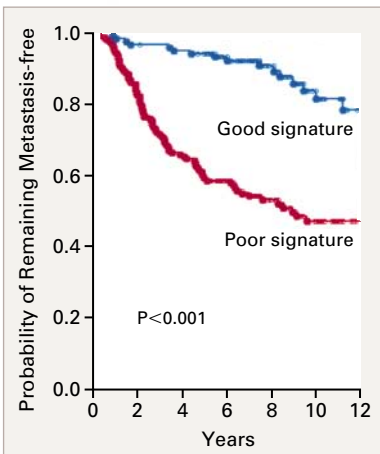




# This Week in the Journal

December 19, 2002

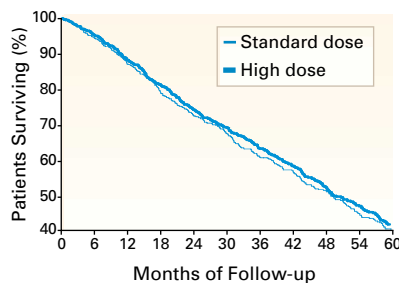


## Gene-Expression Signature as a Predictor of Survival in Breast Cancer

The patterns of expression of 70 genes in almost 300 breast-cancer specimens revealed two genetic signatures: one correlated with a good prognosis, and the other with a poor prognosis, as judged on the basis of overall survival and the development of distant metastases. These signatures correlated with outcome independently of the involvement of axillary lymph nodes and standard clinical and pathological prognostic indicators.

*This work represents a considerable advance in the clinical application of microarray technology. The finding that the genetic signature of a breast cancer correlates with outcome independently of the presence or absence of lymph-node involvement has important biologic and clinical implications.*

see page 1999 (Perspective, page 1995; editorial, page 2067)



## Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis

Both the amount of dialysis and the size of the molecules removed may influence morbidity and mortality among patients receiving long-term hemodialysis. The multicenter Hemodialysis Study randomly assigned 1846 patients, according to a two-by-two factorial design, either to the standard dialysis dose currently recommended in the United States or to a high dialysis dose, with either a high-flux or a low-flux dialyzer. Neither mortality from any cause nor morbidity differed between the groups during a mean follow-up of 2.84 years.

*These data suggest no major benefit from increasing the prescribed minimal dialysis dose from that in current U.S. guidelines or from switching from low-flux to high-flux dialysis membranes.*

see page 2010 (editorial, page 2068)

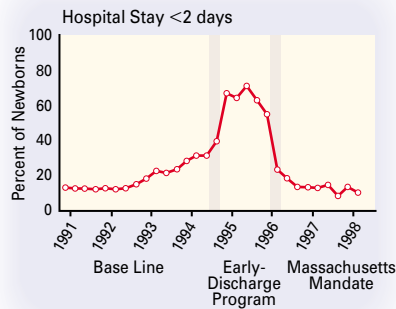
*“Inclusion in the study required evidence of proven invasive candidiasis.”*

## A New Agent for the Treatment of Invasive Candidiasis

Caspofungin is a new echinocandin drug that has activity against the cell wall of candida species. This double-blind trial evaluated whether caspofungin is as effective as amphotericin B, which has substantial toxicity. Among 224 patients with invasive candidiasis, the outcomes were successful in 73.4 percent of those treated with caspofungin and in 61.7 percent of those treated with amphotericin B. The frequency of nephrotoxic effects was lower with caspofungin than with amphotericin B.

*Caspofungin appears to be at least as effective as amphotericin B, and it has considerably less toxicity. Few of the patients in this trial had neutropenia, so further evaluation of caspofungin therapy in this high-risk group will be required.*

see page 2020 (editorial, page 2070)



### Special Article: Effects of a Law against Early Postpartum Discharge

Examinations of newborns three or four days after birth occurred less frequently after a Massachusetts law requiring two-day postpartum hospitalizations eliminated the early-discharge program at a health maintenance organization (HMO), which had provided one postpartum night and one home visit. However, the HMO and state policies had little effect on the health outcomes of newborns or on HMO expenditures.

