In Defense of a Department of Geriatrics

TO THE EDITOR: Dr. Cassel writes in support of geriatric medicine (1), which has always been subsumed as a major aspect of internal medicine. She maintains that “geriatricians . . . must have substantial knowledge of . . . psychiatry, rehabilitation, ophthalmology, audiology, gynecology, urology, orthopedics” and many other areas. I think her patients would best be served by referral to appropriate specialists in those fields. No evidence is provided that the elderly are better treated by physicians with geriatric training. The conditions Dr. Cassel considers to be “geriatric,” such as congestive heart failure, osteoarthritis, and urinary incontinence, are not restricted to any age group. Nor are preventive medicine, early diagnosis of disease, and awareness of the advantages of shorter hospitalization specifically geriatric subjects. In brief, I find no reason to expect better medical care in my senior state from a geriatrician than from a competent internist.

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Reference

IN RESPONSE: Dr. Gilson asserts that geriatric medicine has always been subsumed as a major aspect of internal medicine. Although internists see an increasingly large number of elderly patients, unfortunately that in itself does not mean that most internists are well trained in the content and principles of geriatric medicine. Early leaders in the field of geriatrics, such as eminent internist Paul Besson, pointed out that the specialty of geriatric medicine as recognized in other developed countries around the world includes a significant body of knowledge about aging and age-related syndromes, as well as a different approach to the patient in which functional assessment and functional goals are coupled with diagnosis and treatment. Such leaders as Besson and Hazzard would argue that internal medicine ought to incorporate this body of knowledge and approach to care, especially in light of the aging of the population. I also share that view and articulated it during my term as president of the American College of Physicians. Unfortunately, however, many internists have not had this training and are unfamiliar with functional assessment and with recent advances in aging research. Furthermore, while this situation is improving somewhat, there is still a great deal of room to enrich the curriculum in medical schools and internal medicine residencies, making it more useful for physicians caring for patients of advanced age. Geriatricians do not replace the other specialties in medicine, but they must have extensive familiarity with these other disciplines in order to effectively coordinate the care of the patient who requires multiple referrals. Many internists have learned the principles and content of geriatric medicine through continuing medical education courses, reading of the literature, and relationships with other colleagues. I suspect that Dr. Gilson’s definition of a competent internist may be very close to my definition of a good geriatrician.

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Placebo-Controlled Trials

TO THE EDITOR: I was surprised that in a series of four articles devoted to the ethics of placebo-controlled trials in the 19 September 2000 issue of Annals, including those by Temple and Ellenberg (1, 2), none referred to equipoise, a fundamental ethical and scientific principle of human experimentation (3). This principle states that the patient should be enrolled in a randomized, controlled trial only if there is substantial uncertainty (“equal bet”) about which of the trial treatments would benefit a patient most (3). This principle applies to any randomized trial, regardless of whether it is placebo-controlled. However, it is in placebo-controlled trials that we should be particularly vigilant about applying the uncertainty principle (4), in light of recent empirical data suggesting that placebo arms may indeed constitute inferior comparative therapy (5). Acknowledging equipoise (that is, that true uncertainty about effects of competing treatment alternatives exists) is the best mechanism available for choosing an adequate control group. When the principle of equipoise is applied, patients do not lose out prospectively and are not required to sacrifice themselves for the benefit of others (3, 4). By amending the Declaration of Helsinki to explicitly acknowledge the principle of equipoise, we will remain in a position both to protect patients’ individual rights and autonomy and to advance science by ensuring that the most credible results are obtained (4). In my opinion, improvement in the ethics and science of clinical research will come with further understanding of the equipoise principle—a fundamental principle on which nearly the entire system of human experimentation is based (5). This discussion was sorely neglected in all four Annals articles.
TO THE EDITOR: The debate over the ethics of randomized, placebo-controlled trials focused on clinical settings where treatment does not affect the patient’s long-term health or where delay or omission of active treatment would not increase mortality or irreversible morbidity (1). Unfortunately, this discussion ignored the issue of the use of a placebo in randomized, controlled trials when an effective treatment known to prevent reversible but highly clinically relevant morbidity is available. A specific example graphically makes this point.

