INTRODUCTION

Ageing is a multistep, multifaceted and time dependent phenomenon (process) and is characterized by the decreased ability of a living system to respond to exogenous and endogenous stresses viz., physical, chemical or biological. The process of ageing involves perhaps multiple factors (Kirkwood and Holliday 1979; Hayflick 1973; Gordon 1974; Obriest 1980; Tiniras 1974). Changes in morphology, biochemistry, physiology at the cell and tissue levels have been found to be associated with old age (Davison 1980; Kanunyo 1976, 1980). From a gerontological point of view, these changes are presumed to be the basis for signs and symptoms of growing old i.e., ageing. For instance decline in the physiological effectiveness of cells and tissues, the changes in enzyme activities, the deposition of unwanted substance etc. are conspicuous features which are observed during ageing. Ageing influences practically all body systems. The age-related changes in the organ systems made up of post-mitotic cells, however, are of particular interest (Verzar, 1964, 1968). Age-related deteriorative changes in an organism's adaptation to old age are linked to the changes in the nervous system (Verzar 1965). Experimental evidence has been presented to show that most essential manifestations of ageing are related to the appearance of imbalances in the central nervous system, viz., age-related changes in the psychic behaviour, memory, intellectual and muscle working abilities, responsiveness to environmental stimuli, motor activity, reproductive ability, adaptation to the changing living conditions.
development of age-related pathology etc. (Frolkis 1981; Roth 1979). Moreover, an important concept is emerging that primary age-related changes in the brain lead to secondary manifestation of ageing in other organs and tissues. The experimental data have also shown that the impairment of neural control over the metabolism and function of other organs lead to deterioration of their function (Frolkis 1973).

The central nervous system is, however, also quite sensitive to, and is affected by, many metabolic disorders and hormonal imbalances that arise in other organs (Roth 1979; Samorajski 1978; Samorajski et al 1980). These disorders and imbalances can have significant impact on the brain with time but at younger age-levels they have only negligible effects on other organs of the body (Samorajski 1971). Neurobiology of ageing is a promising nascent field of gerontology. Understanding of the mechanism of ageing in brain requires a concrete analysis of age-related changes in various structures and involvement in the shifts of the organism's activity with ageing. The studies of molecular mechanisms underlying age-related disturbances of neuronal metabolism should throw light on phenomenon of ageing as a whole in higher organisms.

AGE-RELATED MORPHOLOGICAL CHANGES IN BRAIN: With advancing age various morphological changes at the cell and tissue levels have been observed in brain. These changes are: decrease in brain weight, loss of nerve cells, loss of dendritic processes and synaptic contacts, formation of neuritic plaques, formation and accumulation of unfavourable intracellular substances like lipofuscin and so on. In the present work, we have been particularly
concerned with the least rational than that in lipofuscin.

The accumulation of lipofuscin, which is also known as the age-pigment, is one of the conspicuous and consistent morphological change in the nerve cells of cerebral and also the (Adams 1965; Brody 1969; Whitford and Getty 1966; Goraja et al 1964, 1970; Ando and Getty 1974; Jackson and Axford 1974; Brinza et al 1976; Boyal 1982). The presence of lipofuscin is, however, not limited to the nervous tissue alone. It has been well documented that lipofuscin pigment, which is a copolymer of proteins and peroxidized lipid (Adams 1965; Shio et al 1965; Tedball 1973; Alcock 1982), accumulates with age in a wide variety of tissue viz., brain, heart, liver, testis, adrenal cortex etc. (Chen et al 1965; Jezeretel 1974; Iberi et al 1968; Brinza et al 1976; Jexson and Axford 1974; Jacky et al 1976; Miguel et al 1976) and also plant tissues (Aquino and Garcia 1972; Umbre and Ibanez 1972). Lipofuscin has been thought to be possessing some metabolic and physiological significance (Kim 1967; Sino and Subbarjoe 1972; Mann and Yates 1974, 1978). Since lipofuscin contains peroxidized lipids with proteins derived largely from membranes of the cells, lipofuscin deposition can be considered as an index of the peroxidative damage (Chen et al 1965; Jezeretel 1974; Iberi et al 1976; Jason et al 1938). It is conceivable that lipid peroxidation leads to the formation of lipofuscin. It is believed that oxidized lipids are engulfed by lysosomes to be eventually transformed into lipofuscin coposit. (Adams 1965; Sino and Subbarjoe 1972). Further lipofuscin has been prepared in vitro (Shio et al 1965) by the action of certain enzymes on the
unsaturated fats and the lipofuscin so prepared appears to have properties similar to those occurring in vivo. The lipofuscin shows fluorescence characteristics similar to those of the products of peroxidated mitochondria and microsomes (Dillard and Tappel, 1977), of the products of the peroxidated polyunsaturated fatty acids reacting with phosphatidylethanolamine (Dillard and Tappel 1975), of the products of synthesized conjugated Schiff base (Nalsheet and Tappel 1973), of the products of nucleic acid (DNA) and peroxidated arachidonic acid (Rice and Tappel 1973) and also of the products of peroxidated fatty acids and phospholipids (Bidlack and Tappel 1973).

