MERGERS AND ACQUISITIONS — WHO BENEFITS? WHO LOSES?

INSTITUTIONS that have been longtime rivals are merging. In Massachusetts, Brigham and Women's Hospital and the Massachusetts General Hospital have merged, and two of the state's largest health maintenance organizations (HMOs) — Harvard Community Health Plan and Pilgrim Health Care — have merged. In Philadelphia, Hahnemann Medical School and the Medical College of Pennsylvania have merged. Glaxo merged with Burroughs Wellcome, and Upjohn merged with Pharmacia. Many health care organizations are also expanding their range of services by acquiring other organizations. Hospitals across the country are acquiring groups of primary care physicians, outpatient clinics, rehabilitation units, nursing homes, and home health agencies. By combining these units and integrating the hospitals with their staffs (into physician–hospital organizations), a great many are developing vertically integrated delivery systems. In addition, enormous for-profit HMOs and hospital systems have sprung up, virtually overnight.

New combinations appear every day. Rumor even has it that on the East Coast Columbia and Cornell are considering combining their medical schools, and on the West Coast Moffitt Medical Center in San Francisco is "talking" with Stanford Medical Center in Palo Alto. And we used to think that politics made strange bedfellows!

Mergers and acquisitions are now among the dominant strategies for capturing managed-care dollars as health care funds progressively shrink. These strategies are based on the assumption that when it comes to survival, bigger is better. Hospitals, no longer the central focus of care, are under great pressure as occupancy rates decline. Driven by the imperatives of the marketplace, hospitals hope that merging will help them reap economies of scale by reducing expenses for personnel, overhead facilities, and marketing. By becoming larger, yet leaner and more efficient so that they can lower the prices of their services, they hope to beat out the competition in negotiations with insurers, employers, and HMOs. To preserve their roles in training students and house officers and supporting research, many academic medical centers are also developing integrated delivery systems. Although many have managed to remain in the black so far, most of these institutions have not yet felt the full impact of capitation arrangements. The pace is quickening. In 1994 alone, 674 U.S. hospitals were involved in mergers and acquisitions, as compared with fewer than 60 in the previous three years.[1]

The responsibility for regulating mergers and acquisitions in health care is determined by antitrust legislation, and at the federal level rests with the Federal Trade Commission and the Department of Justice. Virtually all the states also have antitrust laws. The federal agencies assess economic competition in a given health care market and prosecute institutions that they believe have acted in an "anticompetitive fashion" — for example, by either colluding with competitors or creating a monopoly that fixes prices. These agencies permit transactions that promote institutional efficiencies and cost containment. The federal antitrust guidelines in health care,[2] the cases that the federal agencies prosecute, and the agencies' letter rulings become standards against which institutions can judge the chance that their mergers or acquisitions will be challenged.[3-5] In recent years, only a handful of ventures have been challenged by the federal agencies, a fact that has been attributed to political pressure by hospitals and physician groups.[6] On the other hand, many states are beginning to enforce antitrust policies more stringently.[7]

Who benefits from the merger–acquisition frenzy and who loses? With their huge salaries and handsome perquisites, the biggest winners are the corporate executives of the huge (and still expanding) for-profit HMOs and hospital systems. Other winners include stockholders, lawyers who broker consolidations, and health care consultants. Some estimate that management consultants receive as much as 2 to 3 percent of the revenues generated by the organizations they serve and that these revenues are growing by 20 to 25 percent per year.[8]

Physicians generally are placed at a disadvantage. Merged hospitals frequently find they have too many physicians, with the result that some — especially specialists and subspecialists — lose income or even their jobs. Joining with hospitals in physician–hospital organizations can also be problematic for physicians. They may lose some autonomy in individual clinical decision-making, and they must often surrender financial authority in arrangements that require dividing the capitation dollar with other physicians and their hospital. Needless to say, most of them feel that this loss of autonomy is necessary to avert even worse personal financial consequences.

In many instances, merging overbedded hospitals has been the only way to preserve patient care in a community, and trustees of some not-for-profit hospitals have risen to this challenge. Nonetheless, expanding an institution's market share through merger or the acquisition of new facilities does not guarantee survival. Purchasing necessary facilities is expensive and often requires borrowed capital. When borrowed capital is used for such ventures, an institution may be left with such large debts that it becomes noncompetitive in terms of the rates it must charge to insurers or payers. Moreover, as hospital use continues to decline under the influence of capitation, hospitals will have to close facilities, lay off more workers, and eliminate marginal programs.

Clearly, there is a limit to how much a health care delivery system can reduce the number of personnel and still provide optimal care. It is in this environment that the patient can be hurt. Because physicians are torn between providing care and minimizing cost, patient care may be threatened.[9] Moreover, when local not-for-profit institutions are acquired by for-profit com-

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panies with headquarters far from the site of care, long-term support of community services may be jeopardized. And, of course, when merger or acquisition is insufficient to maintain solvency, failed institutions can take the premiums of their patients down with them.