In 1993, a randomized trial comparing oral ondansetron with placebo demonstrated that the serotonin antagonist significantly reduced emesis caused by moderately emetogenic cancer chemotherapy (2). However, two previously published peer-reviewed randomized trials had shown that dexamethasone resulted in a statistically significant improvement in emesis in the same general patient population, compared with either placebo (3) or prochlorperazine (4). Thus, in the oral ondansetron study, patients receiving placebo were exposed to a well-defined risk for considerable short-term discomfort, solely for the purpose of satisfying the “drug approval process”—an inexpensive, well-tolerated, and documented effective antiemetic agent was available at the time. Were patients entering this trial able to provide truly “informed” consent?

No patient died as a result of participating in this phase III antiemetic study, and “irreversible morbidity” was not observed. However, on the basis of solid clinical data, patients entering this study experienced a totally unnecessary risk for serious impairment in their quality of life. Was this an ethical study design (4)?

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References

IN RESPONSE: Dr. Djulbegovic argues that the principle of equipoise must be of particular concern in placebo-controlled trials because placebo-treated patients may be disadvantaged and should not “sacrifice themselves for the benefit of others.” It seems important, as we emphasized in our papers, to distinguish between studies of treatments for serious illness and studies of symptomatic treatments. Exposure to placebo in the former requires genuine uncertainty about the outcome. Exposure to placebo in a trial of headache, anxiety, or seasonal allergy, however, cannot reasonably be said to constitute “sacrifice” of oneself. It is, at worst, the sort of choice to defer or omit therapy that people with symptomatic conditions make every day. Moreover, at least in the first trial carried out, there is, in fact, equipoise—uncertainty as to whether the drug or placebo will be superior. There may be knowledge that some other treatment is effective, but that is a different question. It should, however, be appreciated that during treatment development, studies are replicated and there are often multiple placebo-controlled trials of various doses and regimens in diverse settings and populations. These studies help define safe and effective use of the drug, but the favorable results of these trials are at least strongly suspect. Nonetheless, despite possible lack of equipoise, such trials have been conducted, have been considered ethical, and are valuable. In contrast, if in the course of drug development it becomes known that a treatment enhances survival or decreases significant morbidity, relevant equipoise no longer exists and another placebo-controlled trial cannot be conducted.

Dr. Markman asks whether placebo controls are justified where available therapy is “known to prevent reversible but highly clinically relevant morbidity,” such as “emesis caused by moderately emetogenic cancer chemotherapy.” He specifically questions the conduct of a placebo-controlled trial of ondansetron in preventing emesis after cyclophosphamide regimen–induced emesis, since dexamethasone had been shown to be effective in that population. He asks whether patients in the trial gave truly informed consent and why they should have endured emesis when an inexpensive existing treatment was available. In this setting, Dr. Markman suggests that the appropriate comparator was dexamethasone, not placebo, but does not state whether these should have been noninferiority trials or superiority trials. A superiority trial (or a trial seeking evidence of greater efficacy when ondansetron is added to dexamethasone) would have been informative and interpretable, perhaps particularly desirable given...
TO THE EDITOR: Rockville, MD 20857
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agent, and no such trial would be needed for regulatory approval. If a consistent benefit were established, most patients and physicians with placebo-controlled trials of the proposed active control. If a therapy. This could be shown by a thorough review of experience with placebo-controlled trials of the proposed active control. If a consistent benefit were established, most patients and physicians would not want to participate in a placebo-controlled trial of a new agent, and no such trial would be needed for regulatory approval.

Whether patients or physicians accept a trial of a particular design depends on the trial’s value and necessity. It may be that an active control design is interpretable in the initial treatment of patients receiving moderately or markedly emetogenic cancer chemotherapy. This could be shown by a thorough review of experience with placebo-controlled trials of the proposed active control. If a consistent benefit were established, most patients and physicians would not want to participate in a placebo-controlled trial of a new agent, and no such trial would be needed for regulatory approval.