The accumulation of lipofuscin in the intracellular compartment would seem to have a deteriorative effect on the physiological effectiveness of the cell since lipofuscin is mostly a metabolically inert dead substance.

AGE-RELATED BIOCHEMICAL CHANGE IN BRAIN: With advancing age, an increasing biochemical imbalance manifests itself in cells and tissues (Tolman and Roche 1973). The biochemical imbalances may consist of: the presence of altered molecules, absence of certain necessary molecules, appearance of some new and unfavourable molecules and so on (Houben, Menaclle 1978; Kirkwood and Holliday 1977; Roth 1979; Sharma and Sharma 1979).

Whether biochemical imbalance is a cause or effect of the ageing process has, however, not been clear. Despite numerous biochemical changes that may occur in cells with passage of time, no unique or primary factor related to ageing has yet been identified (Kirkwood and Holliday 1979).
a. Oxidative Damage in Relation to Age: Increasing peroxidative damage occurring with age in body tissue has been thought to contribute significantly to the age-related impairment of structure and function (Tappel et al. 1975; Bondaroff 1964; Zeman and Dyken 1969; Armstrong 1974; Chance et al. 1979; Nohl and Negner 1979; Kong and Devison 1980; Valdimirov et al. 1980). The peroxidative damage can result from the action of several agents (oxidants) such as $\text{H}_2\text{O}_2$, $\text{O}_2^-$, $\text{OH}^-$ which arise from the reduction of oxygen (Chance et al. 1979; Folbergrova et al. 1979; Ribav et al. 1982; Bernofsky and Sanda 1983). It is known that under physiological conditions significant levels of potentially dangerous oxidants exist in cells and tissues. In vivo, defense against the oxidants is provided by protective enzymes such as catalase, superoxide dismutase, glutathione peroxidase etc. (Chance et al. 1979; Horak et al. 1979; Kappus and Jics 1981) which detoxify the oxidants. In spite of in vivo defense, age-related damage tends to occur and potentially influences the cells.

Oxidative damage with which the tissues are likely to suffer during the course of their life span has been thought to be responsible for considerable degree of reduction in their physiological functioning (Zeman and Dyken 1969; Ryan et al. 1970; Armstrong 1974; Kappus and Jics 1981). The oxidative damage is a consequence of the oxidation or peroxidation of lipids of cell membranes or cell organelles (Tappel 1975; 1978). Peroxidation of lipids is the reaction of oxidative deterioration of polyunsaturated fatty acids (Sato et al. 1983).
and particularly affects the cell membranes. Membranes possess certain features which make them more susceptible to oxidative damage, for example high content of unsaturated lipids which are more oxidizable than other saturated compounds (protein), continuous diffusion of oxygen through them and location of high energy producing system in them (Jazrawski and Rolsten 1976). One of the manifestations of the oxidative damage can be seen in the nerve cells as intracellular accumulation of lipofuscin, popularly known as age-pigment, which can be, as already discussed above, considered to represent the accumulation of altered (oxidized) membranes (Fryor 1976; Tappel 1980; Johal 1980; Koestler et al 1988). The accumulation of lipofuscin has been considered integratively proportional to the occurrence of lipid peroxidation (Chance et al 1979; Leibovitz and Siegel 1980).

