proper calcium metabolism.

5. Phosphorous is essential for normal bone and tooth development since it is a component in hydroxyapatite, the main calcium salt found in bone and teeth.

Serum Phosphate and Calcium Levels

There is a correlation between serum phosphate levels and calcium levels. Whenever calcium concentrations are not within normal range, serum phosphate will either be too high or too low. In plasma, there is a reciprocal relationship between calcium and phosphate.

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Hyperphosphatemia may be caused by;

1. Hypervitaminosis D increases intestinal phosphate absorption along with calcium.
2. Renal failure due to the inability to excrete phosphate into the urine, Phosphate excretion is impaired.
3. Hypoparathyroidism, the lack of parathyroid hormone permits renal tubular reabsorption of phosphate which results in decrease of urinary phosphate and a rise in serum concentration.
4. Haemolysis may occur intravascularly in the patient, or may be a consequence of an improper sampling procedure.
5. Pseudohyperparathyroidism. There is tissue resistance to PTH.

Hypophsphatemia is uncommon because a balanced diet contains adequate amounts of phosphate. Only in patients on IV solutions hypophosphatemia may arise. It causes marked alterations in erythrocyte metabolism and may be seen in;

1. Vitamin D deficiency (rickets) probably caused by decreased intestinal calcium absorption.
2. Hyperparathyroidism, increased levels of parathyroid hormone further inhibit renal tubular phosphate reabsorption, resulting in increased urinary phosphate excretion, hence decreased serum phosphate levels.
3. Lack of phosphate reabsorption by kidney tubule from other causes e.g. infection and cancers.

4. Long-term aluminum hydroxide gel antacid therapy. This compound forms insoluble aluminum phosphate salts from dietary phosphate therapy hence preventing phosphate absorption from the intestinal tract.
Dibasic calcium phosphate is given orally as a source of calcium and phosphorus in pregnancy and lactation and calcium deficiency states.
Tribasic calcium phosphate is used a an antacid as well as a source of phosphate and calcium, usual dose 1-5 grams three times a day.

Lecture 3
Introduction of Radiopharmaceuticals
Chapter Eleven

Definitions

Isotopes are elements that have the same atomic numbers but different mass numbers. For example, Hydrogen-1, Hydrogen-2 and Hydrogen-3 are isotopes of hydrogen. They have 0,1, and 2 neutrons respectively Similarly Chlorine-35 and Chlorine-37 are the two isotopes of chlorine. For examples chlorine has two isotopes of masses 35 and 37 in the ratio of 3:1 respectively. Radioisotopes are unstable isotopes. Hydrogen-3 is an unstable isotope hydrogen.
Radiopharmaceuticals contain one or more radioactive elements instead of the stable isotope. For example, when some of the stable iodide ions are replaced by the 131 isotope then sodium iodide becomes a radiopharmaceutical.

Chemical versus Nuclear Stability

Chemical stability depends on the outer electronic shell or orbital. Atoms with full shells of outer orbitals are chemically stable. Atoms need to lose or gain electron(s) to achieve stability.
On the other hand, nuclear stability depends on the difference between the number of neutrons and protons. The bigger the gap the less stable the nuclei will be. For example carbon-14 with 8n + 6p is less stable than carbon-12 (6n + 6p). Nuclei need to reduce the gap by converting excess neutron(s) to protons and vice versa.
Most elements have isotopes. The latter are of two types;
1. Stable isotopes (maintain their elemental integrity and do not decompose to other isotopes or elemental forms).
2. Unstable isotopes or radioactive isotopes decompose, decay or emit nuclear particles into other isotopes of the same mass or different elements.

Some metastable isotopes exist or pass through metastable states which are characterized by slow rates of decay. The metastable forms decays at a rate significantly slower than the parent isotope.
Radioisotopes are found naturally or produced synthetically, usually by the bombardment of isotopes with subatomic particles.

The Products of Radioactive decay, emissions

To be stable radioactive elements (the parents) are converted the corresponding daughters with loss of one or more of the particles or radiations.The four products of radioactive decay are;

1. α particles are the nuclei of helium. They have relatively low speed and low penetration power that can be stopped by a sheet of paper.
Therefore they are useless for biological applications. Usually elements of atomic mass > 82 emit alpha particles. An example of an alpha decay is by radium-226.

…… → …… + α

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Therefore they are useless for biological applications. Usually elements of atomic mass > 82 emit alpha particles. An example of an alpha decay is by radium-226.

…… → …… + α

2. Beta particles are electrons of nuclear origin. They are either negatrons (……) or positrons (……). They are faster (~ 0.9 the peed of light) and have more penetrating power than alpha particles. They can be stopped by a thin aluminum sheet (~ 1 inch thick). For example carbon-14 undergoes decay into nitrogen-14 as follows:

…… → …… + ……

To stabilize the nucleus, beta decay converts excess neutrons into protons and excess protons are converted into neutrons.

