STUDIES ON THE METABOLIC RESPONSES TO HAEMORRHAGE IN EXPERIMENTAL ANIMALS

THESIS

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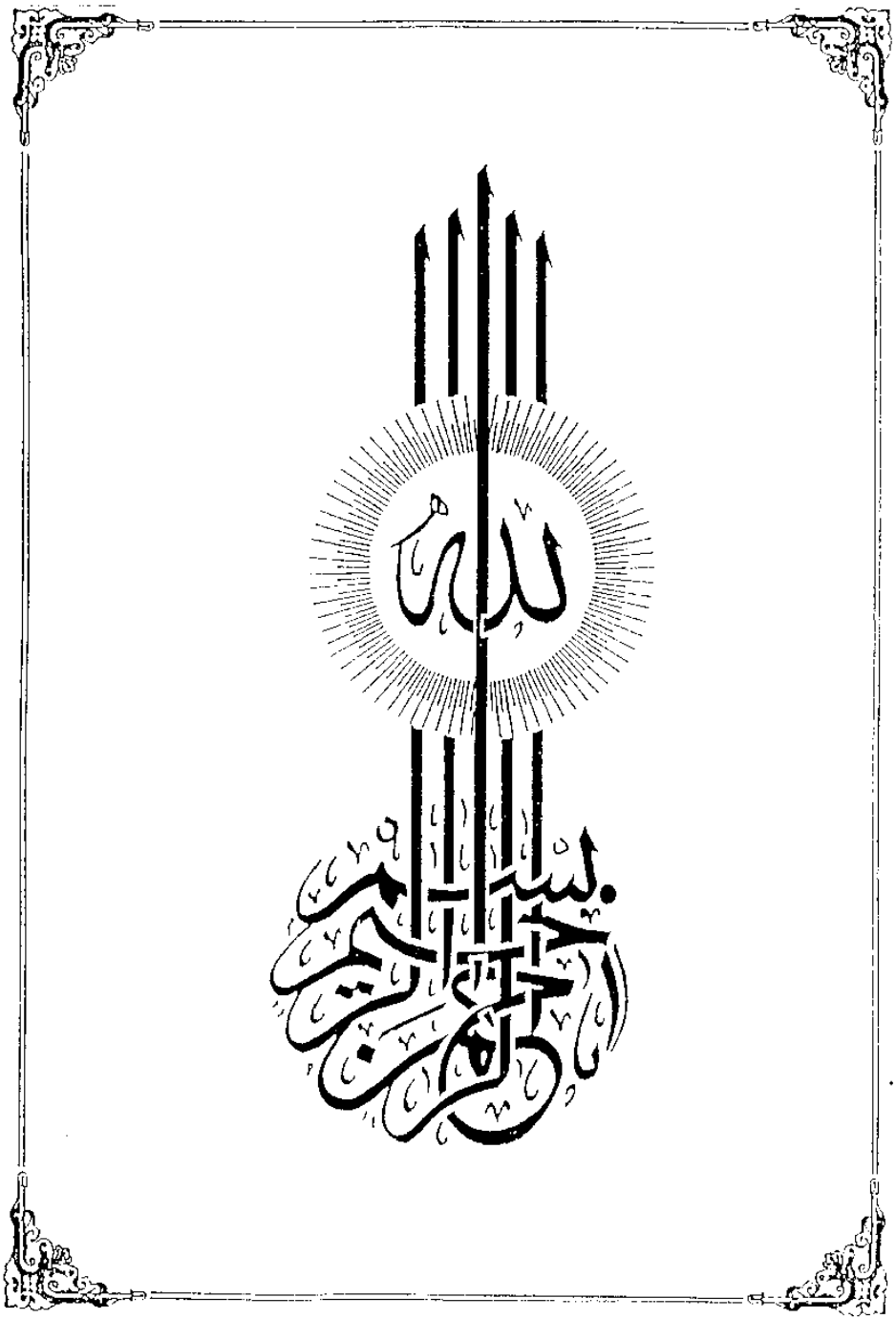

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PREFACE

As early as 1877 Claude Bernard described the metabolic response to haemorrhage. Since that time experimental studies on haemorrhagic shock in laboratory animals were carried out. This helped in understanding the basic disturbances in carbohydrate metabolism, and the deleterious effects of excessive accumulation of lactate have been realised.

In the last decade, as a result of experience gained through lessons during the Vietnam War, interest in research on haemorrhagic shock was renewed. Much work has been done on the metabolic effects of severe haemorrhagic shock in experimental animals and the use of therapeutic measures applied. However, during the whole of this period studies were devoted almost exclusively to degrees of blood loss resulting usually in irreversible shock, and only occasional references were made to lesser degrees of haemorrhage.

