

## Correspondence



### Outcomes in Young Adulthood for Very-Low-Birth-Weight Infants

*To the Editor:* Hack et al. (Jan. 17 issue)<sup>1</sup> report that 20-year-olds who had very low birth weight have a lower rate of risk-taking behavior than their normal-birth-weight peers, and the authors describe this finding as “reassuring.” McCormick and Richardson, in their editorial,<sup>2</sup> suggest that the avoidance of risk-taking behavior indicates a special “resilience” in very-low-birth-weight children and their families.

I disagree. As the parent of a very-low-birth-weight adult, the moderator of an Internet list for parents of preterm children, and the author of a book on prematurity, I am in close contact with many families with very-low-birth-weight children. Our children, even when they do not have major neurosensory handicaps, often have cognitive and behavioral deficits that isolate them from both their peers and their peers’ risk-taking behavior. Our children’s isolation and withdrawal are actually caused by a lack of social and intellectual resilience. As a result, many of us worry that our children will never become fully functioning members of society.

Unfortunately, recent research supports our fears. In a report on a national cohort of prematurely born teens in the Netherlands, Walther et al.<sup>3</sup> estimate that, because of social and cognitive problems, 40 percent of very-low-birth-weight children will never live independently. This Dutch cohort was born only a few years later than the group studied by Hack et al. and has a similar rate of neurosensory impairment (10 percent).

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1. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. *N Engl J Med* 2002;346:149-57.
2. McCormick MC, Richardson DK. Premature infants grow up. *N Engl J Med* 2002;346:197-8.
3. Walther FJ, den Ouden AL, Verloove-Vanhorick SP. Looking back in time: outcome of a national cohort of very preterm infants born in the Netherlands in 1983. *Early Hum Dev* 2000;59:175-91.

*To the Editor:* Hack et al. use either a general equivalency diploma or a standard high-school diploma as a measure of academic achievement. The two are not equivalent.<sup>1</sup> If the authors had used only the latter criterion as a measure of academic success, it is likely that the shortfall in academic achievement among very-low-birth-weight persons would be even more dramatic than that presented. In a nationally representative study,<sup>2</sup> we found that a low-birth-weight child is 74 percent less likely than his or her normal-birth-weight sibling to complete high school by 19 years of age.

In addition, it is not surprising that the less fortunate very-low-birth-weight adults who have chronic disabilities such as blindness, cerebral palsy, or lung disease would be unlikely to be found on the wrong side of the law. Hack and her colleagues state that the relation persisted when they limited their comparison to healthy very-low-birth-weight adults and normal-birth-weight adults. These results should be presented.

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1. Cameron SV, Heckman JJ. The nonequivalence of high school equivalents. *J Labor Econ* 1993;11:1-47.
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*To the Editor:* Hack and colleagues state that very-low-birth-weight babies have a significantly lower mean IQ at

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20 years of age than do the members of a control group (87 vs. 92). Although this difference may achieve statistical significance, such a difference is not considered meaningful by those who specialize in assessing cognitive development. Both scores are rated as falling within the average range. IQ scores are not finite measures of a characteristic in a given person; they are merely scores of someone's performance on a given test at a given time and are subject to errors of measurement. In this case, the range of "true" scores results in considerable overlap between the two groups of subjects.

It is known that low-birth-weight babies are at risk for cognitive deficits. What parents of these babies want to know is the nature and extent of this risk. Hack et al. do not emphasize that 120 of the low-birth-weight adults had normal IQs of 85 or higher.

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*To the Editor:* Hack et al. report higher rates of neurosensory impairment among very-low-birth-weight infants. Since premature infants frequently have retinal problems that may have lifelong consequences, I wonder whether the authors were able to identify visual impairment as one of the serious neurosensory problems.

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The authors reply:

*To the Editor:* We agree with Harrison that social isolation may have a role in the study subjects' tendency to engage in less risk-taking behavior. However, we do not have information on social relationships.

