Special Feature

Reflections on Errors in Neonatology: II. The ''Heroic'' Years, 1950 to 1970

Alex F. Robertson, MD

This series errors in neonatology since the 1920s. Three historical periods are defined: the ''Hands-Off'' years from 1920 to 1950, the ''Heroic'' years from 1950 to 1970, and the ''Experienced'' years from 1970 on. In this article, the ''Heroic'' years, we discuss the Blossom air lock, sulfisoxazole, chloramphenicol, novobiocin, hexachlorophene, Epsom salts enemas, feeding gastrostomy, diaper laundering, and equipment cleaning.
Journal of Perinatology (2003) **23,** 154–161. doi:10.1038/sj.jp.7210843

INTRODUCTION

The first article of this series dealt with errors in neonatology, which occurred during the ''Hands-Off'' years, 1920 to 1970. In this period, premature infants were protected by the nurses who provided food, warmth, and isolation. The only routine treatments were silver nitrate eye drops to prevent ophthalmia neonatorum, oxygen for apnea and cyanosis, and vitamin K to prevent hemorrhagic disease of the newborn. The introduction of the exchange transfusion in the 1940s for Rh isoimmunization was the first remarkable intervention by pediatricians. Antibiotics (sulfas developed in the 1930s and penicillin in the 1940s) were quickly incorporated into newborn infant care. The retrolental fibroplasia disaster and its explication led to research in blood gas monitoring and the development of infant ventilators. These years were exciting. Silverman[1] refers to ''therapeutic exuberance''; Baker describes a ''great spirit of innovation, somewhat lacking in discipline'' and refers to the ''heroic'' era (2). All treatments were new, untested, and we marched on without fear! As a result of our uncritical enthusiasm for treatment, many errors occurred.

This article details several unusual treatments, problems related to prophylaxis of infectious disease, and two episodes of poisoning.

Departments of Pediatrics, Brody School of Medicine, East Carolina University, Greenville, NC, USA.

Address correspondence and reprint requests to Alex F. Robertson, MD, Department of Pediatrics, Brody School of Medicine, East Carolina University, 600 Moye Boulevard, Greenville, NC 27858-4354, USA.

BLOXSOM AIR-LOCK

I remember, as an intern, having my obstetric rotation in the factory town, Ypsilanti, MI. I was the only doctor staying in the hospital at night and was told what to do by a substantial nurse, a Swedish lady, who, apparently, thought I was as deaf as she. One night we delivered a baby who was depressed and needed resuscitation. I had no idea what to do other than suction the mouth, blow oxygen toward the nose, and stimulate the baby by rubbing its back. The nurse brought in two pans, one containing warm water and the other containing ice water. She proceeded to resuscitate the baby by immersing the infant, alternately, in each pan. Dr. Silverman mentions that using ice water was a favorite resuscitation method of Dr. Virginia Apgar in the 1950s (Silverman, personal communication).

Blundell described endotracheal intubation and insufflation in 1884.[2] In 1871, Bernard Schultze described the ''swinging'' method of resuscitation.[3] The Kreiselman resuscitator, which I used in early 1960 was described first in 1940.[4] Since mouth-to-mouth ventilation was often unsuccessful and endotracheal intubation by inexperienced personnel was dangerous, there was great variation in resuscitation techniques in the 1950s.

The strangest resuscitation device was the Bloxsom air-lock (Figure 1), introduced in 1950.[5] This machine was a tightly closed chamber with humidified oxygen at $\sim$60%. To mimic uterine contractions, the pressure in the chamber was cycled regularly between 1 and 3 lb/in^2. The air lock was proposed as a method of resuscitation; ''The infant is placed gently in the lock, preferably not later than 30 seconds after failure to breathe or breathe properly.'' The machine received publicity in Newsweek and became popular around the country. Kendig et al.[6] have described the brief life of this innovation. Subsequently, Apgar and Kreiselman[7] showed no improvement in oxygenation or CO_2 excretion in anesthetized dogs placed in the air lock. Dr. Bloxsom and Sister Mary Angelique responded.

> *In January, 1953, an adverse critical evaluation of the air lock from New York City appeared, based on attempts to make the air lock function as a barospirator for apneic adult dogs. Such a function, of course, was never intended or claimed for the air lock.*

Bloxsom and Angelique[8] suggested that the reduction in the 48-hour neonatal death rate in term and premature infants at their hospital from 1949 to 1952 was because of the use of the air lock. An appropriately designed study showed no beneficial effect of the

Journal of Perinatology 2003; 23:154–161

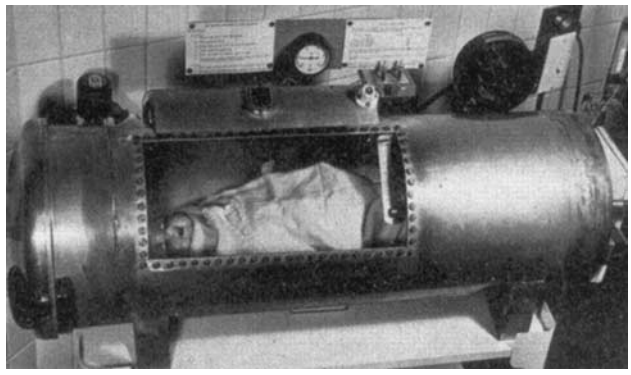

Figure 1. Bloxsom Air Lock Legend: Reproduced with permission: Pediatrics, Vol. 108, Page(s) e116, Figure 1, Copyedited 2001.

air lock in 1956.[9] In this study, all infants received adequate resuscitation before entering either the Bloxsom air lock or an Isolette. This study and the realization that RLF was caused by oxygen led to the abandonment of the device. As the authors state, ''All too often the availability of such a device as the air lock furnishes a panacea for the management of all infants with respiratory difficulty. It may at times be substituted in place of a careful diagnosis of the nature of the difficulty and for the use of well-established resuscitative procedures such as providing a clear airway for the onset of respiration''. There is no way to know how many infants were harmed by this device.

