

as an integral part.

- The Academy endorses the need for good M Sc courses in different branches of science, similar to the DBT programme.

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1. *Statistical Outline of India: 1988–89*, Tata Press, Bombay.
2. *National Policy on Education*, Ministry of Human Resource Development, Government of India, 1986.
3. This is an annual average from the total 8th Plan outlay on school education. See, for instance, *Journal of Educational Planning and Administration*, 1993, 7, 18.
4. Report of the Working Group constituted by the Planning Commission to suggest ways and means to improve undergraduate courses in science at Indian Universities, 1989.
5. Kumar, A. and Nigavekar, A. S. on 'Physics Education' in *Physics in India* (ed. Jha, S. S.) Diamond Jubilee Publication, INSA, New Delhi, 1994, chapter 2, pp 13–35.
6. Reports of the Curriculum Development Centres, University Grants Commission (1991)
7. Deb, B. M., *Curr. Sci.*, 1994, 67, 427.
8. *Curr. Sci.*, 1992, 63, 270.
9. 'Reforms in our Universities: A New Perspective', A Report submitted to the Governor of Maharashtra, March 1993.
10. The Report of the University Education Commission (December 1948–August 1949), Government of India Press, Simla, 1949.
11. Report of the Education Commission 1964–1966, Government of India Press, Delhi, 1966.
12. After preparation of this document, there has been considerable discussion of a proposal to set up a National Science University (NSU), (cf *Current Science*, 1994, 67, 502–519. In Council's view, the proposals contained in the present document are wider in scope, more feasible, and take into account all aspects of this situation in a balanced way.

The ascent of molecular cardiology

C. C. Kartha and O. M. Najeeb

The techniques of molecular biology are increasingly employed to delineate the molecular basis of both normal and abnormal cardiovascular function. Thanks to the knowledge gained in these realms, remarkable progress has been made in recent years to understand the cellular and molecular mechanisms of diseases of the heart and blood vessels. Novel therapeutic options are also on the horizon. This article highlights the major advances made in the field of molecular cardiology.

THE year 1628 is a milestone in the history of medicine. It was then that a physician in St. Bartholomew's Hospital, London, William Harvey, demonstrated the function of the heart and circulation of blood using quantitative experimental methods. That marked the beginning of cardiology. Harvey's revolutionary ideas

did not immediately lead to dramatic changes in either the diagnosis or treatment of heart diseases. Three hundred years elapsed before a second revolution transformed the practice of cardiology. The golden age in the discipline was heralded by the invention of the electrocardiogram by William Einthoven. The four decades that followed witnessed a technological explosion which led to newer diagnostic methods involving catheterization techniques and application of the ultrasound. In the field of treatment, the invention of the heart–lung machine opened up new avenues for the

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repair of developmental and acquired defects in the heart. Non-operative techniques also evolved over the years. The use of balloons, laser and rotary drills began to dominate the practice of cardiology.

And now, we are at the threshold of yet another revolution. Cardiologists have joined hands with molecular biologists to usher in the era of molecular cardiology which is rapidly taking a place in the centre-stage of medical science.

Thanks to the joint venture, we have a better understanding of the normal and abnormal structure and function of the heart at cellular, molecular and genetic levels. The knowledge gained is being applied to develop novel therapeutic strategies.

Various reasons contributed to the delay in the application of molecular biology techniques in the study of the cardiovascular system¹. Molecular biologists were not initially attracted towards a terminally differentiated cell like the myocardial cell which does not proliferate. Neither was there a model available to study myocyte growth and proliferation, since the heart rarely develops tumours. Genetic cardiac diseases were also found uninteresting for investigative studies. Another major handicap was the non-availability of viable cardiac tissue which could provide intact nucleic acids.

Changing scenario

Invention of the cardiac biptome by Konno led to the introduction of cardiac biopsy as an investigative tool. The biopsied tissue provided the much awaited viable material for exploring the molecular basis of diseases using techniques like polymerase chain reaction (PCR) and *in situ* nucleic acid hybridization. Nucleic acid probes and PCR made diagnosis of disorders such as viral infections of the heart sensitive and specific.

Another important development was the recognition that cardiac hypertrophy, an adaptive accompaniment of most heart diseases, is an excellent model to unravel clues to cardiac growth.

Developments in molecular biology techniques also had their impact. Linkage analysis provided a means to identify the chromosomal loci for genetic cardiac diseases. Once the chromosomal locus was identified, it also became possible to isolate the disease gene and identify the mutation through recombinant DNA techniques. Recombinant DNA techniques also provided opportunity for delineating structure-function relationships and developing specific biomolecules for therapeutic use.