In clinical practice blood loss amounting to 30% of the blood volume or less is commonly seen. Knowledge of the effects of smaller grades of haemorrhage on carbohydrate metabolism is still lacking; and the

importance of such studies is thus self evident. First an understanding of the resulting disturbances in intermediary metabolism is an essential prerequisite to the management of such conditions. Secondly, realizing the large amounts of blood, needed for volume replacement, which is usually in short; the need for an intravenous fluid therapy is apparent. This form of volume restoration must satisfy the requirements of correcting the prevailing anoxic metabolism and maintaining an adequate arterial blood pressure. This ideal fluid substitute may serve to minimize transfusion requirements or even totally replace blood. However, its discovery is still a dream and worthy of research trial.

PART I

INTRODUCTION

DISTURBANCES IN CARBOHYDRATE METABOLISM FOLLOWING HAEMORRHAGE

No problem in medicine can have excited so much interest throughout the ages as loss of blood. From the very dawn of man's history he must have known of the dangers of haemorrhage, though his acquaintance with physiological bleeding -during menstruation and childbirth- no doubt taught him that less severe losses are not fatal and indeed have little effect on health.

Interest in the metabolic effects of haemorrhage started in the nineteenth century when Claude Bernard (1877) showed that after haemorrhage there is a sustained increase in blood sugar concentration. This observation has since been confirmed in various species of animals by diverse shock-inducing procedures. With the passage of time it has been recognized that the problem of blood loss concerns each and every tissue and organ in the body; and that haemorrhage may lead to profound disturbances not only at the moment of the catastrophe but also at varying periods afterwards.

Advances in understanding the disturbance of metabolism after haemorrhage were the result of the rapid

progress in knowledge of the normal metabolism and its hormonal control. There is a tendency to regard all the metabolic consequences of haemorrhage as being designed to aid recovery, in other words biochemical observations are often given teleological interpretation.

The biochemical changes that occur in haemorrhagic shock have been ascribed to the effect of hypoxia from the characteristic reduction in blood flow. Other functions are impaired, including nourishment of the tissues in its broadest sense and inadequate removal of various metabolites because of diminished venous and lymphatic flow. Various intracellular metabolites escape into the extravascular space and these induce local and systemic reactions. Hormonal factors are also involved and these may exaggerate the already present metabolic changes.

This review of literature will be restricted to a consideration of the alterations of carbohydrate metabolism following haemorrhage. This subject has been reviewed by Wilhelmi (1948), Engel (1952) and Levenson et al (1961).

Hyperglycaemia following haemorrhagic shock has been repeatedly shown in man (Carey et al, 1970, 1971), dogs (Beatty, 1945 a,b; Seligman et al , 1947; Bauer et al,

1969a; McCormick et al, 1969 a), sheep (Halmagyi et al, 1966, 1968), Baboons (Moss et al, 1970; Cerchio et al, 1971; Hiebert et al, 1972), rats (Engel et al, 1943; Russell et al, 1944; Le Page, 1946; Strawitz et al, 1961) and in pigs (Carey and Wallack, 1970).

The magnitude of the blood sugar rise is dependant in part on the level of liver glycogen, and in part on the integrity of the adrenal cortex (Engel et al, 1943; Selye and Dosne, 1941). Although it is well established that there are certain differences in the metabolic activity of the various species of animals, their hyperglycaemic response to blood loss in surprizingly similar.

The blood sugar rise usually persists into advanced shock until the terminal stages when blood glucose may fall to subnormal levels (Engel, 1952, Engel et al, 1943; Beatty, 1945 a,b; Bauer et al, 1969 a; Strawitz et al, 1961), especially when the environmental temperature is high (Trusler et al, 1939). The fall in blood sugar may be related to depletion of liver glycogen following haemorrhage (Wiggers, 1950; Engel 1952; Levenson et al, 1961; Le page 1946) and to increase in the utilization of carbohydrate by peripheral tissues.

Russell et al (1944) showed that fatal haemorrhage in the eviscerated rat brings about a greatly increased rate of fall of blood sugar, indicating rapid utilization by this peripheral tissue preparation. Beatty (1945 a) demonstrated a progressive increase in A-V glucose difference followed by a terminal decline in dogs after haemorrhage, changes which were also interpreted in terms of increased glucose utilization by muscles. Additional evidence is provided by the frequent observations of depleted muscle glycogen (Le page, 1946), and increased glucose uptake by muscle (Drucker and De Kiewiet, 1964) of animals during haemorrhagic shock.

