Apoptosis and Inflammation. James D. Winkler (ed.). Birkhäuser Verlag, P.O. Box 133, CH-4010, Basel, Switzerland. 1999. 244 pp.

In human society, suicide often seems an irrational and impulsive act. Not so in the society of cells in an organism. Like obedient soldiers making a personal sacrifice for the common good, excess cells, or those that pose a threat to the well being of the organs, often commit suicide on command via an orderly process called programmed cell death/apoptosis. Although recognized in 1842 by Carl Vogt, the most recent re-discovery of cell suicide was in 1972 when the term apoptosis was adopted. A couple of years ago people had real doubt about apoptosis being involved in disease. Now almost everyone is sold on the idea. The past few decades have seen a spontaneous rise in the number of papers being published in the field of apoptosis. The vulnerability to different death signals and the ability to be saved from death by different inhibitors of apoptosis varies from cell type to cell type.

Apoptosis is a highly regulated process that is involved in physiological as well as in pathological conditions. There is extensive and growing understanding of the role of apoptosis and apoptotic signals in inflammatory and immune cells. This book has concentrated on this aspect and also focused on the key role of apoptosis in inflammatory and immune diseases. James D. Winkler set out in this book, to provide a comprehensive, conceptual, introductory account of the characteristics of apoptosis, its regulation and its role in diseases. This is followed by 12 chapters. Each chapter deals with a specific topic and the links between the topics and chapters are strong. Although the morphological characteristics of apoptosis are fairly universal across cell types, the molecular events that initiate, mediate and execute an apoptotic signal are intricate and vary between cell types. A series of intracellular changes that activate a proteolytic cascade which progressively dismantles structures and the cell ultimately degrades its DNA and dies.

The chapter on signalling cascades of apoptosis has focused on glucocorticoids, Fas and T cell receptor. Glucocorticoids stimulate apoptosis in immune cells and are used to suppress inflammation. Activation of a protease cascade is a biochemical hallmark of glucocorticoid-receptor induced apoptosis and is also common to Fas and T cell receptor (TCR). The protease caspase-3 cleaves a number of downstream targets such as poly ADP ribose polymerase (PARP), laminin B1, serum response element binding proteins (SREBPs), DNA fragmentation factor (DFF). Agents which inhibit dATP, cytochrome C release from mitochondria or block caspase action, block DNA degradation and apoptosis. Findings suggest a role of Fas-mediated apoptosis in induction of peripheral tolerance and/or in the antigen-stimulated suicide of mature T cells. Mutation in *Fas* gene leads to autoimmune disorders.

Thereafter the book is organized essentially into two major parts; one dealing with apoptosis in the regulation and function of T and B lymphocytes, granulocytes, haematopoietic cells, chondrocytes, keratinocytes and the second deals with involvement of apoptosis in diseases related to these cell types, i.e. rheumatoid arthritis (RA), osteoarthritis (OA), lupus and lupus-like syndromes, psoriasis and renal disease, dealing with the fundamental analysis and with clinical and therapeutic correlation by different authors working in these fields. There is also a chapter on arachidonic acid which has reviewed *in vitro* and *in vivo* studies that have examined the relationship between arachidonic acid metabolism and cell proliferation with special emphasis on apoptosis.

There has been a major focus in understanding the association of total dietary fat and specific types of fat with cancer risk. In regard to inflammatory cells, proliferation of T cells is suppressed by poly-unsaturated fatty acids (PUFA) in several studies and a pro-apoptotic effect of PUFA has been reported. It is important to point out that major molecular events that link arachidonic acid metabolism and PUFA to cell proliferation or apoptosis are currently poorly understood, further progress needs to be made to resolve controversial findings and inconsistencies in this area to provide new opportunities to utilizing old and new drugs that influence arachidonic acid metabolism and to treat diseases such as inflammatory and cancer.

There is sufficient evidence establishing granulocyte apoptosis leading to phagocytic clearance as an important injury limiting granulocyte disposal mechanism capable of promoting resolution of inflammation as discussed in the next chapter. There does seem a realistic prospect of being able to direct granulocyte apoptosis for therapeutic gain and researchers are looking at the prospect of selectively triggering cell death in population of granulocytes which are causing the injury. In hematopoiesis inflammatory cytokines can induce many of the changes by regulating apoptosis of hematopoietic cells. Thus cytokine inhibition can provide a potential means to interfere with cytokine network and offer relief of systemic complications associated with increased or decreased blood cell numbers. Chondrocytes are differentiated mesenchymal cells which play a role in skeletal development, maintenance and repair. Apoptosis can be induced in chondrocytes by several distinct mechanisms. Keratinocytes, the epithelial cells prevent the entry of toxic environmental agents. Keratinocyte apoptosis is seen in many biological circumstances such as epidermal differentiation, certain skin diseases and graft vs host disease. Recent evidence suggests that keratinocytes can modulate the epithelial immunological environment by expression of Fas ligand and granzyme B and can kill cytotoxic lymphocytes.