The estimate of Walther et al. that 40 percent of very-low-birth-weight children will not live independently was based on the responses to questions asked over the telephone of parents of 14-year-old children.<sup>1</sup> We interviewed and tested young adults. Although fewer very-low-birth-weight men than control men were in college, more were working (47 percent vs. 27 percent,  $P < 0.01$ ). Very-low-birth-weight women did not differ significantly from control women in terms of rates of college enrollment or employment. These results indicate that most very-low-birth-weight adults will be able to work and live independently, although men might lag behind in educational attainment.

In response to Conley and Bennett: we performed additional analyses excluding subjects with a general equivalency diploma. The rates of high-school graduation for very-low-birth-weight and normal-birth-weight men were 60 percent and 68 percent, respectively ( $P = 0.28$ ); the rates for women were 77 percent and 84 percent, respectively ( $P = 0.07$ ). When subjects with neurosensory impairment, a subnormal IQ, or both were excluded, the rates of alcohol use for very-low-birth-weight and normal-birth-weight subjects were 69 percent and 84 percent, respectively ( $P =$

0.001), and the rates of illicit-drug use were 37 percent and 47 percent, respectively ( $P = 0.02$ ). Fewer men with very low birth weight than with normal birth weight had been in contact with the police for drug-related or alcohol-related offenses (13 percent vs. 29 percent,  $P = 0.008$ ). When we excluded all subjects with chronic conditions (neurosensory, medical, or psychiatric conditions or subnormal IQ), subjects with very low birth weight still had lower rates of alcohol use (68 percent vs. 83 percent,  $P = 0.001$ ) and illicit-drug use (36 percent vs. 49 percent,  $P = 0.009$ ) than normal-birth-weight subjects. Among men, the rates of contact with police for offenses related to drugs or alcohol were 14 percent and 28 percent, respectively ( $P = 0.04$ ).

Tasman asks about visual impairment. Four very-low-birth-weight subjects (1.7 percent) had blindness due to retinopathy of prematurity (bilateral in one subject and unilateral in three).

We agree with Zach that many of the very-low-birth-weight subjects had normal IQs in young adulthood. However, as we noted in the discussion, our results are applicable only to current survivors of neonatal intensive care with birth weights between 1000 g and 1500 g. We have serious concern about children born during the 1990s weighing less than 1000 g, who may not function well as young adults.<sup>2,3</sup>

In Table 3 of our article, the total number of normal-birth-weight men with postsecondary study should have been 56 rather than 57.

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1. Walther FJ, den Ouden AL, Verloove-Vanhorick SP. Looking back in time: outcome of a national cohort of very preterm infants born in the Netherlands in 1983. *Early Hum Dev* 2000;59:175-91.

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3. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.

The editorialists reply:

*To the Editor:* Ms. Harrison offers an alternative hypothesis for the relative absence of risk-taking behavior observed in the group of young adults studied by Hack et al. Both our somewhat more optimistic hypothesis of resilience and hers of social isolation are testable in follow-up studies of very-low-birth-weight children now approaching adulthood. Her letter underscores the importance of not simply reporting on the outcomes of these vulnerable children, but also exploring the mechanisms that cause them, as we have argued elsewhere.<sup>1</sup> Well-targeted interventions have been demonstrated to effect changes in preschool cognitive and behavioral outcomes in very-low-birth-weight children.<sup>2</sup> Understanding the mechanisms behind other adverse out-

comes could lead to the development of strategies for amelioration.

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1. McCormick MC. Conceptualizing child health status: observations from studies of very premature infants. *Perspect Biol Med* 1999;42:372-86.
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### Oral and Topical Corticosteroids in Bullous Pemphigoid

*To the Editor:* Joly et al. (Jan. 31 issue)<sup>1</sup> report mortality rates among patients with bullous pemphigoid that are substantially higher than those in four previous British and American studies (a one-year mortality rate of 19 percent, a two-year mortality rate of 6 percent, and three-year mortality rates of 28 percent and 30 percent<sup>2</sup>) but similar to that in another French study (a one-year mortality rate of 41 percent<sup>3</sup>), suggesting that survival of patients with bullous pemphigoid may vary according to the ethnic background. Thus, the findings reported by Joly et al. cannot be extrapolated to all patients with bullous pemphigoid, and additional randomized trials are necessary for validation.

