Knowledge is proud that he has learned so much; Wisdom is humble that he knows no more.

William Cowper, 1731–1800

The second half of the last century was a period of tremendous excitement and accomplishment in the fight against cardiovascular diseases. Looking back, one can point to three major events that provided the foundation for this era of great progress in medical as well as surgical approaches to these diseases.

One of those events was the introduction of cardiac catheterization into clinical medicine by Andre Cournand and Dickerson Richards in the late 1940s. Its importance was appropriately noted by Liljestrand in his Nobel prize presentation speech in 1956: “Professors Cournand, Forssmann, and Richards: the Karolinska Institute has decided to award this year’s Nobel Prize in Physiology or Medicine to you jointly for your discoveries concerning cardiac catheterization and pathologic changes in the circulatory system. . . . Together, they signify the initiation and development of a new and important approach to our understanding of heart disease.” Indeed, as we reflect on our accumulated knowledge of the pathophysiology of heart disease, we must recognize that much of it is the result of the ever-wider use of cardiac catheterization.

The second memorable event of the last century was the introduction of open heart surgery. A myriad of pioneers in many countries contributed to the surgical wonders that we, today, consider ordinary, but the surgeons who took the first steps must be recognized—John Lewis, for the first open heart surgery using hypothermia in 1952, and John Gibben, for the first open heart surgery using a heart-lung machine 1 year later.

These two great medical advances would probably not have flourished as quickly, or even possibly as well, if a third truly defining event had not occurred—the creation of the National Heart Institute by the United States Congress in 1948. Supported by the American people and their elected representatives, that organization catalyzed and sponsored most of the advances that have occurred in the last 50 years. This was accomplished by developing a brilliant workforce and supporting its research. Undoubtedly, the Institute has had both direct and indirect impacts on the worldwide cardiovascular disease burden.

Today, at the beginning of the 21st century, cardiac catheterization and open heart surgery have become so routine that they are hardly noticed. In fact, both may be soon replaced by more innovative approaches.

The support of research has broadened and is shared by countries, voluntary organizations, and relevant industries. Biomedical research, including that on cardiovascular diseases, has itself become an industry stimulated by a greater understanding of those diseases and by the emergence of extraordinary scientific opportunities. These opportunities in the cardiovascular field are derivatives of discoveries and new approaches not only in that field but in other fields as well.

A little more than 2 years ago, the successor to the National Heart Institute, that is, the National Heart, Lung, and Blood Institute, convened a group of prominent cardiovascular researchers to chart a blueprint to guide the Institute’s programs. This group, known as SPARK, identified a number of scientific opportunities and enabling approaches on which specific research directions and activities are built. The future of cardiovascular research is completely dependent on maximizing the utilization of new approaches and technologies and on building multidisciplinary research teams. But the future is now, and already, multidisciplinary teams are assembled.

It is not possible to list all of the research avenues that are currently being pursued and will be pursued in the years to come. The Figure displays some of the most exciting areas of research related to the diagnosis, pathogenesis, and treatment of heart disease. It would be imprudent to attempt to predict which of these directions will bring the greatest benefit to patients with heart disease or to individuals likely to develop this condition. The wisest prognostication is that each and all will contribute to this goal.

One area of investigation, however, has received tremendous attention—genomic and genetic research. Leaders in this field have unambiguously stated that the completion of the human genome will lead to “the development of rational strategies for minimizing or preventing disease phenotypes altogether.” That this forecast may be correct is in part substantiated by some very interesting studies which have demonstrated that specific polymorphisms may confer a higher risk for disease in the presence of environmental or lifestyle risk factors. Conversely, other polymorphisms have been associated with a protective effect. Likewise, other DNA variations may enable us to predict the course of a condition and, thus, guide therapeutic strategies. The practical value of these observations is very hard to predict, especially...
the notion of tying a genotype to a customized preventive regimen. Indeed, we already have extremely compelling evidence that controlling some risk factors such as lifestyle can reduce, if not prevent, disease development. Yet, we know how difficult it is to change behavior, and there is some doubt that the knowledge of a genetic determinant would overcome or reduce this difficulty.

Perhaps the most promising outcome of genomic research, gene sequencing, and the study of polymorphisms is to establish whether and to what extent there may be inherited differences in drug response or sensitivity. The individual and societal benefits of being able to prescribe (only) the right medication(s) to patients are enormous. Undoubtedly, this line of investigation is filled with scientific opportunity and public health value. But much more research is needed first to understand the interplay of multiple single nucleotide polymorphisms and then to assess how their interaction determines the therapeutic phenotype.

Gene therapy has been and remains one of the most fascinating byproducts of genomic research. Since the first attempt at human gene therapy in the late 1980s, the field has progressed—but very slowly, indeed. Cardiovascular medicine has been one of the largest targets of the attempt at gene transfer for therapeutic purposes. Although gene therapy may have received bad press in the last year or so, further work must continue and be accelerated, because the object of the very much warranted criticisms was not the concept of gene therapy, but the process of its application and the methods of those who practiced it.

