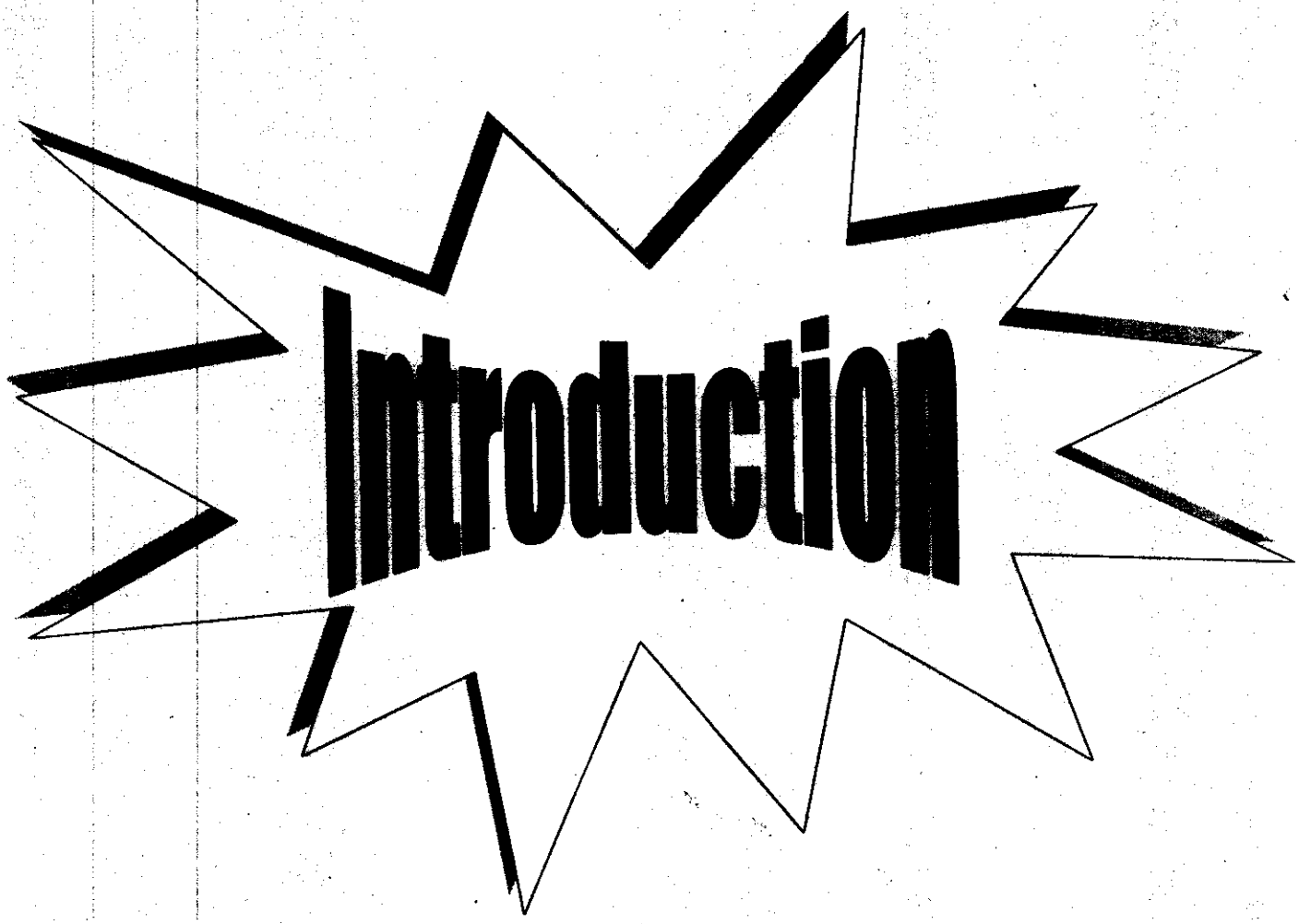
Introduction

INTRODUCTION

The leukaemias are a group of disorders characterized by the accumulation of abnormal white cells in the bone marrow. These abnormal cells may cause bone marrow failure, a raised circulating white cell count and infiltrate organs. Thus common but not essential features in acute leukaemia include abnormal white cell in peripheral blood, a raised total white cell count, evidence of bone marrow failure (i.e. anaemia, neutropenia, thromocytopenia) and involvement of other organ (i.e., liver, spleen, lymph nodes, meninges, brain or skin) ***(Wiernik et al., 1995).***

