

finds a set of 'definitions'. Among them are:

'Quantum mechanics: A branch of physics in which the systems studied can have only discrete values of energy, separated by forbidden regions; it is distinguished from continuum mechanics in which a continuum of energies is assumed possible.'

'Wave mechanics: A branch of mathematical physics involving the statements and solutions of differential equations describing wave behavior.'

Who says science is humourless?

V. BALAKRISHNAN

*Department of Physics,
Indian Institute of Technology,
Madras 600 036, India*

Myocardial Ischemia: Mechanisms, Reperfusion, Protection. M. Karmazyn, ed. Birkhauser Verlag, P.O. Box 133, CH-4010, Basel, Switzerland. 1996. 528pp. Price: SFR 198, DM 238.

Myocardial infarction is one of the most common causes of hospital deaths. Thirty years ago it was generally accepted that insufficient blood flow due to coronary artery obstruction by atherosclerotic process is the cause of myocardial ischemia and that infarction is precipitated by occlusion of coronary artery by thrombus. Therapeutic approaches were aimed at thrombolysis and limiting the infarct size. Recent clinicopathological, angiographic and experimental studies indicate that additional structural and functional alterations are superimposed on chronic atherosclerosis and these are responsible for the development of various ischemic syndromes. Considerable clinical and experimental data have accumulated which make apparent that prognosis following infarction depends on the amount of residual viable normally functioning myocardium and that interventions which would decrease the extent of tissue death will reduce mortality in patients. It has also been recognized that restoring blood flow to the ischemic myocardium is not always associated with recovery but may lead to further damage, recognized as reperfusion injury.

Karmazyn has edited a book which reflects the growth of understanding of

pathophysiological mechanisms in acute myocardial ischemia and the current approaches to define rational therapeutic strategies to salvage ischemic myocardium. The book contains 31 articles grouped in 9 sections with distinctive titles. The contributors are all internationally recognized investigators.

The first, third and fifth articles are on nitric oxide. Zhao, Hintze and Kaley examine evidences for mediation of reflex coronary artery dilatation in ischemic conditions by nitric oxide produced by vascular endothelium. Several studies have earlier shown that activation of sympathetic or parasympathetic nervous system controls the resistance of coronary arteries. Bezold-Jarish reflex, carotid chemoreflex, arterial baroreceptors and ventricular receptors participate in this regulation. The observation that selective impairment of vagal control of coronary blood flow is due to the impairment of nitric oxide synthesis suggests that nitric oxide is a mediator of neural regulation of coronary vascular resistance.

Dusting provides a more extensive review on nitric oxide; its biosynthesis, role in inflammation and pathological conditions such as atherosclerosis, reperfusion injury and heart failure. Studies have demonstrated that atherosclerosis leads to disturbances in the activity of isoforms of nitric oxide synthase in the artery and can contribute to vasospasm, thrombosis and cell proliferation. These defects may be reversed, thus offering a promising target for therapy against some manifestations of vascular diseases. There is also evidence that derangement in nitric oxide function is associated with the development of atherosclerosis and vascular remodelling after angioplasty. Production and actions of nitric oxide are also abnormal in chronic heart failure. Nitrate, the stable end product of endogenous nitric oxide production is elevated and endothelium dependent vasodilatation impaired in patients with heart failure and the levels are proportionate to the severity of heart failure. The causes for enhanced release of nitric oxide from vascular endothelium and its functional consequences are still unclear.

Pabla and Curtis survey experimental studies in animals which imply a role for endogenous nitric oxide as a mediator for cardiac protection in atherosclerosis, myocardial infarction, reperfusion induced arrhythmias and coronary artery restenosis

after angioplasty. Studies using inhibitors of nitric oxide synthase suggest that reduction of nitric oxide production exacerbates the disease state. Probably, to protect cardiac function in disease conditions, it may be of value to mimic nitric oxide function or induce its synthesis or block its degradation. Interestingly, in experimental animals short term exercise training increases the production of nitric oxide in the coronary vasculature and enhances nitric oxide synthase gene production in endothelial cells. Nitric oxide dependent coronary vasodilatation is also improved. These mechanisms may be responsible for improvement of cardiac function and reduction in incidence of coronary diseases, seen in patients who undergo exercise training.

