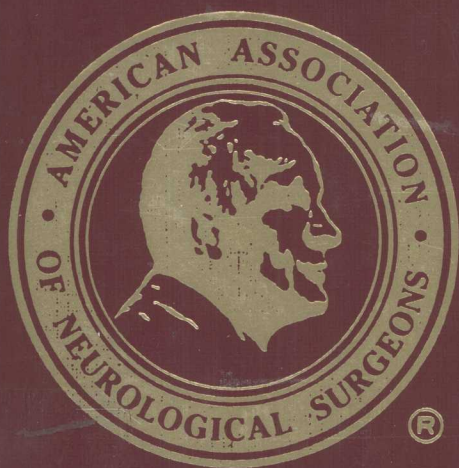
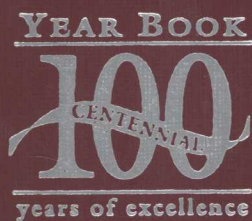


YEAR BOOK[®]

YEAR BOOK OF NEUROLOGY AND NEUROSURGERY[®]

2001



WALTER G. BRADLEY
SCOTT R. GIBBS
ASHOK VERMA

Published in cooperation with
The American Association of Neurological Surgeons.

2001

The Year Book of NEUROLOGY AND NEUROSURGERY®

"Published without interruption since 1902"

Neurology

Editors

Walter G. Bradley, DM, FRCP

Professor and Chairman of Neurology, University of Miami School of Medicine; Chief of Neurology Service, Jackson Memorial Hospital, Miami Fla

Ashok Verma, MD, DM

Assistant Professor of Neurology, University of Miami School of Medicine; Attending Neurologist, Jackson Memorial Hospital, Miami, Fla

Neurosurgery

Editor

Scott R. Gibbs, MD, MA

Director, Regional Brain and Spine Center, Chairman, Division of Neurosurgery, Southeast Missouri Hospital; Attending Staff Neurosurgeon, St Francis Medical Center, Cape Girardeau, Mo

M Mosby

St. Louis Baltimore Boston Carlsbad Naples New York Philadelphia Portland London
Madrid Mexico City Singapore Sydney Tokyo Toronto Wiesbaden



Dedicated to Publishing Excellence

Publisher: Susan Patterson
Developmental Editor: Jennifer Richardet
Manager, Periodical Editing: Kirk Swearingen
Senior Production Editor: Pat Costigan
Project Supervisor, Production: Joy Moore
Production Assistant: Betty Dockins
Manager, Literature Services: Idelle L. Winer
Illustrations and Permissions Coordinator: Chidi C. Ukabam

2001 EDITION

Copyright © 2001 by Mosby, Inc

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Permission to photocopy or reproduce solely for internal or personal use is permitted for libraries or other users registered with the Copyright Clearance Center, provided that the base fee of \$4.00 per chapter plus \$.10 per page is paid directly to the Copyright Clearance Center, 21 Congress Street, Salem, MA 01970. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collected works, or for resale.

Printed in the United States of America
Composition by Thomas Technology Solutions, Inc
Printing/binding by Maple-Vail
Mosby, Inc
11830 Westline Industrial Drive
St. Louis, MO 63146
Customer Service: periodical.service@mosby.com
www.mosby.com/periodicals/

International Standard Serial Number: 0513-5117
International Standard Book Number: 0-8151-0930-X

Associate Editors

Saleh A. Aldasouqi, MBBS

Consultant Endocrinologist, American Boards of Internal Medicine and Endocrinology, King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia

Juan C. Bartolomei, MD

Spine Fellow, Barrow Neurological Institute, Phoenix, Ariz

Joseph R. Berger, MD

Professor and Chairman, Department of Neurology; Professor, Department of Internal Medicine, University of Kentucky College of Medicine, Lexington

John P. Blass, MD, PhD

Burke Professor of Neurology and Neuroscience and Medicine, Weill-Cornell Medical College; Director, Dementia Research Service, Burke Rehabilitation Institute, White Plains, NY

