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neonatal INTENSIVE CARE

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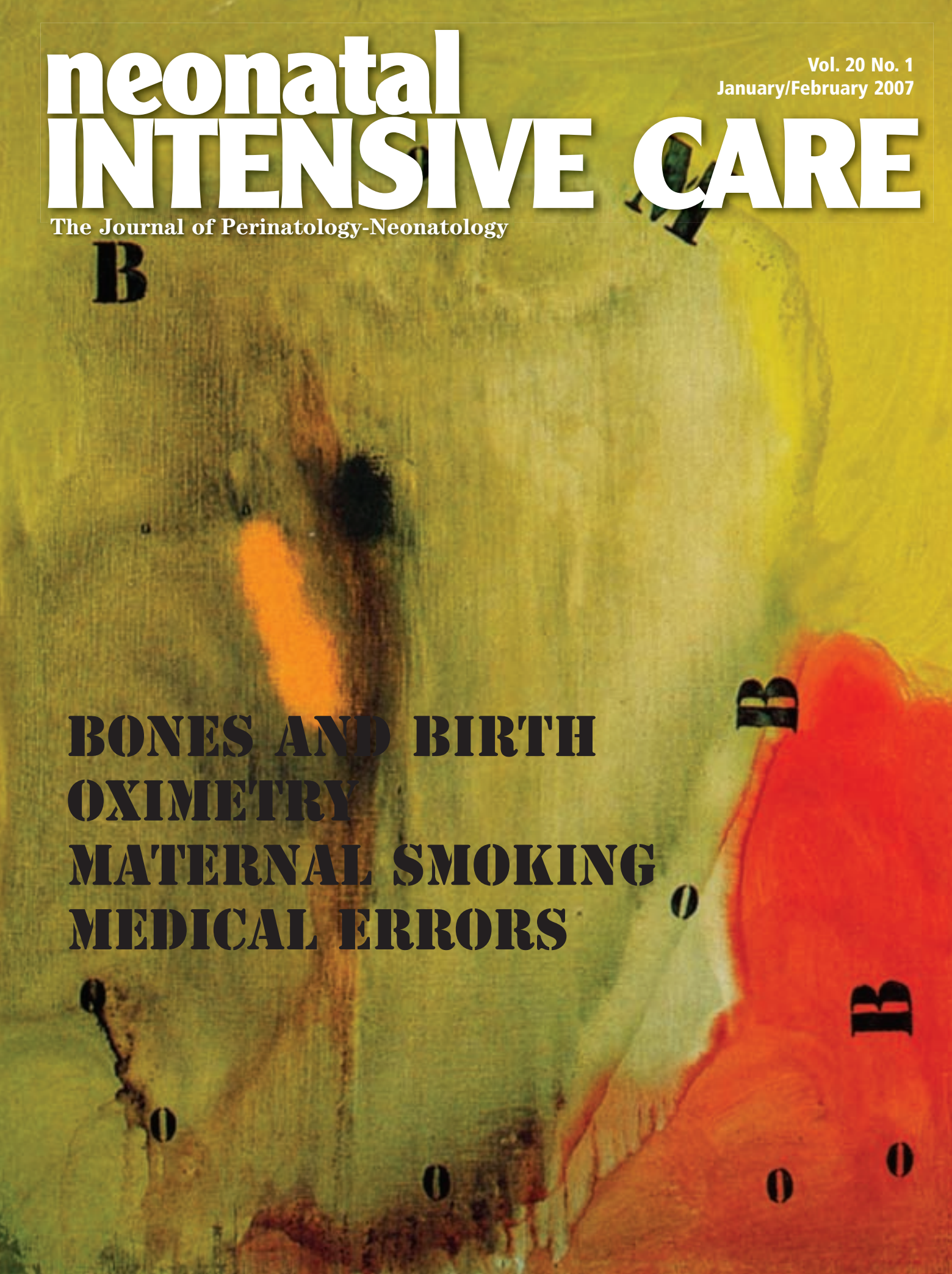

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neonatal
INTENSIVE CARE

Vol. 20 No. 1
January-February 2007

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Editorial

Sea Change?

With Democrats reclaiming both houses of Congress, will there be a sea-change in attitudes toward neonatal/perinatal care? There ought to be. According to a news item in this issue, scientists now say one-third of infant deaths are because of premature births – a much larger percentage than the 20% previously thought. The rate should be 34% or more, according to the Centers for Disease Control and Prevention, because at least a dozen causes of newborn death are actually problems that go hand-in-hand with premature births, such as RDS. The revised statistic might lead to greater educational efforts, as well as expansion of federal research into preterm labor and delivery and the care and treatment of premature infants.

Of course healthcare for infants doesn't exist in a vacuum but is affected by other social, political and demographic forces. Under new federal regulations, for instance, children born to undocumented mothers must apply for Medicaid. Under previous policies, all children whose mothers received emergency Medicaid coverage for the delivery were automatically entitled to insurance for the first year of birth. The new policy would require parents to prove the newborn is a US citizen. Doctors say many undocumented parents would be afraid to submit applications. According to Angela Bonavoglia, writing on Huffingtonpost.com: "The new law withholds insurance for routine healthcare from infants born into poor families until the newcomer is approved for Medicaid coverage, which can take weeks. It was intended as a weapon against illegal immigration… Is this the way to treat "innocent life?" Where are all the troops who descended on Florida to keep poor Terry Schiavo alive when she was actually braindead? Where are all the holier-than-thous who don't want scientists to touch a single cell on a blastocyst in the interest of saving other lives? Where are all those pro-life people to whom all life is supposedly so damn sacred? Silent, obviously. Giving more proof, as if we needed it, that they could really care less what happens to children once they're born. Taking care of children takes money and creativity and commitment and community. It takes a social justice contract with America."

Along the same lines, according to the conservative social critic Donald Light, with the Center for Bioethics, "The United States remains the only industrialized or second-tier country in the world that fails to guarantee its citizens access to medical services. This is a curious omission for a country based on rights and liberty. It is equally strange from an economic and business point of view. For while foreign competitors get full medical benefits at one-third less the cost, American employers are weighed down by ever-growing expense for healthcare… A conservative argument for universal access to healthcare can be put quite simply: When people are ill, in pain, or disabled, they are less able to take care of themselves or others. In such circumstances, individual liberty and personal responsibility are quickly compromised. Even small disorders can turn liberty and responsibility into dependency. Needed medical care can be a great financial burden on the seriously and chronically ill. Losses in wages and earned income make matters even worse, particularly when able-bodied citizens can no longer care for themselves and their dependents.

Medical bankruptcy is quite common in the United States but unknown in the rest of the modern world where there is universal access. Voluntary health insurance has been abandoned [outside the US] long ago as incapable of protecting individual liberty, fostering personal responsibility, and promoting economic opportunity. Universal access to needed medical services is essential to achieve traditional conservative moral principles."

Les Plesko, Editor

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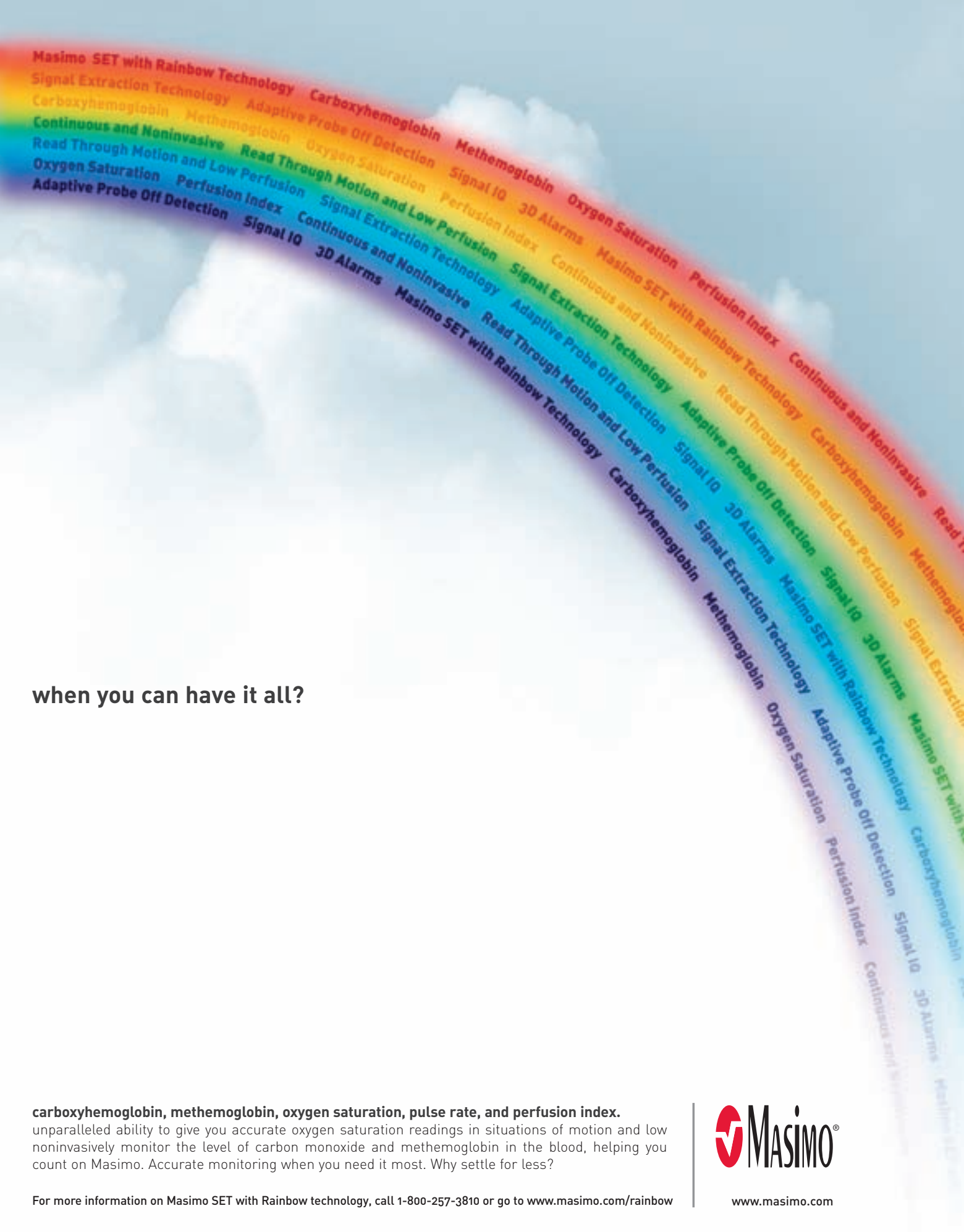

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Prevention
In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

Rescue
To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

CONTRAINDICATIONS
None known.

WARNINGS
SURVANTA is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS
General
Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 1). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been performed with SURVANTA. SURVANTA was negative when tested in the Ames test for mutagenicity. Using the maximum feasible dose volume, SURVANTA up to 500 mg phospholipids/kg/day (approximately one-third the premature infant dose based on mg/m^2/day) was administered subcutaneously to newborn rats for 5 days. The rats reproduced normally and there were no observable adverse effects in their offspring.

ADVERSE REACTIONS
The most commonly reported adverse experiences were associated with the dosing procedure.

In the multiple-dose controlled clinical trials, each dose of SURVANTA was divided into four quarter-doses which were instilled through a catheter inserted into the endotracheal tube by briefly disconnecting the endotracheal tube from the ventilator. Transient bradycardia occurred with 11.9% of *doses*. Oxygen desaturation occurred with 9.8% of *doses*.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 1.

TABLE 1

	All Controlled Studies		
Concurrent Event	**SURVANTA (%)**	**Control (%)**	***P*-Value[a]**
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a] *P*-value comparing groups in controlled studies

When all controlled studies were pooled, there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% *v* 30.8%, *P* = 0.001; and 48.8% *v* 34.2%, *P* = 0.047, respectively). The rate in a Treatment IND involving approximately 8100 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 4300 pretreatment and post-treatment serum samples from approximately 1500 patients were tested by Western Blot Immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

Respiratory: lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

Cardiovascular: hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardio-respiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

Gastrointestinal: abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

Renal: renal failure, hematuria.

Hematologic: coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System: seizures.

Endocrine/Metabolic: adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal: inguinal hernia.

Systemic: fever, deterioration.

Follow-Up Evaluations
To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies
Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies
Six-month adjusted-age follow-up evaluations have been completed in 631 (345 treated) of 916 surviving infants. There were significantly less cerebral palsy and need for supplemental oxygen in SURVANTA infants than controls. Wheezing at the time of examination was significantly more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Final twelve-month follow-up data from the multiple-dose studies are available from 521 (272 treated) of 909 surviving infants. There was significantly less wheezing in SURVANTA infants than controls, in contrast to the six-month results. There was no difference in the incidence of cerebral palsy at twelve months.

Twenty-four-month adjusted-age evaluations were completed in 429 (226 treated) of 906 surviving infants. There were significantly fewer SURVANTA infants with rhonchi, wheezing, and tachypnea at the time of examination. No other differences were found.

OVERDOSAGE
Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

HOW SUPPLIED
SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 4 mL (NDC 0074-1040-04) or 8 mL (NDC 0074-1040-08) of SURVANTA. Each milliliter contains 25 mg of phospholipids suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

May 2004

Manufactured by:
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For:
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ABBOTT LABORATORIES INC.
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News

☐ January-February 2007

CORRECTION
The wrong advertisement for Dräger Medical appeared on the back cover of our October 2006 issue. The correct advertisement, for Dräger Medical, appears on page 4 of this issue, with the headline, "Impact your entire perinatal care process." Neonatal Intensive Care apologizes for the error.

C SECTION REDUX
Regarding the statistically high number of C-sections in the US, an obstetrician responded in a recent issue of the New York Times that doctors are often falsely accused of a "rush to the knife" at minimal changes in the fetal heart rate during labor, which she noted was "certainly not true" in her practice. She noted that women often went through horrors when there was no alternative to vaginal birth, and wrote, "not every term fetus in utero is able to fit through the maternal pelvis and deliver vaginally. The reason instruments to cut the mother's symphysis pubis and crush the fetus's skull are a part of history is that now we have a safe procedure to deliver babies abdominally. It's called Cesarean section." In a letter to The New Yorker, a doctor wrote, "The decision to go ahead with the procedure [is] heavily influenced by our fear of and desire to control natural processes, financial incentives for operative procedures, turf battles within the healthcare community, and societal pressure to produce more in less time." Regarding C-section versus natural birth, another doctor wrote, "The 'natural' course of life, ie, without medical intervention, is brutal and short. The 'natural' course of childbirth, as evidenced in the Third World today, and in the centuries before modern medicine, is just as brutal, often resulting in fistulas, uterine prolaspe, and infection and death of the mother, the child, or both. Let us not romanticize this."

CARE DENIED
Under new federal regulations, children born to undocumented mothers must apply for Medicaid. Under previous policies, all children whose mothers received emergency Medicaid coverage for the delivery were automatically entitled to insurance for the first year of birth. The new policy would require parents to prove the newborn is a US citizen. All children born in the United States are eligible automatically for citizenship but doctors say many undocumented parents would be afraid to submit applications. According to Angela Bonavoglia, writing on Huffingtonpost.com: "From our avowedly pro-life, -pregnancy, -snowflake-baby, -fetus, -embryo, and -blastocyst Administration has come a brand new law concerning babies. In the throes of a tight election year, we might expect an attempt to garner some votes by replacing the inane idea of health-care accounts as the solution to 40 million people without health insurance with a proposal for more, not less, health care for American babies. No such luck. The new law actually withholds insurance for routine healthcare from infants born into poor families until the newcomer is approved for Medicaid coverage, which can take

weeks. The new law, written by Rep Charlie Norwood (R-GA), is nestled, improbably, in the Deficit Reduction Act. It was reportedly intended as a weapon against illegal immigration. Heretofore, children born in the US – citizens all – who had the misfortune of belonging to illegal immigrant parents were entitled to immediate Medicaid coverage for up to one year. The principle was that tending to the routine health care needs of our most vulnerable citizens can only help create a healthier citizenry. Instead, with the new law, the child is not covered immediately, through, for example, an application made by the hospital social worker on the child's behalf. No. The illegal immigrant parents must now bring a birth certificate or hospital record to the Medicaid office and apply for coverage for their child. That must be scary to someone who is in the US illegally, whose greatest fear must be deportation. This means some parents will not apply for Medicaid for their newborn, who will thus have to go without. Is this the way to treat "innocent life?" Where are all the troops who descended on Florida to keep poor Terry Schaivo alive when she was actually braindead? Where are all the holier-than- thous who don't want scientists to touch a single cell on a blastocyst in the interest of saving other lives? Where are all those pro-life people to whom all life is supposedly so damn sacred? Silent, obviously. Giving more proof, as if we needed it, that they could really care less what happens to children once they're born. Taking care of children takes money and creativity and commitment and community. It takes a social justice contract with America, which you won't find on the Republican agenda."

SIDS BREAKTHROUGH

Scientists believe that they have found the underlying cause of SIDS, a condition that claims the lives of hundreds of babies every year. Research into dozens of fatalities identified as the result of sudden infant death syndrome showed that the victims had a brain abnormality that prevents the detection of insufficient oxygen levels in the body. As a result, babies with the condition can be smothered in their bedclothes, especially if sleeping on their fronts. The researchers said yesterday that this was the strongest evidence yet of a common cause for cot death, and that it opened up the possibility of detecting those at risk and treating them. The US team, led by David Paterson, of Boston Children's Hospital, examined postmortem samples from the brainstems of thirty-one babies who had suffered a cot death, comparing them with ten babies who had died of other causes. They were following up research suggesting that cot-death babies had an innate difference in the brainstem, the part of the brain responsible for controlling breathing, heart rate, blood pressure, temperature and arousal. Three studies had found that cot-death babies had a reduced ability to use and recycle serotonin, a chemical best known for regulating mood but which has other roles. Scientists said the new study, published in the Journal of the American Medical Association, offered the most convincing confirmation yet of the link. The babies examined had twice as many brain cells that either manufacture or use serotonin as did those of the babies who died of other causes. But the cells that use serotonin also had significantly fewer binding sites — places on the outside of the cells where serotonin "docks" and acts as a signalling chemical. Dr Paterson said that the group's hypothesis was that they were observing a "compensation mechanism". He said: "If you have more serotonic neurons, it may be because you have less serotonin and more neurons are recruited to correct this deficiency." Boys who had died of cot death had significantly fewer serotonin receptors than girls, a finding that would be consistent with the fact that cot deaths are more common among boys. Hannah Kinney, the paper's senior author, said: "These findings provide evidence that sudden infant death syndrome is not a mystery but a disorder that we can investigate and some day may be able to identify and treat." The study suggests that the slight abnormalities in the brainstem may impair a baby's ability to sense high carbon dioxide and low oxygen levels. This would increase the risk that a baby will inhale its own exhaled breath and become deprived of oxygen.

"A normal baby will wake up, turn over, and start breathing faster when carbon dioxide levels rise," Dr Kinney said. But in babies who die from sudden infant death syndrome, defects in the serotonin system may impair these reflexes. Such circumstances are far more likely to arise if a baby is placed face down in the cot. Campaigns to put babies on their backs have had great success, halving the numbers of cot deaths in the past decade. The Foundation for the Study of Infant Deaths called the findings important and said that they were unlikely to be due to chance or sampling error. The Scottish Cot Death Trust, which part-funded the new research, said: "It looks like a really interesting piece of work and we welcome it as a way of starting to sift out the many possible factors in cot death." Marian Willinger, of the US National Institute of Child Health and Human Development, which funded the study, said that putting babies to sleep on their backs was important but as yet doctors could not target high-risk infants because of problems identifying them. Dr Willinger said that the research improved the understanding of the processes that underlay cot death, and the chances of helping at-risk infants. However, George Haycock, scientific adviser to the Foundation for the Study of Infant Deaths, added that a brain abnormality was unlikely to be the sole cause." Much more research is needed to understand and, ultimately, to prevent these tragedies," he said.

A SMALL SURPRISE

Scientists now say one-third of infant deaths are because of premature births – a much larger percentage than previously thought. In the past, "preterm birth" has been the listed cause of death in fewer than 20% of newborn fatalities. But that rate should be 34% or more, said researchers at the Centers for Disease Control and Prevention. That's because at least a dozen causes of newborn death are actually problems that go hand-in-hand with premature births, such as respiratory distress syndrome caused by underdeveloped lungs.

"This brings preterm birth, as a cause of death, to the kind of level that we think it deserves," said the CDC's Bill Callaghan, the lead author of a study that appeared in Pediatrics. The revised statistic might lead to greater efforts to counsel pregnant women about taking care of themselves and avoiding actions that can lead to preterm births, such as smoking and drug use. It also may help organizations lobbying for more research into why some women who follow medical advice still have preterm babies. The March of Dimes is advocating to expand federal research into preterm labor and delivery and the care and treatment of premature infants. Researchers examined birth and death certificates for about 28,000 US infants who died in 2002. More than 4,600 of those were attributed only to preterm birth. But the researchers also grouped in thousands of other deaths that were attributed to preterm-related conditions, including respiratory distress syndrome, brain hemorrhage and maternal complications such as premature rupture of membranes.

OLD FORMULA

Medication errors, blood-stained equipment, expired baby formula and inattentive care were just a few of the reasons why Martin Luther King Jr/Drew Medical Center flunked a make-or-break federal inspection this summer. Among other problems, inspectors at the Los Angeles hospital found 66 bottles of baby formula in the neonatal intensive care unit that had an expiration date of July 1. Hospital officials blamed housekeeping staff for not notifying the neonatal staff. The report underscored the extent of the hospital's problems, which started with management and extended to the pharmacy, nursing, infection control and other operations. The document cited shortcomings throughout the hospital but focused mainly on the way medicine was administered, errors by staff and the hospital's general lack of upkeep.

THE END

Britain's Royal College of Obstetricians and Gynaecology has reportedly called on doctors to consider euthanasing "the sickest of newborns" which it says can disable healthy families. The Sunday Times newspaper said the proposal was in reaction to the number of such children who were surviving because of medical advances. The college argued "active euthanasia" should be considered for the good of families, to spare parents the emotional burden and financial hardship of bringing up the sickest babies. The proposal was contained in the college's submission to an inquiry into ethical issues raised by the policy of prolonging life in newborn babies. Euthanasia of newborns is illegal in Britain. "A very disabled child can mean a disabled family," the submission says. "If life-shortening and deliberate interventions to kill infants were available, they might have an impact on obstetric decision-making, even preventing some late abortions, as some parents would be more confident about continuing a pregnancy and taking a risk on outcome. We would like the working party to think more radically about non-resuscitation, withdrawal of treatment decisions, the best interests test and active euthanasia as they are ways of widening the management options available to the sickest of newborns." The newspaper reported that the college was not formally calling for active euthanasia to be introduced, but wanted the mercy killing of newborn babies to be debated by society. In the Netherlands mercy killing was permitted for a range of incurable conditions, including severe spina bifida and the painful skin condition called epidermolysis bullosa, The Sunday Times said. The British Council of Disabled People told the newspaper if euthanasia were introduced for certain conditions it would tell people with those conditions "they were worth less than other members of society." Reported in Medical News Today.

PREVENTIVE MAINTENANCE

A program designed to help parents care for their premature infants in the neonatal intensive care unit (NICU) can lead to healthier babies and parents, and save more than $2 billion in U.S. healthcare costs annually. A new study published in the November issue of the journal Pediatrics shows that an educational-behavioral program called Creating Opportunities for Parent Empowerment (COPE) can improve the mental health of parents and decrease the length of stay in the NICU by four to eight days for premature infants. Based on the 480,000 premature infants born in the United States annually, potential healthcare savings could total $2.4 billion if the program were implemented as standard practice in NICUs, according to the study's authors. The average per day hospitalization cost for infants in the NICU is approximately $1,250. Prior evidence suggests low-birth-weight infants experience adverse physical, mental and behavioral outcomes that persist beyond school age, according to the study, and that parents of preterm infants also experience high stress levels and are usually inadequately prepared for the experience. When parents are stressed, anxious or depressed the result is increased rates of dysfunctional and over-protective parenting. Interventions to enhance coping and mental health outcomes in parents or premature infants have lagged behind the rapid technological advances to sustain survival in the NICUs. The study involved a randomized clinical trial from 2001 to 2004 conducted with 260 families with preterm infants in two NICUs in the northeast United States. All families received four intervention sessions of audiotape and written materials. Parents in the COPE program received information and behavioral activities about the appearance and behavioral characteristics of preterm infants and how best to parent them. An educational/behavioral intervention was used because information reinforced with behavioral activities has been shown to be more effective in producing change than information alone, the authors report. In addition to COPE parents reporting less stress in the NICU and interacting with their infants in a more developmentally sensitive manner than comparison group parents, the study found that COPE mothers had significantly fewer anxiety and depressive symptoms when their infants were two months of age. Both mothers' and fathers' parenting beliefs/confidence and how they interacted with their infants in the NICU were related to a shorter length of stay. Post study discussions were held with unit neonatal healthcare teams involved in discharge planning of all NICU babies. These teams indicated that criteria for discharge not only includes that the preterm is physiologically stable, but that the parents are ready to assume care for their infants. Reported in Medical News Today.

LITTLE TWEAKERS

Babies can be exposed to methamphetamine or crystal meth while in the womb, reveals an analysis of hair samples, published ahead of print in the Fetal and Neonatal Edition of Archives of Disease in Childhood. Unlike hair, the most commonly used detection methods (blood and urine), cannot register long term use, nor can they always distinguish among different drugs, say the authors. Bleaching or straightening the hair will not erase the chemical evidence it holds. Long term crystal meth abuse damages nerves in the brain and can lead to psychotic behaviour and aggression. The drug is very easy to manufacture in home laboratories, and global use has soared, particularly among young women, say the authors. An estimated half a million Americans alone are thought to use it every week, including 5% of pregnant women. The authors carried out hair sample analysis on more than 8,000 people, totalling more than 34,000 test results between 1997 and 2005. In all, 396 samples tested positive for crystal meth, accounting for 8% of the total during this period. This number included 11 mother and baby pairs. All but 14 of the samples testing positive for crystal meth had been sent for analysis in 2005. The first positive cases dated from 2003. Wide ranging levels of the drug were found in both the mothers' and the newborns' hair samples. But the levels matched, indicating that the drug is able to cross the placenta directly to the developing fetus, say the authors. The precise effects of crystal meth on a fetus are not fully known, but the evidence to date points to restricted fetal growth and developmental problems. Crystal meth users were also significantly more likely to use other drugs, the results showed.

Most (85%) of the 396 samples positive for crystal meth also tested positive for at least one other illegal drug, predominantly cocaine.

STICKS AROUND

Premature babies born with bronchopulmonary dysplasia continue to exhibit respiratory symptoms after three years of life, according to a new study from Baylor College of Medicine. The lung disorder is most commonly seen among premature infants with very low birth weight, who have received prolonged mechanical ventilation. Researchers followed 31 children with BPD for 36 months following discharge. Eighty-two percent of these children were less than 2.2 pounds at birth. Visits were conducted every three months, from three months of age to one year; and every six months, from one year to two years; and then concluded with a visit at three years. Pulmonary function tests were performed at 6, 12, and 24 months. Results showed that 45 percent of children showed persistent airway obstruction at 24 months, and 75 percent of children reported cough at 36 months.