…..→ …..+ ….. ……→ … + …… and

An example of the positron beta decay is the conversion of zinc-65 into copper-65.

…… → …… + ……

Positrons are very short-lived and converted into gamma rays as follows:

…… → …… + ……

3. Gamma radiation ( ) is a high energy electromagnetic radiation. Thick lead or concrete shielding is requiresd to protect against this harmful radiation. An example of gamma decay is the conversion of metastable cobalt-60, ^{60m}Co, into cobalt-60.

…… → …… + ……

Gamma rays emitters are used frequently in biological applications because they have sufficient penetrating power to reach deep into tissues and be detected outside the body.

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4. K-capture is produced by isotopes with unstable proton/neutron ratio but with insufficient energy to emit a positron. An inner electron (from K or L shell) is captured by the nucleus with the subsequent rearrangement and release of energy. An example is the decay of mercury-197 into gold-197. …… → …… + ……

Kinetics of Isotope Decay

A radioactive sample decays spontaneously into a stable or a metastable form by a rate depending on the type and concentration of the radioisotope.

$- dA/dt = \lambda A$ where A is the radioactivity and λ is the decay constant

It is a first order kinetics. Integration and rearrangement of mathematical equations will give;

$\log A = \log A_o - 0.301(t/t_{1/2})$ where A is the radioactivity at any time t, A_o is the initial rate, and $t_{1/2}$ is the half-life.

Radiation Units

The unit of radiation is the curie (c) which is equivalent to 3.7 disintegrations per second(DPS). The units of radiological health are exposure dose measured in roentgen (r) and the unit of the absorbed dose is the rad (radiation absorbed dose).

As different types of nuclear decay have different biological effects on tissues, the Biological Effectiveness (RBE) was introduced with X-rays, gamma rays and beta have RBE of 1 unit while alpha particles have RBE of 10-20 units depending on the particular tissue involved. Their product, the rem is commonly used to describe doses received by those working with radioisotopes. The Sv/h or Sv/a is the SI unit of instead of rem.

The radiation from a radioactive source is inversely proportional to the square of the distance from the source.

Q: A source radiating $2.0x10^5$ rads at 20cm. Calculate the radiation at a distance of 2.0m from the source.

The Biological Effect of Radiation

The destructive effect of radiation is directly related to its interaction with molecules present in the tissue to form ions and or free radicals. The later can change the local pH or initiate chain reactions forming reactive species including peroxides and ROS leading to necrosis or complete destruction of cells or whole tissues.

For example when water is subjected to radiation hydrogen peroxide and other harmful products are produced.

While alpha particles have strong ionizing power, they have low penetration. Therefore alpha emitters must be applied directly to the tissue or organ concerned. The opposite is true for gamma particles i.e. the penetration is high while the ionization is low.

Therefore alpha particles can cause more damage internally but it is not harmful if it is not in contact with body tissues because it can be absorbed, stopped, by air.

Effect of Radiation on Bilogical Tissues

The effect of radiation on a particular tissue depends on:

1. the energy of the radiation
2. the type of radiation,
3. the tissue exposed
4. the surface area exposed
5. the dose rate of the radiation

Monitoring radiation

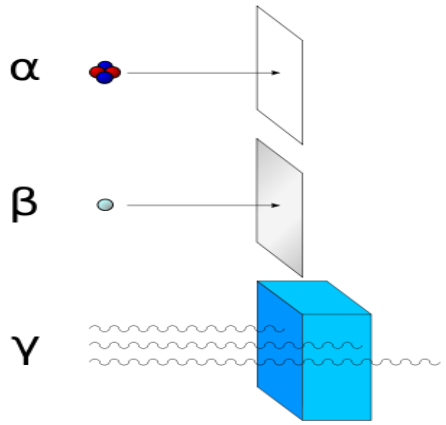
Work areas are usually monitored with Geiger Counters, GMs. The latter measure the amount of ionization caused by radiation.

Film badges and pocket dosimeter are usually carried by worker in the field of radiation. The film badge provides a permanent record of exposure based on darkening of the emulsion on the film. The darkening is proportional to the amount of radiation received.

Shielding

Shielding is a main requirement for work involving radiation. High atomic mass materials e.g. lead or concrete are widely used in this regard to protect from ionising radiation, gamma or X-rays.

The half-thickness is the thickness of material required to reduce the radiation into half its original value.



Internal Administration of radiation:

Radiopharmaceuticals are preparations containing radioisotopes which are used internally for therapeutic purposes.

Radiopharmaceuticals have the following features:

1. They are mainly gamma emitters. However, beta viz the negatron is sometimes used. In some special cases positrons emitting compounds are used.

2. Radiopharmaceuticals usually concentrate at target tissues. Areas are either of heavy or light concentrations are called **hot or cold spots** respectively. Sometimes the radioisotopes are tagged to aid in reaching the target tissue. For example serum albumin is a widely used tag material.
3. The isotopes should be able to be released from the body to be monitored.

