Serum Nitrate, a nitric oxide generation product as a new prognostic marker in liver cirrhosis

Thesis

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Clinical and Chemical Pathology

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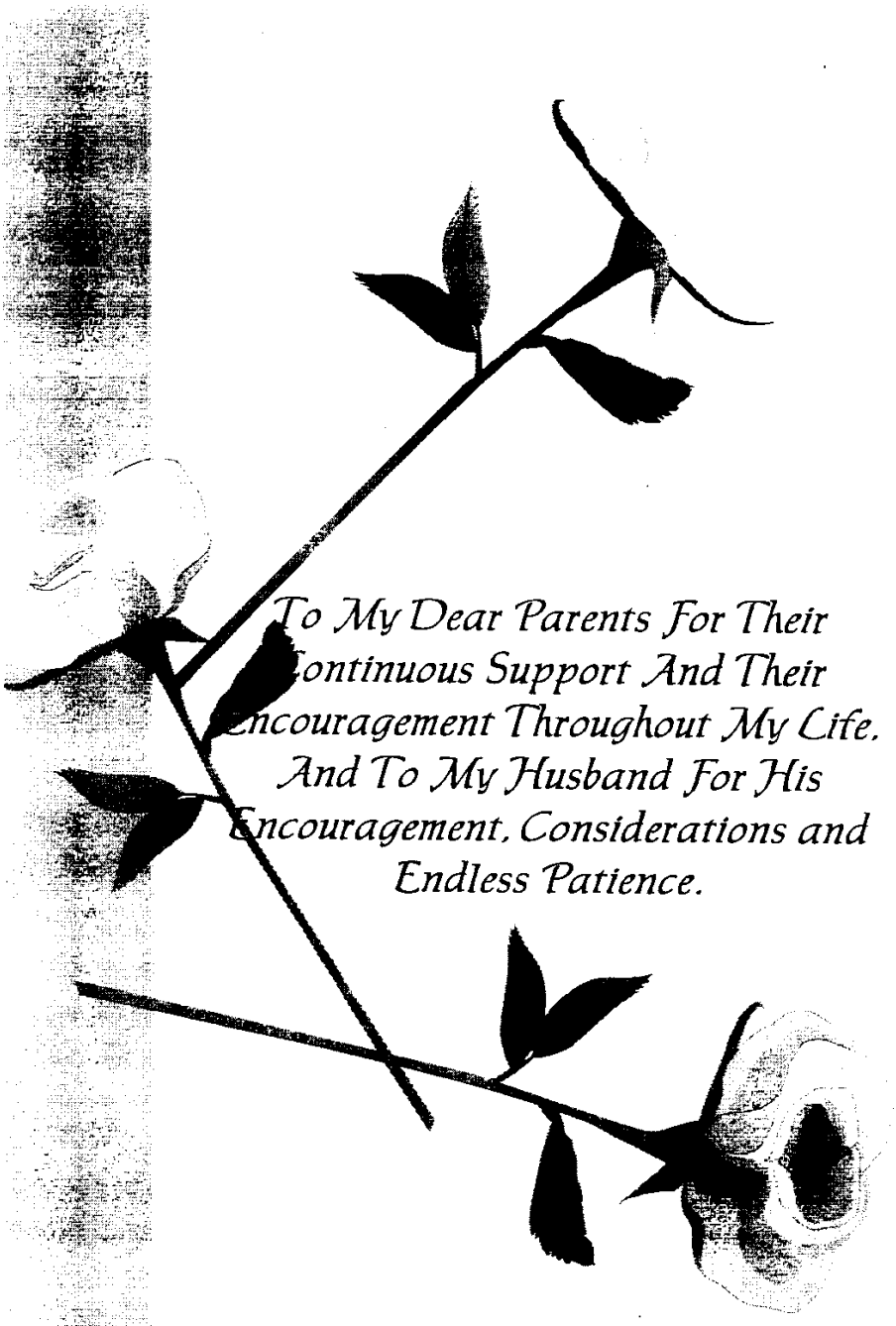

