Hepatic Arterial Infusion of Chemotherapy for Metastatic Colorectal Cancer

To the Editor: The study of hepatic arterial infusion of chemotherapy after resection of hepatic metastases in patients with colorectal cancer, reported by Kemeny et al. (Dec. 30 issue),1 represents a positive development in the management of colorectal cancer. However, clinicians planning to use this therapy may be confused by the dosages reported in the article. By convention, the dosage for hepatic intraarterial chemotherapy is based on the amount of drug delivered to the patient. Since infusion devices have variable flow rates and deliver only part of their contents in 14 days, the total dose of fluorouridine placed in the device is much more than the dose the patient receives.

Kemeny et al. state that the infusion pump was filled with “0.25 mg of fluorouridine per kilogram of body weight per day for 14 days in combination with 20 mg of dexamethasone; 50,000 U of heparin, and enough normal saline to result in a volume of 50 ml.” This does not mean that the dose delivered to patients was 0.25 mg per kilogram per day for 14 days. Because the average flow rate for these devices is approximately 2.0 ml per day, the dose of fluorouridine that each patient received was about 0.14 mg per kilogram per day.

Given the risk of hepatobiliary toxicity and the narrow therapeutic index for this treatment,2 the dose of hepatic intraarterial fluorouridine is a critical factor in the safe administration of regional chemotherapy. The dose of fluorouridine should be based on the flow rate of the pump used to deliver the drug.

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To the Editor: Kemeny et al. report that among patients with resected liver metastases, the survival rate at two years was higher for the patients who received the combination of systemic chemotherapy and hepatic arterial infusion of fluorouridine than for those who received systemic chemotherapy alone. However, the curves in Figure 1 of their article show that the overall survival rates for the two groups did not differ significantly by either the Wilcoxon test or the log-rank test. Furthermore, the appearance of the curves suggests that the survival rates for the treatment groups did not differ significantly at one year or at three years. Although the rate at five years appears to be better for the combined-therapy group, this difference was probably not statistically significant, since the median follow-up was only 62.7 months.

More bothersome is the fact that although the treatment groups appear to have been well balanced with respect to the base-line characteristics enumerated by the authors, the difference in the survival rate at two years was significant only after adjustment by multivariate analysis with the use of the “best subgroup-selection method.” The authors provide no reference for this method, but their description suggests a stepwise approach that may have diminished the value of the multivariate analysis.1 Their inclusion of some variables in the models for disease progression but not in the model for survival is counterintuitive. Certainly, the length of time since the diagnosis of primary cancer, the length of time since the last course of chemotherapy, and the lactate dehydrogenase level are all potentially important enough to be included in a multivariate model of survival. It is particularly disturbing that the location of the primary tumor, the size of the largest liver metastasis, the length of time since the diagnosis, and the length of time since the last course of chemotherapy were not reported as base-line characteristics. In addition, the authors do not mention any tests for the assumption of proportional hazards.2

Kemeny et al. suggest that hepatic arterial infusion of fluorouridine improves the outcome for patients with colorectal cancer and resected liver metastases. However, the au-
Theors’ data seem unconvincing. Even assuming the appropriateness of their multivariate adjustment, the difference in survival between the treatment groups appears to be small in relation to the morbidity and inconvenience associated with hepatic arterial infusion.

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To the Editor: According to the results of the single-institution study reported by Kemeny et al., hepatic arterial infusion plus intravenous chemotherapy results in a significantly lower rate of hepatic relapse and a higher rate of survival at two years than systemic chemotherapy alone in patients with resected hepatic metastases from colorectal cancer. Unfortunately, because of extrahepatic spread, differences in disease-free survival and overall survival were not significant. Thus, the main finding of this study is that hepatic relapse is delayed with the combined treatment.

