Correspondence

Prevalence of Hepatitis C Virus Infection in the United States

To the Editor: Alter et al. (Aug. 19 issue) present valuable data on the prevalence of hepatitis C virus (HCV) infection in the United States. However, their analyses of risk factors for HCV infection are flawed because the third National Health and Nutrition Examination Survey (NHANES III) data did not contain information necessary to control for confounding by the single most important risk factor for HCV infection — namely, injection-drug use. Their conclusions regarding the transmission of HCV by illegal drug use and sexual promiscuity should not be used to counsel patients or to set public health policy.

Although the omission of a question of injection-drug use from NHANES III is unfortunate in itself, the inability to control for injection-drug use should have led the authors either to omit this analysis or to be much more circumspect in their conclusions. They acknowledge in the discussion that injection-drug use is the single most important risk factor for HCV infection; other authors have estimated that the odds ratio for HCV seropositivity associated with injection-drug use is more than 100. Since injection-drug use is also associated with smoking marijuana, inhaling cocaine, and sexual promiscuity, it is likely that the associations with these variables were confounded by its omission from the logistic-regression model.

The authors correctly discount marijuana use as a means of HCV transmission and recognize that the previously reported associations of cocaine inhalation with HCV infection may have been confounded by injection-drug use. In contrast to the findings in the few references cited by Alter et al., a broader review of the literature suggests that transmission to sexual partners is inefficient at best. Of these facts and the probable confounding mentioned above, the conclusion of Alter et al. that “the strongest factors independently associated with HCV infection were illegal drug use and high-risk sexual behavior” is unfortunate.

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To the Editor: Alter et al. acknowledge the biologic implausibility of the transmission of HCV through marijuana use and suggest that the associations between transmission and the use of illegal drugs may be due largely to an association with a history of injection-drug use. In contrast, the authors appear to dismiss the considerable biologic and epidemiologic evidence that sexual transmission of HCV occurs rarely. First, HCV is uncommonly found in either seminal fluid or vaginal secretions, even among persons who are coinfected with human immunodeficiency virus type 1 or transplant recipients, in whom the serum viral load is generally higher. Second, prospective and cross-sectional partner studies among HCV-infected groups without injection-drug use, such as women infected through the receipt of contaminated anti-D immune globulin and men with hemophilia, suggest that transmission to sexual partners is

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rare. Third, although a relatively high prevalence of HCV infection has been found among people treated in sexual health clinics and homosexual men, after adjustment for a history of injection-drug use, there is often no association with the number of sexual partners or sexual practices.

Associations between HCV infection and the number of sexual partners or reported sexual contact with an HCV-positive person are most likely the result of confounding by injection-drug use in studies in which no history of injection-drug use is sought or the result of residual confounding in studies in which such a history is sought. Recent evidence suggests that survey methods can considerably influence the reporting of illegal and stigmatized behavior. In a national survey of adolescent boys in the United States, participants who were randomly assigned to computer-assisted self-interviewing were almost four times as likely to report a history of injection-drug use as those who were randomly assigned to the more traditional self-administered questionnaire.

Other independent associations with HCV infection in the study by Alter et al., such as those of marital status, level of education, and the poverty index, are also almost certainly explained on the basis of confounding by injection-drug use.

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To the Editor: Italy has a different epidemiologic pattern of HCV infection from the United States. Community-based surveys (and unpublished data) of samples of the general population selected from the census by a systematic random sampling procedure have shown much higher prevalence rates, particularly among the elderly (Table 1). The risk of HCV infection seems to be lower in the recent past than in the distant past. The now-abandoned practices involving risk of percutaneous exposure, such as repeated use of a nondisposable glass syringe for medical purposes, were a strong predictor of HCV infection in the communities studied. The decreased use of glass syringes over time may explain the change in prevalence rates in the youngest age groups in Italy. Thus, HCV infection was widespread in the distant past in Italy, whereas in most cases in the United States transmission was recent. Moreover, the modes of transmission have differed. A similar increase in the prevalence of HCV infection with age has been observed in a community-based survey in Spain: subjects who were 50 to 65 years old were more than eight times as likely to be positive for HCV infection as those who were 18 to 29 years old.

