by Moo-Young Han and the Appendix by Nambu); and the idea in 1970 of one-dimensional strings as the ultimate building blocks of the content of the universe (articles by Paul Frampton, Lars Brink, Pierre Ramond and Lay-Nam Chang). The first was developed with Jona-Lasinio, the second with Han. The article by Brink is especially valuable as it recounts in some detail the steps that led to Nambu being awarded the 2008 Nobel Prize. Brink was on the Committee from 2001, later its chairman, and was especially concerned about Nambu's state of health as the announcement date drew near. It is justifiably felt by many that this prize should have been given to him earlier.

As for Nambu the person, we read:

'He was surprisingly soft-spoken and modest for someone so wise and important.'

'His keen insights were driven by a marvellous and unique form of intuition. In a typical Japanese manner Yoichiro was unable to use the word "no".'

'Nambu had great human empathy.'

'…extraordinary display of physics, originality and conceptual power.'

'He was the ultimate gentleman scientist, with a big heart. And a unique perspective on all aspects of physics.'

All in all, this is a precious little book, giving us a fine portrait of a great and visionary physicist of the second half of the 20th century, insights into his ways of thinking and philosophy, and his wonderful human qualities.

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Given the flood of medical literature in recent times, physicians face the continuous challenge of keeping up with the advances in general medicine. An efficient way to update is to read the *Annual Review of Medicine*. *Annual Reviews* integrate, scrutinize and evaluate a wide range of studies of current interest and published during the recent past.

This volume has 33 articles. Nine of them deal with treatment of different types of solid and haematological malignancies. Three articles discuss therapy related to HIV infection. Mechanisms and treatment of immune or autoimmune diseases are the subjects of four reviews. Two articles focus on new vaccines. Pathogenic mechanisms, new pharmacological strategies, novel diagnostic tools and issues of public health are the other themes included.

Neglected tropical diseases (NTDs) such as malaria, tuberculosis, rota virus, HIV, respiratory syncytial virus and parasitic infections (hook worm, schistosomiasis and leishmaniasis) are the most common chronic and debilitating diseases of extremely poor people. Development of vaccines against these diseases confronts distinct challenges with respect to their manufacture, preclinical and clinical trials as well as successful marketing. Progress, opportunity and challenges in these areas are described by Hotez *et al.*. They point out that despite tremendous potential for the development of novel NTD vaccines, there is no specific road map for ensuring that they are made accessible to the needy.

Approaches and challenges for the development of vaccines against dengue are the theme of an article by Guy *et al.* They begin by defining the questions which need to be answered during vaccine development and conclude with presentation of issues raised by clinical trials. One or more vaccines for dengue are likely to be available soon.

Given the undoubted increase in the burden of obesity, type-2 diabetes and non-alcoholic fatty liver disease (NAFLD) in India and the link of these risk factors with hepatocellular carcinoma (HCC), the article on mechanisms underlying their relationship would be of considerable interest to both clinicians and medical scientists. Notable findings of several studies on the association among HCC, NAFLD, type-2 diabetes and obesity are presented by Manengo *et al.* They also describe the molecular mechanisms of hepatocarcinogenesis in the absence of liver cirrhosis. These include adipose tissue-derived inflammation, oxidative stress and lipotoxicity, and stimulation of IGF-1 axis by hyperinsulinemia. Diet, gut microbiome and genetic factors are also relevant. The authors emphasize the importance of developing surveillance and prevention strategies.

Recent reports which suggest that a cure for HIV infection is possible have renewed optimism in developing treatment strategies and methods to evaluate interventions. Martin and Siliciano review the efforts in exploiting shock and kill strategy targeting latent HIV and developing small molecule latency reversing agents such as HDAC inhibitors, vaccines and genome editing tools for restoring memory $CD4^+$ T cells.

The article by Luzuviago focuses on recent advances in our understanding of the basis of HIV-1 persistence in children and the usefulness of very early combination anti-retroviral therapy in restricting generation and preservation of long-lived $CD4^+$ T cells that contain HIV-1 DNA and replication competent virus in children.