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Update in Infectious Diseases

TO THE EDITOR: Dr. Bartlett’s update on infectious diseases (1) was very much appreciated, but I was troubled by its omission of any mention of the link between antibiotic resistance and the widespread use of antibiotics to promote growth in livestock. Roughly one third of all antibiotics produced in the United States are fed to animals solely to enhance weight gain (2). A September 1999 advertisement in Swine Practitioner boasted about a product containing a tetracycline, a sulfanamide, and penicillin to enhance “growth and feed efficiency”—available without a prescription. Since 1998, the European Union has prohibited for use in animal growth promotion all antibiotics used in human medicine (3). The United States, by contrast, allows 19 different antibiotics to be used for growth promotion, and of these, 7 are from classes used in human medicine (3). The economic use of antibiotics, not to cure sick animals but to promote weight gain, is especially problematic in an age of unprecedented antibiotic resistance. Although this practice translates into cheaper meat prices, the economic advantage seems to be minimal.

Denmark has banned the use of human antibiotics for growth promotion for 5 years and has seen productivity actually increase (3). A National Research Council study (4) estimated that a similar ban in the United States would increase per capita costs by $5 to $10 per year. Use of antibiotics as growth promoters in livestock has been linked to the emergence of antibiotic-resistant diseases, helping the Centers for Disease Control and Prevention to conclude that antimicrobial use in food animals is the dominant source of antibiotic resistance among foodborne pathogens (5). Both the Centers for Disease Control and Prevention and the World Health Organization have called for an end to the use of antibiotics for growth promotion in animals. It is time for our leaders in medicine to include this problem in discussions about antibiotic resistance.

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References

IN RESPONSE: Dr. Lodato makes a good point regarding the contribution of antibiotic abuse in animals to antibiotic resistance and antibiotic-resistant infections in people. Agricultural antibiotic use seems to have been particularly important in vancomycin resistance (Europe but not the United States), as well as fluoroquinolone resistance in Salmonella species and Campylobacter jejuni. Nevertheless, to keep perspective, the overuse of antibiotics in patients, particularly those with viral respiratory infections, and extensive use of broad-spectrum antibiotics in hospitals probably account for the lion’s share of our current dilemma. Having said this, I acknowledge that the publication by Mølbak and colleagues (1) should have made my listing.

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Reference

Testosterone and Resistance Training in AIDS

TO THE EDITOR: There are two points of interest in the article by Grinspoon and colleagues (1), which examined the effects of testosterone supplementation on muscle mass and strength in patients with AIDS cachexia. First, all patients had normal free testosterone levels (that is, they were eugonadal). Second, the dosage of testosterone enanthate used (200 mg/wk) was twice the physiologic replacement dosage.
Eight published randomized, controlled trials have examined testosterone supplementation in men at doses that produced physiologic serum concentrations and assessed the effects of such supplementation on muscle mass and strength. Results from these trials suggest that testosterone supplementation at these doses increased muscle mass and strength in hypogonadal but not eugonadal patients. Testosterone doses that produced supraphysiologic concentrations of testosterone in eugonadal patients had inconsistent effects on muscle. Earlier studies had several shortcomings and produced inconclusive results (2, 3). In 1996, Bhasin and coworkers (4), in a well-designed study, reported that a supraphysiologic dosage of testosterone enanthate (600 mg/wk for 10 weeks) increased muscle size and strength in a group of eugonadal normal men. The study by Grinspoon and colleagues reports similar findings in a group of eugonadal men with AIDS wasting. The short-term administration of these supraphysiologic dosages of testosterone did not cause adverse events in either study sample.

These two studies suggest that short-term administration of supraphysiologic doses of testosterone may have beneficial effects in eugonadal men with wasting caused by such conditions as cancer, AIDS, or age-related sarcopenia. The safety of long-term administration, however, is not known. Potential side effects include increased hematocrit levels, stimulation of benign prostatic hypertrophy, and prostate carcinoma, as well as angry behavior.