*Shorter hospital stays were not associated with adverse outcomes for newborns. Because hospitals' prices changed, the changes in hospital use had little effect on HMO expenditures.*

**see page 2031**



### Clinical Practice: Community-Acquired Pneumonia

A 65-year old man with hypertension and degenerative joint disease presents to the emergency department with a three-day history of a productive cough and fever. His temperature is 38.3°C (101°F), his blood pressure is 144/92 mm Hg, his respiratory rate is 22 breaths per minute, his heart rate is 90 beats per minute, and his oxygen saturation is 92 percent while he is breathing room air. Physical examination reveals only crackles and egophony in the right lower lung field. The white-cell count is 14,000 per cubic millimeter, and routine chemical tests are normal. A chest radiograph shows an infiltrate in the right lower lobe. How should this patient be treated?

**see page 2039**

### Drug Therapy: Herbal Remedies

*“Most herbal products in the United States are not regulated as medicines.”*

Conservative estimates suggest that at least 12 percent of the U.S. population uses herbal medicines, and the number is increasing, yet these products are not regulated by the Food and Drug Administration. This review considers the evidence on the safety and efficacy of herbal medicines, focusing on four — *Ginkgo biloba*, hawthorn, saw palmetto, and St. John’s wort — that have been evaluated in a sufficient number of randomized, controlled trials to permit an assessment.

*Controlled data that support or refute the use of herbal medications remain limited, at best. More research is required to support the claims currently being made.*

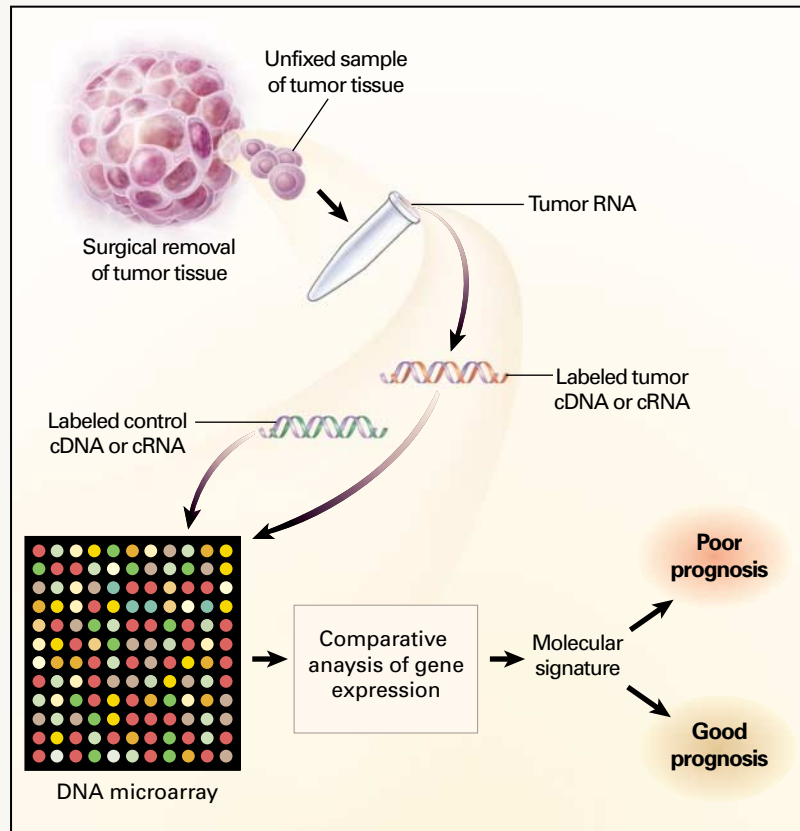
**see page 2046 (Perspective, page 1997; Sounding Board, page 2073)**

## PERSPECTIVE

## Predictive Molecular Pathology

The search for markers that can predict the outcome in an individual patient with cancer or the response of an individual tumor to specific therapies is a major focus of cancer research. Despite these efforts, estrogen and progesterone receptors and the *HER2/neu* gene are the only molecular targets that are analyzed routinely in newly diagnosed breast cancers. Thousands of studies of putative prognostic or predictive markers have failed to identify useful molecular markers in tumors, either because the selected genes were noninformative or because initially promising data could not be reproduced in other laboratories.