Myocardial ischemia and reperfusion are associated with increased production of another endothelium derived peptide, endothelin. Reperfusion of ischemic myocardium is a potent stimulus for increased release of endothelin as is evident by elevated plasma levels of endothelin in patients with coronary artery disease who have had thrombolytic therapy or angioplasty. Elevated plasma levels are associated with diminished ventricular function and increased mortality. A number of investigations have been carried out in animals to assess the effects of endothelin receptor antagonists and other inhibitors in ischemia and reperfusion. Results imply that modulation of endothelin synthesis or its actions could represent novel therapeutic strategies. The topic is exhaustively dealt by Karmazyn.

Oxygen-free radicals have been extensively examined as potential mediators of injury in ischemia and during reperfusion. Free radicals can cause cellular dysfunction directly by oxidation of cell structure components. Another mechanism which has gained attention in recent years is alteration or destruction of second messenger pathways in the cell which affect cellular ionic homeostasis, contractile function and viability. Czubyrt, Panagia and Pierce discuss the studies which address the deleterious effects of oxidants on various components of the second messenger system. The second messengers are important for regulation of normal cardiac function. Changes that occur in the signal transduction system during ischemia and reperfusion have possibly a role in arrhythmogenesis and other functional abnormalities. Recent evidences that reac-

tive oxygen species and nitric oxide are linked to cellular second messenger system and that non-receptor mediated signal transduction is important as a mediator of ischemic and reperfusion injury point to new levels for pharmacological intervention.

Pettersson, Ostlund Lindquist and Westerlund in their article focus on experimental investigations which assess the antiatherosclerotic effects of probucol, a lipophilic and an antioxidant compound. Studies in Watanabe heritable hyperlipidemic rabbits as well as animals in which atherosclerotic disease was induced by hyperlipidemic diet reveal that antioxidants may inhibit development of lesions in aorta. However, it is not clear whether antioxidants can cause regression of pre-existing lesions. Also, there are no reports on the effects of antioxidants on progression or regression of coronary artery atherosclerosis either in animals or man. In animals, antioxidant therapy can prevent restenosis following angioplasty and also restore endothelial regulation of vascular tone which is impaired in atherosclerosis.

Myocardial dysfunction in ischemia and subsequent reperfusion result from a multitude of cellular abnormalities involving ionic homeostasis, metabolism and bioenergetics. Altschuld reviews calcium transport systems of mitochondria and sarcoplasmic reticulum and summarizes how they are altered during ischemia and reperfusion. Damage to mitochondria consists of alterations in the permeability of mitochondrial inner membrane which leads to uncoupling of oxygen consumption from the phosphorylation of ADP. In the sarcoplasmic reticulum, changes in the calcium efflux channels or ryanodine receptors could be responsible for contractile abnormalities.

Soon after the discovery of potassium channels, the potential link between ischemia induced potassium efflux from myocytes and ATP sensitive potassium channels (K_{ATP}) was realized. Modulators of potassium channels are being used for treatment of myocardial ischemia. Grover reviews the data which denote that K_{ATP} openers have potential to be used as protective agents in myocardial ischemia. However there is also the possibility that K_{ATP} openers may enhance arrhythmias.

Membrane phenomena at cellular and subcellular levels have been extensively explored, thanks to the availability of techniques such as NMR spectroscopy,

voltage clamp measurements, etc. and use of channel blockers and fluorescent dyes. Alterations in potassium and calcium homeostasis which lead to reduced conduction velocity, a decrease in duration of the action potential and refractoriness, are important among the multiple cellular mechanisms involved in ischemia-induced electrophysiological abnormalities. There are two articles which address electrophysiological responses and cellular mechanisms of arrhythmias in ischemic and reperfused heart.

Lemasters *et al.*, using cultured myocytes and perfused papillary muscles have probed for mechanisms, other than calcium overload, sarcolemmal injury and free radical damage, for loss of cell viability after reperfusion. Their results signify that reperfusion injury is linked directly to changes in intracellular pH. They hypothesize that naturally occurring acidosis during ischemia inhibits degradative enzymes such as phospholipases and proteases. After reperfusion, this inhibition is released as the pH returns to physiological levels and as a result plasma membrane gets damaged leading to cell death. The change in intracellular pH may also activate myofibrillar ATPase and cause permeability transition in mitochondrial membrane. Avkiran, in his article highlights the role of Na^+-H^+ exchanger which regulate intracellular pH and the possible therapeutic benefits of inhibition of the exchanger in myocardial ischemia and reperfusion.