TINY BREATHS

Babies born at term with low birth weight (LBW) have minimal risk of experiencing poor lung function as adolescents, shows a new cross-sectional study. Researchers from the Philippines performed pulmonary function tests on 41 children, ages 10 to 14, to determine their FEV1 and FVC. All of the children were delivered healthy and at term, but with LBW. Other information, such as present height and weight, body mass index, smoking, and illness were recorded. Researchers concluded that there is a weak correlation between LBW and lung function among early adolescences, and only those children who experience pneumonia at less than two years showed a statistically significant change in FVC.

GIVE AND TAKE

Maryland is reinstating a $7 million Medicaid program that provides health benefits to legal immigrant children and pregnant women, state officials said Thursday, the Washington Post reports. The state's decision is in response to a state Court of Appeals ruling last week that upheld a Montgomery County Circuit Court's preliminary injunction blocking the cuts. The rulings stem from a lawsuit filed by the Maryland Legal Aid Bureau and Bethesda attorney Douglas Bregman alleging the Medicaid cuts were discriminatory. In the lawsuit, families of 13 immigrant children alleged that Maryland discriminated against non-U.S. citizens by cutting a Medicaid program that provided health benefits for pregnant women and about 4,000 children who are legal, permanent residents. Gov Robert Ehrlich (R) later reinstated coverage for pregnant women enrolled in the program. The court's decision is "not only a victory for the 13 plaintiffs; it is a sweeping victory for an entire class of people similarly situated," Bregman said.

GET TOGETHER

The development of safe and effective medicines for newborn babies requires stronger cooperation between researchers, developers and regulators. This was one of the main conclusions of a workshop, organized by the European Medicines Agency (EMEA), which looked at scientific issues related to the investigation of medicinal products intended for the treatment of neonates. Highlighting the agency's commitment to stimulate multidisciplinary cooperation in the development of medicines for children, the workshop brought together some 70 experts from academia and learned societies, industry and regulatory authorities, and also healthcare professionals involved in looking after and treating newborn babies, including babies born prematurely. The participants discussed the impact of organ immaturity and the rapid changes in the first days and weeks of life when investigating medicines for neonates. The outcome of the workshop - together with a series of concept papers on the impact of brain, liver, kidney, heart and lung immaturity prepared by the Agency's Paediatric Working Party (PEG), will form the basis of a future EMEA guideline on this issue. Other aspects covered during the workshop included formulations appropriate for neonates, ethical aspects in relation to the conduct of clinical trials in newborn babies, novel study design methods and safety and pharmaco-vigilance aspects. The EMEA neonates workshop was organized in the framework of the Agency's preparation for the entry into force of the new European legislation on medicines for children. The new legislation introduces incentives aimed at the stimulation of research, development and authorization of medicines for children. It is expected that this will result in an increase of clinical trials in children, including neonates. The workshop provided a platform for a multidisciplinary scientific dialogue among European experts, to identify appropriate measures to encourage high-quality research into medicines for neonates.

OLDIE BUT GOODIE

Women over 50 who give birth can be just as good as younger women when it comes to motherhood, said researchers from the University of California, at the annual meeting of the American Society for Reproductive Medicines. There was no evidence that women in their fifties experience higher levels of stress or experience greater health risks, compared to younger women who give birth. The researchers examined data on 150 mothers who had received fertility treatment between 1992-2004. They gave birth in their thirties, forties and fifties. The women were surveyed to determine their physical and mental functioning and parental stress. Their findings revealed that the women in their 50s were not less capable as parents - neither did they experience higher levels of stress than the other women. The researchers suggest that public prejudice is the problem, not poor capacity on the part of older mothers. A large percentage of the older mothers in this study had younger partners.

MYSTERY

How are babies made? Except that there was semen involved, we didn't always know. It wasn't until the mid 17th century that it was discovered that all female animals produce eggs. In the late 1600s, actual swimming semen was seen in a microscope. However, the connection between sperm and egg wasn't put together for a while. For a century and a half, "ovists" and "spermists" dueled about which component was necessary for conception. The spermists though the egg was just food for the sperm, while ovists said that sperm were merely parasitic worms in the semen. According to Matthew Cobb with the University of Manchester, writing in the Los Angeles Times, "thinkers could not understand what they saw because they did not have the right ideas to interpret their observations. People could not realize that egg and sperm were equivalents because they did not believe that both parents contributed equally to the offspring." It wasn't until the early 1830s that scientists discovered the notion of heredity, a concept that necessitated a two-party contribution. Finally, it was the discovery of cells that

sealed the deal, and shortly thereafter, fertilization could be observed. Cobb concludes, "How many of today's ideas will turn out to be similarly misunderstood? Today's certainties may be reinterpreted in the light of tomorrow's discoveries."

BIG BABY

A Norwich, CT woman recently gave birth to a 14-pound, 13-ounce boy and broke the record at the local hospital. He was nearly 23 inches long. "He's built like a linebacker," said Dr David Kalla, who delivered the baby by Caesarean section. After nine months of carrying the kid, the mom said she was more tired and happy to have given birth than all the attention her baby was receiving. "I was miserable," she said. "I couldn't sleep at night. My 13-year-old son had to help me get in and out bed." The baby's size came as no surprise to his mom. Her oldest son weighed 9 pounds at birth, her 8-year-old twin sons each weighed 8 1/2 pounds and her youngest son, 3, was nearly 12 pounds. At less than 24 hours old, the baby was fitting into clothes for a 6-month-old and was too big for newborn diapers. "I have baby clothes, but I don't think they will be able to fit," his mom said. "I think I will have to return them."

BOWELS AND BIRTH

Irritable Bowel Syndrome (IBS) is linked to low birth weights, according to a Norwegian study. Scientists have discovered that people born weighing less than 2.5kg (5.5lb) were at a greater risk of developing IBS than heavier babies. They believe this may be related to development of the digestive system. The study, published in the journal Gut, looked at 3,334 pairs of female and male identical and non-identical twins born between 1967 and 1979. Researchers compared the recorded birth weight of the volunteers with whether they had gone on to suffer from IBS. Roughly one in 20 had suffered from IBS, a common and painful condition that has a wide range of symptoms, including regular abdominal pain, diarrhea and constipation. Women were more likely to have IBS than men. The researchers found that babies born weighing less than 2.5 kg were more likely to have had IBS. For those born weighing less than 1.5 kg, the difference was more marked: they were 2.5 times more likely to have had IBS when compared with those weighing above 2.5kg. The study also found that the twins with the low birth weight were more likely to develop IBS about eight years earlier than those weighing over 1.5 kg. Researchers also said the study also revealed that genes could play a role in IBS in women.

YOUR OWN GRANDMA

A Japanese woman in her 50s gave birth to her own grandchild last year, using an egg from her daughter and sperm from her son-in-law. It was the first time a woman has acted as a surrogate mother for her daughter in Japan. The woman gave birth last year, Reuters reported. She had agreed to in vitro fertilization and to act as a surrogate mother because her daughter had her uterus removed due to cancer and was therefore unable to bear children. The woman had first registered the baby as her own and then the child was adopted by her daughter and son-in-law.

BITE AND BIRTH

Oral health and the connection to whole body health is becoming a hot topic in the media, specifically as it relates to pregnancy, according to a press release by Procter & Gamble. Recently, insurance companies announced new medical/dental integration plans with enhanced dental benefits for pregnant women. Procter & Gamble Oral Care, Crest and Oral-B have partnered with Scientific American to create a special issue providing comprehensive information and expert opinions regarding the relationship between oral health and whole body wellness. As it relates to women, pregnancy and obstetrics, growing evidence suggests that poor oral hygiene during pregnancy can adversely affect the health of newborns. In fact, oral infection can now be added to a list of possible risk factors.

VITAMIN WHEEZE

Children whose mothers consume more foods containing vitamin E during pregnancy are less likely to develop wheeze or asthma by the age of five, according to researchers. Those born to mothers who had the lowest vitamin E intake were 3.47 times more likely to have persistent wheeze and five times more likely to have early-onset persistent asthma than those born to mothers with the highest levels, according to researchers at the University of Aberdeen. Higher maternal dietary vitamin E intake, assessed at 32 weeks gestation on a dietary questionnaire and nonfasting blood sample, was associated with less wheezing in their children after five years of follow up, even after adjustment for a full range of variables including breast feeding. Dietary vitamin E rather than supplements containing the antioxidant appeared to be key.

Children of mothers who had more intrapartum vitamin E intake were also less likely to have asthma outcomes at age five. The 2,000 mothers who were recruited at Scottish antenatal clinics were also measured for other antioxidant levels including vitamin C, beta carotene, alpha tocopherol, and zinc. Of these, zinc had the strongest associations with early respiratory function. Late onset asthma (after age 2) was correlated with lower maternal zinc intake during pregnancy. The children's own nutrient intake had no impact on their asthma, wheezing, eczema, or other outcomes. While breastfeeding was not associated with wheezing or asthma outcomes at the five-year follow-up overall, breastfed children (74.6%) had greater magnitude associations between maternal antioxidant intake and outcomes than those who had not been breast fed. The researchers said their results were consistent with the notion that early life nutrient intake, both in utero and in the early postpartum period, modifies the risk of developing childhood asthma. Other studies have found that supplementation with antioxidants including vitamin C and E and trace elements like selenium and magnesium does not consistently improve asthma outcomes for adults. Dr Devereux and colleagues said that their study may offer an explanation for the inconsistencies between epidemiologic and dietary intervention studies.

PRODUCTS

A BIG PLUS

Casmed offers a comprehensive family of products for apnea monitoring. For home use, the Amni Plus monitor provides a built-in modem, is lightweight, portable and easy to use. In the hospital environment, the Casmed 511 monitor offers heart and respiration monitoring, can be configured with an optional pulse oximeter, and can easily interface with a nurse call system. The Casmed Express software allows users to quickly access, review and analyze data. Contact http://casmed.com.

CLINICAL DATA

Surfaxin treated preemies require fewer re-intubations and experience improved key clinical outcomes compared to those treated with animal-derived surfactants, according to clinical trials of Discovery Laboratories' Select and Star Phase 3 Surfaxin (lucinactant). The findings were presented at the Europaediatrics conference in Barcelona, Spain. According to data provided by Discovery Labs, in a pooling of studies, re-intubation rates for Surfaxin-treated vs animal-derived surfactants were 34.2% and 43.9%. In the Select trial, re-intubation rates for Surfaxin vs animal surfactants were 34.6% vs 42.8%, and for the Star trial, they were 32.7% vs 47.2%. Long-term clinical data was also presented showing significant survival benefit through one year of life. For more information, contact DiscoveryLabs.

BETTER SAFE THAN…

Viasys offers its Corflo Anti-IV Enteral Feeding System, designed to prevent the accidental administration of enteral feeding into an IV line or parenteral drugs into an enteral feeding tube. The Viasys feeding tube has an anti-IV male connector that's compatible only with the Corflo Anti-IV Feeding set, and minibore tubing on the feeding set uses an orange stripe to indicate enteral use. When used as an integrated system, the Corflo Anti-IV Feeding System is designed to eliminate accidental injection of IV meds into the enteral tube or that enteral feeding will be mistakenly infused into an IV line. For more contact viasyshealthcare.com.

SPOTLIGHT ON OXIMETRY

CEREBRAL AND SOMATIC

Somanetics' INVOS System's Cerebral/Somatic Oximeter enables critical care clinicians to noninvasively monitor site-specific blood oxygenation. With the only simultaneous cerebral/somatic oximeter, clinicians may place up to four sensors to gather oxygenation data from the areas that interest them most. The resulting regional oxygen saturation (rSO2) is a vital sign that helps clinicians detect potentially harmful oxygenation issues. When rSO2 values dip toward threshold levels, the care team can intervene to potentially lessen or prevent ischemic complications such as those associated with seizures, neurologic damage, renal failure, low cardiac output and shock. For information visit somanetics.com, (800) 359-7662.

WIRELESS

Nonin's Avant 4000 System is a wearable digital pulse oximeter that connects wirelessly to a tabletop display. Using Bluetooth technology, the Avant 4000 provides continuous monitoring for your smallest patients – even in a Kangaroo Care setting. The lightweight, durable system features PureSAT signal processing technology, 120 hours of battery life and 33 hours of memory. In addition, the Avant 4000 is compatible with Nonin's full line of PureLight sensors. The company's slogan is: NONIN - Opening new horizons in connectivity. For more information, contact Nonin Medical, Inc at (800) 356-8874 or visit nonin.com.

TAKING THE PULSE

Maxtec Inc, Salt Lake City, UT is excited to announce the release of the all new Pulsox-300i pulse oximeter from Konica Minolta Sensing. For years, the Pulsox-3 series provided the perfect solution for spot checking and recording heart rate and blood-oxygen saturation. Now, the Pulsox-300i offers even more! The Pulsox-300i comes complete with 300 hours of non-volatile data storage, 30 hours of battery life on one AAA battery and provides connection to a PC via USB port for faster downloading and report printing! Contact a Maxtec representative today for details. 866.4.maxtec, maxtecinc.com.

ALL SET

Masimo develops innovative monitoring technologies that significantly improve patient care. In 1995 the company introduced Masimo SET Read-Through Motion and Low Perfusion pulse oximetry, virtually eliminating false alarms and increasing pulse oximetry's ability to detect life-threatening events. More than 100 independent studies confirm that Masimo allows clinicians to accurately monitor blood oxygen saturation in critical care situations—establishing SET as the "gold standard" while substantially contributing to improved patient outcomes. With the 2005 introduction of Masimo Rainbow SET Pulse CO-Oximetry, clinicians can noninvasively monitor carbon monoxide and methemoglobin in the blood, allowing early detection and treatment of potentially life-threatening conditions.

WHAT'S THAT ON YOUR HEAD?

Finding an appropriate site for a pulse oximetry sensor on tiny neonates and infants can be challenging. Now Nellcor offers a new solution: the OxiMax NeoMAX forehead sensor. Designed for the forehead – a preductal monitoring site – the NeoMAX forehead sensor provides an effective alternative to sensors intended for hands and feet. The sterile, single-patient-use NeoMAX forehead sensor is nonadhesive and is built into a soft, fabric cap that holds it in place. In addition to offering a preductal monitoring site, the OxiMax NeoMAX forehead sensor addresses other clinical challenges as well: The forehead is less affected by motion than hands or feet for wiggling preemies and infants. When it's difficult to obtain a signal from the hands or feet, a forehead sensor can be an effective option. Swollen hands and feet can affect SpO2 readings, so using a less edematous site like the forehead can improve monitoring reliability. For patients with fragile skin, the NeoMAX sensor provides a gentle alternative because it is nonadhesive. The OxiMax NeoMAX sensor, available in three sizes, features an easy-to-apply, one-piece design. It is compatible with Nellcor OxiMax pulse oximeters and OxiMax-enabled patient monitors from leading third-party manufacturers. Learn more by calling (800) NELLCOR.

NONINVASIVE

The USCOM noninvasive hemodynamic monitor uses the well-validated science of continuous wave Doppler to accurately measure cardiac output through either the aortic valve or the pulmonary valve to assess both left and right heart hemodynamics. The operator simply places the transducer in the suprasternal notch to access the aortic valve and at the left parasternal edge to access the pulmonary valve. The patient may be awake, sedated or ventilated, facilitating examination in a variety of settings. Weighing just twelve pounds, USCOM is highly portable and is designed to be operated by paramedical staff; all measurements are automatically stored and trended for subsequent review by clinicians. The USCOM has been validated against flow probes in animals, the pulmonary artery catheter, echo, artificial hearts and transesophageal Doppler in children

and adults. USCOM may be applied to patients of any size or weight and reliable hemodynamic information will be obtained in clinical conditions where other monitoring methods fail. Applications include trauma, burns and sepsis in adults and children, patient transport and preclinical evaluation in primary rescue, optimization of hemodynamics in potential organ donors, and management of post-op cardiac surgery patients. Contact uscom.com.

CLINICAL TRIALS REVIEW

A look at the latest in clinical trials. For more information see clinicaltrials.gov.

- Intervention to Decrease Anxiety in Parents of Infants in the Neonatal Intensive Care Unit (NICU)
  Conditions: Anxiety; Acute Stress Disorder; Posttraumatic Stress Disorder; Depression
- The Impact of Implementing NIDCAP on Preterm Infants in the NICU
  Condition: Infant, Premature
- Fetoscopic Tracheal Balloon Occlusion in Unborns With Severe Congenital Diaphragmatic Hernia - EUROTRIAL I
  Condition: Diaphragmatic Hernia
- Comparison of Infant Pain Responses Between Two Different Methods of Urine Collection
  Conditions: Infant, Newborn; Infant, Premature; Infant, Low-Birth Weight; Intensive Care, Neonatal
- Brain Manganese Deposition in High Risk Neonates
  Conditions: Parenteral Nutrition; Prematurity; Necrotizing Enterocolitis; Digestive System Abnormalities; Cholestasis
- Neurodevelopment and Neuroimaging in Parenterally-Fed Infants and Young Children
  Conditions: Parenteral Nutrition; Prematurity; Necrotizing Enterocolitis; Digestive System Abnormalities; Cholestasis
- Evaluation of Pulse Oximetry Sensors in Neonates
  Condition: Premature Birth
- Vermont Intervention: Effect on Joint Attention Skills Between Parents and Preterm Babies in the First Year of Life
  Condition: Premature Birth
- Emotional Experiences in Fathers of NICU Infants
  Conditions: Stress; Depressive Symptomatology
- Study Protocol Evaluating Transient Tachypnoea of the Newborn in Term and Near Term Neonates
  Condition: Transient Tachypnoea of the Newborn
- A Study to Test the Pain-Relieving Effect of Laughing Gas in Infants
  Condition: Analgesic Affect
- Clinical, Biochemical, Histological and Biophysical Parameters in the Prediction of Cerebral Palsy in Patients With Preterm Labor and Premature Rupture of Membranes
  Conditions: Preterm Labor; Infant Neurological Disorders
- Comparison of Different Oxygen Delivery Strategies During Resuscitation of Babies
  Conditions: Prematurity; Oxidative Injury; Respiratory Distress
- Cysteine Supplementation in Critically Ill Neonates
  Conditions: Sepsis; Bronchopulmonary Dysplasia; Necrotizing Enterocolitis; Retinopathy of Prematurity; Systemic Inflammatory Response Syndrome
- Music's Effects on Premature Babies.
  Conditions: Stress; Sleep
- Preterm Infants' Weight Gain Following Massage Therapy
  Condition: Premature Birth
- Fat Tolerance From Lipid Emulsion Infusion Packaged in Glass or Plastic
  Condition: Hypertriglyceridemia
- Two Dose Regimens of Nifedipine for the Management of Preterm Labor
  Condition: Labor, Premature
- Effects of Massage on the Immune System of Preterm Infants
  Conditions: Premature Birth; Stress
- Improving Asthma Care for Very Low Birth Weight Infants
  Condition: Asthma
- Nasogastric Tube Vs. Orogastric Feeding Tube in Preterm Infants: Which is Best?
  Condition: Infant, Premature
- Fetoscopic Tracheal Balloon Occlusion in Unborns With Severe Congenital Diaphragmatic Hernia - EUROTRIAL II
  Condition: Diaphragmatic Hernia
- Impact of Heparin on the Need of Mechanical Ventilation in Neonates
  Conditions: Respiration, Artificial; Hemorrhage
- NO Need to Ventilate: A Trial of Non-Invasive Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn
  Condition: Pulmonary Hypertension
- Preterm Fetal Growth Restriction and Developmental Care
  Condition: Preterm Birth

EXECUTIVE PROFILE

B&B Medical Technologies

David Thompson, Beth Keifer

David Thompson is President and Beth Keifer is Vice President, Sales & Marketing, B&B Medical Technologies.

A new team has assumed ownership and management of B&B Medical Technologies. Continuing B&B's legacy as a respiratory therapist-owned company are David Thompson and Beth Keifer, who together bring more than 50 years in clinical, educational and technical expertise in the respiratory care field. Thompson and Keifer are joined by Robert Sprowls, a Carlsbad, CA businessman with over 40 years in business development, manufacturing and distribution experience. Stephen Briggs III along with Dr. Ernie Bodai created B&B Medical Technologies in 1985 to ensure that specialty airway related products had a pathway to the clinical community. The foundation formed by Briggs through his lifetime in the respiratory therapy community will be carried on in the new ownership and management.

Describe your product(s) and their unique features.
Since 1985, B&B Medical Technologies has been a leading designer of specialty airway management devices and nebulizers for infants, pediatrics and adults. B&B products are designed for easy, one person application, helping to minimize the risk of accidental disconnects and unplanned extubations. B&B's StabilTube, LockTite, E.T.Tape for Adults and Infants and the Bite Block provide clinicians simple solutions for comfortably securing the endotracheal tube, prevention of ventilator disconnects and a convenient answer to prevent endotracheal tube biting. B&B's TrachGuard and TrachStay comfortably secure the ventilator circuit to the tracheostomy tube while preventing accidental disconnects. B&B's patented Hope nebulizer technology provides efficient delivery of continuous medication combined with the ability to blend gases such as Heliox without affecting medication delivery. The Hope Nebulizer is the first nebulizer specifically cleared by FDA for Heliox administration.

How do your products directly affect patient care?
B&B's airway management product line offers a complete package for rapid access to stabilizing the airway. The "all-in-one package" solution provides the tools necessary for the clinician to rapidly secure the endotracheal tube and tracheostomy tube to the patient and ventilator circuit, saving time for patient assessment and care. The B&B products take into account the need for patient comfort with our selection of materials used to manufacture our products.

The B&B ET Tapes comply with the new AHA guidelines recommending the use of a commercial device for "securing the endotracheal tube for preventing accidental tube disconnects when compared with traditional methods of securing," ie, tape. B&B specialty products have been incorporated into many hospital based quality improvement processes to economically minimize the incidence of sentinel events in the ventilated patient.

The HOPE Nebulizer has become the gold standard for continuous medication and Heliox therapy in respiratory care. The patented supplemental gas delivery port for the delivery of specialty gasses, such as Heliox, in a closed dilution nebulizer greatly enhances the performance of the nebulizer providing a significant amount of medication in the respirable range for the moderate to severely compromised patient. The utility of Heliox has potential as supportive therapy, allowing time for other medications to take effect. The HOPE Nebulizer can achieve cost savings during continuous nebulization and provide a useful clinical adjunct for non-intubated patients.

What sets your products apart from others in the field?
The value of our products is in the economic design, manufacturing processes and time savings provided by a packaged product ready for use when the clinician needs it most. B&B products provide efficient solutions to allow the clinician the ability to provide patient focused care at the bedside, in the emergency department and by first responders in the field. Our convenient kits are both time and cost saving.

Discuss your R&D process, including end-user input.
The original founders as well as B&B's new team began in the bedside trenches and we believe the best ideas continue to come from our colleagues working day in and day out in the clinical arena. Taking the ideas and fine tuning them with B&B's engineering, production and clinical staff results in the quickest, most economical way to get the solution to the problem. We call on both domestic and international resources to provide a steady stream of product ideas and recommendations for materials and technologies required to provide the highest quality and most cost effective products.

What are your goals for R&D in the near future?
From the onset of the company, B&B has always valued the clinical and engineering input from the end-user. B&B's first products were conceived from bedside experience in critical care units. The lack of useful tools for patient safety in maintaining a closed airway started the process for product development and still drives a division of the company. We continually work with clinicians and our clinical and engineering consulting team to provide feedback for us on the impact and ease of use of B&B products. We plan to increase communication throughout the health care community and we invite existing and new users to contact us with ideas for new products and suggestions for improving current ones. We have several new products in development that we expect to introduce in early 2007. Each one bears the stamp of end user input.

Discuss the educational services you offer for use of your product.
We believe that supporting the respiratory therapy schools is the key building block for smooth transition of new technologies into the clinical area. With the simplicity and ease of use of the B&B specialty airway management devices, we have found that multimedia tools, such as educational CDs and DVDs with tutorials provide a consistent method for training today's health care practitioners. These tutorials are developed with input from B&B's team of clinical consultants who provide the educational support tools needed by the clinician. On the CD, each B&B product is identified with a separate training module. Each module provides a visual display of the applicable training material along with an audio portion to allow the clinician to

view the material at the clinicians' own speed. A basic competency program has been developed as an adjunct to the product CD with a focus on application of each product. As part of the B&B Value Add program, Policy and Procedure Protocols that focus on patient care are provided to the hospital clinical education department.

Clinical, technical and educational materials are available upon request and many of the support documents can be downloaded from the B&B Medical Technologies website at www.bandb-medical.com.

Discuss the role of critical care providers in developing and upgrading your product.
B&B was founded over 30 years ago by critical care clinicians interested in finding a solution to everyday problems that needed an easy to use tool. All of the current B&B products have imprints from clinicians worldwide that have allowed us to continue to manufacture cost effective and time efficient products for clinicians with the primary focus of patient comfort and safety.

Talk about how you test and evaluate your product in actual day to day use.
Long before a product is released into general distribution it will go through a series of end user practical tests and evaluations to ensure that it will safely and effectively meet its intended use claim. This testing encompasses a wide variety of clinical settings from major teaching institutions to community based hospitals and clinics to first responders. After release, product performance is an ongoing process. This process includes technical performance assessment as well as operator errors, effectiveness of labeling and training materials. Corrective action plans, if required, are implemented as a standard course of business.

What new technology do you see as having the greatest impact on your area of expertise?
Necessity is the mother of invention and this applies to our area as well. The development of new materials to combat skin allergies, for instance, brought about new materials with characteristics that have allowed cheaper, smaller, higher quality components for fields such as our airway security and medication nebulization devices. The rising price of petroleum based materials has resulted in an entire new class of plastics that will soon result in a "green" solution to the current discarding and recycling problems of many medical consumable products.

Discuss the international scope of your testing/marketing/development efforts.
Thomas L. Friedman's book, "The World is Flat" stated that thanks to fiber optics and high speed digital networks the difference in communicating and doing business around the corner or around the world now amounts to about 630 milli-seconds. This has greatly impacted how we are able to take advantage of worldwide resources and meet the growing demands of our customers. This includes intellectual and academic resources, unique and specific research, engineering, availability of materials, manufacturing, international testing, certification, distribution and an almost instantaneous link to and from our customers. The development, supply and distribution chains now go around the world the way they did around the neighborhood at the beginning of the previous century.

Tell us how you utilize conferences, seminars and such to promote your product.
Conferences, seminars and other off site gatherings without the pressure of the clinical schedule are unique venues for exchange of ideas with clinicians to focus on new products and new applications of current products. We have found that the time invested in gathering market research prepares B&B for assuring that our current and future products meet the needs of the users. These meetings allow us to also look at the post market assessment of our products, training tools and support and at our distribution channels to ensure quality customer care. We look forward to meeting you at the next congress.

Unexpected Detection of a Newborn with Multiple Rib and Clavicular Fractures: Birth Injury?

Ben K Rajegowda, MD; Poornima Chintalapalli, MD; Dinabel Peralta, MD; Wilhelmina Hernandez, MD

Introduction

Bony fractures in a newborn may occur during the process of birth and delivery. The most common bone to be fractured is the clavicle because of its superficial location and less commonly skull, spine, long bones and rarely the rib bones. Rib bone fractures were uncommon in the past and more so now due to improvement in perinatal and intrapartum management. When rib fracture does occur it is unintentional, almost always in difficult deliveries, macrosomic infants and instrumental applications. Rib fractures are frequently asymptomatic and missed on a routine palpation of the chest. We report an infant with ipsilateral clavicle and multiple rib fractures diagnosed on the second day of life with brief review of the literature.