ANTIBIOTIC ERRORS

Charles and Larsen[10] present an interesting review of the history of puerperal sepsis (pelvic infection following delivery) and neonatal infections. As the authors point out, the industrial revolution led the migration of large numbers of people into cities and childbirth moved into the hospital. Puerperal sepsis became epidemic. In the mid-1800s, an early advocate of puerperal sepsis' contagiousness was Oliver Wendell Holmes, at that time dean of the Harvard Medical School. A few years later, Semmelweiss, in Vienna, showed that hand washing before pelvic examination reduced the mortality in the obstetric ward. In 1879, Pasteur demonstrated bacteria in the blood and lochia of puerperal sepsis victims. The organism was Group A *Streptococcus*. The use of careful antiseptic practices was the only recourse against infection until the introduction of sulfonamides in the 1930s and then penicillin in the 1940s. The use of antibiotics may have changed the pattern of infection with gram negative organisms and penicillin resistant *Staphylococcus aureus* becoming more prevalent. By the end of the 1950s hospital nurseries around the world were experiencing cross-infections with virulent *S. aureus.* More recently Group B *Streptococcus* has been the primary infectious agent among mothers and babies. As a result of this experience with infections, there have been numerous trials of antibiotic prophylaxis in newborn infants. The infants usually chosen for such prophylaxis were those at increased risk (infants born after prolonged rupture of the placental membranes or premature infants).

SULFISOXAZOLE PROPHYLAXIS

As recounted by Dr. Silverman[1] (pp. 79–81), when the premature center at Babies Hospital in New York opened, all babies transferred in were treated with penicillin and oxytetracyclene or chloramphenicol. In 1953, a newly available sulfonamide, sulfisoxazole, was introduced and had the advantage of requiring less frequent dosing to maintain adequate blood levels. No problems were recognized with its use. When the use of subcutaneous oxytetracyclene was suggested, a controlled study was begun comparing this drug to the accepted regimen of penicillin and sulfisoxazole. ''Much to our amazement, the first trial gave a definitive result. To our horror, the mortality rate was highest (and strikingly so) in infants who received the established treatment!'' The cause of the increased mortality rate was kernicterus which, at autopsy, was nine times increased. There was, at that time, no plausible explanation for this effect. The results of this study are shown in Table 1.[11] The increased death rate (46 compared to 20) and increased incidence of kernicterus (36% compared to 6%) in the sulfisoxazole-treated infants are seen in the table.

In 1959 O'Dell[12] demonstrated that sulfisoxazole competed with bilirubin for albumin binding, thereby increasing the unbound bilirubin concentration in the blood, which was quickly deposited in the brain. The national impact of sulfisoxazole use in jaundiced infants was never reported but was undoubtedly great] Sulfisoxazole was removed from use in newborn infants. There was another important byproduct of this work. Stern[13] emphasized publically that all drugs used in newborns should be tested for their effect on bilirubin binding. He suggested to Professor Rolf Brodersen at the University of Aarhus, Denmark that he devised a practical method of testing drugs for this displacing effect. Brodersen[14] dedicated many of his later years to this question and screened many drugs for their effect. This work led to the realization that ceftriaxone had a displacing effect similar to sulfisoxazole and prevented its use in jaundiced newborn infants.[15] Unfortunately, the FDA requires no screening of new drugs for their effect on bilirubin binding and few laboratories are currently involved in this effort.

From 1982 until his death in 1998, Professor Brodersen was my mentor and I have saved the many letters we exchanged regarding

Table 1 Principal Diagnosis at Necropsy

	Oxytetracyclene	Penicillin/sulfisoxazole
Number of deaths	20	46
% necropsies	80%	72%
Kernicterus	6%	36%

Adapted from Silverman et al.[11]

experiments in progress. Although, outwardly, a very formal man and a rigorous scientist, he was always friendly and frequently humorous in his responses to my ideas. For example, when I asked him what animal to use in studying in vivo bilirubin displacement (animal models had been suggested by some skeptics of his work) he wrote, ''If you nevertheless, against all sense, find that you have to satisfy the skeptics, I would recommend the pig. It is in several respects related to man (at least to some men) and has the advantage that we do not yet know that binding to porcine albumin is different from that to the human protein''. ''You wanted an inexpensive animal model. I believe that pigs are expensive but you can eat them afterwards thus eliminating your animal budget totally!''

CHLORAMPHENICOL PROPHYLAXIS

Dr. Silverman[1] (p. 81) recounts the suggestion made by Dr. Alexander in 1956 that a trial be performed using chloramphenicol, erythromycin, and sulfadiazine as infection prophylaxis in infants weighing less than 2000 g at birth. Instead of a trial, the widespread use of this combination spread across the country.

