of disciplines backed by experimental research, and slow and deliberate recruitment of faculty who can synergize research, teaching and education.

The course design of IISERs is an outstanding innovation aimed at a totally new way of addressing the issues in higher education in science in the country (Box 1).

The working of IISERs has proved the cynics wrong. It has provided a refreshing contrast to the negative image of the potential in higher education in India.

Going by the progress reported in the book, several contributory factors for the success of the experiment may be identified: full academic freedom in course planning and implementation with no political interference; adequate funding with minimum oversight; freedom from micro-management of the institutions by outside agencies; proactive and helpful higher layers of State bureaucracy sensitive to the needs of science education; sustained and dedicated hard work of the founding Directors, who have endured the teething troubles of building institutions from the scratch, including the agonizing delay and hurdles in land acquisition, and completion of regular buildings as well as securing the latest laboratory equipment for undergraduate education, and above all, intake of the creamy layer (top 1%) of bright students (who have taken State and Central Board examination and those who have secured high ranks – within 10,000 – in the JEE Advanced examinations; provision of generous scholarships (100% in the early years); admission of girl students (40%); and self-motivated staff of international calibre. The involvement of undergraduates in research has proved a success as evidenced by peer-reviewed research papers showing their participation[2]. In a short period, IISERs have acquired a brand name for excellence in education. In the Nature Index-2018 ranking (publications in top journals), IISERs as a group are placed at the top of Indian institutions. Several IISER graduates have secured coveted research positions abroad.

This raises the question of utilizing the world-class talent at home as well as building a strong science base. The book indicates that IISERs are likely to be called upon to play an increasing role in taking up sponsored projects. IISERs have attracted several such projects worth crores of investment, indicating the high level of confidence of the sponsors in these institutions. Recently, technology business incubators have been set up in some of the IISERs. It is hoped that some ground rules would ensure that the sponsored projects would result in a win–win situation for both IISERs and the sponsors, and avoid potential use of these institutions to serve the vested (commercial) interests of the private sector.

In the long run, as the number of IISER graduates increases, it is hoped that institutions in the country like ISRO, BARC, DRDO and CSIR would make the best use of their talents and experience. There is an ever-present risk of under-utilization of their skills by involving these graduates in the run-of-the-mill projects that have little scope for their creativity.

The authors have made a valuable contribution that is reassuring, as the country undertakes to reform and revitalize the education sector.

Box 1. Unique features of the IISER course design

In the first two years of the five-year BS–MS course of IISER, students study nearly 'everything', including physics, chemistry, biology, mathematics, computer science, and become ready to solve any problem without viewing it as outside their subject. At the end of two years, they choose 'majors' (and electives) irrespective of what they liked earlier and take summer internships along with electives.

Even in the beginning of the third year, students have the flexibility to change their 'major'. They have the opportunity to take up interdisciplinary studies in line with the world trends during the third and fourth years, with strong inputs of research experience gained from internship in other institutions at home and abroad. In the final year, students undertake research at an institution of their choice, including those abroad and submit a thesis (not a project report). The BS–MS degree certificate of some of the IISERs does not mention any specific discipline. In fact, this enables the students to take up any subject of their choice for the post-M Sc–Ph D.

About 50% of the IISER graduates go for higher studies in India or abroad. They can join IITs or IIMs or IAS or teaching. They can also join technical institutions like ISRO and BARC at appropriate levels.

1. Mohan Sundara Rajan, *Science as a Way of Life; A Biography of C.N. R. Rao*, Prism Books Pvt Ltd, 2003.
2. Sathyamurthy, N., *Curr. Sci.*, 2016, **110**(5), 747–748.

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Annual Review of Immunology, 2017. Dan R. Littman and Wayne M. Yokoyama (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. Vol. 35, vii + 572 pages. Price: US$ 112.

The *Annual Review of Immunology* is a yearly compendium that is eagerly awaited. For several years now, its contents have included definitive and exhaustive reviews by leading researchers, more particularly in fields of the immunological sciences which have witnessed signature advances over the last couple of years. This volume is no different. While we review several contributions, we apologise to the authors not cited due to a paucity of space.

