Learning is a relatively permanent change in behaviour that occurs as a result of experience. In order for learning to take place, first of all, it is necessary that the sensory system should process the stimuli and then sensation should be processed by the information processing system into some kind of permanent physical change so that it can be stored and later expressed in behaviour. Thus, the normal functioning of
the sensory system appears to be a prerequisite for
learning to occur.

Anecdotal reports and clinical studies of learning
in humans under general anaesthesia have failed to provide
unequivocal evidence for learning in this state. Apparently
learning occurs only if the stimuli (usually auditory)
have a high emotional content and their presentation
coincides with the lightening of anaesthesia (Trustman
et al.,1977). Animal studies have also yielded similar
findings (Miller, 1947). However, recently some
researchers like Weinberger, Gold and Sternberg (1984)
reported that learning is also possible in the
deep anaesthetic state. It seems somewhat unbelievable
because the term anaesthesia means loss of sensation.
The first anaesthetic drug was discovered by Priestley
in 1776. He discovered the first inhalation anaesthetic,
Nitrous Oxide, and accurately described the sensations
following its inhalation. Among its initial users was
Horace Wells (1844) a dentist in Hartford, U.K. who
used it for painless extraction of a tooth. Morton, in
1846 successfully showed the use of ether as a general
anaesthetic in the first classic demonstration held in
the operating room of the Massachusetts General Hospital,
Boston, U.S.A. Since then the science of anaesthesiology has progressed considerably and many better agents are now available for use. These anaesthetics can be divided into two broad categories, i.e. local anaesthetics and general anaesthetics. Local anaesthetics are drugs which, when applied directly to peripheral nervous tissue, block nerve conduction and abolish all sensations in the part supplied by that specific nerve. They are generally applied to somatic nerves and are capable of acting on axons, cell-bodies, dendrites and synapses. The general anaesthetic agents are capable of depressing all the functional elements of the central nervous system (CNS). It has been postulated that anaesthetics inhibit the ascending reticular activation system (RAS), which normally maintains a state of wakefulness. It is very difficult to formulate a single theory about the mechanism of action of the general anaesthetics, as the individual agents differ widely in their physical and chemical properties. Generally, it is believed that anaesthetics, probably, act by blocking excitatory synaptic transmission, but a few agents may act by prolonging synaptic inhibition. Both pre-synaptic and post-synaptic actions are likely.
The anaesthetics do not react immediately, rather, they take some time, or in other words, we can say that there are various stages of anaesthesia. Guedel in 1920, referring mainly to the anaesthetic activity of ether, outlined four stages of general anaesthesia. These can be distinctly discriminated with the majority of volatile general anaesthetics, although there are certain important differences among them.

The first stage is known as the stage of analgesia. This stage stretches from the beginning of inhalation of the anaesthetic to loss of consciousness. The gradual depression of the cortical centre is manifested as a sensation of remoteness, feeling of suffocation or as visual or auditory aberrations. A feeling of warmth is experienced by some individuals.

The second stage is known as the stage of delirium or excitement. This stage is associated with excitement, shouting, increased muscular activity, breath holding and hyperventilation. Some of these manifestations are due to release of the lower centres from the inhibitory control of higher centres as a result of cortical depression. The pupils may dilate and marked hypertension
Figure 1 Showing the Classification of General Anaesthesia
and tachycardia may develop, probably due to the release of adrenaline. However these can be minimised by proper pre-anaesthetic medication.

The third stage i.e. the stage of surgical anaesthesia is characterized by a gradual loss of reflexes, regular respiration and relaxation of the skeletal muscles. Reflex activity is lost. This stage is usually employed for surgical interventions.

The last stage is known as the stage of respiratory paralysis. This stage is characterized by severe depression of the vital medullary centres.

Broadly the general anaesthetics can be classified into two groups (Figure I) i.e. the inhalation anaesthetics, which may be volatile liquids or gases and the nonvolatile anaesthetics which includes the barbiturates and non-barbiturates. The inhalation anaesthetics are administered through a mask, which may simply consist of a few layers of gauze or might be a complex instrument which fits the face. The non-volatile barbiturates are administered intravenously to produce anaesthesia. The most commonly used ultra-short acting barbiturate is Thiopentone. The sodium salts of the ultra-short acting
Barbiturates are readily soluble in water but the solution deteriorates on keeping. The clinically used solutions of barbiturates are intensely alkaline with a pH varying from 10.5 to 11. High alkalinity causes local irritation and thrombosis.