Charles P. Bondurant, MD

Clinical Assistant Professor, Division of Neurosurgery, University of Missouri-Columbia School of Medicine, Columbia, Mo

Robert A. Davidoff, MD

Professor of Neurology, University of Miami School of Medicine; Chief, Neurology Service, Jackson Memorial Hospital, Miami, Fla

Igor de Castro, MD

Department of Neurosurgery, University of Arkansas for Medical Services, Little Rock

Nicolas de Tribolet, MD

Professor and Chairman, Department of Neurosurgery, University of Geneva; Chief, Department of Neurosciences, University Hospital of Geneva

Curtis A. Dickman, MD

Director of Spinal Research, Division of Neurological Surgery, Barrow Neurological Institute, Phoenix, Ariz

Alexandre Elias, MD

Department of Neurosurgery, University of Arkansas for Medical Sciences, Little Rock

Myron D. Ginsberg, MD

Peritz Scheinberg Professor of Neurology, Director, Cerebral Vascular Disease Research Center, University of Miami School of Medicine; Attending Neurologist, Jackson Memorial Hospital, Miami, Fla

Donald Goodkin, MD

Senior Clinical Scientist, Immunex Corporation, Seattle

Thomas J. Grabowski, Jr, MD

Associate Professor of Neurology and Radiology, University of Iowa College of Medicine, Iowa City

David F. Jimenez, MD

Associate Professor of Neurosurgery, University of Missouri School of Medicine; Residency Program Director, University of Missouri Hospitals and Clinics, Columbia, Mo

Andrew H. Kaye, MD, FRACS

Professor and Head, Department of Surgery and Neurosurgery, Royal Melbourne Hospital, University of Melbourne, Parkville, Australia

Boris Klun, MD, PhD

Professor Emeritus of Neurosurgery, Medical Faculty, University of Ljubljana, Slovenia

Richard Leblanc, MD, MSc, FRCSC

Professor, Department of Neurology and Neurosurgery, Montreal Neurological Institute and McGill University; Neurosurgeon, Montreal Neurological Hospital

Raul Marino, Jr, MD

Professor and Chairman, Division of Neurosurgery, University of São Paulo Medical School; São Paulo Neurological Institute, Brazil

Marc R. Mayberg, MD

Professor, Cleveland Clinic Foundation; Chairman, Department of Neurological Surgery, Cleveland Clinic Foundation, Ohio

Shahan Momjian, MD

Department of Neurosurgery, University Hospital of Geneva

Bruce Nolan, MD

Associate Professor of Neurology, University of Miami; Director, Sleep Disorders Center, Jackson Memorial Hospital, Miami, Fla

T. Glenn Pait, MD

Associate Professor, University of Arkansas for Medical Sciences; University Hospital of Arkansas, Arkansas Children's Hospital, and John L. McClellan Memorial Veterans Administration Medical Center, Little Rock

Michael Payer, MD

Department of Neurosurgery, University Hospital of Geneva

Miguel-A. Perez-Espejo, MD, PhD

Associate Professor of Neurosurgery, Senior Neurosurgeon, University Hospital "V. Arrixaca," Murcia, Spain

Ryszard M. Pluta, MD, PhD

Senior Researcher, National Institute of Neurological Disorders and Stroke, Surgical Neurology Branch, Bethesda, Md; Associate Professor, Neurological Department Medical Research Center, Neurosurgical Department, Warsaw, Poland

Jerome D. Posner, MD

Professor of Neurology and Neuroscience, Cornell University Medical College; Attending Neurologist, Memorial Sloan-Kettering Cancer Center, New York

Robert M. Quencer, MD

Professor and Chairman, University of Miami School of Medicine; Chief, Radiology Service, Jackson Memorial Hospital, Miami, Fla

R. Eugene Ramsay, MD

Professor of Neurology and Psychology, Director, International Center for Epilepsy, University of Miami; Director, Inpatient Epilepsy Monitoring Unit, Jackson Memorial and Miami Veterans Administration Medical Center, Miami, Fla