The normal mammalian heart has an aerobic metabolism. According to energy demand, the rate of ATP production is regulated by pathways which use fatty acids, lactate and glucose as energy substrates. During ischemia, oxidative metabolism ceases and anaerobic glycolysis is stimulated. Other metabolic derangements also occur. These include inhibition of mitochondrial oxidative phosphorylation, reduction in the capacity to oxidize fatty acids, alterations in triacyl glycerol and phospholipid metabolism, and defective utilization of glucose and free fatty acids. There is accumulation of lactate, protons, nucleosides, inorganic phosphate and acyl carnitine. There is additional tissue injury during reperfusion. Das and Maulik discuss the impairment of bioenergetics in ischemia. Vander Vussue and colleagues detail lipid metabolism in ischemic heart and indicate the possible relationship between altered lipid metabolism and

irreversible damage of myocytes.

Another review is centred on arachidonic acid metabolism and how alteration in the production of arachidonic acid metabolites can affect heart function in health and disease. Under ischemic conditions and during reperfusion, blood cells are activated and their migration and interaction with endothelial cells increase eicosanoid biosynthesis. Their precise functions are not known. Prostaglandins have been implicated as mediators of reperfusion associated dysfunction. Inhibitors of prostaglandin synthases improve ventricular function.

Cardiac injury in ischemia is often extended and complicated by inflammatory reaction. Leucocytes may also damage potentially viable myocardium especially when coronary blood flow is reestablished by reperfusion techniques. Frangogiannis, Youker and Entman elucidate the role of the neutrophil in myocardial infarction and propose a hypothesis which describes the events that mediate post-perfusion inflammatory injury. Attempts are being made to identify specific cellular and molecular targets for therapeutic intervention. Pharmacological approaches include the use of neutrophil antibodies, neutrophil depleting anti-metabolites, neutrophil filters, free radical scavengers, lipooxygenase inhibitors, agents to deplete complement, and leukotriene B antagonists. Prostacycline analogues and adenosine are being tried to alter neutrophil function. Recent studies suggest that monoclonal antibodies against CD 18 and adhesion molecules L-selectin and P-selectin are effective in reducing myocardial necrosis, preserve coronary endothelial function and attenuate neutrophil accumulation in ischemic regions.

Investigators the world over have found that if myocardium is subjected to brief periods of ischemia followed by reperfusion, myocardium develops resistance to infarction from a subsequent severe ischemic episode. This phenomenon is termed preconditioning. The protection includes reduction in cellular damage, ventricular dysfunction and arrhythmias. The mechanism of preconditioning is being intensively explored in numerous laboratories. Several studies are focused to find clues to design pharmacological approaches for preconditioning in patients with ischemic heart disease. Miura and colleagues present the current understanding about preconditioning mecha-

nisms. Adenosine A1 receptor has a key role in preconditioning. Protein kinase C and ATP sensitive potassium channel are possibly important effectors.

Animal studies have revealed that protection in ischemic preconditioning is biphasic. There is an early, rapid onset but transient protection and a second delayed protective adaptation. Both are dependent on adenosine receptor activation. The delayed protection is also associated with increase in myocardial heat shock protein-HSP-70 and increase in activity of the enzyme superoxide dismutase. Interestingly, in experiments using myogenic cell lines transfected with a cDNA encoding human HSP-70, it has been demonstrated that a single stress-related gene product can protect cells against both lethal heat stress and simulated ischemia. There are also reports of improved post-ischemic functional and metabolic recovery or increased resistance of the heart to ischemic injury in transgenic mouse models which overexpress HSP-70. Heads, Latchman and Yellon in their article on the role of stress proteins and antioxidants in adaptation to ischemia, suggest that identification of the genes which are important in mediating ischemic preconditioning and determination of how their promoters are regulated will lead to possible gene therapies for myocardial ischemia.

Currently, there are several attempts to harness endogenous protective mechanisms and considerable knowledge has accumulated on the role of adenosine which has numerous cardiac effects. Cook and Karmazyn review the mechanisms implicated in cardioprotection by adenosine and the potential role of adenosine analogs as protective agents in ischemia. Cardioprotection from ischemia is important in preservation of donor hearts intended for transplantation, and during various cardiac operative procedures using cardiopulmonary bypass. An overview of approaches to myocardial protection in such conditions is provided by Myers and Fremes.

A major factor which influences survival of patients with ischemic heart disease is, ventricular function. Any improvement in ventricular function is associated with better survival. In about 42% of patients, abnormalities of ventricular contraction may not necessarily mean dead tissue or a scar. Ischemic tissue may down-regulate its function and metabolism for survival. This adaptive phenomenon has been termed hibernation of the myocardium.

