

Annual Review of Medicine: Selected Topics in Clinical Sciences. Edited by Cecil H. Coggins, William E. Hancock and Lee J. Levitt. Annual Review Inc., 4139, El Camino Way, P. O. Box 10139, Palo Alto, CA 94303-0139, USA. 1997. vol. 48. Price: Individuals, US\$ 65; Institution, US\$ 130. 590 pp.

Every year *Annual Review of Medicine* provides physicians a means to have a sweeping glance at the advancing frontier of medicine. The book would include not only the results of clinical trials of new drugs and approaches of medical treatment but also pathogenetic concepts, diagnostic criteria for difficult clinical conditions, surgical treatment, public health issues and advances in medical technology. This year is no exception.

There are 42 articles in this year's edition. Among them, the paper by Ted Steiner and colleagues from University of Virginia School of Medicine is of great concern. They draw attention to the outbreak of diarrhea in 1993 at Milwaukee in which 403,000 people developed the illness from drinking water that met all the federal safety standards of that time. This was the largest outbreak of water-borne disease ever reported in the United States. The authors discuss the threat posed by the emergence of protozoal pathogens, which can cause outbreak of water-borne diarrhea. They call *Cryptosporidium parvum*, the cause of the outbreak in Milwaukee, the 'water industry's new super bug'. There are several other water-borne protozoal pathogens such as *Giardia lamblia*, *Entamoeba histolytica*, *Cyclospora cayetanensis* and *Microrosporidia* that are potential threats. Evidently, there is compelling need to search for improved methods for water purification.

Three of the topics included in the book have come to the attention of clinicians only recently and may not be found in general texts of medicine. During the last decade, study of programmed cell death (apoptosis) has gained increased attention. In the pathogenesis of many human diseases, apoptosis has been implicated. These diseases include acquired immunodeficiency syndrome, autoimmune disorders, developmental anomalies,

neurodegenerative diseases, some types of cancers, cardiac failure and viral diseases. Specific mutation of genes critical for apoptosis has been identified in association with several autoimmune diseases including systemic lupus erythematosus. Aberrant control of apoptosis is implicated in Alzheimer's disease, Parkinson's disease and schizophrenia. Therapeutic efficacy of almost all antineoplastic agents is linked to induction of apoptosis. Charles Rudin and Craig Thompson in their article focus on recent exciting developments in our understanding of regulation of apoptosis in health and disease. They discuss the central pathways of apoptosis, apoptotic-signaling pathways, viral modification of apoptosis, cross talk between cell cycle regulation and apoptotic pathways and role of apoptotic mechanism in chemotherapeutic resistance of cancers. The authors speculate that in the future, modulation of apoptosis would be a strategy in the treatment of diseases and that it would have impact on the prognosis of many important diseases.

Molecular genetic techniques have revealed a non-traditional inheritance pattern by a novel mechanism of gene control, which has been termed genomic imprinting. Human beings normally inherit two different copies of each gene, one copy from each parent. In genomic imprinting, only one gene is expressed and depending on which parent the gene comes from, the same genetic information can result in a different phenotype. The phenomenon is observed in a number of developmental abnormalities, cancer, behaviour disorders and disorders of growth. Genomic imprinting should be suspected when a disease is always expressed when inherited only from the male or only from the female parent. Another clue is when one of a monozygotic twin is affected and the other is not. Several types of cancers appear to have effects of genomic imprinting. Hereditary paragangliomas are exclusively inherited from the father. Selective losses from maternal chromosomes are associated with loss of heterozygosity for the retinoblastoma gene and for the Wilm's tumour gene. J. G. Hall in his article comments on the clinical relevance of genomic imprinting.

