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Review Article

ROLE OF COPPER IN THE CLINICS OF NEUROLOGICAL DISORDERS

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INTRODUCTION

Copper is a trace element and belonging to d-block in the periodic table. It holds the 25th position in terms of amounting to about 68ppm by weight in the earth's crust. It is an essential trace element playing a major role in the body, whether be it metabolically, physiologically or functionally. It was one of the elements discovered in the ancient times and is since then known for its curative properties. In biological terms, copper is an essential metallo-element is a reddish-brown since all animal and plant cells require it to live and function[1]. It has been used in medicine for thousands of years — apparently since before the beginning of recorded history. Just as the ancients were able to derive pharmaceutically active compounds from plants, they also relied on compounds of metals such as copper, manganese and zinc for their medicines. In ancient times, copper was found useful for its curative powers — largely due to its antibacterial and antifungal properties — in the treatment of wounds and skin diseases. In modern times, it is becoming more widely recognized for its effectiveness in the treatment of a number of internal diseases including anemia, cancer, rheumatoid arthritis, stroke and heart disease. In addition, current research is confirming the role of normally ingested copper in the prevention and moderation of disease. Much of this research is based upon an improved understanding of the role of copper in the human body, *i.e.*, its role as an essential trace element needed for healthy growth and function.[2]

Biochemistry of Copper

Copper the metabolically active form exists in 2 different ionic forms Cu+ and Cu+2 due to its exhibition of 2 oxidation states which differ by units of one.[1] In the body, it moves between these two states i.e. cuprous and cupric. The latter being the most important one for Cu to induce its effect in the body. It is this state which is referred to as "metabolically active copper". But only a fraction < 1% includes this form. In the body,almost all the Cu is bound to either ammino acids or peptides or proteins decreasing the concentration of unbound proteins to almost zero. It is the bound Cu which changes its character from a biologically useful to toxic form. Thus the bound fraction of copper is high in healthy individuals and diminishes in persons with inflammatory diseases like arthritis.[3]

Biological role of Copper

Cu is known to play a major role in biological activities These include anti-oxidant effects, energy generation, tissue regeneration, incorporation of Fe into Hb and maintenance of elasticity of vessel walls. It is also known to play a major role in nerve conduction, cardiovascular system, immune system and is related to estrogen metabolism. It is very much required for women's fertility and to maintain pregnancy. It is one of the most important stimulants for monoamine oxidase, neurotransmitters like dopamine, epinephrine and nor epinephrine. Other copper containing enzymes synthesised in the liver is cytochrome oxidase necessary for reducing oxygen to water in muscles and other tissues, superoxide dismutase that yields peroxide & oxygen after degrading superoxide and

metallothionein. Cu containing protein Cu-Zn superoxide dismutase is the primary anti-oxidant defense in the human body. Though Cu-Zn superoxide dismutase requires two Cu and Zn atoms, only Cu seems to regulate the expression of functional anti-oxidant activity. It has a great role to play in energy production also. This is brought about by Cu because it forms an integral part in cytochrome oxidase synthesis. This enzyme is a part of complex IV of electron transport chain and thus in the process generates ATP by biological oxidation. Cu is essential for tissue regeneration as it plays a major role in collagen formation, which is an integrated part of connective tissue. Dopamine, epinephrine and nor-epinephrine are mainly synthesized from tyrosine by various enzymes. Tyrosinase is the first enzyme acting in the hydroxylation of tyrosine, which is a Cu containing enzyme.

Tyrosine → DOPA → Dopamine → Nor-epinephrine → Epinephrine

In a similar metabolism, melanin can also be synthesized using the enzyme tyrosinase. Hence the pigmentary disturbances during deficiency or toxicity is the result of disturbances in enzyme formation.

Cu is required for the maintenance of the elasticity of major vessel walls. This is brought about by the Cu containing enzyme Lysyl oxidase. This oxidizes 4 lysine residues together to form desmosine which makes cross-linkages in elastin.

Cu also has a role to play in normal functioning of CNS. There are two important roles that it plays.

1. It increases the concentration of HDL.
2. It forms an integral part of Lysyl oxidase and maintains the fibrous nature of Myocardium.

