

# Special Feature

## The Importance of Iatrogenesis in the Founding of Modern Neonatology

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There is enough interest in *iatrogenesis* in adult medicine today. The press echoes this, too. In the late 1950s, a new field of medicine in pediatrics began to emerge — Neonatology. The technology and information gained from research in physiology and biochemistry, pharmacology and antibacterial drugs and capability for micro-monitoring and micro-chemistry gained from aviation and space research contributed to the increased interest in the study and treatment of newborns. The infants of that time were already being looked upon as “Therapeutic Orphans” as a burst of harmful and disastrous results were being reported, not only from new drugs and technology, but from the old and accepted ones. This body of knowledge needed to be coordinated and controlled for education and research. Thus, *iatrogenic* observations truly served as an impetus for the cartoon, “Neonatology — A Six-Finger Exercise” in 1958, which showed the importance of thinking about *iatrogenesis* when looking at each sick infant along with the traditional clinical conditions, each body system and for birth defects. An appendage was tied with a suture and appropriately called *pediatrica iatrogenica*.

Why I did this must go back to my formative years with Dr. Wilburt C. Davison, Dean and Professor and Chairman of Pediatrics of the Duke University School of Medicine and the Medical Center, which he built and led for over a quarter century. I translated the German pediatric literature and also read and abstracted the English pediatric literature, too, for the *Compleat Paediatrician* which Dr. Davison wrote for eight editions. Dr. Davison was one of the last two Americans to study with Sir William Osler at Oxford and mentioned Osler daily. Osler was interested in Pediatrics, was the fourth president of the American Pediatric Society and greatly contributed to the diagnosis and

understanding of many neonatal problems. My first birthday gift from my wife Faye was Osler's *A Way of Life* and at Christmas she gifted me with Harvey Cushing's *The Life of Sir William Osler* in two volumes which I read over the holidays. These books had a great influence on my life.

I spent an academic year during medical school in cardiopulmonary physiology under Dr. Otto Gauer, discoverer of volume receptors, and inventor of miniature blood pressure devices, pressurized flight suits, the Jobst Stocking for varicose veins, etc. He also believed research should first be performed on animals, then on himself, his associates and fellows. The subject's consent was most important to Dr. Gauer, but young children could not give consent.

A special tour during medical school was spent with Dr. Jay M. Arena, a great pediatrician, accidents and poisoning specialist, inventor of a bottle to prevent children from opening, writer of a textbook of pediatrics, founder of poison control centers in the US and champion of children's healthcare and prevention, who let me know that all accidents, poisonings and mistakes should be reported *and* to be prevented in the future, if possible. He allowed me to see his work with the North Carolina Legislature to prevent fire works and lye injuries. The legislature stopped the sale of fire works but not the sale of lye. Dr. Arena helped me to obtain grants as a young chairman of pediatrics. He later became president of the American Academy of Pediatrics. What a great advocate for children he was!

I did my pediatric residency at Walter Reed under Colonel Ogden C. Bruton, discoverer of agammaglobulinemia and one of the first to perform exchange transfusions and liver biopsies on infants, who always stressed, “The patient is first, last and always” and “Give every patient your best effort.”

Colonel J.P. Henry, MC, USAF, became chief of medical aviation and space research for the USAF. He was once an associate of Dr. Otto Gauer and made it possible for me to spend time in physiology and research at the Walter Reed Army Medical Research Center during my pediatric residency. Colonel Henry certainly made possible many of my inventions there — the best known were the infant oxygen hood, the pilocarpine sweat induction test for cystic fibrosis and a micro-osmolometer to study blood and body fluids even in small animals and infants.

My consultant in the nursery at Walter Reed was Dr. Harry Gordon, who had been exposed to infants with retrolental fibrous dysplasia from excess oxygen while in Colorado in the early 1950s. He had also developed several infant formulas and done nutritional

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research which benefited pre-matures. I learned much about nutrition from him. While Dr. Gordon was Dean at The Albert Einstein School of Medicine, he invited me to the first meeting on Medical Ethics at the Hastings Institute for Medical Ethics at White Plains, New York. He always stressed the teachings of Hippocrates and Maimoides, especially Hippocrates' statement, "If you cannot help, then do no harm," and the importance and need for good research.