An editorial by Marbán in early 2000 emphasized that gene therapy must be approached with as much caution as enthusiasm. This can be reduced to a single prescription: more research is needed. A recent publication by Vale et al illustrates the potential of gene transfer to restore in humans the viability and function of damaged myocardium. But the companion editorial, appropriately subtitled “Moving on Down the Road,” underscores the “rocky adolescence” this field is experiencing and the many questions to be addressed.

Elsewhere, Holtzman and Marteau asked the question “Will genetics revolutionize medicine?” and they concluded, “Those who make medical and science policies in the next decade would do well to see beyond the hype.” This is true, but what is there to see? Carol Ezzell said it well in her Scientific American article “Beyond the Human Genome.” She made the point that the future challenge is to uncover all the proteins encoded by the genes and to identify their function. To my mind, here is the true and lasting value of the genomic revolution—it is proteomics that will revolutionize medicine, because that is the tool that will lead to the understanding of pathological processes at the cellular level. In the past, great progress was made by observing and analyzing pathological alterations; proteomics will permit the molecular dissection of pathogenic pathways. This, in turn, will open the door to many more effective therapies. It is with this in mind that the National Heart, Lung, and Blood Institute launched its flagship Program of Genomic Applications. There are good reasons to believe that the understanding and knowledge of gene expression will be to cardiovascular medicine of this century what cardiac catheterization and open heart surgery were to the last century.

But this is not all. Indeed, there are many other research directions that have remarkable potential. Just as molecular dissection of pathogenic pathways will provide novel and probably very effective therapies, further research in cell biology—defined broadly—can also be expected to lead to other therapeutic options. Fifty years ago, extracorporeal circulation permitted open heart surgery and later heart transplantation. Over the years, many patients with end-stage heart disease have benefited from transplants, but many more failed to have access to this therapy because of the paucity of available donated hearts. Cell transplantation opens a new, huge window of opportunity to repair injured myocardia long before end-stage disease occurs.

During the last few years, we have witnessed previously unthinkable progress and achievements in cell transplantation biology. Fetal myocytes, bone marrow cells, skeletal myocytes, and intraventricular septal cells have all been transplanted into the hearts of animal models. Although embryonic cells may offer the best outlook, their use is not readily possible for societal rather than scientific reasons. The transplantation of other cell types has shown significant success but also considerable limitations, albeit surmountable ones. The plasticity of many cell types has been demonstrated, but, as yet, it is not fully understood. However, it is encouraging to note that cells derived from mature animals appear to have broader differentiation potential than previously thought. The surprising ability of cells from adult animals to develop into various types of tissue—something that was thought to be unique to embryonic stem cells—is already being reported for cells derived from bone marrow and mouse brain. The critical next steps—already showing promising results—are to determine methods to induce stem cells to develop into cardiomyocytes in the large numbers of cells needed for transplant.

The other issues that warrant further and intense investigation are cell viability, integration, and function. For example, elegant studies have established that gap junctions develop between myocytes and transplanted embryonic and stem cells; however, major questions remain about the functionality of these cell junctions. Work on animal models, especially rats, has been quite promising, and already phase 1
human trials are in development. But, clearly, because of the lack of understanding of the biology, the selection of patients and the near-term goals of the trials must be prudent. What the clinical applications of these investigations will be remains to be demonstrated, but the potential of the research is enormous. Tissue generation and tissue repair are now in sight, and if this is successful, scores of patients will be the beneficiaries.

The last promising research area I would like to mention is molecular imaging. Cell fusion and functionality are nothing but a molecular process. Indeed, communications between cells depend on the movement of molecules and the capacity of one molecule to interact with another. The only way to understand the signaling that occurs between cells is to identify the relevant molecules and to image the molecular pathways and interactions of these molecules. Only then can we expect to understand and influence (pharmacologically or otherwise) processes at the cellular and subcellular levels.

As well, there is the promise of being able to literally see the activation of genes of interest using positron emission tomographic imaging. Already with this technology it has been possible to visualize specific gene activation in the mouse. Such approaches are expected to be generalizable to cardiovascular research. We can then anticipate that specific molecular imaging techniques will provide key diagnostic information to permit the implementation of appropriate molecular/cellular/genetic therapies as well as dictate the evolution of therapies to a favorable outcome. This is what the emerging field of molecular imaging will permit us to do.

One can safely predict that molecular imaging will be to the molecular medicine of today and tomorrow what light and electron microscopy of biopsy samples has been to tissue pathology for more than 100 years. Unquestionably, tissue/organ imaging, coupled with molecular imaging, is bound to enhance beyond expectations our understanding of pathogenetic processes and diagnosis as well as therapeutic interventions. Specific research areas that can be expected to benefit enormously include study of acute or chronic inflammatory processes, genetic expression of congenital cardiovascular malformations, and molecular and genetic processes associated with plaque.

This brief and grossly incomplete description of some challenging research avenues does not do justice to the many research opportunities that are before the cardiovascular research community. If these opportunities are pursued and if, as expected, they are successful, patients with cardiovascular diseases will greatly benefit and enjoy longer and healthier lives. But for this to be achieved, much greater attention must be given to the translation of the research outcomes into medical practice. We must all do our best to ensure that research findings do not remain locked in the laboratory. Short of that, it is likely that the support of the biomedical research by the public will be difficult to sustain.

References

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