Cu role in neurological disorders

Metals play a pivotal role in neurodegenerative disorders, metals like Aluminium(Al), Cadmium(Cd) and Lead(Pb) are highly toxic and are reported to be associated with neurological disorders. Recent studies revealed that copper imbalances lead to chronic depression, Wilson's hepatolenticular disease. It has neurotoxic effects, which causes neurodegenerative disorders such as Alzheimer's, familial amyotrophic lateral sclerosis, unipolar depression.[4,5] . Abnormal interactions of copper or iron in the brain with metal-binding proteins (such as amyloid-beta peptide [Abeta] or neuromelanin) that lead to oxidative stress have emerged as important potential mechanisms in brain ageing and neurodegenerative disorders.[6] Oxidative stress has been implicated in the progression of Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.[7]

Copper containing enzymes and its functions in metabolism

Cu containing enzymes	Functions
1. Tyrosinase	Synthesis of dopamine, epinephrine, norepinephrine which are the important neurotransmitters. It also assists the synthesis of melanin.
2. Dopamine hydroxylase	Dopamine for normal brain function.
3. Ceruloplasmin	Required for normal Fe metabolism
4.Cytochrome oxidase	Energy production through electron transport chain in the mitochondria. Reduces Oxygen to water in muscle and other tissues.
5. Superoxise dismutase	Has an anti-oxidant property
6. Lysyl oxidase	e normal elasticity of major blood vessels.

A number of reactions essential to normal function of the brain and nervous system are catalysed by cuproenzymes such as Neurotransmitter synthesis. Dopamine-b-monooxygenase catalyses the conversion of dopamine to the neurotransmitter norepinephrine.[2]. Further, metabolism of neurotransmitters: monoamine oxidase plays a major role in the metabolism of norepinephrine, epinephrine, dopamine. MAO also functions in the degradation of the neurotransmitter serotonin, which is the basis for the use of MAO antidepressants.[5] It is also involved in the synthesis of myelin sheath which is made of phospho lipids whose synthesis depends on cytochrome c oxidase activity.[3]

Role of Genetics in diseases of Cu involvement

Diseases of copper involvement include both genetic & non-genetic abnormalities of copper. The most important of the genetic abnormalities of copper are Wilson's disease and Menke's disease. Wilson's disease is an autosomal recessive genetic disorder caused by mutations in both copies of the ATP7B gene. This gene has a role to play in a pathway in the liver for biliary excretion of excess copper. But Wilson's disease cannot be

diagnosed based on the mutation screening, it is because these mutations vary amongst populations and in almost all populations, no one mutation dominates to a level accounting for 50% or more of all mutations. New mutations involved in Wilson's disease are constantly being found and it is said that there are now about more than 200. Many syndromes result from heterozygosity for the wilson's disease gene, causing mild Cu accumulation , but causing no medical problems with the usual intakes of Cu. When main source of nutrition or water has a high content of Cu, Wilson's disease can become dominant and manifest in heterozygotes. To keep upto date information on mutations discovered that cause Wilson's disease (www. geneclinics.org/profiles/Wilson/details. html can be referred).

Menke's disease is an X-linked inherited disorder which is caused by a mutation in the ATP7A gene. Both the protein made by ATP7B gene are membrane -bound, Cu -transporting ATPases. Failure of ATP7A function in intestine leads to a failure of Cu efflux from intestinal cells, accumulation of Cu in the intestine, a failure of Cu absorption into the blood. In those mutations, where some function of ATP7A function is retained, it causes a milder syndrome called the occipital hormone syndrome. Aceruloplasminemia is an autosomal recessive disease caused by mutations in the Cp gene. There will be total absence of Cp in the blood. It is an iron accumulation disorder causing clinical problems in the brain and liver.

Cu levels in serum, CSF, and urine as diagnostic parameters for neurodegenerative disorders

Diagnosis of neurodegenerative disorder is of a complex phenomenon. Diagnosis of most of the disorders is based on the clinical symptoms eminently, the appropriate knowledge of the 'cardinal signs' and its application in the diagnosis increases the possibility of guessing the disease right, regrettably the definitive approach is only obtained in the autopsy for most of the disorders. A combination of various laboratory parameters is necessary to firmly establish the diagnosis. These laboratory parameters should be coupled with other parameters for accurate diagnosis.