Monitoring Radioactivity

Radioisotopes are used in diagnosis and radiotherapy. Measurement of radioactivity in diagnostic procedures involves:
1. Autoradiography.
2. Scintillation scanning.
3. Detection with GM tubes.

Autoradiography is accomplished by exposing a photographic plate over the appropriate area of the body.The autoradiography picture produced may show an outline of the tissue with heavy concentration of radioactivity (hot spot) indicating possible tumor sites or other areas of abnormal activity.
Scintillation scanning utilizes the ability of gamma radiation to excite certain molecules to higher electronic states and when these molecules return to their ground state, light is emitted (phosphorescence) at low intensity which is multiplied through several stages of a photomultiplier tube. Radiation is detected using a series of photomultiplier tubes. A secondary scintillator (wavelength shifter) e.g., are POPOP is widely used. It has an extended delocalised structure. GM tubes also used to detect and to follow radiation from diagnostic isotopes by measuring the ionizations produced in the gas within the tube.
Therapeutic isotopes are utilized for their destructive effects on tissue.
Its necessary that they have sufficient energy to penetrate throughout the tissue being treated, but radioactivity spreading to surrounding tissue is undesirable.

Effective Half-lives, t_{eff}

The time element involved in the medical use of radioisotopes is an important consideration.
Diagnostic procedure is usually rather short, and it is desirable to have the radioactive compound eliminated from the body within a matter of hours.
Therapeutic procedures usually require the presence of the isotope for a longer period of time (days or weeks). The duration of activity of the isotope in the body is determined by the physical by the half- life of the isotope ($t_{1/2}$) and the biological half-life (t_{bio}) of the preparation with k_b the rate constant of the

elimination of the radiopharmaceutical from the body. These two half-lives are combined to provide an expression for the effective half-life (t_{eff}) as follows;

$$t_{eff} = t_{1/2} \times t_{bio} / (t_{1/2} + t_{bio})$$

Radiopharmaceutical preparations normally have t_{eff} values which are very short lived, short lived and long lived if they have values less than three, up to three, and greater than five times the particular clinical procedure respectively.
After an isotope has gone ten half-lives, it has lost all its radioactivity.

Medical Applications of Radioisotopes

In addition to (i) **oral** and (ii) **intravenous** administration, there are other means of utilizing isotopes for therapeutic benefit. (iii) **Teletherapy** is employing gamma –emitting isotopes , e.g, ^{60}Co with activity as high as 2000 c, focusing radiation directly on the area under treatment for a prescribed period of time using a remote controlled shutter.
(iv) **Implantation** therapy describes various methods for direct introduction of sealed radioactive source in the form of needles, seeds or wires of e.g., ^{198}Au into tumor tissue.
(v) **Contact** therapy uses applicators containing beta-emitting isotopes as topical agents containing β emitters e.g., ^{32}P

Lecture 4
Some Pharmaceutical Preparations
Chapter Eleven

Chromium-51

Preparation sodium chromate Cr^{51} injection $Na_2Cr^{51}O_4$. Trade name is chromitope sodium, Rachromate -51.
Chromium-51 is artificially produced by neutron bombardment of Chromium-50.
The isotope is produced with the emission of γ-Rays, and the reaction is represented by $^{50}Cr\ (n, \gamma)\ ^{51}Cr$.
Chromium-51 decays by emitting a. 0.320 Mev γ-ray by K-capture , and decaying to vanadium V-51. The half –life is 27.8 days.
Uses:
Sodium chromate Cr-51 is used to
(i) diagnostically determine red blood cell mass and volume,
(ii) Determination of RBCs survival time,

(iii) Scanning of the spleen.
Chromium in the +6 oxidation state, Cr(VI), is readily taken by erythrocytes and become fixed to the globin portion of hemoglobin as $Cr^{3+.}$
This process is usually done in vitro and the cells are replaced in the blood to measure blood cell volume and mass.
Survival time is determined as the cells are destroyed, releasing Chromium-51 which is excreted in the urine. The rate of excretion of the isotope is then directly related to the time of survival of the erythrocytes. Radioactive iron will not work in this type because the iron is stored and recycled in the synthesis of new erythrocytes. The uses of sodium chromate Chromium-51 in scanning spleen involves damaging the red blood cells with heat after incubation with the isotope. The damaged cells are then reinjected intravenously where they are rapidly taken up by the spleen. The concentration of radioactivity by this organ is an indication of its ability to function properly.

Radio chromate Serum albumin Cr-51 (chromalbin)
The Chromium-51 labeled sodium chromate is not capable of chemically labeling plasma proteins with the isotopes.
The problem is associated with the Cr(+6) oxidation state and the involvement of the metal in the chromate anion.
When chromium is in the +3 oxidation state [Cr(III)] and available as a ction, i.e, $CrCl_3$ the metal readily interacts with plasma proteins but has virtually no interaction with erythrocytes.
Therefore radioactive $Cr^{51}Cl_3$ can be used to label serum albumin, a plasma protein, to determine plasma volume.
A product containing Chromium-51 labeled serum albumin is utilized in placental localization procedures, that is as a means of visualizing the position and or size of the placenta.
This preparation has the advantage over the commonly employed I-131 serum albumin in that procedures to reduce up take of the iodine isotope by the thyroid gland are unnecessary. Radiation exposure to the mother and fetus is also reduced.

