Letters

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Error in Medicine

TO THE EDITOR: Bates and Gawande's essay (1) deserves close attention in view of the national debate about patient safety energized by the Institute of Medicine (IOM) report on patient safety (2). The authors' positive view of the IOM report differs from comments made by Troyen Brennan in April 2000 (3).

Dr. Brennan, a senior researcher in both studies discussed in the IOM report—the Harvard New York study (4) and the Utah/Colorado study (5)—wrote, "I have cautioned against drawing conclusions about the numbers of deaths in these studies"; "The reliability of identifying errors is methodologically suspect"; and "In both studies (New York and Utah/Colorado) we agreed among ourselves about whether events should be classified as preventable . . . these decisions do not necessarily reflect the views of the average physician, and certainly don't mean that all preventable adverse events were blunders."

The IOM estimated that 44 000 to 98 000 patients died in 1 year because of medical error. The Utah/Colorado study reported 38 adverse event–related deaths, a figure that can be extrapolated to 63 000 national adverse event–related deaths per year. The 17 "preventable deaths" and 15 deaths from negligence that were reported in the same study can be projected to 28 000 preventable deaths and 24 979 deaths from negligence nationally per year. These numbers are in striking contrast to the number of deaths cited by Bates and Gawande—180 000 per year.

Can these imprecisions on such important numbers portend a successful patient safety project? I say yes, because the project will happen. It's time to be honest about the research. Weak data and methods merely require more caution in a project on patient safety.

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IN RESPONSE: Dr. Dunn brings up the controversy over the annual number of deaths related to iatrogenic injuries in the United States. The figure we cited—180 000 iatrogenic deaths—comes from the Medical Practice Study (1) and refers to the total number of deaths due to injury. Just over half of these deaths were deemed preventable, resulting in the Institute of Medicine's upper end figure of 98 000. We believe that given the importance of the problem, too few relevant data are available, and that whatever the actual point estimate is, it is too high. Furthermore, the problem of injuries associated with errors is huge, with an estimated 1.3 million injuries per year (2). Error in medicine is vitally important and is only now getting the attention it deserves.

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Suppose There Were No Printers

TO THE EDITOR: Dr. Davidoff (1) argues well that paper should not be abandoned altogether as a medium, especially as a storage medium. One would assume that at least one copy of *Annals* will forever be archived on a durable analog storage medium such as ink and paper—for historical if not future clinical use. But it is a specious argument to deride the storage limitations of digital media to justify paper publication of *Annals*.

Media transport information across time (storage) and space (distribution and access) and into human minds (presentation). Paper and digital media have varying advantages in each of these three valences. The distribution benefits (Web access, hypertext, searching) and storage shortcomings (degradation in years, not centuries) of

digital media should not overshadow the unique presentation benefits of digital media: user-controlled variation. These presentation benefits of digital text media include not only the obvious choices of font and background for optimized reading but also newer assistive technologies that enable more readers to have cognitive access to the written word: pronunciation cues, instant definitions, and syntactic parsing aides. Although the medical profession sets the reading-performance bar quite high simply for entry, it is not exempt from language processing–based reading disabilities among its members, who face a continual challenge to keep up in an increasingly information-driven field. Indeed, medicine may have a higher rate of such disabilities than other professions, such as law or business.

Publishers should view their content not as medium-dependent artifacts but as time-sensitive information whose window of relevant usability may be short. From this perspective, more can be done to integrate all of the media that *Annals* is built in. I would interpret Edward Wilson's comment about a discovery in quantum terms: It does not truly "exist until it is safely reviewed and in print"—and used.

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IN RESPONSE: As I pointed out in an earlier editorial (1), I agree with Dr. Walker that print and digital media each have important advantages. I also agree that physicians and others who work in health care are not exempt from reading disabilities, and might be helped by the kinds of electronic cognitive assistance he describes. Unfortunately, few medical Web sites (including ours) have actually developed such "assistive technologies," although the opportunity is clearly there (1). Dr. Walker's comments are generally very much on target, but they really don't get at my concerns about the shortcomings of electronic media, which some believe are truly creating a second historical "dark age."