Chloromycetin was discovered by Dr. Burkholder of Yale in 1947. This antibiotic was found in cultures of a new actinomycete isolated from the soil of a field near Caracas, Venezuela and later named *Streptomyces venezuelae*. Unlike penicillin and streptomycin, chloromycetin had a broad range of activity against Gram positive and Gram negative organisms. Clinical trials showed that it was the first drug effective against rickettsial infections and typhoid fever. The drug was synthesized and named chloramphenicol in the research laboratories of Parke, Davis and Company. The drug was marketed in 1949 and was the first broad-spectrum antibiotic available. In 1952 the National Research Council, recognizing the hazard of aplastic anemia caused by the drug, recommended cautionary labeling of the drug and its general use decreased after the labeling was changed.[16] There were no studies or reports at that time of toxicity in newborn infants. Lietman[17] wrote an excellent review of the history of this drug's use in neonates.

The first suggestion of a problem in newborn infants appears to be by Lambdin. In a letter to the editor in Pediatrics in 1960,[18] he states that the recognition of the problem with chloramphenicol ''was brought to the attention of Parke, Davis and Company, and to others by our observation in the early months of 1958''. The problem was publicized by a letter from the company dated 21 January 1959, addressed to all physicians in the US and Canada.

Sutherland published the first description of three cases of cardiovascular collapse in newborn infants receiving large doses of chloramphenicol.[19] The infants were treated because of prolonged rupture of the membranes and concern about infection. A few days after the treatment began, the infants developed abdominal distention, slate-colored or pallid cyanosis (the ''gray baby'' syndrome), cold moist skin, and weak pulse; they died shortly thereafter.

The use of prophylactic chloramphenicol in newborn infants had already spread across the country. Once the possible danger of the drug was recognized, many investigators looked into mortality figures. In 1959 Kent and Wideman[20] at the University of Alabama hospital found the death rate among infants with premature rupture of the membranes rose from 29/1000 to 144/1000 after antibacterial prophylaxis using chloramphenicol was begun. Of 160 infants so treated, 17 died exhibiting the characteristics of the ''gray sickness.'' In 1958 Burns et al questioned the high mortality in infants with prolonged rupture of the membranes who were being treated with antibiotics at the Los Angeles County Hospital. They began a prospective, controlled trial of no antibiotics versus several combinations of antibiotics including chloramphenicol. The mortality in babies weighing 2001 to 2500 g was 2.5% with no antibiotic treatment and 45% with chloramphenicol treatment.[21] A study by Buetow, using vital statistics for the city of Baltimore showed that there was a significant rise in infant mortality in 1957 (Figure 2). This rise resulted in an excess of 118 neonatal deaths, best explained by the use of prophylactic chloramphenicol.[22]

This excess mortality continued into 1958 until the dose of chloramphenicol was reduced to 20 mg/kg/day. The aforementioned reports suggested that a large number of infant deaths across the country were related to the drug. The tragic practice of using chloramphenicol ended in about 1960 as these

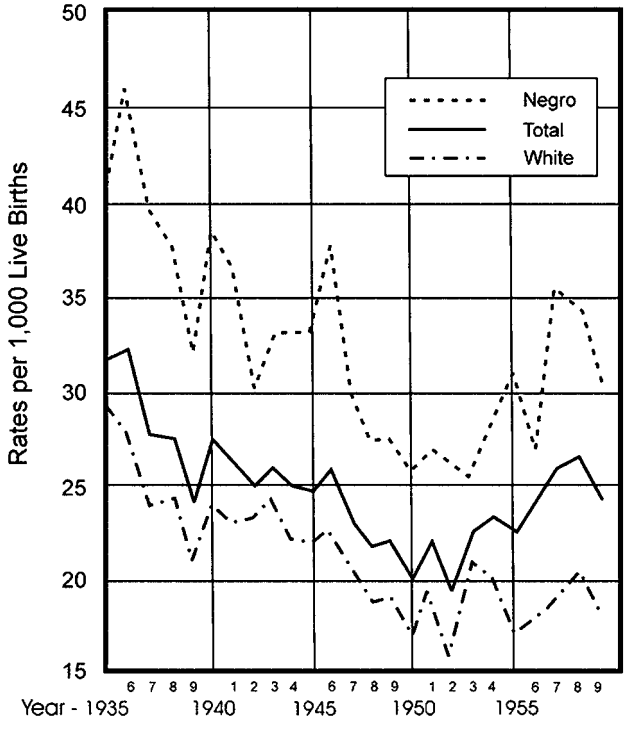

Figure 2. Neonatal Death Rats per 1000 Live Births in Baltimore City, 1935–59. Reproduced with permission: Buetow[22] (p. 218).

reports became common knowledge in medical circles. Not only was the use of chloramphenicol as a prophylactic antibiotic curtailed, the dosage recommendations were changed from 100–150 mg/kg/day to 50 mg/kg/day in term infants and 25 mg/kg/day in preterm infants. Parke, Davis and Company developed an assay for the drug in serum and worked collaboratively with many medical centers to determine the cause of the toxicity.[23] Chloramphenicol's toxicity was related to its accumulation resulting from impaired glucuronidation by the liver of newborns and impaired renal excretion of the drug. The exact biochemical mechanism of the toxicity was never fully explained. An important by-product of this episode was the recommendation that drug levels be determined during antibiotic treatment.

