have no illusions about the complexity. Every time another nation strives to join the nuclear club, it will be making it that much more difficult to reach the worthwhile objective of NWFW.

S. R. VALLURI

Naltech Pvt. Ltd.,
F5 Building, NAL,
Kodihalli Campus,
Bangalore 560 017, India

Annual Review of Medicine: Selected Topics in Clinical Sciences: Cecil H. Coggins, William E. Hancock and Lee J. Levitt (eds). Annual Review Inc. 4139, El Camino Way, P.O. Box 10139, Palo Alto, CA 94303-0139, USA. 1998. vol. 49. Price US $60.

The last century has witnessed rapid advances in various specialities of medicine. The pace of these phenomenal advances has gone beyond the scope and ability of the average physician to keep track of the information and to utilize the same in day to day practice. It is in this context, *Annual Review of Medicine* gains its relevance by giving a comprehensive review of the landmark developments in various branches of clinical sciences. The 1998 edition with its 31 reviews is a valuable addition to this series. It covers a wide range of topics from basic sciences, clinical medicine to public health, so that the clinician is updated and informed about the state-of-art knowledge as he marches on to the next millennium.

Three of the articles are related to coronary artery disease (CAD), the major killer disease of mankind in the 20th century. Phenylketonuria was the first inborn error of metabolism with a dietary cure to be identified. Towards the fag end of the millennium, yet another metabolic disorder of amino acids involving homocysteine (Hcy) is identified to account for at least 10% of the modern CAD epidemic, by epidemiological and biochemical studies. Refsum and colleagues summarize the data to project Hcy levels as a strong but modifiable predictor of cardiovascular mortality and morbidity. Elevated Hcy levels confer a graded risk with no threshold and is independent of conventional risk factors. Evidences from 80 epidemiological studies are consistent, strong and temporally accounts for added CAD risk in general population. Endothelial dysfunction and thrombogenesis initiated by Hcy leads to atherogenesis. The four major enzymes involved in Hcy metabolism utilize B complex vitamins like folate, cyanocobalamine, riboflavine, pyridoxine and cofactor like betane. In addition, a variety of factors like total protein intake, consumption of coffee, alcohol, smoking, age, hormonal status, renal function, drugs and genetic variants in enzymes affect the blood levels. Estimation of blood Hcy levels requires facilities for high performance liquid chromatography. Blood levels more than 15 µmol/li in fasting state is considered abnormal for epidemiologic purposes. The risk conferred by Hcy for coronary, cerebral and peripheral vascular disease is modifiable with lifestyle modification and multivitamin supplementation. Currently fortification of flour and cereal products with folic acid is initiated in developed countries as a major public health measure aimed to achieve further reduction in mortality due to cardiovascular disease.

Solomon and Girsh address an important aspect in clinical cardiology, i.e. the open artery hypothesis. The concept refers to reperfusion of an occluded coronary artery beyond a time when myocardial salvage is no longer possible. This exerts a favourable course on left ventricular function and survival by improving wound healing, decreasing the incidence of ventricular arrhythmias and rejuvenating hibernating myocardium and also by acting as a potential source for future collaterals. This concept is substantiated by experimental and clinical studies like ISIS2, LATE, EMERAS and TAMI. The clinical implications of this hypothesis suggested by circumstantial evidence needs scrutiny of randomized trials.

In their article on monoclonality of atherosclerosis, Schwartz and Murray reexamine the clonal origin of the plaque as proposed by Beniditt and Beneditt as early as 1973. Clones represent focal replication of cells without mixing up with adjacent cells. Initially the proliferating smooth muscle cells of the plaque were identified to represent a single clone of mesenchymal origin. Identification of the onset of this clonal expansion reveals the earliest event in the formation of these critical lesions. The original 'neoplastic theory' did not get wide acceptance and gave way to 'response to injury' hypothesis. But further studies by karyotyping, DNA-PCR technique and X-linked polymorphism have not only confirmed the clonal origin, but also identified large patches of single allotype existing in the arterial wall. These cells do not have rapid cell turnover and therefore should originate early in the natural history or result from natural selection over the years. These cells of the plaque may develop because of migration and trapping in embryonal life, or originate *in situ* from pluripotent cells derived from the vessel wall or circulation, or else apoptotic cell death of other cell lines which cannot adopt to the environment can select a cell line (and such clonal selection does occur in organizing thrombus). Spontaneous or infection-mediated mutation can also select the evolution of a single clone in an atherogenic environment. Thus the revival of monoclonal hypothesis after 25 years unifies the thrombogenic theory, lipid theory, and the response to injury hypothesis and the recent concepts for infectious origin of this deadly plaque. In this context it is important to recognize that atherosclerosis is not a natural disease of other species and animal models of atherosclerosis do not have monoclonality. Thus, understanding of the biology of these cells peculiar to the plaque will go a long way in conquering the disease, elucidating the mechanism of its origin, evolution, determinants of complication and patterns of re-stenosis.

