sequence of immunosuppression, which has implications for all so-called nonpersistent pathogens. Previously, we observed prolonged and possibly chronic shedding of human metapneumovirus in two patients with cancer who were immunosuppressed because they were receiving chemotherapy.[2] Furthermore, it was recently reported that immunosuppression induced by lactate dehydrogenase–elevating virus led to increases in the severity and duration of the acute phase of friend virus infection in mice, most likely because of diminished CD8– responses.[3] Such observations may provide support for earlier assumptions that if the CD4+ defense is insufficient because of immunosuppression, the CD8– response is unlikely to eliminate infection.[4] The study by Kamar et al. revealed significantly reduced CD4– counts in patients with chronic HEV infection. Under these specific circumstances, so-called nonpersistent viruses may cause chronic colonization and recurrent infection. Hence, reducing drug-induced immunosuppression during acute HEV infection might be a strategy to prevent the progression to chronic hepatitis.

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THE AUTHORS REPLY: With regard to the comments by Schildgen et al., prolonged acute hepatitis A virus and HEV infections have been reported previously in both immunocompromised and nonimmunocompromised patients.[1,2] Our report indicated that HEV infection may evolve to chronic hepatitis in organ-transplant recipients. In addition, a unique case of HEV-related cirrhosis has recently been reported.[3] Schildgen et al. suggest that the evolution of HEV infection to chronic hepatitis is related to marked immunosuppression. They base their assumption on two studies of viral infections that appear to be unrelated to those that have been observed in organ-transplant recipients. We agree that the evolution of HEV infection to chronic hepatitis in the setting of marked immunosuppression may be a mechanism, since we have found a lower CD4+ cell count in patients in whom chronic hepatitis evolved than in patients who were clear of the virus. Hence, in HEV-infected transplant recipients, we suggest reducing immunosuppressive therapies that target T cells (i.e., mainly calcineurin inhibitors) in order to allow clearance of the virus.

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Phototherapy for Neonatal Jaundice

TO THE EDITOR: In their Clinical Therapeutics article on phototherapy for neonatal jaundice, Maisels and McDonagh (Feb. 28 issue)[1] describe various mechanisms for maximizing the efficacy of phototherapy. They state, "The dose and efficacy of phototherapy are also affected by the infant's distance from the light (the nearer the light source, the greater the irradiance)." However, this statement must be applied with great care. Indeed, guidelines from the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia specifically urge caution when halogen lamps, which

can generate significant amounts of heat, are used.[2] Placing these lamps as close as possible increases the risk of burns. Thus, physicians should be aware of this untoward side effect when positioning a halogen light to obtain maximum irradiance of a newborn with jaundice.

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TO THE EDITOR: In their review of phototherapy for neonatal jaundice, Maisels and McDonagh cite our work, suggesting that this form of therapy may influence the development of dysplastic nevi.[1,2] We have now investigated the prevalence of melanocytic nevi among 11 monozygotic twin pairs in which one twin received phototherapy for neonatal jaundice and the other did not. Neonatal blue-light phototherapy was associated with a considerably higher number of common and clinically atypical nevi (Table 1). The increased number of nevi on persons receiving phototherapy might well be due to the effects of light on neonatal skin. Ultraviolet A light has profound immunosuppressive effects and is sufficient to induce melanoma and melanoma precursors in animal models.[3] Moreover, visible light has also been shown to exert indirect DNA damage through the generation of reactive oxygen species.[4] In view of the immaturity of the skin and immune system in newborns, intensive neonatal phototherapy could markedly influence melanocytes and nevus development.

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Table 1. Prevalence of Common and Clinically Atypical Melanocytic Nevi in 11 Monozygotic Twin Pairs in Which One Twin Received Neonatal Blue-Light Phototherapy (BLP) and the Other Twin Did Not.*

Twin Pair No.	Sex	Age	No. of Common Melanocytic Nevi		No. of Clinically Atypical Melanocytic Nevi		Total No. of Melanocytic Nevi	
			No BLP	BLP	No BLP	BLP	No BLP	BLP
		yr						
1	M	6	0	3	0	0	0	3
2	F	8	1	4	0	0	1	4
3	M	11	4	17	1	3	5	20
4	F	14	26	28	0	5	26	33
5	M	14	12	27	2	4	14	31
6	M	18	3	3	0	1	3	4
7	M	20	11	12	0	1	11	13
8	F	23	21	15	1	3	22	18
9	M	24	8	9	0	1	8	10
10	F	24	9	27	0	3	9	30
11	M	30	3	12	3	13	6	25
P value			0.03		0.008		0.02	

