

# This Week's Citation Classic

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Silverman W A, Andersen D H, Blanc W A & Crozier D N. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics* 18:614-25, 1956.  
[Babies Hosp., and Dept. Pediat., Columbia Univ., Coll. Physicians & Surgeons, New York, NY]

**A controlled clinical trial to evaluate the relative effectiveness of two prophylactic antibacterial regimens in premature infants resulted in an unexpected and inexplicable outcome: kernicterus (and death) occurred significantly more often among infants who received penicillin/sulfisoxazole. [The SCI® indicates that this paper has been cited over 240 times since 1961.]**

William A. Silverman  
90 La Cuesta Drive  
Greenbrae, CA 94904

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"In 1949, a logical, but unevaluated, practice began in American premature infant nurseries: administration of antibacterial drugs to all small newborn infants. Previous results of treating identified infections had been poor; the principal difficulty was the vague nature of early signs of invasion. Improved survival rates were attributed to the new practice and the approach spread rapidly. In 1954, it was learned that routine oxygen treatment, begun 12 years earlier, had been responsible for blinding 10,000 premature infants. This led all to wonder about other bombs which might be ticking away in American nurseries.

"When, in the same year, a new recommendation for antibacterial prophylaxis was made, we, at Columbia University, seized upon the opportunity to begin a long-delayed examination of this element of care. The grounds for using preventive treatment were reasonable; only the ideal agent(s) seemed in doubt. Consequently, we decided to make a formal comparison between the new proposal and the 'established' regimen (used for 1 1/2 years with no recognizable hint of difficulty). We

anticipated this would be the first in a plodding series to find an ideal regimen. Much to our amazement, the first controlled trial gave a definitive result. Much to our horror, the mortality rate was higher in infants who received the 'established' treatment (penicillin plus sulfisoxazole). Moreover, kernicterus occurred nine times more often in this group. It was clear that this unexpected (and, at the time, completely inexplicable) complication accounted for the increased fatalities. We took no comfort in the knowledge that the formal trial saved half of the infants from exposure to the unsuspected hazards of a treatment which had been used so confidently in our institution and others throughout the country. If a controlled trial had been carried out at the time of the original shift in practice, the saving in lives would have been truly impressive. It was not until 1959 that the mechanism underlying the disaster was uncovered by Odell who conducted *in vitro* studies demonstrating that sulfonamides uncouple protein-bound bilirubin permitting extravascular diffusion of the neurotoxic pigment.<sup>1</sup> In the same year Johnson and co-workers demonstrated the effect in newborn Gunn rats.<sup>2</sup>

"I found it interesting, in the years which followed our report, that it was cited because of the startling finding—the first demonstration that bilirubin-related kernicterus could be produced by a potentiating factor—rather than as a striking demonstration of the inherent safety of the hedging strategy of controlled trials in clinical studies. I can recall the initial skepticism about our bizarre findings—'mere statistics.' Naively, I thought the antipathy toward use of controlled trials would surely change. The methodology had been so well validated by R.A. Fisher<sup>3</sup> in agricultural research and was so well accepted in pre-clinical studies, I was certain a double standard could not last for long. I can see how wrong I was to be so optimistic."

1. Odell G B. Studies in kernicterus: I. The protein binding of bilirubin. *J Clin. Invest.* 38:823-33, 1959.
2. Johnson L, Sarmiento F, Blanc W A & Day R. Kernicterus in rats with an inherited deficiency of glucuronyl transferase. *Amer. J. Dis. Child.* 97:591-608, 1959.
3. Fisher R A. *The design of experiments*. Edinburgh: Oliver and Boyd, 1935. 252 p.