It is an age old saying that the body is made up of elements combined together in varying concentrations, and any change from their physiological limits lead to a disturbed homeostasis. Few decades earlier, when sophisticated analytical instruments were not available, the element present in minute amounts could not be measured and were said to be present in traces. These were referred by the term"Trace Elements". Today, we can almost accurately measure the concentration of these elements but, it has become customary and traditional to still designate these element as Trace Element. Metals constitute major part of the trace element spectrum. Metal ions deficiency has been known to produce various diseases in man. Since ancient times metals have been used to treat various diseases of the body in the form of 'Kushtah' or 'Bhasm'. Normally, man has always been exposed to metals through natural concentration in soil, water and food and some metal concentration is persistently present in different parts of the body. Trace metals were always considered important because they could produce poisoning when ingested in large amount or for sufficiently long period. Nevertheless, these metals are believed to develop their toxic manifestations on a variety of body system, much emphasis has been attributed on their effect on the nervous system.
due to apparent relation of relatively low level of metallic exposure with behavioral and physiological disorders. The biochemical mechanism of neurotoxic effect of trace metals is not clearly understood. Similarly, the interrelationships between various trace metals in different brain areas are also obscure. Experimental study has also shown that metals produce behavioral disorders by disturbing the metabolism of brain neurotransmitters, however the story still gives gloomy picture. Since lead and zinc occur together/or alone in nature, it was assigned to explore their individual/combined effect on the levels of various trace metals, enzymes, lipid peroxidation and neurotransmitters. Modifications of some behavioral patterns following the administration of metals also forms a part of this study. Finally, we also tried to explore the effect of certain external stimuli like alcohol, datura and hormones on the regional concentrations of these metals in the central nervous system.

Brain is a unique body organ which is regionally characterized into specific functions. Because of the regional heterogeneity brain is suitable organ for correlating metal ion distribution to specific function. Such specificity seems to be correlated to the non-homogeneous distribution of
metals in the brain. Present study shows heterogeneous distribution of zinc, copper, manganese, cadmium and lead in the brain. The hypothalamus showed the highest concentration of zinc, copper, manganese and lead, while amygdala had maximum level of cadmium. The amygdala, hippocampus and spinal cord exhibited high contents of these metals. The cerebellum, cerebral cortex and brain stem were observed with low concentration of these metals. Interestingly, the hippocampus and spinal cord were shown to have equal level of each of the zinc, copper and lead.

Rats were exposed to lead (1% lead acetate in drinking water) for a period of 30 days. Lead levels were markedly increased in all the body organs with a maximum retention in kidney. Most parts of the body showed elevated concentrations of Zn, Cu, Cd and Mn ions. But reduced amounts of Cu and Mn in kidney and Cd in the lung were observed. In the blood, lead ions were aggravated while Zn, Cu, Cd and Mn ions were reduced. The activity of d-ALAD was significantly reduced in the blood. In the brain, the highest concentration of Pb was shown in the spinal cord followed by cerebellum, cerebral cortex and brain stem. While the maximum per cent increase was noticed in the cerebellum. Zn was increased in the brain
stem and spinal cord and decreased in the cerebral
cortex. The concentration of Cu was enhanced in the
cerebral cortex and cerebellum and reduced in the
spinal cord. Cd ions were depressed in the cerebral
cortex while Mn ions were enhanced in the cerebral
cortex and cerebellum. It seems that the normal-
distribution-system of trace metals has been disturbed
and shifted to an impaired-state of equilibrium in lead
poisoning. It has been suggested that inorganic lead
poisoning is associated with an altered topography of
trace metals.

The effect of lead (8mg/Kg i.p.) alone and in combination
with zinc or copper (1mg/Kg i.p.) for 7 days were studied
on the regional concentration of zinc, copper and lead ions
in the CNS and blood of rabbits. Although highest
concentration of lead was detected in the hypothalamus
when it was administered alone; combined lead and copper
caued remarkable depletion of lead level in this region.
Combined lead and zinc caused elevation of lead ions in
the cerebellum, brain stem, hippocampus and spinal cord.
Following lead exposure copper levels were elevated in the
cerebral cortex, cerebellum and hippocampus, and
depressed in the amygdala and hypothalamus. However,
combined lead and copper administration resulted increment
of copper in the hippocampus and brain stem. Depletion of zinc levels were seen in the cerebellum, cerebral cortex and hippocampus after lead exposure. Zinc and lead exposure caused a concordant increase of zinc levels of hypothalamus and amygdala. Similar effects were also noticed in these regions when lead was administered alone. After the administration of a single higher dose of zinc (8mg/Kg i.p.) in combination with lead (8mg/Kg i.p.) the animals were hyper-exciteable, restless, incoordinated and died within 6 to 12 hours. Surprisingly, when a single higher dose of copper (8mg/Kg i.p.) were administered along with lead (8mg/Kg i.p.) all the animals developed convulsions and died within 60 minutes.