Copper has been implicated as one of the important etiological factor in many of the neurodegenerative disorders. Evidence for changes in the copper levels of the brain are associated with the neurological symptoms is available from both human and animal studies.[8] Also, altered concentrations of Copper in the CSF in the diseased conditions are reported.[9] It is understood that copper is normally resorbed in the proximal convoluted tubules of the kidney, as under normal conditions very little copper is excreted in the urine.[10] Copper levels in blood are very misleading in the sense that blood levels can be very low in persons who have severe copper overload. The classic example for this is Wilson's disease in which copper accumulates in liver but exhibits very low levels in blood. As per Carl Pfeiffer Cu toxicity is more common, but Cu deficiency extremely rare.[11]

In the event of above facts Cu levels in serum, CSF and urine should be used as very important diagnostic tools along with other clinical, molecular techniques to diagnose the neurodegenerative disorders. Copper in the blood is in the unbound form. Serum copper indicates the total amount of copper in serum. Serum ceruloplasmin indicates the fraction of serum Cu that is bound as ceruloplasmin. It is reported that the normal or healthy situation is to have about 80-95% of the serum Cu present as ceruloplasmin.[11] Copper availability may not have an impact on the rate of synthesis and secretion of apoceruloplasmin but this metal is critical for the stability of the protein and an inability to incorporate copper results in the secretion of an unstable apoprotein, which is rapidly degraded.[12] Decrease in serum ceruloplasmin levels will give an indication of the copper homeostatic imbalance which is noticed in the neurodegenerative disorders like AD, PD etc. Ceruloplasmin is also involved in the normal brain iron metabolism.[13] So altered serum ceruloplasmin level is a pathway to diagnose and consider the thinking towards the diseases resulting due to impaired iron homeostasis. Serum copper and urine copper contents are important reference index for diagnosing the disease, with guiding significance for timely monitoring and controlling serum and urine copper excretion. This will be of great help in making the comprehensive diagnosis.[14]

Damage to the tight regulation of copper transport in the cell may lead to the neurodegenerative conditions.[15] Ceruloplasmin does not cross the blood brain barrier.[13] However, increased concentrations of copper may be found in brain and CSF which

may be due to the fact that alterations in the concentrations of copper in the blood.[8] Weisner et al., reported decreased serum copper level during the initial stages of treatment in Wilson's patient but CSF copper level was high in the initial stages of treatment, which decreased as clinical symptoms improved. This suggests transport of copper from CNS to the CSF.[16] So CSF analysis for copper levels becomes very important tool giving an idea indirectly regarding the concentration of copper in the brain. One of the most important diagnostic tests used in Wilson's disease is 24-hour urine copper test.[17] Since there is very little copper excreted in urine in normal conditions alteration in the level of copper in urine gives very valuable information. This is not only useful in diagnosis but also helpful during the treatment regime of any neurodegenerative disorder. Various rapid, simple and reliable methodologies have been reported to measure serum and urine copper levels.[19]

Therapeutic role of Cu

The first modern research on the subject of copper medicinal substances was by Professor John R. J. Sorenson, of the University of Arkansas for Medical Sciences, College of Pharmacy, who, in 1966, demonstrated that copper complexes have therapeutic efficacy in the treatment of inflammatory diseases using doses that are nontoxic. Since then, copper metallo-organic complexes have been used to successfully treat patients with arthritic and other chronic degenerative diseases. More than 140 copper complexes of non-steroidal anti-inflammatory agents (aspirin and ibuprofen, for example) have been shown to be more active than their parent compounds. Copper aspirinate has been shown not only to be more effective in the treatment of rheumatoid arthritis than aspirin alone, but it has been shown to prevent or even cure the ulceration of the stomach often associated with aspirin therapy.[2]

Cu is an essential trace mineral and is needed for good health and wellness. It can be of great therapeutic significance when used judiciously. It is an essential metallo-element since all animal and plant cells require it to live and function, and it cannot be synthesized in the body but must be obtained through the diet.[20] Copper is not only required for normal metabolism but is also a vital factor in the cure of a number of diseases. It has been used in medicine for thousands of years — apparently since before the beginning of recorded history. Pharmaceutically active compounds were derived from metals like Cu in the earlier days In ancient times, copper was found useful because of its curative powers — largely due to its antibacterial and antifungal properties — in the treatment of wounds and skin diseases. In modern times, it is becoming more widely recognized for its effectiveness in the treatment of a number of internal diseases including anemia, cancer, rheumatoid arthritis, stroke and heart disease.[2]

Copper can help with the following:

Aneurysm / Increased Rupture Risk- copper should be taken for the connective tissue strengthening effect as it acts as a co-enzyme for lysyl oxidase. Hence is of great help in cases of improper circulation.