Jean Régis, MD

Praticien Hospitalier, Hôpital la Timone, Marseille, France

Damianos E. Sakas, MD

Professor and Chairman, Department of Neurosurgery, University of Athens Medical School, Evangelismos General Hospital, Athens, Greece

Juan R. Sanchez-Ramos, MD, PhD

Helen E. Ellis Professor of Neurology, University of South Florida College of Medicine, Tampa

Norman J. Schatz, MD

Voluntary Professor of Neurology, University of Miami; Mount Sinai Hospital, Miami Beach, Fla; Bacon Palmer Hospital, Miami, Fla; Adjunct Professor of Neurology, University of Pennsylvania, Philadelphia

Nina Felice Schor, MD, PhD

Professor of Pediatrics, Neurology, and Pharmacology, University of Pittsburgh; Carol Ann Craumer Professor of Pediatric Research; Scientific Director, and Director, Pediatric Center for Neuroscience, Children's Hospital of Pittsburgh, Pa

Volker K. H. Sonntag, MD

Professor, Clinical Surgery, University of Arizona; Vice Chairman, Division of Neurological Surgery; Chief, Spine Section, Division of Neurological Surgery; Director, Neurosurgery Residency Program, Barrow Neurological Institute, Phoenix, Ariz

Julio Sotelo, MD

General Director, National Institute of Neurology and Neurosurgery, Mexico City

Philipp Gilles Tanner, Dr Med

Research Neurosurgery, BrainLAB-AG, Munich

Vincent C. Traynelis, MD

Professor of Surgery (Neurosurgery); The University of Iowa; University of Iowa Hospitals and Clinics, Iowa City

Ronald J. Tusa, PhD

Professor of Neurology, Emory University and Yerkes Research Center; Emory Hospital, Atlanta, Ga

Patrick Van Schaeybroeck, MD

Department of Neurosurgery, University Hospital of Geneva

Kim M. Vognet, RN

Department of Neurosurgery, University of Arkansas for Medical Sciences, Little Rock

Clark Watts, MD, JD

Clinical Professor, University of Texas Health Sciences Center, San Antonio

Journals Represented

Mosby and its editors survey approximately 500 journals for its abstract and commentary publications. From these journals, the editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

Acta Neurologica Scandinavica
Acta Oto-Laryngologica
Acta Radiologica
American J
American Journal of Human Genetics
American Journal of Neuroradiology
American Journal of Obstetrics and Gynecology
American Journal of Pathology
American Journal of Physical Medicine & Rehabilitation
American Journal of Respiratory and Critical Care Medicine
American Journal of Roentgenology
American Surgeon
Annals of Internal Medicine
Annals of Neurology
Annals Surgery
Archives of Neurology
Arcives of Ophthalmology
Archives of Physical Medicine and Rehabilitation
Brain
Canadian Medical Association Journal
Cancer
Cephalalgia
Chest
Clinical Endocrinology (Oxford)
Clinical Radiology
Critical Care Medicine
Developmental Medicine and Child Neurology
Epilepsia
Headache
Hypertension
International Journal of Epidemiology
Journal of Clinical Endocrinology and Metabolism
Journal of Clinical Investigation
Journal of Computer Assisted Tomography
Journal of Laryngology and Otology
Journal of Neurology, Neurosurgery and Psychiatry
Journal of Neurosurgery
Journal of Neurosurgery: Spine
Journal of Pain and Symptom Management
Journal of Pediatric Surgery
Journal of Pediatrics
Journal of the American Medical Association
Journal of the Neurological Sciences
Lancet
Multiple Sclerosis
Nature
Neurology

Neuroradiology
Neurosurgery
New England Journal of Medicine
Otolaryngology - Head and Neck Surgery
PACE - Pacing and Clinical Electrophysiology
Pediatric Infectious Disease Journal
Pediatric Neurology
Pediatric Research
Plastic and Reconstructive Surgery
Proceedings of the National Academy of Sciences
Psychological Medicine
Radiology
Regional Anesthesia and Pain Medicine
Science
Sleep
Spine
Stroke

STANDARD ABBREVIATIONS

The following terms are abbreviated in this edition: acquired immunodeficiency syndrome (AIDS), cardiopulmonary resuscitation (CPR), central nervous system (CNS), cerebrospinal fluid (CSF), computed tomography (CT), deoxyribonucleic acid (DNA), electrocardiography (ECG), health maintenance organization (HMO), human immunodeficiency virus (HIV), intensive care unit (ICU), intramuscular (IM), intravenous (IV), magnetic resonance (MR) imaging (MRI), ultrasound (US), and ribonucleic acid (RNA).