b. Age-associated changes in enzyme activities: Measurements of enzymatic activities in several tissues of adult and senescent animals have mostly failed to demonstrate very marked or systematic differences with age (Timiras 1974; Faris 1980; Kanungo 1986). It has been observed that depending upon the enzyme system studied, various species studied and the methodological approach adopted, the activities of various enzymes may increase, decrease or remain unchanged (Timiras 1974; Rothstein 1977). Since each enzyme is synthesized under the direction of a specific gene (Finch 1969, 1971; Adelman 1971, 1972; Wilson 1973), an understanding of the causes of changes in the enzyme levels may shed some light on the molecular mechanism(s) of ageing (Barrows 1966; Kanungo and Kaur 1975; Kanungo 1976
The changes in the levels of the antioxidant enzymes viz., catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase and the oxidative enzymes—glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase of pentose phosphate pathway have been reported in ageing rats (Shukla and Kenungo, 1962; Wang et al 1971; Lisenback 1976; Yagal 1976; Yelvia and Rosenthal 1979; Mothersal et al 1981; Al-Hashan et al 1981).

(i) **Antioxidant enzymes**: With advancing age, there seems to be no uniform patterns of changes in the antioxidant enzymes. Antioxidant enzymes showed decrease, increase or no change at all with age. One of the antioxidant enzymes, superoxide dismutase known to cause dismutation of superoxide radical ($O_2^\cdot$) was found to show no change in its activity in the brain of ageing rats and mice (Reiss and Gershon 1976; Kellong and Fridovitch 1976; Petrovitch et al 1982). But there have been other reports indicating age-related increases in the activity of superoxide dismutase in the brain of rat (Pavelli et al 1978; Vanella et al 1982; Sullivan 1982). Recently an increase was shown in the levels of glutathione peroxidase activity upto one year of age and decline in the activity afterwards in old age; an age-related increase in glutathione reductase, however, has also been reported (Mothersal et al 1981). Age-related changes in the catalase activity in the brain of rat or mice, so far, have not been reported (Biard 1971; Chance et al 1979). Like brain, in other tissues viz., lung, liver, heart, age-related changes in the antioxidant enzymes (Reiss and Gershon 1977; Yam et al 1978) have been reported.
(ii) **Oxidative Enzymes of Pentose Phosphate Pathway**: Besides just-mentioned antioxidant enzymes in tissues, there are also other enzymes viz., oxidative enzymes - glucose 6-phosphate dehydrogenase (G6-PDH) and 6-phosphogluconate dehydrogenase (6-PGDH) of the pentose phosphate pathway which can also afford protection against peroxidative damage (Nethersol et al. 1982). It has been shown that G6-PDH activity increases in the brain during growth and declines thereafter (Shukla and Kanungo 1968). But recently an increase was shown in G6-PDH whereas no change was observed in 6-PGDH in the brain of ageing rat (El-Hassan et al 1981). In some tissues (e.g., liver) opposite change in G6-PDH activity were reported in two different strains of the rat (Wang et al 1977). Although there were variations in the enzymatic activity with age within the same tissue and animal species, variation may also depend on a number of other biological factors - such as diurnal cycle, cell population shift, diet etc. (Finch et al 1969; Falzone et al 1967).

**AGE-RELATED ELECTROPHYSIOLOGICAL CHANGES IN BRAIN**: Nerve cell represents the fundamental structural and functional unit of the nervous tissues. It receives signals, processes and transmits them. The modern gerontologists know much more about the structure and metabolism of neuron than about their functions. Thus a full understanding of senescent behavioural changes is likely to be facilitated by information obtained from in vivo physiological studies, particularly electroencephalography (Cebriol 1966).

To date, a number of observations have been made on the age-associated changes in the spontaneous electroencephalogram-
phic activity (Thomas et al. 1976; Obriet 1980). During ageing, one of the most prominent changes is the general slowing of the rhythmic activity, particularly alpha rhythms in man and analogous rhythms in animals. In aged animals, EEG trace shows the abundance of slow waves or of increase in their amplitude (Coton 1966; Frolik 1972a,b; Zelkin 1972; Bellong 1974; Copper et al. 1975; Eleftheriou et al. 1975; Hughes et al. 1977; Thompson 1977; Andriola 1978; Obriet 1980). In adult and old women both frequency and alpha rhythm's index are somewhat higher than in adult and old men (Hubbard 1977; Hughes et al. 1977). Deceleration of EEG rhythm, appearance of slow waves is not represented uniformly in all the areas of the brain (Obriet 1980). Diffuse slow activity which is seldom seen in early life shows higher incidence in older men and animals, similar to the situation seen in some psychiatric patients (Thompson 1976).