With regard to the editorial by Stern,<sup>4</sup> since linear deposition of IgG and C3 are found in the epidermal basement membrane in patients with diseases other than bullous pemphigoid, indirect immunofluorescence studies of salt-split skin, not positive histopathological studies demonstrating such deposition, are considered to be the diagnostic standard.<sup>2</sup> One study found that 15 percent of patients with linear IgG or C3 deposits in the basement membrane had epidermolysis bullosa acquisita or bullous systemic lupus erythematosus.<sup>5</sup> Although patients with cicatricial pemphigoid, linear IgA disease, or chronic bullous disease of childhood may uncommonly have autoantibodies against type VII collagen, most would classify these patients as having epidermolysis bullosa acquisita. LAD-1 is part of bullous pemphigoid antigen 2,<sup>6</sup> not a 97-kD protein distinct from bullous pemphigoid antigen 2. Bullous pemphigoid and herpes gestationis are not immunologically identical, since patients with herpes gestationis have specific HLA associations, avid complement-fixing IgG antibodies, and linear C3 deposits, whereas patients with bullous pemphigoid have no HLA associations, less avid complement-fixing IgG antibodies, and linear deposits of C3 and IgG.

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1. Joly P, Roujeau J-C, Benichou J, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002; 346:321-7.

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6. Zone JJ, Taylor TB, Meyer LJ, Petersen MJ. The 97 kDa linear IgA bullous disease antigen is identical to a portion of the extracellular domain of the 180 kDa bullous pemphigoid antigen, BPAG2. *J Invest Dermatol* 1998;110:207-10.

*To the Editor:* A recent systematic review of treatments for bullous pemphigoid<sup>1</sup> highlights the increased mortality associated with higher doses of oral prednisolone. There is good evidence to support the use of 20 to 40 mg of prednisolone (0.5 mg per kilogram of body weight) in combination with topical therapy and other nontoxic antiinflammatory drugs, such as minocycline and nicotinamide.<sup>1,2</sup> Given that Joly et al. did not compare prednisone at a dose of 1 mg per kilogram per day with prednisone at a dose of 0.5 mg per kilogram per day for the treatment of extensive bullous pemphigoid, one cannot conclude that the lower dose would not be appropriate. Further evaluation is required to determine the optimal dose and the optimal proportions of corticosteroids to be delivered by the oral and topical routes.

The serious drawback to topical therapy alone in the study by Joly et al. was that some patients required nursing assistance. The authors do not report the number of patients who required such care or the cost of delivery. We do not believe that the main conclusion, that oral corticosteroids are no longer justified for treatment of severe bullous pemphigoid, is correct.

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*To the Editor:* An overlooked explanation for the finding that clobetasol, a highly potent topical corticosteroid, is as effective as prednisone for the treatment of bullous pemphigoid is that the medication is absorbed through the skin, resulting in blood corticosteroid levels similar to those achieved by systemic therapy.

Topically applied clobetasol is absorbed rapidly; 12.5 mg applied to normal skin results in peak plasma levels one fourth as high as those attained with 10 mg of prednisone (i.e., 6 to 7 ng per milliliter vs. 24.5 ng per milliliter).<sup>1,2</sup> Blood levels in patients with bullous pemphigoid are probably higher than that, since corticosteroid absorption is increased by a factor of 16 when skin is blistered,<sup>3</sup> as it is in this disease. Furthermore, the potency of clobetasol is much

greater than that of prednisone — 360 times as high, according to assays of vasoconstriction. Thus, the daily topical application of 20 mg of clobetasol (40 g of 0.05 percent clobetasol cream per day) might well have a systemic effect similar to, or perhaps greater than, that achieved in the patients in the control group treated with 60 mg of prednisone per day.

If the therapeutic effect of clobetasol results from its systemic absorption, the safety of this approach may be no greater than that of conventional therapy with systemic corticosteroids and may be outweighed by its disadvantages — cost (a wholesale price 110 times that of prednisone<sup>4</sup>) and the difficulty involved, particularly for the elderly, in applying cream twice daily to the entire body.