NOVOBIOCIN

In 1955 two pharmaceutical research laboratories isolated an antibiotic from *Streptomyces*, a fungal organism. Interest in this finding was high because of the new antibiotic's effect on *S. aureus* which was becoming resistant to other antibiotics. Historically, this period was the time that resistant strains of *S. aureus* were causing nosocomial hospital infections around the world. The generic name, novobiocin, was given to the drug. Animal studies showed little toxicity but it was noted in dogs that ''A yellow color has been noted in the serum of dogs given Novobiocin but this is probably due to some metabolite of the antibiotic; it produces an indirect reaction for bilirubin and is not related to liver damage.'' The same yellow pigment was noted in the serum of humans given the drug.[24]

In 1959, there was a staphylococcal infection epidemic in a term newborn nursery at the Cincinnati General Hospital. To abort the outbreak, novobiocin was given to all infants admitted to the nursery since the organism was resistant to penicillin and erythromycin. An increase in the number of infants with hyperbilirubinemia was quickly noted by Dr. Sutherland, who had earlier been one of the first to recognize chloramphenicol toxicity. The icterus increased not only in incidence but also rose to higher levels more quickly. During the period of novobiocin administration, 60 babies or 9% of admissions had marked jaundiced, whereas before and after the administration of novobiocin, 3 to 4% of admissions were so jaundiced. As Sutherland and Keller[25] explains in the article there was much controversy previously published about the nature of this yellow pigment in the serum of those receiving novobiocin. Actually, in the package insert of the drug, the manufacturer included a description of the procedure they recommended for removing the yellow color from the serum so that the color would not interfere with other laboratory analyses!

With multiple chemical methods, Sutherland and Keller showed that the pigment was indeed bilirubin. They also showed that the clearance of intravenously administered bilirubin was delayed in rabbits receiving novobiocin. In the summary they state that this is ''another instance of an epidemic among the newborn from an incompletely understood metabolic effect of a drug''. In 1962, Hargreaves and Holton[26] showed that the drug directly inhibited the bilirubin conjugating enzyme in rat liver preparations. Fortunately, none of the infants in the Cincinnati epidemic developed kernicterus during their hospitalization and only 12 babies required exchange transfusion. It was fortunate that this effect was recognized before the drug was used widely in newborn infants.

HEXACHLOROPHENE

In 1965, I arrived at the Ohio State University Hospital and took over the care of babies in the newborn nursery. At that time, the babies were bathed on admission and afterwards every other day with 3% hexachlorophene (HCP) soap and then rinsed off with water. To monitor the colonization rate with *S. aureus*, each infant had an umbilical stump culture done at the time of the discharge physical examination. The usual colonization rate was about 10%. If the rate went up significantly, we looked for a cause, generally an environmental change (such as crowding with high census) or a procedural change (such as inadequate hand washing).

In 1969, we noted the first case of a blistering skin lesion in a full term infant. This blistering was obviously the ''scalded skin'' syndrome usually caused by a specific phage type of *S. aureus*. Over the next 6 weeks 33 more cases occurred.[27] Cohort care of the infants (admitting to one nursery and discharging all infants from that nursery and then cleaning before resuming admissions to that nursery) was unsuccessful. Ultimately, the epidemic was stopped by colonization of the umbilical stump and nares in the delivery room with a benign strain of *Staphylococcus*. This approach had been successful in several other hospitals.[28] Since I had to explain the procedure to each of the mothers, I became known at the hospital as the ''friendly Staph doctor.''

As we looked back over our colonization data, we were able to pinpoint the week in which the colonization rate had begun increasing. The apparent precipitating event was the change from 3% liquid HCP bathing to 0.75% bar HCP bathing. After the epidemic was controlled, we changed back to using 3% liquid HCP bathing and water rinsing. Then the liquid HCP was applied as a lotion to the body and allowed to dry without rinsing. At that time I had no idea what was to follow.

HCP [2,2′-Methylene-bis (3,4,6-trichlorophenol)] was patented in 1941 in the US. The chemical was widely used as an antibacterial in soaps, cosmetics, and antiseptic solutions throughout the world. In 1952 Farquharson et al.[29] showed that HCP bathing of newborn infants markedly reduced the rate of impetigo in the nursery. Gluck and Wood[30] reaffirmed that finding in 1961 and presented their bathing method as appropriate for

decreasing staphylococcal colonization. This method was quickly adopted in hospitals around the world and was in place at our hospital when I arrived.

Kimbrough,[31] working for the FDA, reviewed the toxicity of HCP in 1971. Reports of HCP toxicity were first limited to accidental oral ingestions. The signs of poisoning were primarily gastrointestinal, but some neurological signs occurred. In 1959 Herter described an infant treated with HCP as a lotion for 4 days resulting in skin excoriations followed by twitching and convulsions. In 1968, Larson reported HCP transcutaneous absorption and neurological toxicity in burn patients. This syndrome had been previously called ''burn encephalopathy''.[32] In his review, Kimbrough also details the animal studies done up to 1971. In rat studies Kimbrough and Gaines showed HCP toxicity caused hind limb paralysis and spongy degeneration of the white matter. The final recommendation of Kimbrough[33] was that ''the unnecessary use of concentrated HCP preparations should be curtailed''.

Two other studies in 1971 raised concern. Hart[33] reported cystic changes in the white matter of monkeys washed daily with HCP and Curley et al.[34] showed that infants bathed daily with HCP absorbed the chemical into the blood. On December 8, 1971 the FDA mailed a warning to all US physicians. The letter concluded by recommending (jointly with the Committee on Fetus and Newborn of the American Academy of Pediatrics) not to use HCP for total body bathing of infants. In a review by Plueckhahn,[35] the author cites a report by the French Ministry of Health that HCP, over 6%, had been accidentally included in certain batches of a baby talcum powder and was implicated as the cause of death in 40 infants aged 1 to 15 months.