Recently, besides EEG changes associated with waking state, much attention has also been paid to the sleep patterns and EEG changes during sleep. In old age, relative proportion of various phases of sleep is altered. In old age decreases were observed in paradoxical sleep (REM), in spindle bursts and in non-rapid eye movement sleep (NREM) (Thompson 1976; Obriet 1980).

PHARMACOLOGICAL ASPECTS OF AGE-RELATED CHANGES IN BRAIN: The nature of the mechanism(s) underlying the origin of age-associated changes in brain is largely unknown. With increasing age, the central nervous system (CNS) loses its ability to adapt to increased metabolic and functional demands made upon it. This leads to cellular changes or vice versa. The validity of this
principle in relation to ageing can only be established by the correlation of specific cellular changes with rates of ageing. In order to achieve these goals, it may be imperative to study the effects of changes produced experimentally.

A number of pharmacological agents used in geriatrics are known to have beneficial effects on age-related impairment or deterioration of function. Generally most geriatric drugs are said to have normalizing effects on the central nervous system. For example, several drugs used in psychogeriatric therapy are used to treat elderly persons who are afflicted with physical and mental disorders, neuropsychiatric disorders of organic brain syndromes etc. These agents are centrophenoxine, dimethylaminoethanol (Deconol), chlorpromazine, promazine, procaine, hydergine etc. Of these drugs, in the present work we have studied only the first three, since they are supposed to have some common antiageing pharmacological effects, e.g., reduction of the neuronal content of lipofuscin, increase in life span etc. (Mandy 1963; Mandy and Sal 1977; Hochschild 1973; Samorajski and Holsten 1976). Pharmacological intervention in gerontology permits a study of the selected aspects and thus affords only an incomplete insight into the processes occurring in the ageing brain and the possibility of modifying them with drugs. Any consideration of the effects of geriatric drugs on the life span should draw distinction between its effects on the ageing process, and the effects on renewable substances. If geriatric drugs act on the rate of ageing process, then they can be considered to modify the mechanism determining the life span.
Life span of experimental animals (particularly of rats and mice) are subject to modification by geriatric pharmacological agents (Nandy 1978; Hochschil 1973a,b). The major difficulty in understanding the underlying mechanism of ageing is that specific morphological, biochemical or physiological events which may be landmarks have not yet been established. Whatever the underlying mechanism may be, experimental alteration of life span or of age-associated changes by geriatric drugs provide a useful approach in the study of the pharmacology of the ageing process. Therefore, before going into the discussion of other relevant points, it will be appropriate to discuss the known effects of geriatric drugs viz., centrophenoxine, dimethylaminethanol and chlorpromazine on age-related changes in the brain.

(a) Effects of geriatric drugs on Life span: The long-term treatment with centrophenoxine resulted in a significant extension of median life span of 357 B16 mice, whereas no change in maximum life span were found (Nandy and Lal 1977). Hochschil (1973) also studied the effects of centrophenoxine on median, mean and maximum survival times of male Swiss Webster albino mice and observed a significant extension of all the three.

In vitro also it was shown that centrophenoxine could extend the life span of neuroblastoma cells in culture and also of fibroblast cells of lung (Nandy et al 1978; Gill and Hassan 1977).

Dimethylaminoethanol, a molecular structural constituent of centrophenoxine, has been reported to extend life span of
Drosophila and mice (Hochschild 1971, 1973a). However, a recent study has shown a decrease in life span of Japanese quail after dimethylaminoethanol treatment (Cherkin and Sherman 1977).

Recently, Narra and Holsten (1976) showed that chronic treatment of mice with chlorpromazine (5 mg/kg) did not affect percentage survival of mice but the dose of 10 mg/kg showed a decrease in percentage survival, which could be due to sedation, since this condition may restrict food intake.