**Letters**

**To the Editor:** To investigate "the effect of garlic on total cholesterol level in persons with elevated levels," Stevinson and colleagues (1) performed a thorough meta-analysis of trials conducted with garlic supplements. Such an undertaking assumes that consumption of garlic supplements and consumption of garlic cloves result in similar levels of active compounds in the body. However, no clinical trial has yet used a garlic supplement that has demonstrated bioavailability of the probable active compounds of garlic. This is a crucial point because considerable evidence indicates that most of garlic's effect on cholesterol reduction is due to allicin (2), a compound that is readily present when garlic is chopped or crushed but that must be enzymatically formed in the body from alliin when dried garlic is consumed in supplement form. This transformation by alliinase cannot be assumed to take place without bioavailability studies, since alliinase is inactivated immediately by gastric acid and in 1 hour by intestinal proteases (3). Unlike many other brands, the brand used in 10 of the 13 trials that qualified for inclusion in this meta-analysis does not use a coating that protects alliinase from exposure to gastric acid. Because of this, in vivo allicin formation depends on gastric pH and gastric emptying time and is therefore in considerable doubt. The second powder supplement included in the analysis was prepared by spray-drying, a process that results in loss of most of the alliin. Of the two studies that used allicin-derived garlic oils, the one that showed no effect (4) used an unusual solid form of the oil that has since been demonstrated to have low bioavailability in a 48-hour breath test (5). The conclusions derived from this meta-analysis can be applied only to the particular supplement brands used in the studies and not to garlic itself.

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**Garlic for Total Cholesterol Reduction**

**In Response:** We agree with Dr. Kamel that our data demonstrate a significant effect of supraphysiologic testosterone on muscle mass and strength in eugonadal men with AIDS wasting. The use of testosterone may therefore be considered to reverse sarcopenia in this population. However, we also agree that the long-term safety of supraphysiologic testosterone is unknown. Although our data do not show adverse effects on prostate-specific antigen and hematocrit levels, the study was short and the longer-term safety effects remain unknown. Furthermore, our data do suggest a decrease in high-density lipoprotein cholesterol level, which may adversely affect such patients. In addition, long-term use of high-dose testosterone may result in suppression of gonadal function. In contrast, we have shown that progressive resistance training increases muscle mass and improves levels of high-density lipoprotein cholesterol. How these strategies will be best used in long-term clinical care remains to be determined.

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**References**


TO THE EDITOR: If wine drinkers experience lower mortality rates than drinkers of beer and spirits (1), it may be because these beverages affect body tissue distribution differently. Two cross-sectional studies in the United States have reported that beer and spirit consumption was positively associated but wine consumption was inversely (or nonsignificantly) associated with the waist-to-hip ratio among men and women in young adulthood (2) and middle age (3). These beverage-specific associations persisted after adjustments for several factors, including age, education, smoking, and body mass index. An elevated waist-to-hip ratio might be the result of relative enlargement of the upper body (waist) or relative reduction in the size of the lower body.

Our 10-year follow-up of 44,080 middle-aged healthy white women (4) explored how regular consumption (≥5 days per week reported across a 10-year interval) of these three alcohol types was associated with risk for weight gain in the waist and in the periphery (predominantly hips and thighs). Compared with nonconsumers, regular drinkers of wine, beer, and spirits had similar, nonsignificant likelihoods of weight gain in the waist, with odds ratios of approximately 1.0, but the beverage-specific groups differed notably in the likelihood of weight gain in the periphery. Regular wine drinking was not associated with peripheral weight gain. However, women who regularly drank beer or spirits had a reduced likelihood of peripheral weight gain (odds ratios, 0.59 [95% CI, 0.43 to 0.81] and 0.54 [CI, 0.44 to 0.65], respectively).

These consistent findings suggest that the apparent advantage of wine drinking might be related to the preservation of muscle or adipose tissue in the lower extremities. Large hips and thighs may be protective (5). Whether these differential effects are related to the alcoholic beverage itself or to behaviors associated with its consumption remains to be determined.