Some argue that rather than use capital to acquire facilities, integrate vertically, and create new governing structures, hospitals are better off developing joint ventures with other facilities, making contractual arrangements with physicians, specifying clearly the care to be given, and developing an information system that tracks the outcomes of care.[10] In fact, no matter whether integration occurs through formal acquisition or through contractual arrangement, the true test of these efforts is whether the care of patients is optimized as a consequence. It is far more difficult to develop a delivery system that provides high-quality, thoroughly coordinated, and cost-effective care than it is to acquire facilities, create new governing bodies, and decide who will be the new institution's chief executive officer.

Market forces will be the chief influence on the way health care is delivered for some time to come, and it is clear that institutions will continue to respond to these influences with more mergers, acquisitions, and other integrative approaches. The principal responsibility for inspection and oversight of institutions after consolidation rests predominantly with accrediting bodies, especially the Joint Commission on Accreditation of Healthcare Organizations and the National Committee for Quality Assurance. Although these organizations have no official governmental status, hospitals in most states must continue to be accredited to keep their licenses. Unfortunately these accrediting bodies are ill equipped to monitor newly reorganized, complex systems of care, and they are not independent of the health care industry. Our system of health care regulation and accreditation has been aptly described as "too expensive, too grounded in the past, too concerned with old forms, and too little addressed to new ones."[11] The accrediting bodies are trying to adapt, but they must speed up the evolution of their practices to conform to new realities. Since the rapid changes in health care began, there has been too little attention to the consequences of mergers, acquisitions, and other consolidations. Health services researchers have gathered few data on the effects of these shifts, and few others have voiced concern that oversight may be inadequate. If voluntary organizations cannot step up to the plate, state health agencies should improve their analytic capabilities so that they can assess the consequences of these consolidations. Detailed proposals to redesign inspection and accreditation have been made[11] (see review of *New Rules: Regulation, Markets, and the Quality of American Health Care*, in Book Reviews, page 740) and should be considered.

Decisions about mergers, acquisitions, and vertical integrations in health care are largely in the hands of an oligarchy of executives who are reacting to the vicissitudes of the marketplace. Many trustees of not-for-profit institutions are overwhelmed by the complexity of these issues and have relinquished responsibility to consultants who focus narrowly on the bottom line. Our health care system continues to change rapidly without a coherent national approach to the structure of the delivery of care. There is little doubt that in some small towns and rural communities, mergers of institutions have preserved health care services within the region, but whether the great majority of mergers and acquisitions will add value to our health care system is yet to be determined. Given the rapidity of change in our delivery system, we should insist on a comprehensive review of the adequacy of our regulation and accreditation mechanisms.

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LOW-MOLECULAR-WEIGHT HEPARIN — AN OPPORTUNITY FOR HOME TREATMENT OF VENOUS THROMBOSIS

VENOUS thromboembolism, a disease now recognized in most cases to have a genetic basis,[1] is the discharge diagnosis of more than a quarter-million patients in U.S. hospitals annually.[2] Heparin has been the standard initial therapy for this condition since the 1940s. For many years, evidence of the efficacy of heparin in these patients was based on experimental studies in animals and uncontrolled clinical experience. Not until 1992 did a randomized, double-blind trial demonstrate that patients with deep-vein thrombosis do indeed require initial treatment with full-dose heparin.[3]

Admission to the hospital has been deemed necessary for patients with deep-vein thrombosis in order to treat them with dose-adjusted heparin administered parenterally. Even in the 1980s, such patients were usually hospitalized for 7 to 14 days of heparin therapy[4] before being discharged taking oral warfarin for longer-term anticoagulant therapy. More recently, it was determined that the duration of heparin therapy and hospitalization could be safely shortened to five days if oral anticoagulant therapy was started simultaneously with heparin.[5,6] The advent of preparations of low-molecular-weight heparin has now made it possible to begin heparin therapy in an outpatient setting. This issue of the *Journal* includes reports of two multi-institutional randomized trials demonstrating the efficacy and safety of fixed-dose low-molecular-weight heparin administered at home to selected patients as the initial therapy for acute proximal deep-vein thrombosis.[7,8]

As Figure 1 shows, heparin acts as an anticoagulant by binding to plasma antithrombin III. This interaction induces a conformational change in antithrombin III that greatly increases its ability to inactivate coagulation enzymes, including thrombin and factor Xa. Preparations of standard (unfractionated) heparin consist of a heterogeneous mixture of polysaccharide chains ranging in molecular weight from about 3000 to 30,000. Preparations of low-molecular-weight heparin are fragments of standard heparin produced commercially by controlled enzymatic or chemical depolymerization, a process that yields chains with mean molecular weights of about 4000 to 6000.[9,10] The anticoagulant activity of both standard heparin and low-molecular-weight heparin resides in a unique pentasaccharide sequence that is randomly distributed along the heparin chains and binds with high affinity to antithrombin III.