The search for prognostic and predictive markers may soon become much more successful. The Human Genome Project has revealed detailed information about the structure of all human genes. On the basis of this knowledge, powerful new high-performance screening techniques have been developed for molecular analysis. One of these new methods is the DNA microarray, used in the study reported by van de Vijver et al. in this issue of the *Journal* (pages 1999–2009). DNA microarrays allow simultaneous analysis of the expression of tens of thousands of genes in a tissue in a single experiment. Microarrays are small glass plates or nylon membranes to which specific sequences of thousands of genes adhere. Two different kinds of target DNA sequences are widely used: complementary DNA (cDNA) sequences prepared by reverse tran-



### Gene-Expression Profiling.

Unfixed samples of tumor tissue obtained during surgery are the starting material for gene-expression profiling. The expression levels of a set of prognostically relevant genes are determined by DNA-microarray analysis. The resulting molecular signatures allow the patients to be classified into groups with a poor prognosis or a good prognosis, thus facilitating therapeutic decision making.

scription of the full-length messenger RNA sequences corresponding to the target genes, or oligonucleotide sequences representing small but highly specific segments of the target genes. Both types of DNA microarrays are widely available from commercial vendors but are also manufactured in many research laboratories. As probes, complementary DNA or complementary RNA (cRNA) prepared from RNA derived from tumor tissue and the appropriate control tissue are used. Simultaneous hybridization of the

tumor-derived probes and the control probes, which are labeled with different fluorescence dyes, results in differential staining of each gene spot. For each gene, the relative intensity of the different colors reflects its RNA expression level.

In principle, there are two ways of using data from a DNA microarray. First, one can systematically search for single genes that may be related to the prognosis or that may be useful as therapeutic targets. This approach is limited by the variable suitability of DNA sequences for

precise measurement on a DNA microarray. The second approach is to use the entire set of expressed genes to classify tumors — that is, to use the microarray to derive gene-expression profiles. Powerful statistical methods have been developed to classify tumors on the basis of similarity in expression profiles (see Figure). This approach, used by van de Vijver and coworkers, is technically much more robust than analysis of individual genes. Imprecise analysis of a few hundred genes within a set of 25,000 is unlikely to affect the outcome of cluster analysis.

What can be expected from a study of the expression of 25,000 genes in each of 295 women with breast cancer for whom information about clinical outcome is available? A lot. It is generally believed that the malfunctioning of specific genes drives the development and progression of neoplastic disease. Indeed, the study by van de Vijver et al. showed dramatic differences in survival between patients whose tumors had previously established “good” and “poor” gene-expression profiles. The DNA-microarray data predicted prognosis much better than such classic prognostic indicators as grade, stage, and nodal status in a multivariate analysis. Intriguingly, the set of genes that dis-

tinguished the good-prognosis and poor-prognosis groups consisted of only 70 genes. The majority of genes do not obviously affect the clinical course of breast cancer. The small number of genes for which the RNA expression level is prognostically relevant raises strong hope that a robust, affordable, commercially available testing system could soon emerge.

The data reported by van de Vijver et al. are fascinating in themselves. However, this study is just one example of how gene-expression profiling can provide highly useful prognostic information. It is almost certain that analogous studies will yield similar results for virtually all other types of tumors. Moreover, we can anticipate that simultaneous expression analysis of the majority of human genes will identify molecular profiles that are linked to the response to treatment.