Two other articles of relevance to cardiologists are related to arrhythmias, one on molecular genetics of long QT syndrome (LQTS) and the other on the pathophysiology and therapy of atrial flutter. LQTS are congenital autosomal disorders of electrical repolarization caused by mutation of six genes. This is a frequent, but overlooked cause of syncope and sudden cardiac death (SCD) in children and young adults during exercise, emotional upset, and rarely during sleep. The morphologic study of SCD victims at autopsy is normal. The diagnosis can be made only by genetic studies and family screening. The

prevalence is around 1 in 10,000. Characteristic ECG findings are QT prolongation and T wave changes. But the electrocardiogram is normal in 10% and boderline in 30%. Mortality in untreated symptomatic patients exceeds 60% in 10 years and reduces to 3–4% on treatment, a variety of commonly used drugs like erythromycin, septran, broncodilators, terfenadine, astemizole, azole antifungals, amitryptyline, phenothiazines, diuretics and hypokalemia further prolongs QT interval. The genotypic characteristic, the channel abnormalities, phenological features and therapy of these uncommon disorders are summarized in the article by Michael Vincent.

As we approach the next millennium, emerging and reemerging infections pose a major public health problem. The chapter on evaluation of a patient with recurrent bacterial infections is exhaustive in this regard, though the disorders enlisted are rare if not uncommon. A variety of aquired immune deficiency disorders secondary to diabetes, aging, chemotherapy, irradiation and HIV infection are more common. The close interaction of humans with nature has increased the incidence of enzootic diseases like lyme disease and ehrlichiosis. J. S. Dumler and J. A. Galin summarize currently available information on human granulocyte ehrlichiosis. Whotherspoon's article on gastric lymphoma of mucosa associated lymphoid tissue and its relation to *Helicobacter pylori* is of great public health importance. Eradication of *H. pylori* infection leads to regression of > 60% of these uncommon tumours. Dyspepsia is a common symptom affecting 25% of the population and the role of *H. pylori* is well known and summarized in the same issue by Agreus and colleagues. *H. pylori* infection precedes the development of mucosa associated lymphoid tissue (MALT) in the stomach. Low grade non-Hodgkin's lymphomas of this lymphoepithelium occurring in the stomach is therefore amenable to antibiotic therapy if not prevention.

Obesity is perhaps the most important public health problem of the developed countries where it affects 25% of the population and accounts for 45% of the health care costs. Two interesting articles address two distinct aspects of this problem. Obesity is associated with increased mortality as well as increased risk for CAD, hypertension, diabetes, obstructive sleep apnoea, hyperlipidemia, osteoarthritis, abdominal wall hernias, benign intracranial hypertension, and depression. In addition, incidence of several malignancies including that of colon, breast and ovaries are increased in obese subjects. The article by L. Flanebaum and P. S. Choban deals with finer aspects of surgical implications of obesity, stressing the importance of proper preoperative precautions and monitoring to minimize serious cardiovascular and pulmonary complications. Obese patients can be treated safely and effectively as normal weight counterparts and should not be denied of any surgical treatment when it constitutes the most appropriate therapy. Best long-term results for weight reduction and amelioration of comorbidity is again achieved by surgical treatment, like Roux-en y gastric bypass and vertical band gastroplasty.

Other related topic, exercise, glucose transport and insulin sensitivity is reviewed by L. J. Goodyear and B. B. Khan. Elucidation of cellular mechanism for the changes in insulin sensitivity occurring in skeletal muscle in response to exercise, paves the scientific foundation for advocating long-term regular exercise programme as a mode of reducing the risk of developing non insulin dependent diabetes mellitus (NIDDM). This has been substantiated in earlier epidemiological studies. Translocation of a glucose carrier protein from transverse tubules to plasma membrane by an insulin independent mechanism forms the basis of this alternate mechanism of improved glucose uptake by the skeletal muscle. In the post-exercise period, insulin delays the internalization of these receptors and this augments insulin-mediated glucose uptake for several hours proportional to the degree of glycogen depletion.

