

Recommendations for Vitamin C Intake

To the Editor: The article by Dr Levine and colleagues¹ on recommendations for vitamin C intake provides strong rationale for raising the recommended intake for vitamin C from the current level of 60 mg/d to as high as 200 mg/d. However, several statements made by the authors may create misconceptions. In the United States it is unlikely that the consumption of 5 servings of fruits and vegetables daily would provide 210 to 280 mg of vitamin C. The fruits and vegetables commonly consumed in the US diet are low in vitamin C, typically only 10 to 20 mg per serving.² For example, the total amount of vitamin C in 1 apple, 1 banana, a lettuce salad, a serving of corn, and a serving of green beans is only 30 to 35 mg. Although the campaign to consume "5-a-day" is commendable, consumers need to be aware of the importance of including 1 or 2 vitamin C-rich fruits and vegetables in their diet daily, a list that includes citrus, cantaloupe, strawberries, broccoli, cauliflower, and peppers.

Attention to diet is important because recent national survey data indicated that 10% to 13% of Americans are vitamin C deficient and at high risk for developing scurvy (plasma vitamin C <11 $\mu\text{mol/L}$).³ The authors' recommendation for the daily intake of vitamin C (100-200 mg/d) would provide for tissue saturation but not plasma saturation. This is an important distinction since an accepted functional marker for vitamin C nutriture is not available. It is not known whether plasma saturation confers added physiological benefits for humans beyond that achieved at tissue saturation. The cofactor functions of vitamin C occur intracellularly and are likely influenced more by tissue levels than plasma levels. However, the antioxidant and reduction actions of vitamin C in extracellular fluids could be maximized by plasma saturation, as some literature suggests.⁴

Finally, gram doses of vitamin C are well tolerated by healthy individuals, and epidemiological data indicate that individuals who regularly supplement their diets with vitamin C may be at lower risk for all-cause cancer deaths, colon and bladder cancer, lens opacities, and kidney stones.⁵ The tolerable upper intake level, as defined by the Food and Nutrition Board of the Institute of Medicine, is not designed to protect individuals with pathologies exacerbated by nutrient supplementation.⁶ Hence, the upper intake level for vitamin C should not be defined based on a potential adverse effect of vitamin C supplementation in patients with preexisting hyperoxaluria, as indicated by the authors.

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To the Editor: The comments by Dr Levine and colleagues¹ regarding an appropriate recommended daily allowance for vitamin C are controversial. The data reported in the previous study by Levine et al² support earlier published data,³ and indicate that plasma saturation with vitamin C does not occur until consumption of a dosage of 500 mg twice a day. A critical protective effect of vitamin C is its synergistic role in regenerating vitamin E in plasma low-density lipoprotein. Oxidation of plasma low-density lipoprotein is a key step in deposition of plaque in arteries. Thus, maintaining a maximal level of vitamin C in the plasma significantly reduces free-radical generation leading to low-density lipoprotein oxidation.⁴ There is considerable evidence that taking vitamins C and E in supplement form may reduce the risk of cancer, heart disease, and death.⁵ Dosages of less than 500 mg twice a day do not provide plasma saturation, and do not reduce free-radical formation in plasma as effectively.

Although Levine et al raise concerns about the formation of oxalate at high levels of vitamin C, existing studies⁶ indicate that those without a history of urinary tract calculi who are taking dosages of vitamin C greater than 1500 mg/d have a significantly lower incidence of kidney stones. On the basis of existing studies, there is no evidence that taking 1000 mg/d of vitamin C or more increases the risk of kidney stones except for specific at-risk populations, for which the risk remains unknown. A safe upper limit for vitamin C remains undefined at present for lack of any evidence of hazard.

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In Reply: Dr Johnston is concerned that 5 servings of fruits and vegetables would provide less than 200 mg of vitamin C daily. If US Department of Agriculture and National Cancer Institute guidelines for 5 fruits and vegetables are followed, predicted vitamin C intake exceeds 215 mg/d.¹ While it is possible to select fruits and vegetables with lower vitamin C content, National Cancer Institute and US Department of Agriculture guidelines recommend consumption of a variety of fruits and vegetables, and we agree wholeheartedly. If this advice is followed, average vitamin C intake will not be as low as Johnston's rather extreme example. We also indicated that vitamin C food content could be decreased by factors such as season, transport, and cooking.