Case Report

A full term, large for gestational age, infant was delivered vaginally by vertex presentation in ROA position. Mother was a 34 year old, G2 P1. She received full prenatal care and all of her labs and prenatal fetal sonograms were normal. A recent fetal sonogram documented macrosomia and polyhyhramnios.

The neonatal team was called because of maternal type 1 diabetes and fetal macrosomia. During delivery the obstetrician experienced shoulder dystocia and delivery was accomplished by McRoberts Maneuver. There was also one loop of tight cord around the neck. At birth, the infant was depressed requiring PPV with FiO_2 of 50%. The infant's condition improved from an APGAR score of 5 at 1 minute to 8 at 5 minutes. In the delivery room some weakness of upper limb movements were noted and the infant was otherwise stable. The infant was transferred to the newborn nursery for further evaluation and management.

The authors are with the Department Of Pediatrics/Division of Neonatology, Lincoln Medical and Mental Health Center, Bronx, NY. The principle author sincerely thanks Muhammad Aslam, MD for his technical and literature search support. He is a fellow at Harvard Neonatal-Perinatal Medicine Program at Children Hospital Boston/ Harvard University. Thanks also go to Robert Leggiadro, MD for his final review of the paper. He is the Chief of Department of Pediatrics at Lincoln Medical and Mental Health Center.

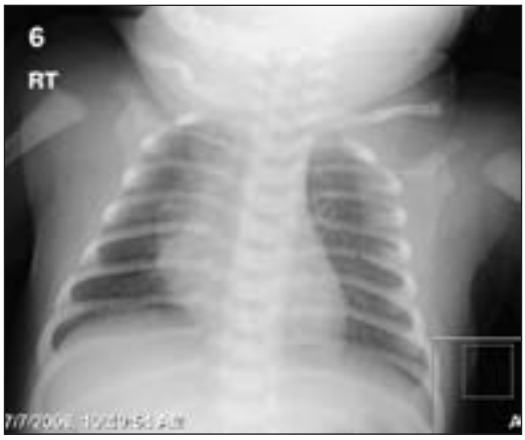

Figure 1. ACXR taken first showing multiple left sided rib fractures. The lungs and heart are normal

The infant had a weight of 4285 grams (> 90th percentile), head circumference 35 cms (50th percentile) and length 53 cms (> 90th percentile). The vital signs were normal and physical examination was essentially within normal limits. Both upper limbs were moving equally and she had good and equal Moro and Grasp reflexes. There was no evidence of swelling or crepitation on clavicular exam. The infant had a routine stay of 48 hours in the hospital with her mother and no complaints or any other problems were brought up by the parents or health care staff.

During a thorough discharge examination, the infant was active, slightly jaundiced with stable vital signs and good reflexes. Systemic examination was normal except for auscultation of a thud like noise in the precordial area with no murmur or additional heart sounds. A feathery feeling was felt on the palm while palpating the precordium and lateral aspect of left chest. A repeat palpation of clavicle and exam of the chest did not reveal any evidence of clavicular fracture, swelling of chest or redness. A chest radiograph was ordered to rule out pulmonary leak or any chest trauma (Fig 1).

A complete bone survey was done to rule out metabolic and genetic bone disorders or possible suspicion of intentional injury. The bone survey was essentially normal except for the additional finding of left clavicular fracture (Fig 2).

Consultation with pediatric orthopedic surgery, genetics and social services was done. Infant was managed and parents were supported. She was discharged home in good condition and was seen and evaluated in follow-up clinic and was doing well.

Discussion

Rib fractures in a healthy newborn occur very rarely and are often unrecognized clinically. Rubin and Levine and our own study documented no case of rib fractures among 15, 435 infants, 13, 870 infants and 18,293 infants examined for birth injuries respectively. [1, 2, 3] On the other hand Thomas reviewed rib fractures in children less than one year of age over a period of 6 years. He identified 25 cases of which there was one newborn and one 3 weeks old infant. The newborn baby's diagnosis was osteogenesis imperfecta, whereas the 3 weeks old infant had a birth weight of 5860 grams and was delivered by mid-forceps. This infant was asymptomatic in the nursery. [4]

In my experience as a neonatologist for over 37 years caring or supervising for over > 150, 000 infants, I did not come across a healthy baby with fractured ribs. It does not mean that it never happened but may not have been detected clinically.

We have not identified any citations on rib fractures or how to detect them on active review of the literature over the last 15 years. So any fractures noted in an infant before discharge from the hospital should be attributed to the process of labor and delivery until proven otherwise.[5] Usually the infants do not manifest any signs and symptoms. A routine radiograph of the chest is not usually done to look for rib fractures unless signs like swelling, redness, tenderness and crepitation on palpation exist. In our case there was a feathery feeling on palpation and a thud like noise on auscultation which gave a clue to request a radiograph of the chest. Detection before discharge may suggest birth trauma and detection at a later age with healing fracture in a child may suggest child abuse.[6, 7] It is very important to distinguish these two by reviewing birth history by documenting a difficult labor and delivery, birth weight and any instrumental use. In addition a careful examination including palpation of ribs in addition to clavicles should be performed in all difficult deliveries. One should also look for other risk factors like macrosomia, shoulder dystocia, prolonged second stage, small inadequate pelvis and instrumental delivery.

It was postulated that the rib fractures occur when the head is delivered and the shoulder is stuck requiring traction maneuver to deliver. In this way the rib cage passes under pubis by squeezing with lateral compression of the chest resulting in fragile rib fractures. In a questionable case one should exclude conditions associated with multiple fractures like osteogenesis imperfecta, congenital hypophosphatasia and other rare fragile bone diseases. These diagnoses were ruled out by history and radiological studies. A skeletal survey would be helpful to distinguish these conditions from birth trauma. In addition possible intentional injury by parents or employees must be considered.[8, 9] In our case the mother was healthy, happy and affectionate and loving to her child and she had a stable home environment from social service evaluation and we see no reason to suspect any abuse. One can detect asymptomatic rib

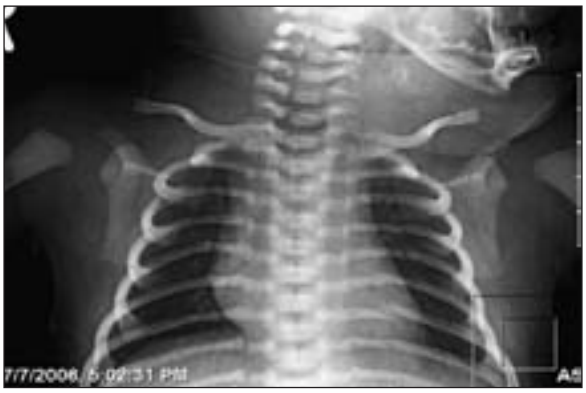

Figure 2. Chest and clavicular radiograph taken as a part of skeletal survey showing fractures involving fractures of the mid shaft left clavicle and posterior aspect of left 4th, 5th, 5th, 7th and 8th ribs

fractures by clinical suspicion if perinatal risk factors are present further assisted by good examination and radiological studies.[10] As in our case we did not find a clavicular fracture clinically at initial examination, but identified it by radiograph on the same side of the rib fractures.

Conclusions

We believe rib fractures secondary to birth trauma do occur but are difficult to detect clinically unless routine examination of the chest including palpation of the ribs is included in all difficult births.

ACOG committee on practice guidelines issued a statement that delivery of all estimated fetal weights of more than 4500 grams if they are diabetic and more than 5000 grams if they are non diabetic are at risk for unanticipated shoulder dystocia and prone to birth injuries. They suggest delivering such babies preferably by C section to avoid birth injuries. However birth weight between 4000-4500 grams is also a risk and a careful maneuvering of baby's decent and delivery may prevent or avoid birth trauma.[11]

References

1 Rubin A: Birth injuries: Incidence, mechanisms, and end results. J Obstet Gynecol 1964; 23:218-221

2 Levine MG, Holroyde J, Woods JR, et al: Birth trauma: incidence and predisposing factors. Obstet Gynecol 1984; 63:729-795

3 Samir.al-Absi, Marilyn Guerrero, Ronald bainbridge & Ben.Rajegowda.Assessment of clavicular fracture in a high risk population. APS-SPR # 1070 May 4-7-2002

4 Thomas PS: Rib fractures in infancy. Ann Radiol 1977; 20:115-122

5 Valman HB: Birth trauma. Br Med J 1979; 2:1566-1567

6 Cumming WA: Neonatal skeletal fractures. Birth trauma or child abuse? J Can Assoc Radiol 1979; 30:30-33

7 Merten DF, Radkiwski MA, Leonidas JC: The abused child: A radiological reappraisal. Radiology 1983; 146:377-381

8 Leonidas JC. Skeletal trauma in the child abuse syndrome. Pediatr Ann 1983; 12:875-881

9 Kogutt MS, Swischuu LE: Patterns of injury and significance of fractures in battered child syndrome. Am J Radiol 1974;121:143-149

10 Feldman KW, Brewed DK: Child abuse cardiopulmonary resuscitation and rib fractures. J Pediatrics 1984; 73:339-3422

11 ACOG Practice Bulletin 22:2000

Prevalence of Smoking During Pregnancy in a New York Inner City Hospital

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Abstract

Objective: We assessed the actual prevalence of smoking and passive exposure to cigarette smoke among postpartum mothers in our hospital.

Design/Methods: Using a questionnaire on smoking habits and exposure to cigarette smoke, we conducted a systematic interview of 846 postpartum mothers of babies admitted to our Well Baby Nursery from December 1, 2004 to June 30, 2005. Resident physician interviewed the mothers in a private room and at the end of the interview counseled them regarding the effects of active and passive smoking.

Conclusions: The overall prevalence of cigarette smoking during pregnancy among our study population was 12.6%, which is much higher than the reported prevalence of 11.4% for all racial groups in the United States (CDC 2002 data). We also found a higher prevalence between Hispanics 110/616 (16.3% vs. 2.5% nationally) and Blacks 25/210 (11.9% vs. 8.5% nationally). We obtained higher prevalence rates because the mothers were more forthcoming with information to the pediatricians. Although many mothers were aware of the hazards of smoking and of passive smoke exposure during pregnancy, many of them continued their smoking habits.

Introduction

Tobacco use in the form of cigarette smoking, once considered as a symbol of social status, is now associated with a wide variety of public health issues. It is one of the leading causes of morbidity and mortality in infants, adolescents and adults including pregnant women. In the United States, as much as 30% of women smoke and many of them do so even when they are pregnant. Smoking during pregnancy costs the US over $350 million annually for neonatal care and results in additional indirect costs due to infant lives lost.[1,2]

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According to the 2002 CDC data, the prevalence of active smoking among women has declined from 18.4% in 1990 to 11.4% in 2002.[3] This decline was reported in all racial and ethnic populations, with the lowest prevalence among Asians (2.3%), followed by Hispanics (2.5%), Blacks (8.5%) and Whites (14.5%). However, the Healthy People 2010 goal is to reduce the prevalence of smoking to 12% in adults and to ≤2% in pregnant women.[4] To reach this goal, an accurate assessment of the prevalence of smoking during pregnancy is necessary in order to determine the success of any public health initiatives to reduce the problem.

Lincoln Medical & Mental Health Center in New York City is an inner-city hospital in the South Bronx that provides medical care to a patient population that is largely of low socio-economic status. Based on the hospital's 2004 birth certificate data, the prevalence of smoking during pregnancy was reported to be about 2.5%. However, our interaction with the mothers during the postpartum period indicated that the actual prevalence could be much higher. We believe that many mothers do not readily volunteer smoking-related information to non-medical personnel when they are casually questioned about their smoking habits. Therefore, we decided to conduct a study using a systematic interview conducted by health care providers to assess the prevalence of smoking and passive exposure to cigarette smoke among postpartum mothers in our hospital.

Materials and Methods

The mothers were interviewed individually on the day of their babies' discharge from the hospital by the study authors (LV and RS). To ensure privacy and confidentiality, the interviews were conducted in each mother's private postpartum room. Using a questionnaire, specific information was obtained about the mother's smoking habits and passive exposure to cigarette smoke before and during pregnancy. The study included all mothers (n = 846) of infants who were discharged from the Well Baby Nursery from December 1, 2004 to June 30, 2005. At the end of the interview, each mother was counseled on the effects of active smoking and exposure to passive smoke on the baby. If the mother was a smoker, she was encouraged to quit smoking

Table 1. Study Period – December 1, 2004 to June 30, 2005

Mothers	Number	Percentage
Interviewed	846	
Active smokers	140/846	16.5%
Passive smokers	37(P)/846 44(P+A)/846	4.4% 5.2%
Stopped smoking before this pregnancy	33/140	23.6%
Continued smoking after knowing of pregnancy	107/140	76.4%
Stopped smoking during this pregnancy 1st trimester 2nd trimester 3rd trimester – tried stopping but continued	70/107 50/107 20/107 7/107	65.4% 46.7% 18.7% 6.5%
Continued throughout pregnancy	37/107	34.6%
Ethnic Groups Total No. of Hispanics Smokers Total No. of Blacks Smokers Total No. of non-Hispanics/non-Blacks Smokers	 616/846 110/616 210/846 25/210 20/846 5/20	 72.8% 16.3% 24.8% 11.9% 2.4% 25.0%
Age <19 yrs 19-30 yrs >30 yrs	 13 105 22	 9.3% 75.0% 16.0%
No. of cigarettes smoked per day 0 - 5 6 -10 >10	 79 32 29	 56.4 % 23.0% 21.0%

*P- Passive smokers
*A- Active smokers

and to participate in a smoking cessation program.

Results

In our study, 140 of 846 women were active smokers, resulting in an overall prevalence of active smoking among women of 16.5%, among which 12.6% had smoked during pregnancy. It is higher than that reported by the CDC 2002 data (11.4%).[5] Of this group 33/140 (23.6%) stopped smoking before this pregnancy. 107/140 (76.4%) continued to smoke after finding out that they were pregnant. 70/107 (65.4%) women who actively smoked at the beginning of their pregnancy gradually cut down on their smoking and eventually stopped during the first or second trimester. Seven of these women, however, were unable to stop completely or resumed their smoking habits during the third trimester. 37/107 (34.6%) continued smoking cigarettes throughout their pregnancy. Thus, in this study the overall prevalence of cigarette smoking during pregnancy was 12.6% (107/846), which is higher than what the hospital had reported based on its 2004 birth certificate data (2.5%).

Comparing racial groups, the majority of our subjects were Hispanic (73%) with a smoking prevalence of 16.3% (higher than the reported prevalence of 2.5%). We also found a higher smoking prevalence of 11.9% among Black mothers compared to what has been reported (8.5%), although Blacks comprised only 24.8% of our study subjects. In addition to active smokers, the exposure to passive cigarette smoke occurred in 4.4% of the non-smoking group and in 5.2% of the active smokers group in the household. The results are summarized in Table 1.

Discussion

Active smoking and passive exposure to cigarette smoke during pregnancy and beyond can cause a wide range of harmful effects on the growing fetus and child. Cigarette smoke contains several hundred components. Of these, nicotine and carbon monoxide appear to have the most significant effects on a developing fetus. Nicotine is vasoconstrictive; it constricts the utero-placental arteries, thereby reducing blood flow to the fetus. Carbon monoxide reduces the delivery of oxygen to fetal tissues. The reduction in blood flow to the fetus and the concomitant oxygen deprivation can affect fetal development, resulting in low birth weight and other adverse fetal, neonatal and post-neonatal outcomes (Table 2).[6,7]

In 2001, 11.9% of babies born to smokers in the U.S. were low birth weight compared to 7.3% of babies born to non-smokers. Smoking during pregnancy nearly doubles the risk of IUGR by lowering the birth weight by as much as 200 grams. Low birth weight babies weighing less than 5 pounds face an increased risk of health problems including an increased risk of SIDS, chronic disabilities (such as cerebral palsy, mental retardation and learning problems), and even death. Pregnant women who do not smoke should avoid exposure to passive smoking. Studies suggest that exposure to secondhand smoke may reduce

Table 2. Effects of smoking on fetus and neonate

Fetal Effects	Neonatal Effects
Abortion	LBW
Still birth	Prematurity
SGA	Nicotine withdrawal
Placental insufficiency	Abdominal colic
Abnormal fetal development	Club feet
Optic nerve hypoplasia	Lower IQ
Fewer brain cells	ADHD
	Hyperkinetic disorder
	Asthma
	Middle ear infection
	Behavioral problems
	SIDS

the fetal growth and increase a women's chances of having a low birth weight baby.[7]

The prevalence of active smoking among women in our study population is significantly higher than the national average reported by the CDC in 2003. The prevalence of active smoking among pregnant women in our study population is also higher than our hospital's official report based on its 2004 birth certificate data and the NYC data. We obtained higher prevalence rates because the mothers were more forthcoming with information to the pediatricians.

There are several factors that are associated with smoking habits during pregnancy. Major factors include starting to smoke at a younger age, younger age at pregnancy, having a spouse or partner who smokes, lower level of education, lower income, and stress. Although many mothers were aware of the hazards of smoking and of passive smoke exposure during pregnancy, many of them continued their smoking habits even after knowing that they were pregnant. Early education in the prenatal period by the maternal health care providers and postpartum counseling by the pediatrician along with public health initiatives may have a greater impact in motivating mothers to quit smoking and to avoid exposing their infants to passive smoke, thereby reducing the morbidities associated with cigarette smoking.[8]

References

1 DiFranza JR, Lew RA. Effect of maternal cigarette smoking on pregnancy complications and sudden infant death syndrome. J Fam Pract 1995; 40(4): 385–94.

2 Adams EK, Miller VP, Ernst C, Nishimura BK, Melvin CL, Merritt R. Neonatal health care costs related to smoking during pregnancy. Health Econ 2002; 11(3): 193–206.

3 Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births: final data for 2002. Nat'l Vital Stat Rep. 2003; 52:1-113.

4 U.S. Department of Health and Human Services. Healthy People 2010. Washington, DC: USDHHS;

5 MMWR weekly 2004; Oct 53(39); 911-15.

6 Ananth CV, Savitz DA, Luther ER. Maternal cigarette smoking as a risk factor for placental abruption, placenta previa, and uterine bleeding in pregnancy. Am J Epidemiol. 1996 Nov 1; 144(9): 881-9.

7 Ventura SJ, Hamilton BE, Mathews TJ, Chandra A. Trends and variations in smoking during pregnancy and low birth weight: evidence from the birth certificate, 1990—2000. Pediatrics 2003; 111:1176-80.

8 Lorrain V. Klerman, and Judith P Rooks. A simple, effective method that midwives use to help women stop smoking. J Nurse Midwifery. 1999 Mar-Apr;44(2):118-23.

The Continuing Development of Neonatal and Pediatric Ventilation Therapies

The very first pediatric intensive care unit in Germany was established at the Children's Hospital of The Johannes Gutenberg University in Mainz in 1965. Ever since that milestone, the center has been involved in great advances in neonatal and pediatric research and patient treatments, which has led to rapid expansion and the establishment of the current interdisciplinary pediatric intensive care facilities. The institution recently celebrated its 40th anniversary by means of a two-day symposium with international experts. Critical Care News met with some of the staff members of this remarkable ICU, including Ralf G. Huth, Director of Pediatric Intensive Care.

Can you tell us about your 40th anniversary celebrations?
Ralf Huth: The background story is quite simple: in 1965, the Director of Pediatrics had a job offer at the University Hospital in Frankfurt, and in the negotiating period, he established an emergency department here. This building was only intended as a provisional solution for five to ten years, but it grew and became well established over the years. This was the first pediatric intensive care unit in Germany, and the fifth in Europe. Our recent anniversary symposium was not only a celebration, but also an overview of what pediatric intensive care is all about, from disease and therapeutic perspectives. We reviewed not only disease situations but also the therapy options we have today, compared to the past and with a view to the future.

What has been your experience of ventilation therapy, in regard to past history as well as your future requirements?
If we review our own experiences in mechanical ventilation, we always used as a standard ventilator the old SERVO 900 device. But the problems with weaning meant that ventilation with infants was not that easy with this device. We were looking for another device. At that time there were only the old Draeger Babylog devices available. We then tested other ventilators; such as the Infant Star, the Engström ventilator and the Sechrist. We decided to go with the Infant Star, which in those days had the combination of flow-interrupted neonatal ventilation with the possibility of High Frequency Oscillation (High Frequency Flow Interruption HFFI). We had four devices aboard for neonates, and for older children we had Servo Ventilator 900 C.

This worked well in the early days. But when we moved to this new facility, we needed to redesign and that was the time that the Servo 900 C was getting older, and the Servo Ventilator 300 came on the market, so we would have a combination of treating even neonatal patients with the Servo Ventilator 300. The issue of weaning was important, especially when we started with pediatric cardiac surgery here in 1985. At that time it was necessary in controlled ventilation to start up with the Servo 900 C, and when it was time for spontaneous ventilation we would switch to a neonatal ventilator. The subject was almost solved with the Servo Ventilator 300 as a very good device covering a large range of patients.

Non-invasive ventilation was not regularly in use at that time. We were the first center in Germany to try out HFO with the Sensormedics 3100A. Oscillation came from neonates, as well as high frequency jet ventilation. It was transferred to Europe, and increasingly used in neonatal and pediatric ventilation, but never connected with the adult patient population. As there was some interest in our anesthesia department, I tried to show the benefits of oscillating flow. At that time, we had a sophisticated system that provided nitric oxide in combination with HFO. In the adult departments, we came to help out with our equipment for the especially difficult cases, like the ARDS patients. I had an opportunity to take part in one of the first scientific and education symposia on HFO, and convinced some of my colleagues in the adult department to come with me. In a workshop with lung lavage model in a big pig, HFO was initiated and you could see improvement and we almost understood how HFO could work. Normally technology comes from the adult sector to the pediatric, but in this case it was the other way around.

Dr. Ralf G. Huth, Director of Pediatric Intensive Care.

After this experience, we were then focusing on the neonatal and pediatric noninvasive ventilatory care. We found one device that was ready to do this at that time, the Hamilton Gallileo that offered noninvasive ventilation and also automated ventilation or adaptive support ventilation (ASV) for bigger children, for weaning after operations for instance. A little later, we started looking at SERVO-i since this device offers the possibility of noninvasive therapy in addition to controlled ventilation, even in the neonatal age group. Different ventilation treatments for all age groups combined in one device was the goal. Currently we have a problem with too many models for different therapies. We need to define how to reduce to fewer devices, but providing the same treatment performance.

How large are the children's intensive care units, and how many staff members do you have to run them?
We have up to 150 patients in the pediatric department, including 10 pediatric ICU beds, 10 neonatal beds and up to eight intermediate care beds, all arranged on the same floor, in two wings. For nursing staff, we have 33 regular full time positions which means 44 people including part time staff. Many of our pediatric ICU nursing staff have longstanding experience. We have very high standards in terms of professional intensive care nursing education. Over 90% have not only pediatric specialty, but also pediatric ICU nursing certifications. So this is a very special background, which contributes to a true team effort together with the physicians.

In regard to the number of physicians here, we share the facilities between neonatology and pediatric intensive care, and all together we have 18 fulltime physicians, including consultants. Some of the consultants working in cardiology and neonatology also have duty during the night shifts here, which comprises a total of 22 people. We have a focus on pediatric intensive care, especially the surgical cases, and a focus in neonatology on the perinatal problems. Our patient occupancy is rougly 90% with a changing turnover of nearly 500 a year.

What types of patients do you most frequently encounter?
Dr Jan-Helge Höpner, pediatric intensive care physician: Our main focus is on pediatric post-cardiac surgery, or post-neurosurgery. We do have general surgical cases, and everything that comes otherwise: infections, oncology patient with ALI or ARDS, trauma patients (fortunately decreasing rates over the past years), orthopedic surgery, urological surgery, oro-facial deformities, and other birth defects. We have a separate burn unit for two patients.

How long have you been doing nasal CPAP therapy here?
Ralf Huth: Since the introduction of this therapy, Nasal CPAP therapy had a big impact on controlled ventilation with all the complications. We were among the first to introduce transcutaneous CO_2 measurements and transcutaneous O_2 measurements. Being early involved with nasal CPAP therapy, we then gathered additional information by noninvasive monitoring to know when to reduce invasive ventilation therapy and change to noninvasive ventilation. Previously, we were flying blind. I can remember in the past how we did blood gas analysis. I started at bed number one, finished at bed number ten and went back to bed number one again. What has changed from that time is the add-on information from noninvasive monitoring; like saturation monitoring and CO_2 monitoring. This gives us a sense of security when it's possible to reduce invasive ventilation therapy and go over to noninvasive support.

Based on your experiences, when is nasal CPAP therapy best indicated? Which types of patients and which types of situations?
I think the question is rather when do you indicate invasive ventilation? Ventilatory support is something that is needed if you have an additional oxygen requirement, if you have exertion and exhaustion. In the early years, we would say, "this child needs ventilatory support," which automatically implied invasive ventilation. We were not secure about interfaces: masks, nasal prongs and the like. Gradually we got experience and saw that it could work. By introducing PEEP and opening the lung, we could also give these children support that was feasible by noninvasive measures, with less oxygen requirement, fewer ventilatory problems, and less exertion.

So is noninvasive ventilation therapy generally always preferred over invasive therapy?
Yes, generally, we go for noninvasive when we can, and if this doesn't work, we apply invasive therapy. In some cases, such as post-op patients, they are intubated anyway and need invasive therapy to start out with. But in other cases we want to avoid invasive ventilation when possible; for example, oncology patients, patients with chronic respiratory problems needing support due to oxygen requirement and CO_2 retention.

In light of some of your experiences with nasal CPAP, is there an advantage of being able to provide nasal CPAP and invasive ventilation therapy with the same equipment?
Yes – right now we have too many devices, and the storage rooms are too small. Offering combined therapies with the same ventilator is an advantage.

Susanne Frey, pediatric intensive care nurse: When there is a new patient coming, we have to decide which ventilator to use. If you have too many devices, you almost have to decide before you see the patient, which is difficult because we need to know if they will need noninvasive or invasive ventilation. If you have too many machines, it is difficult and time-consuming. Now we see the chance of choosing one device and doing pretty much everything with it. In Mainz we are looking for everything in one unit, from the newborns to the ninety kilo children, for the

Susanne Frey, pediatric intensive enteral nutrition and pneumonia. care nurse.

noninvasive and the invasive support.

Dr Höpner: It's an advantage to have a unit mounted behind the bed, with the interface at the head of the bed. You can start with noninvasive and go to invasive if needed, or scale down from invasive to noninvasive without having to move the whole unit.

How many different ventilators have you had in inventory, and as a nurse what are the challenges in training on these different devices?
Susanne Frey: Plenty of models: the Infant Star, the Servo Ventilator 300, the Hamilton Galileo Gold, the SensorMedics 3100 A and B with HFO, the Breas transport ventilator LTV 1000 and a CPAP device Vital Flow. This is a problem because if you get new staff members you have to teach them all different devices. Each model functions a little different, in terms of modes, and user interface. It is a challenge for the nursing staff. And each device model has special tubing, which requires training and logistical management as well.

Dr Höpner: It is also a challenge for the doctors. We need to decide which therapies the nurses should monitor. The other thing is that we physicians have to rotate between the different wards as well, which means that it is easier if there is some standardization – not only within the unit, but in our neighboring units too.

Ralf Huth: The difference between the devices is a problem, which we are trying to overcome by finding one device that suits all. There are not only the technical aspects, but also how the user interfaces for these devices are designed for easy understanding and operating.