The crucial information was reported in 1973 in the *Morbidity and Mortality Weekly Report*.[36] A pathological specimens review from the University of Washington revealed that vacuolation of the brain's reticular formation was present in 63% of autopsied infants who had been exposed 3 or more times to 3% HCP by bathing and under 1% in those less exposed. Of 21 cases, 18 were infants weighing less than 1400 g at birth. The details of this study were reported by Shumann et al.[37] in 1975. In 1973, Powell et al.[38] (including Gluck who had instituted the bathing method) reported seven cases of spongiform myelinopathy of the brainstem in infants under 1400 g exposed to HCP. Figure 3 shows the typical lesions. In 1976, Gowdy and Ulsamer[39] reported a study of 76 brains from infants bathed with HCP and 69 control specimens. They found no statistically significant increase in vacuolization of infants bathed with HCP. However, they did find detectable levels of HCP in 5 brains showing vacuolization. In 1980, Anderson et al.[40] reported additional cases of spongiform myelinopathy with HCP detectable in the brain in premature infants. In none of these reports was there a clinical condition that could be related to the pathological findings. Lockhart[41] presents a fascinating history of the involvement of the FDA in this saga.

When HCP was no longer available for bathing babies there was great concern that the rate of staphylococcal infections would increase and there were some reports verifying a resurgence. However, other reports questioned whether HCP appeared effective only because the pattern of infections around the world was beginning change again for unknown reasons. Most nurseries reverted to using triple dye for cord stump treatment and the concern gradually faded.

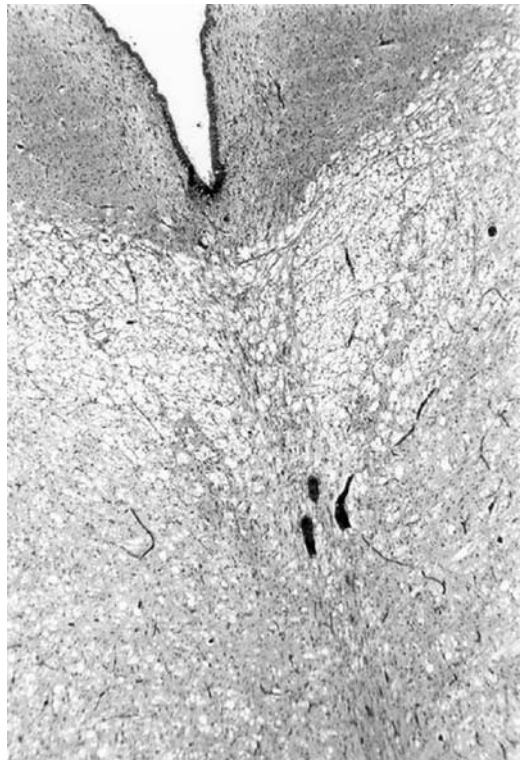

Figure 3. Spongiform Myelinopathy of the Braistem. Photograph provided by Dr. H. Powell.

EPSOM SALTS ENEMAS

In 1963, President Kennedy's son, Patrick Bouvier, died of respiratory distress syndrome (RDS), then known as hyaline membrane disease. The publicity attending his illness raised the popular interest in neonatology, which had not yet received that name. As Dr. Silverman[1] (p. 87) details, publicity is often dangerous in medical affairs. A paper given in October 1964 at the annual meeting of the College of American Pathologists described the beneficial effect of Epsom salts enemas on RDS. This startling idea was reported on p. 1 of the *New York Times* and subsequently in *Time magazine*, *Medical Tribune* and the *Lancet*. I remember hearing these reports and dismissing them as absurd. However, the news spread rapidly and use of the enemas was frequent.

Van Gelder[42] wrote a letter published in *Pediatrics* asking for a report of other physicians' experience with what he considered a ''potentially hazardous'' treatment. Dr. Stowens, the originator of the treatment, responded saying, ''I am happy to be able report that since the appearance of the stories numerous other physicians

in all parts of the country who have not shared Dr. Van Gelder's querulousness or inability to analyze and reach independent conclusions have reported to me of their successes with this form of treatment''.

In 1965 Dr. Stowens reported his pathological studies in hyaline membrane disease and his hypothesis that ''the basis of the respiratory difficulty in premature infants might be related to inability of the infants to achieve the proper level of total body water necessary for extrauterine existence.'' The treatment originated from Dr. Stowens erroneous analysis of the pathology of RDS. He described the method and results of using the enemas in 28 infants.[43] He stated that all infants improved but no objective measures were presented. In an addendum to the article he noted that he had sent details of the method of treatment to many physicians. ''Reports from 24 physicians have yielded data on 121 infants.'' ''Of the 121 infants, 94 recovered.'' It is startling to realize that these statements were acceptable for publication. Even more startling is his final statement, ''One infant manifested a precipitous drop in respiratory and cardiac rates after enema and was treated with intravenous calcium gluconate. It was believed that this infant developed magnesium toxicity, but magnesium determinations were not performed.'' Dr. Stowens was the first to report the toxicity of his treatment!