Robert Moore describes functional organization of circadian system and

some of the common disorders of circadian function. Circadian system involves pacemakers in the suprachiasmatic nuclei of the hypothalamus, visual and non-visual pathways that project environmental information to the pacemakers and outward pathways which couple the pacemakers to effector systems under circadian control. Pacemaker dysfunction can cause irregular sleep-wake pattern and is also thought to be responsible for fragmentation and loss of sleep in old people. Disorders of entrainment pathways which are involved in resetting the circadian clock are associated with jet lag, work shift syndrome, delayed phase sleep syndrome and non-24 hour sleep-wake syndrome. Recent studies show that melatonin is an effective treatment for some of these disorders. Moore does not cover genetic and molecular aspects of circadian biology. The role of chronobiology in finding new therapies particularly for cancer is also not covered in Moore's article.

Eleven of the reviews are devoted to cardiovascular problems. George Cooper reviews recent progress in unraveling the molecular mechanisms of cardiac hypertrophy. He presents evidences for the view that mechanical load itself is adequate for the initiation of cardiac growth at cellular, tissue and organ levels. A number of endocrine, paracrine and autocrine factors can also stimulate cardiac growth. However, it is unsettled whether any of them are primary stimulus for cardiac hypertrophy. It seems likely that inducible secondary factors intensify the primary response to mechanical load and that cardiac hypertrophic response to abnormal haemodynamic overloads has substantial redundancy. Cooper has also discussed transcriptional and translational regulation of cardiac hypertrophy. The same mitogenic pathways as seen in mitotically active cells mediate most of the qualitative changes in gene expression during hypertrophic response. Protein synthesis in hypertrophy has been linked to changes in both translational efficiency as well as translational capacity. Another interesting information is on the role of integrins and signal transduction pathways in the transduction of mechanical input into growth response. Redistribution and activation of integrin related non-receptor tyrosine

kinases are suggested as key components of the mechanotransduction pathway.

Several disease states such as atherosclerosis, congestive cardiac failure, diabetes mellitus, post-angioplasty arterial stenosis, hypertension and septic shock are associated with abnormalities in endothelial function. In these disorders, the endothelial dysfunction contributes to the alterations in the structure and function of the blood vessel wall. An important regulator of endothelial function is the molecule nitric oxide, which is derived from L-arginine through the action of the enzyme nitric oxide synthase. There is increasing interest in the study of the role of the enzyme in the pathogenesis of vascular diseases because of the possibility of targeting the enzyme in developing new treatment strategies for vascular disorders. J. P. Cooke and V. J. Dzau focus on the role of nitric oxide synthase in modulating vascular resistance and the activity of the enzyme in pathological conditions.

In the early 1950s, an operative treatment was reported to remove atherosclerotic plaques of carotid arteries, the cause for transient ischemic attacks and stroke. Since then there has been an exponential increase in the number of carotid endarterectomies performed. A decade ago, the advantage of the procedure over medical treatment in preventing stroke and death was questioned. Several prospective randomized trials were conducted during the past six years and they helped to clarify the indications for operative treatment of carotid artery disease. C. M. Wittgen and D. C. Brewster summarize the results of some of the large surgical trials and present in a tabular form, the indications for endarterectomy. A proven indication in an asymptomatic patient is stenosis exceeding 75% and proven indications for symptomatic patients are carotid artery stenosis of more than 70% and either mild stroke or one or more transient ischemic attacks within past six months.

It was in the 1970s that Carpentier developed what he termed the French correction for reconstruction of mitral valve. His techniques included ring annuloplasty, leaflet resection, chordal shortening and chordal transposition. Carpentier's techniques are popular for

the treatment of mitral regurgitation and are increasingly preferred over mitral valve replacement. C. Hahn and G. J. Vlahkes from cardiac surgical unit of Massachusetts General Hospital present the results of repair which has a stunning 90% rule: 'Approximately 90% of patients with mitral insufficiency are candidates for reconstruction; after repair 90% no longer have significant mitral insufficiency; over 90% are in NYHA class I or II and the five year survival is nearly 90%; nearly 90% of survivors are free from reoperations at ten years.' Compared to valve replacement, reconstruction is associated with decreased risk of endocarditis and thrombo-embolism. The cost of prosthetic materials used in repairs is only one-third that of prosthetic valves. Surprisingly there is no mention about the role of mitral valve repair in mitral regurgitation of rheumatic etiology.

