

Neonatology In Singapore: The Way We Were, The Way Forward[†]

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Abstract

Singapore has a maternity hospital since 1924, but for many decades the newborns could only receive basic care. Neonatal and perinatal mortality rates were high. Marked improvement in neonatal care began from the 1980s when many neonatal departments were set up to provide intensive care. Improved socioeconomic status, better healthcare facilities, effective infection control, immunisation programmes and availability of potent antibiotics contributed to the decline of perinatal and neonatal mortality. Following the implementation of the glucose-6-phosphate dehydrogenase (G6PD) deficiency screening programme, severe neonatal jaundice and kernicterus were largely reduced. Exchange blood transfusions initiated in the 1960s and phototherapy in the 1970s had saved many babies. Kernicterus is almost not seen now. With more neonatal-trained staff, organised resuscitation teams, advances in respiratory management and better monitoring equipment, more babies have survived. Closer cooperation between obstetricians and neonatologists was a great leap forward towards perinatal medicine. Physicians should endeavour to reduce the incidence and prevalence of birth defects and metabolic errors. Perinatal asphyxia should be promptly detected and managed effectively, including neuroprotective strategies. There should be markers to predict the outcome of asphyxiated babies for decision-making. Neonatologists should be mindful of safe introduction of new technologies and rapid diagnostic techniques for infections, including group B streptococcal screening and chemoprophylaxis when required. Other current issues include prevention of major morbidities, preservation of brain function, improved neurodevelopmental outcome of premature babies, use of blood substitutes, optimal nutrition, fetal surgery, evidence-based medicine, better information systems, avoidance of medication errors, adequate sedation and pain relief of the baby, and the use of nitric oxide. One should bear in mind the need to enhance the neonatal intensive care environment, improve non-invasive monitoring and minimise invasive procedures. Physicians should prioritise neonatal care for their country and utilise less costly neonatal care. Ethical issues in neonatology that arise following advancement in neonatal care deserve attention. Advances in life sciences, such as the completion of the human genome project, cloning of tissues and organs, human stem cell research and technology, gene therapy, deoxyribonucleic acid vaccines and nanomedicine, should benefit neonatology.

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Introduction

Over a span of 35 years of my working life, I have witnessed the growth of, and also grown together with, neonatology in Singapore. As I look at the present-day status of neonatology, it gives me a sense of achievement and accomplishment. I am proud to be associated with neonatology in this country. I am particularly pleased to have worked together with a group of dedicated doctors, nurses and paramedics to build up neonatology for the country. I like to pay tribute to them. I shall be going down memory lane, from when I was then a specialist medical officer in the Paediatric Unit of the General Hospital in 1972, to being sent to work in a nursery in Toa Payoh Hospital, then the Thomson Road General Hospital. I had no inkling of neonatology and all I knew was that I have to look after the newborn babies delivered in the hospital. All

childbirths were expected to be uneventful and all newborns were presumed to be normal. No one used, or knew, the term “neonatology”, first coined in 1960 by Alexandra Schaffer when neonatal intensive care units (NICUs) were first started in hospitals in the United States. That was the decade when many considered the commencement of practice of newborn medicine.

Neonatology in Singapore would have begun in the mid-1970s, although newborn care had been in existence much earlier than this. The Kandang Kerbau (maternity) Hospital (KKH) has been in existence since 1924 and had, in 1966, recorded the most number of births in a single hospital (39,835) per annum in the world. Nevertheless, we did not have NICUs and neonatal ventilators were unheard of. The only neonatal problem at that time was neonatal jaundice.

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Medical students at that time needed to know breastfeeding and neonatal jaundice before they felt comfortable to sit for the written paper in medicine for the final MBBS examination because these questions appeared frequently, if not repeatedly, in the examination paper.

With such primitive standard of neonatal care, it is understandable why the perinatal mortality rate and neonatal mortality rates then were very high. Traditionally, Chinese parents did not consider their baby their own until the baby survived beyond the first 30 days.

The Way We Were

Addressing the way we were in newborn medicine, we have to look back on the many major neonatal problems encountered then and examine what we have achieved in the past 50 years. We had no neonatologist and the general paediatrician with a special interest in newborn infants looked after the babies. Usually, 1 paediatrician, 1 staff nurse and 2 midwives manned the whole nursery.