Wound Healing -Copper works with vitamin C to create strong collagen, and it creates cross-links in collagen and elastin that give strength to proteins. Thus role of copper in the biosynthesis of bone and connective tissue has been well established. A German physician first observed the role of copper in healing by this process. For example, copper complexes heal gastric ulcers five days sooner than other reagents.[2] Copper is also known to play a critical role in the synthesis of the natural antioxidant called copper/zinc superoxide dismutase (SOD).

Osteoporosis – Osteopenia- Copper is required for strong bone formation.

Rheumatoid Arthritis -Copper has a mild anti-inflammatory effect. This can probably explain use of copper bracelets in the treatment of arthritis. Copper in the bracelets reacts with the fatty acids in the skin to form copper salts that are absorbed into the body. The same action of Cu is implied in the treatment of osteoarthritis.

Zinc Toxicity- Low doses of copper will help restore the imbalance between zinc and copper caused by long term excessive zinc intake as the two have actions that are contradictory to each other.

Anticonvulsant Activities of Copper Complexes- The brain contains more copper than any other organ of the body except the liver, where copper is stored for use elsewhere. This fact suggests that copper plays a role in brain functions. Copper has a role to play in the prevention of seizures. It was

found that copper complexes of all anti-epileptic drugs are more effective.[2]

Anticancer Activities of Copper Complexes- The serum levels of Cu are often elevated in animals and humans with cancer.[21] It appears that this elevation in Cu levels occurs as a part of the body's response to the cancer, rather than its cause. Most tumor cells have decreased CuZnSOD activity compared to normal cells, and it has been suggested that the elevation in serum Cu is a physiological response designed to activate CuZnSOD or other copper enzymes in cancer cells to inhibit their growth.[22]

Therapy for Cu deficiency

Cu is a trace element and is hence found in trace amounts .The serum concentration of Cu in males amounts to about 0.99 microgram/ml and in females it is 1.02micrograms/ml.[1] The concentration of Cu is the maximum in brain and liver. But it is as well found in the skeletal system i.e. bone marrow, muscle and spleen.[21] In the brain its concentration is about 6.5 +/- 1.5 mg.[22] It has been found out that the levels of Cu and other metals that are in the body generally tend to be higher in newborns. Its levels keep on decreasing with age. Normal newborn canine hepatic copper concentrations are higher than those seen in mature humans.[23] In pregnancy, the demand for Cu is high as it plays a major role in the normal neurological development of the fetus as small deficits in dietary Cu produces substantial changes in fetal brain enzymes.

We also know that Cu plays a major role biologically and hence its deficiency can lead to imbalances in the body functions.However,clinically evident or frank Cu deficiency is relatively uncommon.Serum cu levels and ceruloplasmin levels may fall to 30% of normal in cases of severe Cu deficiency.One of the most common clinical signs of Cu deficiency is anaemia.[3,26] Symptoms of Cu deficiency mainly leads to impaired body functions such as improper Oxygen carrying capacity of the blood due to improper incorporation of Fe into Hb and subsequently leading to anaemia, Aortic aneurysm can be the result of impaired connective tissue function, Minkey's Kinky Hair Syndrome, precipitation of chronic depression.[25] Cow's milk is relatively low in cu and cases of cu deficiency have been reported in infants and children fed only cow's milk formula. Premature infants,infants with prolonged diarrhoea, malabsorption syndromes patients. Individuals with celiac disease, sprue and short bowel syndrome.[3,24] The basic therapy would be to increase the intake of foods rich in copper, such as legumes (especially soybeans), nuts, cocoa, black pepper, seafood, raisins, molasses, avocados, whole grains, and cauliflower. Nutrients Supplement Suggested Dosage comments that it is important to have an intake of 5-mg Copper daily for 1 month then reduce to 3 mg daily. Take with 100-mg vitamin C for better absorption.[26]

Symptoms of Cu overdose

Acute overdose by ingestion may cause vomiting, abdominal pain, diarrohea, and jaundice. External contamination from copper can result in hair discoloration (green). In body as a whole, its overdose can lead to burning sensation, metallic taste, pain, shock, decreased urine output, convulsions, fever, muscular aches, chills, weakness, anemia, yellow eyes, yellow skin, gastrointestinal disturbances, nausea or vomiting, diarrhea.