Johnston also noted that vitamin C daily intake of 100 to 200 mg would saturate tissues but not plasma, and that plasma saturation could confer added benefit beyond tissue saturation. We cannot conclude from the available evidence that plasma saturation confers physiological benefit. The example Johnston provided is insufficient to support this claim. In addition, Johnston suggests that regular vitamin C supplement users may be at lower risk for cancer and cataracts. Regarding cancer, the evidence cited reveals inconsistent effects of vitamin C. In 1 study,² a protective effect could not be accounted for by vitamin C supplements alone, but only when fruit and vegetable ingestion was included. In another study,³ the only amount of vitamin C found to be protective was far higher than what nearly saturates plasma, suggesting that the observed effect may have been due to something other than vitamin C. Factors not accounted for, such as hypertension, could have been responsible for the observations. We indicated that effects of vitamin C on cataracts are inconclusive.

Johnston and Dr Ordman claim that vitamin C supplement users have a lower risk of kidney stones. In the study cited,⁴ no association was found between daily vitamin C intake and kidney stones. However, it remains possible that subjects who were at risk were not part of this study or were otherwise masked. We remain concerned that people with occult hyperoxaluria could be at risk. One gram or more of vitamin C increased oxalate excretion above normal levels in patients with hyperoxaluria who had oxalate stones.⁵ Because hyperoxaluria may be occult and the first clue to its presence may be a kidney stone, we maintain that the safe upper intake level of vitamin C ingestion is less than 1 g/d.

Ordman also suggested that his study provided evidence that plasma saturation did not occur until a dose of 500 mg twice daily was administered, but this study only reported vitamin C urinary excretion using an insensitive method.⁶ Although low-density lipoprotein oxidation in vitro is inhibited by vitamin C, the mechanism may be independent of vitamin E regeneration, and significance of these findings for patients is uncertain. Ordman maintained that vitamin C and vitamin E supplements reduced risks of cancer, heart disease, and death, but the cited study showed no effect of vitamin C alone, and the data could be explained by use of vitamin E alone.

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Financial Disclosure: Dr Rumsey owns stock in Bristol Myers Squibb, which owns Mead Johnson Nutritionals.

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Increasing Incidence of Renal Cell Cancer

To the Editor: The article by Dr Chow and colleagues¹ demonstrated that the incidence of renal cell carcinoma increased steadily from 1975 to 1995 in the United States, especially among African Americans. The authors determined that increased detection due to ultrasonography, computed tomography, and magnetic resonance imaging did not fully explain the upward trend and suggested that other factors may be contributing.

We agree with their observation and have previously reported similar findings among patients with human immunodeficiency virus (HIV) infection. After observing renal cell carcinoma in a patient with HIV infection, we conducted a retrospective review of our local hospital population to determine if the prevalence of renal cell carcinoma in patients with HIV infection was greater than in the non-HIV-infected population. Of 66 715 adult patient admissions over a 5-year period, we determined that the prevalence of renal cell carcinoma in the HIV population was 8.5 times greater (649/100 000) than in the non-HIV population (75/100 000), with an average age at oc-

currence approximately 15 years younger than that reported in national statistics.² In our study and all of the previously reported cases of patients with renal cell carcinoma and HIV infection, all patients were African Americans.

It is of interest that the incidence of renal cell carcinoma in African Americans parallels the reports of cases of acquired immunodeficiency syndrome (AIDS) in that population.³ We wonder if the increase in incidence of renal cell carcinoma in this group is partially explained by the spread of HIV disease. Chow and colleagues note that the upward trend of renal cell carcinoma began in 1975. In our study, we noted that the mean CD4 cell count was $0.41 \times 10^9/L$, suggesting that renal cell carcinoma can begin in relatively immunocompetent patients with HIV infection before any AIDS-defining illnesses are present. The first cases of AIDS, recognized in the early 1980s, were in individuals who had been infected for 7 to 10 years.⁴ If HIV infection can be correlated with an increased risk of renal cell carcinoma, this may explain why the trend started in the mid-1970s.