James L. Cox is a pioneer in the operative treatment of atrial fibrillation, the most common disorder of cardiac rhythm. He and his colleagues reported the left atrial isolation procedure in 1980 and seven years later the Maze procedure was described. Since then 178 patients were treated by this technique or its modifications. One hundred and twenty five patients were re-evaluated till February 1996. It was found that not only was atrial fibrillation abolished, but also right atrial function was preserved in 98% of patients and left atrial function was preserved in 94% of patients. Cox and T. M. Sundt examine their data and recommend Maze III procedure for the treatment of atrial fibrillation in patients whose arrhythmia is refractory to medical treatment.

The success of cardiac surgery has led to a new population of patients. These are adults whose original complex congenital cardiac problems have been modified by operative treatment. Management of these patients needs special expertise. Jane Somerville has the ROCK recommendations for organizing the services for such patients. She runs a separate unit for the grown up congenital hearts, termed the GUCH unit at Royal Brompton Hospital, London.

There are two articles on venous thrombosis. One of them is about the

most common genetic risk factor for venous thrombosis, viz. inherited resistance to activated protein C. Protein C system is activated by the thrombin-thrombomodulin complex. Activated protein C cleaves and inhibits activated factor V and activated factor VIII, thus downregulating the activity of the coagulation system. Four years ago the link between familial thrombophilia and poor anticoagulant response to activated protein C was recognized. The molecular basis was elucidated shortly. A single point mutation in the gene for factor V accounts for the slow degradation of activated protein C, resulting in hypercoagulability and a life long increased risk for venous thrombosis. Prevalence of factor V mutation is estimated to be 1-15% in populations of Caucasian origin and is more common than all other known causes for inherited hypercoagulability states. The authors suggest that general screening for activated protein C resistance would be beneficial in conditions associated with thrombosis such as pregnancy, trauma, surgery and oral contraceptive usage.

G. F. Pineo and R. D. Hull consider the long term follow up results of six randomized clinical trials which compared low molecular weight heparin with unfractionated heparin for the treatment of proximal deep vein thrombosis. They conclude: 'low molecular weight heparin will undoubtedly replace intravenous unfractionated heparin not only in the treatment of venous thromboembolism, but also in other conditions where heparin therapy is indicated'.

Two articles are perhaps, eye openers for nephrologists. Manuel Pascual and colleagues from Harvard Medical School present results from clinical trials and experimental studies that indicate that the course and outcome of patients with acute renal failure may be influenced by the biocompatibility of dialysis membranes. The potential of dialysis membrane to activate or not activate complement and neutrophils appears to be relevant in influencing patient morbidity and mortality. Donald Vidt of the Cleveland Clinic Foundation draws attention to a common but rarely recognized cause of renal failure, viz. cholesterol embolization (CE). Interventional diagnostic procedures and

operations on aorta increase the risk for cholesterol emboli in the kidneys. Vidt enumerates a number of clinical conditions which can mimic CE and describes how CE can be distinguished from them.

Several reviews pertain to new therapeutic agents such as thrombopoietin, intravenous immunoglobulins, new generation beta blockers, mifepristone (proved useful not only for termination of pregnancy and as contraceptive but also for the treatment of endometriosis, fibroids and as anti-glucocorticosteroid agent), taxanes and naltrexone (approved by FDA for the treatment of alcoholism). There are comprehensive essays in which you will find how to differentiate variant forms of von Willebrand's disease, guidelines for the management of severe pre-eclampsia and evaluating patients for lung volume reduction surgery in emphysema, possible approaches to immunotherapy in paraneoplastic syndromes, a scoring system to objectively assess severity of urinary symptoms in patients with benign prostatic hypertrophy, treatment of primary pulmonary hypertension, temporal lobe epilepsy and pre-menstrual syndrome, the usefulness of oral administration of antigens in the treatment of autoimmune diseases, techniques involved in the transplantation of haematopoietic stem cells, pathogenesis of renal osteodystrophy and criteria for the diagnosis of acute respiratory distress syndrome.