What are your experiences of combined invasive ventilation and nasal CPAP in the same ventilator? Can you share some of your patient experiences?
Susanne Frey: We have treated neonatal patients with ALI or respiratory distress using nasal CPAP and we have treated pediatric patients with muscular disease. We have treated post-op surgical patients with atelectasis, which have started out on invasive ventilation, before we have switched them over to nasal CPAP, as well as oncology patients with pneumonia. Different types of noninvasive therapy have been provided depending on the situation. For instance, in some cases we only needed CPAP to maintain PEEP. In another situation, we needed pressure support too. There is much that can be done with noninvasive therapies, and we have different patient interfaces available: nasal prongs, nasal masks and full-face masks.

PICU nurse Connie Zander and volunteer Frau Diehl, with a 5 month old heart failure patient, treated with nasal CPAP therapy.

Dr Huth and Susanne Frey with a patient soon to be discharged. The baby was born a metabolic birth defect requiring enteral nutrition and pneumonia.

What are the most important practical aspects for nasal CPAP therapy? Is it early application, fixation, or the fitting of the patient interface?
Susanne Frey: The system should be easy to use. The patient interface should fit the patient comfortably but avoid leakage as much as possible. We used a helmet in one girl with chronic myelogic leukemia, who in the course of chemotherapy had leucopenia and ALI/ARDS due to pneumonia with PEEP up to 15cm/ H_2O. Initially she had an oxygen requirement of up to 100%, recovering under NIV. Oxygen was reduced to 30%. The noninvasive therapy with the helmet worked quite well in the acute situation.

Do you have a preference for the types of patient interfaces you are using with nasal CPAP?
Connie Zander, pediatric intensive care nurse: For the small patients (up to 5-6 kg), we use the prongs, which work very well in combination with the pacifier, which manages leakage nicely. For the larger children (bigger than 6 kg), we prefer to use a nasal mask, and in some cases a full-face mask is needed, depending upon the individual facial morphology. Or in cases where they are not fully awake and can keep their mouths closed, we use a full-face mask. We have used the Fisher Paykel nasal CPAP interfaces, and they worked very well since you have different sizes to fit the actual patient, no problems with long or short nostrils.

Susanne Frey: We did have one tricky interface problem with a patient on the SERVO-i. She had been intubated for a very long period, and after extubation, we saw a big difference in the size of the nostrils. This was one specific case that was a little tricky to manage, but we did it.

Ralf Huth: It may not be a matter of which of the interfaces to use, but whether we have the right interface for this new kind of ventilatory support? I would say that a center might want to re-investigate which types of interfaces they are using, since this new combined device for invasive and noninvasive therapy probably gives you some new necessities and possibilities.

I think that we are not yet at the end of discussions on how the patient interfaces between ventilators and children are designed. But hopefully we will see continued interface development. Having a new ventilator on the market, providing different kinds of support, from invasive to noninvasive therapy and back again, may challenge development of interfaces with quality and ease of use, alarm management and patient comfort in terms of application for neonates and small children.

Dr Höpner: I think patient comfort is a very important issue

equal to the ease of use. If it is easy to start up a device, but you need to go back and readjust it every half hour because the patient is awake and moving, you have really gained nothing.

How long have you had the latest combined ventilator for invasive and nasal CPAP therapy?

Ralf Huth: For about six months, in the recent version which we have been evaluating. We have just decided to purchase these units, which we consider an investment into the future. In my point of view, the development of SERVO-i was a straight line in development from the Servo Ventilator 300. It offered the same type of ventilation opportunities, but it was not a re-introduction of ventilation concepts; rather you could see a natural continuation in development. It was significant to us that SERVO-i included the combination of PRVC with SIMV, so that you have the possibility of this mode, which was not available before. This was something we were really looking for. I think the user interface was straightforward, with the easy access knobs to the most interesting parameters. The calibration of the O_2 cell facilitated ease of use. So I think that the development was going in the right direction, and it was very easy to introduce this device after long experience with Servo Ventilator 300, compared to other devices we had been testing before. It was a logical continuation of development, which eased the acceptance of introducing SERVO-i into the ward, compared to other models.

We have one infant patient here who has been extubated after an operation, he was treated with SERVO-i for a long time. He has spinal muscular atrophy with pneumonia, which needed long time support. I think without the SERVO-i we would have had to switch to intubate him. But we were able to easily switch from nasal CPAP to noninvasive ventilation. So we were able to keep him totally on noninvasive support, which is unimaginable with any other device we have had so far.

References

1 Schranz D, Huth RG, Stopfkuchen H, Jungst BK The effect of nifedipine alone or combined with low dose acetylsalicilic acid on endotoxin-induced pulmonary hypertension in the piglet. Intensive Care Med 1988; 14(6): 595-601.

2 Trubel HK, Meyer HG, Jahn B, Knuf M, Kamin W, Huth RG. Complicated noscomial pneumonia due to legionella pneumophilia in an immunocompromised child. Scand J Infect Dis 2002; 34(3):219-221.

3 Wippermann CF, Huth RG, Schimidt FX, Thul J, Bentacor M, Schranz D. Continuous measurement of cardiac output by the Fick principle in infants and children: comparison with the thermodilution method. Intensive Care Med 1996; 22(5):467-471.

4 Wippermann CF, Schranz D, Huth RG. Evaluation of the pulse wave arrival time as a marker for blood pressure changes in critically ill infants and children. J. Clin Monit 1995; 11(5): 324-328

5 Wippermann C.-F., Schmid, F.X., Eberle, B., Huth R., Kampmann, Ch., Schranz, D., Oelert, H.: Reduced Inotropic Support after Aprotinin Therapy during Pediatric Cardiac Operations. (Ann Thorac Surg 1999, 67: 173-176.

6 Bott J, Carroll MP, Coway JH, Keilty EJ, Ward EM, Brown Am. Randomized controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 1993; 341: 1555-1558.

7 Antonelli M, Conti G, Noninvasive ventilation in intensive care unit patients. Curr Opin Crit Care 2000; 6: 11-16.

8 Brochard L, Harf A, Lorino H, Lemaire F, Inspiratory pressure support during weaning from mechanical ventilation. Am Rev Respir Dis 1989; 139: 513-521

9 Heulitt MJ, Sanders RC, Holt SJ, Rhodes SM, Thurman TL. Comparison of total work of breathing during CPAP between two neonatal ventilators in a neonatal animal model. Pediatric Critical Medicine 2000; 1(2): 170-175.

10 Heulitt MJ, Holt SJ, Thurman TL, Wilson SW. Effects of continuous positive airway pressure/positive end expiratory pressure and pressure support ventilation on work of breathing utilizing an animal mode. Respir Care 2003; 48(7): 689-696.

11 Baum, V., Schranz, D., Huth, R., Zimmer, B.,Wippermann, C.-F.: The Use of Norepinephrine as Supportive Therapy in Potential ECMO Candidates. Clinical Intensive Care 1991, 2: 325-330

12 Schranz, D., Huth, R., Michel-Behnke, I., Wippermann, C.-F.: Norepinephrine, Enoximone and Nitric Oxide for Treatment of Myocardial Stunning and Pulmonary Hypertension in a Newborn with Diaphragmatic Hernia. J Pediatric Surg 1995, 6: 801-804.

13 Schranz, D., Huth, R., Michel-Behnke, I., Wippermann, C.-F., Ritzerfield, S., Schmid, F.X., Oelert, H.: Nitrict Oxide and Prostacyclin Lower Suprasystemic Pulmonary Hypertension after Cardiopulmonary bypass. Eur J Pediatr 1993, 152: 793-796.

14 Schranz, D., Zepp, F., Iversen, S., Wippermann, C.-F., Huth, R., Zimmer, B., Jungst, B. –K., Oelert, H.: Effects of Tolazoline and Prostacyclin on Pulmonary and Systemic Hemody-namics after Surgery in Infants with Congenital Heart and Disease and Pulmonary Hypertension. Critical Care Medicine 1992, 20: 1243-49

15 Wippermann, C.-F., Schranz, D., Baum, V., Huth, R., Gehb, C.: Independent Right Lung High Frequency and Left Lung Conventional Ventilation in the Management of Severe Airleak during ARDS. Pediatric Anesthesia 1995, 5:189-192

16 M. Neukirch, B. Schmidt, S. Sonnenberger, M. Knuf, R. Huth, Nicht-invasive Beatmung bei Kindern und Jugendrlichen aug einer interdisziplinären pädiatrischen Intensivstation, Intensivmedizin und Notfallmedizin, Volume 41, Issue 3, Apr 2004, Pages 163-170

17 Bindl L, Buderus S, Dahlem P, Demirakca S, Goldner M, Huth R, Kohl M, Krause M, Kuhl P, Lasch P, Lewandowski K, Merz U, Moeller J, Mohamad Y, Peters M, Porz W, Vierzig A, Ruchard J, Scharf J, Varnholt V; ESPNIC ARDS Database Group. Gender-based differences in children with sepsis and ARDS: the ESPNIC ARDS Database Group. Intensive Care Med. 2003 Oct;29(10):1770-3. Epub 2003 Aug 15.

Assessing the Quality of Research

Paul Glasziou, Jan Vandenbroucke, Iain Chalmers

Inflexible use of evidence hierarchies confuses practitioners and irritates researchers. So how can we improve the way we assess research? The widespread use of hierarchies of evidence that grade research studies according to their quality has helped to raise awareness that some forms of evidence are more trustworthy than others. This is clearly desirable. However, the simplifications involved in creating and applying hierarchies have also led to misconceptions and abuses. In particular, criteria designed to guide inferences about the main effects of treatment have been uncritically applied to questions about etiology, diagnosis, prognosis, or adverse effects. So should we assess evidence the way Michelin guides assess hotels and restaurants? We believe five issues should be considered in any revision or alternative approach to helping practitioners to find reliable answers to important clinical questions.

Different types of questions require different types of evidence

Ever since two American social scientists introduced the concept in the early 1960s, hierarchies have been used almost exclusively to determine the effects of interventions. This initial focus was appropriate but has also engendered confusion. Although interventions are central to clinical decision-making, practice relies on answers to a wide variety of types of clinical questions, not just the effect of interventions. Other hierarchies might be necessary to answer questions about etiology, diagnosis, disease frequency, prognosis, and adverse effects. Thus, although a systematic review of randomized trials would be appropriate for answering questions about the main effects of a treatment, it would be ludicrous to attempt to use it to ascertain the relative accuracy of computerized versus human reading of cervical smears, the natural course of prion diseases in humans, the effect of carriership of a mutation on the risk of venous thrombosis, or the rate of vaginal adenocarcinoma in the daughters of pregnant women given diethylstilbesterol.

To answer their everyday questions, practitioners need to understand the "indications and contraindications" for different types of research evidence. Randomized trials can give good estimates of treatment effects but poor estimates of overall prognosis; comprehensive non-randomized inception cohort studies with prolonged follow up, however, might provide the reverse.

Systematic Reviews

Systematic reviews of research are always preferred. With rare exceptions, no study, whatever the type, should be interpreted in isolation. Systematic reviews are required of the best available type of study for answering the clinical question posed. A systematic review does not necessarily involve quantitative pooling in a meta-analysis.

Although case reports are a less than perfect source of evidence, they are important in alerting us to potential rare harms or benefits of an effective treatment. Standardized reporting is certainly needed, but too few people know about a study showing that more than half of suspected adverse drug reactions were confirmed by subsequent, more detailed research. For reliable evidence on rare harms, therefore, we need a systematic review of case reports rather than a haphazard selection of them. Qualitative studies can also be incorporated in reviews—for example, the systematic compilation of the reasons for non-compliance with hip protectors derived from qualitative research.

Grading Evidence

Level alone should not be used to grade evidence. The first substantial use of a hierarchy of evidence to grade health research was by the Canadian Task Force on the Preventive Health Examination. Although such systems are preferable to ignoring research evidence or failing to provide justification for selecting particular research reports to support

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	Short term outcomes	Long term outcomes
Benefits		
Contraception	☺Effective (2 controlled trials[w1 w2])	Return to normal fertility soon after cessation (nested case-control and cohort studies[w3])
Dysmenorrhoea	☺Possible reduction in pain and work absence (systematic review of 5 poor quality RCTs[w4])	Not applicable
Harms		
Breast cancer	☹Increased risk: relative risk 1.24 (95% CI 1.15 to 1.33) for current users (individual patient data analysis of 54 observational studies[w5])	No increased risk detected 10 years after cessation (systematic review of 45 observational studies[w5])
Venous thromboembolism	☹Increased risk: 2.5-fold to 6-fold increase in relative risk (systematic review of 5 non-randomised studies) and relative risk 1.1 (0.4 to 2.9 in one RCT with 9898 participants[w6])	Return to background risk after cessation[w6 w7]
Minimal or uncertain effects		
Weight gain	☺No weight gain (3 placebo controlled RCTs of 4-9 months[w8])	Unknown
Heavy menstrual bleeding	☺Insufficient evidence (one, 3 armed RCT with 43 participants[w9])	Not applicable

Example of possible evidence table for short and long term effects of oral contraceptives. (Absolute effects will vary with age and other risk factors such as smoking and blood pressure. RCT = randomised controlled trial)

recommendations, they have three big disadvantages. Firstly, the definitions of the levels vary within hierarchies so that level 2 will mean different things to different readers. Secondly, novel or hybrid research designs are not accommodated in these hierarchies—for example, reanalysis of individual data from several studies or case crossover studies within cohorts. Thirdly, and perhaps most importantly, hierarchies can lead to anomalous rankings. For example, a statement about one intervention may be graded level 1 on the basis of a systematic review of a few, small, poor quality randomized trials, whereas a statement about an alternative intervention may be graded level 2 on the basis of one large, well conducted, multicenter, randomized trial.

This ranking problem arises because of the objective of collapsing the multiple dimensions of quality (design, conduct, size, relevance, etc) into a single grade. For example, randomization is a key methodological feature in research into interventions, but reducing the quality of evidence to a single level reflecting proper randomization ignores other important dimensions of randomized clinical trials. These might include:

- Other design elements, such as the validity of measurements and blinding of outcome assessments
- Quality of the conduct of the study, such as loss to follow up and success of blinding
- Absolute and relative size of any effects seen
- Confidence intervals around the point estimates of effects.

None of the current hierarchies of evidence includes all these dimensions, and recent methodological research suggests that it may be difficult for them to do so. Moreover, some dimensions are more important for some clinical problems and outcomes than for others, which necessitates a tailored approach to appraising evidence. Thus, for important recommendations, it may be preferable to present a brief summary of the central evidence (such as "double-blind randomized controlled trials with a high degree of follow up over three years showed that..."), coupled with a brief appraisal of why particular quality dimensions are important. This broader approach to the assessment of evidence applies not only to randomized trials but also to observational studies. In the final recommendations, there will also be a role for other types of scientific evidence—for example, on etiological and pathophysiological mechanisms—because concordance between theoretical models and the results of empirical investigations will increase confidence in the causal inferences.

Unavailable Reviews

What does one do when systematic reviews are not available? Although hierarchies can be misleading as a grading system, they can help practitioners find the best relevant evidence among a plethora of studies of diverse quality. For example, to answer a therapeutic question, the hierarchy would suggest first looking for a systematic review of randomized controlled trials. However, only a fraction of the hundreds of thousands of reports of randomized trials have been considered for possible inclusion in systematic reviews. So when there is no existing review, a busy clinician might next try to identify the best of several randomized trials. If the search fails to identify any randomized trials, non-randomized cohort studies might be informative. For non-therapeutic questions, however, search strategies should accommodate the need for observational designs that answer questions about etiology, prognosis, or adverse effects. Whatever evidence is found, this should be clearly described rather than simply assigned to a level. Such considerations have led the authors of the BMJ's Clinical Evidence to use a hierarchy for finding evidence but to forgo grading evidence into levels. Instead, they make explicit the type of evidence on which their conclusions are based.

Varieties of Research

Balanced assessments should draw on a variety of types of research. For interventions, the best available evidence for each outcome of potential importance to patients is needed. Often this will require systematic reviews of several different types of study. As an example, consider a woman interested in oral contraceptives. Evidence is available from controlled trials showing their contraceptive effectiveness. Although contraception is the main intended beneficial effect, some women will also be interested in the effects of oral contraceptives on acne or dysmenorrhea. These may have been assessed in short term randomized controlled trials comparing different contraceptives. Any beneficial intended effect needs to be weighed against possible harms, such as increases in thromboembolism and breast cancer. The best evidence for such potential harms is likely to come from non-randomized cohort studies or case-control studies. For example, fears about negative consequences on fertility after long term use of oral contraceptives were allayed by such non-randomized studies.

Sometimes, rare, dramatic adverse effects detected with case reports or case control studies prompt further investigation and follow up of existing randomized cohorts to detect related but less severe adverse effects. For example, the case reports and case-control studies showing that intrauterine exposure to diethylstilbestrol could cause vaginal adenocarcinoma led to

Summary points

Different types of research are needed to answer different types of clinical questions

Irrespective of the type of research, systematic reviews are necessary

Adequate grading of quality of evidence goes beyond the categorisation of research design

Risk-benefit assessments should draw on a variety of types of research

Clinicians need efficient search strategies for identifying reliable clinical research

Summary points

Infection with herpes simplex virus type 2 is mostly asymptomatic and cannot be cured

Prevalence by age differs between populations and geographical areas

Serology tests are commercially available with acceptable sensitivity and specificity

Use of the tests to screen low prevalence groups would give high rates of false positive results

Potential biotechnical, medical, epidemiological, psychosocial and ethical advantages and disadvantages must be balanced at both the individual and public health level

Screening cannot currently be ethically justified

further investigation and follow up of the mothers and children (male as well as female) who had participated in the relevant randomized trials. These investigations showed several less serious but more frequent adverse effects of diethylstilbestrol that would have otherwise been difficult to detect.

Conclusions

Given the flaws in evidence hierarchies that we have described, how should we proceed? We suggest that there are two broad options: firstly, to extend, improve, and standardize current evidence hierarchies; and, secondly, to abolish the notion of evidence hierarchies and levels of evidence, and concentrate instead on teaching practitioners general principles of research so that they can use these principles to appraise the quality and relevance of particular studies.

We have been unable to reach a consensus on which of these approaches is likely to serve the current needs of practitioners more effectively. Practitioners who seek immediate answers cannot embark on a systematic review every time a new question arises in their practice. Clinical guidelines are increasingly prepared professionally—for example, by organizations of general practitioners and of specialist physicians or the NHS National Institute for Clinical Excellence—and this work draws on the results of systematic reviews of research evidence. Such organizations might find it useful to reconsider their approach to evidence and broaden the type of problems that they examine, especially when they need to balance risks and benefits. Most importantly, however, the practitioners who use their products should understand the approach used and be able to judge easily whether a review or a guideline has been prepared reliably.

Evidence hierarchies with the randomized trial at the apex have been pivotal in the ascendancy of numerical reasoning in medicine over the past quarter century. Now that this principle is widely appreciated, however, we believe that it is time to broaden the scope by which evidence is assessed, so that the principles of other types of research, addressing questions on etiology, diagnosis, prognosis, and unexpected effects of treatment, will become equally widely understood. Indeed, maybe we do have something to learn from Michelin guides: they have separate grading systems for hotels and restaurants, provide the details of the several quality dimensions behind each star rating, and add a qualitative commentary.

Association of Umbilical Cord Blood Lead with Neonatal Behavior at Varying Levels of Exposure

Archana B. Patel, Manju R. Mamtani, Tushar P. Thakre, Hemant Kulkarni

Abstract

Background: In the light of the ongoing debate about lowering the cut-off for acceptable blood lead level to <5 µg/dL from the currently recommended level of <10 µg/dL, we considered whether prenatal exposure to varying levels of lead is associated with similar or disparate effects on neonatal behavior.

Methods: Using Brazelton's Neonatal Behavioral Assessment Scale (NBAS), an epidemiological approach and robust statistical techniques like multivariate linear regression, logistic regression, Poisson regression and structural equations modeling analyses we estimated the simultaneous indirect effects of umbilical cord blood lead (CBL) levels and other neonatal covariates on the NBAS clusters.

Results: We observed that when analyzed in all study subjects, the CBL levels independently and strongly influenced autonomic stability and abnormal reflexes clusters. However, when the analysis was restricted to neonates with CBL <10 µg/dL, CBL levels strongly influenced the range of state, motor and autonomic stability clusters. Abnormal walking reflex was consistently associated with an increased CBL level irrespective of the cut-off CBL, however, only, at the lower cut-offs were the predominantly behavioral effects of CBL discernible.

Conclusion: Our results further endorse the need to be cognizant of the detrimental effects of blood lead on neonates even at low-dose prenatal exposure.

Background

There is an ongoing debate over the appropriate cut-off of blood lead concentration to detect lead poisoning.[1-6] Starting from 60 µg/dL the cut-off recommended by the Centers for Disease Control (CDC) receded to 25 µg/dL and then to the currently used value of 10 µg/dL.[5] This was essentially due to a series of studies showing that even at low doses of exposure, environmental lead continues to be a biological and social toxicant.[4,5,7,8] Recently, there is a burgeoning recognition that even at low doses exposure to lead has serious implications on a child's behavior pattern. For example, lead exposure in low doses has been convincingly implicated in juvenile delinquency,[9,10] intelligence quotient [IQ] patterns[4,11-18] and crime rates.[19,20] In the light of these findings, Needleman and others recommend that the time has arrived to lower the CDC recommended cut-off for blood lead to 5 µg/dL.[5]

Blood lead has also been considered for a long time to be a behavioral teratogen. Interestingly, however, literature on the putative association of the prenatal blood lead exposure with the behavioral prototypes in the newborns is scant and inconsistent.[2] For example, Ernhart et al,[21] Rothenberg et al[22] and more recently Emory et al[23] could not demonstrate any striking association between umbilical cord blood lead level and neonatal behavior. In contrast, two recent prospective studies have – using the Mental Development Index (MDI) – shown association of low-exposure to lead with neurobehavioral development in early life.[24,25] Additionally, since neonatal behavior is a multi-dimensional construct with several hard-to-measure and correlated domains, the analytical strategy to test the association between blood lead levels and behavioral indicators is not always straightforward.[2,26]

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Table 1: Characteristics of the neonatal study subjects (n = 176)

Maturity in weeks (mean ± S.D)	38.93 ± 3.45
Hours of birth (mean ± S.D)	45.78 ± 15.15
Sex	
Male (n, %)	99 (56.3)
Female (n, %)	77 (43.7)
Birth weight (g, mean ± S.D)	2644.35 ± 413.15
Head circumference (cm, mean ± S.D)	32.47 ± 2.13
Umbilical cord blood lead level (µg/dL, mean ± S.D)	5.15 ± 12.65
Fetal obstetrical problem (n, %)	
Yes	6 (3.4)
No	157 (89.2)
Unknown	13 (7.4)
Specific disorder in fetus/neonate (n, %)	
Yes	17 (9.6)
No	145 (82.4)
Unknown	14 (8.0)
Maternal obstetrical problem (n, %)	
Yes	44 (25.0)
No	119 (67.6)
Unknown	13 (7.6)
Problem noted during labor (n, %)	
Yes	59 (33.5)
No	109 (61.9)
Unknown	8 (4.6)
Use of oxytoxic agents during labor (n, %)	
Yes	44 (25.0)
No	127 (72.2)
Unknown 5 (2.8)	
Rupture of membranes before labor onset (n, %)	
No	135 (76.7)
Less than 24 hours	29 (16.5)
24 to less than 72 hours	5 (2.8)
72 to less than 120 hours	1 (0.6)
More than 120 hours	1 (0.6)
Unknown	5 (2.8)
Maternal medical problem during this pregnancy (n, %)	
Yes	30 (17.1)
No	137 (77.8)
Unknown	9 (5.1)
Tobacco intake by mother (n, %)	
No	164 (93.2)
Yes	8 (4.6)
Unknown	4 (2.2)
Alcohol intake by mother (n, %)	
Yes	3 (1.8)
No	169 (96.0)
Unknown	4 (2.2)
House painted (n, %)	
No or white wash	98 (55.7)
Yes, some	35 (19.9)
Yes, complete	39 (22.2)
Unknown	4 (2.2)
Age of house paint (n, %)	
< 5 years	62 (83.8)
5 – 10 years	7 (9.5)
Unknown	5 (6.7)
NBAS cluster scores (mean ± S.D)	
Habituation	28.91 ± 3.29
Orientation	43.06 ± 8.19
Motor	26.60 ± 3.69
Range of state	16.05 ± 3.83
Regulation of state	18.69 ± 5.38
Autonomic stability	14.12 ± 3.29
Abnormal reflexes	2.37 ± 1.98

We therefore undertook this study to address two research questions: a) Do umbilical cord blood lead (CBL) levels independently correlate with the early neonatal neurobehavioral pattern? b) Do these neurobehavioral associations, if any, continue to be present in neonates with CBL levels below 10 µg/dL? We hypothesized that the behavioral archetypes of neonates are influenced by the level of prenatal exposure to lead even at relatively low doses of exposure. To test this hypothesis, we conducted a cross-sectional study assessing the association between umbilical cord blood lead levels and the neonatal neurobehavioral responses using appropriate measurement scales and statistical models.

Methods

Study subjects

The present cross-sectional study was conducted at the Government Medical College and Hospital, a tertiary care hospital in Nagpur, India. The data were collected over a four-month period starting from January 1998. All consecutively born neonates at the study center whose mother gave an informed consent were included in the study. Overall, 230 children were included. However, blood lead measurements were available on 176 (~77%) of the neonates who compromised our study sample. The study was approved by the Ethical Committee of the Government Medical College, Nagpur, India.

Study variables

Outcomes: We measured the neonatal behavior using Brazelton's Neonatal Behavioral Assessment Scale (NBAS).[27] The scale consists of the 28 behavior-related items scored on a 9-point scale, 18 reflexes and 7 supplementary items. Two trained pediatricians administered the scale. Before the study began, these two investigators independently and together evaluated a separate set of 20 neonates to ensure concordance of observations. The NBAS was administered within three days of birth. Since the arousal state can influence a newborn's performance on the individual items of the NBAS scale,[27] we noted the initial state (the state of the newborn at the beginning of the NBAS evaluation) and predominant state (the state which the newborn was most commonly in over the duration of NBAS assessment and which was recorded at the end of the NBAS evaluation) of the newborn. We converted the raw scores on the NBAS items into the following seven clusters as recommended by Lester et al:[28] habituation, orientation, motor, range of state, regulation of state, autonomic stability and abnormal reflexes. The association of the predictor variables was then assessed with the cluster scores.

Blood lead measurement: Cord blood samples (5 ml) were obtained for each neonate in a metal-free K3 EDTA bulb and analyzed within 48 hours of sample collection for blood lead by flameless atomic absorption spectrophotometry (Hitachi Z-8000) in parts per billion at a wavelength of 283.3 nm with a slit width of 1.3 nm using the method described by Lagesson et al [29]. The detection rate of lead for the instrument was 1 µg/dL, with an average error rate of 5% for reproducibility of results. The samples were analyzed for estimation of the lead concentration within 48 hours of collection.

Covariates: Table 1 describes the characteristics of the study subjects. In multiple linear regression analyses (described below), we used the following covariates: maturity, hours of birth, sex, birth weight, head circumference, fetal and maternal

Table 2: Results of regression analyses for prediction of NBAS cluster scores based on CBL and other covariates† in all neonates (left column) and neonates with CBL levels <10 μg/dL.