We believe that monitoring HIV-1 infection as a possible cofactor in patients with renal cell carcinoma should be considered in future studies. It also will be of interest to see if widespread use of highly active antiretroviral therapy since the mid-1990s will correlate with a decline in the incidence of renal cell carcinoma.

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1. Chow W-H, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. *JAMA*. 1999;281:1628-1631.

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To the Editor: Following the report of Dr Chow and colleagues¹ of an increasing trend of renal cell cancer in the United States, we reexamined trends in mortality from kidney cancer in major European countries, which also have shown upward trends between 1955 and 1989, with an overall average increase of 17%.²

Official death certification data for 17 selected European countries were derived from the World Health Organization (WHO) database. Classification of kidney cancer deaths was recoded for all calendar periods and countries according to the *International Classification of Diseases, Ninth Revision* (code 189). No distinction was possible between renal cell carcinoma, which accounts for 80% to 85% of all malignant tumors of the kidney,³ and transitional cell carcinomas of the renal pelvis.

Estimates of the resident population, generally based on official census data, were obtained from the same WHO database. From the matrices of certified deaths and resident populations, age-specific rates for each 5-year age group and calendar period were computed. Age-standardized rates were based on the world standard population.

Increases in kidney cancer mortality across Europe were observed between the mid-1970s and the late 1980s (TABLE). During the last few years, however, some leveling or decline of rates has been observed in Sweden and other Scandinavian countries, France, and Switzerland, mostly in men. Among the countries considered in 1990-1994, the highest mortality rates were recorded in Hungary (6.5 per 100 000 men and 2.7 per 100 000 women) and Germany (6.3 per 100 000 men and 2.8 per 100 000

Table. Trends in All-Age Mortality From Kidney Cancer in Selected European Countries, 1975-1994*

	Deaths per 100 000 Men				Deaths per 100 000 Women			
	1975-1979	1980-84	1985-1989	1990-1994	1975-1979	1980-84	1985-1989	1990-1994
Austria	5.2	5.6	5.9	5.7	2.6	3.1	2.9	2.8
Belgium	4.1	4.3	4.2	4.3	2.3	2.3	2.6	2.2
Bulgaria	1.5	1.8	2.1	2.3	0.9	0.9	0.9	1.1
Denmark	5.1	5.5	5.5	4.9	3.8	3.5	3.8	3.2
Finland	5.1	5.3	5.5	5.5	2.5	2.8	2.9	2.8
France	3.6	4.0	4.5	4.5	1.7	1.8	1.8	1.8
Germany	4.2	5.2	6.1	6.3	2.0	2.3	2.7	2.8
Greece	1.8	2.3	2.3	2.5	0.9	0.9	1.0	1.0
Hungary	4.4	4.8	5.8	6.5	2.3	2.3	2.7	2.7
Ireland	3.0	2.8	3.3	3.5	1.4	1.6	1.7	1.6
Italy	2.9	3.5	4.1	4.3	1.2	1.5	1.6	1.6
The Netherlands	4.5	5.0	5.2	5.3	2.4	2.6	2.7	2.6
Norway	4.3	4.8	4.7	4.5	2.4	2.4	2.4	2.3
Spain	1.9	2.1	2.5	2.9	1.0	0.9	1.0	1.1
Sweden	6.5	5.9	5.7	5.1	3.7	3.4	3.4	2.8
Switzerland	4.5	4.4	5.1	4.6	2.5	2.5	2.5	2.2
England and Wales	3.3	3.4	3.7	3.9	1.5	1.6	1.8	1.9

*Age-standardized rates of the world population.

women); the lowest rates were observed in Greece (2.5 per 100 000 men and 1.0 per 100 000 women). Truncated rates for persons aged 35 to 64 years also were computed and showed a similar pattern, with slightly more favorable trends over the last few years in several European countries.

