# STUDY OF PLATELET FUNCTION IN ANEPHRIC ANIMALS

**THESIS**

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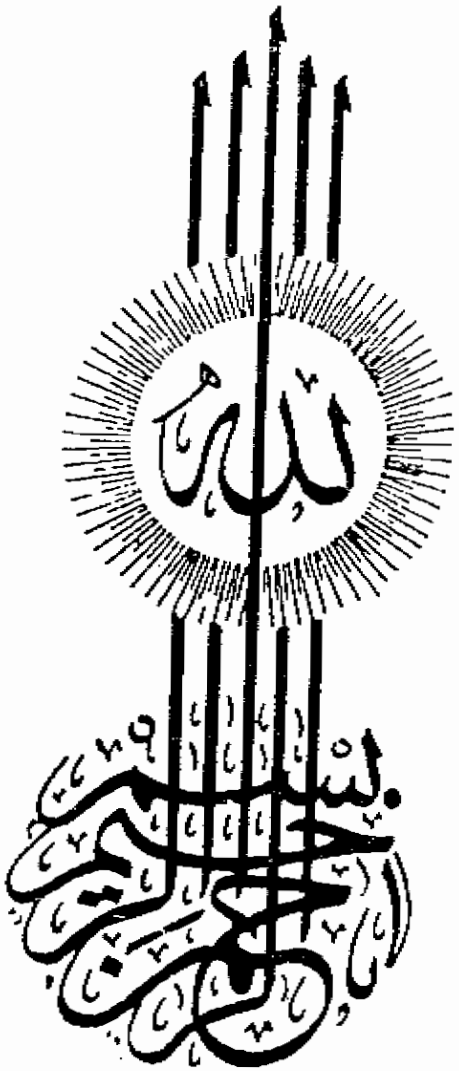

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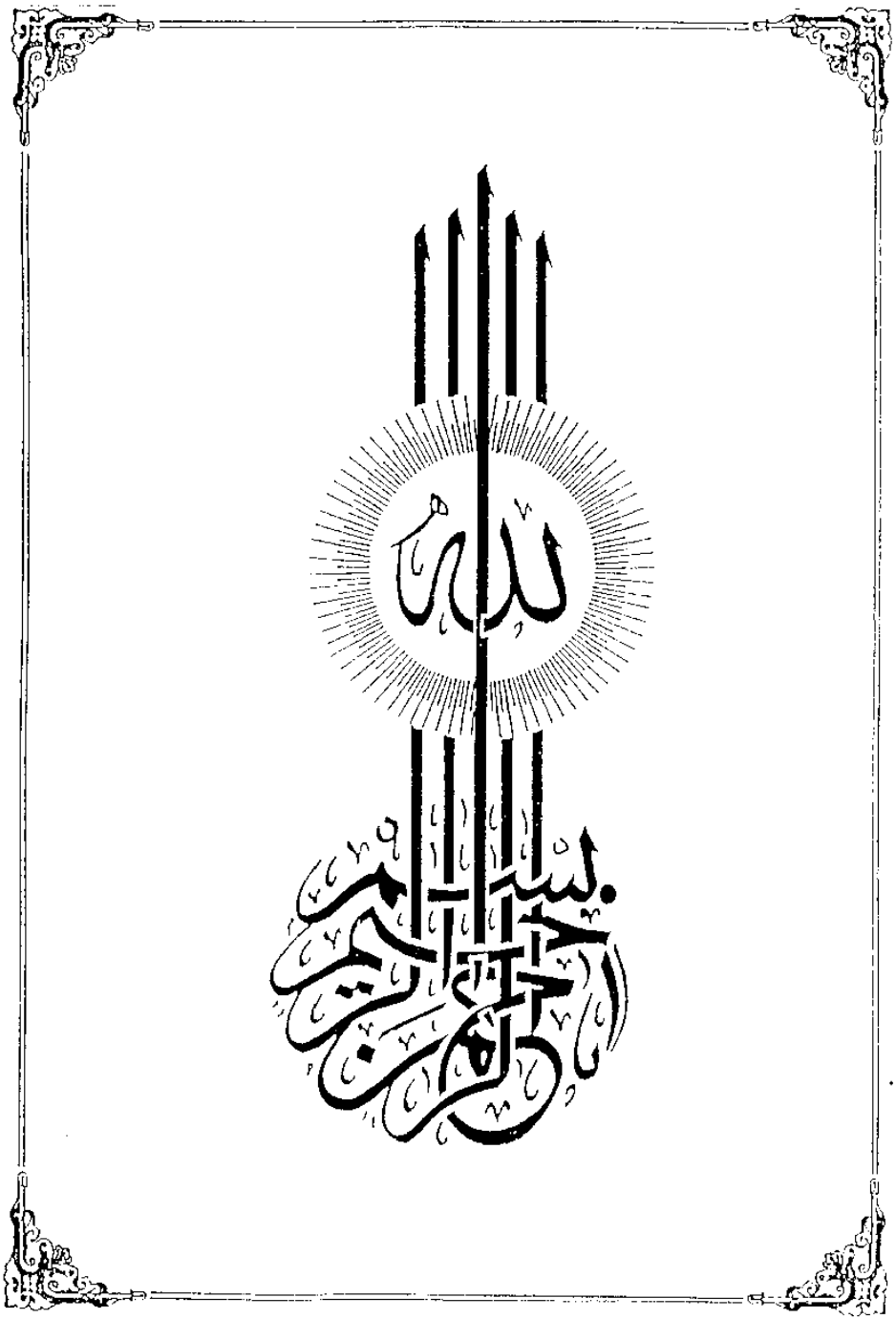

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# Introduction

# INTRODUCTION

A high mortality from hemorrhagic complications is a feature of acute renal failure. Although there is a fairly general agreement that platelet function is inhibited, the pathogenesis of the platelet defect has still not been defined.