* Differences in the prevalence of common and clinically atypical melanocytic nevi between the exposed and nonexposed subjects were analyzed by means of a two-sided Wilcoxon signed-rank test (SPSS software, version 15.0). P values of less than 0.05 were considered to indicate statistical significance. Data concerning the neonatal history of the subjects were based on the official neonatal medical charts. A detailed standardized questionnaire was used to assess data concerning constitutional factors, sun exposure, and other variables; these factors proved to be very consistent in the examined twin pairs.

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TO THE EDITOR: The article by Maisels and McDonagh succinctly summarizes the mechanisms and application of phototherapy for jaundiced newborns. The authors promote the guidelines for using phototherapy that were published in 2004 by the American Academy of Pediatrics,[1] which are based primarily on total serum bilirubin levels. They admit that these guidelines are not evidence-based, but rely primarily on expert opinion, and that "many infants are treated [2 to 3% of term or near-term infants and 150,000 to 250,000 premature infants each year] whose levels of total serum bilirubin would not have reached the threshold for exchange transfusion had phototherapy been withheld."

The authors fail, however, to mention that theoretical considerations,[2] substantial experimental data,[3,4] and increasing evidence in human newborns[5] all indicate that total serum bilirubin is a poor predictor of bilirubin-induced neurologic damage, whereas unbound ("free") bilirubin levels correlate well with neurotoxicity. Establishing evidence-based guidelines for phototherapy (and exchange transfusion), with the use of unbound (free) bilirubin measurements, could significantly improve selection and reduce the number of infants requiring these treatments, as well as decrease hospital readmissions and the associated health care costs.

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THE AUTHORS REPLY: Kapoor draws attention to an important issue. Halogen and tungsten lights should not be placed closer to the baby than recommended by the manufacturer because of the danger of a burn. We noted this in our article (Fig. 3 legend), and it is also a recommendation of the American Academy of Pediatrics guidelines.[1]

As noted by Csoma et al., the development of dysplastic nevi is a concern requiring further investigation. It is difficult to evaluate their findings because of a lack of information about the spectral emission of the phototherapy lights, particularly their ultraviolet output; the distribution of the nevi; and the patients' skin types. Properly shielded fluorescent lamps emit little radiation (<400 nm),[2] and blue light-emitting-diode (LED) lights none at all. Although the findings in twin pairs might appear to be persuasive, the untreated twin is not an adequate control for the effects of phototherapy light on the treated twin. Proper sibling controls would need to be treated identically to their twins but not exposed to blue light or, alternatively, exposed to the same fixtures containing lamps with only long-wavelength visible emission. In the absence of proper controls, the results reported could equally well be attributed, for example, to effects of electromagnetic-field radiation from the light-fixture ballasts as to effects of the phototherapy light. Reassuringly, to our knowledge, there are no reports of increased nevus formation in patients with the Crigler–Najjar syndrome who have received daily phototherapy since birth.

It is well known that the total bilirubin concentration alone is a poor predictor of kernicterus. Nevertheless, the risk of bilirubin encephalopathy increases with the bilirubin concentration at high bilirubin levels. Kernicterus in term and late-preterm infants is almost always associated with bilirubin concentrations higher than 25 mg per deciliter (428 μmol per liter) and rarely occurs at lower concentrations. Therefore, the total bilirubin concentration, which is readily measured, is

not to be ignored. The idea that unbound ("free") bilirubin levels are useful in improving the selection of infants requiring treatment is a long-standing hypothesis that requires validation. Currently, such measurements are not offered by clinical laboratories in the United States, and there is concern that bilirubin photoisomers may complicate their interpretation.[3] Alternatives are the bilirubin:albumin molar ratio and the reserve bilirubin-binding capacity of albumin in serum,[4,5] which are more easily measured and might also facilitate identification of infants at greatest risk. Currently, attempts are being made to refine the American Academy of Pediatrics guidelines and reduce unnecessary treatment.

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