The main significant accomplishments of neonatology in the last 3 decades were:

- the successful management of neonatal jaundice and the decline, or near eradication, of kernicterus in the country;
- close cooperation between obstetricians and paediatricians in the management of newborn babies, including perinatal consultation, thus resulting in the birth of perinatology;
- the success of surfactant replacement therapy (SRT). SRT revolutionised newborn care, dramatically decreasing mortality and morbidity rates;
- the establishment of neonatal units and setting up of NICUs offering assisted mechanical ventilation for the ill babies.

Neonatal Jaundice

Kernicterus is a serious neonatal disorder, often fatal but also devastating in those who survived, causing long-term impact and severe handicap. Almost half a century ago, it was found that kernicterus was a common cause of neonatal deaths in Singapore. When the common causes of deaths in babies and children 0 to 10 years old were examined, kernicterus was ranked third, after pneumonia and congenital malformations. However, kernicterus occurred mainly in the first 2 weeks of life. When one further examined the deaths of babies less than 1 week old, kernicterus stood out as the leading cause of newborn deaths, far exceeding the total neonatal deaths due to pneumonia, congenital heart disease and intracranial haemorrhage.¹

A study of term infants with severe jaundice culminating in kernicterus was conducted. It was perceived that there were “unknown” causes other than those seen in the West,

such as Rhesus incompatibility and ABO haemolytic disease leading to kernicterus. What caused this high prevalence of kernicterus in Singapore? A kernicterus surveillance project was then embarked on in 1964 to study the cause for such prevalence of kernicterus. It took a few years to find out that many babies who developed kernicterus (nearly 50% of them) had glucose-6-phosphate dehydrogenase (G6PD) deficiency and many died.² Immediate action was taken and since then, death from this cause declined sharply.³

In 1988, a study in Singapore showed that G6PD deficiency accounted for 1.5% to 2% of neonatal jaundice. In Toa Payoh Hospital, Singapore, the incidence of G6PD deficiency for Chinese, Malay and Indians was 2.6%, 1.35% and 1.17%, respectively.⁴

Exchange Transfusions for Severe Neonatal Jaundice

It was Diamond who introduced double volume exchange transfusion in the United States, which prevented most cases of kernicterus and saved many lives.^{5,6}

In the 1960s, the available treatment for severe jaundice in Singapore was exchange blood transfusion; the criteria to do so was when the serum bilirubin levels exceeded 20 mg/dl, or approximately 350 mmol/l, in a term baby. It was a beneficial method to prevent kernicterus and, therefore, physical disabilities and mental retardation.

Exchange blood transfusion is a very tedious procedure with its attendant risks and we had encountered deaths in “exchanged” babies as a result of this procedure. In those days, we had 15 to 30 admissions to the paediatric unit each day, the majority of which was due to severe neonatal jaundice. On an active admission day, we had to perform 5 to 10 exchanged blood transfusions, sometimes as many as 15.

As a result of the neonatal jaundice screening programme in Singapore, it is gratifying to note that we have not encountered a single case of kernicterus for more than 15 years.³

Thermal Management of the Newborn

In 1958, William Silverman demonstrated that maintaining body temperature by controlling the thermal environment significantly decreased premature low birthweight mortality;⁷ thermal management has since become a cornerstone of neonatology. In the 1960s, only overhead heating lights were used to keep babies warm and this method was neither scientific nor proper. Subsequently, we received a few “closed space” incubators donated by commercial firms. Then in the late 1970s, we acquired our first open-care radiant warmer.

Paediatricians Attending High-risk Deliveries and Neonatal Resuscitations

Paediatricians attending high-risk deliveries in the labour

ward and operating theatre did not happen until the early 1970s. It was realised that mortality could be reduced if the high-risk babies could be resuscitated promptly at birth. A well-organised neonatal resuscitation team was formed to manage high-risk deliveries expectantly.

Establishment of Neonatal Units and Setting Up NICUs: Offering Assisted Mechanical Ventilation for Ill Infants

The changes in name, from premature nursery to special care nursery or special care baby unit and then to NICU, reflected significant change and advance in the management of critically ill newborns. In the 1960s, newborn infants came to be regarded as patients, and not a delivery room “by-product”. Management of premature infants shifted from simple, if not primitive, care, temperature control, feeding, and vulnerability to diseases to a more comprehensive and scientific approach to modern practice of newborn infant care.