The question remains whether there is a specific uremic toxin which is removed by dialysis or whether a non-dialyzable factor involved in other metabolic or hormonal abnormalities of the uremic state is responsible. Since physiological aggregation has an absolute requirements for calcium, knowledge of the role of calcium in these abnormalities of platelet function in uremia would be of value.

# Aim of the work

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The object of this investigation was two fold. First, to study the time course of changes in platelet function following experimental acute uremia induced by bilateral nephrectomy. Second, attempt to find out any relation between platelet aggregation and the changes in biochemical parameters especially calcium.

# Review of Literature

# PLATELET FUNCTION IN UREMIA

Excessive bleeding in Uremic patients has been recognized for many years, and it became an important problem in renal dialysis. It is responsible for nearly one-tenth of all deaths in acute renal failure; and may be ascribed to several mechanisms, for example, capillary or coagulation defects.

However, the most important cause of bleeding is platelet defect. A large number of mechanisms may account for this defect in platelet function. The present review of literature describes some ways by which platelet function is influenced in Uremia.

## *THROMBOCYTOPENIA*

Low platelet count has been reported as the most common abnormality in uremic patients [Larrian and Adelson, 1956, Kuhlback, 1957, Altschuller et al., 1960].

Altschuller et al., [1960] concluded that the contribution of platelet to the haemorrhagic disorder in the

uremic state is quantitative phenomenon. It is also the feature of some 25 percent of patients with acute renal failure [ Stewart and Castaldi, 1967]. Several investigators have shown normal platelet count in chronic uremic patients [Losowsky and Walls, 1971, Jorgensen and Ingeberg 1979]. No correlation between uremic bleeding and thrombocytopenia was demonstrated. Life span of platelets in uremia was found to be normal [Stewart and Castaldi, 1967]. And such thrombocytopenia as occurs is propably due to defective production.

The origin of the uremic bleeding is still unexplained. Various platelet functional defects has been described that the contribution of platelets to the haemorrhagic disorder in the uremic state is a quantitative phenomenon. Lewis et al., [1956] were the first to report that an abnormality in platelet function was the most consistent finding in patients with uraemia having bleeding problems. Later, Rath et al., [1957] reported that a qualitative platelet defect rather than a quantitative phenomenon in the uremic patients. Cahalane et al.,[1958] demonstrated that the platelets of uremic patients manifested a prolonged bleeding time, short prothrombin consumption time. These platelets appeared to lack platelet

factor 3 (Thromboplastic activity ) and appeared morphologically abnormal under the electron microscope. The platelet factor 3 activity was normal, however, after the platelets had been disintegrated by some oscillations indicating that the platelets possessed platelet factor 3 activity but seemed to be unable to release it.

Cahalane et al., [1958] suggested that the bone marrow can produce normal platelets and that the metabolites in uremic plasma inactivate the platelet factor 3 activity in the circulating platelets. Castaldi et al. [1966] demonstrated that the impaired platelet function could not be attributed to thrombocytopenia, and those tests of coagulation which do not depend upon platelets were not affected. They also suggested that the platelet dysfunction could not be related to either to the duration of renal failure or to its cause. Uremic patients with evident bleeding had a prolonged bleeding time and impaired platelet aggregation and clot retraction, also platelet factor 3 was abnormal. They further demonstrated that the uremic patients who were not bleeding had reduced platelet aggregation and clot retractions, but the bleeding time and platelet factor 3 were usually normal. The same authors

demonstrated that the correction of the bleeding defect by dialysis indicates that a biochemical effect of renal failure is responsible.

Horowitz et al., [1967] demonstrated that patients with uremia have both prolonged bleeding times, suggesting poor platelet plug formation, and impaired prothrombin consumption, ascribed to defective factor 3 activation. They reported that ADP plays a central role in the formation of the platelet plug and also activates platelet factor 3, accelerating fibrin formation. Thus a defective response to ADP in uremia could account for most of the hemostatic abnormalities observed. They also demonstrated that the inhibitory effect of uremic plasma could not be attributed to urea for two reasons, first, no correlation could be found between the platelet factor 3 level and blood urea nitrogen, second, addition of urea to normal platelet-rich plasma did not inhibit platelet factor 3 activation with ADP. The previously inhibitory effect of uremic plasma could be overcome by the addition of calcium. Jerushalmy et al., [1966] investigated a series of guanidines compounds as inhibitory of platelet aggregation, the strongest inhibitors were diguanidins compounds whose inhibitory activity could be overcome by small increments of ionic calcium.

Eknoyan et al., [1969] suggested that the abnormality in platelet function in uremia is due in part at least to the action of elevated blood urea or one of its metabolites. They found that platelet adhesiveness was significantly lower in bleeding subjects than in those without bleeding and that there was a significant inverse correlation between the level of serum urea nitrogen and creatinine, and the adhesiveness of the platelets. The abnormalities of platelet function were improved by dialysis. Their findings confirmed the view that the platelet abnormality was reversible and due to a dialyzable product that accumulates in renal failure. The authors were unable to reproduce the platelet abnormality in vitro by addition of urea, dextrose, manitol, creatinine, urate, phosphate, potassium, or magnesium or by alteration of pH or osmolarity within the range might be encountered in patients with severe uremia.

Horowitz and Bronx [1970] demonstrated several lines of evidence indicating that a circulating toxin is responsible for the poor function of platelets in uremia, platelets from subject with uremia can not be distinguished from those of normal individuals in terms of phospholipids