I know of no other articles in the medical literature describing the results of this treatment but, 1 year later, Andrews et al.[44] showed the devastating effect of this treatment in newborn lambs. There is no way of knowing how many babies died as a result of this treatment but as late as 1973 a report of the fatal use of this treatment was recorded.[45] One problem during that time period, before the extensive use of ventilators, was that babies with RDS would frequently become exhausted from the breathing effort, stop breathing, and die. The same picture would result from magnesium toxicity.

FEEDING GASTROSTOMY

Feeding premature infants has always because a problem since they may have poor sucking and swallowing coordination and strength. In 1900 Pierre Budin described current artificial feeding methods. ''When infants are feeble, they sometimes refuse to suck. Milk is then made to trickle into their mouths, directly from the nipple, by exerting pressure upon it, or they are fed from a small spoon, till they become strong enough to take the breast; but, if they allow the milk to dribble out of their mouths, if they do not swallow, or if they reject what is given to them, gavage, feeding by the stomach tube, must be considered''.[46]

Budin cites Marchant of Charenton in 1851 as the first to use intermittent gavage feeding in premature infants. In 1884 Professor Tarnier introduced this method to the Maternité Hospital in Paris for many premature infants. The method of intermittent gavage feeding was never completely satisfactory because the rubber tubes were relatively large and irritating. Vomiting sometimes occurred when the tube was removed, and the infants could not receive frequent, small volume feedings. In 1951 Royce et al.[47] described successful the using of an indwelling polyethylene nasogastric tube for feeding small (for that time) premature infants.

In 1963, Tomsovic et al reported the use of gastrostomy tubes in small infants; they cited poor tolerance for intermittent gavage or retention nasogastric feedings of infants below 1500 g. In their series the infants were not fed for 3 days and then a gastrostomy was performed. In all, 11 infants were operated on and none died as a result of the surgery.[48] Similar results were reported by Berg et al.[49] in 1964. Jones and Reid[50] recommended this approach for small infants with severe respiratory distress. None of these reported experiences were controlled trials.

In 1969 Vengusamy et al.[51] reported a controlled study of mortality associated with gastrostomy in infants weighing less than 1250 g at birth. A total of 54 infant pairs were matched and sequentially analyzed. In all, 34 pair had similar outcomes. In the 20 pairs with dissimilar outcomes, 13 control infants and seven gastrostomy infants survived. At that point, the statistical criteria were met and the study terminated. The morbidity in gastrostomy infants was also increased with 18 instances of wound infection. Fortunately, this study as well as improvements in gavage feeding brought the episode of gastrostomy feeding for premature infants to an end.

DIAPER LAUNDERING

In 1967 20 infants, all born in a small St. Louis maternity hospital for unwed mothers, developed a sickness characterized by profuse sweating, fever, tachycardia, tachypnea, hepatomegaly and acidosis. This epidemic occurred over a period of almost 5 months. Nine infants were severely affected and two died. The course was rapid once signs of illness developed; one infant died 3 hours after the onset of fever and sweating.[52] Six children had an exchange transfusion and promptly improved. The disease was named the ''sweating'' syndrome.

The first four cases developed between April 17 and 19. The nursery, closed on April 24, was thoroughly cleaned and disinfected, and reopened on May 3. A second cluster of cases followed between May 10 and 15.[53] The only apparent epidemiologic difference between the sick and well infants was that the sick infants had been in the hospital longer when their illness began. This fact suggested toxic material exposure. An incompletely identified phenolic substance was found in the serum and urine of affected infants. It was thought that a phenolic disinfectant used at the hospital was the cause; however a case beginning after that disinfectant was removed suggested it was not the cause. A search for all phenolic compounds in use revealed a hand soap and shampoo containing hexachlorophene, an instrument and general disinfectant containing phenols, and an antimicrobial laundry

neutralizer containing pentachlorophenate (PCP). None of the first four compounds matched the exposure or time pattern of epidemic. PCP was used in a final laundry rinse before drying and all the nursery washables were rinsed in it. The PCP solution had been used for some time in the laundry but in excessive amounts since only shortly before the onset of the epidemic.[54]

PCP was positively identified in the serum and in autopsy tissues. The chemical was absorbable through skin and excreted in the urine where, for infants in diapers, it might reabsorbed. The exact mechanism of toxicity is unknown but is likely because of uncoupling of cellular oxidation and phosphorylation leading to an increased metabolic rate, fever, sweating and dehydration. Owing to the possibility of this compound's further misuse, the manufacturer withdrew it from use in September 1967.

EQUIPMENT CLEANING

In 1972, doctors at a New Jersey hospital performed five exchange transfusions for hyperbilirubinemia in a period of 36 hours. The newborn infants were otherwise normal. Not knowing the cause for this cluster of cases and concerned that an extrinsic factor was at work, the hospital staff changed the brand of infant formula and disposable diapers, stopped giving vitamin K injections, and moved the babies out of the nursery. No unusual feeding or bathing practice or laundering of linen was identified. Staff members reported that, in preparation for one of their colleagues delivery, they cleaned the bassinet reserved for that baby several times with their routine disinfectant detergent (Vestal LpH, Vestal Laboratories, St. Louis MO). That baby needed three exchange transfusions for jaundice. This led to an investigation of the disinfectant which contained several phenolic compounds. Further reconstruction of the events showed that there had been an epidemic of diarrhea in the nursery several months before, and in response to this epidemic the concentration of the disinfectant used for cleaning was increased. The day before the cluster of cases occurred the nursery was vigorously cleaned. The cleaning solution was immediately changed to hexachlorophene and no more cases occurred.