The chief difference between standard heparin and low-molecular-weight heparin is in the inhibitory effect on factor Xa and thrombin. Any heparin containing the pentasaccharide sequence inactivates factor Xa simply by binding to antithrombin III and thereby accelerating the interaction between factor Xa and antithrombin III. In contrast, the inactivation of thrombin by heparin requires heparin to bind to both antithrombin III and thrombin, forming a ternary complex (Fig. 1). This complex can be formed only if the heparin chains are at least 18 saccharide units long and also include the pentasaccharide sequence. Most molecules of standard heparin are at least 18 saccharide units in length, whereas only a small proportion of chains of low-molecular-weight heparin are long enough to bind to both antithrombin III and thrombin. Thus, standard heparin has equivalent inhibitory activity against both factor Xa and thrombin, whereas preparations of low-molecular-weight heparin preferentially inactivate factor Xa.

Low-molecular-weight heparin has been considered theoretically superior to standard heparin in several respects.[9,10] First, it may be more effective as an anticoagulant because, unlike standard heparin, it can inactivate platelet-bound factor Xa and can resist inhibition by platelet factor 4, which is released during clotting. Second, low-molecular-weight heparin may cause fewer hemorrhagic complications than standard heparin, possibly because of its less pronounced effects on platelet function and vascular permeability. Third, low-molecular-weight heparin has more favorable bioavailability and pharmacokinetics, because it binds less readily than standard heparin to vascular endothelial cells, macrophages, and plasma proteins. The plasma half-life of low-molecular-weight heparin is about two to four times longer than that of standard heparin at therapeutic doses. Furthermore, since some of the heparin-binding plas-

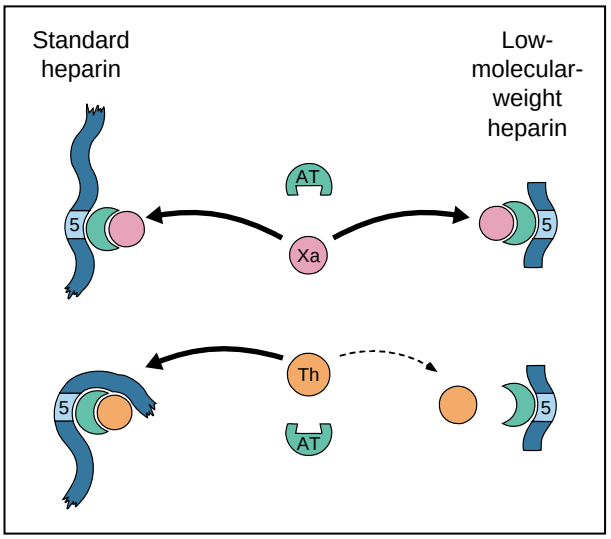

Figure 1. Mechanisms of Action of Standard (Unfractionated) Heparin and Low-Molecular-Weight Heparin.

Heparin (dark blue strands) acts by binding to antithrombin III (AT, green symbols) and changing its conformation, permitting it to bind to specific coagulation factors and inactivate them. The antithrombin III–binding site and anticoagulant activity of both standard heparin and low-molecular-weight heparin reside in a unique pentasaccharide sequence (light blue) that is randomly distributed along the heparin chain. Standard heparin and low-molecular-weight heparin have similar effectiveness in inactivating factor Xa (Xa, pink circles), since this inactivation occurs directly through the binding of antithrombin III to factor Xa. In contrast, the inactivation of thrombin (Th, orange circles) requires the formation of a ternary complex involving heparin, antithrombin III, and thrombin, and most chains of low-molecular-weight heparin are not long enough to form this complex. Thus, standard heparin has equivalent inhibitory activity against both factor Xa and thrombin, whereas low-molecular-weight heparin preferentially inactivates factor Xa.

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ma proteins are acute-phase reactants, standard heparin produces a less predictable anticoagulant response than low-molecular-weight heparin. These properties allow low-molecular-weight heparin to be administered only once or twice daily and without laboratory monitoring.

Can the theoretical superiority of low-molecular-weight heparin be translated into clinical efficacy? Most published experience with these preparations has involved the prevention of venous thromboembolism in high-risk patients. In such patients, low-molecular-weight heparin has been generally found to be at least as effective and safe as low-dose or adjusted-dose standard heparin given subcutaneously.[9] Randomized trials have also been reported that have compared low-molecular-weight heparin with standard heparin for the initial treatment of deep-vein thrombosis. Two meta-analyses of these trials found similar trends indicating improved efficacy and safety with low-molecular-weight heparin.[11,12] Low-molecular-weight heparin is also associated with a lower incidence of heparin-induced thrombocytopenia than is standard heparin.[13]