Inherent factors affecting susceptibility to inflammatory diseases have become the focus of renewed investigation. Genome-wide association studies using SNP arrays, as well as whole genome sequencing and whole exome sequencing have provided insights into genetic factors that influence the response to vaccination, and that enhance the likelihood of primary immunodeficiency and autoimmune disease. It is interesting, as Langlais *et al*. (pp. 1–30) report, that considerable overlap has been documentted between genes that influence inflammation and those that mediate primary immunodeficiency. Epigenetic profiling of immune-mediated diseases has added another

layer of understanding to immune responses in health and disease.

Randolf *et al*. (pp. 31–52) describe the role played by lymphatic endothelial cells in the development of tolerance to self-antigens. These cells are capable of retaining antigen for extended periods of time; dying endothelial cells are phagocytosed by dendritic cells, and the antigens that the former have retained are then cross-presented to enhance CD8 T-cell memory. Living endothelial cells serve an immune purpose as well; though they express MHC Class II, they lack HLA-DM, which compromises their ability to directly present antigen to CD4 and CD8 T-cells. Cooperation with dendritic cells via multiple mechanisms, including 'cross-dressing', contributes to tolerance as well as immunity. It is also intriguing that changes in the lymphatic architecture are associated with the pathophysiology of Crohn's disease.

'Th2 identity' characterizes both the generation of protective immunity against helminth infection, as well as the inflammatory outcomes of allergic diseases, as discussed by Nakayama *et al*. (pp. 53–84). Some evidence suggests that antigen dose during the initial TCR triggering event might influence differentiation outcomes. Dominant activation of the ERK pathway appears to favour a Th2 skew, as do NFAT2 and PKC Θ signalling. Further, epigenetic changes at the *Gata3* locus are closely associated with the appearance of the Th2 differentiative state. The Polycomb and Trithorax complexes bind upstream and downstream respectively, of the *Gata3* promoter in naive T-cells; these complexes have histone methyltransferase activity. Th2 cells play a critical role in the pathogenesis of allergic inflammatory disease, and IL-5-producing Th2 memory cells have been implicated. Interestingly, co-production of IL-17 and IL-4 has been documented; such plasticity is worthy of study as the pathological implications of such phenomena could be significant.

As Abramson *et al*. (pp. 85–118) review the ability to distinguish self from non-self by T-cells that exit the thymus is central to organismal survival. The expression of an impressive spectrum of peripheral antigens occurs in the thymus; while 3000–4000 of these transcripts are driven by the transcription factor AIRE in medullary thymic epithelial cells, a large percentage of thymic transcription appears to be AIRE-independent. An intriguing, stochastic nature of the expression of peripheral antigens in individual thymic epithelial cells, with each cell expressing only a small percentage of the whole repertoire, has been described. The generation and export of Foxp3+ T-regulatory cells is also a significant event that aids in the development of self-tolerance. The role of the thymus in the generation of T-cells with 'un-conventional' T-cell receptors has also been recognized. Given the central role of the thymus in the generation of effective immunity, the ability to re-establish thymopoesis in instances of thymic compromise may be of clinical benefit.

Up to a hundred trillion commensal bacteria inhabit the human intestinal tract, and interaction of these organisms with the gut mucosa, as well as with the host immune system, is the subject of intense study, as Kurashima *et al.* (pp. 119–147) discuss. Intestinal epithelial cells can be either absorptive or secretory, the latter producing mucin, antimicrobial peptides as well as several hormones. Intestinal disorders such as Crohn's disease often manifest as a consequence of abnormalities in these cells, including mutations in genes that ensure the integrity of intestinal tight junctions. Transcytosis of bacteria, mediated by M-cells of the Peyer's patches, initiates contact with host innate immune cells, triggering immune responses and the generation of secretory IgA. A variety of cytokines are considered critical to re-epithelialization after wound healing, with the roles of TGFβ, amphiregulin, IL-33 and IL-36 coming into focus. Further understanding why harmful organisms trigger active immune responses while commensal organisms induce a quiescent, anti-inflammatory state would help in the design of rational strategies for the prevention and treatment of inflammatory mucosal disorders.

