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EDITORIAL

The Seeds of Time
"On the Future of Cardiology"

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"If you can look into the seeds of time,
And say which grains will grow and which will not"
(Shakespeare, Macbeth)

THE GREATNESS OF YESTERDAY (1)

The 20th century witnessed a series of grand achievements in cardiology that have been pivotal in the development of the specialty. Early in the century, Willem Einthoven (1903) designed the string galvanometer and could record the electrical activity of the heart. The first catheterization of the living human heart was performed by Werner Forssman on himself in 1929. Coronary arteriography was introduced by Mason Sones in 1959 and this paved the way to coronary revascularization, first surgical and then percutaneous. In 1977 Andreas Gruentzig developed percutaneous transluminal coronary angioplasty and established the new subspecialty of interventional cardiology. Balloon angioplasty was soon followed by stenting with bare metal stents and later on by drug-eluting stents. The introduction of coronary care units by Desmond Julian in 1961 immediately reduced the in-hospital mortality of acute myocardial infarction by half. The visualization of the heart and great vessels by non-invasive imaging, first through echocardiography by Inge Edler and Helmuth Herz (1952) and subsequently by advanced radiological techniques (computed tomography and magnetic resonance imaging) made many invasive diagnostic procedures unnecessary.

Cardiovascular pharmacology was boosted by the development of beta blockers by James Black in the 1960s, angiotensin-converting enzyme inhibitors by Cushman and Ondetti in the 1970s and the introduction of statins by Akira Endo in 1976.

Cardiovascular surgery was ushered in by Robert Gross' closure of patent ductus arteriosus in 1938 and open heart surgery was born following the introduction of cardiopulmonary bypass by John Gibbon in 1953.

Electrical methods of treating cardiac arrhythmias started with the development of the first external pacemaker by Paul Zoll in 1952. This was followed by introduction of permanent pacing by Elmquist and Senning in 1959 and the implanted cardiovertor defibrillator by Michel Mirowski in 1970.

These dazzling achievements (2) did not develop de novo, but were built on many decades of research by basic scientists, engineers and other talented innovators. They promoted cardiology to be a robust vibrant specialty that provides enormous benefits to humanity. Nevertheless, contemporary cardiology faces several major challenges related to the premature subspecialization of cardiologists, escalating cost of therapeutic strategies and inadequate application of preventive measures. Such vexing problems should be appropriately handled by cardiac specialists and not be left to legislators or regulators. Cardiologists must develop diagnostic and therapeutic strategies that are evidence-based but must also be more mindful of limited resources and economies particularly in developing countries. This will be progressively more momentous as we travel into the 21st century with even more astounding achievements expected.

THE PROMISE OF TOMORROW

In the field of heart failure, the greatest battleground in cardiology today, several drug classes are currently in development. Large scale mortality trials of aldosterone receptor antagonists are underway. Renin inhibitors such as aliskerin are also emerging as the next wave of renin-angiotensin-aldosterone system inhibitors.

Future treatment paradigms may include attenuation of inflammatory and metabolic processes important in the pathophysiology of heart failure and blocking at the molecular signaling level necrotic and apoptotic events that lead to cell death. Immune modulation is a major focus and clinical studies of oxypurinol and celacade are near completion. Metabolic modulators using novel compounds such as glycoprotein-like peptide-1 (GLP-1) and T3 analogue (DITPA) have also emerged. Stem cell therapies in various forms have been the newest development. It is likely that genomic medicine will become part of managing heart failure. The discovery of genetic mutations in dilated cardiomyopathy and exciting genomic-based diagnostic strategies are evolving. Finally, device therapy will be here

to stay and better and more sophisticated pacing strategies will evolve including better positioning of leads, better techniques and pacing modalities (including non-contractile pacing), new targets for electrical therapy and new patient monitoring capabilities.

In the area of coronary (3) artery disease (4), several imaging modalities now provide insight into the extent and structure of coronary atheromatous plaques (e.g. high-resolution intravascular ultrasound, positron emission tomography with labeling of plaque metabolic activity and optical coherence tomography). A critical goal is to distinguish metabolically active plaques with enhanced risk of rupturing and thrombotic events from quiescent plaques with stable anatomical and biological features. Such differentiation would allow targeted therapy of non-stenotic but vulnerable plaques and avoid unnecessary treatment of stable quiescent and non-obstructive lesions. In the management of both acute coronary syndromes and stable angina, it is critically important to determine whether markers of upregulation of the inflammatory and coagulation systems may provide additional and more accurate prognostic information (e.g. hs CRP, CD40, IL-1, serum Amyloid A and markers of platelet activation). Another goal is to establish the extent to which environmental factors modify the expression and the impact of specific genetic characteristics (rather than single gene polymorphism).

Pharmacogenomics represent the "low hanging fruit" of the genetics/genomics revolution. It will probably allow targeting of patients most likely to benefit from therapy. For example factor VII, glycoprotein IIa (PIA2 allele) and thrombospondin genes have all been demonstrated to have clinically relevant single-nucleotide polymorphisms that could guide the use of different antithrombotic cocktails. Eventually, therapies designed to modify or enhance an individual's genetic structure will be created. Angiogenesis has great potential and in conjunction with major developments in gene transfer therapy, it may provide highly innovative future methods of improving myocardial perfusion.

Cytoprotection mechanisms including pre- and post-conditioning have been demonstrated in experimental studies to have a major impact on cell survival in tissues subject to ischemia and reperfusion. As yet, these approaches have not translated into therapeutic intervention, but they have the potential to do so.

Substantial progress has already been made in the diagnosis and management of various cardiac arrhythmias. In the future, non-fluoroscopic multisite mapping for creating three-dimensional maps of specific arrhythmias and improved energy sources and delivery techniques will be forthcoming (5). It would not be surprising if arrhythmogenic substrate could be eliminated through energy delivery from the body surface.