The proposed use of low-molecular-weight heparin as the initial therapy for deep-vein thrombosis in the outpatient setting raises some critical questions. Is it effective? Is it safe? Is the quality of life improved? Is the therapy feasible? Is it cost effective? The reports in this issue of the *Journal*[7,8] answer the first two questions persuasively. Both studies compared standard heparin (administered in the hospital by continuous intravenous infusion, with the dose adjusted on the basis of the activated partial-thromboplastin time) with low-molecular-weight heparin (administered twice daily by subcutaneous injection in fixed doses adjusted for the patient's weight, without laboratory monitoring). In both studies, recurrent thromboembolic events and bleeding complications occurred with similar frequency in the two treatment groups. The studies confirm previous observations that recurrent, life-threatening pulmonary embolism is exceedingly rare during initial treatment with either type of heparin, when traditionally patients would have been hospitalized. Even when deaths occurred, it was not clear whether the patients' being in the hospital would have prevented them. Major, life-threatening bleeding complications were likewise rare with both heparin regimens during this initial period. Because such episodes of bleeding are potentially treatable when the patient is under observation in the hospital, however, it would seem prudent to begin heparin therapy there in patients who have coexisting risk factors for hemorrhage, such as severe liver disease, thrombocytopenia, or other coagulopathies, and in patients with a risk of falling.

Answers to questions about the quality of life, the feasibility of treatment, and cost effectiveness remain somewhat more elusive. The improvement in physical activity and social functioning in the patients receiving low-molecular-weight heparin who were studied by Koopman et al.[8] is not surprising, since the questionnaire used was developed for the evaluation of outpatients, and the questions are phrased in such a way that simply being in the hospital would tend to produce worse scores for a patient, regardless of the level of illness. To assess improvement in quality of life, it will be desirable to develop measures more specific to the disease — that is, to thrombosis. In the two studies, about two thirds and one third of patients were excluded for reasons such as coexisting conditions, potential noncompliance, and geographic inaccessibility, in addition to the risks of bleeding. Therefore, disseminating this approach into routine practice will be difficult in some populations. Finally, the cost-effectiveness analysis attempted by Koopman et al. is incomplete; besides comparing the use of resources, they should attempt a more rigorous cost analysis by applying some acceptable conversion unit to normalize differences in medical costs between countries. In any substitution of ambulatory for inpatient care, it must also be remembered that part of the savings will be derived from shifting the costs of services from the health care industry to the patient or the patient's family.[14]

It will be critical to adopt the flexible, sensible approaches to hospitalization taken in both studies and to resist the temptation to establish rigid practice guidelines based on their findings. These investigators have challenged a time-honored practice and have made a major contribution to the treatment of deep-vein thrombosis.

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ALLERGIES TO TRANSGENIC FOODS — QUESTIONS OF POLICY

FOOD biotechnology, the use of recombinant-DNA and cell-fusion techniques to confer selected characteristics on plants and animals used for food,[1] can be used to increase agricultural productivity. The great promise of biotechnology is that the use of these techniques will help solve world food problems by creating a more abundant, more nutritious, and less expensive food supply. Despite this promise, public concern about the safety, usefulness, and social consequences of genetically engineered food products has led to boycotts, legislative bans, and demands for stronger federal regulation.[2] Such actions have caused leaders of the biotechnology industry to identify public "biotechnophobia" as the most serious threat to commercialization of their products and to view as their most critical challenge the need to reassure people that the new techniques are both safe and beneficial.[3]

Questions of safety vex federal regulators and industry as well as the public. The transfer of genes from microbes, plants, or animals into foods raises issues about the unintended consequences of such manipulations. Allergenicity could be one such consequence. Genes encode proteins; proteins can be allergenic. Biotechnology companies might be introducing allergenic proteins from donor organisms into the food supply. The Food and Drug Administration (FDA) anticipated this problem in 1992 when it devised its policy on transgenic plant foods.[4] But because this policy requires premarketing notification of the FDA, premarketing safety testing, and labeling only of foods with genes transferred from the 8 to 10 most commonly allergenic foods, public-interest groups have cautioned that existing rules inadequately protect people against lesser-known transgenic allergens to which they might be sensitive.[5]

In this issue of the *Journal*, Nordlee and her colleagues confirm that food allergens can indeed be transferred from one plant to another by transgenic manipulation — in this case, from Brazil nuts to soybeans.[6] They identify 2S albumin as the principal allergen of the Brazil nut and demonstrate that people who react to Brazil-nut extracts on standard skin-prick tests have similar reactions in response to extracts of transgenic soybeans that contain 2S albumin. The authors also collected serum from people known to be allergic to Brazil nuts and analyzed the ability of proteins in transgenic soybeans to bind to IgE in the serum samples, using radioallergosorbent tests and sodium dodecyl sulfate–polyacrylamide-gel electrophoresis.