CD4 T-cells were initially considered to exclusively recognize peptides derived from antigens internalized from extracellular spaces (and presented on MHC class II molecules), and CD8 T cells were believed to bind peptides sourced from intracellular antigens (and presented on MHC class I molecules). It soon became clear that strict adherence to such rules would compromise immunity. The phenomenon of 'cross-presentation' is now well-recognized; Cruz *et al*. (pp. 149–176) review current information in the area. Phagocytosis and macropinocytosis (as opposed to fluid-phase pinocytosis) appear to efficiently trigger cross-presentation. While the cross-presentation of antigens from dying cells has been reported and surface receptors (such as the AXL/LRP-1/RANBP9 complex) involved in the process identified, reports also suggest that dendritic cells can cross-present antigens from living cells, possibly by 'nibbling' at the surface. The transfer of peptides from antigen donor cells to antigen presenting cells via GAP junctions has also been reported, as has the phenomenon of 'cross-dressing' or trogocytosis, which involves the transfer of peptide-loaded MHC class I complexes from antigen donor cells to antigen presenting cells. Antigens internalized into the phagosome gain access to the cytosol, either by membrane disruption or via an endoplasmic reticulum-associated protein degradation (ERAD)-like translocation process. Such antigens are then acted upon by the proteasome complex, and the resulting peptides transported to the ER via TAP to be loaded onto MHC class I molecules. Phagocytosed antigens could also be acted upon by proteases subsequent to which IRAP-mediated trimming occurs. MHC class I molecules are then transported to such peptide-containing endosomes and, after peptide loading, to the plasma membrane. Whether peptide exchange occurs, or empty MHC molecules are stabilized by as yet unknown mechanisms, is not clear. As understanding of the underlying processes grows, so does the potential for selectively enhancing cross-presentation to increase the efficacy of therapeutic vaccination; anti-cancer immunotherapy would be an obvious area of interest in this regard.

The fact that microbes play a significant role in the progression of cancer is being increasingly recognized. Dzutsev *et al*. (pp. 199–228) describe that cancer-inducing microbes (such as *Helicobacter pylori*, Hepatitis B and Hepatitis C viruses, human papilloma virus and Epstein Barr virus) have been identified, and some evidence appears to suggest that tumorigenesis is aided by the presence of commensal, non-pathogenic microbes. Indeed, studies in both humans and experimental animals have drawn associations between cancer and the presence of certain microbes. The extensive use of antibiotics has been linked to inflammatory bowel disease and breast cancer.

Although not always based on a clear line of reasoning, the use of particular bacteria in the treatment of cancer has a long and interesting history, beginning with the treatment of patients with soft tissue sarcoma with *Streptococcus pyrogenes* and *Bacillus prodigious*. Indeed, instillation of BCG still forms the first line of treatment for bladder cancer. An interesting concept is the use of anaerobic bacteria (such as *Clostridium* species, which would thrive in the hypoxic environment) to initiate preferential anti-tumour effects in solid tumours. Host microbes appear to be critical influencers of anti-tumour responses, mediated both by drugs and well as upon immunotherapy. In germ-free mice, the effects of platinum-based anti-cancer agents and of cyclophosphamide are attenuated. The positive effects of total body irradiation (which works to disrupt the intestinal mucosa, resulting in TLR4-mediated effects on dendritic cells) on the anti-tumour effects of transferred CD8 T-cells are abrogated in antibiotic-treated mice. Anti-tumour responses consequent to anti-CTLA4 therapy and anti-PD-L1 are also influenced by resident microbiota. An expanded knowledge of how specific microbes potentiate anti-tumour responses will no doubt lead to more efficacious and safer therapies.

Roybal *et al*. (pp. 229–253) review the area of 'immune engineering'. Tumour antigen-specific T-cell receptors have been indentified, and T-cells engineered to express such receptors have been re-infused into the patients from whom they were derived. Most trials have been carried out on melanoma patients, targeting antigens such as gp100, MART1 and MAGE-A3. While encouraging results have been obtained, some studies have also been marred by unexpected, life-threatening, toxicity. Chimeric antigen receptor (CAR) T-cells represent another strategy. Typically, components in such engineered T-cells include an extracellular ligand domain (most often a tumour-recognizing Scfv), and one or more intracellular signalling/co-stimulatory domains. In patients of chronic lymphocytic leukaemia and acute lymphoblastic leukaemia, CD19 has been employed as a target using such approaches, with varying degrees of success. Autoantigens expressed on the surface of T-cells (coupled to signalling constructs similar to those described above) have been employed to specifically deplete autoantigen-specific B-cells, with the aim of eliminating pathogenesis-inducing serum antibodies without the induction of generalized immune suppression. Given that substantial toxicity has been reported in some studies, on-going strategies include the co-introduction of inhibitory CARs which transduce negative signals upon the recognition of antigens on normal cells.