In the 1950s Virginia Apgar, first American professor and chairperson of Anesthesiology, was interested in the asphyxiated newborn and resuscitation of the newborn. She proposed the now famous APGAR score for assessing the condition of the newborn at birth which became internationally accepted. Dr. Apgar was very pleased with my cartoon "A Six-Finger Exercise" and the special emphasis it placed on *iatrogenesis*. She was also pleased with the cartoon on "The Small-for-Date Infant", which gave causes for small premature and term infants which only included those above 28–29 weeks gestation because of lack of experience with survival of younger infants in 1958. She seemed to enjoy repeating that, "The Six-Finger Exercise' cartoon gave definition to the new field and the *iatrogenic* appendage gave a new ethical dimension to newborn care. "The Small-for-Date Infant' cartoon also gave Neonatology a purposeful direction for future research and clinical care." She was truly a great promoter for the newborn and a dear friend. She suggested a group meeting of those interested in care of the newborn at the American Pediatric Society and Society for Pediatric Research Meetings in Atlantic City. Joseph Brazie, a fellow of Joseph Butterfield, and I started these meetings. Mary Ellen Avery asked Clement Smith to come and give an informal talk to this group. Only 25 to 30 came the first year in 1965 and over 300 came in 1969. Drs. Virginia Apgar, Richard Day, Ceciley Williams and William Silverman spoke in the ensuing years. At the last meeting in 1969, Dr. William Silverman gave his famous talk on incubators. Ross Laboratories' Dewey Sehring continued these informal meetings which grew to attendances of thousands over the years.

The Old Children's Bureau and Kentucky Department of Health funded the first Physician and Nurses Training Program in 1965 with a neonatal fellow, lectures and nursery experience. In 1966, the program was extended to visits by a team of pediatricians, nurses and neonatal fellows to regional hospitals. In 1967, The Annual Newborn Symposium became a part of this program. The cartoon "The Hand" has been used ever since, except in 1969 when the "Small-for-Date Infant" was used. Dr. Larry N. Cook, a medical student fellow in nutrition, now chairman of pediatrics at Louisville, spoke at the first meeting and at many others as he became a neonatal fellow and faculty member. David Adamkin continued these meetings after Dr. Cook became my successor as chairman and, now, as the annual Kosair Children's Hospital Newborn and Pediatric Symposium. Both cartoons were also used from the beginning of the Mead

Johnson Perinatal Research Conferences at Lake Barkley started in 1975 and have continued under Drs. Cook and Adamkin to the present.

I would be remiss, especially in Texas, not to mention the great influence of Drs. Murdina Desmond and Abraham "Jack" Rudolph upon our understanding of early adaptation of the newborn and techniques for resuscitation, temperature control, environmental control and so many others.

I also should mention why I'm here. It is because of my dear friend and benefactor who has stimulated and supported my interests in medical history and ethics, Dr. John P. McGovern. Dr. McGovern is also a Duke Graduate and a pediatrician with the same heroes, Wilburt C. Davison and Sir William Osler. He is a Founder of the largest Allergy Clinic in the United States in Houston, Founder of American Allergy-Immunology, the American Osler Society, the Davison Club, and numerous lectureships in the US and abroad. He is also a renowned scholar, educator, medical historian, ethicist and philanthropist. In Texas, especially in the US and abroad his good works can be seen.

It was Dr. Warren Wheeler, Professor and Chairman of Pediatrics at the University of Kentucky, an expert in infectious diseases, writer and Editor of the *American Journal of Diseases of Children*, who kept insisting for many years that I publish "The Hand" with a few comments. Finally, I complied with his request and it was published in the *American Journal of Diseases of Children* in September 1968, and ended with *Primum Non Nocere*.<sup>1</sup> The cartoon of "The Small-for-Date Baby" finally appeared in the preface and an article in *The Small-for-Date Infant* in 1970, the proceeding of the International Meeting on that topic at Louisville in 1969.<sup>2</sup>

