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 Bee- son, 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 Beeson 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.
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References

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 than the comparator) is available at the time. Were patients entering this trial able to give truly informed consent and why they should have endured emesis when an inexpensive existing treatment was available?
dexamethasone’s low cost. An interpretable noninferiority trial, however, would have required a full evaluation of all trials (not just one or two) comparing dexamethasone with placebo. If dexamethasone had consistently been shown to be effective (superior to placebo) in decreasing emesis, an appropriately sized equivalence–noninferiority trial could have been informative. Despite the documented effectiveness of ondansetron in the setting of highly emetogenic chemotherapy, however, there are many situations, primarily postsurgical, in which ondansetron has not been consistently distinguishable from placebo as an antiemetic. In these situations, a comparison with dexamethasone would have been uninformative. To know whether ondansetron was effective in these cases, placebo-controlled trials would be necessary.

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 sulphonamide, 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.

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References

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 in this population. 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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Garlic for Total Cholesterol Reduction

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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References
Letters


IN RESPONSE: Dr. Lawson rightly points out that the results of our meta-analysis refer only to the use of garlic supplements and not the consumption of garlic per se. The question of interest was whether garlic supplements reduce cholesterol levels in patients with elevated levels to the extent that these supplements might be considered a treatment option for hypercholesterolemia, as suggested by previous data (1). This question is a pertinent one, given that garlic supplements are marketed for that purpose. Our results indicated that supplements probably do not reduce total cholesterol levels to a clinically meaningful degree, but clearly this does not imply that eating garlic does not have health benefits. As discussed in our paper, systematic reviews of herbal medicines invariably combine data derived from different preparations. This can be problematic, not least because of the lack of bioavailability data for the possible active compounds of garlic. Dr. Lawson has presented interesting data to suggest that the conflicting results of clinical trials may be related to the quality and coating of the tablets (2). Although he points out that unlike other brands, the tablets used in most of the trials included in our analysis were not enteric-coated, it is worth noting that the efficacy of these other brands has not been demonstrated in rigorous clinical trials. It could also be mentioned that unlike other research, our work in this area is independent of commercial interests.

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References

Wine and Mortality

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
no effect on mortality, as can be seen in our Table 1. Third, the apparent added beneficial effect of wine in our study seemed to apply mainly to death from cancer and not to death from coronary heart disease, which is much more strongly associated with increases in waist-to-hip ratio.

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Smoking and Abnormalities in Renal Function

TO THE EDITOR: Pinto-Sietsma and colleagues recently reported that cigarette smoking is associated with albuminuria in nondiabetic persons (1). They refer to the known adverse effects of smoking in diabetic patients that were previously reported in the literature. Their references, however, are entirely to studies of patients with type 1 diabetes mellitus. Smoking has not consistently been found to be an important risk factor for nephropathy in patients with type 2 diabetes mellitus, which accounts for 90% of the 16 million cases of diabetes in the United States (2, 3).

We would also like to comment on the association between smoking and nephropathy in type 2 diabetes mellitus, which we have reported in a recent article (4). In our study, the multivariate odds ratio for nephropathy was 1.61 (95% CI, 1.01 to 2.58) in smokers with type 2 diabetes mellitus who were enrolled in the Appropriate Blood Pressure Control in Diabetes trial.

Diabetic nephropathy continues to be the leading cause of end-stage renal disease. In patients with diabetes, aggressive blood pressure control, newly defined as a value less than 130/80 mm Hg, is an important cornerstone of any successful program to prevent diabetes-related complications (5). Impressive evidence continues to mount from several clinical trials that show marked benefits from aggressive blood pressure reduction. In addition, since approximately 25% of all diabetic patients smoke, finding another potential hazard associated with smoking gives physicians further impetus to strongly encourage smoking cessation in order to attenuate the rate of decline in renal function. The exact pathophysiologic basis for this association is currently unknown. Smoking may contribute to decline in renal function through its effect on cytokine-transforming growth factor and renal hypertrophy or through an effect on glomerular ischemia and elevations of plasma endothelin-1 levels.

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References
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 albuminuria, both those with diabetes and those without.

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References
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Kava Hepatotoxicity

TO THE EDITOR: Phytotherapeutic 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, Kuessnacht, Switzerland) (210 mg of kavallactones daily) for 3 weeks. The patient reported intake of no other drugs except the homeopathic medication Exsepta (Tentan AG, Rottier, 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 Exsepta. Phenotyping of cytochrome P450D6 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.
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 antianginal agent perhexiline (5).

