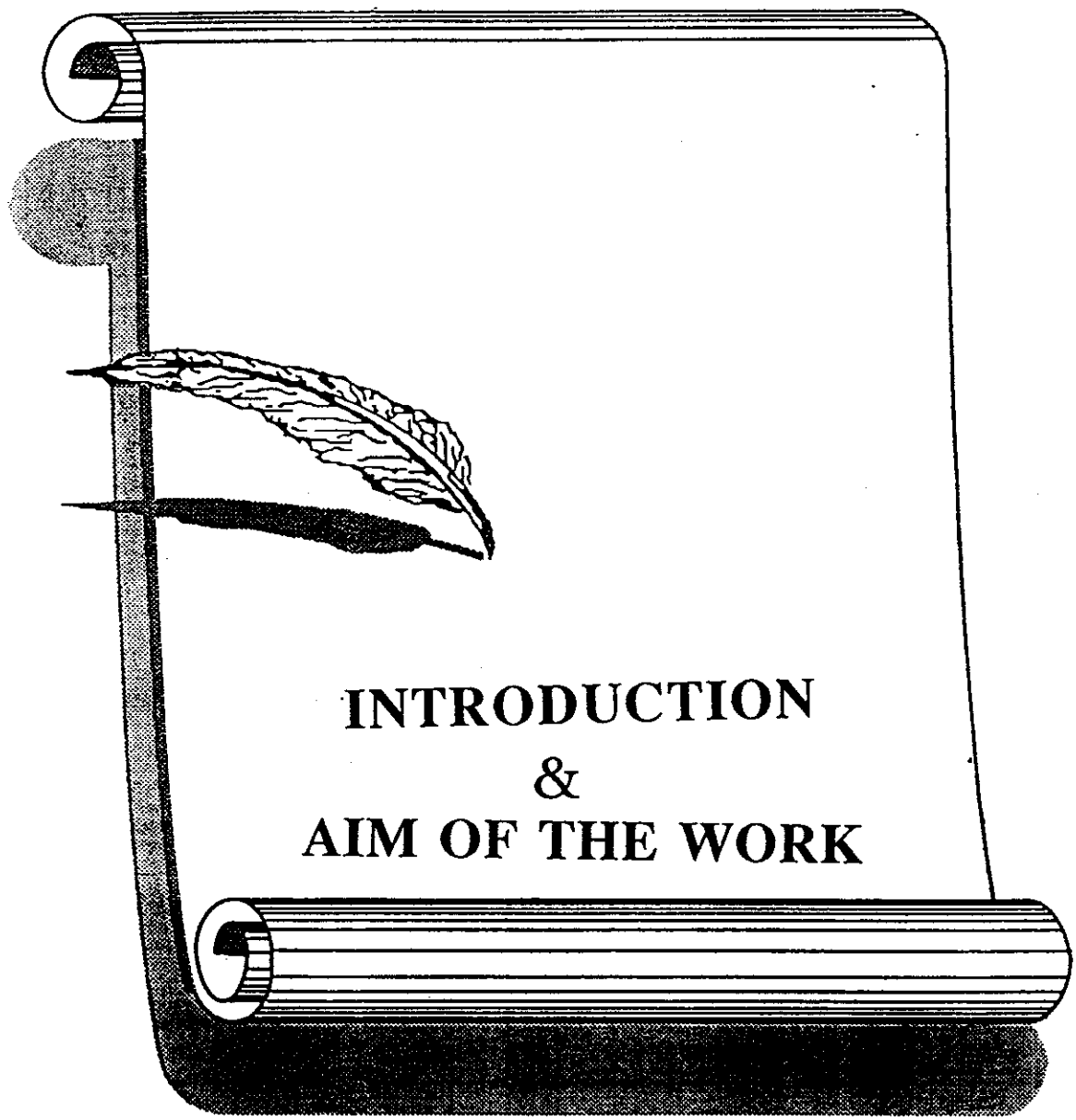

INTRODUCTION
&
AIM OF THE WORK

INTRODUCTION

Host responses to microbial infections, injury, and inflammatory diseases include mounting of specific and nonspecific immune responses against causal agent and dramatic changes in metabolic, hematologic, and immunologic parameters that are often grouped together and called acute-phase response *[Klasing; 1988].*

The intensity of the response can vary with the severity and duration of the particular disease. In general, the full spectrum of the response involves metabolic changes such as aminoacidemia, proteinuria, net nitrogen catabolism, hypoferremia, hypozincemia, and hypercuperemia; concomitant with these changes is the oncet of dramatic increases in hepatic acute-phase protein synthesis, the so-called acute-phase reactants *[Dinarello, 1991].*

Research effort has been shifted from experiments designed to describe the changes in protein, energy and mineral metabolism associated with an immune response, to investigations of mediators responsible for this response *[Klasing, 1988].*

In the past few years, progress in molecular immunobiology has led to the characterization of still growing number of hormonelike proteins that, besides the classical hormones, mediate the interaction between different cells and tissues.