Cobalt -57 and 60
Cyanocobalamin Co-57 capsules and solution.
Trade name: Racobalamin-57 Rubratope-57
also cyanocobalamin Co-60 capsules and solution

Trade name : Racobalamin-60 and Rubratope.60
These two isotopes are both used in the same diagnostic procedure.

Preparation of Co-57

Co-57 can be produced by several methods .one of these methods involving γ – irradiation of Ni^{58}: $^{58}Ni_{28}(\gamma, P)$, $_{27}Co^{57}$,and another is accomplished through proton bombardment of Fe-56 as,

$_{26}Fe^{56}(p, \gamma)_{27}Co^{57}$.

Co-57 decays by K-capture and emits a 0.123 Mev gamma ray. The half-life of the isotope is 270 days.

Preparation of Co-60

Co-60 is produced by bombardment of the stable Co-59 in a neutron reactor,$_{27}Co^{59}(n, \gamma)\ _{27}Co^{60}$.

The isotope has a half-life of a 5.27 years, emitting both beta and gamma radiation. For purpose of diagnostic measurement, the 1.17 and 1.33 Mev gamma rays are the most important.

Co-60 is present in the fallout from nuclear bomb explosions. Its half –life and emissions are responsible for the public health hazard associated with fallout contamination. The official capsules of cyanocobalamin Co-57 and 60 may contain a small amount of solid material or may actually appear to be empty. The solutions are clear, colorless to pink, having a pH between 4.0 and 5.5 and are preserved with a suitable bacteriostatic agent.

Uses: Cyanocobalamin Co-57 or Co-60 is vitamin B_{12} in which a portion of the molecules contains radioactive cobalt in place of the stable isotope of the metal. The radioactive forms of the vitamin are used in diagnostic procedures for pernicious anemia.

The basis of the test was developed by Schilling on the premise that if B_{12} is absorbed from the gastrointestinal tract, it will be excreted in the urine. Therefore, the radioactivity from an oral dose of Co-60 labeled vitamin B_{12} should be detectable in the urine of the normal patient, and absent or at significantly lower levels in the urine of the patient with pernicious anemia, since these patients lack intrinsic factor which is necessary for the proper intestinal absorption of vitamin B12.

Both oral doses of the capsules and injected doses of the solutions may be used alternately to study the effect of the liver on the intestinal absorption of the vitamin.
Recently, Co-57 has become preferred over Co-60 for various reasons:
1. Co-57 offers greater radiation counting efficiency in that the scintillation crystal detects only the singles gamma at 0.123Mev, while in the case of Co-60(has two gamma rays) or other isotopes of Co, interactions of the crystal with the gamma rays produce a scattering of the radiation (Compton effect) which reduced the efficiency of the detector.
2. Also the shorter half-life of Co-57 (270day) Co-60 (5.27Year).
3. No beta radiation and the lower of the gamma emission.
All of these mean a lower radiation exposure to the patient and particularly the patients liver, the organ which stores most of the unexcreted vitamin B_{12} and receives the largest dose of radioactivity.

Iron-59
Ferrous citrate Fe-59 and Ferric Chloride.
Trade name : Ferrutope.
Iron -59 is a beta and gamma –emitting isotope is prepared by neutron activation of Iron-58
$^{58}Fe_{26}$ (n, γ) $^{59}Fe_{26}$, which is a stable isotope in Iron metal occurring in 0.33% abundance. The half-life of $^{59}Fe_{26}$, is 45 days.
$^{59}Fe_{26} \rightarrow {}^{59}Co_{27}$ + 0.462 Mev β^- +0.271 Mev β^- +1.30Mev γ + 1.10Mev γ
The isotope is employed in diagnostic procedures relating to various aspects of iron metabolism and red blood cell formation. The preparation can be administrated orally to study the absorption of iron from GIT, and injected intravenously for determination of plasma iron clearance and turnover, and the incorporation of iron into erythrocyte.
Iron -59 has sufficient gamma radiation energy to allow scintillation counting of the radioactivity in various tissues associated with erythrocyte formation and destruction i.e., spleen, Serum, and liver from outside the body.

Gold-197 and 198
Trade name: Aurcoloid-198, Aurcoscan-198.
Radioactivity Gold-198 is short life isotope 2.7 days emitting both beta and gamma radiation.
Its produce by neutron bombardment of stable

Gold-197 according to the reaction : $^{197}Au_{79}(n, \gamma)\ ^{198}Au_{79}$.