Immunological cytotoxicity is one of the most important consequences of immunological activation producing selective destruction of cellular targets by humoral or cellular effector mechanisms and apoptosis. Apoptosis is also a key mechanism for eliminating autoreactive lymphocytes, activated lymphocytes and non-specific effector cells during different phases of inflammation. Defective induction of apoptosis is believed to allow persistence of autoreactive T cells and production of auto antibodies in autoimmune diseases as discussed in the last few chapters in the second part of the book. The difference in apoptotic susceptibility is used in treatment of many types of inflammatory and immunological diseases. Keratinocyte apoptosis has been described in many immunological skin diseases such as lichen planus, graft vs host disease, photosensitive lupus and psoriasis. Environmental triggers such as viruses, sunlight and drugs can dysregulate apoptotic pathway or pathways for immune clearance and result in chronic inflammatory diseases. A large number of

viruses have been associated with development of chronic infection which lead to autoimmune diseases either by persistent or latent viral antigen or molecular mimicry. Modulation of apoptosis may play a role in pathogenesis of arthritis associated with infection of adenovirus, baculovirus, HIV and influenza virus. Inhibition of apoptosis is associated with persistent infection, latency enhancement of viral production whereas promotion of apoptosis facilitates virus spread and release. Rheumatoid arthiritis (RA) is a chronic inflammatory disease affecting synovial tissue in multiple joints. There is a strong evidence to suggest a role of CD_4^+ T cells as well as of activated macrophages and fibroblasts like synviocytes which destroy articular structure in chronic RA disease. Inadequate apoptosis appears to play a significant role in the increased cellularity in the synovial tissue. Interventions aimed at enhancing apoptosis in the synovium are emerging as potentially effective forms of treatment. Osteoarthritis (OA) is the most frequent musculoskeletal disorder, especially in the aging population. There is reduction in chondrocyte cell number due to apoptosis involving a number of multiple molecular pathways. The pathogenesis of systemic lupus erythematosus (SLE) is multifactorial and multigenetic. Chronic inflammation associated with it is thought to be due to loss of self-tolerance and apoptosis defects. Fas and Fas ligand regulate NFkB, kinases, phosphatases, bcl-2 family members, interleukin 1-β converting enzyme (ICE) and FLICE (FADD-like ICE) family members which may be dysregulated in patients with SLE. There is strong evidence for involvement of apoptosis in acute renal failure but it is not clear whether it is involved in disease progress or the repair process or both. Thus a direct connection of apoptosis with numerous disease states has been established and the number of examples will probably increase as more apoptosis and disease regulation genes are identified, and their biochemical activities established. Opportunities for novel therapy may then become apparent.

I trust that both experienced and new researchers alike will read this book as a primer on what is new and possible in apoptosis and immune system. This book will serve as a useful resource material and guide for biochemists/researchers who wish to understand the role of apoptosis, particularly in immune/inflammatory disease. The number of references to the primary literature is fairly large, i.e. more than 850. It covers a small number of topics in depth and with relevant detail. In summary this book will find an appreciable but limited audience.

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Proton Pump Inhibitors: Milestones in Drug Therapy. L. Olbe (ed.). Birkhäuser Publication. 1999. 264 pp. Price: SFr 188/DM 238.

Innovation has become the industrial religion of the new millennium. Healthcare business sees it as the key to increasing profits and market share. For more than 100 years it has been known that gastric acid secretion is not the only but an essential causative factor in the pathogenesis of acid-related diseases. Thus reduction of acid secretion became a major therapeutic goal. For quite sometime, surgical procedures (gastric resection and vagotomy) were used as effective interventions in the management of peptic ulcer diseases. The introduction of potent inhibitors of acid secretion, that is the H_2 receptor blocking agent cimetidine and its analogues in the late seventies and the even more potent proton pump inhibitor omeprazole and its analogues in the late eighties have revolutionized therapy. Around the world, the rhetoric of innovation has replaced the redundant products or surgical approaches in the management of peptic ulcer disorders.

This new monograph series – *Milestones in Drug Therapy* – highlights new therapeutic developments of proton pump inhibitors, which have provided significant steps forward in the fight against peptic acid disease. Each book in this series generally deals with an individual drug or drug class, which has altered the approach to therapy. Experts in the field place emphasis on the scientific background to the discoveries and the development of the therapy, with an overview of the current state of knowledge of the drugs. The series is aimed at a broad readership, covering biochemistry, pharmacology and clinical aspects, as well as revealing the personal stories behind these milestone developments.

This book *Proton Pump Inhibitors* presents the story starting from the initial observation of classical experiments to the launch of four proton pump inhibitors in six chapters namely: the discovery and development of the proton pump inhibitor; mechanism of action; the pharmacology of proton pump inhibitors; pharmaceutical considerations; clinical experience with proton pump inhibitors and socio-economic impact of acid-related diseases. Modern drug discovery mostly relies on identification and characterization of potential targets by genome research, molecular biology, combinatorial chemistry and automated screening. But the first chapter takes the reader back by thirty-three years and gives narration how director Ivan Östholm initiated an innovative research project in the gastrointestinal field at Astra Hässle using classical screening methods. It is worthwhile for all researchers engaged in drug discovery research to read the development of the first proton pump inhibitor – omeprazole – starting from a chemical structure with an observed antisecretory effect but also severe toxic effects that had to be eliminated. As always, the basic and the applied research operate hand in hand to optimize the delicate balance between efficacy and safety of a new drug.

The second chapter starts with the landmark paper of William Prout presented at the Royal Society Meeting on 11 December 1823, stating that 'On the Nature of Acid and Saline Matters Usually Existing in the Stomach of Animals'. He was the first to identify the hydrochloric acid in the gastric juice of many species and was able to quantify the free and total acid. Further, work on acid secretion in isolated frog mucosae in the 1960s paved way to identify the molecular target involved in acid production. This chapter gives a detailed biochemical description of the gastric H^+, K^+ ATPase