Though the exact mechanism underlying hibernating myocardium remains controversial, both animal and human studies reveal that prompt establishment of blood flow improves function of the hibernating myocardium and survival of patients. A similar phenomenon is myocardial stunning. While hibernating myocardium occurs in a hypo-perfused heart that reduces its oxygen demand by decreasing contractility, stunned myocardium is a feature of an ischemic heart but with normal perfusion. Differentiation between stunned and hibernating myocardium is critical. Leor and Kloner review the current views on the hibernating myocardium. New non-invasive techniques for detecting and treating stunned myocardium are analysed by Allen, Cox and Kloner.

The last section of the book deals with the healing processes in the infarcted myocardium and the compensatory changes that occur in the remaining tissue. These alterations or remodelling occur at three levels, viz. in the chemical composition of the myocytes and extracellular matrix (biochemical and subcellular remodelling), in the microscopical structure (structural remodelling) and in the three-dimensional configuration of the ventricular chambers (geometrical remodelling). It is now realized that remodelling is mediated by the activation of sympathetic nervous system, circulating renin-angiotensin-aldosterone system (RAAS), locally generated tissue angiotensin II and formation of growth factors. Studies on remodelling in the infarcted heart are summarized in three articles.

Recognition that changes associated with ventricular remodelling are responsible for ventricular dysfunction in the post-ischemic period has prompted search for therapeutic strategies aimed at improving the healing process after myocardial infarction. Novel approaches are scrutinized by Jugdutt. Pharmacological agents which influence the inflammatory infiltrates, fibroblast activation, myocyte growth, nutrient flow, cellular metabolism and integrity of collagen matrix appear to have potential to modify healing and remodelling after infarction.

Diabetes mellitus and cardiac hypertrophy are two common pathological conditions which affect cardiac function and are vulnerable to ischemic injury. Feuvray presents myocardial metabolism as well as disturbances in membrane mechanisms

which regulate intracellular pH in diabetic rats and their influence on the response to ischemic injury. Allard and Lopashuk discuss alterations in energy metabolism that occur in pressure overload-induced cardiac hypertrophy and how these changes increase susceptibility to ischemic injury. They also examine the relationship among altered energy substrate utilization, dysregulation of ionic homeostasis and functional recovery of the left ventricle. They suggest that glucose utilization may be useful target for pharmacological modulation in the hypertrophied heart.

On the whole, the book provides a rapid means to grasp the current level of understanding in a number of important areas related to myocardial ischemia. Many of the chapters are noteworthy for their detailed presentations, discussion of very recent developments and for providing future directions for investigations. An extensive and up-to-date reference list is available at the end of each article which facilitates search for the original studies. Each chapter is self contained and designed to be independent. Hence unavoidably, there are some areas of overlap in coverage. Some of these are cross-referenced by mentioning the author's name in brackets. Some of the chapters are crammed with information, that it will require substantial effort by readers with no background in pharmacology or physiology.

The book would have benefited from a chapter on pathological anatomy of myocardial ischemia and infarction with special emphasis on the effects of reperfusion. Similarly, a contribution from a practising cardiologist on clinico-pathologic correlates of acute ischemic heart disease syndromes would have made it more appealing.

The articles are not organized in the traditional format and the sections are uneven. The other deficiencies of the book are (1) the inconsistency in the format and style of various chapters (some of them have a summary, others do not. Most of the chapters have subtitles such as introduction and concluding remarks while these are absent in others), (2) an apparent over-emphasis on the possible therapeutic implication of each and every mechanism discussed, (3) an inadequacy of the index, and (4) occasional typographical errors.

There is no doubt that the book is an excellent addition to the available cardiology books. The extraordinary wealth of

basic knowledge provided in the book could serve as a definitive reference to physiologists, pharmacologists, biochemists, pathologists and cardiologists interested in mechanisms of myocardial ischemic injury and treatment of related disorders.

C. C. KARTHA

Division of Cellular and Molecular Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram 695 011, India

Indian Food: A Historical Companion.

K. T. Achaya. Oxford University Press, Walton Street, Oxford OX2 6DP, UK. 1994. 325pp. Price: Rs 750.

There is an old story about an international group that was assigned the task of writing an essay on the subject of elephants. The Frenchman wrote on 'Love among the elephants'; the Jew wrote on 'Elephants and the Jewish question'; the American wrote 'Bigger and Better Elephants'; and the German scientist wrote 'An Introduction to the Bibliography of the elephant': Achaya's excellent book is not about elephants but it furnishes such a rich background in an area so close to our hearts that it appeals to all, to each in a different way. There is meat aplenty for the historian, main dishes for the social scientist and desert for the food scientist. Added to his previous detailed accounts of various other aspects of our food and culinary heritage he has given us, as one reviewer has noted. 'A superb repast'.