Therapy for Cu toxicity

Although copper is an essential micronutrient normally subject to effective homeostatic control, excess dietary intakes can in some circumstances be toxic. Susceptibility to copper toxicosis depends, however, on many factors, including species, genetics, age, and diet. This appears to reflect not only variations in the efficiency of the absorption and excretion of copper but also differences in the intake of other hepatotoxic or protective factors, differences in the cellular distribution of copper, and differences in the expression of specific copper transport and storage proteins. Many of the toxic effects of copper, such as increased lipid peroxidation in cell membranes and DNA damage, are related to its role in the generation of oxygen free radicals.[27] It should be determined if the poisoning is life-threatening or poses a potential hazard or is esentially harmless.

Chelation therapy

Chelation therapy removes toxic metals from the body and can be used to ramove excess copper. If the Cu levels are higher than normal, but not extreme, this can often be managed with supplements.If cu levels are very high, treatment with DMSA, penicillamine or EDTA may be needed. The

trace minerals manganese,molybdenum and Zinc can prevent excess Cu from accumulating in the body. Chelates are a complex of an organic ligand(electron donor) and a metal (electron acceptor) in a ring structure formed by the positive-negative attraction of the electrons. Certain metals like Cu form very strong chelates.[28] The chelating agents compete eith the binding sites inthe body for complexing the metals, producing a water-soluble complex which is then excreted in the urine or bile.[29] Clioquinol was identi fied as a prototype metal-protein-attenuating compound (MPAC). The development of optimal second-generation MPACs is a desirable goal and may permit greater insights into the significance of metal-protein interactions across several neurodegenerative disorders.[6]

Clioquinol, a 8-hydroxyquinoline derivative, is producing very encouraging results in the treatment of Alzheimer's disease (AD). Its biological effects are most likely ascribed to complexation of specific metal ions, such as copper(II) and zinc(II), critically associated with protein aggregation and degeneration processes in the brain. We report here, for the first time, a structural characterization of the zinc(II) and copper(II) complexes of clioquinol. A ligand to metal stoichiometry of 2:1 is found in both cases, though in the presence of quite different coordination polyhedra. The present findings are discussed in the frame of modern approaches to AD treatment.[31]

The home treatment is to induce vomiting unless the patient is unconscious or experiencing convulsions. Before inducing vomiting, contact Poison Control to verify that is the correct treatment. If instructed to induce emesis, proceed as follows or as otherwise instructed: First, give the usual dose of ipecac syrup: 15 mL (1 tablespoon) for children and 30 mL (2 tablespoons) for an adult. Follow with 1/2 cup (4 oz) of water for children or 8-12 oz. of water for adults. Repeat if vomiting has not occurred in 1/2 hour. Poison control: Induce vomiting, Administer activated charcoal, Use gastric lavage, administer an antidote, Dialysis, Treat the symptoms.

Case studies

The following case studies will help us understand the role of Cu in medicine.

Menopause/PMT- Vahida Starcevic is one of the 20 therapists practising with me at Castle Street Clinic in Guildford and uses MET alongside acupuncture. She comments, “I have used MET for many years, and I have trust in their effectiveness. They are easy to use, safe, inexpensive and effective in a gentle way and also suitable for children, since they have no taste. I have also regularly found them very helpful for the menopause and premenstrual conditions”. Maria, aged 45, came to see her two years ago suffering with hot flushes, tiredness and irritability. She also suffered regularly from common colds and infections and was recently diagnosed as having asthma. “I gave her MET Ga-Pb-Sn, to which she responded almost immediately, and now manages to control her hormonal symptoms. The MET Cu-Au-Ag has also been very beneficial in as far as it supported and strengthened her immune system. She no longer has asthma and has only had one cold since we started treatment.”[24]

Immunodeficiency/ME- Alongside health kinesiology desensitization for residual viral toxins, I have found that ten drops of MET H (Holmium) taken first thing in the morning has shown extraordinary results. Typically most of these clients suffer from hypoactive thyroid conditions and MET Holmium or MET Molybdenum (M), in my view, is fundamental to aiding recovery. I also give MET Cu-Au-Ag (Copper-Gold-Silver) for adrenal dysfunction and immune support, and, in cases of extreme depletion (and resistance to any form of treatment), MET TOTAL 72, which is designed to give a natural stimulus to try and restore cellular integrity and normal mineral absorption.[24]