Accompanying the enhanced utilization of carbohydrate, there is an increase in blood lactate and pyruvate, which increase in parallel fashion until late in shock when the lactate rise becomes much more steep resulting in a striking rise in lactate-pyruvate (L/P) ratio (Engel et al, 1943; Russell et al, 1944; Beatty, 1945 a; Root et al, 1947; Seligman et al, 1947). The increasing L/P ratio being indicative of a shift towards anaerobic metabolism in the tissues. This situation is the result of tissue anoxia. As anoxia develops glucose conversion to pyruvate continues, but pyruvate cannot enter the Krebs cycle

because of oxygen deficit. The pyruvate is converted to lactate, which diffuses readily to tissue fluid and plasma. This metabolic pathway produces only a fraction of the energy produced by aerobic metabolism, but does allow for cellular survival if conversion to aerobic metabolism is not too long in coming.

Although the magnitude of lactate elevation is not a reliable predictor of survival, there seem to be a relationship between the severity of shock and the degree of lactic acidaemia. There is, however, no specific level of arterial lactate that is incompatible with survival and no advantage is gained by deriving excess lactate or L/P ratio. If lactate levels do not fall promptly as volume is restored prognosis is extremely poor (Carey et al,1971).

The development of metabolic acidosis in shocked patients was observed early in this century by Henderson (1910) and Cannon (1918). It is widely believed that in haemorrhagic shock acidosis mainly results from increased production and accumulation of lactic acid in the blood stream (Beatty, 1945 a; Hardaway, 1961; Broder and Weil,1964; Cloutier et al, 1969), due to inadequate oxygen supply to the cells, yet it is not affected by hyperbaric oxygen (Cain and Connolly, 1967).

The contribution of peripheral tissues to these changes in intermediary carbohydrate metabolism is illustrated by the steep rise of the blood lactate in eviscerated rats after haemorrhage (Russell et al, 1944), and by the high levels of muscle lactate and pyruvate found in rats subjected to haemorrhagic shock (Le page, 1946).

Beatty (1945 b) presented evidence that late in shock the ability of the liver to remove lactate fails progressively. Seligman et al (1947) do not agree with this latter view, they showed that during haemorrhagic shock dogs cleared injected lactate as the normal animals. They suggested that the altered L/P ratio is due in part to impairment of volume and velocity of blood flow. Also intravascular glycolysis as a consequence of prolonged hypoxaemia may contribute to this change. Corday and Williams (1960) showed that the lowered blood flow to the liver during shock influences hepatic lactate metabolism in two ways: first the amount of this substrate presented to the liver is lowered; and second, the low hepatic blood flow may be a causative factor because the oxygen supply to the liver is lowered. Schröder et al (1969) lowered hepatic blood flow and oxygen consumption in dogs by inducing cardiac tamponade, this results in hepatic lactate

production and lactic acidosis. They concluded that the liver is the organ responsible for the development of lactic acidosis in low flow states by either failing to clear lactate from the portal blood or by lactate production.

A large increase in serum inorganic phosphorus after haemorrhage was noted by various groups of workers (Seilgman et al, 1947; Root et al, 1947; Bauer et al, 1969 a). Allison et al (1947)in a careful study on dogs after haemorrhage or trauma, noted the coincidence of the early increase in plasma inorganic phosphorus with the fall in blood pH. The authors suggested that depression of renal function in the shocked dogs may be responsible for the observed increase in phosphate. Other factors may be the breakdown of ATP and creatine phosphate in muscle and other tissues (Le page, 1946), depression of liver function, and possibly some alteration in parathyroid activity during shock (Engel, 1952).

It is apparant from the standpoint of survival, that the above changes during shock may prove to be critical.

Recently, it was shown that profound ultrastructural changes occur in mitochondria after prolonged haemorrhagic shock (Holden et al, 1965; Strawitz and Hift, 1965).

Oxidative phosphorylation in heart mitochondria from dogs in shock is lowered (Strawitz and Hift, 1956; Packer et al, 1958). These findings indicate damage to mitochondrial enzyme system.

Insulin response during haemorrhagic shock:

Although blood sugar elevation has been a uniform finding in shock, both clinically and experimentally, there is some conflict in regard to insulin kinetics. One potent stimulus to insulin release is hyperglycaemia; in opposition to the hyperglycaemic stimulus is the suppressive effect of catecholamines. The fact that exogenous insulin reduces blood sugar in rats shocked by clamping(Haist & Hamilton, 1944) and in dogs during haemorrhagic shock (Spigelman and Ozeran, 1970); the presence of the hyperglycaemia suggests that during shock the blood sugar level is either not regulating endogenous insulin secretion or that normal insulin activity may be deranged or blocked (Levenson et al, 1961).

Studies in dogs have shown that haemorrhagic shock is associated with a rise in insulin levels (Bauer et al, 1969 a; McCormick et al, 1969 a) indicating that the pancreas is capable of responding to the stimulus of hyperglycaemia despite any reduction of splanchnic circulation and the high levels of catecholamines (Bauer, et al 1969 b).