*Why and when* did I use these cartoons? Both cartoons were first used for a joint Obstetric – Pediatric Morbidity and Mortality Conference in October 1958 in which I had to discuss a premature infant who was given 100 mg/kg Chloromycetin on several occasions and died with the gray baby syndrome. No cause was found on *post mortem*. Dr. Robert Moser, internist, writer and editor had used the word *iatrogenesis* in the *JAMA* earlier, but I had not seen this. I had later made a thorough search of *iatrogenesis* and found Bleuler's textbook from Germany from 1924. I then asked many people with psychiatry and other training who said they had never heard or mentioned *iatrogenesis*. Many years later, when at Duke to deliver the first lecture in Medical Leadership,<sup>3</sup> I asked Dr. Ewald Busse, my former psychiatry professor and later dean at Duke University School of Medicine, how long he had used the word *iatrogenesis*. He quickly replied, "Since the 40s from a *Textbook of Psychiatry* by Professor Eugene Bleuler translated by A.A. Brill, McMillan Co., New York, 1924." I must have remembered it from Dr. Ewald Busse and I told him so. He seemed very pleased that I had paid attention to him.

"The Hand" was used to point out problems in many body areas and how to look for them on all habitable continents. The

thumb was relegated to cardiopulmonary problems to point out the most imminent dangers of oxygen, retinopathy of prematurity, c-sections resulting in prematures, dangers of respirators, tubes, nasal and tracheal necrosis, broncho-pulmonary dysplasia, MgSO<sub>4</sub> enemas, diuretics, etc.

The second finger was for hematological dangers — transfusion, hepatitis, cytomegaloviruses, HIV, syphilis, etc., white cells causing host vs graft reaction, platelets, intravenous E-ferol and Imferon, etc. The New Zealand experience of giving too much Imferon led to disastrous consequences as had the intravenous E-Ferol; even blood volume changes by handling of the umbilical cord could lead to anemia *and/or* plethora. Without tight control of volume and concentration of the blood during exchange transfusion, anemia or hemo-concentration could occur. The question was, “To shake or not to shake to control volume and concentration during exchange transfusion?” Gentle, frequent shaking throughout the exchange led to more normal values. Eventually, even hydropic and hemo-concentrated infants began to live with proper care.

The third finger pointed to dangers from nutrition, metabolism, liver, kidney and endocrine glands. Problems with formulas, concentration, Na, proteins, intravenous formulas, etc. Also problems from vitamins, synthetic vitamin K with hyperbilirubinemia, lack of folic acid, special spinal defects, maternal treatments for hyper- and hypo-thyroidism, infants with thyroid and adrenal problems, and from mothers with diabetes with special problems.

The fourth finger represented infections which we must look for as well as the antibiotics chosen for therapy. Major problems with Chloromycetin, the gray baby syndrome, sulfonamides — hyperbilirubinemia, Declomycin, cerebral edema, Tetracycline, stained teeth, even with Hexachlorophene, a long-used antiseptic which when absorbed from the skin of prematures produced a vacuolization of the brain, even physical massage of the chest, left broken ribs, etc.

The fifth finger represented congenital anomalies occurring from trauma, genetic or use of drugs, such as Amphotericin, Dilantin, Thalidomide, etc. Helen Taussig exposed the phocomelia and internationally denounced Thalidomide. Now, we must look for deficiencies, too, such as the recent discovery of prevention of spinal cord defects with folic acid during pregnancy.

The small appendage, *pediatricia iatrogenica*, which is appropriately tied-off, is used to point out the dangers from procedures, equipment and drugs, etc.

The palm of the hand represents problems that can come from all of these areas to affect the central nervous system as well as specific problems such as infections, hemorrhage, clotting, hyper-

and hypoxia and eventually to scarring, hydrocephalus, seizures, retardation and palsies.

After about 30 years of stressing the importance of *iatrogenesis* on many continents, some associates began to address me as “Doctor *Iatrogenesis*.” To dissuade such references at The International Meeting on Perinatology in South Africa in 1985, I replied, “*Obniti Iatrogenesi et Primum Non Nocere*” (“To strive against *iatrogenesis* is much akin to first do no harm”). When I learned Dr. David Adamkin was to edit a Festschrift for me, I wrote and dedicated this poem to him.<sup>3</sup> Maybe the comment has become less frequent, unless such reports as this will stimulate its perpetuation.

Neonatology has evolved into a well-established subspecialty of pediatrics. Excellent reviews have chronicled many episodes of *iatrogenesis*.<sup>4,5</sup> *Iatrogenesis* will continue and may be expected as part of progress, but we must minimize it. Even with today's reduction of infant mortality from 27/1000 in 1958 to 7/1000 in 1999, the survival of infants under 28 to 29 weeks gestation was near 100% in 1958, and in 1999 even infants at 22 to 23 weeks were surviving in Japan. We must continue to be vigilant. From a med-line search, over 50 articles were written about *iatrogenesis* in infants and children in the past 5 years in the English-speaking literature. Maybe even more could have been written. Any new therapy or procedure requires testing. Teaching about *iatrogenesis* must be emphasized and continued.

