

面向21世纪高等医药院校精品课程教材

浙江省高等教育重点建设教材

ESSENTIALS OF INTERNAL MEDICINE

简明内科学

(英文版)

主 编 薛树仁 Xue Shuren

副主编 李荣山 Li Rongshan



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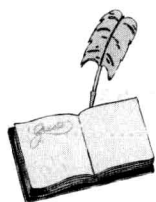
前 言

在医学双语教学中,如何在繁重的专业课与英语教学之间取得平衡,是很值得探讨的一个问题。其中,首要的是必须明确,双语教学是用英语学习专业知识而并非是学习英语,语言学习不能脱离专业知识而独立存在。双语教学的主要目的不是学习语言,而是以外语为工具进行知识技能、思维方法的训练。

原版国外教材共同的特点是内容先进且广泛,注重多学科融合,提供多个观察视角和对问题的共同处理方法;但是与国内教材相比,国外教材篇幅太长。在单一汉语语言环境中学习大部头的外文原版教材对本科学生而言是很困难的。多数学生的外语运用水平还不高,提高外语应用能力是学生在双语课程中客观上首先面对的任务。

为了配合国内医药院校开展双语教学和留学生教学,我们在做了充分的调研之后设计了双语教材的编写思路,即参考引进国外优秀教材,邀请教学一线教师,编写既适合国内教学实际,又吸收原版特色的内科学教材。本书保留内科学的精华部分,还增加了当前人们普遍关注的内科学新理论、新技术、新观念、新进展。本书内容和编排符合国内教学实际,适合双语教学,是医学生及临床医生用于掌握内科专业知识及提高专业英语的必读教材。

编 者



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SECTION I

Introduction to Molecular Medicine

1 Changes to Medical Practice in the Age of Genomics

Xue Shuren

1 **Changes to Medical Practice in the Age of Genomics**

Given the great effort needed to define allelic variants contributing to complex disease, it is reasonable to ask whether such a large investment of resources is warranted. To be able to answer in the affirmative, it is necessary to demonstrate that benefits will accrue to everyday medical practice and patient health. Understanding genetic factors that contribute to disease could help establish a more rational basis for many aspects of patient care by providing deep insights into molecular pathogenesis and through improved molecular diagnostic tools that allow individually tailored preventive and/or therapeutic regimens.

Better Understanding of Molecular Mechanisms of Disease

Despite the extraordinary advances in our understanding of the functions of cells and organ systems in states of health and disease, it is somewhat humbling that fewer than 5000 human genes have been functionally characterized—many in only a cursory fashion. Clearly, it is difficult to provide full descriptions of the ways in which disease processes perturb cellular function in the absence of a comprehensive catalogue of genes that are either affected by these disease processes or are involved in the response to disease. The Human Genome Project provide such a catalogue, giving a complete description of the DNA and protein sequences of all of these genes.

The genome project is providing important tools that will help researchers discover functions of novel proteins. About half of the new genes identified by large-scale DNA sequencing bear some resemblance to other genes that have previously been studied, either in humans or in model organisms. Sequence similarity to previously characterized genes can provide important clues to protein function. In addition to comparisons of primary DNA and protein sequences, computerized approaches to predicting three-dimensional protein structures are becoming increasingly feasible, and may also allow generation of testable predictions about gene function.

Of course, many novel genes do not have any (or enough) similarity to known genes for useful predictions to be made, and direct experimental investigation may be required to determine their function. To deal with the large number of new genes that are being identified by the Human Genome Project, an innovative set of methods has emerged, known collectively as functional genomics, which explore the roles of many genes in parallel. Functional genomics experiments will obtain a great deal of information about patterns of gene expression, protein interactions, and metabolic pathways.