The advances made in cardiovascular medicine, thanks to molecular biology, can be grouped under four headings, viz. cardiac function, molecular basis of pathologic states, new avenues for treatment and animal models.

Cardiac function

We have learned a great deal about how the contractile function of the heart is regulated. New insights have been obtained into the function of adrenergic and muscarinic receptors, which form the interface between the autonomic nervous system and the cardiovascular system²⁻⁴. Earlier, it was not possible to purify these receptors, since they were present in small numbers in the tissues. Neither could they be characterized. The receptors were identified by observing the response to agonists and antagonists. Later, the development of radioligand assays provided a means to characterize them. As ligand affinity chromatography was developed and detergents capable of extracting receptor proteins were identified, these proteins could be purified, their amino acid sequence obtained and DNA probes designed. Cloning work ensued and complementary DNA clones were obtained for muscarinic and adrenergic receptors. It is now possible to investigate the functional role of these receptors by artificially expressing the cloned DNA in cell lines⁵.

The function of these receptors is to detect extracellular hormones or neurotransmitters. The information is transmitted across the cell membrane through changes in the receptor structure, which is detected by membrane-associated G proteins. These proteins modify the activity of an intracellular enzyme, which in turn influences several processes in the cell.

Several types of G proteins are now recognized. The G proteins which are expressed in the heart have been identified and incisive studies are being carried out. In addition to the presence of G proteins which are either stimulatory or inhibitory to adenylyl cyclase, there is evidence for the existence of Gp that regulates phospholipases in the ventricular tissues of the heart. The interactions between the receptors, G proteins and intracellular effector systems which regulate cardiac function are yet to be unravelled.

With respect to molecules which mediate ionic currents across the cell membrane, cDNA encoding cardiac sodium and calcium channels have been cloned, expressed in *Xenopus* oocytes and their functional properties characterized⁶⁻⁸. Cloning of cardiac potassium channels has also been carried out⁹.

Thanks to detailed molecular studies on how the chemical energy of ATP hydrolysis is coupled to protein conformational changes and physical alterations of ion binding sites, the complex role of ion transport in cell physiology is being delineated. Sequencing and mutagenic analysis of three cation pump enzymes (calcium ATPase of the sarcoplasmic reticulum, calcium ATPase of the plasma membrane and the Na-K ATPase) which catalyse the reaction coupling ATP hydrolysis to transmembrane movement of cations has helped to

improve our understanding of the mechanisms of ion transport¹⁰⁻¹⁵.

Molecular basis of pathologic states

Much light has been shed on molecular mechanisms of cardiac growth and hypertrophy, cellular basis of hypertension, paracrine and autocrine interactions in atherosclerosis and molecular genetics of cardiomyopathies.

Cardiac growth and myocardial hypertrophy

Cardiac muscle does not have the capacity to increase its mass by division. Adaptive growth is through myocyte enlargement, i.e. hypertrophy. Experimental studies in animal models and tissue culture systems have revealed that hypertrophy is associated with re-expression of a substantial subset of 'foetal' cardiac genes and reappearance of myofilament isoforms associated with embryonal contractile apparatus¹⁶. Myosin is the major contractile filament in the heart. Molecular cloning and sequencing of the α - and β -myosin heavy-chain genes have increased our understanding of the regulation of cardiac myosin isoforms in physiological adaptation and in clinical disorders¹⁷.

Myocardial growth is considered to be regulated by acidic and basic fibroblast growth factors as well as transforming growth factor β , which are expressed in the heart^{18,19}. The peptide growth factors selectively induce foetal contractile protein genes²⁰. The trophic signals of the growth factors are mediated by proteins encoded in cellular oncogenes²¹. The expression of a number of proto oncogenes, viz. *c-fos*, *c-myc*, *c-jun* and *ras* is identifiable in the heart.

Thus, there is a better knowledge of the initiating events, coupling mechanisms and regulation of gene expression in cardiac hypertrophy²². When we understand completely the factors that regulate cardiac growth during normal development and cardiac gene expression during response to injury, it might be possible to develop methods for stimulation of myocyte regeneration after cell death as occurs in myocardial infarction.