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1. Olsen EA, Cornell RC. Topical clobetasol-17-propionate: review of its clinical efficacy and safety. *J Am Acad Dermatol* 1986;15:246-55.
2. Ferry JJ, Horvath AM, Bekersky I, Heath EC, Ryan CF, Colburn WA. Relative and absolute bioavailability of prednisone and prednisolone after separate oral and intravenous doses. *J Clin Pharmacol* 1988;28:81-7.
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4. 2001 Drug topics red book. Montvale, N.J.: Medical Economics, 2001: 253-4, 474.

*To the Editor:* The protocol used by Joly and colleagues required the initial application of 20 g of clobetasol cream twice a day until 15 days after control of the disease had been established, followed by a gradual decrease in the dose and frequency to 10 g twice a week until the end of 12 months of therapy. As a rule of thumb, 30 g is enough to cover the average person's body once. How did subjects manage to apply considerably less than that and cover the entire body? Does the "entire surface of the body" include the palms, soles, face, scalp, and intertriginous areas? If patients have just a few blisters or localized disease, I often treat them locally with a topical corticosteroid. How do the authors treat localized disease? Finally, the cost of a 45-g tube of generic clobetasol cream at our local pharmacy is about \$45. The cost of 60 mg of prednisone (an average dose) in the form of 20-mg tablets is about 70 cents a day. At these rates, treatment for 30 days with topical clobetasol cream would cost \$1,350, as compared with about \$21 for the oral prednisone. I wonder whether the cost differential justifies the use of topical corticosteroid, particularly in the case of moderate disease, for which the outcomes are similar.

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The authors reply:

*To the Editor:* Korman comments that the mortality rate among our patients treated with high doses of oral corticosteroids seems higher than the rates reported in British

and American studies. Unfortunately, the studies cited by Korman are either retrospective studies with a substantial number of patients lost to follow-up or therapeutic studies testing immunosuppressive drugs in very limited numbers of selected patients (one study included only 26 patients).<sup>1</sup> We suggest that these studies underestimated the actual mortality rate associated with bullous pemphigoid. Other large prospective studies of nonselected patients would be needed in order to permit meaningful comparisons of the mortality rates in various countries.

Arderm-Jones et al. suggest that patients with severe bullous pemphigoid could be adequately treated with the use of 20 to 40 mg of prednisolone per day. We agree that in a few patients, extensive bullous pemphigoid may occasionally be controlled with these low doses of oral corticosteroids. However, to date, these doses cannot be considered or proposed as standard, since the only randomized study reported in the literature that tested such low doses of corticosteroids showed that severe bullous pemphigoid was not controlled by 0.3 mg of prednisolone per kilogram per day in any of the 15 patients who received this regimen.<sup>2</sup>

It is likely that the extremely high efficacy of clobetasol propionate cream is due to the combination of local and systemic effects, as suggested by Bystryn et al. Indeed, basal cortisol levels were reduced in 19 of the 20 patients who were treated topically in our study. Treatment with topical corticosteroids has the advantage of achieving high skin levels that influence local factors of inflammation, whereas systemic absorption may suppress the synthesis of antibodies to the basement-membrane zone.

Spigel notes the high cost of topical treatment. However, the decrease of, on average, seven days in the hospital stay for patients who receive topical treatment (as compared with those who receive oral treatment), observed in patients with moderate or extensive bullous pemphigoid, should more than outweigh the higher cost of topical treatment. Moreover, this added cost pales in comparison with the overall cost of treatments such as intravenous immune globulin and mycophenolate mofetil, which have been proposed despite the lack of data from randomized trials.<sup>3</sup>

Finally, we agree that most patients with bullous pemphigoid can probably be adequately treated with lower doses — from 10 to 30 g of clobetasol propionate cream daily — depending on the extent of disease. We are currently testing the efficacy and safety of these reduced doses in a randomized, controlled trial. Our findings, based on results in more than 300 patients, indicate that a dose of 10 to 15 g is sufficient to cover the entire surface of the body, excluding the face, which is usually not involved in bullous pemphigoid.<sup>4</sup>

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1. Korman NJ. Bullous pemphigoid: the latest in diagnosis, prognosis, and therapy. *Arch Dermatol* 1998;134:1137-41.
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The editorialist replies:

*To the Editor:* Dr. Korman appears to equate higher resolution with superiority. In clinical practice, the most appropriate test may not have the highest resolution or be the most expensive. Rather, if a test is required to confirm or rule out a diagnosis with greater precision than can be done on the basis of clinical criteria alone, that test should be selected according to factors such as sensitivity and specificity, the probability of the diagnosis under consideration, and the cost.