Novel vaccine designs aim to mimic natural evolution of protective neutralizing antibodies against HIV-1. Sadanand *et al.* describe the structural characteristics of neutralizing antibodies against HIV, their viral targets and strategies to elicit these antibodies in the development of an HIV vaccine.

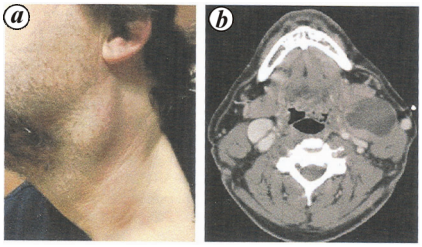
A fascinating review is on new pharmacological strategies to increase cGMP. Impairment of the cGMP pathway is linked to pathogenesis of a variety of diseases which include obesity, dementia and cardiovascular diseases such as hypertension and heart failure. For treatment of these diseases, agents that enhance cGMP generation are being developed and evaluated. These drugs are either guanyl cyclase activators or phosphodiesterase inhibitors or neprilysin inhibitors. Progress in research in this area indicates that distinguishing between cGMP in different compartments of the cell could lead to intervention in a specific selected pathway.

In lower- to middle-income countries, young adults and women are particularly vulnerable to acute kidney injury and are at risk of death. Those who survive could develop chronic kidney disease and end-stage renal disease. Zuk and Bonnentre focus on novel pathogenic mechanisms for acute kidney injury and progression to chronic kidney disease discovered

from animal models. These mechanisms relate to renal blood vessels, cellular stress responses which include unfolded protein response, mitochondrial dysfunction, autophagy and innate immune response. Progression to chronic kidney disease seems to be a sequel to persistent maladaptive repair mechanisms involving macrophages, endothelium and surrounding pericytes, and growth-arrested tubular epithelial cells. Progress in the understanding of these mechanisms is expected to lead to the discovery of useful biomarkers and therapeutic interventions.

Todd and Kay provide a comprehensive description on a systemic fibrotic disorder in patients with kidney disease who had exposure to gadolinium-based contrast agents. Their article includes a historical perspective, description of demographic, clinical and histological features, discussion on mechanism, evidences for a causal association, differential diagnosis, prevention strategies as well as emerging antifibrotic therapies.

The exciting field of non-invasive prenatal testing is reviewed by Wong and Lo. The increasingly popular approach sans amniocentesis or chorionic villus sampling for screening or diagnosis of foetal chromosomal or genetic conditions employs analysis of cell-free foetal nucleic acids in maternal plasma or serum. Advent of massively parallel sequencing facility has enabled the growth of a number of applications for prenatal testing and discovery of genetic information on the foetus, from chromosomal errors to single-gene disorders. Deep sequencing of maternal plasma has revealed whole foetal genome, transcriptome and methylome as well as specific foetal genetic disorders.



(***a***) Left neck mass in a patient diagnosed with HPV-positive oropharyngeal cancer; (***b***) the computed tomography scan correlate demonstrating the cystic appearance of cervical lymph node metastases commonly seen in patients with HPV-positive oropharyngeal cancer.

Natalizumab, fingolimod, teriflunomide, dimethyl fumarate and alemituzumab are new agents approved by the US FDA for the treatment of relapsing forms of multiple sclerosis, a leading cause of disability among young adults. Dalizumab, ocrelizumab and ofatumumab are currently promising in late-phase clinical trials. One review is on the mechanisms of action of these agents, clinical trial data, safety concerns and monitoring requirements for these agents. Clinical trials do not yet suggest a significant effect of these new agents on disease progression. Future research is expected to aim at developing agents which promote remyelination or have neuroprotective properties.

Barrat *et al.* discuss the significance of recognition of nucleic acids by the innate immune system to mount an immune response appropriate to pathogens and the mechanisms through endosomal and cytosolic sensors. Autoimmune diseases result from inflammation driven by uncontrolled mechanisms of recognition of self nucleic acids. They examine the therapeutic potential of targeting nucleic acid sensors using agonists and antagonists.

