Etiology of Bronchopulmonary Dysplasia

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cases were aware of the social and legal interests being debated. Finally, the later cases make reference to the earlier cases; this is the manner in which the law is created or changed.

4. Drs De Ville and Moskop are troubled by the ages of some children in the cases I reported. It is true that the standards proposed by the FCAA apply only to infants under 1 year of age. Outside the FCAA the law usually defines an infant as anyone under the age of 18 years.[1] The same legal reasoning would have been used if Joelle Rosebush had been 10 days, 10 months, or 10 years old. I believe I have found six pertinent cases.
5. I never claimed to review any state's administrative codes (rules and regulations). It is the function of legislatures to enact statutes and judges to interpret them. I did review N. C. Gen. Stat. @ 7A-516, 517, 542, 543, 544, 549, and 7A-550 for my article and they do not track the FCAA definitions. North Carolina has a statute [143B-153 (6)] that empowers their Social Service Commission to issue rules and regulations for the purpose of complying with federal grants-in-aid. 10 N.C.A.C. 41I0303 represents an administrator's attempt to bootstrap the FCAA definitions onto existing statutes; it states on its face that its authority is derived from the very statutes I reviewed. Although Drs De Ville and Moskop confuse statutes and regulations, their comment underscores my point that it does not matter if states rewrite their statutes to comply with federal suggestions. My research found that a charge of abuse or neglect for failing to provide appropriate medical treatment could be brought under the existing statutes in all 50 states. *Rosebush* proves it can be done.[1] I do not advocate that these statutes be used for this purpose. I only demonstrate that the interests of infants and children in receiving appropriate medical care are already sufficiently protected without creating new laws.
6. It is true that the conflict between the federal and state standards T reported will remain a matter of conjecture until such time as a judge might actually apply the FCAA. Nonetheless, both standards do exist. The federal standard makes the physician the decision-maker and in theory rests solely on objective reasoning. The state standard retains the parent as the decision-maker and allows the subjective determination of the child's best interests. It is this well-documented apparent conflict that has confused a significant number of doctors[6] and lawyers.[1] I do not recommend or personally utilize the federal standard in my medical practice.
7. I make the following observation only because Drs De Ville and Moskop raise the point. A law professor suggested I submit my earlier article[1] to a journal whose primary readership is comprised of juvenile court judges. It's editorial board (mostly judges) felt it had sufficient merit to overcome a prohibition on accepting prior publications.[7]

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REFERENCES

1. Clark FI. Withdrawal of life-support in the newborn: whose baby is it? *Southwestern Law Rev.* 1993;23:1–46
2. Developments in the law-medical technology and the law. *Harv. Law Rev.* 1990;103:1519–1676
3. Child abuse and neglect prevention and treatment. 45 C.F.R. sec. 1340.15 (1993)
4. Pub. L. No. 98–457, 98 Stat. 1749
5. *In Re Doe*, No. GU 8204-0004A (Ind. Cir. Ct. Apr. 12, 1982), *cert denied*, 464 U.S. 961 (1983)
6. Kopelman LM, Irons TG, Kopelman AE. Neonatologists judge the "Baby Doe" regulations. *N Engl J Med.* 1988;318:677–683
7. Clark FI. Withdrawal of life-support in the newborn: whose baby is it? Reprinted in *Juvenile Fam Court J.* 1994;45:29–53

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To the Editor.—

We read with great interest the article by Groneck et al (*Pediatrics.* 1994;93:712–718). The authors concluded that an inflammatory reaction is present in the lungs of preterm infants prone to develop bronchopulmonary dysplasia (BPD), and they suggested that this concept of inflammation could link the pathophysiological gap between barotrauma- and oxygen toxicity-induced injury and subsequent lung fibrosis. In their study, a total of 12 neonates developed BPD: 11 of 24 neonates in the BPD-risk group and 1 of 35 in the control group. BPD was defined according to Bancalari's criteria established since 1979.[1] As the definition involves typical changes on chest radiograph as a crucial component of the disease, we wonder if all infants observed by the authors as having BPD fit into Bancalari's definition. The question arises because in recent years several authors have described in infants who still required supplemental oxygen beyond postnatal day 28 a wider spectrum of radiographic abnormalities often consistent with milder forms of the disease.[2,3] In such instances, the functional term of chronic lung disease (CLD), which includes any pulmonary parenchymal abnormality on chest radiograph has been thought to be more appropriate.[4,5] Moreover, several neonatologists have been coming to the realization that CLD is a more complex disorder than lung injury associated with oxygen toxicity and barotrauma. Indeed, it represents a wide spectrum of clinical entities caused by a variety of insults and predisposing factors the relative importance of which is yet poorly understood.[6,7] Relevant to this, we would like to report our preliminary findings of an ongoing prospective study investigating the acute inflammatory reaction in the lungs of mechanically-ventilated preterm infants through a daily analysis of some inflammatory mediators in the bronchoalveolar lavage (BAL) fluid from postnatal day 1 to 10. Compared with infants without CLD (11) those developing CLD (9) began to show on day 5 of life significantly higher interleukin-8 (mean level, 0, 990 ± (SD) 0, 545 vs 2770 pg/mL ± 0, 849, $P < .01$) and neutrophil (range, 0.3–0.7 10^6 vs 1–1.7 10^6; mean level, 0.5 10^6 vs 1.4 10^6/mL, $P < .01$) BAL fluid concentrations. Peak inspiratory pressure and forced inspiratory oxygen mean values were not found to be significantly different between the two groups through the period they were lavaged except for days 1 and 10, respectively. Seven of the nine infants who developed CLD presented clinical findings of infection during the first week of life. Of these seven infants, five had positive BAL fluid cultures (three for *Ureaplasma urealyticum* alone, one for *U urealyticum* in association with *Pseudomonas aeruginosa*, one for *Chlamydia trachomatis*), one had two consecutive blood cultures positive for *Staphylococcus epidermidis*, and one had clinical evidence of infection not confirmed culturally. Of the remaining two infants without any evidence of infection, one developed pneumothorax on day 3 of life and one had persistent pulmonary hypertension. Among the 11 control-infants, there was only one whose BAL fluid cultures were positive for *C trachomatis*. On postnatal day 28, the radiographic features of patients with CLD consisted of mild signs of both fibrosis and emphysema. Our study suggests that at least in the mild forms of CLD the resolution of acute lung disease may be disturbed by the persistence of lung inflammation in part sustained by infectious agents. More important, our findings reinforce the concept that the development of CLD may be triggered by different factors and that their relative importance may considerably vary among susceptible infants.