Diagnostic Tests

One advance in genomics that is already finding its way into clinical practice is the use of diagnostic tests based on DNA sequence changes. Such tests can be used for several purposes. As with

more conventional tests, genetic tests can confirm a specific diagnosis or contribute to the evaluation of problematic differential diagnoses. Presymptomatic diagnostic testing can also be performed in subjects without disease. However, even in the case of high penetrance mutations, such as those found in Huntington's disease, it may be difficult to predict the time at which clinical signs or symptoms will develop. In some cases, measures may be available that will prevent or ameliorate the onset or course of illness. Examples of such conditions include haemochromatosis, in which regular venesection can prevent the sequelae of iron overload, or hereditary non-polyposis colon cancer, in which case colonoscopic removal of premalignant lesions can help to prevent the development of cancer. In the absence of such effective interventions, especially careful consideration must be given to the circumstances in which predictive genetic testing is performed. Some patients find presymptomatic genetic diagnosis helpful because it gives them the opportunity to make long-term plans which include the likelihood (or not) of developing illness. Others prefer "not to know" and would rather forego testing unless an intervention is available. In many centres, teams that include qualified genetic counsellors are in place to ensure that patients receive appropriate education and non-directive counselling before and after making decisions about whether to undergo testing for serious illnesses.

An important way that DNA testing can differ from conventional diagnostic investigations is in its implications for relatives of the tested proband. A positive (or negative) result may allow one to infer the genotype of individuals other than the proband.

To date, most conditions being investigated with DNA-based tests are relatively uncommon, single-gene disorders, and the tests are usually carried out in specialized centres with considerable experience in their execution and interpretation. As the technologies needed to perform these tests become more widely available and the sequence changes being evaluated more frequent, attention will be needed to ensure that procedures relating to DNA-based diagnostics continue to be carefully executed. Such concerns include issues related to quality control, skills in the interpretation of complex test results, provision of adequate genetic counselling, and other matters such as control of record-keeping systems to ensure genetic privacy. As the use of predictive genetic testing becomes more widespread, the associated obligations will fall to an increasingly diverse range of health-care professionals and it is important that they receive adequate training in this area.

Pharmacogenomics

Although not generally thought of in the same way as DNA variations that predispose to complex disease, germ-line sequence changes can also be important determinants of response to pharmacological treatment. The study of DNA sequence polymorphisms affecting metabolism of, and response to, drugs has become known as pharmacogenomics. It has long been recognized that individuals metabolize pharmacological agents at different rates. A substantial proportion of this variation can be due to genetic effects. A classic example of this phenomenon was described well before the modern era of molecular genetics and genomics, with the division of the population into slow and rapid acetylators groups. Approximately 60 percent of Caucasians, but only 5 to 10 percent of Asians, show reduced rates of N-acetylation and elimination of a number of drugs, including isoniazid, hydralazine, and caffeine, compared with the remainder of the population who exhibit comparatively rapid N-acetylation. Although initially characterized by standard biochemical tests, the genotypic bases for these metabolic differences in drug metabolism are now known to be several polymorphic variants in the gene N-acetyl-transferase-2 or NAT2.

In addition to showing different rates of metabolism and clearance of drugs from the system,

subjects are often found to show variable therapeutic responses to these agents. In some cases, this may be due to subtle changes in the structure of drug targets between subjects. In diseases such as essential hypertension that are treated symptomatically, rather than with specific measures, some patients respond better to certain interventions than to others. If the genetic factors that are responsible for different forms of hypertension could be identified, then it might prove possible to tailor treatment regimens specifically directed towards generating responses in the physiological pathways that are perturbed in particular patients. For instance we might be able to predict that a particular patient would be more likely to respond to the antihypertensive effects of β -blockers than ACE inhibitors. We may then be able to use relatively inexpensive, one-time DNA tests, to determine which drugs can be used safely and efficaciously in patients with chronic illness. Such approaches promise to be more effective than the trial and error processes that are now often needed to discover optimal drug treatment regimens.