$^{198}Au_{79} \rightarrow\ ^{198}Hg_{80} + 0.959$ Mev β^- + 0.412 Mev γ

The solution is categorize as both a diagnostic preparation for scintillation scanning of the liver , and a therapeutic preparation in the treatment of disorder secondary to neoplastic disease.

Au-198 solution is most frequently used therapeutically.

The solution is administered by intra cavity injection into the pleural and peritoneal cavities as an aid the management of pleural effusion and ascites.

Note pleural cavity is the potential space within the membrane enveloping the lung. Peritoneal cavity space of viscera.

Effusion is the accumulation of serous fluid in the pleural cavity . As cites is the accumulation of fluid in the peritoneal cavity. Theses fluid accumulation , when secondary to neoplastic disease in the area can be inhibited by the effect of the beta – radiation on the cancerous tissue cells.

Another uses for this preparation is based on a possible prophylactic benefit against the growth of more tumors after surgical removal of tumors from a major activity.

Intracavitary administration of gold -198 solution is contraindicated in the presence of (1) unhealed surgical wounds.

(2) exposed cavities (3)ulcerative tumors, the solutions should not be used until healing of the surgical wound is well under way.

Other preparation radioactive colloidal gold solutions are also used at a lower dose of radioactivity to perform diagnostic scanning of the liver.

This colloidal solution, as well as many other colloidal solutions of dyes e.g: rose bengal is taken up by and stored in the reticuloendothelial cell of the liver, which are called kupffers cells(these are phagocytic cells sometimes called macrophages)

Iodine -125 and -131

Sodium iodide I-125 solution .its trade name is Iodotope.

Sodium Iodide I-131 capsules and solution(Iodotope I-131 ,Radiocaps-131.

Iodine-131,and some extent iodine-125, occurs as an isotope in numerous radio-pharmaceutical for diagnostic and therapeutic purpose.

Iodine-131, presently the most frequently employed of the two isotopes, emits both beta and gamma radiation to produce a rather complex emission spectrum.

The isotope is present in the products of uranium fission or it may be produce through neutron bombardment of tellurium 130 yielding the isotope along with gamma and beta emission:
$^{130}Te_{52}$ $(n,\gamma)\beta^{-}$ $^{131}I_{53}$ the important emission from iodine-131 for medical purpose are the 0.608Mev beta and the 0.364 Mev gamma (from metastable xenon-131)and the half-life is 8.08 days.
Iodine-125 emits significantly lower energy radiation than iodine-131.
Produced in a neutron reactor, the isotope is formed from the conversion of xenon, with the emission of gamma and k-capture x-Radiation: $^{124}Xe_{54}(n,\gamma)K$ $^{125}I_{53}$.
The iodine-125 then decays with a half-life of 60 days, first emitting 0.027 Mev x-ray produce by k-capture and yielding ^{125m}Te.
The meta stable tellurium decays to the ground state, ^{125}Te with emission of a 0.035-Mev gamma ray.
In contrast to iodine-131, there is not beta radiation from this isotope.
Both iodine-125 and -131 can be produce in the reactor to yield essentially carrier-free isotopes that is they are free of ,or contain only trace amount of no radioactive isotopes of the same element (iodine-127) in the same chemical form.

Preparations of Iodine -125 and -131

1. Sodium iodide-131 is the most common isotope and chemical from in uses as a diagnostic aid in the study of the functioning of the thyroid gland, and in scanning the thyroid to determine size, position, and possible tumor location.
The usual procedure in the study of thyroid function is to measure the uptake of radioactive iodine in a 24-hour period. The thyroid (normal) patient will take up from 10 to 15% of the administered dose in 24 hours.
If the uptake is less than 10% the patient is hypothyroid, and an uptake of over 50% is an indication of hyperthyroidism. If the up take .
Modifications of the up take study using thyroid-stimulating hormone or blocking agents must be done to discover the etiology of any abnormality conclusively.
Thyroid scanning procedures require about two to three times radioactive dose used in uptake studies.

Iodinated I 125 and 131 Serum Albumin

2. Iodinated I 125 and 131 Serum Albumin. These preparation contain no more than 1: 60000 radioactive iodine to albumin. On IV injection of iodinated serum albumin, the radioisotope will mix homogenously with the plasma proteins in 10-15 minutes. When the radioactivity of a withdrawn sample is compared to a standard will determine the circulating blood volume. It can also be used to determine the plasma volume and simultaneous use with Cr(VI)-57 and ferrous citarte Fe-59 to determine total blood volume.
This isotope can also be used to determine blood circulating time and cardiac output.
Iodinated serum can also be used for diagnosis of neoplasms in the brain and circulating cerebrospinal flood.
In this radiopharmaceutical iodine 125 or 131 serves as the radioisotope and serum albumin as the carrier and not used for thyroid scan.