(b) Effects of Geriatric Drugs on Lipofuscin: A number of reports have shown that centrophenoxine inhibits the accumulation of lipofuscin in the nerve cells of the brain of aged guinea pigs, rats, and mice (Sandy 1968, 1976; Hassan et al 1974; Riga and Riga 1974), in C3H mouse neuroblastoma cells in culture (Schneider et al 1977; Sandy et al 1978), in human lung fibroblasts in culture (Gill and Hassan 1977) etc. Recently, Chino et al (1983) found that centrophenoxine reduced the accumulation of lipofuscin in the neurons of rat cerebral hemisphere in primary culture. Reduction of lipofuscin has been found to correspond with experimental modification of life span (Hochschild 1973b, Sandy 1978, 1979). It has been shown that centrophenoxine can only reduce the formation of lipofuscin, but cannot stop its formation completely both in vivo and in vitro (Sandy 1976, 1978). Studies were also made by several investigators on the mechanism of action of drugs on neuronal lipofuscin. Chomitsus et al (1976), Heir and Gless (1971) and others reported that centrophenoxine treatment resulted in the disintegration of pigment mass into small particles and a final disappearance of the pigment was seen after increasing period.
of treatment and thus suggested that possibility of drug-induced removal of these pigments from the nerve cells. Hassan et al (1974a,b) reported the presence of vacuolated pigment granules in the capillary endothelium of treated animals and suggested that the endothelium probably participated in the removal of the pigment from the cells. Spoerri and Sies (1975) suggested that lipofuscin was eliminated to extracellular space by cytoplasmic protrusion in addition to the removal by phagocytosis.

To date, there has been no direct report on the lipofuscin reduction by dimethylaminoethanol. However, Hochschuld (1973b) tried to explore the influence of Deanol on lipofuscin indirectly by oral administration of hydrolysed centrophenozone (by hydrolysis centrophenozone breaks into DMAE and chlorophenoxy acetic acid), and found no effect on the brain lipofuscin. However, lipofuscin content in the heart showed some change.

Jamorajski and Holsten (1976) have shown the reduction of lipofuscin in nerve cells of the brains of mice after chronic treatment with chlorpromazine. Recently, Uhtani and Kawa-china (1983) demonstrated that chlorpromazine reduced the accumulation of lipofuscin in the neurons of rat cerebral hemisphere in culture.

(c) Effects of Geriatric Drugs on Enzyme Activity: To understand the mechanism of action of the drug, the effect of centrophenozone on enzymes in the neurons of the J53 of guinea pigs was studied by Nandi (1968). The histochemical studies showed that the drug reduced the activity of succinic dehydrogenase, cytochrome oxidase, lactate dehydrogenase, mono-
amino oxidase but increased the activity of glucose-6-phosphate dehydrogenase. It can, thus, be suggested that centrophenoxygen enhances the cellular metabolism by activating the pentose phosphate pathway. This effect was similar to the enzymatic changes that occur in regenerating cells (Sandy 1978). and thus it was suggested that centrophenoxygen acted by increasing the flux through the pentose phosphate pathway. Study of the effect of centrophenoxygen on the human lung fibroblast cells showed a slight decrease in the level of lysosomal enzymes viz., acid phosphatase and β-glucosaminidase but the long-term treatment appeared to elevate the levels of these enzymes. It would thus appear that possibly centrophenoxygen influences lysosomal enzyme functions (Gill and Manan 1977).

Recently it has been shown that like centrophenoxygen, nial also enhances the oxidative enzymes - glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase of the pentose phosphate pathway (Roy and Singh 1983).

Inhibition by chlorpromazine of succinic dehydrogenase, cytochrome oxidase, ATPase, adenyl cyclase have been reported (Abood 1955; Bershen et al 1956; Fabien and Chemisca 1970).

(d) Effect of Geriatric Drugs on Physiological Changes and Function: Physiological and pharmacological effects of centrophenoxygen on animals and humans have been studied by several workers (Kossaros and Lajawaka 1972; Polish 1962). Centrophenoxygen therapy has been found to result in beneficial effects in various states of hypoxia or anoxia of cats (Nichon 1960; Polish 1962; Nickel et al 1963). Beneficial effects of this drug in sodium or potassium cyanide intoxication in rabbit has
also been reported (Nikajama and Thuillier 1964; Rumpf and Adolwojn 1968). The drug enhances the resistance to various forms of \( \text{O}_2 \) deprivation in cerebral cells of \( \text{C}7 \) of rats (Bersenker et al. 1962; Scott 1979). It improves memory function and raises level of mental alertness (Sandy and Lal 1977; Sandy 1978). Cyanido intoxication-caused changes in EEG were reversed to normal by centrophenoxine (Rumpf and Adolwojn 1968; Scott 1979). It accelerates the tolerance in rats (Polis 1962), activates respiratory oxidative metabolism (Berrshahft 1974; Hoyer 1979; Nickel et al. 1963; Geriu et al. 1973).

