Hypertension Research

The Next Five Years

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Hypertension is both a disease and a risk factor. Long-term research objectives are to understand blood pressure homeostasis and the pathogeneses of the various forms of hypertension. Short-term research objectives center around enhancing methods for detection, evaluation, treatment, and control of high blood pressure because, even in the absence of precise knowledge of the etiology of hypertension, its control results in substantial reductions in morbidity and mortality. Therefore, a multifaceted national research strategy has been developed that includes basic science, applied research, clinical research, clinical trials, and demonstration and education research approaches. Complementing this research strategy is a congressionally mandated program to facilitate the application of the products of research to the clinical care setting by promoting educational activities aimed at health care providers, patients, and consumers. (Hypertension 1990;15(suppl I):I-25–I-28)

As illuminated elsewhere within these proceedings, there is good evidence to suggest that hypertension should be thought of as both a disease and a risk factor. Long-term research objectives are to understand blood pressure homeostasis and the pathogeneses of the various forms of hypertension so that eventually hypertension can be prevented. Short-term research objectives center around improving methods for detection, evaluation, treatment, and control of hypertension because of the abundant evidence suggesting that blood pressure control is associated with substantial reduction in hypertension-related morbidity and mortality.

To achieve these multiple objectives, the National Heart, Lung, and Blood Institute (NHLBI) has conceptualized an approach for addressing needs and opportunities in cardiovascular research including hypertension (Figure 1). The entire biomedical research enterprise is a cooperative venture involving government, universities, the private sector, and industry, which by a combination of simultaneous efforts in a variety of research areas, yields new knowledge that is eventually transmitted to the clinical health care sector.

Basic research focuses on classic as well as new research disciplines aimed at uncovering mechanisms of blood pressure homeostasis and hypertension.

Applied research often represents a spinoff from basic science investigations, and currently, a large portion of this research is supported by industry. Clinical research is the fulcrum of the biomedical research spectrum in that observations made clinically can serve either to direct investigators back to the bench to uncover mechanisms or can propel them forward to test and further evaluate interventions that appear to be promising on an anecdotal basis.

Clinical trials are used to evaluate efficacy of interventions under controlled circumstances, whereas demonstration and education research evaluates effectiveness under real world conditions. Knowledge dissemination or technology transfer refers to the facile application of the products of research to the world of clinical practice. In the United States, a congressionally mandated program, the National High Blood Pressure Education Program, helps to accelerate technology transfer by providing educational materials not only to physicians but also to patients and consumers.

Molecular Biological Technologies

Among the newer research disciplines, molecular biology will play a very important role in future hypertension research. Modern molecular biology has profoundly influenced the course of basic and applied biomedical research by providing experimental techniques and strategies to analyze gene organization, modification, regulation, and expression, as well as protein structure-function relations with greater efficiency and precision. Consequently, the past decade has witnessed an impressive array of research advances that include the
identification and chromosomal localization of specific genetic sequences linked to certain human diseases; the development of a new generation of sensitive and accurate diagnostic tests; the production of new or increased quantities of biologically active compounds such as human growth hormone, human insulin, and tissue plasminogen activator; the exploration and development of novel therapeutic strategies such as gene transfer techniques to correct genetic abnormalities; and the development and use of transgenic animals to study human disease processes and to ascertain the biological activity of a particular gene at the molecular, biochemical, cellular, and whole-animal levels with the attendant opportunities for devising new diagnostic and therapeutic approaches.

All of these advances are possible because of recombinant DNA (rDNA) technology. Examples of the use of rDNA technology include the synthesis of antisense molecules to regulate gene expression; the use of chimeric genes to produce hybrid polypeptides; and site-directed mutagenesis to study structure-function relations.

Molecular Genetics

Molecular genetic approaches are now available for identifying defective genes even in the absence of knowledge about the primary gene product or the biochemical mechanisms of the disease. This approach, known as "genetic linkage analysis," is responsible for significant advances in our understanding of important human genetic diseases.

Genetic linkage analysis combines two complementary research approaches. The first is to identify families in which the disease phenotype of interest follows a clear pattern of inheritance. The second is to use molecular biological techniques to search for a DNA-based genetic marker that is physically close to the defective gene such that it is almost always inherited along with the disease. The genetic marker can be any variation, or polymorphism, in the DNA.

These structural variations are detected by using restriction endonucleases that cleave DNA at specific sites to produce a pattern of fragment lengths. Variations in these DNA fragments because of the presence of polymorphisms are called restriction fragment length polymorphisms or RFLPs. If a DNA polymorphism is physically close to a single mutation responsible for a phenotypic abnormality, the polymorphism can be used as a genetic marker regardless of whether it is or is not causally related to the disease phenotype.

Genetic linkage analysis can be used in hypertension research. One approach and the subject of a recent NHLBI research initiative is to locate and characterize families for which pedigree analysis indicates an inheritance pattern of a hypertension-related phenotype. DNA within white blood cells from these families can then be analyzed for the presence of RFLPs, of which more than 3,000 are currently cataloged. The pattern of RFLP inheritance is then compared with the pattern of inheritance of the hypertension-related phenotype. A match in patterns suggests that the RFLP and the gene responsible for the hypertension-related phenotype are located on the same chromosome. Thus, the RFLP can be used as a marker for the hypertension-related phenotype, regardless of whether or not it is causally connected to the genetic abnormality accounting for the hypertension-related phenotype.