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References

IN RESPONSE: Dr. Kahn adds to the long list of possible explanations for the apparent beneficial effect of wine compared with beer and spirits on morbidity and mortality. His opinions are of great interest. However, I doubt that the beverage-specific differences in waist-to-hip ratio can explain some, if any, of this effect. First, although there truly do seem to be differences, as found in the two studies mentioned by Dr. Kahn, they would need to be quite large (larger than those reported) to be able to explain our findings. Second, we did consider body weight in the analyses, but since participants who did not drink wine had a mean body mass index of 26 kg/m² and those who did had a body mass index of 25 kg/m², it had...
TO THE EDITOR: Pinto-Sietsma and colleagues (1) found that smoking was associated with albuminuria and abnormal renal function in nondiabetic patients. This fine report adds to a body of evidence showing that tobacco smoking causes structural and functional abnormalities in the kidneys, increases the risks for primary and secondary renal disease, hastens end-stage renal failure, and worsens the outcome for patients receiving dialysis and for recipients of kidney transplants (2). However, neither Pinto-Sietsma and colleagues nor other recent authors have cited early studies that strongly suggested that the kidneys were a target for the adverse effects of tobacco smoking.

Researchers in the 1800s observed effects of tobacco and nicotine on renal structure and function. By the early 1900s, reviews of tobacco-related diseases included information that linked cigarette smoking and renal dysfunction (3, 4). In the famous 1964 Report of the Surgeon General’s Advisory Committee on Smoking and Health (5), among prospective studies in which mortality ratios (MRs) for nephritis were analyzed, the median MRs among smokers and former smokers were 1.5 and 1.1, respectively. These MRs, although unadjusted for passive smoking, were similar to median MRs for coronary artery disease (MR, 1.7), cancer of the kidney (MR, 1.4), and cerebrovascular disease (MR, 1.3). The relationships between tobacco smoking and these vascular and neoplastic diseases have been studied extensively over the past 35 years; however, despite 100 years’ worth of evidence about the adverse effects of tobacco smoke and nicotine on the kidneys, the findings in the 1964 report were largely ignored.

One can only speculate why researchers failed to investigate the renal effects of smoking until recently. The good news is that active research into basic mechanisms and therapeutic interventions related to tobacco smoking and kidney disease has finally begun (2).

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References
Letters

IN RESPONSE: We appreciate the interest in our recent article on smoking and renal abnormalities in nondiabetic persons. As Drs. Mehler and Estacio point out, smoking has been found to have adverse effects on renal function not only in patients with type 1 diabetes mellitus but also in those with type 2 diabetes mellitus (1).

We agree with their plea that physicians should strongly encourage cessation of smoking in patients with type 2 diabetes mellitus. Our finding that smoking is also associated with both albuminuria and renal function changes in patients without diabetes argues that smoking has renal effects independent of the diabetic setting. It adds to our knowledge about the mechanism of albuminuria. Increased urinary albumin excretion seems to be a phenomenon related not only to diabetes and hypertension but also to smoking, central obesity (Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE. A central body fat distribution is related to renal abnormalities. Unpublished data), and the use of oral contraceptives and hormone replacement therapy (2). This may partly explain why microalbuminuria may also be found in 5% to 6% of nondiabetic and nonhypertensive persons.

We thank Dr. Jay for drawing attention to the medical literature as early as 1922. At that time, it indeed was already reported that smoking could cause Bright disease, known in those days as congestion, degeneration, and damage of the kidney. Furthermore, it was described that tobacco induced a pronounced contraction of the vessels of the kidney (3). These and other historical data, as pointed out by Dr. Jay, underline the importance and difficulties of the struggle for smoking cessation. Microalbuminuria is thought to be an early marker for worsened renal and cardiovascular prognosis. Therefore, our finding that patients who stopped smoking no longer had an increased risk for microalbuminuria argues for a more aggressive and intensive approach to encourage smoking cessation in patients with microalbuminuria, both those with diabetes and those without.