Cardiac failure

Investigations on the molecular basis of the failing heart have also made remarkable progress. Selective down-regulation of adrenoreceptors, fluctuations in the levels of various G proteins and altered membrane ATPase gene expression have been observed in the failing heart²³⁻²⁶. A major cause of altered calcium handling in cardiac failure has been identified as alteration, in a

gene-specific manner, the expression of mRNAs encoding calcium transport proteins of the sarcoplasmic reticulum²⁷.

Hypertension

A complex integrated system involving cardiovascular, renal and neurohumoral mechanisms is responsible for the regulation of blood pressure. The cellular and molecular bases of these mechanisms are being delineated²⁸ and the pathogenesis of primary or essential hypertension is beginning to be understood.

The role of the renin-angiotensin system for maintenance of normal blood pressure is well documented. Renin genes have been cloned and sequenced²⁹. Detailed studies on how various stimuli induce secretion of renin have been carried out. Using cultured cells and reporter gene approach, interaction between intracellular signal transduction pathways and renin mRNA expression and secretion has been demonstrated³⁰. Various components of the renin-angiotensin system have been localized in tissues employing *in situ* hybridization histochemistry^{31,32}. This would help to elucidate the function of these systems, their regulation and role during development and in disease states. Another advance is the identification and characterization of angiotensin II. Gene structure and molecular action of other major peptides such as atrial natriuretic peptide and endothelin have also been identified.

Chronic hypertension is characterized by an increase in thickness of the arterial wall. The thickening is a result of hypertrophy and/or hyperplasia of the smooth muscle cells as well as an increase in extracellular matrix components³³. In large arteries the predominant structural adaptation is hypertrophy, whereas in small arteries and arterioles, hyperplasia is observed. Mechanisms that initiate the structural changes involve mechanotransduction processes at the level of the endothelial cells lining the blood vessels. Transduction of a mechanical event such as a shear stress to the underlying smooth muscles may involve activation of electrical signalling mechanisms and release of growth factors. It is found that vasoactive agents which modulate vascular growth are synthesized by the endothelial cells. Autocrine and paracrine mechanisms involved in smooth muscle cell replication are being delineated.

Restriction fragment polymorphisms (RFLPs) technique and linkage analysis are used to investigate the genetic basis of hypertension³⁴. DNA probes for known genes such as renin, angiotensin, endothelin and atrial natriuretic peptide, which are involved in the regulation of blood pressure, are used to examine the occurrence of RFLPs and their linkage to phenotypic variation in blood pressure in large family pedigrees. A polymorphism

in the ACE (angiotensin-converting enzyme) gene which explains the development of essential hypertension has been identified³⁵.

Cardiomyopathies

To investigate the molecular genetics of a variety of inherited cardiomyopathies, the techniques of reverse genetics and positional cloning are employed.

A fatal cardiomyopathy is associated with Duchenne and Becker muscular dystrophy, which is an X-linked recessive disorder characterized by degeneration of skeletal muscle. Dystrophin, a cytoskeletal protein which complexes with several membrane glycoproteins and is involved in excitation-contraction coupling, is greatly reduced in this disease. The gene responsible for the myopathy has been localized to the short arm of the X-chromosome³⁶. Mutation in the gene results in either complete absence of the protein in the affected muscle or in the production of an abnormal protein.

The genetic locus for hypertrophic cardiomyopathy, an autosomal dominant disorder characterized by increased myocardial mass in the interventricular septum, has been identified as the gene on chromosome 14 which codes for cardiac β -myosin heavy chain. Mutations in this gene which result in abnormal myosin proteins have been detected in patients with hypertrophic cardiomyopathy. Missense mutations are the predominant defects that cause hypertrophic cardiomyopathy³⁷. Major deletions or rearrangements of the cardiac myosin heavy chain locus are not responsible in most affected individuals.

Linkage analysis has helped to localize the responsible gene in two other cardiomyopathies. Myotonic muscular dystrophy, a disease with features of muscular weakness, frontal baldness, cataract and dilated cardiomyopathy, is found³⁸ to be linked to chromosome 19q. Long QT syndrome has been³⁹ linked to the short arm of chromosome 11.

It is expected that these findings will help not only in the diagnosis of these diseases but also in the identification of individuals at risk. They would also provide insights into the pathophysiology of these disorders.

As the molecular genetic basis of muscle diseases of the heart is clarified, many questions emerge⁴⁰. Do heritable differences in contractile proteins or heritable genetic alterations in energy producing enzymes determine the susceptibility and severity of cardiomyopathy?

Atherosclerosis

The last decade witnessed delineation of the cellular events that initiate and lead to the characteristic structural

lesion of atherosclerosis, viz. growth of smooth muscle cells in the subendothelial region of the arterial walls. Also, several inherited abnormalities in lipid metabolism responsible for atherogenesis were identified.