In our opinion, these results are partly biased by the heterogeneity of the patients enrolled in the study and by the difference in the duration of treatment. Since 21 patients (13 percent) had positive margins, the surgery they underwent was palliative.1 More than half the patients had previously received chemotherapy, and the median interval from resection of the primary tumor to the development of liver metastases was short (6.8 months in the combined-therapy group and 9.1 months in the monotherapy group). These two points constituted poor prognostic factors with respect to a response to intravenous chemotherapy and survival.2 On the other hand, hepatic arterial infusion has been recommended as an effective second-line therapy in patients with liver metastases that are resistant to systemic chemotherapy,2 and some of the patients enrolled in the recent study by Kemeny et al. were probably in this category.

We suggest that the improvement in survival at two years in the combined-therapy group, reported by Kemeny et al., may have been due to the advantage of hepatic arterial infusion in the subgroup of patients with positive margins. We understand that the data were analyzed on an intention-to-treat basis, but we would like to know either the rates of survival at two years for the subgroups of patients in whom surgery was palliative or curative or the results of a test of the interaction between treatment and positive or negative surgical margins in the multivariate analysis. The key point is whether there is a survival advantage with the use of adjuvant hepatic arterial infusion after curative resection. In addition, the duration of treatment was longer for the combined-therapy group than for the monotherapy group (55 weeks vs. 21 weeks), a difference that may have been particularly important for the subgroup of patients in whom surgery was palliative.

The initiation of postoperative chemotherapy was delayed in some patients, and others did not receive it because of surgical complications, refusal, or technical problems with hepatic arterial infusion. Therefore, the results of this interesting study should also prompt an investigation of the use of fluoropyrimidine-based preoperative chemotherapy, including new drugs such as irinotecan or oxaliplatin, in order to increase both the number of patients in whom subsequent surgery is curative and the overall survival rate.

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To the Editor: Kemeny et al. have previously reported on the benefit of additional hepatic arterial infusion of fluorouridine and dexamethasone as compared with systemic fluorouracil and leucovorin. The authors should be credited for performing this important randomized study, and in particular for their excellent surgical results. However, the use of hepatic arterial infusion of fluorouridine after liver resection, despite the fact that there is no clear overall benefit of this approach, requires some comment about the design of the study and the interpretation of its results. We had different results and are convinced that hepatic arterial infusion with fluorouracil and leucovorin is at least as effective as hepatic arterial infusion with fluoruridine when one considers hepatic and extrahepatic disease.1,2

To assess internal validity, we would like more information with regard to the Consolidated Standards of Reporting Trials (CONSORT) statement; the method of masking treatment assignments and the details of the main analyses as indicated in the study protocol are particularly important. The projected sample size was based on survival rates at two years, rates of progression, and one-sided tests without adjustment for the censoring of data and for the use of two main end points. The use of two-sided tests in the final analyses seems to be more appropriate, but the authors did not adjust the sample size in order to achieve the desired statistical power when they changed the study protocol. The interpretation of the study findings as positive is based on the improvement in the results at two years in the combined-therapy group, although for the comparison of overall survival at two years (P=0.03), statistical significance was not actually demonstrated because there was no outline of the multiple-testing procedure.

The authors do not explain their rationale for selecting the main end points and the statistical methods used in their analyses. The differences in the event rates at two years are particularly important, if there is the possibility of a cure. However, the data shown in Figure 1 of the article do not support the hypothesis that additional treatment with hepatic arterial infusion has a curative potential. We were also
The tick marks on the curves indicate censored data. The difference in survival between the two study groups was not significant (P=0.59 by the log-rank test).

Figure 1. Kaplan–Meier Estimates of Overall Survival According to the Treatment Received.