NOTE

The YEAR BOOK OF NEUROLOGY AND NEUROSURGERY is a literature survey service providing abstracts of articles published in the professional literature. Every effort is made to assure the accuracy of the information presented in these pages. Neither the editors nor the publisher of the YEAR BOOK OF NEUROLOGY AND NEUROSURGERY can be responsible for errors in the original materials. The editors' comments are their own opinions. Mention of specific products within this publication does not constitute endorsement.

To facilitate the use of the YEAR BOOK OF NEUROLOGY AND NEUROSURGERY as a reference tool, all illustrations and tables included in this publication are now identified as they appear in the original article. This change is meant to help the reader recognize that any illustration or table appearing in the YEAR BOOK OF NEUROLOGY AND NEUROSURGERY may be only one of many in the original article. For this reason, figure and table numbers will often appear to be out of sequence within the YEAR BOOK OF NEUROLOGY AND NEUROSURGERY.

Publisher's Preface

The publication of the 2001 YEAR BOOK series marks the 100th anniversary of the original Practical Medicine Series of Year Books. To commemorate this milestone, each 2001 Year Book includes an anniversary seal on the cover. The content and format of the Year Books remain unchanged from the beginning of the last century—each volume consists of abstracts of the best scholarly articles of the year, accompanied by expert critical commentaries.

The first Year Book appeared in 1900 when Gustavus P. Head, MD, produced the first *Year Book of the Nose, Throat and Ear*, a volume consisting of highlights from the previous year's best literature, enhanced by expert observations. Dr Head assembled a small group of distinguished physicians to serve as editors, and the first series of Year Books was published in 1901. The first volumes of the Year Book series—*General Medicine*, *General Surgery*, *The Eye*, *Gynecology*, *Obstetrics*, *Materia Medica and Therapeutics*, *Pediatrics*, *Physiology*, and *Skin and Venereal Diseases*—appeared at monthly intervals, with 10 volumes published in 1 year. The entire series was met with critical enthusiasm.

In 1904, Dr Head's brother, Cloyd, assumed responsibility for the management of the Year Books. In 1905, the volumes began to appear at regular intervals during the calendar year instead of on a monthly basis. By World War I, the Year Books had been established as an authority on medical and surgical progress.

The postwar period brought about a significant change in the practice of medicine: specialization. To accommodate the rise of specialization in medicine, the Year Books were now sold as individual volumes rather than only as a complete set. This change brought about a tremendous response and sales of the books increased. In 1922, the Year Books became even more specialized, as the books now had different editors for the different medical specialties covered in each volume. Later, in 1933, the title of the series changed from the Practical Medicine Series of Year Books to the Practical Medicine Year Books to reflect these new designs.

The Year Books have grown significantly from the first 10-volume series in 1901 to a diversified series of 32 volumes in 2001. That the Year Book series is the only series of their kind to have survived is a testament to the vision and commitment of its founders. Some minor changes in format and design have occurred throughout the years, but the mission of the Year Book series—to provide a record of exceptional medical achievements distinguished by the reflections of many of the great names in medicine today—has remained constant.