Unique circumstances permitted this demonstration of transgenic allergenicity. Pioneer Hi-Bred International developed the transgenic soybeans used in this study in an attempt to increase the amount of sulfur-containing amino acids — methionine and cysteine — in soy-based animal feeds. Such feeds must otherwise be supplemented with methionine (which can be converted to cysteine) to promote optimal growth. The Brazil-nut 2S albumin is exceptionally rich in methionine and cysteine; its gene was a logical choice as a donor. Nuts are known to cause IgE-mediated hypersensitivity reactions that range from mild itching to sudden death.

This study highlights gaps in our current knowledge of food allergies. Stored serum samples from people with specific food sensitivities are limited; in the absence of such samples, the demonstration of the allergenicity of a food is less compelling. Thus, although about one fourth of Americans believe that they or their children are allergic to specific foods, adverse reactions to the food are confirmed by testing of serum samples or the more precise double-blind challenge tests in no more than 2 percent of adults and 8 percent of children.[7] Many more people may have food sensitivities, however, especially since the prevalence of such conditions seems to be increasing as more proteins are added to commercially prepared foods.[8] Furthermore, most biotechnology companies use microorganisms rather than food plants as gene donors, even though the allergenic potential of these newly introduced microbial proteins is uncertain, unpredictable, and untestable.[4]

Pioneer Hi-Bred developed its soybeans for use in animal feeds, but there is no easy method of separating soybeans destined for animals from those slated for human consumption. Soy proteins, which are less allergenic than milk proteins, are used in infant formulas, meat extenders, baked goods, and dairy substitutes. Because the consumption of soy-based foods appears to reduce the risks of heart disease and cancer,[9] the prevalence of soy proteins in foods consumed by infants and adults is sure to increase.

From the standpoint of human nutrition, soybeans are just fine the way they are. Their methionine content is sufficient and not a problem; even if used as the sole source of dietary protein, soy foods maintain nitrogen balance and support growth in adults, children, and full-term infants and must be supplemented only in feeding premature infants.[10]

The results of the study by Nordlee et al.[6] have important regulatory implications. The 1992 FDA policy on transgenic plant foods begins with the premise that the techniques used to create these products raise no new or unusual safety issues.[4] As is the case for other foods generally recognized as safe, the FDA has the authority to remove transgenic foods from the marketplace if unexpected problems arise. When transgenic foods contain genes transferred from donors that are commonly allergenic, the FDA considers them to be governed by food-additive regulations and requires premarketing notification, testing, and labeling.[4] Figure 1 shows the FDA protocol for gene transfers involving donors that are commonly allergenic. Under this policy, Pioneer Hi-Bred was required to — and did — consult the FDA about the need for premarketing safety testing. Given the results of the present study, the company would have had to label its trans-

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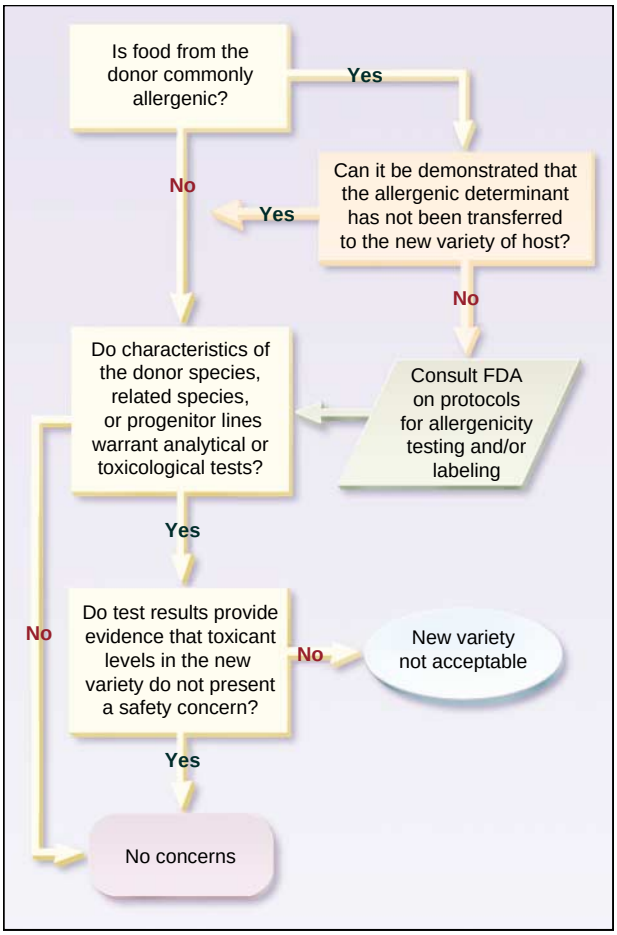

Figure 1. The FDA Protocol for the Development of Potentially Allergenic Transgenic Foods by Biotechnology Companies.
If a gene from a commonly allergenic food is likely to be transferred to a host plant, this protocol requires companies to consult the FDA, test for allergenicity, and label the product. Reprinted verbatim from the Food and Drug Administration.[4]

genic soybeans. Instead, it discontinued plans to market them.