After 3 years, a pediatrician in a Wyoming community reported an unusual incidence of unexplained hyperbilirubinemia in their nursery. Also, there had been three exchange transfusions within a 1-month period. This episode was not as dramatic as the New Jersey epidemic but careful analysis of the nursery records showed that the incidence of hyperbilirubinemia was unusually high in April and May of that year. Again, there was no known change in procedure or medication that might give an explanation. However, because of the previous experience in New Jersey and the fact that the hospital used the same disinfectant, the investigators concentrated on cleaning methods. In this hospital, individual nurses cleaned with either hexachlorophene or the phenolic solution. And several nurses used inappropriately high concentrations of the phenolic solution for cleaning. Review of the staffing records showed that the affected infants had significantly more care by the nurses using the phenolic compound. Additionally, it was found that the exhaust air registry in the nursery was blocked and that the clothes used for cleaning may have been laundered with the nursery linen. Once the disinfectant was removed from use, the epidemic ceased.[55]

The phenolic compounds probably caused jaundice by a toxic effect on the liver, inhibiting the enzymes responsible for conjugating and excreting bilirubin. These cases demonstrate the unique susceptibility of newborn infants. As the investigators mention,[56] newborn infants absorb materials easily through their epidermis. Also, their respiratory rate is higher than adults so newborn infants may inhale larger amounts of environmental contaminants. And finally, the newborn's liver conjugates chemical substances more slowly than an adult.

Acknowledgements

I am grateful for the helpful comments and suggestions of Dr. WA Silverman and Dr. Jeffrey P. Baker, and for the extensive grammatical review by Alex F. Robertson IV.

References

1. Silverman WA. Retrolental Fibroplasia: a modern parable. New York: Grune & Stratton, 1980.
2. Dunn PM. Dr. James Blundell (1790–1878) & neonatal resuscitation. Arch Dis Child 1989;64:494–5.
3. Baskett TF, Nagele F. Bernhard Schultze and the swinging neonate. Resuscitation 2001;51:3–6
4. Kreiselman J. An improved apparatus for treating asphyxia of the newborn infant. Am J Obstet Gyn 1940;39:888–90.
5. Bloxsom A. Resuscitation of the newborn infant. Use of the positive pressure oxygen-air lock. J Pediatr 1950;37:311–9.
6. Kendig JW, Maples PG, Maisels MJ. The Bloxsom air lock: a historical perspective. Pediatrics 2001;108:e116.
7. Apgar V, Kreiselman J. Studies on resuscitation. An experimental evaluation of the Bloxsom air-lock. Am J Obstet Gynecol 1953;65:45–52.
8. Bloxsom A, Angelique SM. Neonatal infant mortality. Before and after the use of the air lock for the treatment of newborn infants in a large maternity hospital. Am J Obstet Gynecol 1954;67:647–50.
9. Reichelderfer TE, Nitowsky HM. A controlled study of the use of the Bloxsom air lock. Pediatrics 1956;18:918–27.
10. Charles D, Larsen B. Streptococcal puerperal sepsis and obstetric infections: A historical perspective. Reviews of Infectious Disease 1986;8:411–22.
11. Silverman WA, Andersen DH, Blanc WA, Crozier DN. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics 1956;18: 614–25
12. O'Dell GB. Studies in kernicterus: I. The protein binding of bilirubin. J Clin Invest 1959;38:823–33.
13. Stern L. Drug interaction: II. Drugs, the newborn infant, and the binding of bilirubin to albumin. Pediatrics 1972;49:916–8.
14. Brodersen R, Robertson A. Chemistry of bilirubin and its interaction with albumin. In: Levine RL, Maisels MJ, editors. eds. *Hyperbilirubinemia in the*