Induction by these compounds is very quick and pleasant. The subject passes through the stages of hypnosis and deep sleep to anaesthesia. Consciousness is lost first, then the reflex activity and muscle tone and lastly the medullary centres are depressed. Though the reflexes return in 10-30 minutes, the organism remains disoriented for several hours. There are many uses of these type of anaesthetic agents like, induction of general anaesthesia for operation of short duration and also as an anticonvulsant in the emergency treatment of convulsions. There are many advantages of these intravenous thiobarbiturates, i.e. ease of administration; non explosive; induction is rapid and pleasant with no irritation of mucous membranes; quiet respiration, no sensitization of myocardium to adrenaline and speedy recovery after small doses. However, there are certain disadvantages of these anaesthetics. The stage of surgical anaesthesia is
reached very quickly, thereby, making constant supervision necessary. During induction unpleasant and even fatal reactions like apnea, coughing, laryngospasm and bronchospasm may develop. The respiratory centres are depressed and they become less sensitive to carbon dioxide. However, muscular relaxation with barbiturates is not adequate. It also produces hallucinations and other restlessness. Also, silent regurgitation may occur due to relaxation of gastro-esophageal sphincter.

From the above discussion it is clear that the sensory as well as central nervous system functions are depressed by the anaesthetic drugs. Also a majority of investigations in the area of learning and retention accepted the idea that the memory trace is localized within the central nervous system (CNS). Thus the fact that learning can occur under anaesthesia appears to be farfetched. Before we examine the possibility of this learning a perusal of the physiological bases of learning in the normal state is necessary.

A great deal of research have been directed at examining the chemical or physiological mechanisms by which the trace is initially recorded in the CNS and
subsequently preserved. The well accepted theory about the neural changes associated with memory is the synaptic theory according to which learning results in some kind of changes at the synapse. These neurophysiological memory changes may involve potentiation of existing synapses, unmasking of previously ineffective synapses or formation of new synapses. Since the synaptic transmission is mediated through the neurotransmitters, and if learning results in changes at the synaptic level, then changes in these transmitter substances must affect learning. Researches in the last 30 years have revealed that changes in the brain neurotransmitter affect retention.

The brain norepinephrine (NE) concentrations have been found to be sensitive to training procedures and correlated with later retention performance (Gold and van Buskirk, 1978). Dopamine (DA) agonists injected into the hippocampus immediately after training improve retention performances whereas administration of DA antagonists impairs retention (Grecksch and Matthies, 1982). Significantly high levels of hippocampal serotonin (5HT) levels are observed in animals with good retention as compared to animals with poorer retention (Dunn, 1980). Similarly
acetylcholine (ACh) has also been found to affect retention depending on type of organism, dosage, degree of training, time between training and drug administration and time between training and testing (Deutsch, 1971; Stanes, Brown and Singer, 1976; Gold and Zornetzer, 1983).

However, peripheral endogenous substances, the physiological responses of the organism to the learning situation, are also found to play an important role in modulating memory processes. A variety of hormones have been reported to modulate memory processes when administered peripherally (Gold and Zornetzer, 1983; McGaugh and Gold, 1986).

There is extensive evidence indicating that peripheral epinephrine (E), derived primarily from the adrenal medulla, can regulate the neuronal mechanisms responsible for storage of new memories (Gold and Zornetzer, 1983; McGaugh, 1983; McGaugh and Gold, 1986). Posttraining peripheral injections of E can modulate memory for appetitive (Sternberg, Isaacs, Gold and McGaugh, 1985; Sternberg et al., 1985) and avoidance tasks (Gold and van Buskirk, 1975, 1976, 1978; Izquierdo, 1984; Izquierdo and Dias, 1984) in juvenile (Gold, Murphy and
Cooley, 1982), adult and aged (Sternberg et al., 1985) rats and mice. Peripheral administration of E can also enhance long term potentiation, a neurophysiological analog of memory (Delanoy, Gold and Tucci, 1983).

The peripherally administered E modulates memory in a dose and time dependent manner. An inverted 'U' shaped relationship has been found between the dosage of E and later retention performance in which memory enhancement is seen at moderate doses and amnesia observed at higher ones. (Gold and van Buskirk, 1975, 1976; Gold, van Buskirk and Haycock, 1977; Yadava, 1985). The memory modulating effect of E has been found with immediate but not delayed injections indicating that E modulates the consolidation process (Gold and van Buskirk, 1978). Also posttraining E levels have been found to be sensitive to footshock levels and later correlated with retention proformance (McCarty and Gold, 1981). A dose of E which enhances memory of training with low footshock has been found to impair memory of more intense footshock (Gold and van Buskirk, 1976) suggesting that endogenous responses to the training footshock interact with the exogenously administered E to determine the consequences of E on memory.
Further, McCarty and Gold (1981) found that an E dose (0.1 mg/kg) that enhances memory results in plasma E levels comparable to those found after high footshock training while a higher dose (0.5 mg/kg) that impairs retention results in exaggerated plasma E levels. This indicates that there is an optimal level of circulating E below or beyond which memory consolidation is poor (Gold and Zornetzer, 1983).