Because FDA requirements do not apply to foods that are rarely allergenic or to donor organisms of unknown allergenicity, the policy would appear to favor industry over consumer protection. In a discussion of 3300 public comments on the policy, one report noted that biotechnology companies generally supported the policy but that consumer groups thought it delegated too much of the responsibility for premarketing safety testing to industry.[5] As a result, the report recommended a review of federal oversight of food biotechnology in order to develop a more equitable regulatory balance between promoting industry and protecting the public.

In 1993 the FDA requested public comment on whether and how to label food allergens in transgenic foods,[11] but the agency has not yet reported or taken action on the responses. Although the labeling of transgenic foods raises complex regulatory issues, surveys indicate strong public support for doing so.[12] One reason for labeling is that avoidance is still the best — and sometimes only — defense against food allergies.[7] In 1994 the FDA and several other federal agencies held a conference on scientific issues related to the allergenicity of transgenic foods. The participants discussed the gaps in information on food allergies and the need to find ways to identify less common allergens, but they reached no firm conclusions about how to deal with these issues. The FDA has released a transcript of the conference[13] but has not issued a formal report or recommendations.

The FDA has recently drafted a premarketing-notification rule that would require companies to inform the agency when they are developing transgenic foods, in part to help resolve the safety issues related to allergenicity.[14] In the current climate of deregulation, the implementation of any new premarketing-notification rule seems unlikely, particularly since the biotechnology industry is demanding that such a requirement be limited in scope and end after three years.[15] The unresolved status of this regulatory policy means that the responsibility for protecting the public against uncommon or unknown allergens in transgenic foods will continue to be delegated to industry and largely voluntary.

This situation illustrates the pressing need to expand basic and clinical research on food allergies. More information about incidence, prevalence, dietary exposure, antigenicity, immune responses, diagnosis, and treatment would help researchers, regulators, and biotechnology companies predict whether transgenic proteins are likely to cause harm. In the special case of transgenic soybeans, the donor species was known to be allergenic, serum samples from persons allergic to the donor species were available for testing, and the product was withdrawn. The next case could be less ideal, and the public less fortunate. It is in everyone's best interest to develop regulatory policies for transgenic foods that include premarketing notification and labeling. Industry benefits when the public is convinced that transgenic foods are safe, and stronger federal regulations would encourage such public confidence.

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TREATING SMALL HEPATOCELLULAR CARCINOMAS

MANY factors influence the survival of patients with hepatocellular carcinoma, quite apart from treatment, the most important being the size of the tumor at the time of diagnosis and the severity of the underlying cirrhosis.[1] Small hepatocellular carcinomas have relatively long tumor-doubling times, as compared with large, symptomatic hepatocellular carcinomas. In a recent study, the three-year survival rate among 260 patients with well-compensated cirrhosis and hepatocellular carcinomas 5 cm or less in diameter was 79 percent with surgical treatment and 26 percent without treatment; among 131 patients with more advanced liver disease, the comparable rates were 40 percent and 13 percent.[2]

Screening programs that use ultrasonography and serum alpha-fetoprotein assay detect small hepatocellular carcinomas in an increasing number of patients with cirrhosis. The most attractive option for the treatment of these patients is orthotopic liver transplantation, because the procedure can cure both the tumor and the underlying cirrhosis. In a series of patients treated in our unit,[3] none of 14 patients with single small tumors (<4 cm) had recurrence of cancer during a mean follow-up period of 23 months. The results reported in this issue of the *Journal* by Mazzaferro and colleagues from Milan[4] confirm the effectiveness of liver transplantation in patients with cirrhosis and small hepatocellular carcinomas. The criterion for eligibility was the presence of a single tumor 5 cm or less in diameter or no more than three tumor nodules, each 3 cm or less in diameter. The actuarial rates of overall and recurrence-free survival at four years were 75 percent and 83 percent, respectively. These figures were higher — 85 percent and 92 percent, respectively — when the criteria used for the selection of patients for transplantation were subsequently confirmed by pathological examination of the explanted liver. Survival was similar for patients with single tumors and those with multiple tumors.

In early series, patients with multiple tumors had a very poor prognosis; the rate of recurrence within two years after transplantation was 80 percent.[3] The present results from Milan suggest that it is the total bulk of tumor tissue rather than the presence of more than one tumor nodule that determines recurrence. This is an important issue that needs to be addressed in more patients, since 20 to 60 percent have multiple tumors at the time of diagnosis. It must be kept in mind that the accuracy of radiologic procedures in detecting small tumors is poor. In a retrospective study, we found that ultrasonography, computed tomographic scanning, and angiography had failed to demonstrate multiple tumors in 80 percent of patients who were discovered to have them when the explanted livers were examined,[5] and in almost 30 percent of the patients studied by Mazzaferro et al., tumor bulk was larger than predicted before transplantation.