Newborn. Report of the 85th Ross Conference Of Pediatric Research. Columbus: Ross Laboratories; 1983. p. 91–8.
15. Brodersen R, Robertson A. Ceftriaxone binding to human serum albumin: competition with bilirubin. Molecular Pharmacology 1989;36:478–83.
16. Woodward TE, Weisman CL. Chloromycetin (Chloramphenicol). In: Antibiotics Monographs. No. 6. New York: Medical Encyclopedia, Inc;1958.
17. Lietman PS. Chloramphenicol and the neonate — 1979 view. Clinics in Pharmacology 1979;6:151–62.
18. Lambdin MA. On the ''gray syndrome'' and chloramphenicol toxicity. Pediatrics 1960;25:1090.
19. Sutherland JM. Fatal cardiovascular collapse of infants receiving large amounts of chloramphenicol. Am J Dis Child 1959;97:761–7.
20. Kent SP, Wideman GL. Prophylactic antibiotic therapy in infants born after premature rupture of membranes. JAMA 1959;171:1199–290.
21. Burns LE, Hodgman JE, Cass AB. Fatal circulatory collapse in premature infants receiving chloramphenicol. New England J Med 1959;261: 1318–21.
22. Buetow KC. An epidemiological approach to the problem of rising neonatal mortality in Baltimore. Am J Public Health 1961;51:217–27.
23. Weiss CF, Glazko AJ, Weston JK. Choramphenicol in the newborn infant. A physiological explanation of its toxicity when given in excessive doses. New England J Med 1960;262:787–94.
24. Finland M, Nichols RL. Current therapeutics CXIV. Novobiocin. Practitioner 1957;179:84–92.
25. Sutherland JM, Keller WH. Novobiocin and neonatal hyperbilirubinemia. Am J Dis Child 1961;101:447–53.
26. Hargreaves T, Holton JB. Jaundice of the newborn due to novobiocin. Lancet 1962;1:839.
27. Albert S, Baldwin R, Czekajewski S, van Soestbergen A, Nachman R, Robertson A. Bullous impetigo due to Group II Staphylococcus aureus: an epidemic in a normal newborn nursery. Am J Dis Child 1970;120:10–3.
28. Light IJ, Walton LR, Sutherland JM, Shinefield HR, Brackvogel V. Use of bacterial interference to control a staphylococcal nursery outbreak. Am J Dis Child 1967;113:291–300.
29. Farquharson CD, Penny SF, Edwards HE, Barr E. The control of staphylococcal skin infections in the nursery. Canad MAJ 1952;67:247–9.
30. Gluck L, Wood HF. Effect of an antiseptic skin-care regimen in reducing staphylococcal colonization in newborn infants. N Eng J Med 1961;265:1177–81.
31. Kimbrough RD. Review of the toxicity of hexachlorophene. Arch Environ Health 1971;23:119–22.
32. Larsen DL. Studies show hexachlorophene causes burn syndrome. Hospitals J Amer Hosp Assoc 1968;42:63–4
33. Hart ER. Toxicity of pHisoHex on 90-day skin application to infant rhesus monkeys. Report submitted to Sterling-Winthrop Research Institute by Bionetics Research Laboratories, Dec. 3, 1971.
34. Curley A, Hawk RE, Kimbrough RD, Nathenson G, Finberg L. Dermal absorption of hexachlorophene in infants. Lancet 1971;2:296–7.
35. Plueckhahn VD. Hexachlorophene and skin care of newborn infants. Drugs 1973;5:97–107
36. Anonymous. Neuropathology in newborn infants bathed with hexachlorophene. MMWR 1973;22:93–4.
37. Shuman RM, Leech RW, Alvord EC. Neurotoxicity of hexachlorophene in humans II. A clinicopathological study of 46 premature infants. Arch Neurol 1975;32:320–5.
38. Powell H, Swarner O, Gluck L, Lampert P. Hexachlorophene myelinopathy in premature infants. J Pediatr 1973;82:976–81.
39. Gowdy JM, Ulsamer AG. Hexachlorophene lesions in newborn infants. Am J Dis Child 1976;130:247–50.
40. Anderson JM, Cockburn F, Forfar J, Harkness RA, Kelly RW, Kilshaw B. Neonatal spongiform myelinopathy after restricted application of hexachlorophene skin disinfectant. J Clin Pathol 1981;34:25–9.
41. Lockhart JD. Hexachlorophene and the Food and Drug Administration. J Clin Pharmacol 1973;13:445–50.
42. Van Gelder DW. Magnesium sulfate enemas for the respiratory distress syndrome. Pediatrics 1965;35:355–6.
43. Stowens D. Hyaline membrane disease. Morbid anatomy, hypothesis of its pathogenesis, and suggested method of treatment. Am J Clin Path 1965;44:259–70.
44. Andrews BF, Campbell DR, Thomas P. Effects of hypertonic magnesium-sulphate enemas on newborn and young lambs. Lancet 1965;2:64–5.
45. Outerbridge EW, Papageorgiou A, Stern L. Magnesium sulfate enema in a newborn. Fatal systemic magnesium absorption. JAMA 1973;224:1392–3.
46. Budin P. The Nursling. Edinburgh: The Caxton Publishing, 1907, translated by WJ Maloney.
47. Royce S, Tepper C, Watson W, Day R. Indwelling polyethylene nasogastric tube for feeding premature infants. Pediatrics 1951;8:79–81.
48. Tomsovic EJ, Barringer ML, Gay JH, McBride WP, Nomura FM. Feeding gastrostomy in small premature infants. Amer J Dis Child 1966;112:56–60.
49. Berg RB, Schuster SR, Colodny AH. The use of gastrostomy in feeding premature infants. Pediatrics 1964;33:287–9.
50. Jones PF, Reid DHS. Gastrostomy in neonatal respiratory failure. Lancet 1966;2:573–4.
51. Vengusamy S, Pildes RS, Raffensperger JF, Levine HD, Cornblath M. A controlled study of feeding gastrostomy in low birth weight infants. Pediatrics 1969;43:815–20.
52. Robson AM, Kissane JM, Elvick NH, Pundavela L. Pentachlorophenol poisoning in a nursery for newborn infants. I. Clinical features and treatment. J Pediatr 1969;75:309–16.
53. Anonymous. Pentachlorophenol poisoning in newborn infants — St. Louis, Missouri, April–August 1967. MMWR 1996;45:545–9.
54. Armstrong RW, Eichner ER, Klein DE, Barthel WF, Bennett JV, Jonsson V, Bruce H, Loveless LE. Pentachlorophenol poisoning in a nursery for newborn infants. II. Epidemiologic and toxicologic studies. J Pediatr 1969;75:317–5.
55. Anonymous. Neonatal hyperbilirubinemia, New Jersey, Wyoming. MMWR 1975;24:293–4.
56. Wysowski DK, Flynt JW, Goldfield M, Altman R, Davis AT. Epidemic neonatal hyperbilirubinemia and use of a phenolic disinfectant detergent. Pediatrics 1978;61:165–70.