It is likely that gene-expression profiling will increasingly be used for clinical decision making. For this purpose, adequate reporting of DNA-microarray data to clinicians will be necessary. Such reports are not likely to include expression data on thousands of genes; rather, they will probably be limited to a simple tumor classification, such as “RNA high risk” or “RNA low risk.” Even though a fraction of

cases will be difficult to classify, gene-expression profiles may be more reproducible than well-established but highly subjective variables, such as the histologic grade.

The major obstacle for broad application of gene-expression profiling and other new techniques will be the requirement of fresh tumor tissue for the analysis. Today, morphologic and molecular analysis is based almost entirely on formalin-fixed tissues in diagnostic laboratories. Formalin fixation is an established, inexpensive method of tissue handling in universal use. However, fresh tissue is highly preferable for DNA-microarray analysis, and its use may become mandatory in future assays to allow investigation of the status of drug targets. A global change in the handling of tumor tissue is desperately needed and will be the principal challenge for the emerging field of predictive molecular pathology. Substantial resources are needed to adjust the logistics of diagnostic pathology to the requirements of the new millennium.

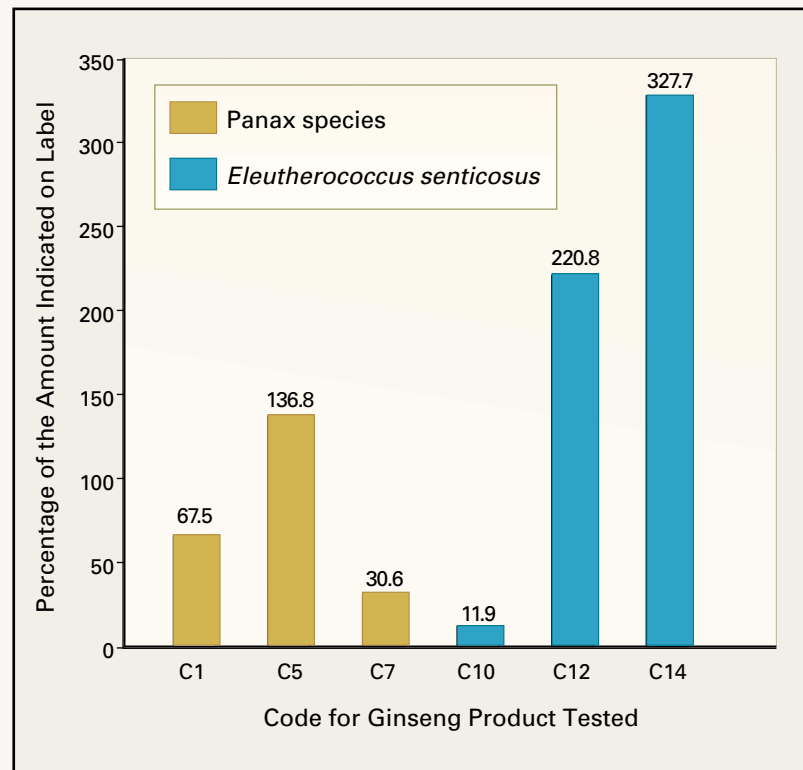
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## PERSPECTIVE

Herbal Medicines —  
What's in the Bottle?

We are in the midst of a public health experiment that much of academic medicine has failed to acknowledge until recently. In spite of the greatest health and longevity in history in the United States and Europe, millions are turning back to traditional herbal medicines in order to prevent or treat a host of illnesses. Thus, the review by De Smet (pages 2046–2056) and the accompanying Sounding Board article by Marcus and Grollman (pages 2073–2076) in this issue of the *Journal* are very timely. Both articles identify serious problems with the overall quality, safety, and efficacy of herbal products. In the United States, herbal products are regulated as dietary supplements and are therefore not subject to most of the requirements that proprietary drugs must meet before they can enter the marketplace. With herbal medicines, what is on the label may not be what is in the bottle (see Figure). Just because an herb is natural does not mean that it is safe, and claims of remarkable healing powers are rarely supported by evidence.