Not all patients with small hepatocellular carcinomas have the option of receiving a transplant: many countries do not have a liver-transplant program, and in those that do, the waiting lists are getting longer because demand is exceeding the number of donor organs available. In patients for whom transplantation is not possible, partial resection is the next best choice. This procedure can be performed only in patients with well-compensated cirrhosis who can withstand the stress of the operation. The results in a series of patients in Japan who had mild cirrhosis and small tumors (<5 cm) and who underwent resection are, at first sight, quite reasonable, with a five-year survival rate of 26 percent; 60 patients (28 percent) died from recurrent or new cancer.[6] However, in a European series of 121 patients with cirrhosis and fewer than three hepatocellular carcinomas less than 3 cm in diameter, the three-year rates of overall and disease-free survival were lower after resection (35 and 10 percent, respectively) than after transplantation (both 83 percent).[7]

The poor results with resection are due to the progression of the underlying liver disease and to the new tumors that arise in the remaining liver tissue. Metastases can also be left in place at the time of resection. The advent of intraoperative ultrasonography has improved rates of tumor detection considerably, with almost 100 percent of tumors 1 cm or more in diameter being identified by this technique. Survival after surgical treatment may be improved by the use of preoperative chemoembolization and postoperative chemotherapy. In a retrospective study, however, we found that tumor size predicted survival after transplantation regardless of whether the patient underwent chemotherapy.[8]

For patients to whom surgery cannot be offered, either arterial chemoembolization or percutaneous ethanol injection is a worthwhile palliative treatment. Pa-

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tients with small tumors are good candidates for chemoembolization, as Levin and Amos discussed in an editorial in the *Journal* last year.[9] Percutaneous injection of ethanol with ultrasound guidance is a relatively simple and safe technique. The results in a large series from Italy[2] are encouraging, with a three-year survival rate of 71 percent among patients with well-compensated cirrhosis and tumors less than 5 cm in diameter, as compared with 26 percent in a group of patients who were not treated.

Cirrhosis is present in 90 percent of patients with hepatocellular carcinoma, and in the absence of cirrhosis the tumor is usually diagnosed at a very late stage. Therefore, the diagnosis of a small hepatocellular carcinoma in a patient without cirrhosis is extremely rare, but cases may still occur in patients with chronic hepatitis B or hepatitis C virus infections and hemochromatosis, or in patients receiving gonadal steroid hormones. In one series of 68 patients without cirrhosis but with hepatocellular carcinomas, the median tumor diameter was 8.8 cm.[10] In that study, 72 percent of patients underwent partial resection, with three-year rates of 52 percent for overall survival and 43 percent for disease-free survival.[10] These patients may have late recurrence, but aggressive surgery is nonetheless justified.

In the longer term, the prevention of hepatocellular carcinoma is surely the proper approach. The widespread use of the hepatitis B vaccine should reduce the frequency of hepatitis B–related cirrhosis and hepatocellular carcinoma. With respect to patients with hepatitis C–related chronic active hepatitis and cirrhosis, who are at high risk for hepatocellular carcinoma, there is an encouraging recent report that interferon alfa can reduce the frequency of hepatocellular carcinoma.[11]

In conclusion, in patients with cirrhosis and small hepatocellular carcinomas, liver transplantation is potentially curative; partial resection, chemoembolization, and percutaneous alcohol injection improve survival. Treatment is therefore justified, but the optimal strategy remains to be defined.

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IMPROVING THE OUTCOMES OF CARE FOR PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

A WIDE spectrum of specialists and generalists are now delivering care of increasing complexity for patients infected with the human immunodeficiency virus (HIV). Few of these physicians have had any formal training in what is, in many respects, a new multidisciplinary medical specialty. Within health care organizations, there is often little coordination among practitioners who treat HIV-infected patients. In some systems, such patients are intentionally "mainstreamed" by assigning their care to generalists regardless of the experience or training of the physicians or their interest in this disease. When this happens, important recent advances in management may never reach the patients.

Survival is improved when patients with AIDS are hospitalized in facilities that have more experience with AIDS,[1,2] but the effect of the physician's experience on outcome has only recently been investigated. The report by Kitahata et al. in this issue of the *Journal*[3] examines physicians' experience in treating HIV infection as a predictor of survival among their patients with AIDS. With the restructuring of American medical care, we must reassess the allocation of patients to specialists or generalists. Data on outcomes can support rational recommendations about the training of physicians in the care of HIV-infected patients and about the optimal numbers of patients for each doctor to treat.

Kitahata et al. analyzed survival among more than 400 HIV-infected men as a function of the estimated level of experience of their primary care physicians in treating patients with AIDS. In the staff-model health maintenance organization (HMO) they studied, patients were assigned, essentially at random, to family physicians and general internists. Referral to specialists was possible and not actively discouraged, but overall re-

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sponsibility for care remained with the primary care physician. Most patients remained in the HMO throughout the study period. The experience of each physician was estimated according to the number of patients with AIDS that he or she had treated previously and the time and location of his or her residency training. Those trained in cities with a high incidence of AIDS were assumed to have cared for more patients with the syndrome.