Therapeutic drugs which target IL-23, IL-17 and their receptors, important contributors to the pathogenesis of several common immune-mediated disorders, are either in present clinical use or are undergoing trials. They are found to be effective in psoriasis and promising in treating spondylo arthropathies. Properties of these drugs are enumerated in one of the reviews. The authors also deliberate on the lessons learnt during clinical trials on the safety and utility of these agents.

Rho kinases (ROCKS) modulate a wide range of biological processes and are important coordinators of tissue responses to injury. Dysregulation of their activity is implicated in several diseases. The role of ROCKS in the pathogenesis of autoimmune diseases and the approaches to inhibit ROCKS are surveyed by Pernis *et al.*

An exciting review is on intraoperative fluorescence imaging. This is an emerging tool which improves surgeons' visualization of tissues and thus surgical precision. Authors detail the technique and compare methods that utilize non-specific fluorescent dyes such as indocyanine green for monitoring anastamotic procedures and lymph-node mapping, with those that employ targeted agents such as folate receptor targeting agents, useful to identify molecular biomarkers, outline tumours and probe pathophysiological features of disease.

In another stimulating review, the authors discuss current concepts of epigenetic regulation in cancer cells and approaches of cancer epigenetic therapy, which involve primarily inhibitors of DNA methylation and histone deacetylation. Examples of epigenetic therapy trials in different types of solid tumours are also enumerated. Increasing recognition of clinical efficacy indicates that reversal of cancer-associated epigenetic alterations by reprogramming neoplastic cells can be achieved.

Several drugs targeting the PI3K/AKT pathway are under clinical trials in patients with solid tumours as well as haematological malignancies. A comprehensive review by Mayer and Arteaga considers how genetic alterations in the PI3K/AKT pathway lead to tumorigenesis, cancer progression and drug resistance. They also comment on the mechanisms of actions of various therapeutic PI3K inhibitors and results of clinical trials on the evaluation of the role of these inhibitors. Challenges remaining for therapeutic targeting of PI3K/AKT are also enumerated.

Another major target in cancer therapy is *B-Raf*, an oncogene. *B-Raf* mutations are highly prevalent in malignant melanomas, and papillary and anaplastic thyroid carcinomas. *B-Raf* mutations are also reported in patients with hairy cell leukaemia and Langerhans's histiocytosis. Fiskus and Mitsiades provide an account of drugs that suppress *B-Raf* and small-molecule inhibitors of MEK, a downstream signalling mediator of the *Raf* pathway, mechanisms of resistance, adverse effects, future prospects of overcoming resistance and combinatorial therapies, including immunotherapy approaches.

Incidence of human papilloma virus (HPV) positive oropharyngeal cancer (OPC) is increasing. The reasons for this are not clear. Patients with HPV-positive OPC are younger males, less likely to smoke, of higher socio-economic status and have specific associated lifestyle factors. Maxwell *et al.* provide an update on contemporary views regarding the natural history of HPV-related OPC and strategies for risk stratification for planning treatment. They also comment on

the present status on the development of immunotherapy and HPV vaccines.

Basic design of chimeric antigen receptor (CAR) on T cells, and advantages and disadvantages of their use compared to other immunotherapies for lymphomas are reviewed by Ramos *et al.* They also present the results of clinical trials using CARs and strategies to enhance their efficacy and safety.

Bisphonates are widely recommended to treat bone loss in patients with osteoporosis. They have been also tried for adjuvant therapy in women with hormone receptor-positive breast cancer to prevent bone-related complications secondary to cancer treatment, as well as to prevent recurrence and metastases. The first article in the volume summarizes the results of randomized clinical trials involving many thousands of patients as well as a recent meta analysis by Earl Breast Cancer Trialists' Collaborative Group (EBCTCG). Meta analysis by EBCTCG of data from about 19,000 patients reveals the beneficial effect of bisphonates on recurrence of bone metastases and overall survival in patients with breast cancer, who are post-menopausal at diagnosis or pre-menopausal women who received ovarian suppression treatment, i.e. in a low oestrogen environment at baseline of their treatment.