Direct immunofluorescence testing is used to confirm (or rule out) the clinical diagnosis of various autoimmune blistering skin diseases. Since such testing was first described 35 years ago, modifications, including so-called salt-split tests, have become available. These modifications may permit more precise localization of immunoreactants in the basement-membrane zone, but I judged discussion of this arcane topic to be of limited interest to the intended readers of my editorial. In addition, immunofluorescence testing of salt-split skin has not been demonstrated to have a higher predictive value than clinical criteria alone.<sup>1</sup>

Patients with bullous pemphigoid, epidermolysis bullosa acquisita, or bullous lupus typically have distinctive clinical features. When an autoimmune blistering skin disease is suspected, clinical data along with traditional direct immunofluorescence testing are usually sufficient for an accurate diagnosis. In the rare case of a patient with a clinical presentation compatible with multiple autoimmune blistering skin diseases, the more expensive salt-split skin study or even higher-resolution studies are useful and indicated.

I have always thought that elderly and pregnant patients with autoimmune, subepidermal blistering diseases differ from other patients in many clinical and some immunologic aspects. As I noted, their antibodies do share the same principal antigenic targets.

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### Antibiotic-Associated Diarrhea

*To the Editor:* Dr. Bartlett (Jan. 31 issue)<sup>1</sup> notes that "occasional cases [of *Clostridium difficile* infection] follow treatment with methotrexate or paclitaxel for cancer chemotherapy." As a medical oncologist, I encounter many cases of diarrhea associated with *C. difficile* infection in patients who have received broad-spectrum antibiotics because of

neutropenic fever. I have yet to document a case after chemotherapy in the absence of a history of broad-spectrum antibiotic therapy. Moreover, I cannot find any well-documented cases in the literature. Is Dr. Bartlett aware of any such cases that are clearly documented?

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1. Bartlett JG. Antibiotic-associated diarrhea. *N Engl J Med* 2002;346:334-9.

Dr. Bartlett replies:

*To the Editor:* I, too, have never encountered a case of *C. difficile*-associated diarrhea that was clearly due to cancer chemotherapy. The statement that "occasional cases" are ascribed to *C. difficile* infection was based on multiple reports in the literature.<sup>1,2</sup> Higher doses of paclitaxel were more frequently associated with this complication than were lower doses.<sup>1</sup> In these and most other reports, it is often unclear how well antibiotics were exonerated. I suspect that some cases are truly associated with antineoplastic chemotherapy, but only rarely.

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### The Antiphospholipid Syndrome

*To the Editor:* In their review article, Levine et al. (March 7 issue)<sup>1</sup> state that the prevalence of antiphospholipid antibodies increases with age and is especially high in the elderly population. This statement overlooks data on the prevalence of antiphospholipid antibodies in children. In particular, anticardiolipin antibodies can be found in a high percentage of children without any discernible disease. We observed positive values for anticardiolipin antibodies in 11.4 percent of 61 apparently healthy children at their regular preventive visits.<sup>2</sup> In addition, Rapizzi et al. found anticardiolipin antibodies in 28 percent of 100 healthy children.<sup>3</sup> It has generally been assumed that such naturally occurring anticardiolipin antibodies could be the result of previous infections or vaccinations that are common in this population.<sup>4</sup>

Furthermore, recent evidence suggests that alternative responses of the developing immune system to dietary antigens can result in the production of specific antiphospholipid antibodies during childhood. We showed that the mean value of IgG anti- $\beta_2$ -glycoprotein I antibodies is highest in preschool children and that, in this group, it is significantly higher than in adolescents and healthy adults.<sup>2</sup>