Table of Contents

ASSOCIATE EDITORS.	ix
JOURNALS REPRESENTED	xv
PUBLISHER'S PREFACE	xvii
NEUROLOGY	1
<i>Walter G. Bradley, DM, FRCP</i>	
<i>Ashok Verma, MD, DM</i>	
INTRODUCTION: HUMAN GENOME PROJECT, BRAIN RESEARCH, AND CLINICAL NEUROLOGY IN THE NEW MILLENNIUM	3
1. Cerebrovascular Disease	9
2. Neuromuscular Disease	35
3. Pediatric Neurology	65
4. Multiple Sclerosis	73
5. Alzheimer Disease and Dementia	89
6. Movement Disorders	99
7. HIV Infection and AIDS	111
8. Infectious Diseases of the Nervous System	117
9. Headache	123
10. Epilepsy and Seizure Disorders	135
11. Sleep Disorders	143
12. Neuro-otology	153
13. Neuroradiology	159
14. Neuro-ophthalmology	171
15. Neurogenetics	173
16. Neurorehabilitation	189
17. Neuro-oncology	197
18. Miscellaneous Conditions	199
NEUROSURGERY	213
<i>Scott R. Gibbs, MD, MA</i>	
INTRODUCTION: ENROLL IN THE VISION	215

A FEW JOURNALS REVISITED	217
19. Brain Tumors/Cysts	253
20. Cranial Operative Techniques	271
21. Head Trauma	299
22. Hydrocephalus	303
23. Neonatal/Pediatrics	309
24. Neuroimaging	319
25. Neurovascular	333
Arteriovenous Malformations	333
Carotid Occlusive Vascular Disease	339
Cerebral Aneurysms/Subarachnoid Hemorrhage	346
Intracranial Hemorrhage	362
26. Peripheral Nerve Surgery	367
27. Spinal Disorders	371
Cervical Spine	371
Thoracic Spine	387
Lumbar Spine	393
Spine Trauma	399
Spinal Surgical Technique	403
Miscellaneous Spine	405
28. Transsphenoidal Surgery	415
29. Trigeminal Neuralgia	421
30. Miscellaneous	427
SUBJECT INDEX.	439
AUTHOR INDEX	467

NEUROLOGY

WALTER G. BRADLEY, DM, FRCP

ASHOK VERMA, MD, DM

Introduction: Human Genome Project, Brain Research, and Clinical Neurology in the New Millennium

Medical history is replete with sagas of physicians and scientists who doggedly pursue dreams to understand and alleviate human suffering. In these pursuits, at some point between the first glimpse of true success and the final maturation of an important concept, many enthusiasts smile and a few skeptics frown. It is in this context that we stand today with regard to the human code of life. The first draft of the human genomic sequence has just been released. Now we must come to terms with what it means and how it is going to change the way we practice medicine in the 21st century. The question is: Is this the dawn of a new medical era, or are we still dreaming? Separating fact from fancy is central to this question.

In 1988, the history of biology was forever altered by the bold congressional decision to fund the greatest scientific effort in modern biology—one that would, in ultimate detail, decipher the complete human genetic code. On October 1, 1990, the Human Genome Project (HGP) officially began. Ten years later, the HGP is closing in on the goal with the release of the working draft ($\geq 90\%$ complete sequences), which holds some 80,000 human genes (the number of genes remains contentious) embedded in more than 3.2 billion nucleotides. The genetic alphabet alone would fill 200 telephone books if printed out, without annotations describing what those sequences do. Our current knowledge of tissue-specific gene expression tells us that at least 50% of these genes are expressed in the brain, and at least 25% may be specific to the nervous system. It is therefore not surprising that we, the neurologists, encounter the majority of the known human genetic diseases and, by analogy, will have major stakes in this new genomic science. Neuroscientists in general and neurologists in particular will have to be capable in this century of gleaning the useful genomic information and of transferring it to the clinical practice—to prevent and treat neurologic disorders. In this editorial, we overview the immensely useful offshoot of the HGP that we have witnessed along the way during the last 6 years. We consider how the dream will become reality in coming decades, and we conclude with the cautionary note of the skeptics.