The human environment is exposed to constant contamination of high concentrations of lead which has been recognised as a principal toxicological factor to the central nervous system. The most common toxic effects of lead lead to the production of behavioral abnormalities in humans. Cerebral norepinephrine (NE) concentrations have been shown to be associated with behavioral hyperactivity in lead exposed rodents. Regional NE levels in brain and its association with circadian rhythm of ambulatory activity in open field situation were observed in young adult male rats. The ambulatory activity with an initial transient increase forming a parabolic response during first week
of lead exposure (2% lead acetate in drinking water for 30 days) was significant from day 2 to 6. After peak activity on day 3, the ambulation progressively declined. The hypo-ambulation response was although observed significantly from day 9 to 17 as compared to control. A rapid increase was noticed on day 18 and then remaining significantly higher from then onward. When circadian rhythm was studied it was found that hyper-ambulation appeared at 6 and 22 hours on day 3, and at hours 10, 14, 18, and 22 on days 23 and 30. Further, the hypo-ambulation was also recorded on the 13th day at 2, 6, 10 and 14 hours. When lead-intoxicated rats exposed to simultaneous light and noise stimuli a progressive decrease in ambulatory response was noticed. There was a gradual but marked increase in the concentration of lead in all parts of the central nervous system of lead-intoxicated rats. The highest accumulations of lead ions were obtained in the cerebellum and spinal cord. Although, the maximum per cent augmentation of this ion was noticed in the cerebral cortex on day 30. Surprisingly, a quick increase and retention of lead ions appeared in the cerebellum on day 13. Moreover, the cerebral cortex was the only brain region which showed a significant enhancement of lead ions on day 3. The NE levels of the cerebral cortex was significantly enhanced on day 3. However, on day 13 the
cerebellum and spinal cord exhibited diminished contents of NE. On day 23, the levels of NE were increased in all brain regions. Moreover, the increased concentrations of NE were discernible in the cerebellum and the brain stem on day 30. It appears that the increased levels of NE have been implicated in modifying the ambulatory behavior and at present a reasonable explanation of such effect may be through modification in circadian rhythm of ambulatory activities observed at different test hours. This may support the role of NE in the evaluation of both hypo-and hyper-ambulatory activity.

In recent years the study of the effect of toxic substances on behavior has been intensively studied to understand more and more about the toxic effects of metals on behavior. Little effort has been made to know and understand the kind and genesis of behavioral disturbances in human beings following environmental and occupational lead exposure. The animal stereotypy in correlation with regional brain dopamine response may constitute a valid model for lead neurotoxicity in humans. Ingestion of 2% lead acetate in drinking water to rats for a period of 30 consecutive days produced significant changes in behavioral stereotypy and dopamine levels in various brain regions. During first week of lead exposure, the rearing response diminished with a significant change on day 3. Subsequently, this response depressed
until day 22. Significant augmentation of rearing response was obtained on day 26 which was gradually aggravated until day 30. Preening, on the other hand, showed irregular pattern until day 6. Then a progressive increase in preening response was noticed until day 30. There was a significant augmentation of scratching behavior showing a parabolic response during first three weeks. Subsequently, this response remained consistently higher until day 30.

A typical biting behavior has been shown to be developed in rats after lead exposure. Biting was usually either on the abdomen, on the back, near the base of the tail, or on the external reproductive organs. A parabolic pattern was observed similar to that of scratching response. Dopamine contents were increased in the cerebral cortex on days 13, 23, and 30, in the cerebellum on day 30 and in the brain stem on days 3, 13, 23 and 30. Surprisingly, the cerebellum showed depressed dopamine levels on day 13. The observations obtained in this study are of importance in this context that, developed responses may attribute for symptoms of neuropsychiatric dysfunction of lead poisoning.

Rats exposed to lead (2% lead acetate in drinking water for 30 days) showed impaired motor behavior and reduced regional brain GABA. Ambulatory activity (i.e., gross movements) was initially increased for the first 5 days and then reduced (hypoactivity) until the 17th day.
augmentation of gross motor activity was observed on day 18, which remained consistently high until day 30. Fine movements (representing mainly behavioral stereotypies such as rearing, preening, scratching and biting) exhibited a parabolic pattern which culminated after 2 weeks. GABA levels were significantly diminished in the cerebellum on day 3, 23, and 30. Brain stem GABA was also significantly reduced on 13, 23, and 30th day. Decreased contents of GABA was also found in the spinal cord on days 13 and 23 only. The cerebral cortex, on the other hand, showed decreased GABA contents at different test periods. It seems that decreased cerebellar GABA may be related to increased total and gross motor activity whereas GABA in the brain stem and spinal cord showed an association with fine movements in rats chronically exposed to lead.