These hormonelike proteins are called peptide regulatory factors or cytokines *[Klasing, 1988, and O'Garra, 1989].*

Cytokines form a complex network of mediator molecules which constitute a communication system coordinating different cells and tissues within the body, thus maintaining or restoring physiological homeostasis *[Green, 1989].*

Most of these cytokines are glycoproteins with a molecular mass below 80,000 Da. Cytokines usually act in picomolar concentrations through specific high affenity cell surface receptors. In contrast to the classical hormones, they act mainly in a paracrine and autocrine manner on neighboring cells and themselved, but they can also act in endocrine manner on distant cells *[Andus, et al., 1991].*

Although, a regulated cytokine response to pathogens or toxins is essential to host defense and tissue repair, cytokine excess can lead to tissue damage and fibrosis *[Wong, et al., 1989 and Van Snik, 1990].*

Cytokines are responsible for the changes of the hepatic protein metabolism, which are observed in response to trauma or infection. These changes are characterized by an impaired uptake of amino acids and an accelerated protein breakdown in muscle and by an amino acid shift from the periphery to the liver. Concomitantly, acute phase protein synthesis and gluconeogenesis in the liver are inhanced *[Bibby, et al., 1989].*

Inflammatory states are often associated with an increase in the plasma levels of free fatty acids and with hyperlipidemia, the latter being primarily due to the accumulation of very low density lipoproteins *[Klasing, 1988].* Several cytokines stimulate hepatic fatty acid and cholesterol synthesis *[Feingold, et al., 1989].*

Some cytokines augment glucose uptake in hepatocytes, leading to a decrease in plasma glucose and insulin [Jacob, et al., 1989], also promote gluconeogenesis in isolated rat hepatocytes through in activation of pyruvate kinase [Moule, et al., 1988] and activate glycogen synthase through a mechanism distinct from that of insulin, leading to increased glycogen synthesis *[Chowdhury, et al., 1987].*

Many transport proteins of minerals and trace elements are acute phase proteins. Changes in their synthesis lead to cosiderable changes in plasma levels of iron, copper and zinc. Administration of many cytokines produce a transient depression of zinc in the plasma and a concomitant up take of zinc by liver *[Klasing, et al., 1984 and Bibby et al., 1989].*

Some cytokines may interact synergistically at their targets with certain classical hormones of endocrine system. Glucocorticoids play a permissive and synergistic role with respect to induction of hepatic acute phase protein synthesis. On the otherhand, glucocorticoids exert a feedback inhibition

on cytokine production in inflammatory cells *[Heinrich, et al., 1990]*. In absence of glucocoticoids, the induction of acute-phase protein synthesis is abolished or impaired both in vivo and in vitro *[Bauer, et al, 1984]*.

Cytokines from cells of the immune system are often further subclassified as monokines and lymphokines, which are produced by a monocyte / macrophage and lymphocyte lineages, respectively *[Klasing, 1988]*.

It is well-known that monocytes and tissue macrophages play important roles in the regulation of various cellular functions by vitrue of synthesizing unique cytokines. Two major monocyte /macrophage - derived cytokines, tumour necrosis factor (TNF) and interleukin-1 (IL-1), have been well characterized. *[Le, et al., 1987]*.

An enormous amount of new information about the structure and function of TNF and IL-1 has surfaced during the last few years. Much of this new information was obtained as a result of successful purification of these cytokines and, mainly, the successful cloning and expretion of cDNAs for TNF and IL-1; *[Beutler et al., 1986]*.

Evidence of altered cytokine metabolism in human liver disease is now available. McClain and Cohen reported that in vitro cultured monocytes isolated from patients with alcoholic hepatitis secreted more TNF-α than monocytes from controls.

[*McClain et al, 1989*]. Tumour necrosis factor is produced and secreted by infiltrating mononuclear cells in focal inflammatory areas of liver. TNF production by peripheral blood monocytes is increased in chronic liver diseases and correlated with the activity of hepatitis. So, TNF-α may have a role in the inflammatory activity of chronic liver disease *[Yoshioka et al., 1990]*.

AIM OF THE WORK

To determine whether elevated tumour necrosis factor levels contribute to the clinical manifestations and complications of chronic liver diseases and to evaluate the relation between tumour necrosis factor and serum levels of interleukin-1β , interleukin-6 and C-reactive protein.