Moreover, IgG anti- $\beta_2$ -glycoprotein I antibodies can be found in a high percentage of infants with atopic dermatitis who have exaggerated immune responses to nutritional antigens. These findings indicate that dietary  $\beta_2$ -glycoprotein I may act as an oral immunization agent and induce transitory production of anti- $\beta_2$ -glycoprotein I antibodies in infants, whose intestinal mucosa is more permeable to large molecules than that of adolescents and healthy adults.<sup>4,5</sup>

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1. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002;346:752-63.
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3. Rapizzi E, Ruffatti A, Tonello M, et al. Correction for age of anticardiolipin antibodies cut-off points. *J Clin Lab Anal* 2000;14:87-90.
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The authors reply:

*To the Editor:* Dr. Avcin and colleagues note that we omitted mention of the prevalence of antiphospholipid antibodies in children. They also suggest that the relatively high prevalence of anticardiolipin antibodies in this population may be the result of previous infections, vaccinations, or exposure to dietary antigens, including dietary sources of  $\beta_2$ -glycoprotein I.<sup>1</sup>

Our review focused on adults, in whom the prevalence of antiphospholipid antibodies increases with age. However, the implication that we should have made specific reference to the problem of antiphospholipid antibodies and the antiphospholipid syndrome in children has merit. As summarized by Dr. Avcin and colleagues, the prevalence of antiphospholipid antibodies may be biphasic with respect to age, with an initial peak occurring before adolescence. Although the presence of antiphospholipid antibodies does not mean that a patient has the antiphospholipid syndrome, the current diagnostic criteria<sup>2</sup> may be deficient with respect to their application in children.<sup>1</sup>

Though worthy of speculation, the potential link between oral antigens and antiphospholipid antibodies has not, to our knowledge, been proved. Another attractive theory, for which there is experimental evidence, is that there is an infectious trigger for the production of antiphospholipid antibodies. Viral<sup>3</sup> and bacterial<sup>4</sup> peptides induced antiphospholipid antibodies in murine models. In fact, the antiphospholipid antibodies induced in response to a cytomegalovirus peptide caused thrombosis and endothelial-cell activation in mice.<sup>3</sup> In adults, high levels of antiphospholipid antibodies have been described in association with

cytomegalovirus infection in recipients of allogeneic stem-cell transplants.<sup>5</sup> Finally, cytomegalovirus infection is found in approximately 1 percent of newborns and is common in young children.

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## Pharmacy Compliance with a Prescription-Drug Discount Program

*To the Editor:* California Senate Bill 393 requires "presentation of a valid prescription for the patient and the patient's Medicare card" as the basis for discounted prices.<sup>1</sup> Since the design of the study reported by Lewis et al. (March 14 issue)<sup>2</sup> did not include the presentation of prescriptions, and since the "standardized patients" identified themselves only as Medicare enrollees, it is not possible to interpret the results as a measurement of compliance with Senate Bill 393. A more valid design would have included the presentation of both prescriptions and Medicare cards. Furthermore, it was inappropriately implied that pharmacists should be able to deduce patients' ages and Medicare-enrollment status solely by observation.

For pharmacies, the logistics of obtaining Medicare discounted prices are complicated. They involve entry into the computer of information about the patient obtained from the Medicare card and specific prescription information; electronic transmission of the information to plan-specific processors, with a charge (\$0.15 to \$0.25 per prescription); and finally, receipt of the discounted price. Without prescriptions and Medicare cards, obtaining discounted prices requires the creation of "dummy prescriptions," completion of the procedures listed above, and payment of charges.

In addition, the authors fail to consider in their discus-

sion the possible effects of the national shortage of pharmacists and the related recent surge in retail prescriptions on the findings.<sup>3,4</sup>

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The authors reply:

*To the Editor:* We were unable to have the standardized patients present prescriptions at pharmacies for legal reasons. Nonetheless, we performed a valid test of whether pharmacies would offer the legally mandated discounts. As we stated in our article, both Title 16 of the California Code of Regulations<sup>1</sup> and California Business and Professions Code 4122<sup>2</sup> “stipulate that pharmacies must provide prescription-drug prices when asked, whether or not the customer presents a prescription.”

