Indian biology research at cross roads

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THE latter part of the 20th century has witnessed a tremendous excitement in biological research. A revolution in approach and technology giving birth to modern biology has taken place and this revolution is continuing. It is predicted that the 21st century will witness mind-boggling advances in the understanding and exploitation of biological phenomena, when the conventional biologist cannot claim anymore that biology is his/her prerogative. One has seen distinct signs of this gold rush with chemists, physicists, and engineers joining hands with biologists to conquer mother nature. It is true that nature is smarter than all scientists put together, but has a seductive appeal giving the illusion that one is about to conquer, when something dramatic turns up to put us back in square one.

What are the frontiers of biology?

The gene is still occupying the central stage and it will continue to do so, till answers are sought to understand the molecular basis of biological phenomena. The fundamental questions are: How is the gene organized? How is it expressed? How is it repressed? How does it evolve? How many genes are there and how are they coordinated? How are biological phenomena related to gene activity? The present century has seen concerted efforts in understanding the genetic basis behind uncontrolled cell multiplication and the functioning of the immune system. The emphasis now is towards understanding development, differentiation and behaviour in terms of gene activity. This has all been possible due to rapid evolution of technology, whereby one is able to handle small and large chunks of the genome with facile techniques of cloning, mapping and sequencing at one level, studying features of gene expression *in vivo* and *in vitro* at another level and examining pathways of signal transduction from the environment to the genome at yet another dimension. While, gene is the holy bible, proteins and membranes are the actors in the field and therefore, their structure, assembly and activity also constitute a major field of interest. Technologies to study protein structure using X-ray crystallography, NMR and computer graphics have become common place. Protein engineering to design novel catalytic sites on either novel or existing proteins is attracting a lot of attention. Strategies to separate and isolate chromosomes and visualization of the genomic and cellular worlds using scanning tunnelling microscopy and confocal microscopy are exciting pursuits. One is moving to understand the biology of the total organism, since the total is definitely lot more than the sum of the individual components in biology.

In this scenario of basic research, biotechnology looks like a perversion. It is a perversion in the sense of corruption introduced by commercialism. The cut-throat competition, secrecy, litigation to claim prioriy and teachers wanting to become millionaires, quite out of tune with the classical image of the profession, have made science a serious business but not really enjoyable. But, the implication of biotechnology for solving problems of human health and disease, food and agriculture and environment and industry are so enormous that no country can afford to take this field lightly. The recent saga of identification of the genetic defects in Cystic Fibrosis and Duchenne Muscular Dystrophy affirms our faith in science as a vehicle for betterment of the quality of life. But, can there be a meeting ground where science and application can go together without generating a feeling of being cheated or exploited or dominated? Perhaps, these are expressions of a bewildered mind used to an old-fashioned sense of values and idealism, but baffled when arriving at the cross roads in the path of modern biology and biotechnology. Well, this is the global scenario.

Funds for biology research

Whatever science structures we see in the country, are because of the personal faith of the Nehru family that science can deliver. However, as a Society I am not sure that we really believe that science is an instrument for progress. Thus, one sees successive governments in the recent past being preoccupied with ever so many problems, having little time to worry about science. This will have disastrous consequences in the long run and the industry is not going to get excited overnight to shower funds on scientists. Nevertheless, there is a feeling that Life Sciences have received a greater share of funding available from the government. This feeling probably stems from the visibility of the Department of Biotechnology as an independent entity and the extramural research funding received from other agencies. But if one considers the total scenario of funding going to research, which includes the

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establishments of Defence, Space, Atomic Energy and CSIR, the amount coming to Life Sciences cannot constitute a larger share. In any case, these are arguments over, who is better among those sharing the poverty.

Nevertheless, allocation of funds to Life Sciences has seen a quantitative increase in the eightees. There has been a sustained support of a larger scale from DBT and DST. The DBT has gone in for the establishment of centres of excellence, national infrastructural facilities and manpower training. Since, DBT's own institutions are just a couple, it has been able to support research on a big scale in national laboratories and selected universities. DST, on the other hand, has concentrated on individual funding and established certain national facilities. Extra-mural research funding from CSIR, DAE and ICMR has been helpful. In a gross sense, biological research has also been carried out in some ICAR, ICMR, DST and CSIR institutions.

Where are we in basic research?

Real statistics is not available. But, one sees a distinct improvement in the quality of science being presented in many symposia held in the country. There are at least 50 groups where good recombinant DNA research is progressing. These groups are localized in about a dozen major institutions. There are at least a few groups doing research of international standards in the areas of proteins, biomembranes and cell–surface interactions. There are a couple of institutions with a strong base in the area of structural biology. I do see good papers from India appearing in good international journals. The total number may not have significantly increased. But, we have to run that much faster to stay where we are. It is my personal bias to state that it is easier to publish good physicochemical papers in biology which are gadget-dependent or good but straightward enzymology or papers based on theory than to publish molecular biology-oriented papers in reputed journals. The latter requires intricate experimentation of different kinds, dependent on a wide variety of consumables, long periods of study and fierce competition. It is much easier to carry out studies with artificial model systems and publish good papers, but I am once again biased to state that these do clarify real biology only after the event, i.e. only when the experimental results are available from real systems.