The authors reply:

To the Editor: In our study, the recommended dose of floxuridine was the total dose, and it was not adjusted for the flow rate. To make an adjustment for the flow rate, the dose should be 0.14 mg per kilogram multiplied by the pump volume and divided by the pump flow rate. We chose two-year end points because they were used in many other reports. The rate of survival at two years was significantly higher in the combined-therapy group than in the monotherapy group (86 percent vs. 72 percent, P=0.03). A study with many more patients than the 156 in our study would be necessary to show a significant increase in overall survival. The difference in the median period of survival (72.2 months in the combined-therapy group vs. 59.3 in the monotherapy group) may have clinical importance. The best subgroup-selection method is described by Furnival and Wilson.\(^1\) We chose the stepwise approach to pick the factors for the multivariate analysis because we believed that this approach would result in the selection of the best factors, which can differ in the models for overall and progression-free survival. With a multivariate analysis that included the potentially important variables suggested by Dr. Atkins, the risk ratio for death was 2.33 in the monotherapy group as compared with the combined-therapy group (P=0.028). We used Cox’s proportional-hazards model for easy interpretation of the variables.

Conroy et al. suggest that we selected patients who had characteristics associated with resistance to systemic chemotherapy. If such patients can benefit from hepatic arterial infusion, then it is a useful treatment. The duration of treatment was longer for the combined-therapy group than for the monotherapy group. However, the patients in the combined-therapy group were treated every five weeks rather than every four weeks. We did not report the results of subgroup analyses of data at two years because we had too few patients to do so.

We believe hepatic arterial infusion with floxuridine is better than hepatic arterial infusion with fluorouracil plus leucovorin because of the higher hepatic extraction rate of floxuridine (minimizing toxicity elsewhere and allowing for combination with new agents such as irinotecan or oxaliplatin) and because of the poor results of the study by Lorenz et al.,\(^2\) in which only 30 percent of patients completed treatment.

As outlined in the CONSORT statement, all enrolled patients were eligible and were followed. As for the method of assignment to a treatment group, sealed envelopes were picked from boxes in the operating room; the envelopes were labeled according to the number of metastases (1, 2 through 4, or more than 4) after the surgeon had confirmed how many liver metastases were present.

A one-sided statistical test was initially chosen, because we believed the combined therapy would be better than systemic therapy alone. P values for one-sided tests in the final analyses would have made our already significant results even more pronounced. The study showed improved outcome at two years. No multiple-testing procedures were used. Data on a patient were censored if death occurred before the end point, without evidence of disease. Many pa-

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patients would disagree with the comments of Lorenz et al. concerning the curative potential of treatment and would choose the treatment that offered a greater chance of being alive at two years, even if it were not curative.

We would also like to note that the first sentence of the Methods paragraph in the Abstract of our article should have referred to six cycles of similar systemic therapy, not six weeks.

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Volume of Procedures at Transplantation Centers and Mortality after Liver Transplantation

To the Editor: Edwards et al.1 (Dec. 30 issue) compared the one-year survival at centers performing 20 or fewer liver transplantations per year with survival at centers performing more than 20 transplantations per year and found excess mortality in the former group.

The authors seek to determine a turning point for experience. Unfortunately, they did not choose a priori categories. They justified their choice of the number 20 by appealing to their Figure 1. They state that “mortality rates stabilized at centers that performed more than 20 transplantations per year and increased inversely with transplantation volumes of less than 20 per year.” However, this choice appears to have been arbitrary. To our eyes, in fact, the graph may very well “stabilize” beyond 20, perhaps at 30, transplantations per year, with the result that those sites with mortality rates above 30 percent would be included. The authors offer no statistical definition of “stability.”

Moreover, Figure 1 simply reflects the greater statistical variability of small samples than of large ones; the choice of cutoff point should not be based on it at all. For example, all the excess mortality may be attributable to centers performing 1 to 10 (or 1 to 15) liver transplantations, with those performing 11 to 20 (or 16 to 20) at no disadvantage. A statistical analysis that carefully compared proper subgroups, which Edwards et al. do not report, would be required for the accurate identification of a turning point for experience.

Hunsicker, one of the authors of the study by Edwards et al., was reported in the New York Times to have said that medical research shows that patients fare best in centers that perform at least 20 liver transplantations per year.2 Hunsicker has used the number 20 to argue that there should be one liver transplantation program in Iowa, not two, because the number of usable donated organs is about 40 per year. Hunsicker was quoted as saying, “So if we had two programs and we split evenly, then we would both be at the very lowest end of the numbers necessary to maintain competence.”2 Thus, we are concerned that the number 20 may have been chosen for political, not scientific, reasons.