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References

Kava Hepatotoxicity

TO THE EDITOR: Phytorheapeutic preparations for sleep and anxiety disorders that contain kava-lactones are available over the counter in many countries. A 33-year-old woman took the drug Laitan (Schwabe Pharma AG, Kuesnacht, Switzerland) (210 mg of kava-lactones daily) for 3 weeks. The patient reported intake of no other drugs except the homeopathic medication Exsippa (Tentan AG, Rottweil, Switzerland). Two months later, she restarted use of the kava preparation. After another 3 weeks, 1 day after intake of 60 g of alcohol, she developed malaise, loss of appetite, and jaundice. Levels of aminotransferases, bilirubin, and alkaline phosphatase were elevated 60-, 15- and 3-fold, respectively (aspartate aminotransferase, 40.8 μkat/L [2450 U/L]; alanine aminotransferase, 40.5 μkat/L [2430 U/L]; total bilirubin, 399 μmol/L [23 mg/dL]; alkaline phosphatase, 4.98 μkat/L [299 U/L]). Prothrombin time was normal. Tests for autoantibodies and results of viral serologic tests were negative, except for low titers of Epstein–Barr virus IgM. Liver biopsy showed infiltrated portal tracts, bridging necroses, destruction of interlobular bile ducts, and canicular cholestasis (Figure). Liver enzyme levels returned to normal within 8 weeks after withdrawal of Laitan. A lymphocyte transformation test (1) performed after recovery indicated strong and concentration-dependent T-cell reactivity to Laitan (stimulation index, 13.2) but not Exsippa. Phenotyping of cytochrome P4502D6 activity with debrisoquine showed that the patient was a poor metabolizer. We also performed phenotyping in a patient who had had positive results on a rechallenge test (3) and found that she was a poor metabolizer of debrisoquine. Since the local prevalence of CYP2D6 deficiency is 9% (4), the probability that two consecutive patients are deficient is less than 0.01%.

Figure. Liver biopsy specimen showing an inflamed portal tract.

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IN RESPONSE: We appreciate the interest in our recent article on smoking and renal abnormalities in nondiabetic persons. As Drs. Mehler and Estacio point out, smoking has been found to have adverse effects on renal function not only in patients with type 1 diabetes mellitus but also in those with type 2 diabetes mellitus (1). We agree with their plea that physicians should strongly encourage cessation of smoking in patients with type 2 diabetes mellitus. Our finding that smoking is also associated with both albuminuria and renal function changes in patients without diabetes argues that smoking has renal effects independent of the diabetic setting. It adds to our knowledge about the mechanism of albuminuria. Increased urinary albumin excretion seems to be a phenomenon related not only to diabetes and hypertension but also to smoking, central obesity (Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE. A central body fat distribution is related to renal abnormalities. Unpublished data), and the use of oral contraceptives and hormone replacement therapy (2). This may partly explain why microalbuminuria may also be found in 5% to 6% of nondiabetic and nonhypertensive persons.

We thank Dr. Jay for drawing attention to the medical literature as early as 1922. At that time, it indeed was already reported that smoking could cause Bright disease, known in those days as congestion, degeneration, and damage of the kidney. Furthermore, it was described that tobacco induced a pronounced contraction of the vessels of the kidney (3). These and other historical data, as pointed out by Dr. Jay, underline the importance and difficulties of the struggle for smoking cessation. Microalbuminuria is thought to be an early marker for worsened renal and cardiovascular prognosis. Therefore, our finding that patients who stopped smoking no longer had an increased risk for microalbuminuria argues for a more aggressive and intensive approach to encourage smoking cessation in patients with microalbuminuria, both those with diabetes and those without.