Thus, trends and rates in kidney cancer mortality were heterogeneous across Europe and only partly consistent with the increases in incidence and mortality observed in North America. Tobacco smoking is the most recognized risk factor for kidney cancer, and the trends in several Nordic countries are consistent with the decline in tobacco use in those countries.²⁻⁴ Prevalence of overweight is also lower in Europe compared with the United States.⁵ However, the potential role of other risk factors for kidney cancer in national trends in incidence and mortality, as well as the roles of improved diagnosis and certification, remain unclear.

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In Reply: The finding by Drs Katner and Baynham of a higher prevalence of renal cell carcinoma among HIV-positive vs HIV-negative patients is intriguing and should be evaluated in future epidemiological studies of renal cell cancer. However, we note that an excess risk of kidney cancer has not been reported in population-based studies of HIV-infected persons.^{1,2} Thus, the association between HIV infection and renal cell cancer in a hospital-based series may be spurious, perhaps due to selective referral of patients or extensive medical surveillance of HIV-positive patients. Further information on the clinical stage of the renal tumors, the time sequence of disease events, and the characteristics of the general source population would help in drawing inferences about a possible relation to HIV infection. However, the available incidence and mortality data from the United States indicate that the increase in kidney cancer started many years prior to the AIDS epidemic.³

The upward trend in renal cancer mortality in several European countries, as reported by Dr La Vecchia and colleagues, is

consistent with our findings. The heterogeneity in the temporal patterns across Europe is attributed by the authors to variations in risk factors, such as smoking and obesity. However, it is important to note that mortality trends also are affected by variations in death certification practices and survival time.

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Moderate- vs High-Dose Methadone for Opioid Dependence

To the Editor: Dr Strain and colleagues¹ addressed the importance of methadone sodium dose in retaining persons dependent on opioids in treatment. In addition to myriad lesser factors, 2 major reasons for patients to discontinue treatment are the level of doses given to patients and the number of times they are required to visit the clinic.²

In a large clinical trial, we demonstrated that low treatment doses and a requirement that patients attend clinic 5 days per week negatively affected retention rates dramatically. Yet, standard care in the United States demands even more stringent requirements of patients than our trial imposed. These requirements originated when the regulations governing the use of methadone to treat heroin users was established. These provisions require patients to visit clinics 7 times per week for the first 90 days. In our study, 3 other groups—those who received 50 mg/d of methadone sodium and made 2 visits per week, those who received 80 mg/d and made 5 visits per week, and those who received 80 mg/d and made 2 visits per week—were equally successful in remaining in treatment. Thus, retention is modulated by either dose or by number of clinic visits required. However, those in both groups that received 80 mg/d of methadone had a lower proportion of opioid-positive urine samples than the 2 groups receiving 50 mg. Higher methadone dose is more effective for its intended and singularly direct effect on reducing illicit opioid use. In another large randomized clinical trial designed to address treating those addicted to cocaine with fluoxetine hydrochloride, we not only found the treatment ineffectual, but we also demonstrated that the requirement for a high number of clinic visits had a severely negative effect on treatment retention.³

In sum, 2 procedures diminish the utility and availability of an effective treatment. Both are inherent in regulation but also are artifacts of stigma and the unsubstantiated belief that low doses of methadone are good and that more visits are better.

Unfortunately, the regulatory load and stigmatization are already major treatment impediments.⁴ Because of these findings, we urge further attention to dismantling the unique enforcement and regulatory components for dispensing this medication by making it available through prescription from any trained physician. Understandably, many physicians would not participate in this opportunity, but others could expand their treatment armamentarium. This might contribute substantially to bringing treatment of opioid dependence, and perhaps related disorders, into the mainstream of treatment.