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1. Davidoff F. www.annals.org [Editorial]. Ann Intern Med. 2000;132:92. [PMID: 0010627259]

Work–Family Balance

TO THE EDITOR: "Children's lives do not wait." This is the theme in Dr. McMurray's essay (1) about her mother's decision to leave medicine in the late 1940s and her father's regrets about not having "picked more daisies" during his 40 years of medical practice. In her response to this poignant essay, Dr. Nagy-Agren gives us a look into our progress in the area of work–family balance over the past 50 years (2). Both Dr. McMurray's mother and Dr. Nagy-Agren were left feeling "scared, unsupported, [and] possibly unwanted" as they tried to adjust their practices of medicine to accommodate the needs of their children.

Our profession has been slow to adopt workplace flexibility. This inaction is contributing to high levels of burnout among women physicians. Long work hours, loss of work control, and lack of professional support for family contribute to burnout (3). Burnout prevention requires an accepting professional culture for working-parent physicians and part-time career opportunities. This approach has been successful in the Netherlands, to the benefit of both men and women physicians with families (Linzer M, McMurray J, Visser MR, Oort FJ, Smets EM, Nanneke CJ. Gender differences in physician burnout in America and the Netherlands. In preparation).

A bright light for working parents is the Mary O'Flaherty Horn Scholars Program in General Internal Medicine. This new career opportunity for physicians centers on work–family balance. A 3-year stipend will be awarded to a physician who chooses to work half-time as an academic generalist and spend "the other half" raising children. Dr. Mary Horn was prepared to leave her full-time academic position to attend to her growing family's needs. Rather than lose a valuable faculty member, her colleagues created a split full-time position. The solution was a dramatic success for all concerned. After Dr. Horn's untimely death in 1998, the Horn Scholars Program was established as a program of the Society of General Internal Medicine.

Our profession must embrace a culture change if we are to offer a wider range of career pathways with appropriately adjusted work schedules, promotion timelines, pay, and benefits for half-time physicians. It will take time to integrate physicians working half-time into academic, clinical, and corporate medical settings. We cannot languish any longer if our daughters and our sons are to experience something different than physicians did 50 years ago. "Children's lives do not wait."

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Seizure Associated with *Ginkgo biloba*?

TO THE EDITOR: Anecdotal reports of seizure in association with *Ginkgo biloba* have recently come to light. The U.S. Food and Drug Administration's Special Nutritionals Adverse Event Monitoring System (SN/AEMS) describes seven reports of seizure associated with ginkgo. Four reports were associated with multi-ingredient products, and three were associated with single-ingredient ginkgo preparations, each from different manufacturers (1).

Other anecdotal reports come from Internet discussion boards and electronic mailing lists. For example, on the Massachusetts General Hospital Neurology Web Forum, a patient reported having temporal lobe seizures after taking ginkgo. On the *Pharmacist's Letter* "Who Knows the Answer" discussion board, a pharmacist described a patient who had severe headaches and experienced a seizure after taking ginkgo. On the Idaho State University Ambulatory Care e-mail list, a pharmacist described a woman who had a seizure after drinking tea suspected to contain ginkgo.

Reports of seizure associated with the most commonly used form of ginkgo, ginkgo leaf extract, are not found in MEDLINE, EMBASE, or the International Pharmaceutical Abstracts online database. However, seizure has previously been associated with ginkgo seed preparations (2).

It is unclear how ginkgo might incite seizure. However, ginkgo has been shown to produce changes on computer-analyzed encephalography similar to those seen with the drug tacrine. Tacrine has also been associated with seizure (3, 4). Another possibility is that the ginkgo products used in the cases described were contaminated with ginkgo seeds.

On the basis of these limited data, it is impossible to determine causality with any certainty. Until more is known, ginkgo should be used cautiously or avoided in patients who might be predisposed to seizure or who are using other medicines known to incite seizure. This letter is meant to put health care professionals on the lookout for similar cases and to prompt more thorough communications about possible ginkgo-related seizure.