More than 80 percent of the physicians were judged to have had only minimal or moderate experience (five or fewer patients with HIV infection). To compare the medical care received by the patients of physicians in different experience categories, the authors collected data on the use of prophylaxis against *Pneumocystis carinii* pneumonia, antiretroviral therapy, and CD4+ cell counts. To correct their results for probable confounders, the authors adjusted for both the date of diagnosis and the severity of disease. As expected, patients in whom AIDS was diagnosed more recently had a higher probability of survival than those in whom AIDS was diagnosed earlier in the epidemic.

Kitahata et al. found a direct relation between the physician's level of experience in caring for patients with HIV infection and the rate of survival among his or her patients. For the patients in whom AIDS was most recently diagnosed, the mortality rate was 43 percent lower among the patients of the most experienced physicians than among those treated by the least experienced physicians; the most experienced providers followed CD4+ cell counts more closely and more often prescribed prophylaxis against *P. carinii* pneumonia and antiretroviral therapy. Moreover, even a moderate level of experience with AIDS had detectable consequences, since the earlier patients of a given physician had a higher risk of death than his or her subsequent patients, even when the total number of treated patients was five or less.

Although the improvements in survival for those with AIDS that are documented in this study provide reassuring evidence that we are making progress against this disease, not all patients are getting the benefits of improved treatment strategies. Many physicians are unaware of recent changes in standards of care, such as the use of HIV RNA assays, newer drugs for the prevention and treatment of opportunistic diseases, and the growing benefits of complex combinations of antiretroviral drugs. It is very difficult for doctors who care for only occasional patients with HIV infection to stay well informed. Consider a few of the important changes in the standards of care over the course of the study and what effect a failure to adjust practice styles may have had. Antiretroviral therapy, prophylaxis against *P. carinii* pneumonia, and effective new drugs to treat cytomegalovirus, cryptococcus, and mycobacterial infections can all improve outcome. Each of these developments has generated controversy and conflicting reports. Finding one's way to the appropriate recommendations for patient care can be daunting even for doctors engaged full-time in treating patients with AIDS, not to mention those who rarely care for such patients.

The results of this study should help reopen the debate about the optimal organization of care for patients with AIDS. Medical care is increasingly controlled by large organizations, and changes in organizational structures will affect most HIV-infected patients and their physicians. Lessons from research on the care of patients with AIDS may also be generalized to the care of patients with other complex diseases.

Several conclusions are clear. To begin with, the care of patients with HIV infection should be delivered by experienced physicians, and all health care systems should make the necessary drugs and laboratory tests readily available. Earlier in the debate it was asked whether the supply of adequately trained physicians could possibly keep pace with the AIDS epidemic. The progressive increases in the number of patients with AIDS were assumed to mean that all primary care physicians should expect to deliver care to such patients.[4] In this country, however, the incidence of AIDS is no longer increasing rapidly. The epidemic has remained concentrated in certain population groups, and AIDS will probably not consume an ever-increasing proportion of physicians' time and of space in medical facilities. The problem now is not so much one of the supply of physicians, but of their training and the organization of health care.

Medical subspecialty training is certainly not required for excellent care of HIV-infected patients. Across the country, leading investigators and care givers include general internists and family physicians as well as subspecialists. Yet we must recognize the complexity of the care required by patients with AIDS and the dangers of forcing untrained and inexperienced providers to assume this responsibility. The risks will become more acute as care for HIV-infected patients grows even more technical and as more aggressive therapies and sophisticated methods of laboratory monitoring come into common use. Already, combinations of three or more antiretroviral drugs are becoming routine. Monitoring therapy for HIV requires the use of sensitive assays of HIV RNA titers. Patients often must take 10 or more different medications each day to treat HIV infection, suppress opportunistic infections, and control symptoms. In response to this increasingly complex situation, we must broaden the opportunities for training in treatment strategies for AIDS and make such training available to both generalists and specialists. Rather than simply giving all physicians minimal exposure, we should direct training to those most interested in the care of patients with HIV infection. The experience needed to ensure optimal outcomes for patients must be gained in a supervised setting. Health care organizations should move toward models in which primary care for those with HIV infection is concentrated, rather than widely distributed. These primary care providers will often be generalists and

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may continue to combine the care of patients with HIV with the treatment of other diseases. Patients have the right, however, to expect care that is fully informed by the most recent advances in the field, no matter how complex.

Some have expressed concern that the de facto AIDS specialists will practice more expensive medicine than other physicians. In fact, it did appear in the study by Kitahata et al. that the more experienced physicians ordered more tests and more quickly adopted new therapies. This criticism loses much of its credibility, however, when one recognizes that those same practices were probably responsible for the improvements in survival. Let us not forget that our first responsibility as physicians is to improve and prolong our patients' lives. At least for us, that mission remains more important than the goal of controlling the costs of health care.

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