reversible hypothyroidism? If the hypothyroid state is expected to last only a few weeks or months and if it is not severe (as is usually the case), no treatment is necessary. Alternatively, a small dose of thyroxine — for example, 50 μg daily — can be given. This dose should ameliorate most symptoms of hypothyroidism but not decrease thyrotropin secretion to normal in a patient with severe hypothyroidism. If the patient's serum thyrotropin concentration does decrease to a normal level, there has been at least partial recovery, and the thyroxine therapy can be discontinued.

The situation with regard to hypothyroidism in patients with chronic autoimmune thyroiditis is different. Since their hypothyroidism is chronic, if not permanent, adequate thyroxine-replacement therapy should be given. The routine withdrawal of therapy after some interval — two or five years, for example — is not warranted.

How can the need for thyroxine therapy be assessed for patients or their physicians who want to know whether hypothyroidism persists? As documented by Takasu et al., repeated measurements of thyrotropin-inhibitory antibodies are not a reliable guide, because their disappearance is not necessarily accompanied by the disappearance of hypothyroidism. Alternatively, patients can be tested with thyrotropin or thyrotropin-releasing hormone. Those who have an increase in serum thyroxine and triiodothyronine concentrations can be presumed to have normal thyroid function and therefore should remain euthyroid after therapy is discontinued. These tests, however, are cumbersome and not well standardized. The simpler alternative is to reduce or discontinue thyroxine therapy. It is usually possible to get a clear answer in four weeks,[9] with little risk to the patient, because severe symptomatic hypothyroidism is not likely to develop in this short interval. Perhaps we will eventually learn how to predict which patients are likely to have remissions, and even how to promote remission, but until then withdrawing therapy is the only practical option.

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PROGRESS AGAINST RARE AND NOT-SO-RARE CANCERS

THE use of chemotherapy has resulted in substantial progress in the treatment of certain uncommon cancers, such as childhood leukemia, testicular cancer, and the lymphomas, whereas the more common epithelial tumors of adults have in general proved far more resistant. Only as an adjuvant to surgery has chemotherapy improved the outlook for patients with breast, colon, or rectal cancer. This pattern of dramatic progress against the rarer tumors and more modest gains against common tumors in early stages continues. Two new agents, deoxycoformycin[1] and 2-chlorodeoxyadenosine,[2] are highly effective in patients with hairy-cell leukemia. Another antimetabolite, fludarabine, has clear clinical benefit in patients with chronic lymphocytic leukemia refractory to alkylating agents.[3] Tretinoin (all-*trans*-retinoic acid), a derivative of vitamin A, induces complete remissions in nearly all patients with acute promyelocytic leukemia,[4] which accounts for 10 percent of cases of nonlymphocytic leukemia in adults. These new treatments exploit unique susceptibilities of particular tumors. In hairy-cell leukemia, for example, the neoplastic lymphocytes seem highly sensitive to drugs that disturb the balance of adenosine metabolism, and in acute promyelocytic leukemia, possibly because of an underlying genetic translocation involving the receptor for retinoic acid, the cells are exceedingly sensitive to the "differentiating" activity of a retinoid. With respect to the more common solid tumors, there is empirical evidence that recurrence rates are reduced by a third and survival is improved in patients with node-positive colorectal cancer[5] or breast cancer[6] who receive postoperative chemotherapy. However, in patients with disseminated forms of the common epithelial tumors, both complete remissions and cures continue to elude us.

In this issue of the *Journal*, two interesting reports show that this trend continues.[7,8] Islet-cell carcinoma of the pancreas is a rare, slow-growing neoplasm with a broad range of endocrinologic manifestations. Moertel et al.[7] report that as compared with the standard combination of streptozocin and fluorouracil, a combination of streptozocin and doxorubicin produces a superior response (69 percent vs. 45 percent) and better median survival (2.2 vs. 1.4 years). What seems equally impressive is that 11 of 36 patients who received streptozocin plus doxorubicin apparently had no progression of disease for more than two years, and some had remissions extending beyond five years. Clinical evidence of tumor response was paralleled by biochemical evidence of a decrease in aberrant endocrine function. Although these results by themselves do not represent a major therapeutic discovery, they confirm the responsiveness of islet-cell carcinoma to cytotoxic chemotherapy. Since streptozocin plus doxorubicin induced moderate leukopenia (only 5 percent of patients had white-cell counts of less than 2×10^9 per liter [2000 cells per cubic millimeter] during their initial cycle of treatment), other drugs may be added