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Kava Hepatotoxicity

TO THE EDITOR: Phytorheapeutic preparations for sleep and anxiety disorders that contain kava-lactones are available over the counter in many countries. A 33-year-old woman took the drug Laitan (Schwabe Pharma AG, Kuesnacht, Switzerland) (210 mg of kava-lactones daily) for 3 weeks. The patient reported intake of no other drugs except the homeopathic medication Exsippa (Tentan AG, Rottweil, Switzerland). Two months later, she restarted use of the kava preparation. After another 3 weeks, 1 day after intake of 60 g of alcohol, she developed malaise, loss of appetite, and jaundice. Levels of aminotransferases, bilirubin, and alkaline phosphatase were elevated 60-, 15- and 3-fold, respectively (aspartate aminotransferase, 40.8 μkat/L [2450 U/L]; alanine aminotransferase, 40.5 μkat/L [2430 U/L]; total bilirubin, 399 μmol/L [23 mg/dL]; alkaline phosphatase, 4.98 μkat/L [299 U/L]). Prothrombin time was normal. Tests for autoantibodies and results of viral serologic tests were negative, except for low titers of Epstein–Barr virus IgM. Liver biopsy showed infiltrated portal tracts, bridging necroses, destruction of interlobular bile ducts, and canicular cholestasis (Figure). Liver enzyme levels returned to normal within 8 weeks after withdrawal of Laitan. A lymphocyte transformation test (1) performed after recovery indicated strong and concentration-dependent T-cell reactivity to Laitan (stimulation index, 13.2) but not Exsippa. Phenotyping of cytochrome P4502D6 activity with debrisoquine showed that the patient was a poor metabolizer. We also performed phenotyping in a patient who had had positive results on a rechallenge test (3) and found that she was a poor metabolizer of debrisoquine. Since the local prevalence of CYP2D6 deficiency is 9% (4), the probability that two consecutive patients are deficient is less than 0.01%.

Figure. Liver biopsy specimen showing an inflamed portal tract.

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References
The histologic findings and the results of the lymphocyte transformation test are compatible with an immune-mediated reaction, possibly mediated through a reactive metabolite. In humans, kavalactones are metabolized through hydroxylation (2), but the involved enzymes have not been identified. The present data strongly suggest that kava preparations may be hepatotoxic and that CYP2D6 deficiency is a risk factor, as is the antiangiotal agent perhexiline (5).

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Medication Assistance Programs

TO THE EDITOR: Prescription medications are the most rapidly expanding component of national health care expenses. Ninety billion dollars were spent on prescription drugs in 1998, and this number is projected to increase to $171 billion by 2007, representing 8% of total national health care expenditures (1). Approximately 16% of the U.S. population does not have health insurance, and a greater percentage has health insurance that does not include a prescription medication benefit (2). Therefore, it is becoming increasingly difficult for some segments of the population to purchase the prescription drugs that they need.

Many pharmaceutical companies offer assistance by providing free or reduced-cost medications to patients who meet specific financial criteria. A wide range of medications for many indications are provided in these programs. Drugs may be provided free, or patients may be required to pay a fee or shipment charge. Medications are supplied by direct delivery to the patient or physician, or the patient may be issued a benefit card or voucher that must be presented at a pharmacy. The amount of medications given and the length of time that a patient may be enrolled vary.

Physician involvement is necessary for patient enrollment in these programs, so clinicians must be informed about them to increase patient access to medications. Information concerning medication assistance programs sponsored by pharmaceutical companies can be obtained from a variety of sources, including Pharmaceutical Research and Manufacturers of America, such publications as Reimbursement Assistance Programs Sponsored by the Pharmaceutical Industry and the Directory of Prescription Drug Patient Assistance Programs, and various Internet sites (3, 4). However, the best source of information about assistance programs and specific details concerning patient eligibility and program enrollment is the manufacturer of the medication.

Of course, these programs are not the solution to this universal problem of medication access, and it is important to note that they operate at the discretion of the pharmaceutical company and may therefore be terminated at any time. Nonetheless, it is equally important to be aware of their existence as a possible source for medications. The Appendix Table, available on the Annals Web site (www.annals.org), provides an extensive listing of many medications whose manufacturers offer medication assistance programs (5).

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References


Acute Renal Failure Related to High-Dose Celecoxib

TO THE EDITOR: A 57-year-old woman developed acute renal failure on 6 July 2000. She had been prescribed celecoxib, 200 mg/d, 10 months earlier for symptomatic osteoarthritis and had been followed with bimonthly visits thereafter. Her baseline creatinine and blood urea nitrogen (BUN) levels were normal at 88 μmol/L (1.0 mg/dL) and 3.9 mmol/L (11 mg/dL), respectively. In the last half of June 2000, her orthopedist doubled the daily celecoxib dose to 400 mg. Two weeks later, on 6 July 2000, she presented with marked dependent edema and markedly elevated blood pressure (160/110 mm Hg). Creatinine and BUN levels were elevated to 265 μmol/L (3.0 mg/dL) and 15.4 mmol/L (43 mg/dL), respectively. Celecoxib ther-
TO THE EDITOR:
The concomitant growth of genetic research and clinical practice has accelerated the need for accurate and comprehensive information about genetic disorders. One such database is the Online Mendelian Inheritance in Man (OMIM), a valuable tool for clinicians and researchers. OMIM is a catalog of human genes and genetic disorders, and it is updated regularly to include new findings and updates on existing conditions.