Leukemia is the most common childhood cancers; leukemia accounts for about one third of pediatric malignancies. Acute lymphoblaste leukemia (ALL) represents approximately 75% of all cases in children, and has a peak incidence at age of 4 years ***(William et al., 2000).***

The cause of leukemia is unknown in the majority of patients. several factors are however associated with the development of leukemia these factors are (genetics factors, environmental factors, viral infection, immunodeficiency, drugs and chemicals) ***(Philip, 2000).***

The clinical presentation and mortality in acute leukemia arises mainly from neutropenia, thrombocytopenia and anaemia because of bone marrow failure and less commonly from organ infiltration e.g. of meninges or testes ***(Bain and Catovsky, 1995).***

The disease may be recognized by conventional morphology only when blast cell in the marrow exceed 5% of the cell total. When the

number of leukaemic cells is 5% or less in the bone marrow, the leukaemia is usually undetectable by conventional morphology. Using modern sensitive cytogenetic, molecular biological technique, minimal disease, may however, be detectable although the blood and marrow appear normal ***(Bain, 1993).***

Most of the cytotoxic drugs used in leukaemia therapy damage the capacity of cells for reproduction. Combinations of at least three drugs are now usually used initially to increase the cytotoxic effect, improve remission rates and reduce the frequency of emergence of drug resistance ***(Beltinger et al., 1998).***

The aim of cytotoxic therapy is first to induce remission and then to eliminate the hidden leukaemia cell population by course of consolidation therapy ***(Zittoun, 1993).***

The molecular pathways that determine sensitivity or resistance of tumor cell towards anticancer therapy are not well understood. Irrespective of intracellular targets, most anticancer drugs have been shown to induce apoptosis in chemosensitive leukaemias and solid tumors ***(Debatin and Krammer, 1995).***

Apoptosis or physiological cell death is the way in which unwanted cells are removed. The majority of cell formed during haempoiesis are destined to die by apoptosis before they are fully differentiated and homeostasis of cell number is maintained by a balance between mitosis and apoptosis ***(Minegishi et al., 1995).***

In lymphoid cells the CD95 (APO-1/Fas)/ CD95 ligand (CD95-L) system is a key regulator of apoptosis ***(Friesen et al., 1997).***

The CD95 cell surface receptor is a 45 KD a type I transmembrane protein, expressed on avariety of cells including activated lymphoid cells. CD95 is a member of the tumor necrosis factor/nerve growth factor (TNF/NGF) receptor superfamily of cell surface molecules which mediates apoptosis ***(Bertoni et al., 2000).***

Selective induction of apoptosis via cell surface molecules such as APO-1 may represent a new approach for treatment of malignant diseases ***(Debatin, 1994).***

In order for neoplastic cells to expand their population and subsequently form leukemia, they must escape surveillance by the host defense system. A major mechanism for such escape from growth control, at least in lymphoid cells, is thought to be mediated via apoptosis triggered by the Fas receptor (CD95/APO-1) ***(Kamikira, 1999).***

Changes in propensity to apoptosis have been clearly linked to oncogenesis and most anticancer drugs appear to induce this process ***(Reed, 1995).*** The Fas signaling system probably play a critical role in the natural and chemotherapeutic cell death machinery.

The Fas gene found by ***Nagata and Golstein (1995)*** encodes mainly two isoforms, the membrane (mFas) and soluble (sFas) isoform ***(Papoff et al., 1996).*** The former is translated from the Fas full-length mRNA encoding extracellular (EC), transmembrane (TL) and intracytoplasmic (IC) domains. The latter is translated from alternative

spliced mRNA lackig the TM domain is present in T-cell culture supernatants, and may provide protection from Fas mediated apoptosis in vivo.

Over production of sFas in the tumor via alternative splicing may facilitate tumor progression through a biologic decacy effect similar to that of soluble TNF ***(Heaney and Golde, 1996).*** Thus not only mFas but also sFas may be involved in the relationship between tumor and host.

Soluble form of members of the TNF/NGF receptor family were show to prevent binding of the ligand to the cell surface receptor, and prevent cell from undergoing APO-1 ligand-induced apoptosis. Hence secretion of sAPO-1 may provide a mechanism for tumor cell to escape immunosurveillance and may be involved in leukemogenesis ***(Tamiya et al., 1998).***

Soluble Fas/APO-1/CD95 can be detected in serum or plasma of patients with defective Fas mediated apoptosis by a sandwich enzyme-linked immunosorbent assay (SELISA) ***(Cheng et al., 1994).***