The detection of cell-internal cytoplasmic nucleic acids is crucial to the development of host resistance against foreign microbes. While Toll-like receptors reside on the cell surface and in the endosomes, additional receptors that recognize RNA or DNA moieties reside in the cytoplasm. Impaired functioning of these receptors can lead to failure to distinguish self-derived nucleotides from pathogen-derived nucleotides. Crowl *et al*. (pp. 313–336) discuss recent findings related to signalling via RIG-1-like receptors (RLRs, which act as RNA sensors) and the primary DNA sensor, sGAS. Mutations in these molecules have been associated with inflammation and autoimmunity. Aicardi–Goutieres syndrome (characterized by psychomotor retardation) in humans arises as a consequence of mutations in one of seven genes involved in cytoplasmic nucleotide sensing. In mice, knockout of several enzymes that constitute these pathways results in autoinflammation and/or autoimmunity, as a consequence of conditions sometimes referred to as 'type I interferonopathies'. Insight gained from such monogenic models sheds light on more complex, multi-genic disorders like Systemic lupus erythematosus (SLE), which is also characterized by a heightened interferon signature.

Increasingly, transcriptome analyses using high-throughput technologies are being employed to shed light on interferon and IL1-mediated diseases, both of which can be either monogenic or multigenic, as discussed by Banchereau *et al*. (pp. 337–370). In Kawasaki disease as well as in type-1 diabetes, an IL-1 signature has been identified in peripheral blood mononuclear cells (PBMCs). In psoriasis, stimulation of the IL-23/Th17 axis is considered central to skin-associated damage, and antibodies against the IL-17 receptor can reverse clinical features of disease. Alternative splice variants are also coming into increasing focus due to their association with disease; variants of CTLA-4 with type-1 diabetes and variants of the TCR ζ-chain with SLE are prominent examples. Increasingly, transcriptomics is aiding in disease diagnosis and activity assessment, in monitoring or predicting response to specific treatments, as well as in patient prognosis.

An emerging area involves the influence of metabolite-sensing G-protein coupled receptors (GPRs) on organismal health, as reviewed by Tan *et al*. (pp. 371–402). Ten such receptors have currently been identified, their expression distributed across cells of both immune and non-immune lineages. These receptors, which normally mediate an anti-inflammatory role, recognize dietary and bacterial metabolites (including short-chain, medium-chain and long-chain fatty acids, and break-down products of tryptophan) to regulate gut homeostasis. For example, short-chain fatty acids (derived from dietary fibre) acting via GPR43 ameliorate dextran sulphate sodium-induced colitis, and may play a role in dampening autoreactive cells in NOD mice as well. Lack of GPR109A reduces colonic Treg numbers, and the receptor mediates the modulatory effects of nicotinic acid in atherosclerosis. In the latter case, whether natural fatty acid ligands work in similar ways would be interesting to determine. Increasingly, the combined effects of a 'Western diet' and the increasing use of antibiotics are believed to contribute towards the rising incidence of diseases like asthma and diabetes, as well as of different allergies.

It is recognized that microglial cells play a significant role in brain development. Colonna *et al*. (pp. 441–468) review microglial function in health and neuro-degeneration. The phagocytotic capabilities such cells display enable the clearance of apoptotic cells and invading bacteria, as well as of macro-molecular protein aggregates. The presence of a wide spectrum of pattern recognition receptors, as well as of membrane and cytoplasmic components that mediate disposal of cellular debris, enable these functions. Additionally, neuronal-glial communication is facilitated by the presence of several neurotransmitter receptors. While it is becoming apparent that gut microbiota can greatly influence microglial function, whether treatment with probioitcs in disorders of the central nervous system leads to restorative effects awaits demonstration. Microglial cells may serve both protective and

destructive functions during Alzheimer's disease, initially helping to clear amyloid-β plaques, but prolonged exposure to such plaques may contribute to neuroinflammation.