Laproscopic (keyhole) surgical techniques are landmark developments in the last few decades. These procedures along with other interventional procedures will make the fundamental specialities of surgery and medicine to merge again. They reduce the preoperative morbidity, hospital stay, and cost and are more cosmetically acceptable. Even major procedures like cholecystectomy can be done as a minor surgery with the advent of laproscopes and lasers. Asharaf Memon and R. A. Fitzgibbon present a comprehensive review of laproscopic inguinal herniorraphy. This new and evolving procedure is ideal for recurrent/bilateral inguinal hernia, and when laproscopy is performed for some other reason. But at present this procedure requires general anaesthesia, costly equipments and trained personnel. Bowel injury, adhesions, infection and herniation at trocar site are rare but dangerous complications of this procedure.

Abdominal aortic aneurysms (AAA) are lethal once they rupture. AAAs more than 5 cm diameter should be operated. They occur in the elderly who have major cardiopulmonary, renal and other comorbid factors. The advent of endovascular stents reduces the perioperative risk and hospital stay for these critically ill patients. In several FDA approved trials, more than 800 grafts have been implanted with 80% procedural success. This procedure reduces the anaesthetic complications, operative cardiac stress, blood loss, pain, and the duration of aortic cross clamping. Persistent leak of blood around this graft with the continued risk of rupture is at present a major problem. Future modifications of the current device and techniques of delivery are likely to offer potential advantages over conventional surgical repair. Infra renal AAA with a 15 mm of non-aneurysmal aorta below the renals are suitable for transfemoral graft placement. This new era of arterial prosthetic management is discussed by Trieman and Berhard.

The discussion on the scientific basis of screening for colon cancer by David Leiberman is of relevance to family physicians, gastroenterologists and epidemiologists. Screening of asymptomatic average risk individuals over the age of 50 by faecal occult blood testing (FOBT) and/or sigmoidoscopy (SC) reduces mortality due to colon cancer. But compliance and cost effectiveness are important issues in deciding the best method for screening the population and to develop a public health policy. FOBT has a compliance of 20% and SC10%. Colonoscopy has the highest mortality reduction since majority of the precancerous lesions can be removed in the same sitting, but is costly and is not universally available. Neoplastic disorders are the other major group of killer

disease of this century and four other articles in this review are on interesting basic aspects of oncology. They are on hereditary aspects of breast cancer, angiogenesis in relation to metastasis, minimal residual disease and adoptive immunotherapy following bone marrow transplantation.

Current knowledge on the hereditary aspects of breast cancer is abridged by L. W. Ellison and D. A. Haber. One third of the breast cancers in women less than 30 years and 5–10% of the overall breast cancers have a genetic basis. The current surveillance methods miss the disease because of the early age of onset and the tragedy strikes at the prime of their life. The genes implicated are highly penetrant like BRCA1, BRCA2, P53, and PTEN/MMAC. They function mainly as tumour suppressor genes. Mutation of one of the BRCA1 alleles located on the chromosome loci 17q21 confers a 85% life time risk of development of Ca breast and 50% for ovarian cancer. BRCA2 (13q 12–13) mutations account for 14% of the male breast cancer patients. MMAC gene (Mutated multiple advanced cancer gene) located on 10q23 loci when mutated, leads to the development of Cowden's syndrome. Similarly, the multi cancer familial syndrome described by Li and Fraumeni is linked to mutations of the tumour suppressor gene *p53*. Though the syndrome is rare, *p53* gene is mutated in more than 50% of the sporadic breast cancers, indicating that it plays a major role in progression of the tumour, if not in genesis. Genetic testing as a part of cancer risk assessment in patients with family history or early onset breast cancer, therefore has a number of scientific, social and legal implications.

Angiogenesis, the recruitment of new blood vessels is an essential component of tumour metastasis. A bird's eye view of the biology of angiogenesis with respect to tumour metastasis is given by B. R. Zeller. Vascular density can serve as a prognostic indicator and metastatic potential. Anticancer effects of natural and synthetic angiogenic inhibitors are investigated in various clinical trials, because of their low toxicity and lesser chances of developing drug resistance. Antiangiogenic agents are likely to be used as chronic low dose therapies to cause gradual tumour regression and to provide long term prophylaxis to prevent widespread metastatic growth. The article on minimal residual disease (MRD) by Hirsch-Ginsberg summarizes its relevance in the treatment of human malignancies. This residual tumour burden present after clinical remission determines the chances of relapse, drug resistance, and prognosis. Analysis by tumour markers, chimerism, cytogenetics and morphology helps to identify this MRD and regulate further courses of therapy. Detection of neoplastic cells in lymph node or bone marrow after chemotherapy of hematological malignancies or after bone marrow transplantation portends a poor prognosis, depending on the temporal relation, and increase in their number on serial assays. Well-conducted studies on MRD by bone marrow aspiration after therapy of leukemias has generated good data on duration of remission, survival, curability and prognosis.