Additionally, E has also been found to influence the retrieval processes. A number of researchers found that E produces amnesia when administered in high doses immediately after training. However, when the same hormone is also administered at the time of testing, good retention was observed indicating that E modulates memory, not by interfering with the storage mechanisms but by influencing the retrieval processes (Izquierdo and Dias, 1983, 1985; Nagpal, 1985; Gupta, 1987).

Further support for the role of peripheral endogenous substances in memory modulation is available from investigations in which the effect of memory modulatory treatments are found to be attenuated in animals pre-treated with peripherally administered E (Gold and Sternberg, 1978; Squire, Davis and Spanis, 1980; Sternberg and Gold, 1980, 1981; Sternberg
et al., 1985) suggesting that the effect of these treatments on memory may be mediated by adrenal medullary release of E.

In addition to effects on memory this hormone also has other central nervous actions, such as, influence on electrographic arousal (Baust, Niemezyk and Vieth, 1963), amygdala kindling (Welsh and Gold, 1984, 1985), cerebral blood flow (Berntman et al., 1978) and central noradrenergic activity (Gold and van Buskirk, 1978, 1978b). It has been found that peripherally administered E that affects memory in a dose dependent manner also affects the brain NE concentrations. A 20% decrease in brain NE levels have been observed with memory enhancing doses of E while a 40% decrease in NE concentration was found with a memory impairing dose. Similar transient changes in the magnitude of NE levels has been observed with low and high footshock training suggesting that a central NE response to training may modulate the storage of information and by extrapolation, may mediate the effects of E on memory. (Gold and van Buskirk, 1978).

Alternatively, effect of peripheral E may be mediated through the opioid receptors. Researches
indicate that E causes release of hypothalmic beta-endorphin in the rat (Carrasco et al., 1982). Various forms of aversive and non-aversive training release beta-endorphin from the rat brain but not from the pituitary gland (Izquierdo et al., 1980, 1981, 1982), while systemic or intra cerebro-ventricular (icv) administration of low doses of beta-endorphin cause retrograde amnesia for a variety of tasks (Izquierdo et al., 1980, a, b; Martinez and Righter, 1980; Izquierdo and Dias, 1982; Lucion et al., 1982). These effects are antagonized by naloxone indicating that there is an endogenous opioid mechanism which affects memory processes. Additionally, Izquierdo and Dias (1983) found that beta-endorphin, administered peripherally, potentiated the amnestic effect of E. Naloxone on the other hand potentiated the facilitatory effect and antagonized the impairing effect suggesting that peripheral E influences memory processes through opioid receptors.

Further, the effects of peripherally administered E on memory has been found to be blocked by brain lesions. Liang and McGaugh (1983) studied the effect of stria terminals (ST) on retention facilitation produced
by E. No retention deficits were observed in rats with ST lesions. Retention facilitation was observed in sham ST lesioned rats when treated with E. However the lesions of ST attenuated the facilitative effect of E on retention suggesting that the integrity of the ST is essential for the effect of E on memory processes.

Similarly, Liang et al., (1985) reported retention impairments with posttraining amygdala stimulation in rats with an intact adrenal medulla. However, amygdala stimulation did not impair retention in demedullated rats, but stimulation did impair retention, if E was administered prior but not after the amygdala stimulation. This suggests that peripherally released E interacts with amygdala stimulation either by altering the state of amygdala prior to stimulation or altering the immediate physiological consequences of amygdala stimulation.

Thus, it is clear that peripheral endogenous levels of E affect brain processes underlying memory. However the exact mechanism through which peripheral E effects the central nervous system functioning underlying memory is not yet clear, as E and other hormones cannot readily cross the blood-brain-barrier (BBB) (Dunn and
A more feasible alternative is that peripheral NE might affect brain activity from the periphery rather than direct entry into the brain. This possibility gains support from the fact that alpha-adrenergic antagonists attenuate the amnesia produced by frontal cortex stimulation if administered peripherally but not centrally (Gold and Sternberg, 1978; Sternberg and Gold, 1980).

Thus, it appears that the noradrenergic sympathetic nervous system and/or the adrenal medulla may be potentially important in memory modulation. However a number of studies have demonstrated that adrenal demedullated animals appear to learn and remember as well as intact controls (Orsingher and Fuiginiti, 1971; Sternberg et al., 1981). Even sympathetic blockade with bretylium, a peripheral sympathetic noradrenergic antagonist does not affect retention performance, nor does it attenuate the amnesia produced by frontal cortex stimulation (Sternberg, Gold and McGaugh, 1982).