The development of new anti-arrhythmic drugs that are more effective and less toxic remains an elusive goal. It is likely that the future management of ventricular tachycardia will evolve with even less reliance on such drugs. Refinements in device-based therapy aimed at more effective treatment and prevention of ventricular tachycardia by manipulating the timing and site of stimulation are already underway. More widespread and earlier use of ablation can be expected.

The spectacular success of molecular genetics in unraveling the mechanisms of polymorphic ventricular tachycardia in patients without structural heart disease holds promise for individual risk stratification and tailored therapy based on specific genetic profile. Initial attention has been focused on the impact of single-gene mutation. It is likely that an increasing variety of "modifier" genes with more subtle influence on cardiac electrophysiology will be discovered. This will help guide the exploration of genetic causes of increased arrhythmia susceptibility in the much broader population of patients with ventricular tachycardia and structural heart disease. Such genetic factors will help explain the different vulnerability of these patients to environmental stresses including ischemia, wall tension, autonomic fluctuation, infectious and autoimmune phenomena.
In the field of catheter ablation (6), the next big step will be the fusion of all anatomical and mapping information into integrated systems and automatic targeting by robotic systems. At present, two systems are available (Stereotaxis) or in development (Hansen) to provide remote control of catheter movement in the heart. These systems will be merged with high resolution cardiac imaging from multidetector CT scans or three dimensional intra-cardiac echocardiographs. Mapping and catheter location information from three dimensional catheter positioning systems will be registered with anatomical imagery. At this point, catheter ablation will become completely automated. The operator will interpret mapping and anatomical information and the computer will then direct the movement of the catheter to the desired point or line of ablation.

Pacemakers are becoming increasingly more sophisticated. One of the most significant future developments is likely to be the availability of remote monitoring of these devices. With the availability of automatic capture threshold testing, pacing thresholds could be determined by the device. It might soon be possible to download all this information with conventional or cellular phone lines from the patient's home. This would be revolutionary in the management of these patients by limiting office visits, increasing patient compliance and satisfaction and possibly reducing emergency room visits. It would not be surprising if it is even possible to program these devices remotely in the near future. Pacemaker algorithms for limiting right ventricular pacing are becoming increasingly popular, although their clinical efficacy needs to be more objectively quantified in randomized trials. Device diagnostics will not only store arrhythmia episodes and electrocardiograms, but will also store activity logs and heart failure states with the monitoring of transthoracic impedances.

For valvular heart diseases, a variety of ingenious catheter

HMJ Vol. 1, No. 1, 2007
May, 2007: 2-4

based approaches to valve repair are in the preclinical and clinical testing (7). For the mitral valve, these include percutaneous annuloplasty (via the coronary sinus or directly via the left atrium), techniques to reproduce the edge-to-edge repair (Alferi stitch) and percutaneous valve replacement. Percutaneous aortic valve replacement will soon become a reality for selected patients, at this point mostly as a rescue procedure for desperately ill patients. The limited durability for current bioprosthetic valves may be attributed in part to the absence of "life" tissue able to regenerate itself. Successful tissue engineering of functioning autologous heart valves based on human marrow stromal cells has been recently demonstrated in experimental models. It is conceivable that in the near future, life-tissue heart valves could be custom manufactured using autologous cells.

Future directions in therapy for infective endocarditis include treatment with novel therapeutic agents. Bacterial adherence is central to initiation of infection and metastatic spread and bacterial surface adhesion proteins have been a target for the development of new immunotherapies. In animal models of S. aureus endocarditis, combination therapy with S. aureus human immune globulin and vancomycin significantly increased clearance of bacteria when compared with use of vancomycin alone. Aurexis, a humanized monoclonal antibody against S.aureus protein clumping factor A is currently under trial (phase 2) in patients with MRSA endocarditis. The development and testing of vaccines to target high risk groups may reduce outcomes of infective endocarditis. Immunization with fibrinectin binding protein protects against experimental infective endocarditis in animal models. Such vaccines could have important clinical applications among patients with indwelling venous catheters or prostheses at high risk for S. aureus infections.

For patients with pulmonary hypertension (8), investigational therapies in clinical trials include the selective oralET-A antagonists sitaxsentan and ambrisentan, the long acting PDE-5 inhibitors vardenafil and tadalafil, inhaled and oral treprostenol, inhaled vasoactive intestinal peptide (VIP) and intravenous or inhaled adrenomedullin. Imatinib which is an oral PDGF receptor inhibitor and approved for treatment of chronic myeloid leukemia has been shown to improve haemodynamics in patients with pulmonary arterial hypertension, a prospective double-blind clinical trial is currently underway. The use of bone marrow derived endothelial progenitor cells (EPC) in combination with endothelial nitric oxide synathase (eNOS) gene therapy has shown to decrease pulmonary pressures and pulmonary vascular resistance and to reverse pulmonary vascular remodeling in a rat model. Similar cell based gene transfer strategies in animal models with other vasodilators (e.g. adrenomedullin gene) and angiogenic genes (e.g. vascular endothelial growth factor gene) have also yielded promising results. We look forward to future hybrid cell-gene therapy studies in the human pulmonary arterial hypertension phenotype.

Other areas of remarkable progress in cardiovascular medicine involve lipid disorders, hypertension, peripheral vascular diseases and rehabilitation.

CONCLUSION

As cardiology advances so rapidly, the future of the specialty and more importantly for patients with cardiovascular disorders looks bright. The principle role of the cardiologist will change from recognizing and managing established disease as is the case today to interpreting and applying genetic information in prevention and treatment. The supreme goal, of course is to eliminate cardiovascular disease as a major threat to long productive life.

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