Deanol produced not much improvements in memory or in cognitive functions. It produced behavioural changes involving reduction in the anxiety, depression, irritability and increase in the motivational intensiveness (Sherkin 1978). DFAL, a biochemical central stimulant (Pfioffer 1958) has been reported to decrease the alpha rhythm (Goldstein and Lach 1965).

Nothing is known about the effect of chlorpromazine on the age-related changes, particularly of its chronic doses. It affects sleep-wakefulness cycle, generally by inhibiting awake and REM sleep whereas it enhances REM sleep (Jewett and Norton 1966; Hishikawa et al. 1965; Sagi les et al. 1969; Wallach et al. 1969; Pole et al. 1973). Chlorpromazine has complex neurological effects on brain.

(e) Effects of Geriatric Drugs on Patho-physiological Changes: First study on the effect of centrophenoxine on brain function disorders in patients suffering from organic brain syndromes was reported by Weitek (1965). The drug showed improvements in patients suffering from agitation, aversion from social contacts,
lacg or drive, various cognitive effects due to organic brain syndromes etc. (Ger tenbrand et al 1963; Coirault et al 1962; Rummele 1962; Birner and Siroli 1966). The drug exerts psychotomimetic effects in psychogeriatric patients suffering from various organic brain syndromes (Destrem 1962).

Deanol has been used to treat the minimal brain dysfunction syndrome in children (Lewi and Lewis 1977), for example tardive dyskinesia (Goldstein and Back 1965; Miller 1974; Stefford and Farr 1977) and other involuntary movement disorders (Cherkin 1978). EEG changes in patients suffering from schizophrenia were restored to normal by MAO treatment (Murfhee 1963).

Chlorpromazine, a neurotropic drug was first introduced into clinical psychiatry by Delay and Jenniker (1952). Chlorpromazine has attained a significant clinical use as a sedative agent particularly in emotionally disturbed patients and for controlling a wide range of anxiety symptoms (Jarr 1974). EEG of schizophrenic patients became normal also after treatment with chlorpromazine (Murfhee 1963). It has been reported that chlorpromazine has a regenerating effect on the pentose phosphate pathway of neuroglia, which in turn may reactivate neurons in the brain made dormant by the inactivity of old age or disease (Forrest 1974).

PHARMACOLOGICAL APPROACHES AND DEPRESS MECHANISM AGAINST PEROXIDATIVE DAMAGE: Age-associated increase in oxidative damage to cell and cell organelle membranes in the body tissues by lipid peroxidation can contribute significantly to the age-related impairment of structure and function (Fryor 1971, 1976; Kohn 1971; Hochschild 1973a; Gordon 1974; Uchrost 1980; Tappol
1980; Botbersal et al 1981, 1982; Suzuki and Agar 1983; Yama-
shogi and Kajimoto 1983). Prevention of, or reduction in the
oxidative damage is likely to have beneficial effects in the
sense that it should lead to improvement in physiological effe-
ctiveness, in other words it should result in the retardation
of the ageing process i.e. prevention of physiological impair-
ment to at least some extent.

Use of drugs to retard the ageing process appears to be
an interesting and promising approach in geriatrics. As already
said, there are a number of anti-ageing drugs available for psy-
chogeriatric treatments of various disorders in elderly patients
and those are known to have some beneficial effects on age-rel-
ated changes in brain. From gerontological point of view, geri-
stratic drugs particularly those containing dimethylaminoethanol
moiety in their structure are of major interest because of their
cellular membrane stabilizing effects. Attempts have been made
by several gerontologists to increase life span in experimental
animals and also to reduce age-related accumulation of lipofu-
scin, which is a cytologic index of peroxidative damage by
administration of pharmacological agents such as centropheno-
xine, dimethylaminoethanol and chlorpromazine etc. Evidence
now become available to show that some of these agents have the
potential of increasing life span (DHA and centrophenoxine -
Hochchild 1973a,b ; Hand 1979), and also of reducing cellular
deposits of age-pigment (Handy 1978; Siga and Siga 1974; Hoch-
child 1973b; Ipoerri and Gless 1975; Kamorjuki and Holsten
1976; Ohtani and Kawahima 1983). Reduction of lipofuscin accu-
mulation may apparently correspond to the experimental modifi-
of several known effects of these drugs viz., reduction in lipofuscin accumulation, an increase in life span, membrane stabilization, improvement in physiological disorders, it is worthwhile to investigate the effects of these drugs on the in vivo activity of the antioxidant system in the brain.