3. Sodium Rose Bengal I-131

Sodium Rose Bengal I-131 injections, Rose Bengal is dye which was used for many years as a colorimetric diagnostic aid in liver function determination.
When injected intravenously, the dye is rapidly and selectivity taken up by polygonal cells of the normally functioning liver after 30 min.
After this time the dye is excreted into the intestine.
Sodium Rose Bengal labeled with I-131 is useful as a radioactive tracer in :
The determination of liver function.
Provided information about the hepatic blood follow in the liver.
Used as indication of possible obstruction .
This preparation remains in the liver long enough to provide radioactive scan of the liver.
Sodium Rose Bengal I-131 is used to determine:
the Size , location, and the presences of abscesses, cysts, Tumor.
Since the metabolism of the dye and its uptake by thyroid are possibilities, the patient should be given (Lugol solution) at least 24 hrs before taking the preparation ,I n order to make saturation of the thyroid by iodine from lugols solution.

Sodium iodohippurate 131

4. Sodium iodohippurate 131 injections are used for kidney scan.
It is cleared from the blood, collected and excreted (80% of the administered dose) within 30-90 minutes only by the kidneys..

The resulting renograms which show the rate of absorption and excretion of the radidoisotope is monitored as radioactivity versus time and will tell about the state of the kidneys.

Mercury- 197 and Mercury-203

The main preparations of radioactive mercury are; Chlomerodrin Hg^{197} and Chlomerodrin Hg^{203}.

Hg^{197} is produced by neutron bombardment of naturally occurring mercury -196 . It has a half-life of 2.7 days and emits gamma radiation by K- Capture. Hg-203: is produced by neutron bombardment with the target isotope being naturally occurring Hg-202. This preparation has longer half-life and emits both Beta and Gamma radiation.

The two preparationHg-197 and Hg-203 are special radioactive tracer for making scintillation scans of the kidney and brain and they are considered as Mercurial diuretics

Therefore, in kidney scan mercurial diuretic preparation are taken up by the cells of proximal kidney tubules in the renal cortex.

The excretion is slow enough from these cells to allow scanning procedure of the kidney to determine the presences and location of cysts, Tumor and other abnormalities.

In Brain scan: Neoplastic and non-neoplastic lesions will concentrate radioactive (Chlormerodrin) in less time than radioiodinated serum albumin . Therefore these preparations are useful in scanning procedure to locate brain tumors and other lesion in the brain.

Advantage of Hg preparation over I-131 serum albumin

1. Less time than the radioiodinated preparations needed for concentration.
2. Simple decay pattern which simplifies the instrumentation.
3. Lower radiation exposure to the patient.

Mercurial derivatives, which is Meralluride drug given as IM to prevent being taken up of chormerodrin (used in brain scanning) by the kidney .

Advantage of Hg-197 over Hg-203

1. Shorter half-life.
2. Gamma-radiation is of lower energy.
3. There is no beta emission.
4. Lower exposure of the radioactive isotope to the patient.

Phosphorus -32, P^{32}

(Sodium phosphate P-32 solution) is the preparation of P^{32}.

This preparation is produced by neutron bombardment of element sulfur-32, yielding the radioactive isotope with the emission of a proton, an (n,p) reaction. The isotope decays by beta emission with maximum energy (1.71MeV) and half-life of 14.3days.

$^{32}S_{16}(n , p)^{32}P_{15}$ (14.3 day) $\rightarrow$ $^{32}S_{16} + \beta^{-}$(1.17Mev)

This solution is useful for oral or IV administration and for both diagnostic (the eyes) and therapeutic Red and white blood cells disorders.

Note: P is very useful in cell metabolism so as the metabolism. Therefore, the proliferating cells or cancer cells or cancer cells turnover or accumulate this isotope P-32 more than other cells.

Phosphorus -32 uses

1. Diagnostically: This isotope preparation used in location of intraocular tumor .The beta radiation of P-32 is of sufficient energy and can penetrate the tissue up to 8 mm and since eye tumor is near the surface., so they can be located through beta radiation from the outside of the body by using Geiger Counter when the difference in activity of normal and suspected tumor is 20-30% so it is tumor.

2. Therapeutically:

This isotope is used in the treatment of polycythemia vera in which there is an increase in number and mass of the RBC. The effect of radioactive isotope is to reduce the formation of erythrocytes in the body.

Phlebotomy, removing blood from the body through an incisions in the veins, must be done before or when injection of the Phosphorus-32.

Other use in therapy palliative treatment of chronic granulocytic or myelocytic leukemia but its use is less frequently. This type of leukemia in which there is increase in the number of WBC from the granulocytic series and increase in the number of immature cells.

The leukocytes are quite sensitive to the effect of radiation, giving efficacy to the isotope P-32.

The preparation is also used in chronic lymphocytes leukemia but this form of disease responds better to chemotherapy. The radiation isotope must not be used in acute form diseases. The dose of p-32 should be carefully calculated and it is dependent on:

a. Body weight.
b. Erythrocytes count.

c. Leukocyte count.
d. Platelets count.
e. It must be carefully calculated because the isotope emits high energy ionization Radiation.

