

Still talking of Dirac, the birth of Quantum Electrodynamics is well related, with Anderson's discovery of the positron and Dirac's immediate understanding/explanation of it, invoking the Pauli principle to fill up the infinite 'Dirac sea'.

The historic meeting between Fermi and Pauli in 1933 resulting in the prediction of the neutrino and the β -decay is well documented [p. 194]. One learns of the extreme audacity of the pioneers, e.g. the advocacy of Bohr to give up the principle of conservation of energy to explain these experiments, prior to Pauli's bright idea.

There are several interesting stories on the three Nobel Curies, on Langevin, and the two de Broglies. The role played by Nernst in 'instigating' the Solvay meetings, his rivalry with Arrhenius and the resulting competition between the Solvay meetings and the Nobel foundation are recorded in an interesting way, in the particularly readable essay by Elisabeth Crawford. Nernst's Nobel quest propelled by the third law of thermodynamics, and the specific heat of solids is very interestingly presented.

All in all the book deals with an interesting subject in a way that manages to come through as interesting, despite the fragmentation of the format.

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Annual Review of Pharmacology and Toxicology 1999. Vol. 39. A. K. Cho, T. F. Blaschke, I. K. Ho and H. H. Loh (eds). Annual Review Inc., 4139, El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. pp. 470. Price: Individuals, US \$ 65; Institutions, US \$ 130.

The discovery of new therapeutic molecules demands an understanding of the nature of drug targets, features of detoxification mechanisms, drug toxicology and the regulatory features of the cellular machinery that is involved in all

these responses. *The Annual Review of Toxicology and Pharmacology 1999* has several articles that reflect these elements.

There are two articles which directly discuss molecular targets for drugs. The article on nitric oxide synthase (NOS) examines this enzyme as a potential therapeutic target. Inhibitors of NOS are potentially useful in diseases including septic shock, neurodegenerative disorders and inflammation. The article on phospholipase A2 (PLA2) emphasizes the role of phospholipids as second messenger molecules with key roles in cellular signalling. PLA2 is a key to the synthesis of key inflammatory mediators that include prostaglandins, leukotrienes and platelet activating factors. Inhibitors of PLA2 could potentially block these pathways.

Five articles could be classified under the subject of detoxification mechanisms. The article on 'human cytochrome P-450 3A4' highlights the broad catalytic selectivity, catalytic mechanism, cooperativity, mechanism of induction and possible genetic polymorphism of this protein of major interest. It accounts for the metabolism of 50% of the currently available drugs in use. The article on 'methylation pharmacogenetics' deals with methyltransferases, especially those that catalyse O, S or N-methylation of organic molecules. Phenotyping for the thiopurine methyltransferase genetic polymorphism represents one of the first examples in which testing for pharmacogenetic variant has entered standard clinical practice to decide on therapy of individuals with thiopurine drugs. The article on 'metallothionein (MT)' indicates that contradicting the expectation arising out of the postulated role of MT as a storehouse of zinc and free radical scavenger, null mutants of mice are found to be normal, but highly susceptible to cadmium toxicity. It appears that during evolution, the role of MT against cadmium toxicity has acquired an overriding importance, with compensatory mechanisms perhaps being available to fulfill the other postulated functions. The article on the 'multidrug transporter', P-glycoprotein, that is known to play a role in multiple drug resistance in cancer, highlights the complexity of this pump involved in the efflux of drugs. The full range of exogenous and endogenous substrates for P-glycoprotein is yet to be explored. The article on 'excitatory amino acid transporters' concentrates on the glutamate transport system in neurons

and glial cells. Glutamate has the potential to influence the function of most neuronal circuits in the CNS and to limit receptor activation, extracellular concentrations of excitatory amino acids need to be tightly controlled by appropriate transport systems.

A couple of articles are devoted to discussing aspects of toxicology. One focuses on the cytotoxicity of short chain alcohols and the other on the teratology of retinoids. The damage resulting from acute or chronic exposure to short chain alcohols, including ethanol, is associated with aberrations in phospholipid metabolism, changes in cellular redox state, disruptions of the energy state and increased production of reactive oxygen. Teratology of retinoids including vitamin A governs all the six principles of teratology ranging from the genotype of the conceptus to the sequelae of abnormal development. The retinoid receptors have come into focus in recent years as the mediators of several converging signal transduction pathways and it is of interest to learn that the RAR ligands as opposed to RXR ligands or retinoids that do not bind to receptors, are most potent teratogens.

Majority of the articles deal with the regulatory features of the cellular machinery that respond to and are affected in toxicological responses. Three articles relate to the brain environment. Neurological cells consist of astrocytes, oligodendrocytes and microglia and Schwann cells in the peripheral nervous system. When neurons become severely damaged, microglia become brain macrophages and aid in the disposal of the dying nerve cell. The article on 'genetic regulation of glutamate receptor ion channels' discusses the role of specific glutamate receptor subunits in long term potentiation and depression, learning, seizures, neuronal pattern formation and survival with the use of transgenic and knockout mice. fifteen genes are now known to encode ionotropic glutamate receptor subunits and these together determine the molecular make up of the three pharmacologically defined families of glutamate receptors. The article on 'dopaminergic receptors', that are targets in Parkinson's schizophrenia and hyperlactinemia, elaborates the role of the five different receptors known. D₁ and D₂ receptor subtypes are positive modulators, with antisense treatment or knock out leading to loss of behavioural activity.