NBAS cluster	All Neonates		Neonates with CBL < 10 μg/dL	
	Unadjusted (coefficient, p)	*Adjusted* (coefficient, p)	*Unadjusted* (coefficient, p)	*Adjusted* (coefficient, p)
Habituation	0.0145, 0.468	0.0292, 0.213	-0.0432, 0.812	-0.0057, 0.988
Orientation	0.0092, 0.853	0.0176, 0.753	0.2823, 0.518	1.5972, 0.053
Motor	0.0188, 0.446	0.0108, 0.724	-0.2733, 0.136	0.4154, 0.282
Range of state	-0.0304, 0.196	-0.0419, 0.085	-0.5135, 0.008	-0.1957, 0.548
Regulation of state	0.0030, 0.930	0.0458, 0.336	-0.7138, 0.010	-1.2912, 0.036
Autonomic stability	-0.0567, 0.008	-0.0506, 0.077	-0.1219, 0.462	-0.3156, 0.507
Abnormal reflexes*	0.0118, 6.8×10^{-5}	0.0073, 0.084	-0.0487, 0.163	-0.1049, 0.168

† List of the covariates is provided in the Methods section, Study Variables subsection
* Estimated using Poisson regression analysis

obstetric problems, specific disorder in fetus/newborn, problem noted during labor, use of oxytocic agents, rupture of membranes before onset of labor, tobacco intake by the mother and alcohol intake by the mother. The meaning and description of some of these covariates is provided in details Supplementary Table 1 (see additional file 1, supplementary table 1). The covariates were measured based on the antenatal medical records, labor notes and by interviewing the mothers.

Statistical analysis

Our general strategy for statistical analysis was to test the association between cord blood lead levels and each NBAS cluster score in univariate and multivariate contexts. Since, in theory, the NBAS clusters represent essentially orthogonal i.e. uncorrelated factors, we used the score for each NBAS cluster as an outcome. For estimating the unadjusted influence, we used only CBL level as the predictor. Subsequently in a multiple linear regression model we estimated the adjusted influence of CBL, for each NBAS cluster score by including the covariates mentioned above, the initial and predominant states of arousal (Table 2). It was essential to include both initial and predominant states in the multiple regression models because there two variables were not completely collinear with each other indicating that in a given infant often the initial state was not the same as the predominant state initial state was not the same as the predominant state (Spearman's rho = 0.093, p = 0.1938). Lastly, only for the "abnormal regression" cluster we used single and multiple Poisson regression analyses because the scores for this cluster actually represent the count of the number of abnormal reflexes.

Our next step of analysis was to assess the association of the CBL levels with the NBAS cluster scores in a multivariate context. For this purpose, we first conducted analysis of covariance (ANCOVA) using each NBAS cluster as the outcome and CBL as the predictor – first alone (unadjusted analysis) and then using initial and predominant states as covariates (adjusted analysis). Using the results from these analyses, we tested for the influence of blood lead on multiple outcomes using the Multiple Indicator Multiple Causes (MIMIC) model under the umbrella of Structural Equations Modeling (SEM). Additionally, we used Poisson regression to test the association between blood lead and the number of abnormal reflexes and multiple logistic regression analysis to test the association between various reflexes and dichotomized values of blood lead as described in the succeeding sections. We used State 8.0 (State Corp, College Station, TX) and Amos 5.0 (Amos Development Corp, Spring House, PA) for statistical analyses. Unless specified otherwise, an alpha error rate of 0.05 was used to test statistical significance.

Results

The characteristics of the study subjects are described in Table 1. Only two (1.1%) neonates were premature (<32 weeks), 10 (11.3%) had head circumference less than 30 cm, eight (4.6%) were small (birth weight < 2 kg), three (1.7%) were very small (birth weight < 1.5 kg) and 14 (8.0%) had cord blood lead exceeding 10 μg/dL. In general, therefore our study sample mostly included healthy neonates. This was also reflected by the mean scores for each of the NBAS clusters as shown in Table 1. During the NBAS evaluation, the most common initial states were light sleep (65 neonates, 36.9%), deep sleep (43 neonates, 24.4%) and alertness (35 neonates, 19.9%) while the most common predominant states were alertness (70 neonates, 39.7%), open eyes (49 neonates, 27.8%) and crying (31 neonates, 17.6%).

CBL and NBAS cluster scores

The results shown in Table 2 indicated that when the analyses were conducted in all study subjects, the CBL levels significantly correlated with the autonomic stability and abnormal reflexes clusters even after adjustment for the aforementioned covariates. However, when the same analyses were performed in neonates with CBL levels <10 μg/dL, the unadjusted analyses identified the association of the CBL levels with the range of state and regulation of state clusters but the adjusted model identified the association with orientation and regulation of state clusters. We also considered whether the association of CBL, with each NBAS cluster is specifically influenced by the potential effect of the initial and predominant states of the newborn on the NBAS cluster scores and found, using ANCOVA, that is was not. This first pass analysis through the multiple regression models and ANCOVA thus indicated that i) The CBL levels correlated with specific NBAS clusters; ii) The CBL levels were differentially associated with NBAS clusters in all subjects versus subjects with CBL levels below 10 μg/dL and iii) The association of CBL levels with NBAS clusters varied between the unadjusted and adjusted analyses in neonates with low-dose prenatal lead exposure.

Correlation among NBAS cluster scores

Even though the NBAS clusters are theoretically uncorrelated,

we assessed if the correlations among these clusters were dataset-specific. To consider this possibility and the implications thereof, we first assessed the correlation structure of the seven NBAS clusters in all neonates as well as in neonates with CBL levels below 10 µg/dL (Figure 1). Not surprisingly, we observed that there were a number of statistically significant correlations between pairs of NBAS clusters. Specifically, the habituation, orientation and motor clusters were strongly correlated with each other while the range of state and regulation of state clusters showed a trend towards a significant correlation with each other in all neonates as well as in neonates with CBL levels below 10 µg/dL. Arguably, this correlation structure can alter the interpretations regarding the simultaneous influence of the predictors on the NBAS clusters. Therefore, we chose to conduct further analyses in which we modeled the influence of CBL levels and other covariates simultaneously on the NBAS clusters.

Simultaneous effects of CBL on neonatal behavior: specification of the MIMIC model

To be parsimonious, we wanted to select the most significant NBAS clusters that were least likely to be correlated with each other. For this purpose, using a reverse approach, we first used CBL levels as the outcome and the NBAS cluster scores as the predictors. We conducted stepwise linear regression with a strict retention probability criterion of 0.05. The clusters that were retained in the final model were motor, autonomic stability and abnormal reflexes in all neonates and range of state in neonates with CBL levels below 10 µg/dL. Therefore, we chose these four clusters as outcomes for modeling the simultaneous effects of CBL. This choice of the NBAS clusters was also consistent with the observed correlation structure since habituation and orientation were strongly correlated with the motor cluster while regulation of state was moderately correlated with the range of state.

We then chose four neonate-related predictors which we modeled as the covariates – CBL levels, head circumference, maturity and birth weight. There were three reasons for choosing this set of covariates. First, there exists literature support for a putative association of these covariates with NBAS cluster scores. Second, in a series of stepwise regression models in our dataset, these variables were consistently associated with one or more of the NBAS clusters. Finally, as these variables can be considered to be of a continuous disposition, the correlation matrices to be used in structural equations modeling are more reliable and easier to construct and require no preprocessing of the data.

The path diagram of our model (Figure 2A) thus contained four predictors and four outcomes. In SEM, a model of this nature is referred to as the Mulitple Indication Multiple Cases (MIMIC) model.[28] In the proposed MIMIC model, none of the predictors directly influences any of the outcomes, that is, there exists no direct arrow in the path diagram (Figure 2A) from any predictor to any outcome – they all pass through a conceptual, latent and unmeasured variable. We argue that these four predictors influence a latent (unobserved) trait which we refer to as the "neonatal behavior." In our model, the NBAS clusters were thus considered as indicators of the neonatal behavior.

We modeled the influence of the predictors on neonatal behavior on the four outcomes within the framework of structural equations modeling (SEM). The regression weights (parameters labeled as r_1 to r_7 in Figure 2A) thus measure the influence of the predictors on each outcome in a multivariate context. The random errors of measurement associated with all observed variables – four predictors and four outcomes – were included as shown (parameters labeled as e_1 to e_8 in Figure 2A). Since the measurements of NBAS clusters are correlated, we assume that the measurement errors associated with these variables will also be correlated (shown by the curved arrows in the model and the parameters labeled as c_1 to c_6). Finally, to make the model identifiable we constrained the head circumference à neonatal behavior regression weight to unity.

Results from the MIMIC model

Figure 2B-E shows the results of SEM analyses using the MIMIC model. As the predictor and outcome variables are measured on different metrics, we present the data in the form of standardized estimates of the regression of coefficients (Figure 2B and 2C). We observed that when the analysis was conducted in all neonates, CBL levels and maturity independently influenced neonatal behavior – more mature neonates had a better behavior score. Interestingly, this influence of CBL and maturity was detectable only with respect to autonomic stability and abnormal reflexes – the other two outcomes were not influenced. This analysis thus recaptured the observations from the previous analysis that even in a multivariate and multiple-outcome context the independent influence of CBL on autonomic stability and abnormal reflexes was discernible.

When the analysis was restricted to neonates with CBL levels below 10 µg/dL, we observed a notable shift in the pattern of association. The CBL levels were now the only statistically significant predictor and the influence on the neonatal behavior was limited to the motor, range of state and autonomic stability clusters. Thus, concordant with the earlier results, our results of MIMIC modeling reaffirmed that the dominant effects of CBL were different in all neonates compared to neonates with low-dose exposure to lead.

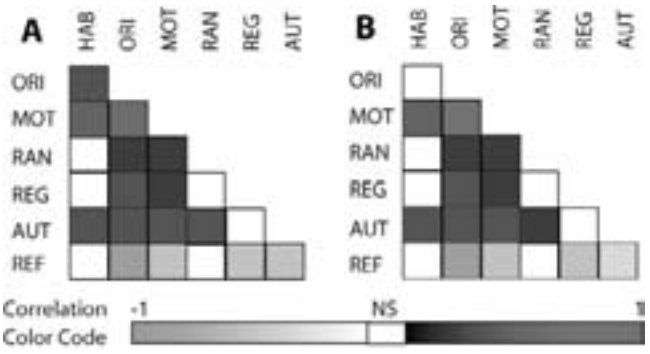

Figure 1
Correlation structure of the NBAS cluster scores in all neonates (A) and neonates with the CBL levels below 10 µg/dL (B). The color codes at the bottom provide a reference for the magnitude and significance of the Pearson correlation coefficients. Open boxes represent statistically non-significant correlation coefficient. The actual estimates of correlation coefficients and their significance values are shown in Supplementary Table 3 (see additional file 1, supplementary table 3). The NBAS clusters shown here are: habituation (HAB), orientation (ORI), motor (MOT), range of state (RAN), regulation of state (REG) and autonomic stability (AUT) and abnormal reflexes (REF).

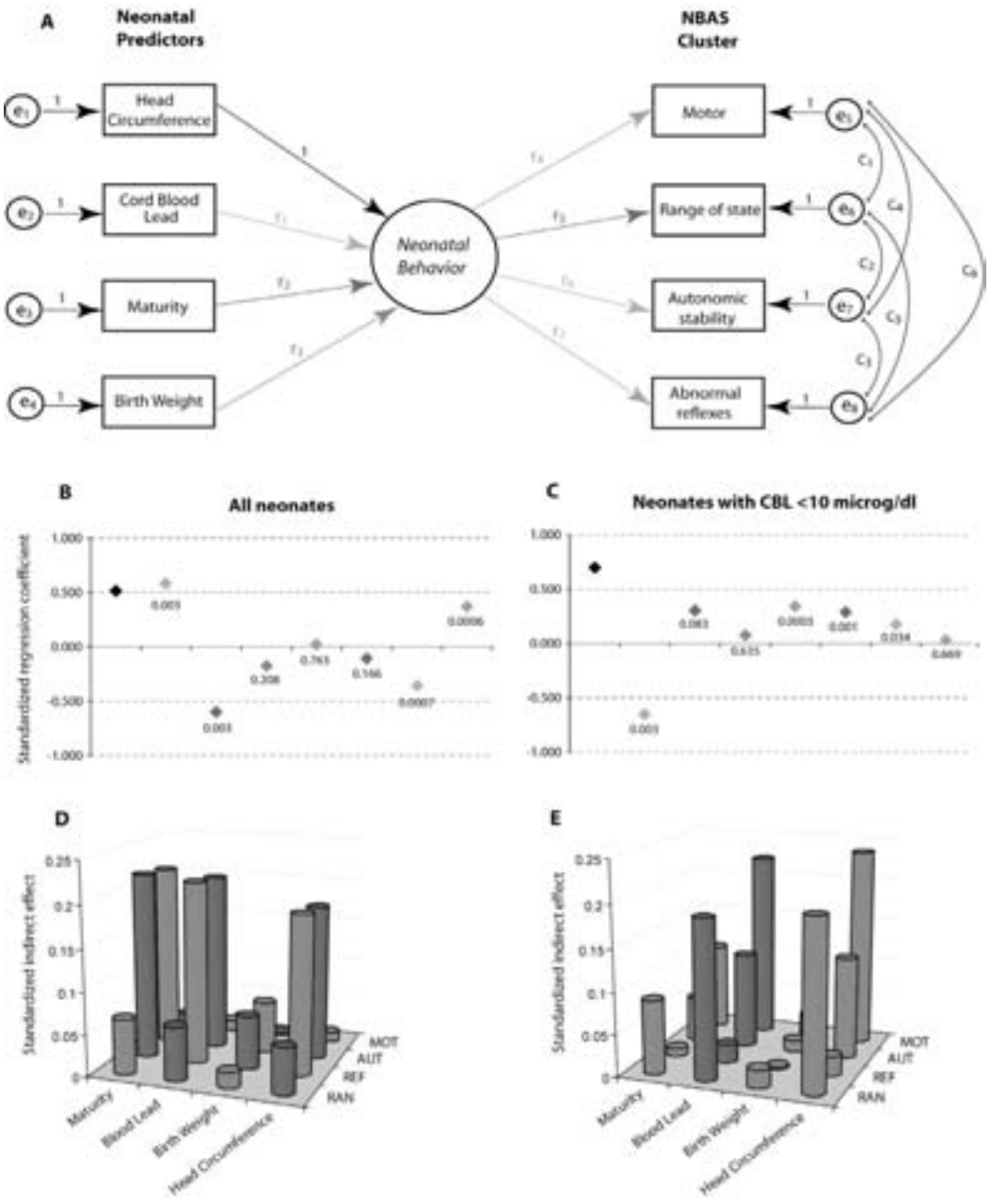

Figure 2

Structural equations modeling of the influence of neonatal predictors on the NBAS clusters. (**A**) The MIMIC model. The details of this model are given in text. Rectangles represent observed variables, circles represent latent variables, one-headed arrows represent influence and double-headed arrows represent covariance. The numbers or identifiers along the arrows are the model parameters. For ease of identification, the one-headed arrows of interest are color coded. Parameters e_1–e_8 represent the errors in measurement of observed variables. (**B and C**) Standardized regression coefficients for the color coded influences shown in panel A. Numbers indicate the statistical significance. The analysis was first conducted in all neonates (B) and then in neonates with CBL levels below 10 μg/dL (C). (**D and E**) Standardized indirect effects of the neonatal predictors (x-axis) on the NBAS cluster scores (y-axis). The z-axis represents the magnitude of the effect. Red cylinders indicate a negative effect while green cylinders indicate a positive effect. The analysis was conducted in all neonates (D) and then in neonates with CBL levels below 10 μg/dL (E). Complete results of SEM are shown in Supplementary Table 6 (see additional file 1, supplementary table 6). Abbreviations for the NBAS clusters are: motor (MOT), range of state (RAN), autonomic stability (AUT) and abnormal reflexes (REF).

Table 3: Association of NBAS items with risk of possessing high CBL levels: results from final models using stepwise multiple logistic regression analyses.

NBAS Item	Risk of CBL levels > the shown cut-off point		
	OR	***95% CI***	***P***
	5 μg/dL		
Range of State cluster			
Peak of excitement	0.60	0.37 – 0.98	0.042
Autonomic stability cluster			
Tremors	0.77	0.63 – 0.94	0.012
Abnormal reflexes			
Moro's reflex	3.37	1.13 – 10.04	0.029
Walking reflex	3.55	1.24 – 10.15	0.018
	10 μg/dL		
Autonomic stability cluster			
Tremors	0.75	0.58 – 0.96	0.023
Abnormal reflexes			
Babinski sign	4.26	1.01 – 17.8	0.047
Walking reflex	5.99	1.44 – 24.9	0.014
	25 μg/dL		
Abnormal reflexes			
Babinski sign	11.3	1.89 – 68.1	0.008
Walking reflex	8.17	1.36 – 49.2	0.022

Our results of the SEM modeling indicated that the model fit was not adequate either for all neonates or for neonates with CBL <10 μg/dL. We further investigated the reason for this apparent lack of fit for which purpose we assessed the predictive performance of 10 other models nested within the model shown in Figure 2A. While constructing the nested models, we considered all combinations of the four predictors taken three at a time and then taken two at a time. A close look at the model fits for these nested models revealed the following: i) Removal of CBL as a predictor from the MIMIC model always worsened the model fit; ii) Inclusion of maturity and head circumference was most of the times associated with a poor fitting model; iii) The best model for all neonates was with two predictors: CBL and maturity; and iv) The best model for neonates with CBL <10 μg/dL contained CBL and head circumference. Thus, the full model with all four predictors was associated with a poor model fit but we have shown it here only because it permitted us to study the effects of CBL adjusted for other potential confounders.

Association of increased CBL levels on items within the significantly associated NBAS clusters

Given the significant multivariate effects of CBL levels on the four NBAS clusters included in the MIMIC model analyses in the previous step, we next considered whether there were any specific items within these clusters that were associated with the risk of increased CBL levels. For this purpose, we dichotomized the CBL levels into high and low using three different cut-off points: 5, 10, 25 μg/dL. Using each of these binary outcomes we used backward stepwise unconditional multiple logistic regression analyses with a probability criterion of 0.05 to identify the NBAS items most significantly associated with the likelihood of possessing CBL levels exceeding these cut-offs. The results of these analyses are shown in Table 3.

We observed that not all items within each cluster were significantly associated with the risk of an increased CBL level. For example, if a high value (>25 μg/dL) for the CBL cut-off was used then only two abnormal reflexes – Babinski's sign and walking reflex – were significantly associated. At the currently used cut-off of >10 μg/dL, tremors were additionally identified to be significantly associated, while at a lower cut-off of >5 μg/dL, the peak of excitement also was significantly associated. Moreover, Moro's reflex rather than Babinski's sign was the significant abnormal reflex.

Discussion

In the process of human brain development the perinatal period characterizes a critical interval during which there is highest rate of brain development, rampant genesis of new synapses widespread neuronal proliferation, and maximum density of the N-methyl-D-aspartate (NMDA) receptors (31-37). The last of these facts bears a special relevance to lead neurotoxicity since it has been argued that the Ca++ permeable NMDA receptors also act as the neuronal gateway for Pb++.[38] Therefore the newborn brain is especially prone to toxic effects of environmental neurotoxicants[26] and can be expected to be sensitive to even low doses of lead exposure. Based on this biological rationale using the NBAS administered within three days of birth and employing multivariate statistical approaches for analysis, we observed that umbilical cord blood lead levels were significantly associated with different aspects of the neonatal behavior even at relatively low doses of exposure.

Study findings

We observed that the association of CBL levels with NBAS clusters was differential in two respects. First, not all NBAS clusters were equally associated with the CBL levels. Biologically, since the development of the newborn brain is neither simultaneous nor equivalent across all areas;[26,39-41] it can be expected that the influence of lead may not be alike on all areas of the developing brain. Indeed, several experimental studies have demonstrated that in the rat models of lead toxicity, the predominantly affected brain areas include the hippocampus,[42,43] the hypothalamus,[44] the prefrontal cortex,[45] the temporal cortex[46] and the cerebellum.[47] In humans, the posterior hippocampus has been shown to be associated with behavior,[48] the prefrontal cortex is known to control cognitive functions like language, abstract reasoning, problem-solving, social interactions, and planning,[49,50] the temporal lobe along with portions of hippocampus and prefrontal cortex has been implicated in object working memory[51] while cerebellum is the known seat of locomotion control. Our findings that the motor, range of state, autonomic instability and the abnormal reflexes NBAS clusters were specifically associated with the CBL: i) corroborate the conjecture that all domains of neonatal behavior will not be equally influenced by exposure to lead; and ii) are consistent with the known behavior-related functions of those areas in the human brain that have been shown in animal studies to be the primary targets for the effects of exposure to lead.

Second, and more interestingly, we found that the NBAS clusters associated with CBL levels in all neonates were not the

same as the NBAS clusters identified by restricting the analyses to low levels of exposure. In neonates with CBL <10 µg/dL, we did not observe an association of the varying CBL levels with the abnormal reflexes cluster but did uncover an association with the motor cluster. These data indicate that relatively higher values of CBL will be needed for lead to demonstrate its influence on the abnormal reflexes; however at a relatively milder dose it may continue to demonstrate an association with the motor, autonomic instability and range of state clusters. Evidence to support the deleterious effects of low-dose lead exposure on human neonatal behavior is continuously increasing[24,25,52,53] however a novel finding of the present study is that the patterns of behavior are different in neonates with CBL <10 µg/dL as compared to those with a higher dose of exposure.

Study limitations

Our study suffers from three limitations. First, for the reasons explained earlier, the main focus of our study was the behavioral patterns in the newborn which we assessed using NBAS. However, this is a cross-sectional study design – a fact that does not permit inferences about the potential causal role of low-dose lead exposure.[25,54,55]

Second, a single measurement of umbilical cord blood lead is unlikely to faithfully capture the overall cumulative exposure to lead[25] thereby making our measurement of lead exposure questionable. We did not have data on serial measurements of the lead concentrations in mother's blood over the entire duration of pregnancy. Our rationale for using umbilical CBL was based on the following observations: i) As reported by previous studies, the correlation coefficient between maternal and umbilical cord blood lead levels ranges between 0.55 to 0.92;[56,57] ii) All through gestation, lead is known to cross the placenta and is considered to be the most important source of umbilical cord blood lead;[58] and iii) independent of the maternal bone lead – an index of the cumulative lead exposure – umbilical cord blood lead has been shown to be a significant predictor of child development.[25] Considering these pieces of evidence from the literature and the absence of serial measurements of maternal blood lead in our study, we used umbilical cord blood lead as a surrogate for the cumulative lead exposure of the newborn.

Third, we did not have data on co-exposure of the newborn to other toxicants like cadmium and polychlorinated biphenyls which can also imitate some of the effects of lead.[54,59,60] In the absence of this data, our study will not be able to definitively point towards a causal role of lead, however the compatibility of our findings with the existing literature and the robust analytical methods used in this study urge the consideration of a plausible role of low-dose lead exposure in determining the patterns of neonatal behavior.

Study implications

With the caveats mentioned in the preceding section, we believe that our study has three important implications. First, it is not currently known whether the neonates who are affected by the low levels of lead exposure grow into children more likely to be affected with regards to their overall mental health. However, it has been observed that children exposed to low doses of lead show suboptimal cognitive functioning and reduced intelligent quotients.[12-14] Further, the following observations indirectly suggest a strong link between the events in early neonatal life and childhood development: gestational low-dose exposure to lead in rats can lead to a significant future risk of alterations in monoaminergic metabolism during adulthood;[61] neonatal infection can result in robust hippocampal-dependent memory impairment in adulthood;[62] neonatal prefrontal cortex lesions can manifest in adult animals as behavioral disturbances;[63] and early life does have an influence on the behavioral patterns in later life.[64] Considering all these observations together, it is conceivable that neonates demonstrating behavioral disturbances secondary to lead exposure may continue to manifest these disturbances in childhood.

We believe that, among others, a possible reason for discordance in the results and interpretations of the effects of low-dose lead exposure on neonatal behavior can be attributed to a lack of standardized analytical protocol. Theoretically, lead can have multiple and simultaneous effects and we suggest that future studies need to be incorporated statistical techniques like SEM to handle the data more efficiently and accurately. The use of Generalized Estimating Equations (GEE) for regressing the predictors[65] on multiple outcomes is another attractive alternative. In either case, the emphasis needs to be laid on the measurement and identification of concomitant influence of blood lead – alone or with other predictors – on multiple outcomes related to behavior.

Another area of interest in the field of lead poisoning relates to the politics and practice of screening. Sergeant and others[66] argue that in order to reduce the false positive error rate, it may be unwarranted to screen for children with blood lead levels between 10 and 15 µg/dL. As an alternative, Binns et al[67] suggested high-risk population screening. In situations where blood lead tests may not be easily or inexpensively available, it has also been thought to consider the use of blood lead questionnaires.[68,69] In that vein, we identified only a few NBAS items to be specifically correlated with the risk of possessing high CBL levels. Our findings imply that peak of excitement, tremors and abnormal Babinski's sign and walking reflexes may together serve as a potential initial screen to identify neonates possessing moderate to high CBL levels. While our study was not designed to address the issue of screening for lead toxicity, our results suggest that neonates with the aforementioned characteristics may need a further evaluation with a special emphasis on lead poisoning.

Conclusion

Needleman[4] believes that we are now into a "fifth cycle" of understanding the effects of this commonest environmental toxicant. Our findings concur with the observation that the effects of reduced levels of blood lead only indicate a possible avoidance of the physical presentation of lead poisoning; they may not however preclude the more subtle behavioral repercussions that can continue to have a high impact on the social realm of the disease. Therefore efforts to reduce exposure to this physiologically redundant but environmentally toxic metal need to be continued.

References

1 Ernhart CB: Lead levels and confounding variables. Am J Psychiatry 1982, 139:1524.
2 Ernhart CB: Inconsistencies in the lead-effects literature exist and cannot be explained by "effect modification". Neurotoxicol Teratol 1995, 17:227-33. discussion 249-251.
3 Ernhart CB: Lead effects research. Am J Public Health 1998, 88:1879-1880.