Chromic phosphate P-32 Suspension [$CrP^{32}O_4$] this is another preparation of P-32 it is used therapeutically by;

(A) Intracvitry injection in the treatment of pleural effusions and ascites in much the same manner as colloidal preparation of golid-198. but this isotope has advantages over Au-198 injection which is:

1. Its beta radiation is more penetrating which will improve its efficacy.
2. It emits gamma radiation only, so less hazard to the personnel.
3. It is more economical than gold.

Interstitially injected into tumors (i.e. directly into the tumor tissue.) This preparation is insoluble (suspension) so it will remain localized because it is not absorbed or transported. So it is not taken as a source of phosphorus. This property is an advantage.

Technetium-99m

Tc-99m is used in 20 million diagnostic nuclear medical procedures every year. Approximately 85% of diagnostic imaging procedures in nuclear medicine use this isotope as radioactive tracer. ^{99m}Tc is used for imaging and functional studies of the brain,
myocardium, thyroid, lungs, liver, gallbladder, kidneys, skeleton, blood, and tumors. Depending on the procedure, the ^{99m}Tc is tagged (or bound to) a pharmaceutical that transports it to its required location.

For example, when ^{99m}Tc is chemically bound to exametazime HMPAO), the drug is able to cross the blood–brain barrier and flow through the vessels in the brain for cerebral blood-flow imaging. This combination is also used for labeling white blood cells to visualize sites of infection. ^{99m}Tc sestamibi is used for myocardial perfusion imaging, which shows how well the blood flows through the heart. Imaging to measure renal function is done by attaching ^{99m}Tc to mercaptoacetyl triglycine (MAG3; this procedure is known as a MAG3 scan. Technetium-99m can be readily detected in the body by medical equipment because it emits 140.5 keV gamma rays (these are about the same wavelength as emitted by conventional X-ray diagnostic equipment), and its half-life for gamma emission is six hours (meaning 94% of it decays to ^{99}Tc in 24 hours). The "short" physical half-life of the isotope and its biological half-life of 1 day

(in terms of human activity and metabolism) allows for scanning procedures which collect data rapidly, but keep total patient radiation exposure low.

The preparations of this isotope include:

1-Tc-99m injection

This isotope is not present in nature but it is an artificial element. All its isotopes are radioactive.Tc-99 is produced by the neutron bombardment of molybdenum -99 (Mo-99) which is also produced by neutron bombardment of Mo-98. The preparation and decay are shown in the following:

The radioisotope is obtained as sodium pertechnetate Tc-99($NaTc^{99}O_4$) by elution with sodium chloride injection from aluminum column which has been loaded with Mo-99. The entire borosilicate glass column with the elution and collection system (packed with Mo-99, sterilized and shielded) is available as Tc-99m generator. This form of preparation provided Tc-99m in an absolutely (carrier-free state).

Advantages of Tc radiopharmaceuticals

1. Short half life, 6 hours is long enough for various medical examinations to be done. Also, it is short enough for the ^{99m}Tc to be eliminated from the system without causing any harm.
2. Single gamma photon which simplifies instrumentation.
2. Absences of beta radiation (which is a powerful ionizing radiation).
4. The penetrating power of the isotope this make it easy to be detected from outside the body.
5. The carrier-free nature of the isotope eliminate the possibility of chemical toxicity.

From these reason, large dose can be given to the patient and increase the resolution and scanning rate to the patient and decrease radiation bad to the patient.

1. Sodium pertechnetate salt ($NaTc^{99}O_4$) mostly used
2. Colloidal preparation of technetium sulfide $Tc_2{}^{99m}S_7$ Tc-99m labeled serum albumin. macroaggregutes.
3. ^{99m}Tc serium albumin aggrigates
4. ^{99m}Tc –iron-ascorbic acid complex.

Sodium pertechnetate, $NaTc^{99m}O_4$

($NaTc^{99m}O_4$) is used to obtain brain scans to detect the presence and location of neoplastic and non-neoplastic lesion. ($NaTc^{99}O_4$) has an initial distribution similar to iodide. Therefore, a small amount of the isotope will be entrapped in the normal thyroid gland, and larger amounts in the hyperthyroid states. Since the perchlorate ions, ClO_4^- have the same distribution as the ($Tc^{99}O_4^-$)ion so a dose of 200-250mg of potassium perchlorate is usually given in order to block the uptake of thyroid gland and stomach to prevent the radiation exposure.
Some of the main benefits of using this radioactive substance are:

a. The radiation dose to the patient remains low because ^{99m}Tc emits gamma ray only with no beta particles.
b. ^{99m}Tc can be tagged or attached to a variety of chemicals so that it can be used for the treatment of various parts of the human body.
c. It emits the 140 keV gamma rays, which is readily detectable.
d. It is one of the most useful radioactive isomers and is widely used in nuclear medicine. It can only be produced artificially for medicinal purposes.
e. Technetium 99m has great contribution in the advancement of nuclear medicine.