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nor), they account for a much smaller proportion of infections because of the relatively small proportion of people with such exposure.

Neither the inability to identify users of injection drugs nor the potential underreporting of illegal behaviors is likely to account for the significant associations we found between HCV infection and both sexual behavior and sociodemographic variables. We used a history of cocaine or marijuana use as a surrogate for injection-drug use. Most users of injection drugs have also used cocaine and marijuana, and the prevalence of cocaine and marijuana use in the United States is much higher than that for injection-drug use alone. Thus, it is likely that our analysis, which included adjustment for sociodemographic characteristics, resulted in more conservative estimates of the adjusted odds ratios for the sexual-behavior variables.

The epidemiology of HCV infection in other countries may differ from that in the United States, as indicated by the results of a randomized clinical trial in which they compared early revascularization with reperfusion independent of myocardial salvage. Circulation 1987;75:299-306.


The authors reply:

To the Editor: We agree that there may be benefits of early revascularization associated with myocardial salvage that are different from the potential for late revascularization to improve long-term ventricular remodeling and electrical stability. The distinction between early and late reperfusion is often blurred, particularly in the setting of cardiogenic shock. Salvage of myocardium can be achieved more than 12 hours after myocardial infarction because of ischemic preconditioning and intermittent opening and closing of the infarct-related artery. Furthermore, relief of the severe ischemia and progressive necrosis that result from the sustained coronary hypoperfusion that occurs in shock may allow myocardial salvage up to 24 to 48 hours after myocardial infarction. In addition, late revascularization for patients who have triple-vessel and left main dis-
ease with impaired left ventricular function should improve long-term survival. We agree that it is also possible that pa-
tency of the infarct-related artery after an apparently com-
plete infarction may improve long-term outcome by mul-
tiple mechanisms.1,2 A randomized clinical trial testing this hypothesis is beginning.

The SHOCK (Should We Emergently Revascularize Oc-
ccluded Coronaries for Cardiogenic Shock) study was not
designed to distinguish between the benefits of early and late opening of infarct-related arteries. Our data can directly
assess only the effect of a strategy of early revasculariza-
tion, a median of 14 hours after myocardial infarction (in-
terquartile range, 8 to 26 hours), as compared with no re-
vascularization or late revascularization, at a median time of
119 hours (interquartile range, 95 to 181 hours). We did not
demonstrate that there was no benefit associated with early revascularization at 30 days; rather, we failed to prove that
there was a benefit. The distinction is important. Although
the difference in survival rate was statistically significant only
beginning at 6 months, the curves were separating by 30
days. We agree with the statement in Ryan’s editorial (Aug-
26 issue)3 that the difference between the groups in survival at 30
days (although only a trend) was large, at 9.3 lives
saved per 100 patients treated, in contrast to 2 lives saved per
100 patients treated with thrombolytic agents.4 For patients
less than 75 years old the difference at 30 days was large
(15.4 lives saved per 100 patients) and statistically significant.

The six-month mortality rate for patients assigned to
medical therapy who survived long enough and were cli-
cally selected to undergo late revascularization was rela-
tively low, at 38 percent (14 of 37 patients), as expected.
The superiority of early revascularization, however, is sug-
gested by the similar 1-year survival rate among 30-day sur-
vivors in the medical-therapy group, whether or not they
underwent delayed revascularization. Analyses are being per-
fomed to try to assess the effect of early as compared with
late revascularization on longer-term survival, but any con-
cussions will be limited because patients in the initial med-
ical-therapy group were not randomly assigned to late or
no revascularization.