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1. Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence. *JAMA*. 1999;281:1000-1005.
2. Rhoades HM, Creson D, Elk R, Schmitz JM, Grabowski J. Retention, HIV risk, and illicit drug use during treatment: methadone dose and visit frequency. *Am J Public Health*. 1998;88:34-39.
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To the Editor: The study by Dr Strain and colleagues¹ seeking an optimal level of medication dose for treatment of patients in methadone maintenance programs ignores that individuals vary in how they metabolize a given amount of medication. Just as there is no optimal insulin or digoxin dose, there is no optimal dose of methadone for all persons in a methadone maintenance program.

In 1984, Tennant et al² reported that equal amounts of methadone resulted in a wide range of methadone serum levels in individual patients. These levels, and not the absolute amount of methadone administered, correlated with clinical success in a methadone maintenance program.

While a fixed-dose methadone schedule may provide successful control for many patients enrolled in a methadone maintenance program, pharmacokinetic variables indicate that a "one size fits all" dosing schedule will result in significant failures.³ In such cases, there is the temptation to label the patients as "drug seeking" when they complain that their symptoms are not controlled when, in fact, their response is due to the variables involved in metabolizing methadone.

For persons whose symptoms are not well controlled while receiving a "standard" methadone dose, measuring the quantitative methadone serum level can provide a guide to an effective dose and help retain persons in the program. This determination (quoted at less than \$40 by 2 commercial laboratories) is extremely cost-effective, considering the high personal and social cost of methadone treatment failure and the patient returning to heroin use.

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1. Strain EC, Bigelow GE, Leibson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence. *JAMA*. 1999;281:1000-1005.
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To the Editor: For more than 50 years, there has been agreement in scientific investigations that "the voluntary consent of the human subject is absolutely essential."¹ The article by Dr Strain and colleagues² comparing different doses of methadone prescribed for the treatment of narcotic addiction raises a fundamental question: Can consent to participate in an experimental protocol be deemed "voluntary" when it is the only means of access to a medication of known efficacy in reducing morbidity and mortality?

The ability to refuse to enter a study always exists, of course; what is essential is that the option be reasonable. In this particular instance, all the subjects were addicts "seeking opioid dependence treatment"—specifically, methadone maintenance treatment in Baltimore, Md, where significant waiting lists exist. Accordingly, the only alternative to accepting the research protocol that was presented was to continue illicit heroin use at substantial risk to health and life.

The specifics of the protocol described by Strain et al are reason for concern. Most notably, adjustments of methadone dose, administered under double-blind conditions, were severely limited in both frequency and amount regardless of clinical indications and patient requests; all patients were detoxified within 40 weeks without consideration of individual therapeutic response, needs, or desires. Half the subjects were assigned to receive a maximum of 50 mg/d of methadone sodium, despite the observation made a decade ago by the National Institute on Drug Abuse that "the most effective dose [of methadone] for the majority of patients is between 50 and 100 mg."³

It is difficult to imagine that many patients addicted to heroin would be inclined to give informed consent and enter a study such as this on a *voluntary* basis, regardless of how one defines that term. The alternative is that they responded to the coercion associated with woefully inadequate availability of treatment. If that indeed is the case, can one maintain that the "absolutely essential" ethical requirement of voluntary consent has been met?

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1. The Nuremberg Code. *JAMA*. 1996;276:1691.
2. Strain EC, Bigelow GE, Leibson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence. *JAMA*. 1999;281:1000-1005.
3. Schuster CR. Methadone maintenance: an adequate dose is vital in checking the spread of AIDS. *NIDA Notes*. Spring/Summer 1989:3.

In Reply: Dr Grabowski and colleagues point out that their work has shown how the required frequency of clinic visits for methadone treatment can affect retention, while methadone dose

influences rates of illicit opioid use.¹ Methadone regulations require patients to attend clinics on a daily basis initially, and months or even years can elapse as patients gradually earn the right to attend on a less frequent basis. Their work suggests these attendance requirements may increase attrition from methadone treatment programs. This is an important point that needs to be considered as federal agencies work to revise current methadone regulations. It is also worth noting that some forms of insurance reimburse daily treatment delivered on-site but do not provide reimbursement for take-home doses of methadone. This can be another factor influencing the current practices of methadone clinics.