Allogenic bone marrow transplantation is the treatment of choice in many hematological neoplasms and a variety of immunologic disorders. Cost, lack of donors, immunosupression and graft vs host disease are the major limitations. Immunodeficiency increases the chances of major life-threatening infections but achieves good host vs graft tolerance. So also graft vs host disease increases morbidity, but has good anticancer effect on residual disease. Adoptive immunotherapy refers to infusion of T lymphocytes of donor origin to reverse general immunodeficiency, and to circumvent tumour unresponsiveness. J. M. Goldmann and F. Dizzi discuss the current knowledge and future potential of this novel mode of therapy.

One of the major advances of this century is organ transplantation. Allogenic organs are available from cadavers and live related donors. Atleast 8 people die per day in the United States because of lack of donors. This has renewed interest in xenografts, the scientific aspects of which are outlined by Bach. Concordant donors like baboons do not produce hyperacute rejection, but have problems like organ size and chances for zoonotic disease transmission. Discordant donors like pigs generate hyperacute rejection mediated by xenoactive antibodies (XNA) and complement. This can be overcome by depletion of XNA, immunosupression, scavenging complement with its soluble receptors, and by donor organs derived from transgenic pigs expressing human complement inhibitors on endothelial surface. Once hyperacute rejection is overcome, delayed xenograft rejection gets initiated by type II endothelial cell activation, platelet aggregation and infiltration by mononuclear cells and NK cells. In addition to immunosupression and antiplatelet drugs, down regulation of endothelial cells and donor organs from transgenic pigs with endothelial expression of thrombomodulin and ATPase are the currently available modes to overcome this reaction. Further advances and refinement of this field of science will lead to the evolution of transgenic forms, as the major source of human organ substitution.

Three chronic disorders which are reviewed in this edition are: a) chronic fatigue syndrome, b) management of chronic pain and c) the newer drugs for the management of seizure disorders. These articles are not only informative but also give useful updated information for the internist as well as for the specialists dealing with these disorders.

Articles on endocrinology like that on extracellular calcium sensing receptors, pre-insulin dependent diabetes mellitus, and congenital adrenal hyperplasia (CAH) deal with the fundamental aspects of understanding these clinical disorders. The article on CAH by Maria I New exemplifies the clinical utility of such knowledge. This disorder comprises a family of enzymatic defects of any of the various steps in the synthesis of steroid hormones from cholesterol, resulting in chronic adrenocortical stimulation, and accumulation of a variety of steroid precursors. These result in various forms of genital ambiguity salt losing syndromes, and secondary hypertension. Understanding of the metabolic abnormalities and the early identification of the genetic abnormalities by PCR technique has paved the way for antenatal therapy to avoid the genital dysmorphism in the new born. A battery of PCR probes are available to identify the common mutations of the concerned *CYP21* gene located on chromosome 6 by chorionic villous sampling (10–12 wks) or by amniocentesis (15–18 wks). Administering dexamethasone orally to mothers at risk, as soon as pregnancy is confirmed, can

prevent abnormal genital virilization of the female foetus. Simultaneous karyotyping is done along with the genetic analysis. If the baby is normal, or if there is genetic abnormality but the foetus is a male, dexamethasone prophylaxis is stopped. This succinct review is an excellent example for the clinical utility of understanding the fundamental basics involved in these disorders. Such articles form the crowning glory of the annual reviews.

S. SIVASANKARAN

Department of Cardiology,
Sree Chitra Thirunal Institute for
Medical Sciences and Technology,
Thiruvananthapuram 695 011, India

The Ecology and Evolution of Inducible Defenses. Ralph Tollrian and C. Drew Harvell (eds). Princeton University Press, 41, William Street, Princeton, NJ 08540, USA. 1999.