Other technitium-99 preparations

$\underline{Tc_2S_7}$ This preparation obtained from sodium pertechnetate in acidic medium using sodium thiosulfate as the source in the generator. When it is IV injected, is taken up by reticuloendothelial cells in the liver, spleen, and bone marrow, in this order. It is like gold-198 preparation, used for the scan of all these 3 organs. Therefore this preparation can be used to scan these three organs with a better quality than gold-198.
Tc^{99m} labeled albumin macroaggrigates are used to obtain lung scans.
Tc^{99m}-iron-ascorbic acid and citrate complex used for renal function and scanning.

Lecture 5
Radiopaque Contrast Media

Radiopaque Contrast Media

Radiopaque media are chemical compounds containing elements of high atomic number which will stop the passage of x-rays. These types of compounds are used as diagnostic aids in radiology or roentgenology. Roentgenology involves

the use of X-rays(roentgen-rays), which are short wavelength electromagnetic radiation, in the imaging or shadowing of various internal organic structures. X-rays are capable of passing through most soft tissue so that when special photographic film or a photosensitive plate is placed on the side of the patient opposite to the x-ray source, the film or plate will become darkened in an amount proportional to the number of x-ray photons that are able to pass. Bone and teeth are the only types of tissue capable of significantly arresting the passage of X-rays.

Radiopaque materials appear light on exposed x-ray film, allowing their visualization for the diagnosis of fractures, malformations, and the like. The chemical-constituents of bone and teeth which give them the ability to stop this type of radiation are the large concentrations of calcium and phosphorus. Although these elements do not have tremendously high atomic numbers, they represent the highest available in biological systems in any significant concentration. Furthermore, they occur in close-packed structures providing large localizations of electron density. As a general rule, the more electrons in an atom or molecule the greater the chance of stopping the passage of x-rays. Soft tissues, being less dense and composed primarily of carbon, hydrogen, and oxygen, which are relatively low in atomic number, do not present a dense enough electron "screen" or barrier. For this reason skin and soft organs appear only as shadows, if at all, on x-ray film.

The most common radiopaque contain barium and iodine. The iodine compounds are covalently bonded organic iodides. These compounds are used for x-ray examinations of the kidney, liver, blood vessels, heart, and brain. Covalent organic iodides are nonionic, and the organic molecule usually has some affinity for the organ system to be studied. Only one compound of barium is useful as a radiopaque, barium sulfate. Other salts of barium exhibit some solubility and thus provide toxic barium ion. Therefore, barium sulfate is essentially the only inorganic compound in this class of agents. Although both barium and iodine do not have the highest atomic numbers, they are the most easily incorporated into molecules exhibiting relatively low toxicity. Their opacity to x-rays is dependent upon their being highly concentrated in the organ to be studied, and they have served quite well as contrast media in the x-ray examination of soft tissues.

Barium Sulphate

Barium Sulfate, U.S.P. XVIII ($BaS0_4$; Mol. Wt, 233.40 Barium sulfate insoluble in water, organic solvents, and solutions of acids and alkalies.

The insolubility of barium sulfate limits the ability of the compound to enter into chemical reactions. It will react with concentrated sulfuric acid to form the soluble bisulfate salt. Barium sulfate is the agent of choice in roentgenographic studies of the "gastrointestinal tract. Its insolubility in acidic gastric juice is a major criterion for this use.

Caution—When Barium Sulfate is prescribed, the title always should be written out in full to avoid confusion with the poisonous barium sulfide or barium sulfite.

Although barium ion generally is not available in this product, certain aspects of its pharmacology should be mentioned with respect to its toxicity.

Barium ion will produce a stimulation of all muscles. In the gastrointestinal tract, this is seen as a stimulation of the smooth muscle resulting in vomiting, severe cramps, diarrhea, and possible hemorrhage.

Stimulation of the heart muscle can produce cardiac arrest as the cause of death. Therefore, caution has been suggested in the use of $BaS0_4$ in cardiac patients. Hypertension can result from constriction of the smooth muscle of the arteries. The effect on skeletal muscle is similar, producing tremors and spasms. The systemic absorption of 800 mg of a soluble barium salt is sufficient to produce death. $BaS0_4$ is employed in suspensions of various concentrations for use in the G.I, tract. A paste of the compound will remain in the esophagus long enough for roentgenbgraphic or fluoroscopic study. The suspensions are administered orally or by enema after fasting. The major side effect associated with the use of barium sulfate suspensions is constipation. Accidental entry of barium sulfate into the peritoneal and other cavities through perforations and the like has produced little in the way of severe reactions or inflammation.

Organoiodine Radiopaque compounds.

There are a number of official iodine-containing organic compounds used in diagnosis by roentgenography. The following is a partial listing of these agents and their primary uses.

Meglumine Diatrizoate and Sodium Iodipamide

These agents are used in cerebral angiography (visualization of cerebral blood vessels) and gastrointestinal studies the meglumine salts is used in coronary angiography.

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