Dr Levinson suggests that methadone serum levels can be useful in guiding methadone dose selection. For patients receiving a stable methadone dose, several studies suggest that better outcomes are associated with 24-hour postdose plasma concentrations greater than 150 to 200 ng/mL.²⁻⁴ In our experience, the primary impediments to the use of methadone blood levels have been cost and venous access for patients with long histories of injecting drug abuse. The current cost for a quantitative methadone serum level at our local laboratory is \$63. Since there can be wide variations in methadone blood levels among patients taking the same dose of methadone, at present, we believe the data are much stronger relating clinical outcomes to dose than to blood level. For patients who report opioid withdrawal symptoms despite a relatively high daily maintenance dose of methadone, a blood level may be useful.

Dr Newman questions whether patients would have participated in this clinical trial if methadone treatment were more readily available. We are in complete agreement with his implied advocacy for improved availability of methadone treatment in the United States. However, we take issue with the other points in his letter. Patients enrolling in our study understood that their treatment was part of a research study, that treatment was limited in time, and that assistance was available to apply for community-based methadone treatment if they did not wish to enroll in our research clinic. Newman argues that voluntary consent is only possible when other options are available to the patient. Unfortunately, the usual care for most people dependent on opioids is no care. Our study provided treatment to 192 patients who otherwise may have remained in the community using illicit opioids. In previous work, we have shown that patients dependent on opioids have significant post-treatment reductions in drug use after a 6-month outpatient methadone treatment/research episode.⁵ Those data support our firm belief that treatment research experiences deliver significant benefit to participants.

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Resource Use in Liver Transplantation

To the Editor. The article by Dr Showstack and colleagues¹ regarding the effect of patient characteristics and clinical practice on resource use in liver transplantation includes several points the authors should address. First, the conclusion that patients with higher medical urgency have higher transplantation cost is not a novel finding and was demonstrated years ago.² The authors have not taken into account sufficient variables in patient characteristics to validate their other conclusion, namely, that variability in center practice accounts for large differences in costs for liver transplantation.

The authors failed to describe comparative interinstitutional demographics of patients undergoing transplantation. Table 1 in their article provides the demographic and clinical data for all study patients, yet the authors do not note whether there are real differences among the 3 institutions. According to United Network for Organ Sharing (UNOS) data, the percentage of patients undergoing transplantation while hospitalized ranged from 25% to 50% among the 3 institutions.³ In addition, among the 3 institutions, during the time of the study, the proportion of hepatitis B virus–positive patients varied from 2.9% to 5% (unpublished data, National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplant Database, May 1999). The use of hepatitis B immunoglobulin prophylaxis would account for \$40 000 worth of differences in pharmacy charges during the hospitalization period.

What were the differences in the percentage of “high-risk” cytomegalovirus (CMV) recipients among the centers and what were the institutional approaches to prophylaxis and monitoring of CMV infection and disease? While it would be unusual to see differences in CMV disease during the initial hospitalization, it is conceivable that program practice differences may be manifested by increased posttransplantation readmissions. The lack of total health care costs for the entire year following transplantation would lead to failure in detecting any potential negative impact of economy-minded decisions on patient care. Although acknowledged by the authors, this represents a significant flaw in the study. Centers can “discharge” a patient to another facility, artificially lowering the cost of the transplantation hospitalization but resulting in a higher overall transplantation cost.

Finally, the conclusions of this report, as well as those in another article,⁴ will create payer pressures to use only “blue-ribbon” donors for “blue-ribbon” recipients. This eventually will lead to declining use of “expanded” donors and limit access of transplantation to higher-risk candidates. This is the logical ex-

tension of applying the concepts seemingly embraced by this article, in which economics drive health care decisions.