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REFERENCES

1. Bancalari E, Abdenour GF, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr.* 1979;95:819–823
2. Edwards DK. Radiographic aspects of bronchopulmonary dysplasia. *J Pediatr.* 1979;95:823–829
3. Heneghan MA, Sosulski R, Baquero JM. Persistent pulmonary abnormalities in newborns: the changing picture of bronchopulmonary dysplasia. *Pediatr Radiol.* 1986;16:180–184
4. Tooley WH. Epidemiology of bronchopulmonary dysplasia. *J Pediatr.* 1979;95:823–829
5. Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease preventable? A survey of eight centers. *Pediatrics.* 1987;79:26–30
6. Silverman M. Chronic lung disease of prematurity: are we too cautious with steroids? *Eur J Pediatr.* 1994;153[suppl 2]:S30–S35

7. Cassell GH, Waites KB, Crouse DT, et al. Association of *Ureaplasma urealyticum* infection of the lower respiratory tract with chronic lung disease and death in very-low-birth-weight infants. *Lancet*. 1988;2: 240–245

In Reply.—

In agreement with other authors who have investigated the mechanisms of bronchopulmonary dysplasia (BPD), we have used Bancalari's definition in our recent publication.[1,2] However, we certainly agree that from a clinical point of view it is much more appropriate to define the disease when clinical symptoms are present at a corrected age of 36 weeks, as recently stated by Merritt et al.[3] Moreover, a more differentiated descriptive definition, as suggested by Weinstein et al,[4] could be helpful for the comparison of pulmonary outcomes in clinical trials.

Secondly, we agree that BPD is a complex disorder resulting from different insults and predisposing factors. Inflammation due to infection will certainly contribute to the development of the disease, at least in some infants. Tracheobronchial colonization of preterm infants with microorganisms, especially *Ureaplasma urealyticum* and *Chlamydia trachomatis*, varies from country to country, and strongly depends on ethnic, social, and a variety of other factors. Thus, the impact of infection on the development of BPD may vary between different populations.

In their preliminary observations, Papoff et al report high levels of interleukin-8 and increased neutrophil count in tracheal secretions of infants colonized with microorganisms. In our experience, there is no principal difference between the inflammatory reaction evoked by microbes, or by unspecific stimuli like hyperoxia or trauma. We have detected high levels of inflammatory mediators in respiratory fluids of patients with BPD without microbial colonization, and of patients with colonization and/or infection of the airways without subsequent development of BPD. The significance of infection with bacteria, *U urealyticum*, and *C trachomatis* in the pathogenesis of BPD should be evaluated in a prospective study including measurements of inflammatory mediators and quantitative analysis of microbial colonization.

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REFERENCES

1. Bancalari E, Abdenour GF, Feller R, et al. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr*. 1979;95:819–823
2. Groneck P, Götze-Speer B, Oppermann M, Eiffert H, Speer Ch.P. Association of pulmonary inflammation and increased microvascular permeability during the development of bronchopulmonary dysplasia: a sequential analysis of inflammatory mediators in respiratory fluids of high risk preterm infants. *Pediatrics*. 1994;93:712–718
3. Merritt TA, Northway W, Boynton BR, et al. The BPD-problem. (Letter). *Pediatrics*. 1991;88:189–190
4. Weinstein MR, Peters ME, Sadek M, Palta M. A new radiographic scoring system for bronchopulmonary dysplasia. *Pediatr Pulmonol*. 1994; 18:284–289

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