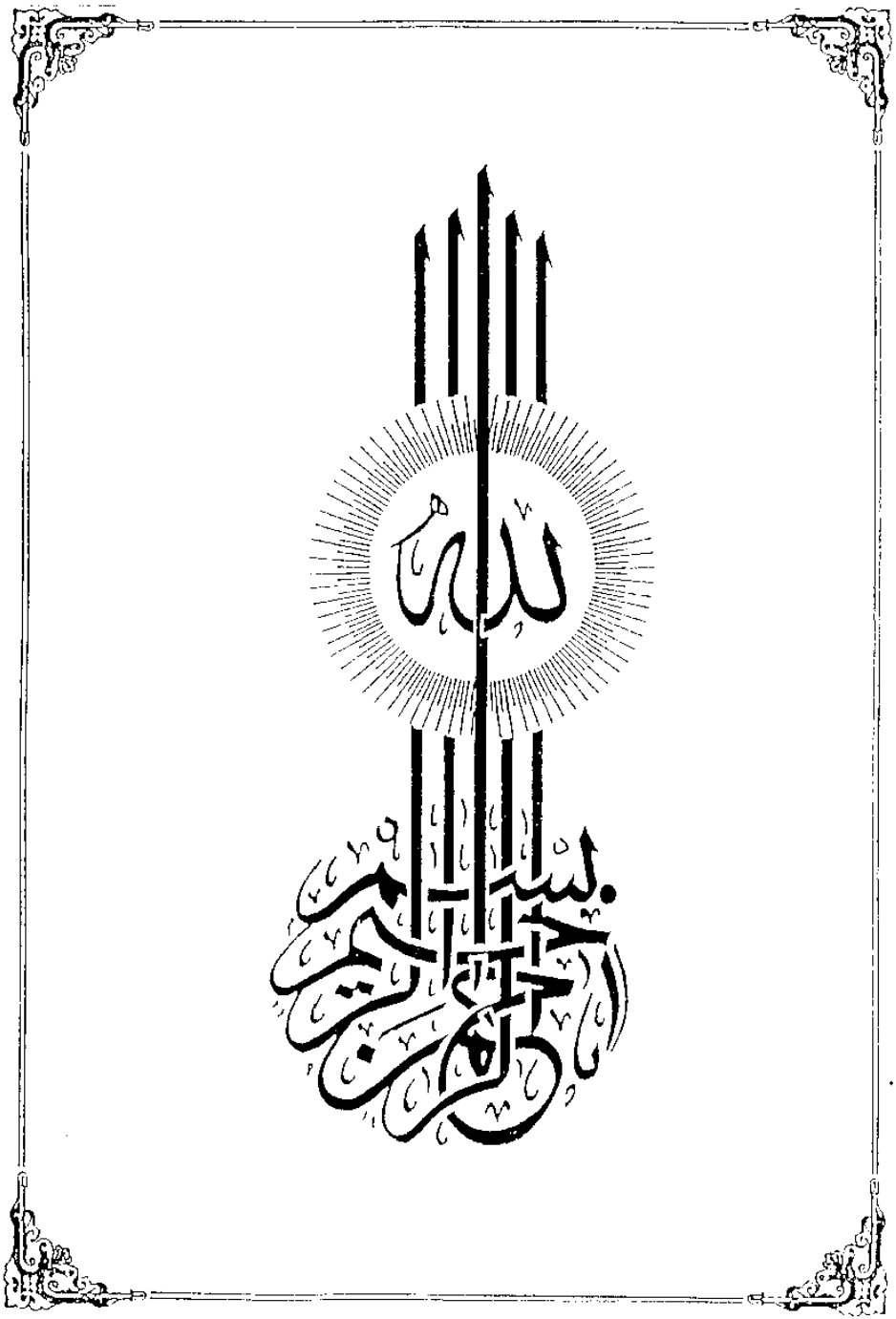

بسم الله الرحمن الرحيم

﴿ ... وَمَا أُوتِيتُم مِّنَ العِلمِ إلاَّ قَلِيلاً﴾

صدق الله العظيم

سورة الإسراء ... من الآية ٨٥

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List of Abbreviations

ALP:	Alkaline phosphatase.
ALT:	Alanine transaminase.
ADP:	Adenosine diphosphate.
AIDS:	Adults immunodefficiency syndrome.
ATP:	Adenosine triphosphate.
AST:	Aspartate transaminase.
BCP:	Bromocresol purple.
BUN:	Blood urea nitrogen.
Ca^{2+}:	Calcium.
DW:	Distilled water.
cGMP	Cyclic guanosine monophosphate.
EDRF:	Endothelial-derived relaxing factor.
FAD:	Flavin adenine dinucleotide.