Herbal medicines are but one component of complementary and alternative medicine, which includes acupuncture, chiropractic manipulation, meditation, homeopathy, and other approaches. The Centers for Disease Control and Prevention reported that 29 percent of adults used complementary and alternative medicine in 1999, with 10 percent ingesting herbal medicines. Women, people with higher levels



Variation in the Amounts of Active Ginsenosides (Panax Species) and Eleutherosides (*Eleutherococcus senticosus*) in Ginseng Products in Relation to the Amounts Indicated on Their Labels.

Adapted from Harkey et al. (*Am J Clin Nutr* 2001;73:1101-6), with the permission of the publisher.

of education and income, and patients with chronic illnesses turn to complementary and alternative medicine most often. Its proponents explain that conventional treatments have intolerable side effects and are delivered too impersonally. Patients seek what the practitioners of complementary and alternative medicine espouse — time, talk, touch, and optimism.

Among the complementary and alternative approaches, herbal medicines present unique challenges that are thoroughly addressed by De Smet and by Marcus and Grollman and that are dramatically illustrated by the case of herbal product PC-

SPES. Until recently, thousands of American men with advanced prostate cancer were using this mixture of eight herbs formulated according to principles of traditional Chinese medicine. Preliminary studies suggested that PC-SPES lowered prostate-specific antigen levels but often at the cost of breast tenderness and loss of libido; these were side effects that many patients considered acceptable. In early February 2002, however, the California Department of Health Services reported that PC-SPES is contaminated with diethylstilbestrol and warfarin. The product was withdrawn from stores, the manufactur-

er ceased operations, and patients were enticed by similar herbal “cocktails” that were marketed promptly by other companies.

What have been the reactions to reports that some herbal medicines are contaminated or toxic or that they interfere with the metabolism of drugs used to treat cancer or AIDS? Understandably, the enthusiasm of consumers for these “natural” cures has been tempered by increasing skepticism, and sales of herbal products in the United States have actually declined during the past two years. The public now seeks more authoritative sources of information, and credible compendiums and data on Web sites are available. We physicians, in turn, ask patients more often about their use of herbal products, and we are less judgmental toward patients who use them. An open dialogue results in better information so that consumers can choose products according to the existing evidence, such as it is, as to which herbal products appear to be least harmful and most helpful.

Despite their many challenges, herbal medicines also afford clinical and research opportunities that

should not be neglected when greater regulation of these products is considered, as Marcus and Grollman recommend. Certainly, the recent discovery in Chinese herbs of artemisinins as a new class of antimalarial drugs indicates that we have not yet surveyed all of nature for its healing potential. However, both the quality of the data and the quality of the herbal products themselves must improve greatly if herbal medicines are to assume a respected place in the contemporary health care armamentarium. The National Center for Complementary and Alternative Medicine at the National Institutes of Health is charged with investigating herbal medicines and other complementary and alternative approaches by promoting rigorous studies of their mechanisms of action, pharmacology, and clinical outcomes; recruiting and training scientists to undertake such work; and disseminating research findings. Most of our funding supports preclinical and early-phase trials, but on the basis of existing data, a few products such as *Ginkgo biloba* and St. John’s wort have been deemed ready for multicenter investigations.

Mounting these studies has not proved to be straightforward. Because commercial sources of herbs often lack careful characterization, we have had to contract for research-grade products. For example, with the National Institute of Diabetes and Digestive and Kidney Diseases, we have contracted for extracts of saw palmetto and African plum to be used in randomized, placebo-controlled trials for the treatment of benign prostatic hyperplasia.

The National Center for Complementary and Alternative Medicine was created to foster and build a research enterprise that subjects complementary and alternative medicine to open-minded, hypothesis-driven investigation. Although some people believe that any such undertaking is a pointless exercise, most have been resoundingly supportive of the center’s efforts.

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