4 Needleman H: Lead poisoning. Annu Rev Med 2004, 55:208-222.
5 Needleman HL, Landrigan PJ: What level of lead in blood is toxic for a child? Am J Public Health 2004, 94:8-9.
6 Scarr S, Ernhard CB: Of whistleblowers, investigators, and judges. Ethics Behav 1993, 3:199-206.
7 Oberto A, Marks N, Evans HL, Guidotti A: Lead (Pb+2) promotes apoptosis in newborn rat cerebella neurons: pathological implications. J Parmacol Esp Ther 1996, 279:435-442.
8 Shen X, Wu S, Yan C: Impacts of low-level lead exposure on development of children: recent studies in China. Clin Chim Acta 2001, 313:217-220.
9 Dietrich KN, Ris MD, Succop PA, Berger OG, Bornschein RL: Early exposure to lead and juvenile delinquency. Neurotoxicol Teratol 2001, 23:511-518.
10 Pabello NG, Bolivar VJ: Young brains on lead: adult neurological consequences? Toxicol Sci 2005, 86:211-213.
11 Bellinger DC, Hu H, Kalaniti K, Thomas N, Rajan P, Sambandam S, Ramaswamy P, Balakrishnan K: A pilot study of blood lead levels and neurobehavioral functions in children living in Chennai, India. Int J Occup Environ Health 2005, 11:138-143.
12 Canfield Rl, Gendle MH, Cory-Slechta DA: Impaired neuropsychological 2004, 26:513-540.
13 Canfield RL, Kreher DA, Cornwell C, Henderson CR Jr: Low-level lead exposure executive functioning, and learning in early childhood. Neuropsychol Dev Cogn C Child Neuropsychol 2003, 9:35-53.
14 Chen A, Dietrich KN, Ware JH, Radcliffe J, Rogan WJ: IQ and blood lead from 2-7 years of age: are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environ Health Perspect 2005, 113:597-601.
15 Chiodo LM, Jacobson SW, Jacobson JL: Neurodevelopment effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol 2004, 26:359-371.
16 Ozmert En, Yurdakok, Soysal S, Kulak-Kayikci ME, Belgin E, Ozmert E, Laleli Y, Saracbasi O: Relationship between physical, environmental and sociodemographic factors and school performance in primary schoolchildren. J Trop Pediatr 2005, 51:25-32.
17 Popcock SJ, Smith M, Baghurst P: Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. BMJ 1994, 309:1189-1197.
18 Schwartz J: Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ Res 1994, 65:42-55.
19 Holmes SE, Slaughter JR, Kashani J: Risk factors in childhood that lead to the development of conduct disorder and antisocial personality disorder. Child Psychiatry Hum Dev 2001, 31:183-193.
20 Stretesky PB, Lynch MJ: The relationship between lead exposure and homicide. Arch Pediatr Adolesc Med 2001, 155:579-582.
21 Ernhart CB, Wolf AW, Kennard MJ, Erhard P, Filipovich HF, Sokol RJ: Intrauterine exposure to low levels of lead: the status of the neonate. Arch Environ Health 1986, 41:287-291.
22 Rothenberg SJ, Schnaas L, Cansino-Ortiz S, Perroni-Hernandez E, de la Torre P, Neri-Mendez C, Ortega P, Hidalgo-Loperena H, Svendsgaard D: Neurobehavioral deficits after low level lead exposure in neonates: the Mexico City pilot study. Neurotoxicol Teratol 1989, 11:85-93.
23 Emory E, Pattilo R, Archibold E, Bayorh M, Sung F: Neurobehavioral effects of low-level lead exposure in human neonates. Am J Obstet Gynelcol 1999, 181:S2-S11.
24 Shen X-M, Yan C-H, Guo D, Wu S-M, Li R-Q, Huang H, Ao L-M, Zhou J-D, Hong Z-Y, Xu J-D, Jin X-M, T J-M: Low level of prenatal lead exposure and neurobehavioral development of children in the first year of life: A prospective study in Shanghai. Environ Res 1998, 79:1-8.
25 Gomaa A, Hu H, Bellinger D, Schwartz J, Tsaih SW, Gonzalez-Cossio T, Schnaas L, Peterson K, Aro A, Hernandez-Avila M: Maternal bone lead as an independent risk factor for fetal neurotoxicity: a prospective study. Pediatrics 2002, 110:110-118.
26 Tronick EZ: The neonatal behavior assessment scale as a biomarker of the effects of environmental agents on the newborn. Environ Health Perspect 1987, 74:185-189.
27 Brazelton TB, Nugent JK: Neonatal Behavioral Assessment Scale 3rd edition. London: Mac Keith Press; 1995
28 Lester BM, Als H, Brazelton TB: Regional obstetric anesthesia and newborn behavior: a reanalysis toward synergistic affects. Child Dev 1982, 53:687-692.
29 Lagesson V, Andrasko L: Direct determination of lead and cadmium in blood and urine by flameless atomic absorption spectrophotometry. Clin Chem 1979, 25:1948-1953.
30 Bollen KA: The General Model. In Structural equations with latent variables John Wiley & Sons: New Yorkl 1989:19-448.
31 Bhutta AT, Anand KJ: Vulnerability of the developing brain. Neuronal mechanisms. Clin Perinatol 2002, 29:357-372.
32 Rice D, Barone S Jr: Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect 2000, 108:511:533.
33 Rakic P: Images in neuroscience. Brain development, VI: radial migration and cortical evolution. Am J Psychiatry 1998, 155:1150-1151.
34 Rakic P, Bourgeois J-P, Eckenhoff MF, Zecevic N, Goldman-Rakic PS: Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 1986, 232:232-235.
35 Gould E, Cameron HA: Early NMDA receptor blockade impairs defensive behavior and increases cell proliferations in the dentate gyrus of developing rats. Behav Neurosci 1997, 111:49-56.
36 Rao H, Jean A Kressler JP: Postnatal ontogeny of glutamate receptors in the rat nucleus tractus solitarii and ventrolateral medulla. J Auton Nerv Syst 1997, 65:25-32.
37 Chahal H, D'Souza SW, Barson AJ, Slater P: Modulation by magnesium of N-methyl-Daspartate receptors in developing human brain. Arch Dis Child Fetal Neonatal Ed 1998, 78:F116-F120.
38 Toscano CD, Guilarte TR: lead Neurotoxicity: from exposure to molecular effects. Brain Dev Brain Res Rev 2005, 49:529-554.
39 Uylings HB, Malofeeva LI, Bogolepova IN, Jacobsen AM, Amunts K, Zillies K: No postnatal doubling of number of neurons in human Broca's areas (Brodmann areas 44 and 45)? A stereological study. Neuroscience 2005, 136:715-728.
40 Travis K, Ford K, Jacobs B: Regional dendritic variation in neonatal human cortex: a quantitative Golgi study. Dev Neurosci 2005, 27:277-287.
41 Guillery RW: is postnatal neocortical maturation hierarchical? Trends Neurosci 2005, 28:512-517.
42 Yu K, Yu SS, Ruan Dy: Opposite effects of lead exposure on taurine- and HFS-induced LTP in rat hippocampus. Brain Res Bull 2005, 64:525-531.
43 Booze RM, Mactutus CF: Development exposure to organic

lead causes permanent hippocampal damage in Fischer-344 rats. Experientia 1990, 46:292-297.
44 Virgolini M, Chen K, Weston DD, Bauter MR, Cory-Slechta DA: Interactions of chronic lead exposure and intermittent stress: consequences for brain catecholamine systems and associated behaviors and HPA axis function. Toxicol Sci 2005, 87:469-482.
45 Schneider M, Koch M: Behavioral and morphological alterations following neonatal excitotoxic lesions of the medial prefrontal cortex in rats. Esp Neurol 2005, 195:185-198.
46 Ma T, Chen HH, Lim DK, Hume AS, Ho IK: Excitatory amino acids and lead-induced neurotoxicity. J Toxicol Sci 1998, 23:181-183.
47 Zhu ZW, Yang RL, Dong GJ, Zhao ZY: Study on the neurotoxic effects of low-level lead exposure in rats. J Zhejiang Univ Sci B 2005, 6:686-692.
48 Strange BA, Fletcher PC, Henson RN, Friston KJ, Dolan RJ: Segregating the functions of human hippocampus. Proc Natl Acad Sci USA 1999, 96:4034-4039.
49 Wood JN, Grafman J: Human Prefrontal Cortez: processing and representational perspectives. Nature Review Neuroscience 2003, 4:139-147.
50 Strange BA, Henson RN, Friston KJ, Dolan RJ: Anterior prefrontal cortex mediates rule learning in humans. Cereb Cortex 2001, 11:1040-1046.
51 Kaldy Z, Zigala N: The neural mechanisms of object working memory: what is where in the infant brain? Neurosci Biobehav Rev 2004, 28:113-121.
52 Factor-Litvak P, Wasserman G, Kline JK, Graziano J: The Yugoslavia Prospective Study of environmental lead exposure. Environ Health Perspect 1999, 107:9-15.
53 Schnaas L, Rothenberg SJ, Flores MF, Martinez S, Hernandez C, Osorio E, Velasco SR, Perroni E: Reduced intellectual development in children with prenatal lead exposure. Environ Health Perspect 2006, 114:791-797.
54 Bellinger DC: Assessing environmental neurotoxicant exposures and child neurobehavior: confounded by confounding? Epidemiology 2004, 15:383-384.
55 Bellinger DC: Lead. Pediatrics 2004, 113:1016-1022.
56 Ernhart CB: A critical review of low-level prenatal lead exposure in the human: I. Effects on the fetus and newborn. Reprod Toxicol 1992, 6:9-19.
57 Gardella C: Lead exposure in pregnancy: a review of the literature and argument for routine prenatal screening. Obstet Gynecol Surv 2001, 56:231-238.
58 Wong GP, Ng TL, Martin TR, Farquharson DF: Effects of low-level lead exposure in utero. Obstet Gynecol Surv 1992, 47:285-289.
59 Carrillo-Ponce Mde L, Martinez-Ordaz VA, Velasco-Rodriguez VM, Hernandez-Garcia A, Hernandez-Serrano MC, Sanmiguel F: Serum lead, cadmium, and zinc levels in newborns with neural tube defects from a polluted zone in Mexico. Reprod Toxicol 2004, 19:149-154.
60 Stewart P, Reihman J, Lonky E, Darvil T, Pagano J: Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. Neurotoxicol Teratol 2000, 22:21-29.
61 Antonio MT, Corpas I, Leret ML: Neurochemical changes in newborn rat's brain after gestational cadmium and lead exposure. Toxicol Lett 1999, 104:1-9.
62 Bilbo SD, Rudy JW, Watkins LR, Maier SF: A behavioral characterization of neonatal infection-facilitated memory impairment in adult rats. Behav Brain Res 2006, 169:39-47.
63 Schneider M, Koch M: Behavioral and morphological alterations following neonatal excitotoxic lesions of the medial prefrontal cortex in rats. Exp Neurol 2005, 195:185-198.
64 McEwen BS: Early life influences on life-long patterns of behavior and health. Ment Retard Dev Disabil Res Rev 2003, 9:149-154.
65 Bull SB: Regression models for multiple outcomes in large epidemiologic studies. Stat Med 1998, 17:2179-2197.
66 Sargent JD, Dalton M, Klein RZ: Diagnostic testing unwarranted for children with blood lead 10 to 14 microg/dL. Pediatrics 1999, 103:e51.
67 Binns HJ, Kim D, Campbell C: Targeted screening for elevated blood lead levels: populations at high risk. Pediatrics 2001, 10:1364-1366.
68 Binns HJ, LeBailly SA, Fingar AR, Saunders S: Evaluation of risk assessment questions used to target blood lead screening in Illinois. Pediatrics 1999, 103:100-106.
69 Litaker D, Kippes CM, Gallagher TE, O'Connor ME: Targeting lead screening: The Ohio Lead Risk Score. Pediatrics 2000, 106:E69.

Emergence of Physiological Rhythmicity in Term and Preterm Neonates in a Neonatal Intensive Care Unit

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Abstract

Background: Biological rhythmicity, particularly circadian rhythmicity, is considered to be a key mechanism in the maintenance of physiological function. Very little is known, however, about biological rhythmicity pattern in preterm and term neonates in neonatal intensive care units (NICU). In this study, we investigated whether term and preterm neonates admitted to NICU exhibit biological rhythmicity during the neonatal period.

Methods: Twenty-four-hour continuous recording of four physiological variables (heart rate: HR recorded by electrocardiogram; pulse rate: PR recorded by pulse oxymetry; respiratory rate: RR; and oxygen saturation of pulse oxymetry: SpO_2) was conducted on 187 neonates in NICU during 0-21 days of postnatal age (PNA). Rhythmicity was analyzed by spectral analysis (SPSS procedure Spectra). The Fisher test was performed to test the statistical significance of the cycles. The cycle with the largest peak of the periodogram intensities was determined as dominant cycle and confirmed by Fourier analysis. The amplitudes and amplitude indexes for each dominant cycle were calculated.

Results: Circadian cycles were observed among 23.8% neonates in HR, 20% in PR, 27.8% in RR and 16% in SPO_2 in 0-3 days of PNA. Percentages of circadian cycles were the highest (40%) at <28 wks of gestational age (GA), decreasing with GA, and the lowest (14.3%) at ≥ 37 wks GA within 3 days of PNA in PR and were decreased in the later PNA. An increase of the amplitude with GA was observed in PR, and significant group differences were present in all periods. Amplitudes and amplitude indexes were positively correlated with postconceptional age (PCA) in PR ($p < 0.001$). Among clinical parameters, oxygen administration showed significant association ($p < 0.05$) with circadian rhythms of PR in the first 3 days of life.

Conclusion: Whereas circadian rhythmicity in neonates may result from maternal influence, the increase of amplitude indexes in PR with PCA may be related to physiological maturity. Further studies are needed to elucidate the effect of oxygenation on physiological rhythmicity in neonates.

Background

Preterm neonates hospitalized in a neonatal intensive care unit (NICU) face many challenges to adapt to the new environment. Heat loss,[1] weight loss,[2] respiratory distress and cardiac instability[3] are very common features for them. An artificial environment in NICU is mandatory to support these neonates; however, external influences such as constant light, noise, and medical intervention may be stressful. Further, neonates are deprived of maternal influences, which are essential for their development. It has been thought that this environmental condition may influence the development of biological rhythm in preterm neonates.[4-6]

Circadian rhythms are generated endogenously by a biological clock, which is located in the anterior hypothalamic suprachiasmatic nuclei (SCN),[7,8] and are modulated by exogenous factors.[9,10] Many physiological processes are now known to be cyclically organized.[11] They show different cycles: circadian cycles last approximately 24 hours, ultradian cycles shorter than 24 hours, and infradian cycles longer than 24 hours.[12] These rhythms interact mutually as well as with the outside fluctuating environment under the control of feed-back systems providing an orderly function that enables life.[11]

Circadian rhythms have been described in the human fetus[13-16] and have been attributed either to the maternal environment or

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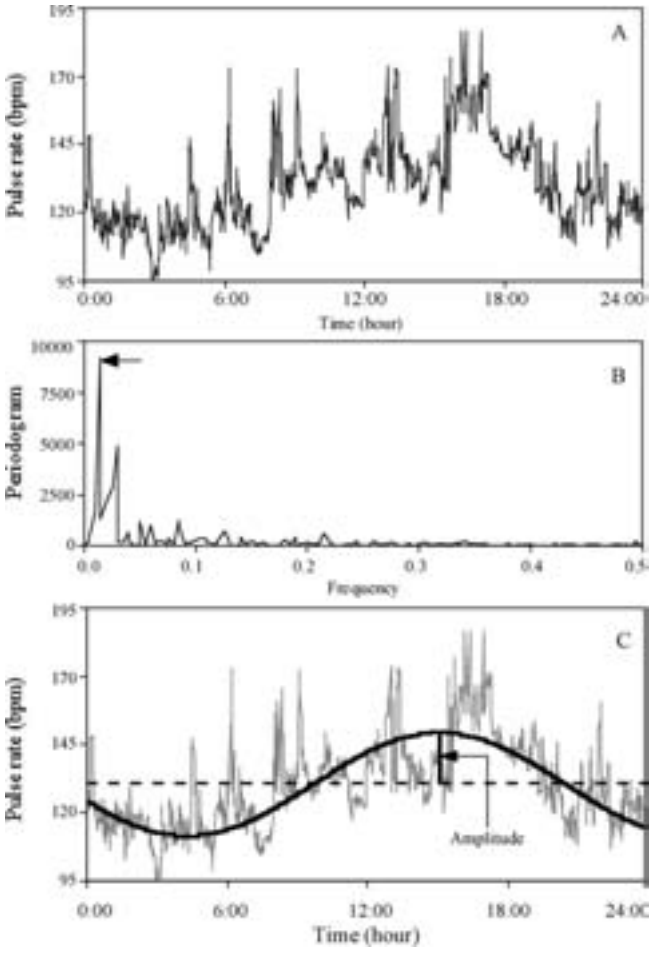

Figure 1
Brief description of steps to determine the dominant cycle using spectral analysis. ***A***: Plot of original data for pulse rate (PR). PR was measured once every 10 seconds and averaged into 1 minute time block for 1440 minutes; N = 1440 observation. ***B***: Periodogram intensities for PR (plotted on linear scale). The largest peak of the periodogram was selected (arrow) as representative cyclic component that represent the largest amount of variance. ***C***: The corresponding cycle of the largest peak in the periodogram intensities was reconstructed from the FFT coefficient to fit the sinusoidal function: $\chi_t = \mu + A\cos(\omega t) + B\sin(\omega t)$. The bold line is the detected cycle (period: 1440 minutes = 24 hours) superimposed on the original data.

to the maturation of the fetal nervous system.[13,17,18] The SCN has been detected as early as 18-20 weeks of gestational age,[19] and primate studies indicated that the SCN is responsive to light at 24 weeks of gestational age.[20] In term neonates, circadian rhythms have been reported to be present immediately after birth but to eventually disappear,[4,21] not being detected again until 3-4 weeks of postnatal life.[22] Some studies showed that circadian rhythms are predominant in preterm neonates,[4,21,23] while others showed ultradian rhythms to be dominant in preterm neonates.[22,24-27] To elucidate the development process of physiological rhythmicities, we studied four physiological variables in preterm and term neonates.

Methods

Subjects and data collection: From January 2004 to March 2006, 520 neonates were admitted to the NICU at Meichuo Medical Center. All of them were monitored with electrocardiogram (ECG) for heart rate (HR), respiration rate (RR), and with pulse oxymetry on the wrist or the feet for saturation of pulse oxymetry oxygen (SPO2) and pulse rate (PR) throughout their stay in the NICU. Monitored physiological information was transformed as measurement variables at 10-second intervals by the Wave Achieving System (WAS-J; Phillips Electronics Japan, Tokyo, Japan) through the local area network in the NICU. The data were recorded for 24 hours for the following postnatal periods: Period 1: days 0-3; Period 2: days 4-6; Period 3: days 7-13; and Period 4: days 14-21. Subjects with continuously disrupted data for more than 1 minute were excluded from the study. A total of 187 neonates (114 boys and 73 girls) were recorded from period 1 to period 4.

Table 1: Demographic characteristics of 187 preterm and term neonates.

Variables/Categories	*n (%)*
Gender (boys/Girls)	114 (61)/73 (39)
Gestational age (wks), median (range)	34 (23–42)
< 28	17 (9.1)
28–32	49 (26.2)
33–36	58 (31)
≥37	63 (33.7)
Birth Weight (g), median (range)	1968 (454–4132)
< 1000	27 (14.4)
1000–1499	31 (16.6)
1500–1999	38 (20.3)
≥2000	91 (48.7)
Apgar score 1 min/5 min, median (range)	8 (0–10)/9 (2–10)
Age at hospitalization (day), median (range)	0 (0–9)
Hospitalization (day), median (range)	32 (5–182)
Caesarian Section	96 (51.3)
Multiple gestation	4 (2.3)
Intubation	111(59.4)
Oxygenation	72 (38.5)
Birth asphyxia	27 (14.4)
Intrauterine growth retardation	23 (12.3)
Respiratory distress syndrome	31 (16.6)
Transient tachypnea of the newborn	38 (20.3)

Data are expressed as mean ± SD or n (%).

The NICU was maintained under a light-dark cycle. The light was dimmed (less than 30 lux) during the night from 21:00 pm to 07:00 am, while it was maintained at a higher level (300-580 lux) during the daytime. NICU staff also varied according to time of day: the number of attendants at night was one third that of attendants during daytime hours. Parent's visitations were allowed three times a day (11:00 to 12:00 in the morning, 14:00 to 15:00 in the afternoon, and 17:00-21:00 in the evenings). Bathing and measurement of body weight were conducted daily in the morning. Medical examinations, such as blood sampling, radiography, or ultrasonography, were mostly provided in the morning if necessary.

Written informed consent was obtained from the parents, and the study was approved by the ethical committee of the institute. Demographics and health status information were obtained from the medical records.

Analysis of rhythms: Physiological rhythmicity was analyzed for HR, PR, RR and SPO_2 with spectral analysis (periodogram) with

Table 2: Descriptive profiles for significant cycles of HR, PR, RR and SpO_2.

Period		Period 1	Period 2	Period 3	Period 4
Sampling		(0–3)	(4–6)	(7–13)	(14–21)
n		116	114	125	106
Eligible sample*	HR	82 (70.7)	64 (56.1)	91 (72.8)	67 (63.2)
	PR	101 (87.1)	88 (77.2)	106 (84.8)	84 (79.2)
	RR	99 (85.3)	85 (74.6)	104 (83.2)	84 (79.2)
	SpO2	103 (88.8)	89 (78.1)	106 (84.8)	85 (80.2)
Significant cycle**	HR	80 (98)	64 (100)	89 (98)	67 (100)
	PR	100 (99)	87 (99)	104 (98.1)	83 (99)
	RR	90 (91)	84 (99)	97 (93.3)	79 (94)
	SpO2	94 (91.3)	86 (97)	103 (97)	78 (92)
Circadian cycle***	HR	19 (23.8)	11 (17.2)	20 (22.5)	13(19.4)
	PR	20 (20)	16 (18.4)	20 (19.2)	16 (19.3)
	RR	25 (27.8)	28 (33.3)	21 (21.6)	11 (13.9)
	SpO2	15 (16)	10 (11.6)	17 (16.5)	15 (19.2)

Data are shown in n (%). Parentheses are percentages of * eligible samples in all samples, ** significant cycles in all eligible samples, and *** circadian cycles in significant cycles.

Table 3: Distribution of circadian cycles according to gestational age groups in each period.

	Gestational age		Period 1		Period 2		Period 3		Period 4
	Groups	n	(0–3 d)	n	(4–6 d)	n	(7–13 d)	n	(14–21 d)
PR	<28 wks	10	4 (40)	12	3 (25)	12	5 (41.7)	13	4 (30.8)
	28–32 wks	26	6 (23.1)	22	6 (27.3)	42	11 (26.2)	39	9 (23.1)
	33–36 wks	29	5 (17.2)	26	5 (19.2)	31	2 (6.5)	23	3 (13.0)
	≥37 wks	35	5 (14.3)	27	2 (7.4)	19	2 (10.5)	8	0 (0)
RR	< 28 wks	7	1 (14.3)	11	1(9.1)	13	5 (38.5)	13	0 (0)
	28–32 wks	24	8 (33.3)	20	9 (45)	38	9 (23.7)	36	8 (22.2)
	33–36 wks	25	8 (32)	27	9 (33.3)	28	3 (10.7)	22	2 (9.1)
	≥37 wks	34	8 (23.5)	26	9 (34.6)	18	4 (22.2)	8	1(12.5)
SpO2	< 28 wks	10	0 (0)	12	3 (25)	12	3 (25)	13	2 (15.4)
	28–32 wks	25	5 (20)	20	3 (15)	40	7 (17.5)	37	9 (24.3)
	33–36 wks	26	5 (19.2)	25	5 (20)	32	4 (12.5)	20	3 (15)
	≥37 wks	33	5 (15.2)	29	4 (13.8)	19	3 (15.8)	8	1 (12.5)

Data are shown in n (%).

SPSS 11.5 software (SPSS Inc, Chicago, IL), as previously reported.[28] Briefly, 24 hours sessions were run in 10-second intervals and were aggregated into 1-minute time series of 1440 minutes (N = 1440 observations). The Fisher test was used to test the statistical significance of the cyclic components (N = 1440, p = 0/05).[28,29] Among the significant cycles, the cycle with the largest peak in the periodogram was considered to be the dominant cycle for each time series data and was used for further analysis.[28] All dominant cycles were confirmed by Fourier analysis, and further circadian cycles were confirmed by cosinor analysis with a significance of $p < 0.05$ by least square analysis (Figure 1). The amplitude, the distance between mesor and the highest value of the cosine curve, was calculated for each dominant cycle. In addition, an amplitude index was calculated as follow:

Amplitude index = amplitude ÷ mean of variables × 100

Statistical analysis: Data were analyzed with SPSS and Statview. ANOVA was used to evaluate the differences between gestational age groups. The Pearson correlation coefficient was used to analyze the relationships between postconceptional age (PCA) and rhythmicity parameters. Univariate analysis using Mann-Whitney U-test for continuous variables or Fisher's exact test for categorical variables was used to compare clinical variables according to the development of physiological rhythmicity. A multiple logistic regression analysis was performed using a step-wise approach to determine the independent relationship of significant variables found in the univariate analysis.

Results

Sample characteristics

The demographics of neonates are shown in Table 1. The median gestational age (GA) was 34 weeks (range: 23-42 weeks), and the median birth weight was 1968 g (range: 454-4132 g). Among these neonates, 9.1% were born at < 28 weeks of gestation age and 14.4% had birth weight of less than 1000 g. The median age at hospitalization was 0 day (range 0-9 day) and the median duration of hospitalization was 32 days (range 5-182 days). One hundred eleven neonates (59.4%) were intubated and 72 neonates (38.5%) received oxygen.

Rhythmicity analysis

Results of the analyses of rhythmicity are summarized in Table

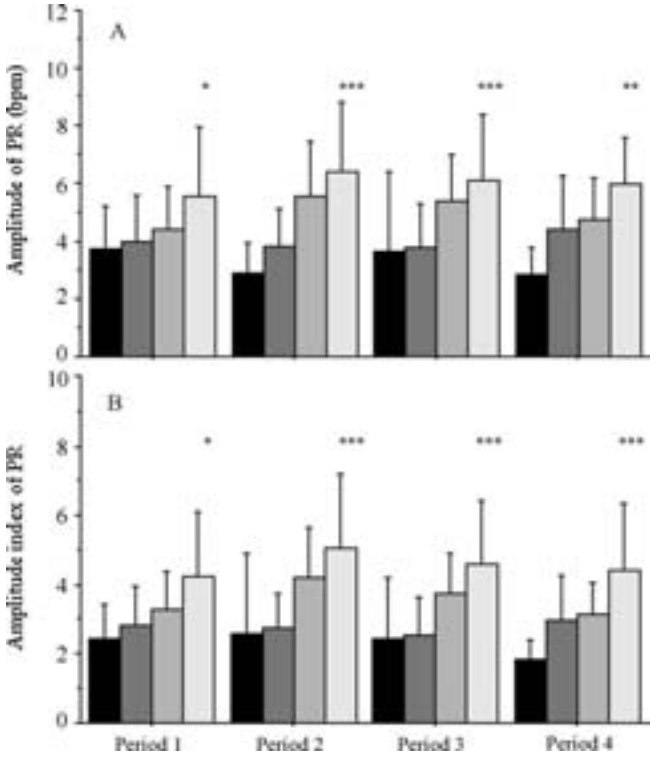

Figure 2
Amplitudes (*A*) and amplitude indexes (*B*) of all detected cycle of PR over the 4 periods for 4 gestational age groups infants. Data are shown in Mean ± SD. The dark bar is for < 28 wks, the gray bar is for 28–32 wks, the light gray bar is for 33–36 wks, and white bar is for ≥ 37 wks. * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$, according to ANOVA. The sample size for each gestational age group is shown in Table 2.

2. To ensure the accuracy of rhythmicity analysis, parameters missing more than 7% of total data were excluded from the analysis in each study. Among 461 time series recorded for each parameter, eligible samples were obtained in 304 for HR, 379 for PR, 372 for RR, and 383 for SPO_2 within the 4 periods. Among eligible samples, rhythmicity was observed in more than 90% of neonates in each period for HR, PR, RR, and SPO_2 (Table 2). The percentage was not much lower (HR: 89%, PR: 90%, RR: 79%, SPO_2: 76%) after Bonferroni correction for multiple testing ($p < 0.0001$).

Without correction for multiple testing, circadian cycle (1440 minutes) was observed among 23.8% neonates in HR, 20% in PR, 27.8% in RR and 16% in SPO_2 in Period 1. Because many samples were excluded from HR analysis, and the percentage of eligible samples was consistently lower than for PR, further analysis of cardiac rhythmicity used PR instead of HR.