Rats exposed to lead (2% lead acetate in drinking water for a period of 10 days) showed altered levels of phospholipids, lipid peroxidation and lead ions. Lead ion concentrations were significantly increased in all brain regions with a maximum retention in the spinal cord and cerebellum. The cerebral cortex showed a high per cent elevation of lead ions as compared to the other areas of the brain. The phospholipids contents were significantly depressed in the cerebral cortex, cerebellum and spinal cord. Subsequently, the rate of lipid peroxide formation has been enhanced in all brain regions. Increased rate
of lipid peroxidation and decreased levels of phospholipids followed the similar rank order as that of increasing lead concentration was spinal cord, cerebellum, cerebral cortex and brain stem after lead intoxication.

The distribution of lead, zinc and copper in the environment has a pronounced biological effects both in man and animals. Anemia is regarded as the major effects of heavy metals in humans. It has long been known that the anemia resulted due to an inhibition of heme synthesis in the blood. The delta-aminolevulinic acid dehydratase (d-ALAD) is one of the principal enzymes involved in the heme synthesis. In the present study, the activity of d-ALAD significantly declined as a result of increased lead content in the blood following lead intoxication (8mg/Kg i.p. for 7 days). Similarly, copper poisoning (8mg/Kg i.p. for 7 days) also inhibited the activity of d-ALAD in the blood. But, on the other hand the activity of d-ALAD was significantly enhanced following zinc administration (8mg/Kg i.p. for 7 days). Whenever one of the zinc, copper or lead ion exerts its toxic effect, the other two ions declined significantly in the blood. It may be possible that the d-ALAD inhibition, caused by either lead or copper poisoning, is related with zinc metabolism.
The effect of zinc (8mg/Kg i.p. daily for 7 consecutive
days) was studied on the levels of zinc, copper and
lead in the blood, spinal cord and different regions of
the brain in rabbits. It was found that with increase in
zinc concentration there was a decrease in copper levels
and an increase in lead levels in almost all parts of the
brain. In the blood, both copper and lead levels were
significantly decreased. The study suggests that the
changes of zinc ion concentration beyond physiological
limits can effect the concentration of other essential
and non-essential metal ions.

Hormones (Estrogen-Progesterone, 5 μg 17α-ethinylestradiol
and 15 μg d-norgestrel per Kg body weight i.m. for 30
consecutive days) was administered to investigate the
redistribution of zinc, copper and lead in different
regions of the brain and blood in female rabbits. It was
noticed that the levels of zinc and lead were decreased
while copper was elevated in the blood. In the brain,
zinc was enhanced in the hippocampus but was depleted in
hypothalamus and brain stem. Copper, on the other hand, was
elevated in the hypothalamus, cerebellum, brain stem and
spinal cord and depressed in the hippocampus and amygdala.
The concentration of lead was augmented in the amygdala
and hippocampus while reduced in the hypothalamus, cerebellum
and brain stem after steroids administration.

Repeated administration of alcohol (4/Kg body weight as 20% v/v solution in deionized water i.p. daily for 10 consecutive days to rats) caused depletion of lead and copper in the whole brain. The concentration of zinc was decreased in the amygdala and hypothalamus and increased in the cerebellum. Copper ions exhibited increased concentration in the spinal cord, on the other hand, hippocampus, amygdala and hypothalamus showed reduced amounts. Increased levels of lead ions were found in the cerebral cortex and cerebellum, while amygdala and hypothalamus exhibited depressed values. The activity of (Na+ - K+) - ATPase was inhibited in the cerebral cortex and cerebellum. Stimulated activity of this enzyme was observed in the hippocampus, amygdala and hypothalamus following ethanol exposure. It seemed that alcohol acts differentially on zinc, copper and lead as well as (Na+ - K+) -ATPase activity in the brain.

The effect of Datura-stramonium (extract of 60mg seeds/Kg body weight i.p. for 7 consecutive days) was examined on redistribution and retention of zinc, copper and lead in the blood, spinal cord and various brain regions. In the blood, zinc, and copper ions were augmented and lead
ion was declined. In the brain, datura administration increased zinc level in the brain stem while decreased in other parts. Copper levels were declined in the hypothalamus and spinal cord while elevated in the hippocampus. Decrements in the content of lead were observed in the spinal cord, amygdala and hippocampus. The hypothalamus showed increase in lead level.