It is likely that the activity of antioxidant enzymes and oxidative enzymes of PPP can play an important role in determining the rate at which lipofuscin deposits can be formed as well as in the rate of aging. Since the above mentioned geriatric drugs decrease the lipofuscin deposits, it would appear that they may do so by influencing the activity of the antioxidant enzymes and of oxidative enzymes of PPP in a way that will favour increased detoxification of free radicals i.e. oxidants. Oxidants of relevance in this regard are superoxide/đžω(O₂⁻), hydroxyl /đžω (•OH), hydrogen peroxide (H₂O₂) etc. In this context, it is therefore, interesting to find out whether geriatric drugs have any effect on the activity of the enzymes: catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, glucose 6-phosphate dehydrogenase and G-phosphogluconate dehydrogenase. Data concerning the effects of these drugs on the activity of above enzymes will help in explaining the mechanism of the possible anti-aging action of these drugs.

Age-related impairment of brain function can also be assessed electroencephalographically. EEG activity shows deceleration with age. Lipid peroxidation, (since it may have adverse effects on membrane function) can also be considered one of the factors contributing to the changes in the electrical activity of brain. Since the above referred geriatric drugs are known to
cation of life span (Gandy 1979). However, the mechanism by which these drugs decrease accumulation of lipofuscin, increase life span, produce beneficial effects in physiological disorders and stabilize cell membranes are not known. The possibility that can be raised here is whether these drugs (viz., centropheno- xine, dimethylaminoethanol and chlorpromazine) and other similar drugs act by activating chemical pathway(s) that are involved in preventing oxidative damage.

In tissues there are defense mechanisms which afford protection against oxidative damage produced by oxidative stress. The mechanisms that protect the tissues against oxidative damage can be broadly categorized into two:

(i) first one consists of the enzymatic pathways detoxifying oxygen-reduction products and (ii) second one consists of the nonenzymatic action such as scavenging by antioxidants and other agents viz., vitamin E, vitamin C, glutathione etc.

In tissues natural defense mechanism for protection against oxidative damage comprises antioxidant enzymes such as catalase, superoxide dismutase, glutathione per oxidase which can metabolise oxygen-reduction product. Besides this, reductive potential generated by pentose phosphate pathway also contributes to the defense potential against action of oxidants. It is, therefore, of interest to find out whether anti-aging drugs such as centrophenoxine, DMAE and chlorpromazine modulate the activity of antioxidant enzymes and also of the oxidative enzymes of pentose phosphate pathway. Our previous preliminary studies have already indicated that the oxidative enzymes of PPP were increased by DMAE (Roy and Singh 1983). Thus in view
have some beneficial effects on various brain disorders, a normalizing effect in cyanide-intoxicated animals and also some inducing effects on the mechanism that retard ageing, the extent to which the beneficial effects of these geriatric drugs are manifested in the brain electrical activity is also of considerable interest.

The objective of the present work was, thus, to determine the effect of above mentioned geriatric drugs on the activity of enzymes: catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, on lipid peroxidation and on lipofuscin accumulation. This was expected to provide an answer to the question whether these drugs produce gerontologically beneficial effects by activating chemical pathways that retard peroxidative damage. Besides enzymatic activity, influence of these drugs on EEG activity and multiple unit activity of the brain has also been studied. The effects of the drugs on the enzymes have been studied in subcellular fractions from different regions of brain in 6, 9 and 12 months rats. Electro cortical activity along with multiunit activity recording have also been studied in the parietal cortex of the brain in three age groups (6, 9 and 12 months) of rats.

In this thesis are, thus, given the age-related changes in the activity of the enzymes - catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase in soluble and particulate fractions. The age-related changes were also studied in lipid peroxidation, the lipofuscin accumulation
and also in the electroencephalographic activity. The effects of the drugs have been studied on these parameters. Most data obtained in this study are new and extend our information concerning the mechanism of action of the given geriatric drugs.