Rhythmicity and gestational age

Rhythmicity was analyzed in four gestational age groups: < 28 wks, 28-32 wks, 33-36 wks, ≥ 37 weeks. The distribution of circadian cycles in each gestational age groups and periods is summarized in Table 3. In PR, the percentage of circadian cycles was highest (40%) at < 28 wks of GA, decreasing with GA, and lowest (14.3%) at ≥ 37 wks of GA in Period 1. A similar tendency was observed in each period in PR; however, there was no consistent tendency in percentages of circadian cycle in RR and SPO_2.

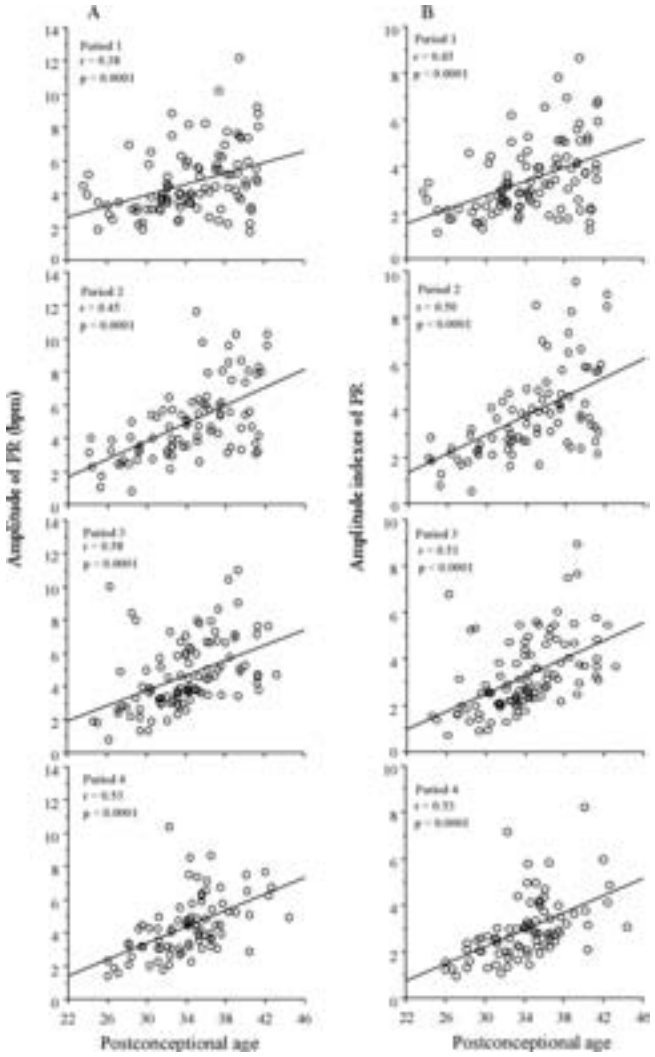

Figure 3
Linear regression (and coefficients of correlation) for amplitudes and amplitude indexes of PR as functions of postconceptional age. A significant increase in amplitudes and amplitude indexes with postconceptional age is present in all period in PR.

Amplitudes and amplitude indexes of all detected cycles in PR in each period are shown in Figure 2. An increase of circadian amplitude with gestational age was observed in PR. Significant differences were present among gestational age groups in all periods (Figure 2A). These changes were not observed in RR and SPO_2 (data not shown). Amplitude indexes showed similar tendency to amplitudes in PR (Figure 2B). There were no significant associations between cycles and amplitudes in any parameter in each period (data not shown).

Relationship between rhythmicity and postconceptional age (PCA), correlation of coefficient was performed using amplitudes and amplitude indexes in each period for all parameters. Amplitude and amplitude indexes of PR were positively correlated with PCA in all four periods (Figure 3).

Clinical conditions associated with rhythmicity

To determine whether clinical conditions may affect the emergence and development of rhythmicity, clinical factors were determined according to cycle length with circadian cycles

Table 4: Univariate analysis for association of clinical parameters with existence of circadian rhythmicities in PR in Period 1.

Clinical variables	Cycle 1440 (n = 20)	≤ 720 (n = 80)	p
Gestational age (wks)	32.7 ± 4.9	34.2 ± 4.6	NS
Birth weight (g)	1930 ± 983	2077 ± 900	NS
Apgar Score < 6 (5 min)	1 (5)	10 (12.7)	NS
Asphyxia	4 (20)	17 (21.3)	NS
RDS	4 (20)	14 (17.3)	NS
IUGR	3 (15)	6 (7.5)	NS
Mean of variables			
Mean PR (/min)	140.2 ± 8.6	135.5 ± 12.8	NS
Mean RR (/min)	45.7 ± 8.5	43.0 ± 8.5	NS
Mean SpO2 (%)	97.9 ± 1.1	97.9 ± 1.3	NS
Treatment of data sampling			
Oxygenation	18 (90)	46 (57.5)	0.02
Intubation	10 (50)	25 (31.3)	NS
Aminophylline	1 (5)	4 (5)	NS
Phenobarbital	0 (0)	1 (1.3)	NS
Midazolam	3 (15)	6 (7.5)	NS

Data are expressed as mean ± SD or n (%). Mann-Whitney U test was performed for continuous variables and Fisher's exact test was performed for categorical variables.

(1440 minutes) or ultradian cycles (≤ 720 minutes). On univariate analyses in Period 1, circadian cycle (1440 minutes) was significantly associated ($p < 0.05$) only with oxygen administration at data sampling in PR (Table 4), while there were no significant associations in RR or SPO_2 (data not shown). In Periods 3 and 4 in PR, gestational age was found to be significantly associated with circadian cycle ($p < 0.05$). Neither gestational age nor oxygen administration qualified as an independent factor for existence of circadian cycle in multivariate logistic regression models. Clinical parameters were not associated with the existence of significant cycles in amplitude or amplitude index.

Discussion

Rhythmicity has been previously studied in preterm and term infants for various physiological variables, such as body temperature,[24,30] blood pressure,[21] heart rate,[18] sleep-wake pattern,[24] rest-activity pattern,[26] melatonin secretion,[31] and electroencephalogram.[32] In this study, we have investigated rhythmicity in PR, RR, and SPO_2. All of these are important parameters in the regulation of human physiology, and yet little is known about rhythmicity of these variables in neonate. We have shown that most of the analyzed neonates had individual rhythmicity for these parameters with variable cycles after birth, even in extremely premature infants.

Emergence of circadian rhythmicity has been reported to be associated with brain maturation of preterm infants.[33,34] In term neonates, circadian cycles are detected immediately after birth and subsequently disappear and are not detectable until 3 to 4 weeks of postnatal life.[22] It has been suggested that circadian cycles in the life of early neonatal period are due to maternal influence in utero and that endogenous rhythmicity appears only later.[13,17,18] However, conclusive studies are limited by subject number because of the difficulty in collecting continuous data in NICU. Our sample size of 187 neonates is larger than that of previous studies. As a result, circadian cycles were observed during early neonatal period in preterm neonates and persisted through the later neonatal period, especially in extremely immature infants, while percentages of circadian cycles decreased through the later period in term neonates. These results partially support the previous studies.[4,21,23] The fact that environmental conditions were rhythmic in our study (ie presence of a light-dark cycle, of a cycle of NICU staffing, of a cycle of bathing, etc) prevents us from making inferences about the endogenous or exogenous nature of biological rhythmicity in our subjects.

Although exact factors for the development of rhythmicity are still unclear, it has been suggested that physiological complications may play a role.[35] Among clinical parameters, disease conditions such as respiratory problems or asphyxia, and therapeutic drugs such as phenobarbital or aminophylline, were not associated with emergence of circadian cycles. Only oxygen administration revealed significant association with emergence of circadian cycles in PR within 3 days of birth. Disruption of circadian rhythmicity by reduction of oxygen supply, and restoration by re-oxygenation, has been demonstrated in rats.[36,37] Reduced oxygen activates hypoxia-inductible factor 1 (HIF-1),[38] which is involved in oxygen homeostasis. Chilov and colleagues also indicated that oxygen supply modulates the circadian clock at the molecular level via HIF-1 in the mouse brain.[39] Our observations support these experimental results and suggested that oxygen supply may also influence rhythmicity in humans. Further analyses are required to explore the influencing mechanisms on emergence of rhythmicities in neonates.

Conclusion

Preterm neonates are at great risk of life-threatening events such as infection, respiratory distress or circulatory failure. As shown in this study, coexistence of circadian cycles with low amplitude in preterm neonates may complementarily support immature homeostasis and function against unstable physiological condition. Our results should aid further research on physiological rhythmicity in neonates.

References

1 Hammarlund K, Stromberg B, Sedin G: Heat loss from the skin of preterm and fullterm newborn infants during the first weeks after birth. Biol Neonate 1986 50:1-10.

2 Bauer K, Versmold H: Postnatal weight loss in preterm

neonates less than 1,500 g is due to isotonic dehydration of the extracellular volume. Acta Paediatr Scand Suppl 1989, 360:37-42.
3 Di Fiore JM, Arko MK, Miller MJ, Krauss A, Betkerur A, Zadell A, Kenney SR, Martin RJ: Cardiorespiratory events in preterm infants referred for apnea monitoring studies. Pediatrics 2001, 108:1304-1308.
4 Mirmiran M, Kok JH: Circadian rhythms in early human development. Early Hum Dev 1991, 26:121-128.
5 Rivkees SA: Developing circadian rhythmicity in infants. Pediatrics 2003, 112:373-381
6 Mirmiran M, Kok JH, Boer K, Wolf H: Perinatal development of human circadian rhythms: role of the foetal biological clock. Neurosci Biobehav Rev, 1992 16:371-378.
7 Panda S, Hogenesch JB, Kay SA: Circadian rhythms from flies to human. Nature 2002, 417:329-335
8 Tousson E, Meissl H: Suprachiasmatic nuclei grafts restore the circadian rhythm in the paraventricular nucleus of the hypothalamus. J Neurosci 2004, 24:2983-2988.
9 Reppert SM, Weaver DR: Coordination of circadian timing in mammals. Nature 2002, 418:935-941
10 Rivkees SA, Mayes L, Jacobs H,Gross I: Rest-activity patterns of premature infants are regulated by cycled lighting. Pediatrics 2004, 113:833-839.
11 Glass L: Synchronization and rhythmic process in physiology. Nature 2001, 410:277-284.
12 Lewy H, Naor Z, Ashkenazi IE: From ultradian to infradian rhythms: LH release patterns in vitro. Chronobiol Int 1999, 16:441-450.
13 Lunshof S, Boer K, Wolf H, van Hoffen G, Bayram N, Mirmiran M: Fetal and maternal diurnal rhythms during the third trimester of normal pregnancy: outcomes of computerized analysis of continuous twenty-four-hour fetal heart rate recordings. Am J Obstet Gynecol 1998, 178:247-254.
14 Visser GH, Goodman JD, Levine DH, Dawes GS: Diurnal and other cyclic variations in human fetal near term. Am J Obstet Gynecol 1982, 142:535-544.
15 Patrick J: Influence of maternal heart rate and gross fetal movements on the daily pattern of fetal heart rate near term. Am J Obstet Gynecol 1982:533-538
16 Patrick J, Campbell K, Carmichael L, Natale R, Richardson B: Patterns of gross fetal body movements over 24-hour observation intervals during the last 10 weeks of pregnancy. Am J Obstet Gynecol 1982:533-538.
17 Seron-Ferre M, Ducsay CA, Valenzuela GJ: Circadian rhythms during pregnancy. Endocr Rev 1993, 14:594-609.
18 D'Souza SW, Tenreiro S, Minors D, Chiswick ML, Sims DG, Waterhouse J: Skin temperature and heart rate rhythms in infants of extreme prematurity. Arch Dis Child 1992, 67:784-788.
19 Reppert SM, Weaver DR, Rivkees SA, Stopa EG: Putative melatonin recepters in a human biological clock. Science 1988, 242:78-81.
20 Hao H, Rivkees SA: The biological clock of very premature primate infants is responsive to light. Proc Natl Acad Sci USA 1999, 96:2426-2429.
21 Dimitriou G, Greenough A, Kavvadia V, Mantagos S: Blood pressure rhythms during the perinatal period in very immature, extremely low birthweight neonates. Early Hum Dev 1999, 56:49-56.
22 Ardura J, Andres J, Aldana J, Revilla MA, Aragon MP: Heart rate biorhythm changes during the first three months of life. Biol Neonate 1997, 72:94-101.
23 Updike PA, Accurso FJ, Jones RH: Physiologic circadian rhythmicity in preterm infants. Nurs Res 1985, 34:160-163.
24 Bueno C, Diambra L, Menna-Barreto L: Sleep-Wake and Temperature Rhythms in Preterm Babies Maintained in a Neonatal Care Unit. Sleep Research Online 2001, 4(3):77-82.
25 Schimmel M, Waterhouse J, Marques MD, Weinert D: Circadian and Ultradian Rhythmicities in very premature neonates Maintained in Intubators. Biol Rhythm Res 2002, 33:83-112.
26 Korte J, Wulff K, Oppe C, Siegmund R: Ultradian and circadian activity-rest rhythms of preterm neonates compared to full-term neonates using actigraphic monitoring. Chronobiol Int 2001, 18:697-708.
27 Weinert D, Sitka U, Minors DS, Waterhouse JM: The development of circadian rhythmicity in neonates. Early Hum Dev 1994, 36:117-126.
28 Warner RM: Spectral Analysis of Time-series Data The Goldford Press, New York, London; 1998
29 Russell RJ: Significance tables for the result of fast fourier transformations. British Journal of Mathematical and Statistical Psychology 1985, 38:116-119.
30 Thomas KA: The emergence of body temperature biorhythm in preterm infants. Nurs Res 1991, 40:98-102.
31 Ardura J, Gutierrez R, Andres J, Agapito T: Emergence and evolution of the circadian rhythm of melatonin in children. Horm Res 2003, 59:66-72.
32 Wakayama K, Ogawa T, Goto K, Sonoda H: Development of ultradian rhythm of EEG activities in premature babies. Early Human Development 1993, 32:11-30.
33 Mirmiran M, Bernardo L, Jenkins SL, Ma XH, Brenna JT, Nathanielsz PW: Growth, neurobehavioral and circadian rhythm development in newborn baboons. Pediatri Res 2001, 49:673-677.
34 Mirmiran M, Baldwin RB, Boeddiker M, Ariagno RL: Development of circadian rhythms in premature infants. Sleep Research Online 1999, 2(Supplement I):
35 Thomas KA: Biological rhythm development in preterm infants: does health status influence body temperature circadian rhythm? Res Nurs Health 2001, 24:170-180.
36 Mortola JP, Seifert El: Hypoxic depression of circadian rhythms in adult rats. J Appl Physiol 2000, 88:365-368.
37 Bishop B, Silva G, Krasney J, Salloum A, Roberts A, Nakano H, Shucard D, Rifkin D, Farkas G: Circadian rhythms of body temperature and activity levels during 63 h of hypoxia in the rat. Am J Physiol Regul Integr Comp Physiol 2000, 279:R 1378-R 1385.
38 Sharp FR, Bernaudin M: HIFI and oxygen sensing in the brain. Nat Rev Neurosci 2004, 5:437-448.
39 Chilov D, Hofer T, Bauer C, Wenger RH, Gassmann M: Hypoxia affects expression of circadian genes PERI and CLOCK in mouse brain. Faseb J 2001, 15:2613-2622.

One Into Two Will Not Go: Conceptualizing Conjoined Twins

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This paper is written in response to controversial judicial decisions following separation surgery on conjoined twins "Jodie" and "Mary." The courts, it is argued, seem to have conceptualized the twins as "entangled singletons" requiring medical intervention to render them physically separate and thus "as they were meant to be," notwithstanding the death of the weaker twin, Mary. In contrast, we argue that certain notions, philosophical and biological, of what human beings are intended to be, are problematic. We consider three compelling conceptualizations of conjoined twins and advocate a model that conceives them as two psychologically separate individuals who happen to share a body, the sharing of a body being integral to the individuality of each twin. While we reject an essentialist view of the conjoined state, a view which might render separation surgery unthinkable in all cases, we nevertheless argue against an adversarial interpretation of conjoined twins' respective best interests. We maintain that the physical entanglement should be regarded as a shared problem rather than one posed by one twin to the other. And if, after deliberation, separation surgery is deemed the least detrimental alternative or the lesser of two evils, then there should be recognition of what conjoined twins will lose, as well as gain, through separation. The current drive to separate twins at all costs may evince a deeper unease with bodily configurations that appear to threaten the premium that the Western ethical and legal tradition places on personal sovereignty, and the physical circumscription that such sovereignty assumes.

This article has been prompted by our deep sense of unease with the reasoning of the Court of Appeal in a case involving conjoined twins, known for legal purposes as Jodie and Mary.[1]

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We think it is a startling example of the strong emphasis in the Western ethical and legal tradition on physical separateness as a constitutive feature of individual identity. It is also, we think, an unusually clear expression of the drive within the law, the medical profession, and the public to customize human anatomy in accordance with norms that associate individuality with the standard – that is, the physically separate, body. With advances in medical technology, a technological imperative seems to have arisen to sculpt conjoined twins in order to make them conform to notions of the standard body. This is so even if such reconfigurations of the human body would result in catastrophic damage to the mobility, reproductive, and life functioning of the people concerned. We believe that this imperative derives, in part, from the desire to make the anatomically abnormal conform to what makes us feel comfortable. We also believe that there are circumstances when separating conjoined twins is not in their best interests and that, in some cases, it is to the benefit of both patients and society that our understanding of what is normal is challenged.

The Legal Judgments

In the case of Jodie and Mary, the Court of Appeal took the unprecedented step of endorsing a lethal assault on an innocent person, Mary. In brief, the case concerned the lawfulness of surgical separation which would have fatal consequences for Mary, because a number of vital organs on which Mary depended were contained within the skeletal structure of her sibling Jodie. Although the High Court and Court of Appeal judges differed in their legal reasoning, they all concluded it would be lawful to kill Mary in order to save Jodie. Synthesising the arguments of the appeal court judges, they thought that in these unique circumstances, killing Mary was a proportionate response to her sibling's welfare requirements and that deliberately fatal surgery, which normally the law would regard as a murderous act, could, with recourse to legal principles, be transmuted into lawful homicide.

A crucial aspect of this case would have been how the judges conceptualized Jodie and Mary's predicament. Was Mary a parasite putting Jodie's life at greater risk? Was Jodie an

individual with an unusual anatomy? Or were Jodie and Mary unique people requiring a unique response from the doctors and the courts? Despite the appeal court's insistence that it was expounding law not acting as arbiter of morals, the legal inferences that each judge was able to draw from the complex facts of the case would have been affected by their imaginative grasp of the dilemma. Did they approach this appalling predicament in terms that properly addressed its unique character, or did they cope by making it conform, inappropriately, to more tractable ethical and legal concepts?

All the judges involved in the case in the High Court and Court of Appeal made their decision on the basis that there were two independent minds, though enclosed within a single continuum of skin. Each twin presented with her own head, brain, lungs, and vital organs, but shared a torso, umbilicus, and bladder. In order to sustain their lives, however, they relied on the cardiovascular system largely located within the skeletal structure of Jodie. Both courts conceived of this as Mary relying on her twin Jodie's heart and lungs for survival. As we argue in greater detail later in this article, we dispute the way in which the courts describe Mary's relationship to Jodie, namely as a physical threat to Jodie through the former's dependence for bodily survival on organs that, by implication, "belong" to the latter. We prefer to describe Jodie and Mary as having a "two in one" body, or bodily survival system, the components of which neither is free to dispose of as she pleases. Thus, the cardiovascular system on which the twins depend is not "Jodie's" but forms part of "Jodie and Mary." While the judges seem to assume that properly constituted individuals ought to have clearly circumscribed physical zones, we would argue that being in the conjoined state forms part of conjoined twins' individuality. In so arguing, we are not adopting an essentialist view of the conjoined state, which would be prohibitive of separation surgery. Rather, we wish to highlight – where separation is called for – what is lost in separation.

In the High Court, Mr Justice Johnson seems to have made his decision on the legal premise that to split Mary from her sister would be analogous to recent cases involving the withdrawal of futile medical treatment, in the knowledge that the patient will almost certainly die as a result. To separate the twins surgically would not be to murder Mary, but rather to allow her to die, which the law allows in certain circumstances. The analogy with treatment withdrawal could be extended to splitting a child off from her organic life support system, her sister.

In the Court of Appeal, all the judges agreed that Jodie and Mary were each a person in their own right and therefore that each had a right to life. As each was liveborn; that is, born with a functioning brain, separate from their mother, and capable of sustaining independent existence, albeit with medical help, each fell to be protected by the law of murder.

In English law, the fetus only acquires full legal protection when it is born and has a separate existence from its mother.[2] This is the so called "liveborn" principle. There is no English case dealing directly with the degree of brain function necessary for birth. The better legal view, it is suggested, is that a person with a functioning brain stem can be liveborn, even if most or all the cerebral hemispheres; that is, the higher brain, are absent. Thus, it is not, for example, lawful to harvest the organs of anencephalic babies.

Mary was not merely a fleshy excrescence that could be separated off from Jodie without legal consequences. It was therefore necessary to reconcile her interests with Jodie's, with whom she was bound together by flesh.

Brooke LJ appears to have derived his notion of bodily integrity (and inviolability?) directly from the sanctity of life doctrine: "the doctrine of the sanctity of life respects the integrity of the human body." He then seems to use a natural rights argument to justify fatal surgery: "The proposed operation would give these children's bodies the integrity which nature denied them." Robert Walker LJ, going further, seems to equate the right to life with the natural right to physical integrity, which he interprets as the right to a whole, physically circumscribed, body, over which the legally competent patient would be sovereign: "Each twin's right to life includes the right to physical integrity, that is the right to a whole body over which the individual will, on reaching an age of understanding, have autonomy and the right to self determination." Thus, restoring Mary's bodily integrity, though it would kill her, was a "good end" which both disposed of the welfare issue and offered a defence to a charge of murder through the application of the doctrine of double effect. "This type of double effect cannot be relevant to conduct directed towards Mary unless the mere fact of restoring her bodily integrity, even at the moment of death, can be seen as a good end in itself and as something which ought to be achieved in the best interests of Mary as well as Jodie."

Although neither court defined with precision the ethical and legal status of Jodie and Mary's fleshly bond, the assumption seems to have been that out of their entanglement of body parts, two singleton individuals could be "liberated," though with fatal consequences for one of the twins. The assumption that Jodie and Mary had detached discrete interests that could be weighed into the balance is especially apparent in the judgment of Ward LJ. His view that the twins were meant to be physically separate people, of whom one (the "parasite" Mary), was unnaturally (and therefore perhaps unfairly?) attached to the other, is reinforced by the use of hypothetical cases, for example, Nazi commandants, cliffhanging climbers, and trigger happy six year olds, designed to capture the predicament. He reconciles their competing interests through a search for the least detrimental alternative, which, in view of Mary's supposed parasitic living, inevitably favors Jodie. Because Mary is "fated for death" she cannot be helped because she is "unnaturally supported" and treating her is "futile," worthless, useless.

Were these court decisions responsible applications of legal principle that captured the ethical dilemma? Or does the judges' reasoning represent a failure of the ethical and legal imagination? How did the court conceptualize the twins, and how should they have done? It is suggested that their lordships based their moral and legal reasoning on the anthropological premise that human beings are meant to be physically separate. As a result, they were led quite easily into using language that suggested that Jodie and Mary (or at least one of them) were in wrongful and harmful contact with each other. The judges might have viewed matters differently, notwithstanding that their decision would probably have been the same, if they had regarded Jodie and Mary's conjoined state as part of a unique relationship requiring a unique response.

Three Conceptual Possibilities

The three possibilities we consider could be applied to the case

of any conjoined twins. The first will definitely only be applicable to some; the second and third are competing conceptualizations of twins who are both regarded as persons. While the second may seem more plausible in some cases and the third in others, we are primarily considering the possibilities with respect of Jodie and Mary's particular situation.

The first possibility is that only Jodie is a person, and that Mary is just some extra flesh attached to her. If the term "parasitic conjoined twins" were taken in its medical sense, this is what it would mean. This scenario would present no ethical problems for separation since there would only be Jodie to consider. The second possibility is that the two should, by rights, be two physically separate people, singletons, who are by some accident joined together. This tends to see both Jodie and Mary as competing for the possession or use of body parts, and having competing and incompatible interests. The third possibility, and the one we would argue for, sees them, and all conjoined twins, as two individuals, psychologically separate but, by degrees, with a shared body. Here, their body is not something they are in competition over, but something they both have interests in, although neither has exclusive rights over it. Also, although they are psychologically individuals, part of what makes them the individuals they are is their conjoined state. This obviously raises questions about the sense in which they are individuals, and whether they would be the same or different individuals after separation, were this to take place.

Almost everyone would agree there are reasons for rejecting the first picture. We argue that although there are temptations to accept the second picture, the reasons in favour of it are difficult to justify philosophically, and tend to lead to deciding in favour of one twin to the detriment of the other. The third picture, we feel, offers the best way of understanding the reality of the situation facing conjoined twins. It also offers the best way of dealing with that situation while respecting both twins as the law and at least some ethical positions claim we should, without consideration of their individual mental and physical abilities or potential. In the next few sections we will consider each case in turn.

(i) Mary as a "parasitic" conjoined twin

Did or should the courts have considered Mary as part of Jodie's body? This interpretation was not open to either court as a matter of law. Both twins had functioning brains, although there is evidence that Mary had suffered brain damage. Mr. Justice Johnson, in the High Court, drew particular attention to Jodie's brightness and alertness. Mary, in contrast, had a "very poorly developed primitive brain" and "reduced cortical development." Nevertheless, as a matter of law, Mary as well as Jodie was to be afforded all the legal protections appropriate to "liveborn" children.

Philosophically, most positions on the person would classify Jodie and Mary as the same. Either both would count as persons, since both are human (by which we mean biologically members of the species Homo sapiens) and alive. Or, according to theories which see as persons only those who have certain mental attributes (the ability to be self reflective, to plan their lives, to make moral decisions), neither would yet be a person. Many philosophical discussions on the nature of the person arise in the context of the abortion debate. For supporters of the first position see Noonan and Beckwith[3, 4] and for supporters of the second position see Feinberg, Warren, and Singer.[5,7] The only way we might differentiate between Jodie and Mary in terms of personhood is by taking account of their potential to acquire the capacities of a person. If we could say that Jodie could grow up to be a person, but Mary would never have the necessary capacities, we might think of them as having different moral statuses. One proponent of this sort of position is Don Marquis.[8] He argues that what has moral standing in debates about abortion (and therefore about killing in general) is what has a future like ours. Here we could perhaps say that Mary is so badly damaged that she will never have a future like ours, and that perhaps it would not be wrong to kill her. Marquis does not address the question of badly damaged fetuses, infants or adults, so it is not clear whether he would hold this position with regard to Mary, but perhaps an argument along these lines could be constructed from his position.

One of the problems with that position, however, is that even a healthy, normally developing fetus has a higher moral status than many adults with mental problems, yet we are reluctant to say that such adults are not persons. Even if we were to think of Mary in this way, this may not allow us straightforwardly to prioritise Jodie's interests over hers. And if we did it is hard to see that Mary would be classed as mere flesh; she would at least be granted the moral status of an animal.