Improved outcome was the result of major developments in neonatal intensive care and improved organisation of perinatal care.^{8,9}

Advances in Respiratory Management of the Premature Infant

Beginning from the 1970s, remarkable advances in the respiratory management of premature infants were seen. George Gregory found success in the use of continuous positive airway pressure (CPAP), resulting in a dramatic improvement in respiratory support of premature infants.¹⁰ The first generation of ventilators designed specifically for neonatal use (Baby Bird I and Bournes BP 200), with time-cycled, pressure-limited, continuous flow and CPAP, and intermittent mandatory ventilation, appeared in the nursery. Respiratory monitoring improved with the introduction of transcutaneous oxygen assessment, followed by transcutaneous carbon dioxide, pulse oximetry, routine blood gas monitoring, and non-invasive apnoea, heart rate, and blood pressure monitoring.

In Singapore, we humbly began building our “intensive care” unit by equipping our nursery with one ventilator. Our first ventilator was the Amsterdam Infant Ventilator. We only realised that the ventilator was meant for bigger infants, not neonates, when complications, including pneumothoraces, arose after several uses. During that time, we also introduced CPAP and used the Gregory box, Carden valve, with little success. In 1980, we finally acquired a neonatal ventilator — a Bird’s respirator — through the generosity of a donor and it heralded the beginning of neonatal ventilation. This reminds me of the Chinese saying: “A thousand miles begin with a first step”.

With technological advances, many models of highly sophisticated ventilators have since come onto the market, helping to salvage many ill neonates whose survival was

considered impossible. Admittedly, technological advances have led to remarkable gains in newborn medicine.

Surfactant Replacement Therapy (SRT): The Singapore Story

It has been almost a century, from the time hyaline membrane disease (HMD) was first described in 1903, to the time when we really had a specific therapy. After HMD was recognised as a disease entity, things did not progress very much over the next 50 years, until the end of the 1940s, when it was felt that hyaline membranes were no longer aspirated amniotic fluid as commonly believed, but rather aspirated vernix. Both Pattle and Clements, in 1955 and 1957, respectively, found surfactant in the lungs.

Then, in 1959, Avery discovered deficiency of pulmonary surfactant as the causative factor of HMD, now appropriately known as respiratory distress syndrome (RDS).¹¹ As a result of this important finding, replacement of deficient surfactant has been widely investigated for the prevention and treatment of RDS, which was the commonest cause of death and handicap in premature infants.

When surfactant was first described in the late 1950s, it was known primarily as lecithin or dipalmitoyl lecithin (DPL) or dipalmitoylphosphatidylcholine (DPCC), the important phospholipid component of pulmonary surfactant. It was thought that replacing deficient DPL would solve the problem of atelectatic lungs in premature babies with HMD.

During that time, KKH attracted American researchers to test the effectiveness of pulmonary surfactant replacement in Singapore because of its high volume of births per unit. Of the 38,849 deliveries in KKH in 1965, 0.5% to 1% had HMD. Dr Josephine Chu and Dr John Clement led the research team from the US to KKH. They used an aerosolised form of surface tension-lowering agent called DPL to treat RDS. Unfortunately, this research was inconclusive and did not help in the use of surface-active agents in RDS.

The research did not produce convincing results because the investigators did not realise the complex nature of human pulmonary surfactant then. We now know that surfactant is more than DPL or DPCC. It also contains four lung-specific surfactant proteins and other phospholipids, such as phosphatidylglycerol and phosphatidyl-ethanolamine. There are also many other substances with specific properties, such as lowering of the surface tension, spreading and respreading, and adsorption. Research in the area of RDS then focussed on these lipids because they were shown to be the most important components of the surfactant in terms of lowering surface tension.

The findings led Chu et al¹² to postulate that HMD or idiopathic respiratory distress in the newborn resulted from and primarily involved pulmonary ischaemia, followed by

secondary changes in structure, composition and physical properties of the lungs. As a result of profound pulmonary ischaemia, prolonged and degenerative changes occurred in the structure and composition of the lung parenchyma. They recommended the use of acetylcholine or other pulmonary vasodilators to improve pulmonary ischaemia.

The pulmonary ischaemia hypothesis had misled many researchers and clinicians and, for many years after, they looked for agents such as acetylcholine hydrochloride, tolazoline and prostaglandin that could improve pulmonary ischaemia. Many papers were published, showing some, albeit marginal, effect of the agents. Nevertheless, these agents did not change the outcome, while many researchers went back to basics to develop the clinical approach of actually replacing surfactant in the lungs. In North America, Enhorning and Robertson¹³ first demonstrated the possibility of replacing surfactant in premature animals. In 1980, Tetsuro Fujiwara of Japan and his colleagues reported the first successful treatment of HMD in premature infants with surfactant replacement.¹⁴

Very few people know that one of the earliest clinical trials of SRT was conducted in Singapore. No progress was made in Singapore after the trial. In 1991, after a lapse of almost 25 years, exogenous synthetic surfactant (Exosurf) was tested again in the same hospital.