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Ibuprofen-Related Hypoglycemia in a Patient Receiving Sulfonylurea

TO THE EDITOR: Several agents, including aspirin, potentiate the effects of sulfonylureas and cause hypoglycemia (1). We describe a case of severe hypoglycemia induced by ibuprofen in a diabetic patient treated with a sulfonylurea.

A 72-year-old man with a 20-year history of type 2 diabetes mellitus was receiving 2.5 mg of glibenclamide per day. His glycemic control had been stable, and he had not experienced any hypoglycemic episodes for several years. He developed a sore throat and arthralgia and took 150 mg of ibuprofen. Half an hour later, he developed severe nausea, sweating, and palpitations that were immediately relieved after the patient consumed sugar. The same symptoms were reproduced again the next morning after the patient took an identical dose of ibuprofen. After taking the same dose again that afternoon, he developed the same symptoms, with greater intensity, and lost consciousness. His blood glucose level was less than 2.2 mmol/L (40 mg/dL). The patient recovered fully soon after receiving intravenous glucose. He stopped taking ibuprofen and has not experienced further hypoglycemic episodes. The patient reported that before this incident, he had never taken ibuprofen. He had never experienced similar episodes with aspirin, acetaminophen, or diclofenac.

Kubacka and colleagues (2) studied the effects of nonsteroidal anti-inflammatory drugs on the pharmacokinetics of glyburide and found that aspirin administration resulted in a 29% increase in glyburide free fraction and ibuprofen administration led to a slight increase. Shah and associates (3) reported that among diabetic patients treated by chlorpropamide, blood glucose levels decreased substantially when phenylbutazone was given; no significant reduction was seen in patients receiving ibuprofen. We could find no published case reports of ibuprofen-induced hypoglycemia, and the effects of ibuprofen on the pharmacokinetics of sulfonylurea have been considered minimal. Readers should note that ibuprofen may cause hypoglycemia when used in patients receiving sulfonylurea therapy.

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Idiosyncratic Acute Hepatitis Caused by Paracetamol in Two Patients with Melanoma Treated with High-Dose Interferon-α

TO THE EDITOR: Acute hepatitis related to paracetamol dose is well documented, whereas idiosyncratic acute liver injury is almost unknown (1–4).

A 47-year-old man and a 64-year-old woman with cutaneous melanoma began receiving adjuvant therapy with interferon-α2b (Intron-A, Schering-Plough, Italy), 20 MU/m^2 daily five times per week during the first month, followed by 20 MU/m^2 three times per week for 11 months. An influenza-like syndrome related to interferon-α was treated with paracetamol (500 to 1500 mg/d). After 2 months (for the male patient) and 3 weeks (for the female patient), liver aminotransferase levels progressively increased. Treatment was suspended and the patients were hospitalized for further investigation.

Blood test results at admission were as follows: For the male patient, alanine aminotransferase (ALT) level was 34 150 nkat/L (2049 IU/L), γ-glutamyltransferase level was 4.83 μkat/L, alkaline phosphatase level was 1.37 μkat/L, and bilirubin level was 17 μmol/L (1.0 mg/dL); for the female patient, ALT level was 36 000 nkat/L (2160 IU/L), γ-glutamyltransferase level was 13.24 μkat/L, alkaline phosphate level was 3.98 μkat/L, and bilirubin level was 212 μmol/L (12.4 mg/dL). Serologic testing ruled out acute hepatitis A, B, C, and E and acute infection with cytomegalovirus, Epstein–Barr virus, and herpesviruses. Other causes of acute liver injury were also excluded; screening for autoimmune disorders (which had yielded negative results before therapy) revealed transient positivity for antimitochondrial antibodies (titer, 80) in both patients. In the female patient, positivity for antimitochondrial antibodies was further characterized by a Western blot showing reactivity with 74-kDa and 55-kDa polypeptides, corresponding to pyruvate dehydrogenase complex-E2 (PCD-E2) and protein X, respectively. Results of liver function tests normalized 1 month later in both patients.