Despite technological advances and progress in our understanding of molecular basis of diseases, some medical problems remain difficult to manage and are important causes for morbidity. Among them are grief reactions in the elderly widowed people and the emotional and behavioural problems that occur following cerebrovascular stroke. These conditions are the themes for two separate articles. I found the rest of the reviews uninteresting.

To sum up, there are several treatises in the recent edition of *Annual Review of Medicine*, which are instructive to the specialists. Primary care physicians in the third world may not find these articles of any practical value. This is not surprising since nearly 85% of the contributors are from the United States and there is none from the developing countries. Possibly there is scope for

another text, maybe an *Annual Review of Medicine in the Tropics*.

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Neotropical Companion: An Introduction to the Animals, Plants and Ecosystems of the New World Tropics. John Kricher. Princeton University Press, 41, William Street, Princeton, NJ 08540, USA. 451 pp. Price US\$ 29.95.

Our yearning for surprise and wonderment is what sets the stage for discoveries. Biology is so attractive to many, perhaps because it is a discipline that is left with many surprises and an often chance for wonderment. What makes biology enchanting are possibilities as wholesome and surreal as our childhood hopes of turning little grasshoppers to parrots or the ant-lion larvae to elephants. Taxonomists made it boring; biochemists and others will squeeze the life out of it. I think one should get initiated in biology without Latin or reference to Lehninger to get the real feel for the wondrous beauty it is. Here is a book that will be an aid for such a pure joy of discovery.

Tropics can be either the 'Emerald paradise' or the 'Green hell' the way you look at it. It is verdant greens, colourful birds and butterflies, exotic fruits and a profusion of animal life forms for the aficionado. It may, however, be disease-carrying mosquitoes, botflies that breed beneath your skin, venomous snakes, vicious crocodiles, spooky spiders, scorpions that sting badly, and a climate reminding one of Dante's favourite place for others. But one thing that every one will agree is that it is not dull. This book is as exciting as the tropics itself. It is not a guidebook but genuinely a companion. One must read it and keep reading it. The writing puts it on par with good books in any class, well written with subtle humour but highly informative. It can be read any time at any page without losing contents. But if you intend to use it as a field-guide in its true sense this is not for you. It is not a catalogue of standard

descriptions and exhaustive illustrations but draws heavily on Kricher's sojourns in the neotropics written with a view to inspire and educate. One misses nice pictures of tamarins and marmosets and many other species but then there are enough photo compilations elsewhere and that absence is made up by such evocative style of writing that reading this volume is bound to be a great satisfaction. The number of new species found, including recently discovered new primates, makes neotropics the region where more is yet to be found and learnt. Kricher's book sketches such a voyage of discovery but not in the style of 'armchair travelogues', which scale great heights in their ability to be boring and monotonous. A few samplers illustrate the style and content of this neat book.

Ant-fungus relationship evolved possibly more than 50 million years ago. Much before we were little furry rats scurrying between giant dinosaur legs, leave alone coconut-flinging monkeys, ants went through stages of hunter-gatherer, pastorals and slave makers. The leaf-cutter ants are really farmers who use the leaves to make media for cultivating a particular species of fungus. Kricher builds a truly wonderful story of co-evolution with this theme. The odd fungus, never found free-living outside fungus garden ant colonies, is the ant's only food. Leaves brought to the colony are cut into small pieces and chewed into soft pulp. Before placing the pulpy mass on the fungus bed, the ants defecate a drop of liquid, that contains all twenty-one essential amino acids, allantoinic acid and allantoin, key ingredients needed for fungal growth. The chewed leaves are then added to the fungus growing bed, and fungal tufts are placed on top of it. Worker ants avoid leaves that contain chemicals potentially dangerous to their fungi. Fungi are always in pure culture, protected from contamination by 'weeding' other fungi. Without the ant's attention the fungi wither away. And finally when a queen ant founds a new colony, she takes some of the precious fungus with her inside her mouth! Some plants have even evolved antifungal compounds that make ants avoid such leaves since their fungus does not grow well even though the leaves are not poisonous to the ants.

The whole chapter on Neotropical Pharmacy is full of informative accounts. 'Tropical rainforests are green.