In 1991, the Neonatal Unit in KKH, Singapore was chosen by the National Perinatal Epidemiology Unit (NPEU) in Oxford, United Kingdom to participate in the Open Study of Infants at High Risk of or with Respiratory Insufficiency — The Role of Surfactant (OSIRIS) trial to test the use of Exosurf.^{15,16} This project has notable significance. First, Singapore was the only country in Asia to be selected by NPEU to take part in the trial. Secondly, after a lapse of almost 25 years, Exosurf was tested again in the same hospital. Thirdly, on 25 March 1991, a premature baby girl was treated with Exosurf for RDS. She became the first patient to receive exogenous surfactant therapy in Southeast Asia! This is a significant milestone in the history of Singapore paediatrics.

This global OSIRIS trial using Exosurf was the largest clinical trial ever conducted in neonatology. It enrolled 6774 babies from 21 countries, including Singapore. Over a period of 9 months, from March 1991 to December 1991, our Neonatal Unit recruited 52 babies with RDS for the trial. The Wellcome Journal credited this synthetic surfactant trial as the first in Southeast Asia (unpublished data — Wellcome Journal 1991; 6:17). Exosurf is a synthetic, protein-free compound, which contains 85% of the key surfactant phospholipid DPCC (lowers surface tension), 9% of hexadecanol (accelerates adsorption) and 6% of tyloxapol (facilitates dispersion). The drug, at a dose of 5 ml/kg of body weight or 67.5 mg/kg of phospholipids, was given at 12-hourly intervals and instilled intratracheally.

The Way Forward

Many early-day neonatal problems in Singapore have been contained or solved. Ahead of us are many problems that we have to focus on. The following are propounded and briefly discussed.

Treatment and Control of Infections

This includes group B streptococcal screening and chemoprophylaxis, and those caused by antibiotic-resistant microorganisms from indiscriminate use of antibiotics.

Better Management of Neonatal Asphyxia

Babies born asphyxiated are at risk of neurological damage. Neuroprotective strategies for the developing brain may offer some help. Many modes of treatment, such as N-methyl-D-aspartate receptor blockers (magnesium sulphate), cerebral cooling, free radical scavengers (allopurinol, desferoxamine), phenobarbital, growth factors of the brain and interleukin antagonists have been proposed.¹⁷ It is helpful if physicians can have reliable clinical markers for decision-making, either withholding or withdrawal of treatment for severe cases, and for counselling the parents if the physicians can predict the outcome of neonatal asphyxia.¹⁸

Safe Introduction of New Technologies

Many unproven therapies and treatment regimens are used commonly in all areas of medicine. This is especially so in neonatology. Premature infants are particularly vulnerable to unanticipated, but potentially devastating, treatment hazards. Many treatment decisions involve highly complex issues that no one adequately understands.

Uncertainty about the value of a therapy is most likely to be resolved by randomised controlled clinical trial (RCT). A controlled trial of an unproven therapy is clearly preferable to haphazard clinical use of the same therapy. Unproven therapies are typically prescribed in clinical practice without any independent monitoring, without consent and with little, if any, effort to inform the parents of what is known and not known about the therapy. In clinical trials, a much more serious effort is made to inform the patient (or surrogate) and to use an unproven therapy in the safest, most effective manner possible, based on a careful assessment of the best available information. The findings of a RCT will foster wide clinical use of this therapy if benefit is shown. If, however, the “therapy” proves to be ineffective or harmful, the number of patients treated with this agent will be minimised, which is an important ethical advantage of clinical trials. It is, therefore, necessary to practice evidence-based medicine or EBM.¹⁹

Prevention and Reduction of Major Neonatal Morbidities

The ultimate goal of neonatal care is to achieve good outcome. This includes reducing chronic lung diseases,

preventing retinopathy of prematurity and intraventricular haemorrhage. Recently, many centres employ exogenous surfactant to treat meconium aspiration syndrome (MAS), to reduce the severity of respiratory illness and decrease the number of infants with progressive respiratory failure requiring support with extracorporeal membrane oxygenation.²⁰⁻²³ The relative efficacy of surfactant therapy compared to, or in conjunction with, other approaches to treatment, including inhaled nitric oxide, liquid ventilation and high frequency ventilation, remains to be tested.