The goals¹ of the HGP were “to complete a detailed human genetic map, determine the complete sequence, and find all genes.” It is wrong to assume that at its inception the major work of the HGP was devoted to large-scale sequencing. Large-scale genomic sequencing began only in 1998, since many other kinds of genomic information were needed before embarking on full-scale sequencing. In the first 8 years, HGP’s scientific goals mostly focused on technical development, genome mapping, and work to characterize the genomes of certain smaller animals. One particular map, known as the *human genetic map*, was particularly helpful for gene hunters even in the early stages. The genetic map consists of a series of sequence-based markers that can be used to pinpoint the likely neighborhood of an altered gene responsible for a disease or other trait. The goal was to establish markers close enough to give a gene researcher a high

likelihood of placing the gene in a reasonably bridgeable interval. By 1994, an international consortium of leading HGP researchers published a genetic map containing more than 6000 markers spaced less than 1 mb (million base) apart. By following the inheritance of a disorder through several generations of a family and by linking its cosegregation with a defined but anonymous genetic locus, the early researchers homed in on several highly penetrant gene mutations with mendelian inheritance patterns.

A second human genetic map, known as the *genomic physical map*, followed soon thereafter. The physical map provides cloned and ordered sets of contiguous DNA that represent regions of a chromosome, a complete chromosome, or the whole genome. Once genetic markers define the region containing the sought-after gene, cloned pieces from the physical map provide a resource from which investigators then can isolate the gene more efficiently. At the end of 1998, the HGP provided a physical map that contained more than 41,000 DNA markers, which are known as sequence tagged sites (STSs). When properly aligned, these pieces covered 98% of the human genome. With this density of DNA markers, most genes in the HGP at its inception had adopted a policy of releasing data every 24 hours to a free, publicly accessible database. In the United States, GeneBank (<http://www.ncbi.nlm.nih.gov>) has served as the public repository of sequence information. The value of this database as a resource for medical research around the world was incalculable. The research community all over the world benefited from this publicly funded effort almost on a daily basis. According to one account, the GeneBank website in mid 1990 was receiving more than 200,000 queries a day for information on gene sequences. Gene discovery by the positional cloning approach once took years to decades, yet an investigator using these powerful tools sometimes mapped and isolated the gene in a matter of weeks. We witnessed the discovery of gene after gene, both common and uncommon, literally every week. We also witnessed the commercial diagnostic laboratories stepping in to offer services at a cost, and we began using this valuable genetic information for accurate clinical diagnosis, informative patient counseling, and effective disease prevention.

During this early learning curve, we also recognized the complexity of allelic and locus heterogeneity in disease expression. Nosologic debates regarding several neurologic syndromes disappeared overnight and newer clinical concepts emerged. Words were replaced by numbers to describe certain hereditary neurologic diseases such as spinocerebellar ataxia and limb-girdle muscular dystrophy. Entirely unforeseen molecular mechanisms in disease expression were discovered. Friedreich ataxia, for example, turned out to result from the expansion of a triplet nucleotide (GAA) repeat in the noncoding region of the mitochondrial "frataxin" protein. Deficient frataxin protein in Friedreich ataxia is now linked to the mitochondrial iron loading and cellular toxicity. Expansion of the triplet nucleotide CAG repeats in several autosomal dominant ataxias leads to nuclear protein aggregates, which ultimately results in neuronal toxicity

and death. An entirely new field of nuclear and mitochondrial intergenomic communication and its many defects that result in mitochondrial diseases with mendelian inheritance is unfolding before us. Now we know how similar phenotypes of Leigh syndrome can be inherited in maternal lineage or in mendelian patterns. On the other hand, clinically different neurological syndromes—cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencephalopathy, familial hemiplegic migraine, and one form of episodic ataxia—can all result from mutations in the calcium channel gene. Miyoshi distal myopathy and one form of limb-girdle muscular dystrophy are both linked to the mutations in dysferlin gene. And there are many other examples. This all brought further questions and challenges, as well as more opportunities. But most important, we witnessed the way we practice neurology changing forever.