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To the Editor: Can Edwards et al. explain more accurately the criteria used in their initial analysis to set the cutoff point at 20 patients per year? In addition, the performance of the multivariate models used was not specified; that is, what proportion of the variation in the outcome was explained by the independent variables? Moreover, the use of better clinical covariates—such as the severity of disease and coexisting illnesses—could have improved the case-mix adjustment.

Edwards et al. also acknowledge that some unmeasured factors may have influenced the relation between volume and outcome. The total number of solid-organ transplantations—not just liver transplantations—done at the hospitals may be an important covariate. Similarly, the volume of liver surgery other than transplantations, the amount and quality of intensive care resources, and the availability of outstanding services for the treatment of infectious diseases and outstanding hematology and interventional radiology services may also be important determinants of the rates of death and complications.

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To the Editor: In an analysis in which a covariate (such as sample size) is related to an outcome (such as patient survival) in a nonlinear way, there is always an element of judgment about which model to use. The least subjective approach is to use a nonparametric method to graph the relation and to divide the centers into two groups according to the apparent inflection point. Those centers with volumes closest to the cutoff point will be less divergent from the reference group.

Laks et al. suggest that the less favorable outcomes in the smaller centers might be the result of greater variability in the outcome because of smaller numbers. This would be true for the outcome at a single center. But the outcomes at the smaller centers, as a class, are less favorable than those in the reference group. The total number of patients at the smaller centers was sufficient for this conclusion to be very robust, as confirmed by the statistical tests of significance that we used. Laks et al. also ask whether political issues in Iowa affected the choice of cutoff point. The initial analyses for this study were done before the issue in Iowa arose, and it therefore had no influence on these analyses.

Hillebrand and Concepcion note that UNOS data on more recent liver transplantations did not show a significant effect of volume. However, that analysis lacks risk adjustment and does not account for center affiliation. Our analysis of data from 1987 through 1991 and 1992 through 1994 demonstrates that the effect of volume has been present during different eras and is unlikely to disappear suddenly.

In response to Bettschart et al.: our multivariate model, which included only donor and recipient factors, accounted for about 40 percent of the variability in center-specific mortality rates. Effects related to the transplantation center, of which the volume is a component, may account for a significant portion of the remaining 60 percent. However, Cox and Wermuth cautioned that the interpretation of \( R^2 \) is misleading in linear regressions with binary responses because “low values are inevitable even if an important relation is present.”

Clearly, many transplantation-center factors that might contribute to variability in outcomes were not included in this model because the data were unavailable in the scientific registry. We agree that having more clinical detail permits better discrimination, but the message is clear: a lower volume of procedures at transplantation centers is associated with higher mortality after liver transplantation.

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Firearms and Suicide

To the Editor: The article by Wintemute et al. (Nov. 18 issue)1 and the accompanying editorial by Rosenberg et al.2 add to the public health literature on firearms. Rosenberg et al. note that we need more information about the circumstances in which suicide with the use of firearms occurs. Clinical studies can complement an epidemiologic approach to help provide such information. One clinical method is to conduct comprehensive interviews with persons who have survived serious suicide attempts involving firearms, in order to determine the psychiatric diagnosis, personality profile, motivation for the attempt, and precipitating factors. These studies illustrate several points.3

First, shootings are often preceded by a crescendo of disputes with an intimate partner, the attempts are often not well planned, and the patients tend to abuse alcohol. These patients are rarely psychotic but have serious domestic and personality problems, often of an antisocial nature.

Second, the fact that the attempts are often impulsive can give the incorrect impression that these are well-adjusted persons who, against the flow of their lives, shot themselves. In fact, long-term clinical history shows that there is a more complicated pattern of long-standing problems and that the suicide attempt was one of several forms of self-destructive behavior.