Development of Therapeutic Agents

In parallel with the government-funded human genome project, much effort has been expended in the private sector to identify and sequence novel genes. A large part of the motivation behind these efforts is the expectation that new therapeutic agents and targets will be discovered. The distinction between therapeutic agents and targets is one that has important implications for the development strategies that must be used. Therapeutic agents developed from genomic sequence information are usually secreted proteins or hormones that can be made for direct in vivo administration. A prime example is the use of recombinant erythropoietin for the treatment of anaemia in chronic renal failure. On the other hand, therapeutic targets can potentially be any proteins that are involved in a disease process or a compensatory response to disease. Once such a target is identified, further effort is needed to develop agents (usually small molecules) that can affect function of the target. Although it remains difficult to predict the three dimensional structure of novel proteins based on amino acid sequence alone, improvements in computational analysis, X-ray crystallography, and nuclear magnetic resonance studies are making it possible to produce increasingly sophisticated models of the active sites of target proteins. Using principles of rational drug design, it will become a more straight forward and less expensive matter to develop new drugs for particular diseases than using the trial-and-error methods that were relied upon in the past. The use of genomic sequence information in identifying targets for drug development is also advancing rapidly in the field of new antibiotic discovery. The genomes of several important microbial pathogens including *H. influenzae*, *S. aureus*, *M. tuberculosis*, and *T. pallidum* have been completely sequenced. Newly identified proteins that are important for bacterial replication or virulence but that do not have close relatives in mammalian cells may provide excellent drug or vaccine targets.

Another exciting possibility that arises from an understanding of the genomic sequence of disease genes is the possibility that the expression of particular proteins might be able to be modulated by developing small molecules that interact specifically with promoter and enhancer elements of the genes coding for these proteins. Considerable advances have been made in both the understanding of factors that influence sequence-specific DNA-binding and the ways in which gene expression are controlled, and it is likely that this knowledge will be used to help develop drugs that can up- or down-regulate gene expression in useful ways for disease treatment or prevention.

Gene Therapy

Though they have been slow to come to fruition, the concepts underlying somatic cell gene

therapy predate the inception of the Human Genome Project. Initial plans to induce expression of normal proteins in patients with rare genetic defects, such as adenosine deaminase deficiency, have been broadened to include a range of more common diseases such as cancer, atherosclerosis, and AIDS. Achieving clinical benefits from gene therapy has proven to be problematic because of technical difficulties preventing sufficiently high-level expression of recombinant proteins in appropriate tissues. Substantial effort is now being directed to the development of viral and other vectors that will allow more effective delivery of introduced genes to the desired sites. A full discussion of gene therapies is beyond the scope of this chapter; but clearly, as our understanding of the human other genomes increases, the range of conditions that are amenable to treatment by various forms of somatic genetic manipulation will also increase.



SECTION II

Decision-making in Clinical Medicine

2 Evidence-based Medicine

Xue Shuren

2 Evidence-based Medicine

To the medical student who requires 2 h to collect a patient's history and perform a physical examination, and several additional hours to organize them into a coherent presentation, the experienced clinician's ability to reach a diagnosis and decide on a management plan in a fraction of the time seems extraordinary. While medical knowledge and experience play a significant role in the senior clinician's ability to arrive at a differential diagnosis and plan quickly, much of the process involves skill in clinical decision-making.

The most important clinical actions are not procedures or prescriptions but the judgments from which all other aspects of clinical medicine flow. In the modern era of large randomized trials, it is easy to overlook the importance of this elusive mental activity and focus instead on the algorithmic practice guidelines constructed to improve care. Today's experienced clinician needs close to 2 million pieces of information to practice medicine. Doctors subscribe to an average of 7 journals, representing over 2500 new articles each year. Computers offer the obvious solution both for management of information and for better quantitation and management of the daily uncertainties of medical care.