We did not expect pharmacists to deduce the age of the standardized patients by observation. Pharmacies were considered noncompliant only if they failed to offer the mandated discount after the standardized patient had specifically asked for it and presented his or her Medicare card. We understood that the logistics of obtaining Medicare discount prices without a prescription are complicated and that pharmacies incur a charge. Therefore, pharmacies were considered compliant if the pharmacist stated that a Medicare discount was available but that he or she could not provide prices without checking the computer. In fact, pharmacists at 345 of the 372 compliant pharmacies stated that the discounted prices were available but failed to provide them.

The reasons for noncompliance are beyond the scope of our study. We certainly expect that a national shortage of pharmacists and a surge in the number of retail prescriptions can only make compliance with this and similar laws more difficult.

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## Case 8-2002: Pleural Effusion

*To the Editor:* In her discussion of Case 8-2002 (March 14 issue),<sup>1</sup> Dr. Quinn includes hypothyroidism in the differential diagnosis of exudative pleural effusions. Hypothyroidism usually causes transudative pleural effusions.<sup>2</sup> Furthermore, the patient had a low level of thyrotropin with normal levels of triiodothyronine and free thyroxine, indicating the presence of subclinical hyperthyroidism rather than hypothyroidism.

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*To the Editor:* Dr. Quinn provides an instructive discussion of a patient with a persistent pleural effusion but does not mention the usefulness of information on adenosine deaminase levels in the diagnosis of tuberculous pleurisy.<sup>1</sup>

It is surprising that the diagnosis of tuberculous pleural effusion was ruled out on the basis of the computed tomographic (CT) findings. We would never rule out pleural tuberculosis on the basis of CT findings without measuring adenosine deaminase levels or performing a closed pleural biopsy.

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## Ooplasmic Transfer

*To the Editor:* In his Sounding Board article (March 7 issue),<sup>1</sup> Dr. Templeton notes that ooplasmic transfer raises novel issues related to family law, kinship, and relationships, in addition to important issues regarding health and safety. A child born after an ooplasmic transfer would have a second genetic mother — the source of the mitochondrial DNA in the donated ooplasm. However, if this technique proves safe and effective for oocyte insufficiency, the rules of family law would easily adjust to it, just as they have with egg donation, a rapidly growing assisted reproductive technique.

Like other egg donors, the woman who provided the ooplasm would almost certainly not have independent standing as a legal parent.<sup>2</sup> Nor, given the small amount of DNA contributed, is it likely that she would psychologically or

socially be viewed as a mother. This viewpoint is similar to the way in which gestational and genetic motherhood is now distinguished in egg donation and gestational surrogacy. Resolving the family-law and kinship issues in ooplasm transfer will be easier than understanding the science or increasing the clinical efficacy of this procedure to an acceptable level.

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### Interferon Alfa-Induced Adverse Effects in Patients with a Psychiatric Diagnosis

*To the Editor:* Two reports in the *Journal*<sup>1,2</sup> have suggested that patients who have psychopathologic symptoms before beginning interferon alfa therapy may have more severe adverse psychiatric effects in response to treatment. This suggestion was based on the observation that patients' scores on psychopathologic rating scales before interferon alfa therapy were positively correlated with the scores after four weeks of treatment.<sup>1,2</sup> However, we and others have found that patients with a psychiatric diagnosis can successfully complete interferon alfa therapy.<sup>3,4</sup> An editorial in the *Journal* has rightly emphasized that withholding interferon alfa inappropriately, especially from members of a stigmatized class, "raises questions about fairness and discrimination."<sup>5</sup>