Finally, a clinical perspective sheds light on prevention. This has implications for the proposed background screening checks before a person can purchase a firearm. A screening process that identifies only admission to a psychiatric unit or documented severe illness such as psychosis will almost certainly not identify a subgroup of persons at high risk. The California procedure rightly casts the net more broadly, attempting to identify persons with substance abuse and a record of violent misdemeanors. Nonetheless, the
clinical studies indicate that even this approach is likely to be insufficient to identify the many people with domestic problems, involvement in custody battles, and alcohol-related problems that may not be severe enough to come to the attention of public authorities but that predispose them to the use of firearms for suicide attempts.

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To the Editor: The comments of de Moore and Robertson emphasize that violence involving firearms results from long-standing personal and interpersonal difficulties and that existing programs will not identify many persons who are at risk for such violence. I agree with both points and will continue their discussion of the second.

In 1998, 63.3 percent of persons who were denied approval for the purchase of handguns were convicted felons; 13.2 percent had been convicted of misdemeanors involving domestic violence or were subject to restraining orders; 6.1 percent were fugitives. Only 0.7 percent of denials were based on mental illness or disability, and only 0.9 percent on drug addiction.

Some 18 states have enacted broader criteria for denial of handgun purchases, which lead to 6.6 percent of all denials. California, for example, prohibits handgun purchases by persons who have been convicted of any misdemeanor on a list that includes most common violent misdemeanors. As compared with handgun purchasers with no criminal history, misdemeanants who buy handguns are much more likely to commit new gun-related or violent crimes. Prohibiting persons convicted of violent misdemeanors from purchasing firearms is widely supported; 75 percent of gun owners favor adding misdemeanors involving assault and battery to the list of criteria for denial, and 91 percent would prohibit handgun purchases by persons with misdemeanors involving the brandishing of a firearm.

In addition, de Moore and Robertson mention the importance of a history of alcohol abuse and a history of other drug abuse as risk factors for suicide; both are risk factors for homicide as well. Federal law already prohibits the purchase of firearms by addicts and unlawful users of controlled substances. The law is rarely applied but should be vigorously enforced. Federal registries of persons registered as addicts or recently convicted of crimes involving the use of controlled substances should be established. A few states prohibit handgun purchases by persons who have been convicted of offenses involving the abuse of alcohol or other substances, but generally only if they have had multiple convictions. Again, such policies are widely supported; 59 percent of gun owners would prohibit gun purchases by persons who have been convicted of driving while drunk, and 89 percent would deny guns to those who have been convicted of possessing equipment for illegal drug use.

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Congenital Autoimmune Diabetes Mellitus

To the Editor: Type 1 diabetes mellitus is an organ-specific T-cell-mediated autoimmune disease characterized by cellular infiltration of pancreatic islets (insulitis) and destruction of insulin-producing beta cells. Congenital diabetes is extremely rare, and very little is known about its pathogenesis.

We describe a neonate in whom hyperglycemia, glycosuria, and moderate acidosis developed 12 hours after birth. He was born at 34 weeks of gestation and was small for gestational age (1600 g). His mother was healthy and had an uncomplicated pregnancy. Congenital diabetes was confirmed by the finding of low serum C-peptide and insulin concentrations. Intravenous treatment with insulin (0.05 IU per hour) was started. Chromosomal abnormalities were not detected in the infant or his parents.

At four days of age he had high serum concentrations of insulin and glutamic acid decarboxylase autoantibodies, whereas the values in his mother were normal. Both mother and infant had negative results on tests for the following autoantibodies: islet cell, anti-IA2 (anti–tyrosine phosphatase–like protein), anti–GM2-1 (islet-specific monosialo-ganglioside), anti–thyroid peroxidase, antithyroglobulin, antinuclear, and anti–extractable nuclear antigen antibodies. Serologic tests for viral infections were negative. At six days of age, persistent, diffuse eczematous lesions, diarrhea, and cosinophilia developed, and the infant died of necrotizing enterocolitis on day 26. A skin-biopsy specimen showed no sign of graft-versus-host disease. His mother had a great-uncle, a second cousin, and two brothers who had died of undetermined causes within six months after birth and an uncle and a daughter who had died before birth.