In clinical practice, OMIM can be particularly useful in identifying potential genetic causes of disease. For example, in the case of a patient with idiopathic thrombocytopenic purpura (ITP), OMIM can help identify genetic variants that may be associated with this condition. By consulting OMIM, clinicians can gain insights into the genetic basis of the disease and consider genetic counseling for the patient and their family.

Additionally, OMIM is an important resource for understanding the genetic basis of complex diseases. For instance, in the case of a patient with duchenne muscular dystrophy (DMD), OMIM provides information on the gene mutations associated with this condition and the clinical features that can be observed in affected individuals.

Overall, the utility of OMIM in clinical practice cannot be overstated. It serves as a comprehensive resource for clinicians, researchers, and patients to understand genetic disorders and their implications for health and treatment.
creased to $0.011 \times 10^9$ cells/L. She was hospitalized and treated with methylprednisolone and intravenous immunoglobulin (2 g/kg of body weight over 5 days). On the fourth hospital day, her platelet count increased to $0.115 \times 10^9$ cells/L. She was discharged on the fifth hospital day with a prednisone taper. At her 3-month follow-up visit, the platelet count was $0.209 \times 10^9$ cells/L. After 1 year of follow-up, the patient remains healthy with a normal complete blood count and no other medical problems.

The annual incidence of idiopathic thrombocytopenic purpura ranges from 1 to 13 per 100,000 persons (1). It usually occurs in women in their second and third decades of life (2). To our knowledge, our patient is the oldest described patient with this disorder. Previously, the oldest described patient was 89 years of age (3). A recent observational study (4) suggests that the incidence of the disorder in adults increases with age. As patients live longer, our patient may be the first of many presenting with idiopathic thrombocytopenic purpura in the second century of life.

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References

Correction: Physicians and Joint Negotiation

In the position paper “Physicians and Joint Negotiations” (1), the third position contained an inadvertent error regarding collective negotiations by residents. The correct policy position that was approved by the Board of Regents of the American College of Physicians–American Society of Internal Medicine on 17 July 1999 is provided below and should be substituted for the position in italics that appeared on the top of page 790. Both the abstract and the conclusion of the paper should also be modified accordingly.

Physicians-in-training should have means available to communicate with their program directors and supervisors to address and resolve concerns about patient care, stipends, hours, and other working conditions. Educational content should remain the purview of the appropriate Residency Review Committee (RRC) and program directors, and should not be subject to negotiations.

The second paragraph of the abstract should be corrected to omit the phrase “collective bargaining is not appropriate for resident physicians” and should read as follows:

The College states that employed physicians should continue to have negotiating rights. It maintains, despite a recent decision by the National Labor Relations Board, that physicians in residency training are protected by accreditation requirements for programs of graduate medical education, and educational content should not be subject to negotiations.

The following revision is also necessary in the conclusion. The sentence “Residents have other mechanisms available to them that are more appropriate than collective bargaining in the educational environment” should read as follows:

Residents have other mechanisms available to them to resolve disputes in the educational environment.

These changes do not represent a change in American College of Physicians–American Society of Internal Medicine policy.

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Reference

Correction: Risk Factors for Coronary Heart Disease in Men 18 to 39 Years of Age

In a recent article on risk factors for coronary heart disease in 18- to 39-year-old men (1), the first line of the figure legend should read “Receiver-operating characteristic curves for prediction of fatal coronary heart disease in young men over 20 years,” not “Receiver-operating characteristic curves . . . in young men older than 20 years of age.”

Reference