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In Reply. Due to changes in clinical practices over time, the data cited by Dr Fung from UNOS center-specific graft and patient survival rates for 1997 are not necessarily comparable with our data for patients who received transplants during 1990 to 1995. For example, hepatitis B immunoglobulin was not used routinely by any of the 3 centers during the first years of the study, and there was little difference among the 3 centers in the number of patients with hepatitis B. Cytomegalovirus prophylaxis did not differ significantly among the 3 centers; all centers used regimens that consisted of intravenous ganciclovir, acyclovir, or both; and analyses controlled for donor and recipient CMV status. Finally, the transfer of patients from the transplantation hospital to a lower-cost facility rarely occurred in this era. Thus, the differences found in resource use among the 3 centers were unlikely to have been caused by the factors suggested by Fung.

Currently, the clinical profile of patients undergoing transplantation in the United States is dictated largely by the criteria used for organ allocation. These criteria represent the efforts of the transplantation community to develop objective criteria by which suitable patients with the most advanced disease can be identified and given the highest priority for transplantation. The current scheme for prioritizing patients is based on the Child-Pugh score.¹ In our study, the most important contributor to increased resource use was more advanced liver disease, defined as patients with a Child-Pugh score of at least 10. In fact, in most parts of the country, few patients with a score of less than 10 have sufficient priority to be offered livers. Thus, national policy is already committed to transplanting livers in patients who are likely to consume greater resources. Moreover, the Institute of Medicine recently acknowledged that if broader sharing of livers for transplantation were to occur, as it recommended, then a greater number of transplantations would be performed in patients with more advanced disease, and the costs of liver transplantation would increase.²

As patients with more advanced disease receive a higher proportion of transplants, there will be increased pressures to deliver cost-effective care, which requires that a program be able to quantify the costs of transplantation, and patient characteristics and clinical services affect those costs. The issue is whether we are most effectively and efficiently using our limited clinical and financial resources for organ transplantation.

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CORRECTIONS

Omission of Investigator Names: In the Original Contribution entitled "The Effect of Raloxifene on Risk of Breast Cancer in Postmenopausal Women: Results From the MORE Randomized Trial," published in the June 16, 1999, issue of THE JOURNAL (1999;281:2189-2197), the names of the study investigators were inadvertently omitted and not acknowledged for their contributions to the article. A full list of the investigators of the study has been subsequently published in the Original Contribution entitled "Reduction of Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis Treated With Raloxifene: Results From a 3-Year Randomized Clinical Trial," published in the August 18, 1999, issue of THE JOURNAL (1999;282:637-645).

Incorrect Wording: In the Original Contribution entitled "Reduction of Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis Treated With Raloxifene: Results From a 3-Year Randomized Clinical Trial," published in the August 18, 1999, issue of THE JOURNAL (1999;282:637-645), there was incorrect wording in 2 tables and 1 figure. On page 640 in Table 2, for study group 1, the relative risk for raloxifene 120 mg/d that read "0.5" should have read "0.6," and the total relative risk for raloxifene 120 mg/d that read "0.6" should have read "0.5." On page 641 in Table 3, the title that read "Nonvertebral Fractures in 4536 Women Receiving Raloxifene Hydrochloride Therapy and 2292 Women Receiving Placebo" should have read "Nonvertebral Fractures in 5129 Women Receiving Raloxifene Hydrochloride Therapy and 2576 Women Receiving Placebo." On page 642 in the legend for Figure 3, the sentence that read "This represents 2292 women who received placebo and 4536 women who received raloxifene therapy for osteoporosis" should have read "This represents 2576 women who received placebo and 5129 women who received raloxifene therapy for osteoporosis."

Incorrect Wording: In the Original Contribution entitled "Clinical and Angiographic Characteristics of Exertion-Related Acute Myocardial Infarction" published in the November 10, 1999, issue of THE JOURNAL (1999;282:1731-1736), there was incorrect wording in the last sentence of the "Results" section on pages 1732-1733. The sentence should read as follows: Patients with an exertion-related MI were more likely to have established coronary artery disease (CAD) risk factors including male sex, obesity, current cigarette smoking, and hyperlipidemia (TABLE 1), and were less likely to use aspirin or β -blockers and tended to have less hypertension ($P = .08$) and established cardiac disease ($P = .06$).