Major Influences on Clinical Decision-making

One of the key roles of the physician in medical care is to serve as the patient's agent to ensure that necessary care is provided at a high level of quality. Factors that influence this role include the physician's knowledge, training, and experience. As would be expected, invasive cardiologists are much more likely to refer chest pain patients for diagnostic catheterization than are noninvasive cardiologists or generalists. The physician beliefs that drive these different practice styles are based on personal experience, recollection, and interpretation of the available medical evidence. For example, heart failure specialists are much more likely than generalists to achieve target angiotensin-converting enzyme (ACE) inhibitor therapy in their heart failure patients because they are more familiar with what the targets are (as defined by large clinical trials), have more familiarity with the specific drugs (including dosages and side effects), and are less likely to overreact to foreseeable problems in therapy such as a rise in creatinine levels or symptomatic hypotension. When conducting rounds with clinical pharmacists, physicians are less likely to make medication errors and more likely to use target levels of evidence-based therapies.

The patient's welfare is not the only concern that drives clinical decisions. For example, a 30-year-old woman who presents with a long-standing history of intermittent headache and a new severe headache along with a normal neurologic examination has a very low likelihood of structural intracranial pathology. Performance of a head CT or magnetic resonance imaging (MRI) scan in this situation would constitute defensive medicine. On the other hand, the results of the test could provide reassurance to an anxious patient. Over the past 30 years, many attempts have been made to develop

computer systems to help clinicians make decisions and manage patients. Conceptually, computers offer a very attractive way to handle the vast information load that today's physicians face. In this era of evidence-based medicine, it is tempting to think that all the difficult decisions practitioners face have been or soon will be solved and digested into practice guidelines and computerized reminders. For the foreseeable future, however, such is not the case. Meta-analyses cannot generate evidence where there are no adequate randomized trials, and most of what clinicians face will never be thoroughly tested in a randomized trial. Excellent clinical reasoning skills and experience supplemented by well-designed quantitative tools and a keen appreciation for individual patient preferences will continue to be of paramount importance in the professional life of medical practitioners for years to come.

Advantages and Disadvantages of the New Approach

Evidence-based medicine can be viewed as a novel form of clinical practice, as a special compendium of approved information, or as a revolutionary change in medical education. In the original proposal for evidence-based medicine, a clinical analysis was divided into four main steps. Each step, as discussed in the next four sections, has its own distinctive advantages and disadvantages when conducted with the current evidence-based medicine compendium.

Formulating a Question to Be Answered

The obvious first step in any process of clinical reasoning is to choose a "prime topic" as the question to be answered. This topic is the doctor's counterpart of the patient's chief complaint. Nevertheless, just as the chief complaint may not always indicate what a patient really wants and expects, the prime topic may not always represent, and may sometimes misrepresent, what is needed for the care of the patient. To be answerable, the chosen question may have to be altered to suit the available data. Thus, the desire to learn about post-therapeutic outcomes, such as relief of symptoms and quality of life, may be diverted to an answer that indicates outcomes such as survival duration and changes in laboratory tests.

A greater, but less apparent, problem is the occasional or frequent mismatch between the available evidence and the nuances of the individual clinical situation. Most published reports of treatment, whether observational studies or randomized trials, will contain results for a stipulated therapy given to patients with a stipulated baseline clinical condition. The stipulations, however, may not include important details—such as concomitant therapy, comorbidity, severity of illness, and functional status—that distinguish the particular patient for whom the question is being asked. The general answer, reflecting results for the larger total group of patients who were treated for the condition, may not be pertinent for the patient's individual distinctions.

This problem is heightened when the evidence comes solely from randomized trials. Designed to answer questions of general efficacy rather than to guide individual treatment, the trials often contain a highly selected group of patients, treated with a relatively rigid therapeutic protocol. Furthermore, with the currently popular intention-to-treat analytic principle, the results of the trials are appraised without regard to whether or how well the patients actually maintained (or even received) the randomly assigned treatment. The results of each trial thus indicate what happens to an "average" patient assigned to the treatment; and the meta-analyses produce an average of the averages. The average results may be satisfactory for the decisions made by economists, health-plan managers, regulatory agencies, and pharmaceutical companies; but averages are often grossly unsatisfactory for