D₃, D₄ and D₅ subtypes are inhibitory. The article on 'pineal gland', often referred to as the third eye, deals with pineal physiology and its role in communicating the effects of light to a variety of biologic rhythms. Its role ranging from free radical scavenger to shifting the sleep-wake cycle resulting in jet lag needs to be understood. A couple of articles address the role of signalling molecules involved in smooth muscle cell and cardiac function. C-Ha-ras and Osteopontin genes are critical molecular targets in oxidant-induced atherogenesis. The induction of atherogenic vascular smooth muscle cell types by chemical injury exhibits remarkable parallels to those seen in other forms of atherogenesis. Similarly, cardiac β -adrenergic receptors, which respond to neuronally released catecholamines, are important regulators of cardiac function. However, whether this is a contributory factor or a result of ventricular dysfunction is not clear. A general article on the 'regulation of gene expression by reactive oxygen' discusses the source of reactive oxygen species (ROS), the signal transduction pathways activated by ROS and the transcriptional regulation of ROS-induced genes of toxicological interest. Finally, the article on 'cyclins and cell cycle' check points elaborates the role of cyclin-dependent kinase inhibitors such as P21 and P16 in cell cycle control. The target sites for anticancer drugs in terms of cell cycle check point controls, cell cycle regulatory proteins and contributory factors to resistance against chemotherapy are all discussed.

This book covers a wide range of topics, but in depth. The unifying theme stems from the progress made at the molecular level in terms of signal transduction pathways and the structural and functional role of a variety of receptor and transducing elements. The new tools available, namely the transgenics and knockouts as experimental animals and approaches based on antisense therapies have ushered in a new era for rational drug discovery. The book is an attestation to the scientific soundness of this rational approach.

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Environmental Governance: The Global Challenge. Lamont C. Hempel. Affiliated East-West Press Pvt Ltd, 104, Nirmal Tower, 26 Barakhamba Road, New Delhi. 1998. pp. 291. Price: Rs 125.

On the threshold of the new millennium mankind is flooded with dismal environmental statistics that afflict the sensitivities of people with numbness and a feeling of resignation. 'In an average day, an estimated 260 thousand people are added to the world's population, 30-100 species of plants and animals are prematurely extinguished, over 90,000 new motor vehicles take to the road, 57 million metric tons of carbon dioxide are released to the atmosphere from the burning of the fossil fuels, over 42,000 hectares (162 square miles) of tropical forests are destroyed . . .', etc.

Lamont C. Hempel, in his finely crafted work *Environmental Governance*, draws us away from highly publicized events like the disasters of Bhopal and Chernobyl and ozone holes of Antarctica, into the rarified field of holistic environmental management. He addresses with equal ease global as well as regional issues. Rightly sensing the shortcomings of a sovereign state-centred approach to environmental problems, which are both transnational as well as local, Hempel advocates political institutions of 'glocal' kind, in which environmental authority is redistributed to both supranational entities and local communities.

Hempel likens the Earth Summit to a climbing expedition 'in which the mountaineers, all linked by a frail rope, were forcefully confronted with the advantages and disadvantages of interdependence. Split into coalitions of the rich and the poor, the participants spent much of their time arguing about how to finance the climb and about which members were most prepared to lead. Reaching an impasse, the expedition eventually succumbed to the law of the "retarding lead," . . . whereby the most cautious and powerful members got to set the pace and to determine the route to the summit.' The major gloomy note at the Earth Summit was struck by the unwillingness of the overconsuming rich and the overpopulated poor to accept responsibility for their own contributions to ecological destruction. The author rates the coming together of the world's NGOs at Rio, several thousand representatives of the people

who negotiated unofficial treaties and strategies in a shadow summit, as one of the achievements of the Earth Summit. Their banners proclaimed, in Gandhi's words, 'If the people will lead, the leaders will follow.'

Environmental destruction is generally attributed to the actions of a relatively small number of thoughtless and careless individuals, or to some passing phase of industrial recklessness that accompanies an otherwise 'benign evolutionary process of economic development'. Hempel, on the other hand, attributes the destruction to driving forces that are 'pervasive, persistent, and deeply ingrained in our values, lifestyles, and institutions'. Deep ecologists, economists, technologists and humanists differ on where to place emphasis in facing environmental problems. The author rightly feels that they can agree on the action required on many different fronts using a variety of strategies and approaches.

The threat of global warming, for instance, is the outcome of several human actions for which the entire humanity contributes. Anthropocentrism, contemporism, galloping population, technological growth, poverty as well as affluence contribute to global warming. Villagers corrode the forest wealth for firewood and clear vegetation for growing crops and grazing livestock. The burning of trees contributes up to 25% of the excess carbon in the atmosphere. Economists have attempted to calculate the impact of climate change and pollution caused by human beings and even advocated environmental taxations like carbon tax but the markets are not designed to accommodate these, thereby passing the buck to posterity.

Despite great progress in international level policy making to counter environmental problems, protection of the earth's environment in the 21st century remains elusive. While expressing satisfaction over the rising environmental consciousness and positive responses from nations, the author urges NGOs to persuade their governments and fellow-citizens that the most pressing challenges we face are largely glocal (global as well as local), that require glocal responses. His main prescription is, 'Utopian as it may seem, a constitutionally based world federation that can link communities and regions.'

There is greater openness in the world's economic structure than in its political structure. The allure of money is so great