Surgery to Cure the Zollinger–Ellison Syndrome

To the Editor: Norton et al. (Aug. 26 issue)1 report 10-
year surgical cure rates of 34 percent in 125 patients with
sporadic gastrinomas and 0 percent in 28 patients with mul-
tiple endocrine neoplasia type 1. The authors’ objective was
limited to the elimination of discoverable gastrinoma, as de-
termined by measurements of serum gastrin, secretin tests,
and imaging studies. A preferable objective would have been
to eliminate reliably the aggressive peptic ulcer disease and
diarrhea that characterize the Zollinger–Ellison syndrome
by suppressing acid secretion with the use of proton-pump–
inhibitor therapy.2

Norton et al. provide little information on morbidity or
the functional outcome after surgery — for example, the
number of patients who still required drug treatment. At
10 years, the rates of cure, or disease-free survival, were
much lower than the rates of disease-specific survival (95
percent in the patients with sporadic gastrinomas and 85
percent in those with multiple endocrine neoplasia type 1).
This good outcome despite the failure to achieve a cure
with surgery can just as readily be achieved by treatment
with a proton-pump inhibitor alone.2

We need a clearer understanding of the true therapeutic
benefit of surgery in patients with the Zollinger–Ellison
syndrome and of when to avoid surgery. Many patients can-
not be cured surgically, and among those who are, only 40
percent no longer require drug treatment postoperatively.2

The authors reply:

To the Editor: We thank Dr. Hirschowitz for his com-
ments. There are two distinct clinical problems with the
Zollinger–Ellison syndrome. First, the hypersecretion of
gastric acid causes severe peptic ulcer disease and diarrhea,
as Dr. Hirschowitz points out. These symptoms can be ef-
effectively controlled with antisercretry drugs in all patients
except those few who cannot or will not take oral medi-
cations.1 However, these drugs have no effect on the sec-
ond problem, which is tumor growth.

In our study of 212 patients with the Zollinger–Ellison
syndrome,2 31 percent of the patients died over a mean
follow-up period of 14 years (range, 0.1 to 31 years); half
the deaths were related to tumor growth, and none to hy-
persecretion of gastric acid. At present, there is no estab-
lished antitumor treatment except effective surgery. In our
study, the morbidity and mortality associated with surgery
remained less than 12 and 1 percent, respectively, as we re-
ported previously.2 In our study comparing the outcome
of medical treatment alone with that of surgical resection,
surgery did not prolong survival (P=0.085);4 however,
surgery decreased the probability of subsequent metastasis
(P<0.003), which is the main prognostic factor for tumor-
related death.2

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Surgery also has important effects on the requirement for antisecretory drugs. We are still determining the exact proportion of patients cured who will be able to stop drug therapy; in our preliminary analysis, it is 40 to 50 percent. With curative resection, there is a 75 percent decrease in basal acid output and a 44 percent decrease in maximal acid output in response to pentagastrin, and among patients continuing to require antisecretory-drug treatment, the majority require a low dose of an antisecretory agent, usually a histamine H₂-receptor antagonist. For the reasons reviewed above and because surgery can cure a substantial proportion of these patients, as demonstrated by our study, we recommend surgery in patients with the sporadic form of the Zollinger–Ellison syndrome.

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Guidelines for Healthy Weight

To the Editor: Willett et al. (Aug. 5 issue) have highlighted the importance of taking early action to prevent increases in measures of obesity and the associated risks, including type 2 diabetes, hypertension, and dyslipidemia. The data to which they refer, however, concern predominantly white populations and are not necessarily representative of other racial or ethnic groups.

Unlike the situation in many Western countries, the prevalence of obesity in Chinese populations remains relatively low. In Hong Kong, approximately 6 percent of the population have a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher, although a third have a body-mass index of 25 or higher. Despite these relatively lower levels of obesity, the disorders associated with the metabolic syndrome are reaching epidemic proportions in Hong Kong. Ten percent of the adult population 25 to 74 years of age have type 2 diabetes (as determined on the basis of a 75-g oral glucose-tolerance test), 17 percent have hypertension (defined as a systolic blood pressure of 140 mm Hg or more and a diastolic blood pressure of 90 mm Hg or more), and more than 50 percent have dyslipidemia (defined as a total cholesterol level of 5.2 mmol per liter [200 mg per deciliter] or more). However, we found that the mean body-mass index and measurements of waist circumference of patients with components of the metabolic syndrome fall near or under the cutoff used to define overweight in whites. Furthermore, when we investigated risk factors among Chinese persons in Hong Kong, the anthropometric levels associated with the lowest prevalence were in subjects with a body-mass index below 22 or a waist circumference below 70 cm.

