CHAPTER I

INTRODUCTION
The rubric 'shock' denotes a wide spectrum of critical events, which if untreated, result in morbidity and mortality. It has been recognised as a clinical syndrome for almost 2000 years, but even today it is a controversial phenomenon in the medical world. A precise definition, continues to change, as the understanding of surgical physiology and metabolism continues to grow. Shock can be best defined, as inadequate perfusion of vital organs, typically associated with marked hypotension and subsequent failure of multiple organ systems (Higgins and Chernow, 1987).

In hemorrhagic shock, there is disproportion between the blood volume and vascular capacity resulting in an overall insufficiency of blood flow and tissue perfusion. Hypovolemic shock is a progression of three physiological conditions. Simple hypotension, impending shock and irreversible shock (Weggers and Ingraham, 1946). The first stage requires no treatment, other than the removal of the immediate cause. The second phase needs treatment to correct, and if left uncorrected, proceeds to the third stage, the irreversible
When the blood loss exceeds 40%, timely intervention is required. Fall in arterial pressure triggers the baroreceptor reflex and sympathetic release of catecholamines. If the shock state persists, a number of regulatory feedback mechanisms are disordered. The severe reflex vasoconstriction which aids in the maintenance of arterial pressure, may itself become a complicating factor, by reducing the tissue perfusion. This may further initiate a vicious cycle leading to widespread cellular injury. Blood flow to brain, heart and kidney is further reduced and severe ischemia to these vital organs leads to irreversible tissue damage. Reduced flow to the medullary vasomotor center, depresses the activity of compensatory reflexes. It involves altered function of the heart and peripheral vasculature. Acute tubular necrosis, caused by the prolonged renal hypoperfusion may result in prolonged post-shock insufficiency. Interruption of renin-angiotensin aldosterone system may also have some adverse effect on kidney. Accumulation of toxic products and metabolic acidosis result from the hypoperfusion of the tissues. These metabolic derangements
ultimately result in failure of energy requiring active transport system of cell membranes. The integrity of the capillary membrane is disrupted and fluid, proteins and blood cells seep into the extravascular tissue space and further aggravate the shock state by reduction in the blood volume.

The treatment of shock, even today is far from clear. There is little doubt that the most effective treatment of hemorrhagic shock is to restore the lost blood volume in time. Since the pathogenesis and the pathophysiology of shock are poorly understood, no therapeutic agent has been found clinically useful, although numerous ones have been tried and reported to be effective. Some of the broad categories of these pharmacological agents that have been studied in an attempt to prevent irreversible phase of hemorrhagic shock include adrenergic agents, adrenergic blockers, glucocorticoids, prostaglandins, angiotensin and its inhibitors.

Adrenergic agents like catecholamines have been used clinically in the treatment of shock. Though experimentally these drugs were shown to improve the
arterial pressure, coronary and cerebral blood flow, renal blood flow decreased and renal resistance increased further (Frank et al, 1956 and Shanbour et al, 1972). These drugs did not improve the survival rate of animals subjected to hemorrhagic shock (Rush, 1967; Daugher and Harrison, 1970). Consequently the free use of these drugs in hemorrhagic shock has been seriously questioned. Then the potential beneficial effect of adrenergic blockade therapy was established in shock. Adrenergic blocking drugs with fluid therapy was found beneficial only as a prophylactic pretreatment in hemorrhagic shock (Hess et al, 1983). Glucocorticoids and its derivatives also have received extensive study in the treatment of shock. In this case, also the best result was seen only with the pretreatment of animals or treatment, very early in the shock state (Lefer et al, 1978). The role of prostaglandins and angiotensin and its inhibitors in oligemic shock, remains to be defined and the field is still very open for investigation (Hess, 1983).

The role of opioids and opioid receptors in shock has just begun to unfold. The release of beta-endorphin into the blood stream, following
hemorrhage is one of the neuroendocrine changes that occur in stress (Faden and Holaday, 1979). This endogenous opioid may mediate some deleterious effects seen in shock. The sudden drop in blood pressure during rapid hemorrhage can not be explained, only on the basis of simple blood loss, which would have given rise to fall in cardiac output—rather the observation is that the fall in blood pressure is due to fall in peripheral resistance. This is inspite of the fact that there are enough circulating vasoconstrictor chemical stores. Faden and Holaday (1979) proved this experimentally by showing that these reserves could be available by annuling the effect of endorphins released, at the opiate receptors by naloxone. The increase in blood pressure by naloxone improves the perfusion pressure for all the organs. Experimentally, naloxone has been credited with the potency to reverse cardiovascular depression associated with hemorrhagic shock (Vargish et al, 1980; Guril et al, 1982). In addition, it has been reported that naloxone, reverses the cellular hypoxia (Rees et al, 1982), improves transmembrane potentials (Alberts et al, 1982), and stabilizes the Na-K pump (Curtis and Lefer, 1980). Naloxone appears to be one of the most promising therapeutic agents to be studied in detail.
Kidney has a very important role to play in regulating the homeostatic mechanism in hemorrhagic shock. Hence any deterioration in the function of kidney will upset the homeostatic mechanism and will act as a vicious cycle for aggravating the already depressed cardiovascular function. Any improvement in the renal circulation will not only improve renal function but also break this vicious cycle, which will enable the kidney to resume its homeostatic function. Though a lot of attention has been given to the role of opioid receptors in stress conditions like hemorrhagic shock, there is no study in the literature which demonstrated the improvement of kidney function by naloxone, the opiate receptor antagonist. The present study was undertaken to explore the impact of naloxone treatment in canine kidneys subjected to hemorrhagic shock and to elucidate its potential role in the control of homeostatic mechanism and survival of animals. An attempt has also been made to compare its effect with clinically used drugs like noradrenaline and dopamine in dogs subjected to hemorrhagic shock.