to this combination. For example, various combinations of fluorouracil plus leucovorin, interferon, cisplatin, and dacarbazine are under investigation at present as treatment for islet-cell cancer. Ultimately, multiagent combinations will probably be developed in which the streptozocin–doxorubicin combination serves as a base. Although the relative rarity of islet-cell tumors (fewer than 1000 new cases annually) makes it difficult to perform single-institution studies, the cooperative group program sponsored by the National Cancer Institute can coordinate and contribute to such trials. It may also be time to reexamine the current practice of withholding chemotherapy from patients with islet-cell tumors until metastases cause discomfort or threaten organ function. The median overall survival of patients given delayed chemotherapy is approximately three years; a few live much longer. In view of the response rates that are now possible, it may be wise to begin chemotherapy earlier in the course of the disease, when performance status and tolerance of treatment are maximal.

In another study in this issue, Schaake-Koning et al.[8] demonstrate an advantage of concurrent radiation therapy and daily cisplatin in patients with a common presentation of a common neoplasm, locally advanced and therefore inoperable non–small-cell lung cancer. More than 130,000 new cases of this cancer are diagnosed yearly in the United States. Standard therapy (radiation to intrathoracic sites of the disease) results in local control of disease in less than 20 percent of patients and in three-year survival of 5 percent. Most patients die with both local and metastatic disease. Until cisplatin was introduced, chemotherapy produced few responses in patients with metastatic disease and had no tangible benefit as an adjunct to radiotherapy.

Theoretically, chemotherapy has two distinct roles in the treatment of locally advanced non–small-cell lung cancer. The first is as a radiation sensitizer to enhance local cell killing; a positive effect would be measured as improved local tumor control. Experimental tumors can be radiosensitized by a variety of drugs, including agents that mimic oxygen in their ability to form toxic radicals when exposed to radiation photons (nitroimidazoles), agents that become incorporated into DNA and retard repair of radiation-induced breaks (halopyrimidines), and agents that deplete cells of glutathione and impair defenses against free radicals (anthracyclines, nitroimidazoles, alkylating agents, and cisplatin).[9] Although the theory of radiosensitization is logical, clinical trials have generally not shown much benefit. The second potential benefit of chemotherapy in locally advanced non–small-cell lung cancer is in the reduction of both local recurrence and distant metastases through direct cytotoxic effects. Several randomized studies[10-12] have examined the value of cisplatin-based combination chemotherapy given before or after radiation, as compared with radiation alone, and have reported that chemotherapy combined with radiotherapy improves survival, although it does not consistently improve local control.

Single-agent chemotherapy with daily cisplatin plus radiation, as described by Schaake-Koning et al.,[8] produced evidence of radiosensitization — namely, a reduction in local recurrence of disease without a measurable effect on distant metastatic disease. There was also a significant improvement in overall survival among patients receiving cisplatin daily, as compared with patients receiving irradiation alone. A regimen of weekly cisplatin appeared less effective. Although it is provocative, this study has apparent shortcomings; the most troubling was the high proportion of patients who could not be evaluated (20 percent). Because of the toxicity of daily cisplatin and its modest benefit, the study should not be regarded as definitive. Larger multiinstitutional trials of cisplatin chemotherapy combined with irradiation are under way.

These results in patients with lung cancer pose a problem for the oncologist. Should therapy be aimed at achieving optimal radiation sensitization (e.g., with daily cisplatin), or is it more important to reduce metastatic disease (with cisplatin plus other agents)? At present, the gain from either approach is inadequate, and better radiosensitization and cytotoxic chemotherapy are both needed. Radiosensitization as described in this report[8] is a useful but not sufficient objective, since non–small-cell lung cancer becomes metastatic in the majority of patients. Thus, the focus must be improved control of both local and systemic disease. New drugs with activity against non–small-cell lung cancer have recently been identified, and clinical trials of CPT-11, edetrexate, and taxol, in combination with cisplatin, could provide important new leads for the control of both local and metastatic disease.