It is apparent from our data that, for Chinese persons, the criteria for obesity should be lowered. Our patients should be encouraged to reduce their body-mass index below 22 and their waist circumference below 70 cm. It is important for clinicians to recognize that cutoff values in guidelines are inherently arbitrary and that those currently used for whites are inappropriately high for Asian patients, including Chinese. Such patients may be within the “normal” range for weight, but their risks of type 2 diabetes, hypertension, and dyslipidemia and the illnesses associated with these disorders are more than double those of persons at optimal weight levels.

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To the Editor: Willett et al. endorse the use of the body-mass index because published studies demonstrate a fairly strong correlation between body-mass index and the results of hydrodensitometry or dual-energy x-ray absorptiometry. At our primary care clinic, we perform direct measurement of body fat using infrared interactance and bioelectrical impedance. We find that the measured percentage of body fat consistently correlates with body-mass index only in persons with a body-mass index of more than 35. As the body-mass index drops, the correlation becomes much weaker. Many people with a “normal” body-mass index have body-fat readings well into the range for obesity. More important, when interventions are introduced, measured body fat and body-mass index can travel in opposite directions. For example, one of our patients recently lost 20 lb (9 kg) by following a calorie-restricted diet only, but her body fat rose from 35 percent to over 40 percent. Virtually every pound she lost came from lean body mass. We believe that clinicians should use the available technology to measure the component that actually creates the risk — elevated body fat.

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To the Editor: The body-mass index is helpful, since it translates the values on the height and weight charts into a single number. But the body-mass index does not dis-
The authors reply:

As Dr. Davis points out, waist circumference can be a useful ancillary measure. The index he proposes is one way to incorporate this information, but it needs further evaluation. The failure of this index to pass the “Shaq” test is a reminder that physicians should not forget to look at the patient and use clinical judgment when interpreting any measurement.

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The Control of Labor

To the Editor: In their review of the mechanisms that control labor (Aug. 26 issue),

Norwitz et al. assert that magnesium sulfate is both safe and efficacious for the management of preterm labor. They also state that it has become the first-line treatment for preterm labor in North America. We were surprised by this unqualified endorsement of the usefulness of magnesium sulfate. A review of the scientific evidence has led us and others to different conclusions.

Although many obstetricians have had the anecdotal impression that delivery is delayed among patients undergoing tocolysis with magnesium sulfate, such an effect has never been proved in a rigorous way. In the only well-designed randomized clinical trial of the tocolytic efficacy of single-agent therapy with intravenous magnesium sulfate, as compared with saline control, Cox and associates found no difference in any measure of therapeutic effect. Similarly, in a recent systematic review of the literature, Kierse and coauthors concluded that “although magnesium sulphate may be efficacious for arresting uterine contractions in women who are not actually in preterm labor, its place in established preterm labor has not been demonstrated and it can have serious side-effects.”

The statements by Norwitz and associates regarding the safety of tocolytic magnesium sulfate are equally controversial, with supportive data lacking. Stating that magnesium sulfate is safe and effective as a means of tocolysis (without citing supportive references) may mislead clinicians into thinking that such conclusions are firmly established.

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The authors reply:

To the Editor: Drs. Pryde and Mittendorf express concern about the efficacy and safety of tocolytic magnesium sulfate and question the statement that magnesium sulfate has become the first-line treatment for preterm labor and, as in all of medical practice, to tailor management to the individual patient. Although no perfect tocolytic drug exists, it is generally accepted, and Mittendorf and Pryde themselves have stated, with colleagues, that “magnesium [sulfate] ranks among the most popular tocolytics in the United States.”

The response rate was 86 percent (62 of 72 questionnaires were returned). Magnesium sulfate was the reported first-line tocolytic agent in 85 percent of the responding institutions (53 of 62) (Ecker J, Greenberg J: personal communication).

In summary, although no perfect tocolytic drug exists, magnesium sulfate probably offers the most favorable benefit-to-risk ratio of all the available first-line tocolytic agents. The first rule of tocolysis is to use it only when indicated (i.e., in a patient with confirmed preterm labor before 34 weeks’ gestation) and, as in all of medical practice, to tailor management to the individual patient.