The biology of respiratory syncytial virus (RSV) has been the subject of focus, as discussed by Openshaw *et al*. (pp. 501–532). The virus has a ubiquitous presence; children are often infected before they are two years old. Repeated infections which occur throughout life are of interest from an immunological standpoint. Why memory responses fail to confer protection (despite the fact that the RSV genome is relatively conserved) is an open question. The ability of nonstructural proteins of RSV (NS1, NS2) to inhibit interferon production and signalling suggests that disruption of innate immune mechanisms may be involved. The extent to which dysregulated immune responses contribute to pathology is also an area of particular concern, given the ability of the virus to cause debilitating disease in the elderly. Ongoing efforts in the development of safe and effective vaccines are hampered by the lack of a good immune correlate of protection.

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PERSONAL NEWS

Raghunath Prasad Rastogi (1926–2018)

Professor Raghunath Prasad Rastogi was born on 4 June 1926 in Lucknow to Purushottam Das Rastogi and Ram Janaki. Raghunath performed exceedingly well in the high school and intermediate examinations. Then completed his B Sc in 1946 and later B Sc (Hons) and M Sc from Lucknow University securing first positions in 1947 and 1948 respectively. In 1952, he obtained Ph D in chemistry under the supervision of A. C. Chatterjee on 'Studies on physical properties of supernatural solution'.

Rastogi's academic career started in Lucknow University as a Lecturer in chemistry (1949–59) and then as Reader in chemistry in Punjab University (1959–62). In 1962, he joined the then Gorakhpur University as Professor and Head of the Chemistry Department. He served the University till 1985, when he moved to Banaras Hindu University (BHU), Varanasi as Vice-Chancellor. He completed two terms in this position until 1991. He wanted to continue his research and joined the Central Drug Research Institute (CDRI), Lucknow and worked as Emeritus Scientist till 1994. He then once again joined Lucknow University as an INSA Senior Scientist in 1995 and continued till 1999. During the same period (1994–96), he served as Chairman of the Pay Commission (UGC) for university and college teachers. From 2006 till 2018, he was INSA Honorary Scientist until he breathed his last on 8 April 2018.

Rastogi has made significant theoretical and experimental contributions in linear thermodynamics of irreversible processes with special reference to electrokinetic, electrophoretic and thermo-osmotic phenomena and Dufour effect, along with equally significant contributions in nonlinear steady-state electrokinetic phenomena. He made important contributions in far-from-equilibrium phenomena (oscillatory reactions, electrokinetic oscillations, pattern formation in chemical reactions, crystal growth and electrodeposition) regarding nonlinear dynamics. His contributions also include

thermodynamics and thermochemistry of eutectic mixtures, addition compounds (including kinetics and diffusion mechanism of solid–solid reaction for compound formation) and on burning rate, ignitability and mechanism of combustion of composite solid, liquid and hybrid propellants.

In view of the fact that classical theory of irreversible processes is valid till linear relations between fluxes and forces are valid, Rastogi studied the nonlinear relation between fluxes and forces, especially, the linear range. However, owing to experimental constraints, nonlinear range could not be studied for all phenomena. In the area of reversible thermodynamic processes, he was enthused to carry out the work on phase diagrams to study the thermodynamic properties of mixtures. So his group initially carried out a study on phase diagrams of binary mixtures of benzene, carbon tetrachloride and cyclohexane. It revealed the formation of molecular complexes between benzene and carbon tetrachloride, which was later supported by American workers. A detailed study on carbon tetrachloride-aromatics and chloroform-aromatics was also carried out. On the electrical effects during dissolution and precipitation of electrolytes, Rastogi with his colleagues published a paper in *Nature*[1]. The work on solid-state processes was a consequence of his work on phase equilibria. This prompted Rastogi's group to go for deeper studies in the chemistry of eutectics and addition compounds. They investigated the thermochemistry, crystallization and microstructure of eutectics. Among addition compounds, novel inorganic reactions lead to the isolation and characterization of mixed halide of mercury and thallium[2]. His work on combustion processes was mainly concerned with ignition, mechanism of pre-combustion reactions,