PREFACE

I. PREFACE

The life of a new individual is initiated by the fusion of genetic material from the two gametes - the sperm and the egg. This fusion called fertilization stimulates the egg to begin development. The subsequent sequence of stages is collectively called embryogenesis. Early embryonic differentiation gives rise to trophoblast, which is the first tissue to differentiate in the early embryo and becomes extra-embryonic with the formation of the placenta forming the foetal side of the interface with maternal blood and tissues. Placenta protects and nourishes the growing foetus.

Abnormal fertilization can lead to a variety of diseased conditions. Gestational trophoblastic disease (GTD) comprises a spectrum of interrelated conditions originating from the placenta as a result of abnormal fertilization. Other terms often used to refer to these conditions include gestational trophoblastic neoplasia and gestational trophoblastic tumour (Soper et al, 2004). GTD includes different clinicopathologic entities such as complete and partial hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumour. The various forms of gestational trophoblastic disease can be defined and related to discrete pathologic aberrations occurring at different stages of trophoblastic differentiation. Some of these lesions are true neoplasms, whereas others represent abnormally formed placentas with a predisposition for neoplastic transformation of the trophoblast (Shih and Kurman, 2002).

John et al, (1993) reports the high prevalence rate of this disease in Kerala, 12 in 1000 deliveries. Since this disease is associated with pregnancy, it affects women of reproductive age, at a time when their social commitments are at a peak. The disease has remarkable features such as high degree of curability with appropriate chemotherapeutic management, consistent production of β-hCG and the tissue of the origin - the foetal chorion, which is genetically different from the host (Alex et al, 2002a). The process of invasion of trophoblast is akin to invasion by cancer cells. At times in hydatidiform moles, the increased trophoblast invasion of the maternal tissue occurs to the extent that systemic chemotherapy is needed for regression of the tumour. The overall situation in these conditions assumes the nature of an invasive tumour (Balaram et al, 2001a). But the pathology of this disease still remains vague. GTD is a borderline disease that can be taken as a model for the study of successful management of neoplastic diseases. Much importance is being focussed on the role of growth factors, in regulating the growth of malignant cells. Over-expression of growth factor receptors have been reported in GTD (John et al, 1997).

Growth factor receptors are important in regulating cellular processes such as proliferation, differentiation and survival. Among growth factor receptors, the most

frequently implicated in human cancers have been members of the epidermal growth factor receptor (EGFR) family. Increased activity of the EGFR receptor has been found in several cancers, including head and neck tumours, colon cancer, breast cancer, prostate cancer, gastric cancer and ovarian cancer (Herbst and Langer, 2002). EGFR over-expression is often correlated with poor clinical outcome (Johns et al, 2004).

EGFR expression has been associated with malignant progression of cells, inhibition of apoptosis, neoplastic angiogenesis, enhanced metastasis potential and both chemo resistance and radio resistance (Herbst and Langer, 2002). This receptor plays an important role in many types of human cancers. Receptor amplification, autocrine activation and / or deletion of exons 2-7 of EGFR gene have all been associated with tumour development. The traditional model of EGFR activation via ligand induced dimerisation and consequential kinase activation does not provide full understanding of its tumourigenicity (Zhu et al, 2003).

Since increasing evidence implicates EGFR signal transactivation in diverse pathophysiological disorders, including GTD (Chen et al, 1990; John et al, 1997; Filla and Kaul, 1997; Tuncer et al, 2000), elucidation of the underlying signalling mechanisms will help us to understand the highly complex network of signal transduction pathways emanating from this receptor and the relevance of its dysfunction in gestational trophoblastic disease, and also to develop novel therapeutic modalities.