The therapeutic role and efficacy of inhaled nitric oxide (INO) in the prevention or reduction of severity of bronchopulmonary dysplasia is also being studied,²⁴ and we expect wider use of INO in neonatology.

Avoidance of Medical Errors and Iatrogenic Causes

Presently, the complexity of our modern healthcare system has contributed to numerous errors. Serious blunders can happen during even the most routine tasks. Errors can also happen when doctors have breakdown in communication with nurses and other staff.²⁵ Mistakes ranged from a simple miscommunication of a drug's name to erroneous programming of a complex medical device at the end of a busy hospital nightshift. Others include wrong diagnoses from mislabelled blood tubes, mistaken treatments because of poorly labelled drugs, wrongly placed decimal point and improper dosing because of faulty calculations. Medication errors are among the most widespread blunder.²⁶

Enhancement of NICU Environment

Undue sound and lighting in the neonatal nursery and NICU environment are stressful to ill babies, parents and staff, especially with prolonged hospitalisation, alterations in parenting and exposure to a technical environment. These babies are dependent on and vulnerable to the intensive care environment to support physiological and neurobehavioural organisation. Concerns about this environment have led to suggestions that it may be a major contributing factor in the persistent incidence of behavioural and learning problems among preterm infants.^{27,28}

Adequate Sedation and Pain Relief for Neonates

Neonates are more sensitive to pain and vulnerable to its long-term effects.²⁹ Provision of adequate sedation and pain relief for babies undergoing surgical procedures is important.

Rapid Diagnostic Methods of Neonatal Sepsis and Newer Therapies

Rapid diagnostic methods are essential to diagnosing serious neonatal infections. Usually, it takes time to get culture and serology results to confirm a specific causative organism. With reliable rapid diagnostic methods,

unnecessary antimicrobial use can be avoided and, with prompt and proper isolation for hospitalised patients, the possibility of nosocomial infection is reduced. With deoxyribonucleic acid (DNA)-based diagnostic tools and newer therapies of management, many expect reduction of healthcare costs. Parents can be advised the expected course of illness.

Improved Monitoring

It is important to improve non-invasive monitoring and to minimise invasive procedures.

To Prevent Malformations, Hereditary Diseases, Metabolic Disorders (Down's syndrome, Thalassaemia, Thyroid Screening)

Congenital malformations are always there. A local 18-year study of congenital malformations had been published more than 10 years ago.³⁰ The Singapore Birth Defect Registry collates all the data of congenital malformations and the prevalence of these defects can be retrieved.

Screening and early diagnosis of congenital malformations is an expanding field in general obstetrics.³¹ Obstetricians' epidemiological knowledge and their awareness of associated risk factors are essential to the primary prevention of birth defects.

Diabetes is responsible for a number of congenital defects and early detection is possible. It is, therefore, important to have proper management of diabetes and to prevent complications.³² Pre-pregnancy counselling, tight glycaemic control prior to conception and during pregnancy and the periconceptional use of folic acid can prevent an excess rate of congenital malformations, fetal macrosomia, birth trauma and RDS. Also, avoidance of alcohol, rubella vaccination and special care for certain maternal disorders can prevent some birth defects.

Neonatal and perinatal statistics reflects the changing pattern of neonatal diseases and guide us to make future plans in neonatology in Singapore. We must know the prevalence of the perinatal and neonatal problems so that relevant measures can be introduced. The major clinical problems for the last decade were RDS, congenital malformations and neonatal infections, many of which were pulmonary infections, hypoglycaemia, neonatal jaundice and asphyxia neonatorum. The major causes of neonatal deaths in the 1980s had been reported.³³

Determination of Viability, End-of-Life Decision and Withdrawing and Withholding of Treatment: The Ethical Issue of How Small is Too Small

Advances in technology in neonatology have enabled more prematurely born babies to survive. Has premature

delivery rate been improved and reduced? What about the associated mortality and morbidity? It is the quality of life of these survivors that matters. Ethical issues deserve considerable attention, such as definition of fetal viability, therapeutic intervention in extremely low birthweight infants, decision-making and practices in withholding or withdrawing therapy during neonatal intensive care, and determining the lower limit beyond which no resuscitation should be done.³⁴ There is a need for long-term follow-up and assistance to the patients and their families.

Looking Beyond: Predicting Future Practice in Neonatology

As we enter the new millennium, wherein life sciences are advancing by leaps and bounds, can these advances benefit neonatology?