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SOUNDING BOARD

REFORMING THE HEALTH INSURANCE MARKET FOR SMALL BUSINESSES

FACED with possible extinction, the private health insurance industry has emerged as a vocal advocate of reforming the way it does business. Since January 1990, the Health Insurance Association of America (HIAA) has proposed extensive regulation of the pricing, marketing, underwriting, and design of policies sold to small-business groups.[1] Similar proposals for reform have been made by the Blue Cross and Blue Shield Association and by the National Association of Insurance Commissioners (NAIC). It is remarkable to see a reform proposal coming from the industry most likely to oppose it. It is also surprising that, with the rest of the debate over health care reform in gridlock,[2] the basic structure of these measures has broad political support and is viewed by many as having a high likelihood of passage, both in individual states and early in the course of federal reform. President Bush and several congressional leaders from both parties have recently endorsed some or all aspects of the industry's proposed reforms. It is therefore imperative to understand precisely what small-group–market reform will and will not accomplish toward the twin goals of universal access and cost containment.

THE PURPOSE OF REFORMS IN THE SMALL-GROUP MARKET

Reforming the small-group market is intended to arrest the disintegration of the health insurance market for small businesses, which is currently in a death spiral. In 1990 only 36 percent of firms with fewer than 25 employees offered their workers health insurance, as compared with 87 to 99 percent of larger firms.[3] Stated even more starkly, among firms that do not offer coverage, 98 percent have fewer than 25 employees.[4] These dramatic statistics result in part from a market dynamic that has forced insurers to treat small businesses more like purchasers of individual policies than like group purchasers, but without the regulatory protections that apply to the individual market.

In previous decades, Blue Cross, health-maintenance organizations (HMOs), and even many commercial health insurers tended to charge one rate for all small groups in a given community, usually adjusting only for age and sex. In recent years, however, commercial insurers and many HMOs and Blue Cross plans have been forced to abandon this modified form of open enrollment and community rating for much more selective marketing practices. The root of these destructive market forces lies in the steeply rising cost of health care. Aggressive price shopping by healthier work forces has forced health insurers to gauge more accurately the actual risks of different groups and to screen out high-risk individuals and groups. Rather than repeat the specifics of widely publicized cases,[5-7] I will describe the general market tendencies.[8-10]

Underwriting (the process of assessing risk) for individual medical conditions becomes more cost effective as the size of the insured group decreases. This follows as a simple application of the statistical law of large numbers. For larger groups, aggregate claims experience is highly predictive of future costs, whereas smaller groups are more likely to have extreme fluctuations from year to year. The consequence of this statistical logic is that insurers (responding to employer demands) have adopted several practices that make it difficult or impossible for some small groups, or individuals within small groups, to obtain sufficient insurance. Insurers sometimes exclude high-risk people in small groups entirely or subject them to lengthy exclusion periods (as long as two years) for preexisting conditions or to permanent exclusions of their major health conditions. In extreme cases, entire small groups are refused coverage or are quoted extremely high prices, either at the outset of coverage or at renewal. More routinely, employees who have lasted through lengthy preexisting-condition periods are afraid to change jobs, producing a phenomenon known as "job lock" that may affect 30 percent of Americans.[11]

Frequently, large price increases and refusals to serve an entire small group are not based on any actual adverse history of claims. Some insurers engage in "tier rating," which classifies various groups on the basis of the insurer's experience that workers in certain occupations and industries are likely to have higher claims. Even favorably rated groups are subjected to "durational rating," which is the practice of offering a low premium to groups identified as low risks at the outset, but raising the premium steeply at each annual or semiannual renewal period, reflecting the tendency of the predictive power of the initial risk assessment to wear off. Medical underwriting tends to wear off because of the statistical phenomenon known as regression to the mean, according to which outliers (both low and high) tend over time to move closer to the norm. Prices also rise over time simply because the initial period during which preexisting conditions are excluded expires. At the most extreme, insurers may refuse altogether to renew the coverage of groups with initial low ratings, which constitutes the phenomenon known pejoratively as churning.

TAKING THE REFORM PROPOSALS AT FACE VALUE

Various proposals to correct these destructive practices share three essential components — guaranteed availability, price regulation, and private reinsurance

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