FN:	False negative.
FP:	False positive.
γ-INF	γ-interferon.
GGT:	γ-glutamyl transpeptidase.
hANP:	Human atrial natriuretic peptide.
H_3PO_4	Phosphoric acid.
HRS:	Hepatorenal syndrome.
IL-1:	Interleukin-1.
KOH:	Potassium hydroxide.
β-NADP:	β-nicotinamide adenine dinucleotide phosphate.
β-NADPH:	β-nicotinamide adenine dinucleotide phosphate (reduced form).
NO:	Nitric oxide.
NOS:	Nitric oxide synthase.
PPB	Part per billion.
RB:	Reagent blank.
S:	Sample.
SB:	Sample blank.
TN:	True negative.
TNF:	Tumor necrosis factor.
TP:	True positive.

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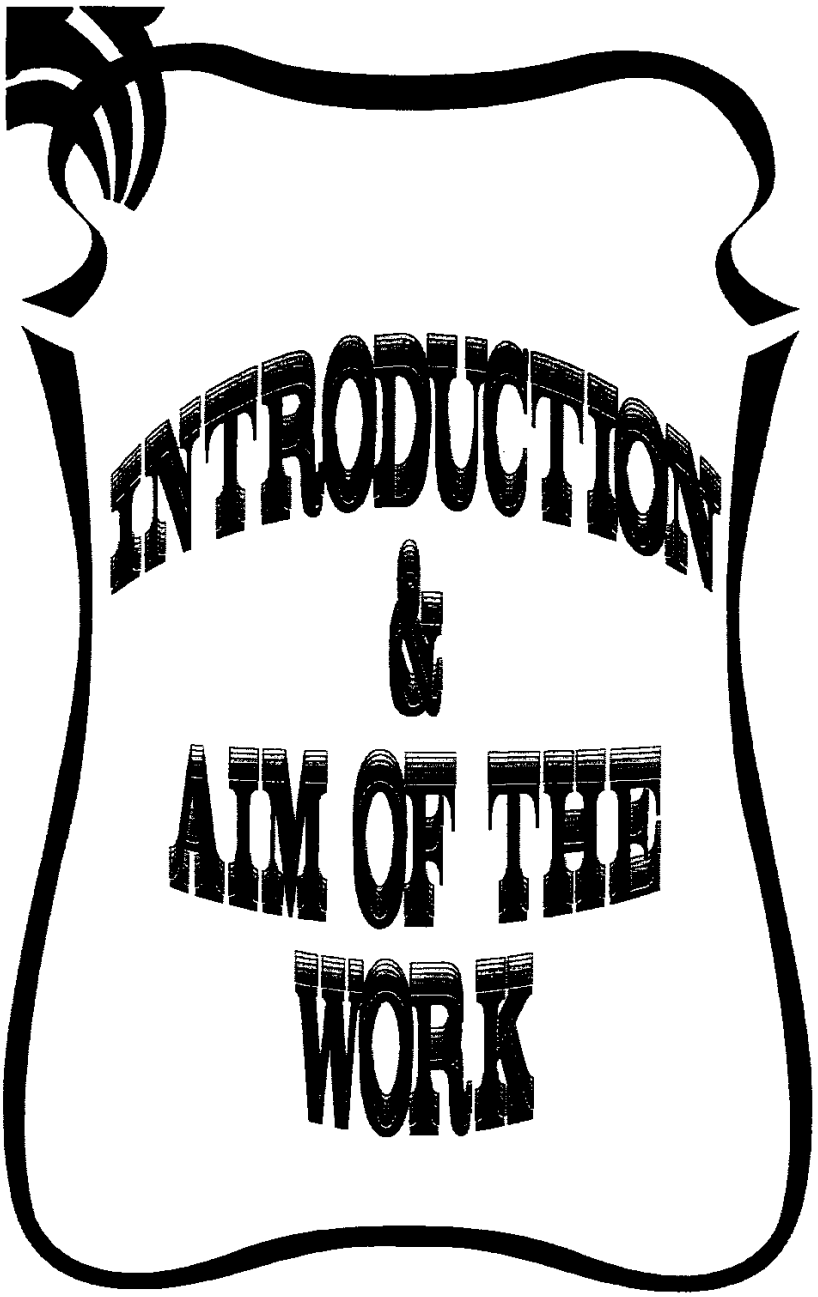