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Back to the Basics

To the Editor: In a Clinical Problem-Solving article by Fisk et al. (Sept. 2 issue),1 a 34-year-old man with paraplegia was admitted because of fever and abdominal pain. The clinician-discussant noted, “It is of interest that palpation of the left lower quadrant elicits pain in the right upper quadrant, and I wonder whether this is a manifestation of impaired innervation of the abdominal wall resulting from the accident.” However, there is another explanation. It was first put forward by Hamilton Bailey, who called it Rovsing’s sign, after Niels Thorkild Rovsing (1862–1927), a professor of surgery in Copenhagen. To test for this sign, even pressure is exerted over the descending colon. If, when the left iliac fossa is pressed, pain is felt in the right iliac fossa, the patient probably has acute appendicitis. The sign appears to be due to the shift of coils of ileum to the right, which then impinge on an inflamed focus in the right iliac fossa. I suggest that the physical findings in this case demonstrated a modified example of Rovsing’s sign.

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To the Editor: I was surprised by the explanations offered for the patient’s heart rate of 95 beats per minute in the context of a body temperature of 38.8°C. In addition to the patient’s relative youth and the possibility of temperature–dysrhythmia dissociation because of enteric fever or atypical pneumonia, should autonomic dysreflexia have been considered as a contributing factor?

Typically associated with lesions above T6, autonomic dysreflexia produces bradycardia in the presence of noxious stimuli, such as an inflamed appendix or, more commonly, an overdistended bladder or impacted bowels. Patients usually have substantial hypertension because an uninhibited sympathetic response below the level of injury produces severe vasoconstriction and then reflexive bradycardia. In the case of borderline sepsis or dehydration, the hypertension may have been mitigated to produce this patient’s blood pressure of 126/68 mm Hg. Autonomic dysreflexia has been reported in a woman with an injury at the level of T10. It may therefore be worth considering...
The Energy Expended in Chewing Gum

To the Editor: Indirect evidence suggests that gum chewing may have greater metabolic effects than has been appreciated. The thermic effect of food is reduced when nutrition bypasses the mouth.1 In cows, chewing increases energy expenditure by approximately 20 percent.2,3 We measured how energy expenditure changes with gum chewing in humans.

Energy expenditure was measured in a temperature-controlled, darkened, silent laboratory with an indirect calorimeter (model 229, SensorMedics, Yorba Linda, Calif) that was calibrated before each measurement with two primary-standard gases (a combination of 4 percent carbon dioxide and 16 percent oxygen and a combination of 26 percent oxygen and a balance of nitrogen) and calibrated for gas flow. Expired air was collected with a specially designed face mask (0.3 by 0.2 by 0.1 m) that allowed unopposed jaw movement. Measurements were performed in seven non-obese subjects with stable weight while they were seated at rest with their arms and legs supported. Energy expenditure was first measured at rest for 30 minutes. The subjects were then provided with 8.4 g of calorie-free gum and instructed to chew at a frequency of precisely 100 Hz (a value than approximates chewing frequency at our institution) with the aid of a metronome. After 12 minutes, the gum was removed from the mouth, and energy expenditure was measured for 12 minutes after chewing.

Mean (±SD) energy expenditure increased in all subjects during chewing, from 58±11 kcal per hour at base line to 70±14 kcal per hour (two-sided P<0.001). After chewing, energy expenditure returned to base line (59±12 kcal per hour) in all subjects (P<0.001). Chewing gum led to a mean increase in energy expenditure of 11±3 kcal per hour (range, 7 to 17), a 19±4 percent increase above base-line values. For perspective, in the same subjects, standing was associated with a mean increase in energy expenditure of 11±11 percent and walking at 1.6 km (1 mile) per hour was associated with an increase of 106±26 percent above base-line values.

Non-nutritional chewing is a behavior that is shared with other primates4 and is a component of nonexercise activity.5 Gum chewing is sufficiently exothermic that if a person chewed gum during waking hours and changed no other components of energy balance, a yearly loss of more than 5 kg of body fat might be anticipated. Chewing of calorie-free gum can be readily carried out throughout the day, and its potential effect on energy balance should not be discounted.

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