After the patients gave informed consent, 500 mg of paracetamol was orally administered. Aminotransferase levels increased suddenly the day after the rechallenge (in the male patient, aspartate aminotransferase level was 5.70 μkat/L [342 IU/L] and ALT level was 7950 nkat/L [477 IU/L]; in the female patient, aspartate aminotransferase level was 5.00 μkat/L [300 IU/L] and ALT level was 7850 nkat/L [471 IU/L]). Thereafter, the male patient restarted full-dose interferon-α treatment plus indomethacin, and he completed the adjuvant therapy without liver toxicity. The female patient declined to restart interferon-α therapy; she died 3 months later because of progression of melanoma.

Our data strongly suggest that paracetamol may cause acute liver damage through an idiosyncratic mechanism.

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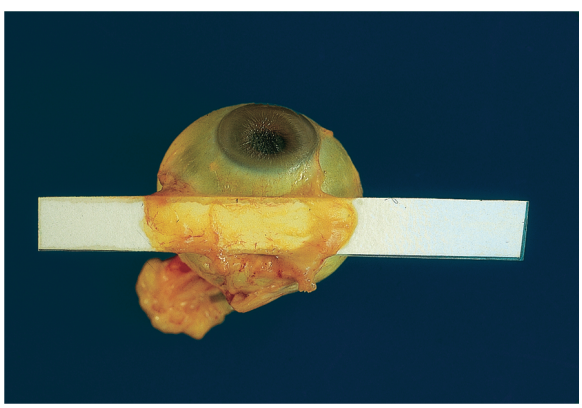
Conjunctival Icterus

TO THE EDITOR: Medical students learn that scleral icterus is an important and often early sign of hyperbilirubinemia. Yet, in each of the eight editions (1892 to 1916) of the classic textbook of medicine that he authored, William Osler defined icterus as yellow "tinting of the skin and conjunctivae." The first six editions (1927 to 1943) of *Cecil's Textbook of Medicine* localize the initial appearance of yellow pigmentation in jaundice to the conjunctiva. In the mid-1940s, sclera displaced the conjunctiva as the site of localization of ocular icterus in textbooks (1, 2)—on the basis of studies published a decade earlier in Germany showing the strong affinity of bilirubin for elastin (3, 4). The higher the elastin content of a tissue, the greater its bilirubin content and the more intense the icteric discoloration. In reality, it is the innermost layer of conjunctiva (the subepithelial lamina propria) and its contiguous, most superficial aspect of the sclera (the episclera) that are endowed with elastic fibers. The sclera proper contains far less elastic tissue.

During postmortem examination of eyes from five jaundiced patients, the conjunctivas were as deeply icteric as their underlying scleras. This is apparent in the photograph (**Figure**) from a patient whose serum bilirubin concentration at the time of death was 374

Figure. **Conjunctival icterus in postmortem examination.**



μmol/L (21.9 mg/dL). A white plastic band has been inserted between the conjunctiva and sclera; sclera at the right margin is free of covering conjunctiva.

My observations of gross specimens and unstained frozen sections are consistent with discussions in current textbooks of ocular pathology, which localize jaundice to the conjunctiva and superficial, fibrovascular episclera. Chronic hyperbilirubinemia will also discolor the relatively avascular sclera proper, presumably reflecting binding of bilirubin to collagen.

Although the underlying icteric episclera may enhance the visibility of early ocular jaundice, as the **Figure** demonstrates it is the icteric conjunctiva that alerts the examining physician to the presence of hyperbilirubinemia.