What makes a people unique and differentiates them from their fellow humans? Surely one of the most distinctive features of a culture is its food – that essential element in life that allows a diversity conditioned by climate, geography and human creativity. This book gives us appetizing glimpses into that hoary past and furnishes us a bridge between all the inventions, innovations and influences of our yesterdays that have made possible the wonderful specialities and daily fare of India today. Achaya, a distinguished oil chemist with a special bent for tradition and history has written with verve and interesting sidelights. Instead of assigning us to the sidelines, as mere consumers, he puts us in our rightful place as innovators

and producers. This is an example of real 'people's science' and helps us to reaffirm our extraordinary capacity to create and evolve culturally and nutritionally balanced and delicious food, in harmony with the natural productivity of the earth. It puts us in touch with the wellsprings of our humanness.

We are now faced with a virtual assault on our traditional foods from TNC's and their universalized burgers, pizzas and fried chicken. Aside from the health issues involved, which arise from the over-consumption of too much salt and animal fat, we are forced to consider the political and economic issues of whether our limited natural resources and food grains should go to feed increasing numbers of battery raised fryers (chickens) or cattle for hamburgers rather than feed people. It takes 7–9 kg of feed to produce one kg of animal food. We are forced to consider whether we need 'ajinomoto' in our packaged foods or other chemicals, flavours and colours to ensure optical attraction and increase the shelf-life of packaged foods. We are forced to ask our government why we need Nestle Company to make our traditional pickles and savouries, why, indeed, we need any TNC in the food business in India! We are forced to ask even more importantly how it can allow others to patent our neem, our parboiled rice, extracts of our turmeric and any other foodstuff which will be mainly to their benefit, and little to ours.

We are also faced with the grim reality of more mouths to feed, less water to irrigate our fields, so-called structural adjustments to allow the market to dictate what should be grown and who can afford to eat it.

Written history ignores much of woman's part in humankind's progress. It undervalues her abilities and contributions as producer, inventor and processor. The arts of food processing and preservation as well as cooking have been mostly women's work. In many areas of the world, even basic cultivation, harvesting and storing of foods are still, today, in the hands of women. The essential quality of these inputs is obvious. It is too bad that few historians, including the one under discussion, have acknowledged this, but, hopefully, in an account like the present one, the real actors and actresses on the scene speak for themselves. In an urban setting, we tend to forget that milk comes out of a cow and tomatoes have to be planted,

harvested and cooked before they become sauce. This book helps us put things afresh into proper perspective and appreciate the intricate hands on 'research' that has shaped our rich culinary heritage.

Achaya has taken us through both archaeological as well as written records, detailing the food of ordinary people and royalty, the influence of religious beliefs on menus and prohibitions, the vedic prescriptions for food as preventive medicine, description of royal feasts, accounts of what surely must be the original 'restaurant', the invention of ice creams and kulfi and descriptions of traditional utensils, and various apparatus used on both household as well as community scale in the preparation of food.

National cuisines and regional specialities are briefly described. We are sure the author himself would be the first to declare he has barely skimmed the surface of all there is to discover about the intricacies of such a vast subject but he has been able to mention some of the highlights of the various areas that will stimulate further research.

Chapters 14 and 15 catalogue the staple foods as well as some specified fruits, spices and vegetables with details of their origins and their adaptation into Indian cuisines. The last chapter lists imports from the Americas and other areas which are now firmly established as normal components of our menus. One of the most interesting facets of the story is the fact that the chilli pepper, an essential component of much Indian cooking, is imported from Central and South America. When and by whom is unknown but its Indian history is very ancient.

There are fascinating tidbits scattered throughout the book in separate boxes so as not to interfere with the text and to highlight related knowledge. There are abundant references, four very useful indexes, and many drawings, illustrations and coloured photos to round out the careful research and comfortable scholarship that is evident throughout. The original price of the hardbound book predicates a rather limited audience. A paperback edition would assure the much wider readership the book deserves.

H. A. B. PARIPIA
CAROLYN W. PARIPIA

*'Suryakanti',
333 Hinkal,
Mysore 570 017, India*