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References

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 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-

www.annals.org
apy was discontinued on 7 July 2000, and a complete work-up for acute renal failure was begun on 14 July 2000. Results of the work-up were negative, and renal function returned to normal; creatinine and BUN levels decreased to 88 μmol/L (1.0 mg/dL) and 6.8 mmol/L (19 mg/dL), respectively. Edema and hypertension also resolved.

A MEDLINE search for celecoxib and acute renal failure revealed only two cases, reported by Perazella and Eras in May 2000 (1). This is the second report and the third case involving this serious problem with a widely used drug. In February 1999, Moreland and St. Clair (2) reviewed the use of analgesics, including the new cyclooxygenase-2 inhibitors, for pain management in patients with rheumatic diseases; the notorious renal side effects of nonsteroidal anti-inflammatory drugs (NSAIDs) were also reviewed. In December 1999, Brater (3) reviewed the effects of NSAIDs on renal function, with a focus on cyclooxygenase-2 inhibitors. All NSAIDs seem to share nephrotoxic side effects, including decreased sodium excretion, decreased potassium secretion, and decreases in renal perfusion. Preliminary data suggest that cyclooxygenase-2 inhibitors also affect renal prostaglandins. It now seems that these shared renal effects also include acute renal failure and that they are dose related.

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References

Usefulness of Online Mendelian Inheritance in Man in Clinical Practice

TO THE EDITOR: The concomitant growth of genetic research and information technology has given birth to electronic genetic databases, the utility of which should not go unnoticed by medical practitioners. Online Mendelian Inheritance in Man (OMIM), a database of human genes and genetic diseases maintained by Johns Hopkins School of Medicine, is freely accessible on the Internet (1, 2). The OMIM gene map is a table of loci of inherited disorders arranged in order. We report a case illustrating the usefulness of OMIM in clinical practice.

A 37-year-old congenitally deaf and mute man presented to our service with bacterial pneumonia. His history was significant for chronic renal failure secondary to primary hyperoxaluria, which was diagnosed when he was 26 years of age. Initial work-up also revealed dilated cardiomyopathy and severe hypothyroidism of uncertain cause. In addition, over an 11-year period, the patient had multiple thromboembolic events, including deep venous thromboses, atriovenous graft thromboses, and pulmonary emboli, that were due to protein C deficiency. Of note, several of the patient’s family members are also deaf and mute. Aware that protein C deficiency was associated with a single gene defect, we used the OMIM gene map to ascertain the location of this gene and to determine whether possible defects in neighboring loci were associated with the other disease entities present in our patient. The search revealed that the long arm of chromosome 2 (2q) includes loci associated with protein C deficiency (2q13-14); type 1 primary hyperoxaluria (2q36-37); type 16 autosomal dominant deafness (2q23-24.3); congenital hypothyroidism due to thyroid dysgenesis or hypoplasia (2q12-14); and dilated cardiomyopathy types 1H, 1G, and 11 (2q14-22, q31, and q35, respectively) (1). A defect affecting 2q may have accounted for the complex clinical picture in our patient.

Electronic genetic databases are a valuable diagnostic tool for the clinician and may suggest appropriate follow-up for patients and families.

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References

Idiopathic Thrombocytopenic Purpura in a 101-Year-Old Woman

TO THE EDITOR: A 101-year-old woman, born on 25 December 1898, presented to our institution with a 2-day history of general weakness and presyncope. The platelet count was $0.0014 \times 10^9$ cells/L, hemoglobin and leukocyte counts were normal, and review of the peripheral smear revealed no clumping or schistocytes. Five months before admission, the patient had a normal platelet count. Her medical history was significant only for hypertension and glaucoma. She was taking calcium carbonate, hydrochlorothiazide, lisinopril, docusate, doxazosin, and aceaminophen and had not received any recent transfusions or intravenous fluids. Physical examination revealed several areas of ecchymoses and petechia on her trunk and upper extremities; lymphadenopathy and hepatosplenomegaly were not present. Findings on computed tomography of the head, serum chemistry tests, and coagulation studies were normal. A presumptive diagnosis of immune thrombocytopenia was made.

The patient received one six-pack of multidonor platelets and 1 g of intravenous methylprednisolone, and her platelet count in-
creased to 0.011 × 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 × 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 × 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