The Battle of Hastings, 1066. 'The courageous leaders mutually prepared for battle, each according to his national custom. The English... passed the night without sleep, in drinking and singing, and in the morning proceeded without delay against the enemy. All on foot, armed with battle-axes, and covering themselves in front by the juncture of their shields, they formed an impenetrable body which would assuredly have secured their safety that day had not the Normans, by a feigned flight, induced them to open their ranks, which till that time, according to their custom, had been closely compacted....Then starting the Song of Roland,...the battle commenced on both sides, and was fought with great ardour,...This alternating victory, first of one side and then of the other, continued so long as Harold lived to check the retreat; but when he fell..., the flight of the English ceased not until night' (William of Malmesbury: cited in Robinson[1]). From a modern-day perspective where stealth, surprise attacks, and superior weaponry are the norm, it appears strange that battles were actually fought in this pre-announced manner, giving time to the enemy camps to prepare themselves. However, historians may tell us based on available technology and contemporary social structure, why ritualized warfare existed.

It is with the same sense of confusion, that one encounters kairomones, those 'infochemicals' produced by predators that announce their presence to prey and which induce prey to don chemical, physical, or behavioural armour. Why should predators reveal their presence to prey; why could not predators have evolved ways of either masking the signal or dampening it altogether? Through many chapters in the book edited by Tollrian and Harvell, this question bothered me; only one paper by Tollrian and Dodson (Inducible Defenses in Cladocera: Constraints, Costs and Multipredator Environments, Chapter 10) and the concept paper by Adler and Grünbaum (Evolution of Forager Responses to Inducible Defenses, Chapter 15) alluded to this fundamental problem. It was with relief then that I later found an answer in Kusch[2]. *Amoeba proteus* preys upon ciliates of the genus *Euplotes*. The amoebae release a signalling molecule (A-factor) or kairomone which the ciliates respond to with predator-avoidance behaviour. Why does the predator betray its presence to the prey? Kusch[2] has shown that the kairomone primarily serves as a self-recognition signal. Particles coated with A-factor escaped phagocytosis, indicating that it is via the A-factor that self-recognition prevents mutual consumption of amoebae many of whom are probably asexual clones. Here the fitness advantage gained by self-recognition is possibly greater than the loss incurred by defence-induction in the ciliate prey. However, not all species of ciliates recognize the A-factor. It is possible that if and when more prey species evolve recognition and subsequent avoidance behaviour, the disadvantage of the kairomone may outweigh the benefits; this would then lead to different evolutionary trajectories for the A-factor. Adler and Grünbaum outline the evolutionary snares that await the predator. The predator might try reducing the cue but the prey could be getting more sensitive or could begin to respond to new cues; the prey may latch on to a cue like a mating pheromone that the predator cannot reduce without facing disastrous circumstances, or reducing the signal may have some energetic or foraging cost for the predator. Subsequent editions of this book, should they be attempted, would do well to incorporate new answers as in Kusch[2] to these old mysteries.

This book has an agreeable mixture of data review, concepts and new ideas, and spans a range of organisms with inducible defences from protozoa, rotifers, carp, larval anurans, barnacles, bryozoans to plants. The volume hinges around one fundamental question – why inducible defences? The conventional *mantra* has been that inducible defences are cost-saving compared to constitutive defences, especially if the attacks are unpredictable and of variable intensity. Agrawal and Karban (Why Induced Defenses May be Favored over Constitutive Strategies in Plants, Chapter 3) attack this conventional point of view for plants and offer six less-investigated hypotheses for the evolutionary origin and maintenance of inducible defences. Among these is the possibility that induced defences slow down the adaptation of herbivores because they do not provide consistent directional selection pressure as would constitutively defended plants. Long-lived animals have a variety-generating immune system which can keep herbivores and pathogens on the evolutionary run; the absence of an immune system in long-lived plants can then perhaps be compensated for by induced defences. It would be worth investigating the relationship between plant reproductive life-span and the constitutive-inducible defence dichotomy. With Agrawal and Karban's provocative and stimulating exposé, the path has been cleared for the investigation of new hypotheses. Yet it appears that the cost-allocation *mantra* cannot be silenced altogether because costs are notoriously hard to measure and although investigators have used various surrogates for costs of defence, the evidence has never been clear cut. Therefore, defenders of the cost-allocation paradigm can always attribute the lack of a pattern or the presence of the 'wrong' pattern to errors of measurement or the employment of the wrong currency. A pluralistic approach to the problem of cost of defences is undoubtedly necessary and, therefore, the views of Agrawal and Karban are very welcome.

Indirect defence in tri-trophic systems has always been characterized by ex-