In 1980, ***Furchgott and Zawadzki*** demonstrated that an endothelium-derived relaxing factor was responsible for acetyl choline dependent vasodilatation. This factor was later shown to be nitric oxide (NO), a molecule which is implicated in certain pathophysiological processes such as control of blood vessel tone, neurotransmission, host immune defense, septic shock and atherosclerosis ***(Mancada and Higgs, 1993; and Lowenstein et al., 1994).***

Nitric oxide is synthesized by the enzyme nitric oxide synthetase from the amino acid L-arginine and diffuses toward the target cells, for example, NO synthesized in endothelial cells diffuses through the smooth muscle cells and is responsible for relaxation by activating the soluble guanylate cyclase ***(Palmer et al., 1988).***

Nitric oxide is important for cellular signaling in non-hepatic tissues, and recent evidence suggests that it may be important regulatory of some liver functions. The liver can produce considerable amounts of NO under both constitutive and inducible conditions and may play a critical role in the arteriolar vasodilatation, high cardiac output and systemic hyperdynamic state of cirrhosis ***(Vallance and Mancada, 1991).***

Nitric oxide is an extremely lipid soluble gas and undergoes rapid oxidative degradation to the stable breakdown products, nitrates and nitrites. Upon entering the vascular system, nitrite react rapidly with

oxyhaemoglobin resulting in the formation of methaemoglobin, while nitrates remain stable in the circulation, therefore NO is best determined in the serum as nitrates ***(Bories and Bories, 1995).***

Increased concentrations of NO breakdown products have been described in patients with sepsis syndrome, in advanced cancer patients receiving interleukin-2 therapy, rheumatoid arthritis, epilepsy, hypoxic ischemic cerebral injury ***(Hibbs et al., 1992; and Evans et al., 1993).***

It has been documented that cirrhotic patients have a significant increase in the concentrations of serum nitrate and nitrite compared with control groups ***(Guarner et al., 1993; and Albillos et al., 1995)*** and consequently, as cirrhosis progresses, vascular resistance continue to fall. Such vasodilatation produced by high NO level may persist, the resulting hypotension may lead to secondary disturbances in renal, hepatic blood flow, and ascites. Indeed, the degree of haemodynamic disturbance correlates with prognosis ***(Bosch et al., 1988; and Knowles et al., 1990).***

Aim of the Work

In this study, measurement of serum nitrate, as an index of nitric oxide generation is done in a trial to establish a relation ship between nitric oxide level and the clinical progression of liver cirrhosis. Moreover, the role of serum nitrate in providing prognostic information to identify those patients at risk of developing hepatorenal syndrome will be highlighted for treatment modulating purposes.