Islet autoimmunity in this infant was first indicated by the presence of insulin and glutamic acid decarboxylase autoantibodies and confirmed by the finding of marked lymphocytic infiltration in the pancreas (with insulitis), heart, and lungs (Fig. 1A, 1B, and 1C). The infiltrates contained many T lymphocytes (CD3+) (Fig. 1D, 1E, and
1F), the majority of which were CD45RO+ (activated [memory]) T cells (Fig. 1G, 1H, and 1I). The islets contained cells that stained with antibodies to glucagon but not to insulin, indicating beta-cell–specific autoimmune destruction. The presence of enteroviruses was excluded by a reverse-transcriptase–polymerase-chain-reaction assay. The infant had high serum IgA and IgE concentrations, probably as a consequence of the massive T-cell activation, but no other abnormalities of immunologic function. The infant also had at least one diabetes-susceptibility HLA allele (DQB1* 0201, DR3) inherited from his father (infant: DQB1* 0501/0201, DR1/DR3; mother: DQB1* 0501/0301, DR1/DR4; father: DQB1* 0301/0201, DR4/DR3).

Because severe beta-cell impairment was present at birth, it is likely that autoreactive T cells had been primed and reacted against self-antigens during fetal life. This rare autoimmune syndrome may have a genetic basis, as suggested by the maternal pedigree. In conclusion, these findings in-

Figure 1. Histologic Appearance of Specimens of the Pancreas, Heart, and Lung of a Neonate with Congenital Autoimmune Diabetes Mellitus.

The sections shown in Panels A, B, and C were stained with hematoxylin and eosin (×50); the sections shown in Panels D, E, and F by indirect immunoperoxidase with anti-CD3 antibodies (×40); and the sections shown in Panels G, H, and I by anti-CD45RO antibodies (×40).
dicate that the fetal immune system is able to mount a pathologic organ-specific autoimmune response.

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Patients 65 Years of Age or Older in Cancer-Treatment Trials

To the Editor: It is surprising that in the article by Hutchins et al. on the underrepresentation of patients 65 years of age or older in trials of cancer treatment (Dec. 30 issue), Table 1 shows that only 42 percent of persons enrolled in the Southwest Oncology Group trials were men. This figure is almost identical to the participation rate for men reported in an earlier analysis of National Cancer Institute trials (43 percent). It is cause for concern that the authors do not mention the fact that their trials include only one man with prostate cancer for every five women with breast cancer.

The issue, it would seem, is not whether women are adequately represented in cancer research but why it is that men are underrepresented, whether the assessment is based on the numbers of men and women with diagnoses of cancer or on sex-specific rates of cancer in the general population.

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To the Editor: We would like to commend Hutchins et al. for highlighting the underrepresentation of patients 65 years of age or older in cancer-treatment trials. The authors did not give information about reimbursement for the care of this group of patients while they were enrolled in clinical trials, and in their discussion, they did not consider financial barriers as the only explanation for the underrepresentation.

We believe that financial coverage is particularly important because half of all cancers occur in patients 65 years of age or older, and more than 60 percent of all persons who die from cancer are Medicare beneficiaries. Currently, the costs of routine care for Medicare beneficiaries enrolled in clinical trials are not covered. Because of the lack of Medicare coverage, we and many of our colleagues have been unable to enroll patients 65 years of age or older in any clinical trial since 1997.