Advances in Current Vaccines

We look forward to new vaccine delivery technology, including easier delivery routes (such as transcutaneous, depot, nasal spray and oral delivery) without compromising efficacy and long-lasting protective immunity. This could help alleviate concerns about vaccine safety and reduce public “anti-vaccine” sentiment! We also hope to see the development of new vaccines against non-infectious diseases, such as cancer, diabetes and even nicotine dependence.³⁵

However, there remains the problem of developing safe childhood DNA vaccines.^{36,37} DNA vaccine technology is still in its infancy and much research needs to be done to improve the efficiency.

Human Genome Project

With the completion of the Human Genome Project, most probably by 2003, 90% of the human genes and its sequence and loci at the chromosomes are expected to be unfolded. Also, the sequencing of the entire human genome could be completed within the next 3 years. The underlying genetic factors of some diseases could be modified and we hope to see many inherited disorders eliminated in the future generation. It is also hopeful that treatment or correction of defective genes will be available within the next 10 years. More reliable gene vectors, such as viral and non-viral DNA nanoballs, and gene therapy will soon be available. It follows that doctors have to make the paradigm shift, to readjust and reorientate the approach and method of practice and to incorporate the benefits of new genomic knowledge into practices.

Some neonatal diseases, including many genetic disorders, could be solved by gene therapy. The clinical experience gained from the use of liposomes to suppress proliferative retinopathy could provide neonatologists with some valuable ideas; it could possibly mean a breakthrough in

the management of retinopathy of prematurity by gene therapy.³⁸

We see the promise and challenges of gene therapy in the perinatal period in this millennium; hopefully, the promise in the long term is of broad applicability across developed and developing countries. Some are even optimistic that gene therapy will be able to replace present technological solutions, such as NICU and ventilators. The neonatal population, susceptible to a number of diseases, may be amenable to transient gene expression, as and when the responsible genes are recognised.

Cloning of Tissues and Organs

Another aspect of advances in the life sciences is the cloning of tissues and organs, where “made-to-order” replacement parts could be created for damaged body parts and rejection problems could be avoided in organ transplantation. It also enables more people to understand and accept this method of treatment, rather than human cloning.

With imperfect and immature technique, there lies a chance of serious gene mutations with birth defects, inborn errors and congenital diseases. Many scientists are presently involved in human stem cell research and improving the relevant technology (mining the embryo to regenerate tissue and to treat diseases). Cord blood is a rich source of stem cells—primitive cells that have the potential to grow into different kinds of cells: red blood cells, platelets, liver and kidney cells. Cord blood banking, as a form of “biological insurance”, is appearing in the market. There are now a couple of companies in Singapore offering parents the chance to bank their baby’s cord blood and keep it in deep freeze, until and if it is needed.

The Age of Nanomedicine

The 21st century is the age of nanomedicine and the medical nano-device will probably be a micron-scale robot assembled from nanoscale parts. It is envisaged that the typical nanomedical treatment, like combating a bacterial or viral infection, will consist of an injection of perhaps a few millilitres of micron-sized nanorobots and therapeutic agents could be precisely transported and delivered to a target cell. Understandably, no actual working nanorobot has yet been built.

The Use of Blood Substitutes

Many aspects of blood substitutes have been studied. These include erythropoietin,³⁹ autologous transfusion and cell salvage, use of artificial oxygen carriers such as perfluorocarbon, haemoglobin-based oxygen carriers and recombinant haemoglobin. The last is haemoglobin with its 2 alpha units fused together, produced by genetically engineered *Escherichia coli*; the amino acid substitution

results in haemoglobin with a high oxygen affinity.

Recently, respirococytes have been mentioned. Respirococytes mimic the action of natural haemoglobin-filled red blood cells. A respirococyte can deliver 236 times more oxygen per unit volume than a natural red cell. The injection of a 5-cm³ dose of 50% respirococyte aqueous suspension into the bloodstream can exactly replace the entire oxygen- and carbon dioxide-carrying capacity of the patient's entire 5400 cm³ of blood.⁴⁰

Conclusion

We are encountering many exciting scientific developments ahead. I am confident that neonatology can benefit tremendously from these achievements. Each country should set their direction towards development in neonatology. The development should be relevant, cost-effective and appropriate.^{41,42} There are many things to be done and I am confident that we can achieve them. I shall end by quoting President Calvin Coolidge, 30th President of the United States: "We cannot do everything at once, but we can do something at once".

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