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Drug-Induced Thrombocytopenia: An Updated Systematic Review

TO THE EDITOR: We previously systematically reviewed all English-language reports, published up to 31 December 1997, on drug-induced thrombocytopenia (1). Our goal was to provide a database describing the level of evidence for a causal role for each drug and clinical outcomes (1). This letter describes our continuing systematic review for 2 subsequent years: 1 January 1998 to 31 December 1999. Through a MEDLINE literature search, we retrieved 58 articles; we identified 71 additional articles by searching the bibliographies of the retrieved articles. Thirty-five of the 71 additional articles had been published since 1966 but had not been identified in our previous MEDLINE literature search (1); 36 were published before 1966 but had not been identified in our previous search of bibliographies of retrieved articles (1). These articles contained 147 patient case reports, of which 78 were excluded because they did not meet previously defined criteria (1). The remaining 69 patient case reports involved 34 drugs. Nine drugs had level I (definite) evidence, and 17 other drugs had level II (probable) evidence. Of these 26 drugs, 15 had not been documented in the previous review as having definite or probable evidence for the drug as a cause of thrombocytopenia (1). Four of these 15 drugs each had one report with level I evidence; 11 drugs each had one report with level II evidence. The **Table** lists the four drugs with level I evidence and the two drugs for which the causal relation to thrombocytopenia was validated by at least two reports with level II evidence.

Table. **Drugs Causing Thrombocytopenia***

Drug	Case Reports, *n*	
	Level I	Level II
Indinavir	2	0
Atorvastatin	1	0
Pentoxifylline	1	0
Mesalamine	1	0
Ticlopidine	0	2
Acetazolamide	0	2

* These six drugs were not reported in the initial systematic review (1). Drugs are listed if the evidence supporting a causal relation to thrombocytopenia was definite (level I, requiring re-exposure to the drug that resulted in recurrent thrombocytopenia) or if the causal relation to thrombocytopenia was validated by at least two patient case reports with probable evidence (level II, requiring all criteria except re-exposure to the drug). Definitions of levels of evidence are described in the previous review (1). The full list of articles reviewed, the complete database, and the previous review are available at http://moon.ouhsc.edu/jgeorge.

This and the previous review were restricted to current therapeutic agents, but foods and alternative medicines may also cause thrombocytopenia. Two such reports—of tahini (pulped sesame seeds) (2) and jui (a traditional Chinese herbal medicine) (3)— both with level I evidence, were found but not included in our database because we had not systematically searched for nontherapeutic agents.

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Who Is a Peer?

TO THE EDITOR: The purpose of peer review is to protect scientific integrity and maintain public trust. This system is charged with preventing dispersal of erroneous data and conclusions. Peer review was constructed as a "checks and balances" system, similar to that used in the U.S. government: Congress (author), the President (reviewer), and the Supreme Court (editor).

What constitutes a peer? Is a peer an "expert" with a competing theory or competing grant? Is it a friend who will disregard missing but important data? Recently, several journals have confronted potential conflicts of interest. Discussion of this issue has focused on

authorship and editorship. Areas in which conflicts among authors and editors arise are many. Positive results of new products published in leading medical journals might increase manufacturers' income by substantiating product effects. Authors' incomes could increase depending on stock ownership; patent rights; consultant relationships; speaking invitations; continued, new, or supplemental research funding; or future employment. Conflicts are not limited to industrial relationships but also extend to grant funding (current and future). Conflicts include theoretical ("I've already made up my mind, don't confuse me with the facts") and financial (grant proposal based on competing theory). Similarly, prevention of publication of studies in which product failure or significant safety issues were encountered could help prevent financial loss.

Although much attention has been given to conflicts of interest among authors and editors, conflicts of interest among manuscript reviewers have not been addressed. Here there are additional potential conflicts. Personal relationships between reviewer and author, for example, may be supportive or in conflict. In addition, in the fight for research dollars, scientists have a vested interest in seeing publication of studies that support their own research theories and data.

All potential conflicts must be minimized. Financial conflicts may be easily identified; others may prove challenging. At a minimum, each reviewer, associate editor, and editor should be required to file a conflict of interest statement that describes relationships with the manufacturer of the product and that lists any research funding (private or government) in the reviewed manuscript's subject area that the involved party has received.

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Correction: Error in Medicine

The article on error in medicine (1) contained two errors. First, Bogner's book, *Human Error in Medicine*, is actually in print (publisher, Lawrence Erlbaum). Second, the Massachusetts error reporting and feedback system is sponsored and run by the Massachusetts Board of Registration in Medicine, not by the Massachusetts Medical Society.

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