Opinion- 72 individual micro-elements are available, together with a further 40 combinations, which have been developed for ease of use and to cater for specific conditions. Frequently used examples include Cu-Au-Ag (Copper-Gold-Silver) for adrenal dysfunction and protection; Ca-F-Mg (Calcium-Fluorine-Magnesium) for calcium absorption; Ga-Pb-Sn (Gallium-Lead-Tin) for menopausal problems and PMT; TOTAL 72 (all 72 micro-elements) for severe imbalance and depletion of minerals, also found helpful as protection during chemotherapy; ‘Sustain’ formula for sports and/or libido; Rh-Ni-Pd (Rhodium-Nickel-Palladium) for arthritis; Al-Br-Mg-Ni (Aluminium-Bromine-Magnesium-Nickel) for asthma; Va-Li (Vanadium-Lithium) for eyes

and improving circulation to the head; and Ce-La-Va-Sc-Y (Cerium-Lanthanum-Vanadium-Scandium-Yttrium) for protection to hands-on therapists, typically with only 2-3drops needed.

Fig. 1: Mechanism of copper In Neurodegeneration

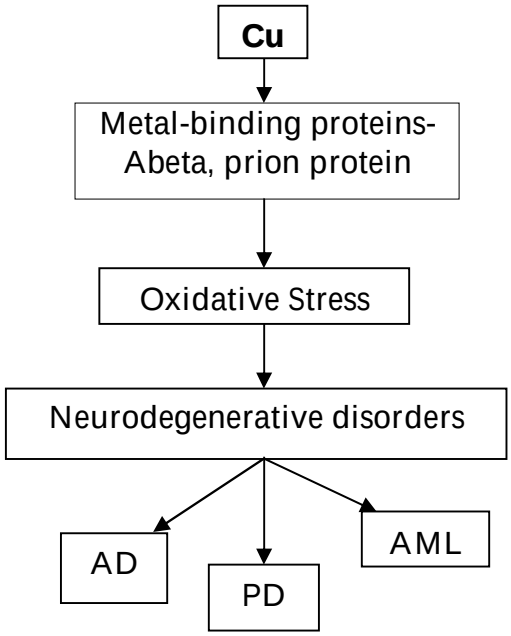
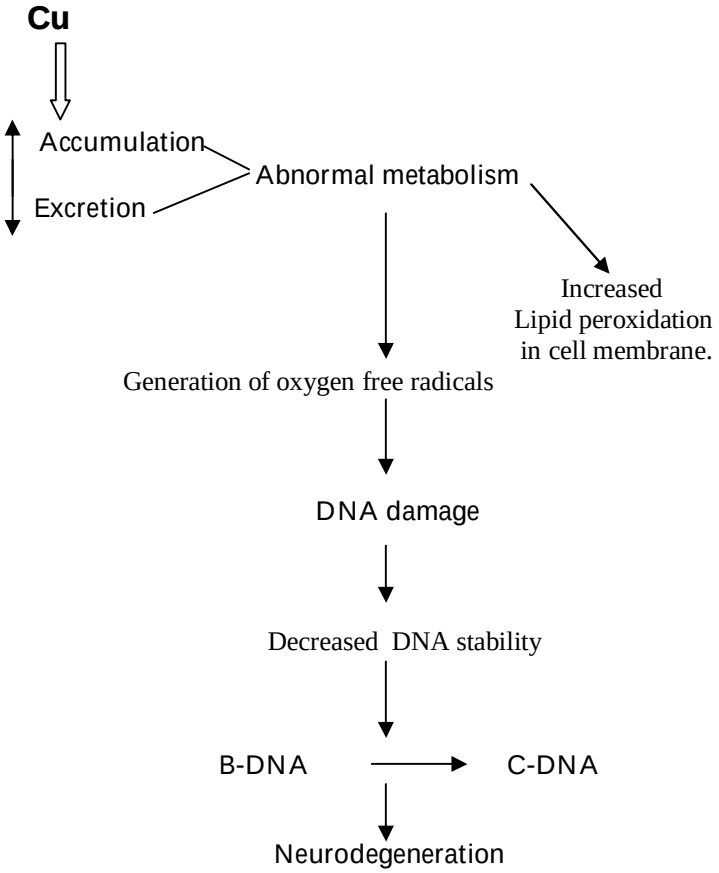


Fig. 2: copper toxicity and DNA damage and Neurodegeneration



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