If we think of them as two people, we still have a problem as to the role the body plays in the concept of a person. The next two possibilities consider whether each person should have their own separate body, or whether two people can share a body. These approaches broadly correspond to the "bodily distinctness" and "bodily relatedness" views described by Cathleen Kaveny in the search for a normative understanding of bodily integrity. Professor Kaveny argues that each view generates different criteria against which the ethics and law of separation surgery can be evaluated. This distinction draws attention to different anthropological premises that may underlie the medical, judicial, and parental thinking. It also provides a principled way of relating the particular issues raised by the case of Jodie and Mary to all cases of conjoined twins.[9]

(ii) Jodie and Mary as two entangled singletons

Did the courts, or should they, view Jodie and Mary as two individuals meant to be physically separate? It is clear, factually, that Jodie and Mary were never physically independent of each other until they were separated through the surgery that resulted in Mary's death. They emerged as a result of a splitting process that was never completed. Thus, there is a "given-ness" about their conjoined state that makes it difficult to claim they were "meant to be physically separate" rather than were "meant never to have physically separated." It seems clear, however, that the Court of Appeal felt it could only think of Jodie and Mary as singletons, physically separate individuals, in order to make an appropriate response. In other words, they seemed to have considered that the only way to think of them was as two separate individuals who were unfortunately joined together. The only model the courts seem to have for thinking about people and their best interests, is that of physically distinct individuals.

On one level, this is not surprising. The model of "one brain, one body" accords with the strong emphasis in the Western ethical and legal tradition on personal sovereignty. The ethical principle of autonomy is usually translated into negative terms as a right of non-interference, a right regulated, for example, by laws

prohibiting non-consensual touching. Within this paradigm, the notion of individuality is linked to a separate body and anything else seems to be unimaginable, or at the very least, implausible. Physical separateness seems to be the indispensable condition for a life of dignity. Thus, physical separation seems to be the primary goal in the case of two persons in one body even if it leads to the death of one twin in certain circumstances. This would entail regarding the body, or parts of the body, as belonging to one of the twins, and the other twin as unjustifiably interfering with the first twin's rights over her body. The appeal court's reasoning could be interpreted as a perfectly intelligible expression of the association within the Western ethical and legal tradition between individuality and physical circumscription.

On another level, such reasoning causes problems. By treating Jodie and Mary as if they were singletons (physically separate), their lordships tended to resolve the predicament in a way that was detrimental to one of the twins. Actually, we argue that separation is detrimental to both twins, since they both lose part of themselves in the process. So conceiving of the twins as singletons both conceives of them as less than they are, and, since it regards separation as the primary aim, tends to ignore the loss to both of them in separation.

Conceptualizing Mary as a "parasite" or one living "parasitically" suggests that Mary attached herself to Jodie for her own benefit. Here, we understand the word "parasite" to refer to a "live" twin, in contrast to its medical meaning, which refers to a fleshy outgrowth, which, while human in form is completely devoid of brain function.

The assumption is that Jodie and Mary ought "by rights" or "by nature" to have been physically independent. By treating them as if they had the discrete interests that are appropriate to physically independent people, those interests could be weighed into the balance and set off against each other with inevitable and deleterious consequences for Mary. By drawing moral and legal inferences on the basis of standard human physiology, the courts found it difficult to avoid conceptualising the twins as adversaries. This adversarial picture was evoked by Ward LJ in his startling speculation on what Jodie might have said to Mary had she been able to utter, "Stop it, Mary, you're killing me," and the vivid confrontational analogies that the court used to capture the predicament.

This suggests that we think persons are somehow intended or meant to be singletons; that is, physically separate, one person to each body and vice versa. Not only does the law work within this paradigm, but so does medicine, and to some extent it has to. In order to deal with people's medical problems we have to operate with some idea of how people are supposed to be. The question is: what idea. We have, and for some circumstances need, an idea of what counts as normal for humans. There are, however, many variations from the norm, some of which we find significant, some not. So is having a single body for two people an acceptable variation from the norm, or a defect that we need to do something about?

A recent philosophical attempt to argue that there is a way nature intended us to be may be found in Philippa Foot's recent book, Natural Goodness.[10] Here she argues that we can distinguish between variations from the norm for a living thing in terms of which characteristics are Aristotelian necessities, and which are not. If a creature lacks an Aristotelian necessity, then it is defective, but other variations from the norm are not defects. An Aristotelian necessity for a creature is a characteristic of that creature which it needs to live the type of life natural to its species. For plants and animals such characteristics are defined as those necessary for survival and reproduction.

Foot allows both that human lives are concerned with more than survival and reproduction, and that either of these can be rejected by humans in pursuit of what they consider a worthwhile life. So does a particular bodily shape, or even a body of one's own, count as an Aristotelian necessity for humans? We argue that this is difficult to maintain. Of course conjoined twins are restricted in the things they can do, in the lives they can lead, and in the reproductive opportunities available to them. This is true, however, of all human beings in one way or another. The fact that being conjoined is statistically of low probability is not enough to make it a defect. Foot's philosophical notion of defect; that is, not having characteristics which are Aristotelian necessities, bears a certain resemblance to the theological notion of ontic evil, instances of which may warrant human correction – for example, a baby being born without the capacity to see or physically joined to his or her sibling. While, however, in the Roman Catholic tradition, bodily distinctness may be the moral norm of bodily integrity, in Foot's analysis such distinctness does not seem to be a necessity in the Aristotelian sense. Neither can we rely on a distinction between what is a natural life, and what is artificially supported, as Foot can do in the case of plants and animals, since it is not clear what would count as natural for humans. Human society, and therefore what is natural for humans, changes as a result of development of human skills, knowledge, and ways of thinking. Admittedly conjoined twins might not even be born or survive without medical intervention. If, however, medical intervention is to count as unnatural, then many others might not survive who we would not consider defective. There seems to be no principled place to draw a boundary between the natural and the unnatural for human beings and therefore to distinguish between differences and defects. A similar argument is used by Ruth Garrett Millikan in her Language, Thought and Other Biological Categories: New Foundations for Realism.[11] She argues:

The business of the biological species of staying in business determines standards for individuals of that species, standards which, though they often correspond to averages, are not defined in terms of mere averages over the species. Consider, for example, how few sperm or immature members of most species actually manage to perform all the functions that nonetheless are proper to them and that help account for the survival of the kind.

The evolution of a species is, however, related to an environment. Our point is that the human environment, within which we evolve, has, through medical science and public health, changed characteristics which would have been so disadvantageous as to preclude the survival of an individual long enough to reproduce. Such characteristics may still be disadvantageous, but they do not rule out survival and reproduction. Thus, the standards for humans are determined in part by developments in human societies and sciences.

This is not to say that we would count nothing as a defect.

When the question arises, however, it is not clear what should guide judgment.

If we cannot say clearly what should and should not count as defects for humans, and in particular whether a physically separate body is something to be aspired to, or as Robert Walker LJ claimed, something to which we have a right, then can we, or should we, assume it is something we should aim for in dealing with conjoined twins? We now consider an argument that it is not, or at least not necessarily.

(iii) Two individuals with a shared body

In a seminal article,[12] Alice Domurat Dreger argues that there needs to be a paradigm shift in the way that doctors (and by extension lawyers and the general public) view conjoined twins. She claims that the medical profession's lust for intercision is driven by powerful cultural assumptions about what it is to be an individual, which often work against the best interests of conjoined twins (Dreger,[12] p 25). It is suggested that her analysis can help us to elucidate some of the hidden assumptions that may have underlain the decisions of the English courts in the case of Jodie and Mary. Her view is that the strong association between individuality and physical separateness is culturally mediated and, in particular, mediated by the medical profession (Dreger,[12] p 4). The medical profession, when encountering unusually configured bodies, plays a pivotal role in deciding what the connection is between anatomy and identity. The meaning of "normal" physiology and individuality is construed and reified surgically in conformity with those prevailing cultural assumptions.

So powerful is the Western emphasis on physical separateness that the medical profession is unable to grasp the concept of a rich worthwhile conjoined life (Dreger,[12] p 11). Dreger makes the startling observation that: [Many twins] old enough to do so express a desire never to be separated because it will result in such a profound change of identity or even the death of one's other half. (Imagine having a vibrant part of your body amputated and lost forever, or else separated and left to lead an independent life!)

In spite of copious evidence that conjoined twins do live lives they value, (see, for example, Smith,[13] and Miller[14]) most doctors find the prospect of conjoined life highly undesirable. Not only are they willing to pursue potentially catastrophic surgery but they are lauded for taking modern surgical expertise to its limits.

For Dreger, however, all this begs a fundamental question: for whose sake is the operation carried out?

The paradoxical fact is that being conjoined is part of conjoined twins' individuality. If we singletons cannot understand that, if we cannot comprehend a life of two consciousness in one continuum of skin, that says something more about us than about them (Dreger,[12] p 26).

The limits of individuality in the case of conjoined twins extend beyond the boundaries of the "standard" body. With reference to the work of Mary Douglas[15] and Stephen Jay Gould,[16] Dreger argues that the body is a flexible concept that cannot be pigeonholed into a discrete category. The accidental fact of conjoined twins puts the definition of individuality itself in issue.

Rather than looking at conjoined twins and noticing how much or how little autonomy singleton's minds and bodies really possess, rather than letting their bodies challenge ours, rather than struggling with the question of what it ever means to have an individual mind or body in an intimate society, we choose to eliminate conjoined twins, to eliminate their accidental and profound questioning of the very concept of human individuality (Dreger,[12] p 25).

This view seems to make a case for considering conjoined twins as two individuals, psychologically separate, part of whose individuality is constituted by being conjoined. That is to see them as essentially, rather than accidentally joined. This may encourage viewing their situation not as one in which each twin is a problem for the other, to be solved by contractual style negotiation, but whether they both face a common problem and in which they have joint interests.

So viewing the twins as entangled singletons, and thus intended to be physically separate, suggests that the primary aim of medical intervention should be separation. Of course, this may not always be possible, as the recent case of Courtney and Natasha shows, and requires assigning organs which both may have enjoyed the use of to one twin or another. Courtney and Natasha May were discovered in utero to have separate arms, legs and head, but to share a four chambered heart, which was distorted and slightly larger than normal. Their parents had originally decided on separation, sacrificing Courtney. In the event, after birth it was decided that the operation was not feasible. In Jodie's and Mary's case, this view of separation as a benefit in its own right adds weight to balance the bad effect of Mary's death.

Viewing them as two psychologically separate individuals with a shared body does not see physical separation as a primary aim; in fact it calls for recognition of what is lost in separation. As such, separation is one of the options to be considered when acting in the twins' best interests. This position also calls for attempting to act in the best interests of both twins, not automatically balancing one person's interests against the other's.

The Way Forward

The problem with the view of twins as entangled singletons is that it assumes something about the nature of human individuality (that having a body physically separate from that of others is an essential part of it) that cannot be philosophically justified. It sees conjointure as a defect to be corrected. If, however, we cannot distinguish between defect and differences, then conjointure surely has to be seen as something that may be a disadvantage in living life in our society, but may also have advantages. It might be argued that what seems advantageous to conjoined twins, only seems so because they cannot conceive of what it is to be separate, and this leads to a distorted view of the conjoined life. It could also be retorted, however, that we singletons cannot conceive of conjoined life and so also have a distorted view of it. We do not see things as they are, but as we are.

The two in one body view sees conjointure as a physical state that has both advantages and disadvantages, while recognizing the value of the advantages. Since the disadvantages are a compound of the twins' physical state and how our society is organised, it must surely be an open question whether the best

compromise is to change conjoined twins physically to conform to society's constraints and views, or to some extent to change the constraints and views of society to accommodate conjoined twins.

It seems that ethical and legal concepts designed to deal with confrontation are not always helpful in elucidating the nature of the conjoined relationship. Unlike most "contractual" relationships, which are premised on arrangements made between physically independent people, conjoined twins have an unbroken history of physical interdependence. There never was a time when they were not together. So it does not make sense to pretend that their conjoined relationship was something entered into through negotiation, or to treat it as something that can be broken on the assumption that their physical entanglement was not negotiated, as it were, at arm's length.

There may well be an intimate relationship between the physical boundaries and the moral boundaries of conjoined twins. If being the individual you are, and if notions of privacy, autonomy, dignity, and individuality are all tied up with the bodies we inhabit, then surely the same should be true of conjoined twins. Dreger argues that their individuality certainly is, in that it is constituted in part by their intimate physical involvement with one another.

In an interesting thought experiment, in response to Judith Jarvis Thomson's celebrated violinist analogy,[18] Kenneth Himma explores this relationship in the case of hypothetical conjoined twins, known as Tom and Joe.[19] While Tom and Joe, who have survived to adulthood joined, could live a long and healthy life together, they cannot be separated without killing Tom, as all the vital organs are contained within the skeletal structure of Joe. The purpose of the thought experiment is to demonstrate that the unbroken history of physical interdependence, common to conjoined twins and the maternal fetal relationship, has moral implications not adequately accounted for by the "contractual" model applied by Thomson. Himma argues that because of that unbroken history, neither has unlimited freedom to dispose of "the shared continuum" as they please. Himma's twins are adult, and able to decide for themselves. If, however, he is right, then it looks as if no one else may decide on behalf of conjoined twins to dispose of their body solely for the benefit of one and to the detriment of the other, as if one has more right to parts of it than the other. In Himma's case all the vital organs are contained within what is identified as Joe's skeletal structure, but they are still not his to dispose of. He has no right to deny Tom their use, since they have never been exclusively his. He argues that the contractual model, which sees the twins as separate agents with separate rights, is inappropriate to their situation and history. In a commentary on this argument Davis claims that what is important is not just an unbroken history of being joined, but the sharing of a body.[20] Himma denies that the twins share a body, but Davis claims that if anyone does, they do, and as a result questions about the disposal of that body have to be settled in the light of the twins' other interests.

Conclusion

Since parasitic conjoined twins do not seem to pose particular moral problems, our concern has been to explore the "entangled singletons" and "two in one body" models for conceptualising conjoined twins. We feel that the entangled singletons model does not do justice to the situation of conjoined twins, and has not, so far as we have discovered, been justified philosophically. It automatically favours physical separation as good in itself, and therefore tends to lead to decisions for surgical separation which play down its disadvantages and ignore the benefits of remaining conjoined. The two in one model reflects better the reality of conjoined twins' situation. It also recognises the losses to twins in being physically separated and calls on us to attempt to resolve their situation without necessarily pitting them against one another, as even Kaveny does in her resolution of the predicament. Cathleen Kaveny's solution to the problem of conjoined twins, even when this is recognised as a case of what she calls bodily relatedness, is to perform a species of utilitarian calculation comparing the benefits to one against the detriment to the other. We have two concerns with this. One is that it pits the twins' interests against each other. The other is that it seems to assume that the twins are the same individuals before and after this calculation. Yet Kaveny herself recognises that "our bodies reflect and shape our identities" (Kaveny,[9] p 758), so the two individuals in one body cannot be the same as the two individuals with

separate bodies who are in some sense created by the separation surgery. This renders the aforementioned calculation not as simple as it looks.

It may be that in the case of Mary and Jodie, the decision would still come down on the side of surgical separation. And cases such as this, where separation will result in the death of one while giving reasonable prospect of healthy life to the other, are always going to be difficult. The difference our approach would make would involve not having to think of one twin as somehow preying on and being a problem for the other. This happens even where one is not noticeably worse off than the other is. In the case of the Lakenberg twins, the medical team painted their fingernails different colours to be sure of saving the right one, (Dreger,[12] p 15) and initial talk of Courtney and Natasha, designated Courtney as the "passenger." In both cases the twins shared a heart and were joined at the chest. The Lakenberg twins were separated, with the survivor nearly reaching her first birthday, although confined to hospital and on a ventilator. It was decided after birth that separation was not feasible for Courtney and Natasha. The main point, however, is that the Lakenberg twins were so indistinguishable that painted fingernails were needed to tell them apart, and Courtney seems to have been designated as a passenger, largely on the basis that it was thought more feasible to donate the shared heart to Natasha. In other words there is felt to be a need to designate one as posing a problem for the other even when this is not clearly the case. Perhaps it makes sacrifice surgery easier to contemplate if the child sacrificed is understood as threatening the potential survivor, however innocently, even though the grounds for saving one rather than the other may be pragmatic. Our approach would encourage seeing the twins as facing a common problem (which may need to be solved by surgical separation to the detriment of one of them) while attempting to value them equally and in order to act in the best interests of both. Their common physiology is a problem for both, and separation will create disadvantages for both, even for a survivor who might otherwise have died.

Of course, our approach is going to raise a host of problems, particularly for notions of individuality, identity, and responsibility. If we can have two individuals in one body, what are the limits of their individuality and identity? When they act, who is responsible for their actions? How does their autonomy function with respect to decisions about their body? What does privacy mean between two who are so intimately connected? Perhaps, however, these problems should be considered in the light of how they are resolved by those twins who have remained conjoined. The fact that such problems are raised by the existence of conjoined twins should perhaps be treated as a challenge to the rest of us to rethink our understanding of these concepts in general.

The ethical and legal thinking that treats conjoined twins as if they were physically separate entities who have unfortunately become entangled and need to have their separate existence restored, seems to have things the wrong way round. Conjoined twins are not separate and never have been. If we separate them, we should at the very least recognise that we are creating two new separate entities from two who were one, and that in doing so we are removing from each of them part of themselves. It may, of course, be a decision that we need to make for the benefit of both twins, but we should be wary of assuming that a physically separate existence is automatically in their best interests. If we are more comfortable faced by singletons, if they conform better to the hidden assumptions of our ethical, legal, and medical notions of what is normal and acceptable, that does not mean these are good enough reasons to change conjoined twins to fit. If medical decisions made on behalf of conjoined twins should be made in their best interests, then we had better be sure that they are, and that they are not made just because they make things easier for us to deal with. It is notable that it was in response to Jodie and Mary's anatomical abnormalities that the Court of Appeal contributed some of the most stringent interpretations of bodily integrity in English law. The court's reasoning is a good illustration of Canguilhem's observation that "the abnormal, while logically second, is existentially first".[21]

We think that the abnormal is defined in terms of the normal, but in fact it is in the face of what is unfamiliar that we are prompted to define more clearly what is normal. This perhaps explains the appeal court's strong affirmation of the connection between physical separateness and personal dignity. However, the unusual anatomy of conjoined twins could, and perhaps should, be taken as an opportunity to question that connection, and challenge our thinking about autonomy, privacy, dignity, and individuality.

References

1 Re A (Children)(Conjoined Twins: Surgical Separation)[2000] 4 All ER 961.
2 Paton v. Trustees of BPAS [1979] QB 276, [1978] 2 All ER 987 [QBD].
3 Noonan J. An almost absolute value in history. The morality of abortion. Cambridge, MA: Harvard University Press, 1970.
4 Beckwith FJ. Politically correct death: answering arguments for abortion rights. Grand Rapids, MI: Baker Books, 1993.
5 Feinberg J. "Abortion" in matters of life and death. In: Regan T, ed. New introductory essays in moral philosophy. New York: Random House, 1986.
6 Warren MA. On the moral and legal status of abortion. Monist 1973; 57: 43-61.
7 Singer P. Practical ethics [2nd ed]. Cambridge. Cambridge University Press, 1993, ch 4.
8 Marquis D. An argument that abortion is wrong. In: LaFollette H, ed. Ethics in practice: an anthology. Oxford: Blackwell Publishers Ltd, 1997.
9 Kaveny MC. The case of conjoined twins: embodiment, individuality and dependence. Theol Stud 2001; 62: 753-86.
10 Foot P. Natural goodness. Oxford: Oxford University Press, 2001.
11 Millikan RG. Language, thought and other biological categories: new foundations for realism. Cambridge, MA: MIT Press, 2001.
12 Dreger AD. The limits of individuality: ritual and sacrifice in the lives and medical treatment of conjoined twins. Studies in the History and Philosophy of Biology and Biomedical Science 1998; 29: 1-29.
13 Smith JD. Psychological profiles of conjoined twins: heredity, environment and identity. New York: Praeger, 1988.
14 Miller K. Together forever. Life 1996 Apr: 44-56.
15 Douglas M. Purity and danger: an analysis of concepts of pollution and taboo. London: Routledge and Kegan Paul, 1966: 122.
16 Gould SJ. Living with connections. Nat Hist 1982; 91: 18-22.
17 http://www.guardian.co.uk/Archive/Article/0,4273,4349873, 00.html (accessed 5 Feb 2002).
18 Thomson JJ. A defence of abortion. Philos Public Aff 1971; 1: 47-66.
19 Himma KE. Thomson's violinist and conjoined twins. Camb Q Healthc Ethics 1999; 8: 428-35.
20 Davis JK. Commentary on Thomson's violinist and conjoined twins. Camb Q Healthc Ethics 1999; 8: 435-9.
21 Canguilhem G. The normal and the pathological [trans Fawcett CR]. New York: Zone Books, 1991: 243.

Nurses, Medical Errors, and the Culture of Blame

Gloria Ramsey

In June 2004, an article in the American Journal of Nursing reported the findings of a three-year study of the organizational culture, attitudes, and assignment of responsibility for patient safety in small, rural hospitals in nine Western states. The study found that most errors fall within the realm of nursing practice and that physicians, administrators, and nurses themselves tend to see patient safety as largely a nursing responsibility. Asked to identify which profession has primary responsibility for ensuring patient safety, 96 percent of the nurses and more than 90 percent of the physicians, administrators, and pharmacists assigned primary responsibility to nurses. Only 22 percent of the respondents believed that physicians, nurses, pharmacists, and administrators share responsibility for patient safety equally.

Unfortunately, however, nurses and physicians differed on the role of nurses in effecting change. Most of the nurses indicated that they had several responsibilities in reducing medical errors, including reporting them, educating themselves and colleagues, serving as role models, making recommendations for changes in procedure and policy, reviewing reported adverse patient-safety events, and participating in investigations. Only 8 percent of the physicians who responded to the survey identified nurses as members of the decisionmaking team.

Nurses have a genuine impact on patient safety. Studies have found a link between patient safety and RN staffing and an increased rate of error when the hospital nursing staff has a smaller proportion of RNs. These are worrisome findings in light of the severe national shortage of nurses. Part of the medical malpractice crisis, then, is the confusion in the health care system and how it affects the role of the nurse.

There is no confusion in the American Nurses Association's code of ethics. This document, first adopted in 1950 and revised in 2001 to reflect and embrace the role of today's nurse, consists of a set of planks that set out nurses' fundamental values and commitments. They also offer a starting point for understanding how nurses should be involved in thinking about medical error, and why nurses blame themselves for medical errors.

The first few planks are the most important. These planks state that the nurse's primary commitment is to the patient (plank 2), and that the nurse promotes, advocates for, and strives to protect the health, safety, and rights of the patient (plank 3). "Interpretive Statements" that accompany the code add that nurses are committed to the patient's health, well-being, and safety throughout the patient's life span, and in all settings in which health care needs are addressed. Further, the code directs that, as an advocate for the patient, "the nurse must take appropriate actions regarding any instances of incompetent, unethical, and illegal practice by any member of the health care team or health care system or any action on the part of others that places the rights or best interest of the patient in jeopardy." For nurses to function effectively in this role, they must be knowledgeable about the code of ethics and their own organization's policies and procedures.

Moreover, when the nurse is aware of inappropriate or questionable practice in the provision or denial of health care, concerns should be expressed to the person engaging in the questionable practice. Attention should be called to the possible detrimental effect upon the patient's well-being or best interests, as well as to the integrity of nursing practice. When factors in the health care delivery system or health care organization threaten the welfare of the patient, concerns should be directed to the responsible administrator. If indicated, the problem should be reported to an appropriate higher authority within the institution or agency, or to an appropriate external authority.

The interpretive statements for the third plank also remind nurses that they have a responsibility to implement and maintain the standards of professional nursing practice. They recommend that nurses "participate in planning, establishing, implementing, and evaluating review mechanisms designed to safeguard patients and nurses, such as peer review processes or committees, credentialing processes, quality improvement initiatives, and ethics committees." Nurse administrators must

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ensure that nurses have access to and are included on institutional ethics committees. Nurses may consider forming their own ethics committee if the organizational ethics committee is not providing them a forum.

Lastly, the interpretive statements for the third plank recommend that when errors do occur, nurses follow institutional guidelines for reporting errors to the appropriate supervisory personnel and for assuring responsible disclosure to patients. Under no circumstances should a nurse participate in, or condone through silence, either an attempt to hide an error, or a punitive response that serves only to fix blame rather than to correct the conditions that led to it.

Given these obligations and duties, it is little wonder that nurses would blame themselves for errors in patient care. Little wonder, too, that nurses are morally burned out when they work in an environment that is not supporting of sound ethical practice. And little wonder that a nurse would feel caught in the middle when reminded about what it means to be a nurse.

In a November 2003 press release, Barbara Blakeney, president of the ANA, said, "improved patient safety and quality of care cannot be achieved without investing in and valuing nursing." Valuing nursing—now there's an idea. Nurses are the pulse of health care institutions. When new models of health care delivery were implemented in the 1990s, RNs represented the largest single expenditure for hospitals. But for exactly that reason, nurses were the first among health care professionals to feel the effects of downsizing. Layoffs, stagnant salaries, and the loss of nurse managers have further decreased the support, advocacy and resources that nurses need to provide good care. Today, nurses are even less involved in the decisionmaking process, yet the pressure on them has increased; and when our attention turns to patient safety, the pressure goes up a notch further. In medicine we blame the person at the end of the sentinel event, and the end point is usually nursing.

But if we look more deeply at what goes wrong in the typical medical error, it is almost never the nurse's actions alone. We must fix the *system* to prevent the error from recurring, and nurses alone should not accept the blame.

A nurse-attorney who conducts both litigation practice and clinical practice recently posed the following scenario to me. A woman in her mid-forties was admitted for chronic pain. At home, she took a medication called Talwin. The hospital did not have any Talwin, so staff allowed the patient to keep her own supply at the bedside. The nurse caring for this patient was a recent graduate with little clinical experience. She had a preceptor—a more experienced nurse who guides the learning and development of a novice—but the preceptor had her own heavy patient load. The physician wrote an order for 50mg intramuscular (IM) Talwin. Not wanting to bother the preceptor, the new nurse attempted to fill the order herself, but she drew up 16cc rather than 1.6cc and gave it intravenously (IV), rather than IM, because the physician's "m" looked like a "v." The patient died, and the nurse was blamed for the death.

Fortunately, the hospital administration sought to identify what had gone wrong in the system to make this error possible. One problem, it concluded, was that the preceptor was responsible for her own patients as well for mentoring a new nurse. Second, the Talwin should not have been kept at the patient's bedside. If the physician's order had been filled by the hospital pharmacist, it would have arrived on the floor prepared for administration. If the medication had to be kept at the bedside, the patient should have controlled the dosage herself via a PCA pump. A third factor was the doctor's illegible handwriting. And lastly, the new nurse needed to be supported more both before *and* after the event. She should have been included in the review of the error and the decisionmaking process resulting from it. If hospitals continue to ignore the role nurses play in quality assurance and elect only to discipline them when an error occurs, they will continue to lose nurses, and the nursing shortage will become even more severe.

Because the ethics of care is the foundation of nursing practice, nurses as independent moral agents are responsible for patient safety and must be vigilant patient advocates. But at the same time, as a careful analysis of this case demonstrates, they and other health care professionals must accept that nurses do not bear the blame for medical errors. The responsibility for medical errors is shared by all.

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Reference: 1. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J.* 2004;23:806–814.

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