Generalities apart, are there examples of original discoveries in the country? I can give a few examples. The unravelling of the unique feature of the DNA repair process in *Vibrio cholerae*. The elucidation of the structure and functioning of osmotic genes in *E. coli*. The discovery of a storage protein gene rich in sulphur amino acid codons in Amaranth. The unravelling of the features of meiotic recombination in the mammalian system. The unique transcriptional regulatory features of a couple of eukaryotic genes. The endocrinology of the human and the basis for contraception using specific proteins. The elucidation of the architecture and behaviour of certain types of ion channels in biological membranes. The features of lectin–carbohydrate interaction on cell surfaces. The role of RNA in ribosomal structure. There are some more examples of research relating to sex-determining genes, genes regulating behaviour and unusual DNA structures, which are in the pipeline and need to the authenticated, but would have a tremendous impact ultimately. How have I chosen these examples as original discoveries? These results have been published in well-rated journals. There is international interest in these findings and hence discussed and commented by peers in international meetings and reviews. Many of these studies have involved years of experimentation, thinking, hardwork and competition against powerful groups with more resources and clout elsewhere in the globe. Most of these studies have been possible only because of the infrastructure being built during the last decade. Time only will tell whether these findings will have the same impact as the Ramachandran plot or the triple-helical structure proposed for collagen in the yester-years. I am not trying to pass judgement here. But, originality and infrastructure need not grow proportionately!

Where are we in real hitech biotechnology? We have achieved some success in low- and medium-level biotechnologies that are not a reflection of our inputs to modern biology. A high standard of research in modern biology should get reflected in hightech biotechnology. Perhaps, one should give some more time to ask this question, since the infrastructure to do real modern biology is being built only during the last 10 years. What do I mean by hightech biotechnology? How many useful proteins have we been able to overexpress and produce in large quantities at least in the laboratory? Have we been successful in the generation of transgenic plants containing genes such as those for BT? How many protein structures have we solved? How many potential drugs have we designed using computer graphics? Can we participate meaningfully in the human genome project?

A couple of years ago the situation was bleak. But, today there is a glimmer of hope. Examples of over-expression of LT gene product in Vibrio, HGPRT of the malarial parasite and EGF from mammalian cells in *E. coli*, etc. have come to light. These are all totally indigenous efforts. We may also have our own overexpression vectors designed in the country. At least, a couple of proteins have been completely sequenced. The first effort on the X-ray structure of a lectin from the country is nearing solution. We are moving towards analysing protein structure using graphics. But, our downstream processing expertise is weak. We have not made good progress with generating transgenic plants. We are dragging our feet to take up the insulin project indigenously.

Where are we in the international scene?

As I am trying to make out, we have made good progress relative to what we were a decade ago. But, elsewhere things have moved by leaps and bounds. Therefore, the differential is even more. Our collective international impact is marginal or none at all. Just on the basis of total number of good papers published by the entire country compared to the voluminous literature pouring out in biology, it would become obvious that it is extraordinarily difficult to get noticed. I can illustrate this with a few examples. The first one is my own area of interest, namely eukaryotic gene transcription, where I am hoping to build a school. It has taken me a decade to clone a gene, characterize the flanking sequences, identify a couple of upstream regulatory elements and transcription factors and come to some conclusion about the possible mode of regulation of transcription of this gene. By this time one would notice that transcription factors themselves have been cloned by the dozen and general models for transcriptional regulation of eukaryotic genes fretted out. I can still survive because I have stuck to a system and may be I have an edge. There are hardly three or four groups working on eukaryotic transcription in the country, which is the current rage all over the globe. By the time we can solve the structure of one single protein as a major effort, dozens of proteins are there for which total structural information is available and which forms the starting point for research elsewhere. While the human genome project is seeking to sequence 3 billion base pairs, the efforts in the entire country for the last five years will not exceed sequencing of 50,000 base pairs.

This is perhaps not the place to give alibi. We have attempted to build big infrastructures on a weak foundation. This weak foundation is because of poor basic facilities such as lack of power and water, poor quality of chemicals and other consumables available in the country, difficulties and delays in the import of biochemicals and administrative inefficiency. Only some institutions are able to address these issues and find at least partial solutions. Many institutions have given up and reconciled to do whatever is feasible under these conditions or do nothing at all.

The solution

I am an optimist. Despite all the problems things did improve in the last decade. Import procedures have become simpler. Labelled biomolecules of reasonable quality are available in the country. Indigenous companies to make biochemicals and plastic ware are slowly taking shape. Biotechnology applications are picking up.

It is clear, however, that our infrastructure will never permit us to close the generation gap between research in India and research in advanced countries. We cannot compete with 'corporate' research, where 40 post docs work round the clock for a single scientist. But, I feel that we can still beat or survive with ideas and working with our own systems. India is rich in flora and fauna and we have all the diseases! Pathogens and parasites throw in lot of surprises in biology. Insect pests and mycobacteria should be as exciting as Drosophila or *E. coli.* Mycobacteria research has become fashionable all of a sudden in view of its importance in relation to AIDS. I think we can ask exciting questions with systems unique and relevant to our society applying all the modern technology that is at our disposal. Perhaps, that way we can tie up basic and relevant research. This approach is essential for young scientists returning from abroad, who feel comfortable with continuing the projects they were handling in the US, but soon find that they cannot get too far competing with their old boss. Biotechnology is an ideal technology for India. It can work out cheap in India and adopted as a small-scale industry.

Most important of all is to get a clear signal from the present government that it has a feeling for science and scientists, so that whatever momentum has been built up is not lost. But there is actually a general feeling of depression among scientists at the benign neglect of their community and the sudden crunch for money for research and the young biologists will emigrate to wherever they are wanted. The older ones will get wasted and perish. There will be no one left even to absorb the imported biotechnology, if research in biology is not supported to sustain the momentum gained in the last decade.