We evaluated 60 patients with chronic hepatitis B and C, some of whom had a preexisting psychiatric diagnosis, in Cagliari, Italy. They received 6 million to 10 million U of interferon alfa three times per week for 12 months. Information on the psychiatric diagnosis was obtained before therapy with the use of the non-patient structured clinical interview from the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised. Interferon alfa-induced adverse psychiatric effects were monitored monthly with use of the 17-item Hamilton Depression Rating Scale, the Beck Depression Inventory, and the Spielberger State-Trait Anxiety Inventory. We analyzed these results using response-feature analysis (maximal scores on psychopathologic rating scales during the therapy) and analysis of covariance. We compared the psychopathologic response of the 25 patients with a preexisting psychiatric diagnosis with that of the 35 patients with no psychiatric diagnosis, while adjusting for base-line differences (Table 1). As expected, patients with a preexisting psychiatric diagnosis had higher base-line scores than patients with no psychiatric diagnosis (all P<0.01) (Table 1). After adjusting for the base-line values, we found no evidence that patients with a preexisting psychiatric diagnosis and patients with no psychiatric diagnosis had different maximal scores on the psychopathologic rating scales (all P>0.5) (Table 1). We also found no significant difference between groups in the incidence of adverse psychiatric effects severe enough to require psychopharmacologic treatment: 3 of the 25 patients with a preexisting psychiatric diagnosis had such effects, as compared with 7 of the 35 patients with no psychiatric diagnosis (12 percent vs. 20 percent; chi-square with 1 df=0.22;

**TABLE 1.** SCORES ON PSYCHOPATHOLOGIC RATING SCALES AT BASE LINE AND DURING INTERFERON ALFA THERAPY IN PATIENTS WITH A PREEXISTING PSYCHIATRIC DIAGNOSIS AND IN PATIENTS WITHOUT SUCH A DIAGNOSIS. \*

| TEST                                      | PATIENTS WITH PREEXISTING PSYCHIATRIC DIAGNOSIS (N=25) | PATIENTS WITH NO PSYCHIATRIC DIAGNOSIS (N=35) | DIFFERENCE IN GROUP MEANS (95% CI) | t-TEST OR F VALUE        | P VALUE |
|---|--|---|------------------------------------|--------------------------|---------|
|   | mean ±SD   |   |                                    |                          |         |
| <b>At base line</b>                       |  |   |                                    |                          |         |
| Hamilton Depression Rating Scale          | 7.1±5.1  | 3.9±3.4                                       | 3.2 (1.0 to 5.4)                   | t <sub>57</sub> =2.9     | 0.006   |
| Beck Depression Inventory                 | 7.2±8.6  | 2.6±3.4                                       | 4.6 (1.4 to 7.8)                   | t <sub>57</sub> =2.9     | 0.006   |
| Spielberger State-Trait Anxiety Inventory |  |   |                                    |                          |         |
| State anxiety                             | 41.7±10.2  | 35.2±8.4                                      | 6.5 (1.7 to 11.4)                  | t <sub>57</sub> =2.7     | 0.009   |
| Trait anxiety                             | 38.6±10.2  | 30.2±6.8                                      | 8.4 (3.9 to 12.8)                  | t <sub>57</sub> =3.8     | <0.001  |
| <b>During therapy</b>                     |  |   |                                    |                          |         |
| Hamilton Depression Rating Scale          | 12.0±5.6   | 9.3±5.3                                       | 0.6 (-2.1 to 3.3)†                 | F <sub>1,56</sub> =0.22  | 0.64    |
| Beck Depression Inventory                 | 10.4±9.4   | 6.0±6.5                                       | 0.8 (-2.8 to 4.4)†                 | F <sub>1,56</sub> =0.20  | 0.66    |
| Spielberger State-Trait Anxiety Inventory |  |   |                                    |                          |         |
| State anxiety                             | 46.5±11.7  | 40.5±10.8                                     | 1.6 (-3.7 to 6.9)†                 | F <sub>1,56</sub> =0.37  | 0.55    |
| Trait anxiety                             | 42.8±12.2  | 36.1±10.2                                     | -0.2 (-5.4 to 5.0)†                | F <sub>1,56</sub> =0.008 | 0.93    |

\*Student's t-test and analysis of covariance were used to obtain 95 percent confidence intervals (CIs) and to evaluate the null hypothesis. On each scale, higher scores indicate a greater severity of symptoms.

†The estimated difference in group means was adjusted for base-line values.

P=0.6). We believe that patients who have psychopathologic symptoms before they begin taking interferon alfa should not be denied this effective therapy.

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