A variety of specific substances were identified and their interactions in atherosclerosis studied⁴¹. These include vasoactive molecules such as serotonin, endothelin, endothelium-derived relaxation factor (EDRF), lipids such as thromboxane A₂ and prostacyclin, and large protein complexes such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF). The role of oxidatively modified low-density lipoprotein in endothelial injury and the role of intercellular adhesion molecules (ICAM) on the surface of the endothelial cells in mediating monocyte attachment and the mechanism of the origin of foam cells are better understood now^{42,43}. The mechanism of smooth muscle replication in atherosclerosis is also better defined.

A feature of atherosclerosis is the elevated levels of low-density lipoprotein (LDL), β very low density lipoprotein and lipoprotein (a) in the plasma. The level of high density lipoproteins is found to be decreased. Recent studies have provided a model for the interaction of these lipoproteins with macrophages and for the formation of the foam cell⁴⁴.

With respect to dyslipoproteinaemias associated with increased risk of development of atherosclerosis, the molecular defect is known in one of them, viz. familial hypercholesterolemia⁴⁵. The discovery of the LDL receptor, its characterization and localization of the LDL receptor gene on chromosome 1 led to the identification of specific mutations in patients with this disease. Sixteen specific mutations have been categorized into four different classes depending upon whether the precursor for LDL receptor is normally or abnormally processed or whether the precursor is detectable or not.

The functional defect in type-III hyperlipoproteinaemia has been traced to mutations that result in the expression of a functionally defective or deficient Apo E, a ligand for the LDL receptor⁴⁶. Considerable knowledge has also been gained with respect to the genetics of lipoprotein disorders and the structure-function relationship for apolipoprotein genes^{47,48}.

New avenues for treatment

The development of new therapies is related to two approaches: (1) targeting molecular processes that are causal to disease states and (2) application of recombinant DNA techniques to develop drugs for specific use and for gene transfer. Gene therapy offers a new approach to the treatment of cardiovascular diseases⁴⁹.

Thanks to the knowledge gained on specific aspects of cardiac function, drugs to selectively modify these

functions are being developed. The search could lead to drugs capable of interacting with adrenergic or muscarinic receptors, or those which can enhance or attenuate calcium ion transport into cardiac myocytes.

Novel therapeutic strategies are on the anvil for hypertension. Since cloned cDNAs for each of the components of the renin-angiotensin system are available, rational design of peptide inhibitors such as peptide-based renin inhibitors is possible⁵⁰.

In the treatment of thrombotic occlusion of arteries, a major change has occurred due to increased awareness of the molecular biology of the fibrinolytic system^{51,52}. Studies on the structure-function relationship of the proteins involved in fibrinolysis inspired efforts to produce genetically engineered proteins with thrombolytic properties. Tissue plasminogen activator (tpA), urokinase and single-chain urokinase are three drugs which are developed using rDNA techniques. Recently, deletion and substitution mutants of tpA have been produced by site-specific oligonucleotide-directed mutagenesis⁵³. These second generation thrombolytic agents have greater fibrin selectivity, greater resistance to inactivation and prolonged clearance time.

Another success is related to the recognition of the role of free radicals in producing ischaemic injury. Superoxide dismutase, an enzyme involved in free-radical degeneration has been developed employing rDNA techniques.

Gene transfer provides a powerful means to introduce new genetic material into the living cells. Recombinant adenovirus holds great promise as vehicles of gene delivery for cells of the cardiovascular system^{54,55}. Gene transfer technique has been used to genetically modify endothelial cells to over-express plasminogen activator activity. Engineered cells are also used to coat vascular stents which are implanted in blood vessels to maintain patency⁵⁶. Another application is prevention of smooth muscle cell proliferation using antisense oligonucleotides to a proto-oncogene *c-myc*, thus paving the way for prevention of re-occlusion of the blood vessel after a successful mechanical dilatation⁵⁷. Direct arterial wall and myocardial transfection are also being tried for gene delivery⁵⁸⁻⁶¹.

There is also the possibility that somatic cell gene therapy may be used to correct familial hypercholesterolaemia. In Watanabe heritable hyperlipidemic rabbits, it has been demonstrated that cDNA for LDL receptor can be transferred into hepatocytes and that these genetically modified cells express LDL receptors *in vivo*⁶².