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More on Chewing Gum

To the Editor: In their analysis of the energy expended in chewing gum (Dec. 30 issue), Levine et al. instructed subjects to chew gum “at a frequency of precisely 100 Hz (a value that approximates chewing frequency at our institution) with the aid of a metronome.” I am curious about the use of hertz, the Système International unit of frequency measured in cycles per second. As defined, a value of 1.0 Hz rather than 100 Hz would be more plausible. Alternatively, if the experimental protocol had called for a setting of 100 Hz on a standard metronome, as might be inferred from the quoted text, the unit of measurement that should have been used is Maelzel’s metronome (MM), which indicates oscillations per minute. A measurement of MM 100 is consistent with calculations based on my own informal observations of gum chewing.

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3. Hertz.” In: Encyclopedia Britannica Web site. (See http://www.encyclopedia Britannica.com/bcom/eb/article/0/0,5716,41115+1+40251,00.html.)

Dr. Levine replies:

To the Editor: Mr. Florman is correct: we did use erroneous units to describe the normal chewing rate at our institution. We should have used chews per minute rather than hertz. The rate of 100 chews per minute at our institution indeed approximates that calculated by Mr. Florman in

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New York City. The rate varies according to body size. In quadrupeds, the chewing rate relates to body mass to the \(-0.128\) power, a relation that relates primarily to jaw mechanics rather than to metabolic needs. Hence, larger organisms chew with greater thermal efficiency than smaller organisms, and I would not want to mislead readers of the Journal regarding any inefficiency at our institution.

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Anabolic–Androgenic Steroids as a Gateway to Opioid Dependence

To the Editor: Athletes who abuse anabolic–androgenic steroids may go on to abuse opioid agonist–antagonists such as nalbuphine\(^1\) or even classic opioids such as heroin.\(^2,3\) We studied this phenomenon among patients treated at Sunrise House, a private inpatient facility for substance-dependence treatment in northern New Jersey. Among 227 men admitted for dependence on heroin or other opioids in 1999, we found that 21 (9.3 percent) had a history of anabolic–androgenic steroid use. In contrast, among 197 men admitted for opioid dependence in 1990, only 1 (0.5 percent) reported prior use of anabolic–androgenic steroids (P<0.001 by two-tailed Fisher’s exact test).

None of the 21 men in 1999 reported any form of substance abuse or dependence before their use of anabolic–androgenic steroids. The mean (±SD) age at the time of their first use of anabolic–androgenic steroids was 20.9±2.4 years and the age at the time of their first use of opioids was 27.0±4.0 years. The information they provided strongly suggests that they were introduced to opioids through anabolic–androgenic steroid use and the bodybuilding subculture: 17 of the 21 men (81 percent) first purchased opioids from the same drug dealer who had sold them anabolic–androgenic steroids; 14 (67 percent) were introduced to opioids by a fellow bodybuilder; 18 (86 percent) claimed that they first used opioids to counteract insomnia and irritability induced by anabolic–androgenic steroids; and 14 (67 percent) had used opioids to counteract depression associated with withdrawal from anabolic–androgenic steroids. All 21 of the men reported at least one of these four attributes.

Demographically, these men appeared atypical for opioid users; they all lived in suburban New Jersey and reported a mean household income of $69,800 (range, $38,000 to $145,000). They reported serious associated morbidity. Since the time of their first use of opioids, 15 (71 percent) had been charged with possession of a controlled substance or prescription fraud; 5 (24 percent) had served time in prison, including 1 for attempted murder; and 7 (33 percent) had made at least one suicide attempt. In the 1 to 11 months since their discharge from Sunrise House, 17 (81 percent) have relapsed into opioid use, and 2 (10 percent) have committed suicide.

These findings suggest an alarming trend: that anabolic–androgenic steroids may serve as “gateway” drugs to opioid dependence, with substantial associated morbidity and even mortality. Although our study cannot establish that anabolic–androgenic steroid use per se led to opioid dependence in these men, the data we report strongly suggest this interpretation. Alternatively, what we observed might be specific to our facility, but our facility is in a region not noted for unusually high rates of either anabolic–androgenic steroid use or opioid dependence. Progression from anabolic–androgenic steroid use to opioid dependence deserves further exploration as a public health problem.

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