Also, once an RFLP is associated with a disease phenotype there are techniques, one of which is known as "chromosome walking," that allow investigators to move from the RFLP locus to the locus on the chromosome responsible for the protein defect associated with the disease phenotype. Once the disease phenotype gene is identified, it can be cloned, and its product can be examined by various techniques including structure-function analyses. The RFLP can also be used as a diagnostic marker of a disease even in advance of full expansion of the disease. Finally, this approach can serve to pave the way for innovative therapeutic modalities such as gene replacement therapy.

It should be noted, however, that an important feature of genetic linkage analysis and one that is problematic in studying hypertension is the need to
identify a discrete, bimodally distributed phenotypic abnormality. Unfortunately, blood pressure is not such a suitable abnormality because of its continuous distribution, thus necessitating the need for identifying other hypertension-related phenotypes when using genetic linkage analysis to study hypertension.

Transgenic Animals

Techniques9,10 for the creation of transgenic animals involve the introduction of foreign genes into the reproductive cell line of mammals to study the mechanisms of biological phenomena including DNA sequences responsible for tissue-specific and temporal-specific gene expression; the identity of neural, hormonal, and transacting factors (proteins that interact with DNA and regulate gene expression); and the mechanisms by which they regulate gene expression. Transgenic animals are also used to determine cell ancestry, cell location, and cell commitment during mammalian development; assess the physiological function of particular cell types using genetic ablation techniques; and generate new animal models of human disease to facilitate better understanding of disease mechanisms as well as the development of novel approaches to therapy. Transgenic technologies are now suitable and ready for application to hypertension research.

Vascular Biology

Because of some of the recent advances made in fundamental biological disciplines, a number of investigators are increasingly focusing their attention on vascular biology per se. This discipline is interesting to the NHLBI because it serves a bridging function. In this context, vascular biology, which views the blood vessel as an organ, refers to the multidisciplinary approach to the examination of cell behavior, primarily endothelial and vascular smooth muscle cell behavior (although there are other important cells such as the platelet, the monocyte, and the macrophage) with an emphasis on communication including signal generation, transduction, and molecular and cellular responses; analysis of the cell cycle in response to hypertension and atherosclerosis, with particular attention paid to vasoactive factors, vasotropic factors, and factors that stimulate smooth muscle replication; and the genes responsible for regulating all of the above. It is anticipated that over the next few years many new advances are likely to emerge from this new discipline with practical application not only for hypertension but for the broad array of diseases that affect blood vessels.

Applied Research

Perhaps the classic example of applied research is the development of angiotensin converting enzyme inhibitors for therapeutic use, and indeed, these agents are quite popular because of their efficacy, safety, and minimal disruption of quality of life.

Of course, angiotensin converting enzyme inhibitors are not quite as specific as they could be because converting enzyme has an effect not only on angiotensin but also on bradykinin. It might be advantageous to develop drugs that are more highly specific, for example, renin inhibitors or angiotensin II antagonists.

With currently available technologies, it is now theoretically possible to synthesize from first principles not only new drugs to block the renin-angiotensin system but also virtually any kind of a polypeptide analogue or antagonist. This entails use of molecular biological methods for primary identification of proteins and receptors and for synthesis of analogues and antagonists, as well as advanced structural analytical techniques (i.e., crystallography, nuclear magnetic resonance spectroscopy, and computer modeling) for identifying the three-dimensional structures of proteins. By using these principles, it is expected that many novel therapeutic agents will be developed over the next few years.

Recommendations for the Future

The aforementioned has been a brief glimpse of new research disciplines and technologies that are currently applied or that are about to be applied to hypertension research. What follows is a concise although not exhaustive listing of future research recommendations.

In the basic research arena, there is a need for better understanding of the genetic determinants of hypertension through aggressive but parsimonious exploitation of new research technologies and integration of these technologies with standard biochemical and physiological disciplines.

Important in applied research, in addition to new drug development, is the need for refinement of current technologies and development of new ones that allow for noninvasive measurement of vascular changes and target organ function not only for diagnostic purposes but because such technologies allow for the creation of intermediate end points in clinical trials that can dramatically reduce sample size requirements when evaluating therapeutic and preventive interventions.

In epidemiological research, it would be useful to stratify hypertensive patients better by both risk and pathophysiology; to develop better insights into the role of environmental variables such as diet, physical activity, and stress; and to learn more about the interaction of hypertension with other cardiovascular risk factors.

In clinical research, there is a need for better matching of drug to pathophysiology, as well as learning which drugs not only lower blood pressure but provide additional benefits with minimal side effects. For example, which drugs are best suited for patients with coronary heart disease, cerebrovascular disease, or hypertensive nephropathy? Additionally, clinical and research approaches
should consider identification and management of other cardiovascular risk factors.

In the area of clinical trials, more information is needed about drug-specific interventions (e.g., the differential effects on morbidity and mortality of the various classes of antihypertensive drugs); about disease-specific interventions (e.g., information on goal blood pressure levels for hypertensive patients with coronary heart disease versus cerebrovascular disease versus nephropathy); about age- and sex-specific interventions (e.g., the differential effects of antihypertensive intervention on the young, the elderly, and women versus men); about the combined effects of nonpharmacological and pharmacological interventions; and about the effects of multiple risk factor reduction interventions.

Demonstration and education research, which refers to evaluation of interventions in the real world, needs to continue to evaluate single and multifactorial risk reduction programs in the community, worksite, and schools.

Finally, continued support of the application of the products of research to the clinical care of the patient by promoting education of health care providers, patients, and consumers is recommended.

References

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**KEY WORDS** • essential hypertension • blood pressure • research