Thus, it appears that individual blockade of adrenal medullary secretion or the release of NE at the
adrenergic synapse in the central or peripheral nervous system, due to training/treatment, does not affect memory. However, the response of the effector cells to circulating levels of E or NE released from either the medulla or sympathetic neurons is more important in modulating memory processes.

Alternatively, effect of peripheral E might be glucose mediated, as a major physiological action of peripheral E is the release of glucose from the liver (Gorbman et al., 1983). Studies indicate that posttraining glucose injections can enhance memory. As with E, glucose modulates memory in an inverted 'U' shaped dose dependent and time dependent manner (Gold, 1986). Hall and Gold (1986) also found that plasma glucose levels show a footshock intensity related increase immediately after inhibitory avoidance training. Further, memory enhancing doses of E and glucose result in increase (about 30%) in plasma glucose levels which are similar to each other and to the values seen after training with a high footshock, which normally results in good retention. Because, glucose modulates memory and because, a major physiological action of E is to increase circulating glucose levels it is reasonable to assume
that glucose represents part of the physiology by which E acts on memory.

Glucose, under normal circumstances is the major fuel for metabolic activity in the CNS (Ingvar and Lassen, 1975; Lowry, 1975; Sokoloff, 1980). Unlike E, glucose is readily and actively transported into the brain (Oldendorf, 1971; Pardridge and Oldendorf, 1975; Lund-Anderson 1979). It has also been reported that glucose injected into the lateral ventricle enhances memory in an inverted 'U' shaped dose dependent and time dependent manner (Lee and Gold, 1986). The ready access of glucose to the brain is particularly important to brain function because glucose is the major source of energy for the CNS (Lowry, 1975; Sokoloff, 1980). A series of studies suggest that pyruvate dehydrogenase which is critical in the production of cellular energy is activated after avoidance training (Morgan and Routtenberg, 1981) and after long-term potentiation (Browning, Bennett and Lynch, 1979; Browning et al., 1979).

Since glucose is the primary precursor of the substrate for pyruvate dehydrogenase in the brain, it appears that circulating glucose levels may regulate the
efficacy of neural processes underlying central processing of information through activation of this or other enzymes, thus indicating that the mechanisms of memory storage may be highly dependent on energy production.

Glucose is also a key precursor of acetyl COA in the CNS which is necessary for acetylcholine (ACh) synthesis and ACh synthesis is sensitive to relatively small changes in plasma glucose levels (Gibson and Blass, 1978). Treatments which affect central cholinergic systems also affect memory processing (Gold and Zornetzer, 1983) and deficits in cholinergic function may contribute to age related memory dysfunctions (Coyle, Price and Delong, 1983). Thus, it appears that peripheral E via glucose release, may exert control over central acetylcholine functions, which in turn, are related to memory storage.

Considered together, these findings indicate that under normal circumstances peripheral E modulates memory processes. Although the ultimate effect of peripheral E must be on brain processes underlying memory storage, it is not yet clear whether E directly affects the brain or this influence is initiated in the periphery.
Recently, Weinberger, Gold and Sternberg (1984) reported that an injection of E also enables learning to occur in rats under deep general anaesthesia, the state during which E secretion is stepped up. Similar results were observed by Gold, Weinberger and Sternberg (1985).

The learning facilitation produced by E, under the state of anaesthesia raised the possibility that E enables learning, under anaesthesia, by reducing the depth of anaesthesia. However, analysis of heart rate and measurement of reflexes during training indicate that E does not lighten the state of anaesthesia. Further the group receiving the lowest dose of E, had the highest retention score, thus further indicating that E did not enable learning merely by lightening the level of anaesthesia -- it would indeed, have had the least anti-anaesthetic action for these animals. Additionally, the animals treated with E but never presented with paired CS-UCS combination showed no retention thus indicating that retention in the experimental group was not due to some non-associative effect of E, such as increased sensitivity to the conditioned stimulus. (Weinberger, Gold and Sternberg, 1984).
Thus the possibilities remain that E enables learning under anaesthetic state either by directly initiating the CNS processes underlying memory and/or initiating peripheral activity such as glucose release. Glucose release, in turn, could affect the metabolic activity of the CNS and thus possibly modulate the memory processes by controlling substrates available for memory storage or through an influence on Acetyl-CoA necessary for ACh synthesis.

With this background, we will pass on to the next chapter dealing with the review of pertinent literature.