Animal models

Animal models which provide excellent means to un-

derstand the pathophysiology of diseases and to test newly developed treatment methods are being developed using transgenic technology. Either by ablation of the causative gene or by over expression of mutant proteins, pathogenetic mechanisms of diseases can be elucidated.

Two approaches are employed for obtaining expression of cloned genes in whole animals. One approach is to transfer genes into somatic cells. For example, endothelial cells removed from the animal are infected with retroviral vectors and then returned to the arteries of the host. Genes can also be directly transferred by liposome mediated transfection or by retroviral infection.

Another approach is to produce transgenic animals by gene injection into a single cell mouse embryo which is subsequently reinserted into the mother. Tissues of the offspring carry the recombinant genes.

A promising technique is gene targeting by homologous recombination⁶³. Embryonic stem cells are used for transfection *in vitro* using previously cloned cells. The modified stem cells carrying the targeted mutation are then injected into the blastocoel cavity of pre-implantation embryo and the blastocyst transferred into the uterus of a foster mother. In successive generations, both heterozygotes and homozygotes for the mutation can be obtained.

Transgenic animals provide models to evaluate the contribution of specific genes to specific disease states. Transgenic mouse over expressing the growth hormone gene has been used to study the role of the hormone in the development of the blood vessel⁶⁴. A transgenic mouse model is also available for osteogenesis imperfecta, an inherited connective tissue disorder of the blood vessel wall⁶⁵.

Animal models of genetic hypertension have also been developed using transgenic technology⁶⁶. Transgenic mice harbouring the rat renin or rat angiotensinogen gene under the control of a metallothionein promoter have been developed. The genes can be activated in these animals by administration of the appropriate metal.

Transgenic mice harbouring human genes implicated in the susceptibility or resistance to coronary artery disease provide ideal models not only for understanding atherogenesis but also for developing gene therapies for hypercholesterolemia. Mechanisms of restenosis after blood vessel dilatation can also be elucidated using these models. 'Knockout' mice that lack the gene for apolipoprotein E, whose structural or functional defect results in Type-III hyperlipoproteinaemia, have been established⁶⁷. These animals are considered valuable for studies on atherosclerosis.

Another expectation is that a genetic approach would advance our present knowledge of developmental defects in the cardiovascular system⁶⁸. Candidate genes for congenital cardiac defects are not well recognized. Once they are identified, gene knockouts of the candidate loci

would shed light on the connection of specific genes with specific defects. A knockout of the Hox 1.5 x gene has been shown to result in abnormal cardiovascular development⁶⁹. In splotch mice, mutations in a homeotic gene (Pax-3) are associated with an abnormal communication between the two great vessels of the heart⁷⁰.

An exciting prospect is the use of zebra fish, *Brachydanio rerio* as a model to study cardiac development^{68,71}. The heart and blood vessels of the fish resemble those of humans in essential features of the primitive heart. The species is considered ideal for embryological studies because fertilization is external and the embryo is transparent. The individual cells of the heart and vessels are visible microscopically. The fish can be raised in large numbers, grown as clonal lethal free lines and is amenable to transgenesis.

Conclusion

As molecular abnormalities responsible for defective cardiovascular structure and function are understood, the therapeutic approach is undergoing a paradigm shift from targeting the organ to targeting the molecules. Strategies are centred around modification of specific aspects of cardiovascular function.

On the horizon are exciting developments. Somatic cell gene therapy holds great promise in inducing the growth of the cardiac muscle by switching on appropriate growth factors. If this succeeds, the benefit would be to patients with cardiomyopathy, in whom the only treatment of choice at present is cardiac transplantation. Gene transfer to promote angiogenesis may provide an alternative to bypass surgery in patients with coronary artery disease.

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Databases in Indian biology: The state of the art and prospects

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Only 0.85% of the scanned 7500 database titles are related to biology and biotechnology developed in India. Of these, 73% are either bibliographic or directory type and the rest are textual, numeric or multimedia in nature. This paper reviews the Indian biology and biotechnology databases and their relation to international databases on the subject. It highlights their limitations and throws more light on their potential for subject experts and information managers in the country to build informative and interactive databases.

THE amount of information being generated in the field of biology and biotechnology all over the world is unprecedented, and its management calls for an efficient system of databases. The present paper reviews the biology- and biotechnology-oriented Indian databases and their relation to the internationally available data

titles on the subject; it discusses their shortcomings and prospects for database developers, information providers and subject experts in creating more informative, user-friendly data titles.

The study

Detailed information about the international databases was gathered through various published and unpublished

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