Now with the decoding of almost the entire human genome, we currently have some 80,000 or so gene sequences in the GeneBank database. It is important to realize that we do not yet know the precise number of functional genes in the sequenced genome. This perhaps is an example of the powerful molecular genetic tools and technology that leaves the gene hunters lagging behind. We currently know the function of approximately 3500 genes. Now will begin the hard work of recognizing all human genes and understanding human diseases at the most fundamental level. How much this will ultimately affect clinical medicine and neurology can only be speculated at this stage.^{1,2} But one obvious area will be the teasing out the genetic components of the so-called “polygenic” and “complex” disorders—hypertension, diabetes, epilepsy, migraine, autoimmune disease, and psychiatric disorders—that result from the interplay of a variable number of genes, as well as environmental factors, human behavior, and lifestyle.

The linkage analysis and positional cloning techniques were suited for discovering monogenic disease with high penetrance (ie, a stereotype disease phenotype). More powerful approaches are required to identify weakly penetrant alleles that contribute to the common polygenic or multifactorial disorders. One new powerful strategy could be mapping the genetic variation in human population to provide a density map of common DNA variants. DNA sequence variations include insertions and deletions of nucleotides, differences in the copy number of repeat sequences, and single-nucleotide polymorphisms (SNPs), which occur quite frequently throughout the human genome. About one in every few hundred bases in the human genome is a SNP. Most SNPs are located outside the protein-coding sequences, but those within coding sequences, known as cSNPs, are of particular interest because they are more likely to affect protein function. One might have surmised that such studies would be of use only in nuclear families or in inbred small ethnic clusters. But this is clearly not the case. SNPs can be used as markers in genome-wide linkage analysis of families, small and large ethnic groups, and in large populations with affected members. Because the human species consists of relatively few generations, recombinations have not disrupted linkage disequilibrium over distances of 3 to 100 kb in most populations. Consequently,

association studies of large human populations for certain disease-associated polygene mapping can be informative. The scope of such research may extend to determine the genetic component even in apparently sporadic disease. For example, more than 90% of amyotrophic lateral sclerosis is nonfamilial. Why rare individuals in all populations and more people in endemic areas like Guam exposed to seemingly identical and different environments, respectively, have ALS develop may be in part due to the interaction of individuals' genotype traits.

In our lifetime, we can expect the transition from genetics to individual genomics. This means that we will be able to identify the individual's genetic variation and its effect on the individual's biological function. The so-called "DNA chip" currently provides a promising approach for a genome-wide search of genetic variations, for the detection of heterogeneous gene mutations, as well as for a gene expression profile.³ The adaptation of dot-blot hybridization on DNA chips, also called microarrays, generally consists of a thin slice of glass or silicone about the size of a postage stamp on which threads of synthetic nucleic acids are arrayed. Sample probes are added to the chip, and the matches are read by an electronic scanner. The microarray chips that can hold thousands of arrays have now been developed. Microarray technology is currently in use to study developmentally expressed genes, genomic comparisons across animal species, genetic recombination, large-scale analysis of gene copy numbers and their transcription profile, as well as protein expression in cells. Microarray technology is being used in clinical practice to detect the oncogene mutations in cancer patients, human immunodeficiency virus sequence variation in AIDS cases, and the expression of cytochrome P-450 genes in patients with potential adverse drug reactions.

The ability to rapidly survey and compare gene expression levels between reference and test samples is moving the drug discovery process toward a more genomic orientation. The microarray technology is currently exploiting collections of known sequences to pinpoint drug effects. Novel disease genes and their expression profile may suggest new targets for drug design. Even if such targets are identified through studies in a subset of patients with a strong inherited tendency to have a given disease develop, new treatments are likely to be discovered. For example, an understanding of the regulation of the receptor for low density lipoproteins that came from genetic studies in familial hypercholesterolemia led to the development of *HMG-CoA* reductase inhibitors (statins), which are now a mainstay for the prevention and treatment of hypercholesterolemia, atherosclerosis, coronary artery disease, and stroke.

The identification of the human genetic variation should eventually allow clinicians to subclassify neurologic diseases and devise therapy best suited to the individual patient. There may be large differences in effectiveness, as well as in toxicity, of medication from one person to the next. This basic concept has spawned the burgeoning new field of *pharmacogenomics*, which attempts to use genetic information to predict response to drug therapies. The scope of human pharmacogenomics ranges from iden-