In this issue

Immunological perspectives: The god in the details

When research in biology is mainly driven by a 'chemical' perspective, more 'physiological' disciplines such as immunology inevitably tend to get the short end of the stick, resulting in a lack of 'profile' even in the scientific community and (partly in consequence, perhaps) a lack of significant rigorous work in them. Immunology in India is an excellent example of such a state of affairs.

And yet, immunology has been and remains one of the most prominent cutting-edge areas in biology worldwide, with burgeoning programmes, new prestigious journals, and an enormous impact (matched only by neurobiology) not only on the understanding of its specialized mechanisms, but also on far more general fundamental processes of life such as DNA repair and rearrangement, intracellular transport, cellular activation and differentiation as well as tissue organization. In consequence, the lack of a corpus of researchers in immunology, large enough to match the scale of the Indian life sciences research enterprise, has been a glaring lacuna for a long time. This gap becomes even more prominent if one remembers that the analysis of infectious diseases, to which many research programmes in the life sciences are ostensibly geared in India, depends intimately on novel insights from immunology.

There are two review articles in this issue of *Current Science* that provide the trigger for these reflections.

The article by Nandi and Sarin (**page 647**) is an overview 'from the treetops' of the current state of immunological insights and dogmas. It is an ambitious journey that starts from elementary definitions of the components of the immune system and ends with some comprehensible predictions of the new directions that will shape immune paradigms. It is the 'low profile' of immunology as a working discipline in India, which makes such an attempt at providing such a futuristic summary of the entire discipline a worthwhile one despite the risk of not satisfying either immunologists or lay readers.

Kanury Rao (**page 639**), on the other hand, takes an entirely different perspective. His is the view of the rigorous analytical examination of a single tree in the forest that Nandi and Sarin fly over. One of the most dramatic events in the functioning of the immune system is the steady enhancement of the binding efficiency of antibodies being generated in the course of an immune response. Thus, early in the immune response to a vaccine antigen, the efficiency of antibody–antigen binding is fairly low, while late in the response, this efficiency can undergo huge, exponential increments. The process involves generation of genetic mutants of the original antibody molecules and the concurrent selection of efficient mutants in a cell population-based dynamic process that is only poorly understood at best. Rao's review leads the reader step by step through the core components of the generation of the antibody response to the current state of the field. He provides an analysis based on a decade of dissection of the antibody response to a peptide antigen, and the account of how the combination of logic and data together drive him to paradigm-shifting kinetic models of selection is riveting. It opens up, as a meaningful hypothesis should, a host of experimentally approachable novel questions on the cellular and biochemical events mediating this selection process. Ironically, both the limitation of writing reviews and the significance of Rao's hypothesis are illustrated by the fact that the review is already outdated by work from Rao's own laboratory providing further thermodynamic dissection of the events involved (Manivel *et al.*, *Immunity*, 2000, **13**, 611).

In the event, one might feel that the single tree reveals more than the forest does, or, to plagiarize poor Einstein, 'god' (which for immunologists as for evolutionary biologists stands for 'generation of diversity') is truly revealed in the little details.

Satyajit Rath

Stress and the shrinking neuron

Stress has become a catchword now. The physicist who is aware of its definition as force applied per unit area, is probably not uncommonly confronted with stress of a biological kind. Stress as a common man understands it, is a condition or situation causing hardship, disquiet and mental exertion, in which he must either adapt or cope. Situations or things that cause stress, called stressors by psychiatrists, can range from missing a flight to even marriage. Psychiatrists use something called a social readjustment rating scale, which gives scores to different stressors that affect one's life, including relationships, illnesses and vacations. Death of a near one figures at the top of the list, marriage somewhere in the middle and vacation somewhere in the bottom. The perception of an event as stressful however, varies among individuals and cultures.

There is stress of modern living in urban areas – overcrowded, polluted and noisy roads, competitive life styles in every sphere with constant struggle for survival, which to an experimental scientist would mean constant ability to attract research grants for his laboratory and getting high output work from his group. We are aware of its effects physically, because the way we react to stress, viz. the fight or flight response, but such constant reactions do have their tell-tale effects, the most commonest being stress-related heart disease.

In an article in this issue, Shankaranarayana Rao *et al*. (**page 653**) probe the effects of stress on the rat brain. Neurons are the basic units of the nervous system and there are about 100 billion neurons in the brain itself. The neurons are special in two ways: (i) their membranes are highly specialized to convey electrical messages in the form of the action potential; (ii) their shapes are unique and varied. Unlike being spherical or cylindrical like many other cells in the body, the neurons have numerous projecting parts like the tentacles of an octopus, with many projections that snake through the brain tissue such that they can make the right connection with the right neurons and transmit signals. Broadly speaking, a neuron has a long axon and it is usually one axon that may branch; while the other type of branching, the dendrites, are so numerous that they represent 90% or more of the neuron's total surface area. Most signals are delivered to dendrites, which have tiny little bumps or projections in them known as dendritic spines. The messages are passed on to junctions called synapses where a chemical (neurotransmitter) is released. The geometry of the dendrites, in a way, determines the shape and also the function of the neuron. The pyramidal neuron in the CA3 region of the hippocampus, which has been morphologically analysed by Shankaranarayana Rao *et al*., for instance, has a roughly pyramidal-shaped cell body or soma, and two widely separated sets of dendrites, the apical and the basal, as well as axon branches. The hippocampus is a region of the brain which in gross anatomical detail is S-shaped, which reminded the earlier histologists of a sea-horse (hippocampus) or a ram's horn (Ammon's horn). Like the annular rings in the tree trunk which are a result of a layer of cells, the pyramidal neurons in the hippocampus are arranged in defined layers, making them amenable to detailed morphological studies.

A stress regimen consisting of 6 h restraint stress every day for 21 days, resulted in atrophy of apical dendrites of the CA3 hippocampal neurons in the experimental rats. Although the authors have not experimentally evaluated the consequences of such atrophy, at the functional level it would translate into a reduction in the number of synaptic inputs to the neurons. It is as if a part of the electrical or telecommunication connection to a buzzing city becomes non-functional with wires being hacked, jeopardizing the communication network in the city as a whole. This was confirmed by using neuroanatomical Golgi staining and quantification of morphological details of dendritic arborization using the well-established Sholl's method, which they describe in the paper. Interestingly, such dendritic atrophy was reversed in the group of stressed rats which were placed in rehabilitating conditions without restraint and access to food and water for 45 days. In the rat group that was subjected to long-term restraint stress for 66 days however, the atrophy extended to the basal dendrites as well.

The role of the hippocampus in brain functions such as cognition, learning and memory, particularly spatial memory, are well established. The vulnerability of the hippocampus to stress, resulting in structural pathology of the neurons is alarming. The human hippocampus essentially has a similar role as the rat hippocampus, although understandably it is related to more advanced tasks such as declarative, episodic, spatial and contextual memory performance. Restraint stress to a human could mean being in an office with a job one does not like and in surroundings that are hostile, for eight hours every day. But there is a catch; the employee still gets his weekend holiday to rehabilitate his atrophying hippocampal dendrites, and for an employee in the Indian Government, there are the numerous festival-related holidays thrown in liberally. Added to this are the numerous coffee and tea breaks with chat and gossip sessions and exchange of pleasantries, making the office quite a rehabilitating centre in itself, and for certain individuals it may well act as a destressor unit.

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