Risk profiling of acute myeloid leukaemia (AML) has evolved from traditional morphologic and cytogenetic analysis to next-generation sequencing studies which have provided significant novel insights into the molecular aspects of AML with normal karyotype. This new knowledge has implications for diagnosis, risk stratification and post-remission treatment of patients with AML. Komanduri and Levine demonstrate how molecular analysis and assessments of somatic mutations in leukaemic cells have helped guide selection of post-remission treatment strategies extending from chemotherapy to a combination of haematopoietic stem-cell transplants and immunotherapy.

Cystic neoplasms of pancreas, increasingly recognized now thanks to the wide use of abdominal cross-sectional imaging tools, are a diverse group of tumours classified according to their potential to turn malignant. Epidemiological and clinical features, classification, risk factors, pathogenesis, different means for diagnostic evaluation (including molecular diagnostics) and management strategies of cystic pancreatic tumours form the theme of one of the reviews.

An article titled 'Molecular profiles of prostate cancer' examines commercially available as well as promising genomic tests in development. Their advantages and limitations in differentiating aggressive from non-aggressive prostate cancer are presented. New molecular profiling tests have better reproducibility compared to pathological or radiological grading. Hence they are promising for risk stratification to assist monitoring of patients and making therapeutic decisions.

Over the last two decades, advances in medical treatment for benign prostatic hyperplasia (BPH) and its related symptoms have led to decrease in surgical interventions. Another article catalogues various surgical and device treatments for BPH, treatment outcomes and associated complications. Pathogenesis of BPH is also discussed.

There are also reviews on other topics of considerable current interest. One of them presents the results of four major cardiovascular outcome trials on incretin-based therapies (with three DPP-4 inhibitors and a GLP antagonist) on cardiovascular outcomes or safety in patients with type-2 diabetes. Wong summarizes the understanding on the biological connection between vitamin D and the cardiovascular system and the results of ongoing prospective randomized trials on vitamin D supplementation in patients at risk for cardiovascular diseases. Surprisingly, accumulating evidence suggests that vitamin D supplementation has no influence on blood pressure.

Other interesting reviews in this volume deal with oral immunotherapy for peanut allergy, mechanisms for opioid analgesia, actions and side effects of opioid receptor agonists and antagonists, public health issues arising from marijuana legislation in USA, epidemiology of cognitive impairment in survivors of critical illnesses and approaches to the management of patients with critical illness brain injury, future of evidence-based therapy for nicotine addiction, mechanisms of action, and evidence for the use and adverse effects of pirfenidone, an antifibrotic agent which provides a new hope for patients with idiopathic pulmonary fibrosis.

In summary, the new edition of *Annual Review of Medicine* contains enlightening chronicles of advancing frontiers of a wide range of common clinical problems as well as simulating topics of contemporary interest. All the articles are lucidly composed. An appropriate background useful to readers unfamiliar to the review topic and a summary at the end are provided. Schematic illustrations of concepts, effective use of tables in presenting data and good quality photographs enhance the quality. All interesting and significant studies referred to in the reviews are brought to the reader's attention by providing their citations in bold font.

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Annual Review of Cell and Developmental Biology, 2015. Randy Schekman, Larry Goldstein and Ruth Lehmann (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. Vol. 31. vii + 842 pp. Price: US$ 105.

This volume comprises reviews covering a wide range of topics. The editors have broadly classified them in different areas pertaining to cell and developmental biology. However, the reviews are highly focused.

The volume begins with a perspective by Lewis Wolpert. His transition from a civil engineer to a biologist makes fascinating reading. It is of interest to note how he began his research by applying the principles of mechanics to cell biology problems. The system in the UK would permit this transition with ease!

Wood and Nurse in their article entitled 'Sizing up to divide: mitotic cell-size control in fission yeast' discuss various aspects of cell size control which has been studied extensively but is yet to be resolved unequivocally. The quantitative aspect of this problem studied from 1900s has been summarized in the introduction. The review suggests that further investigations are necessary for better and clearer insights into the problem.