Pictures in my office show the facies of fetal alcoholism of a baby born in Kentucky to an alcoholic mother and a picture given to me by a fellow from Japan, a child with a distorted body and failure-to-thrive, because of mercury from a mother who ate fish from Minemata Bay outside Tokyo, Japan. Both pictures constantly remind me of what mothers can drink and eat that can harm their infants. In 1986, my neonatal fellows gifted me with a professional cartoon of me in diapers pointing to “The Hand,” which is also on my office wall to constantly remind me of *iatrogenesis*. Will I be thinking of *Iatrogenesis* when the final call for me comes? Thank you.

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# Corrigendum

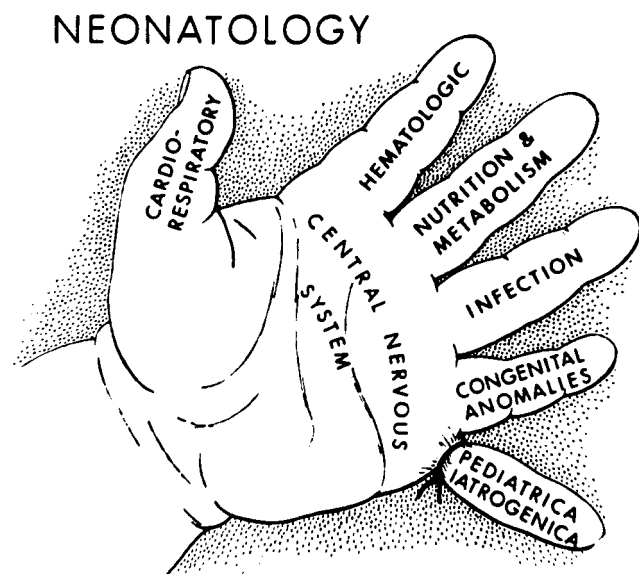
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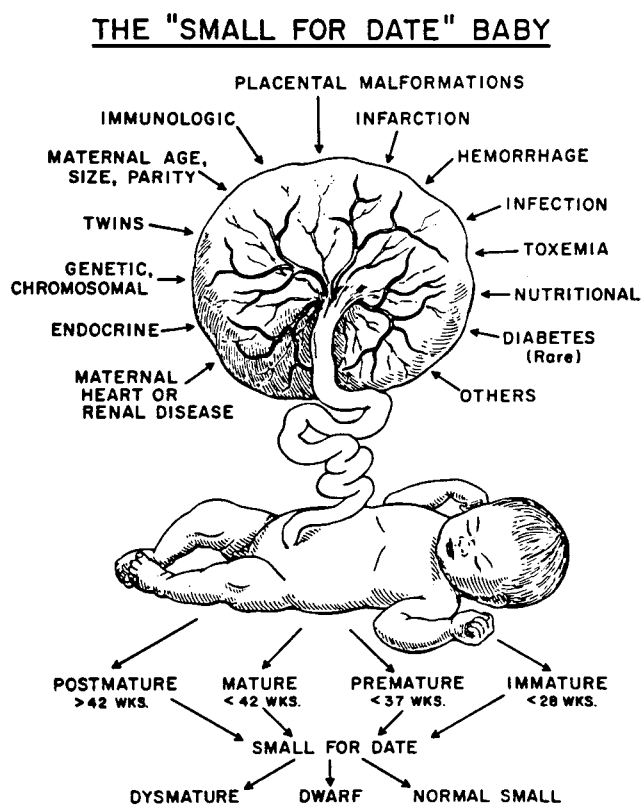
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Following publication of the above paper, the author has realized that two figures pertinent to the article were left out. The figures as they should appear are below. These cartoons have been used in numerous articles and books in the last half century.



**Figure 1.** Andrews BF. Six finger exercise. *Am J Dis Child* 1968;116:334



**Figure 2.** Andres BF, editor. *The small-for-Date Infant*. Philadelphia: WB Saunders; 1970, p. 185-98.

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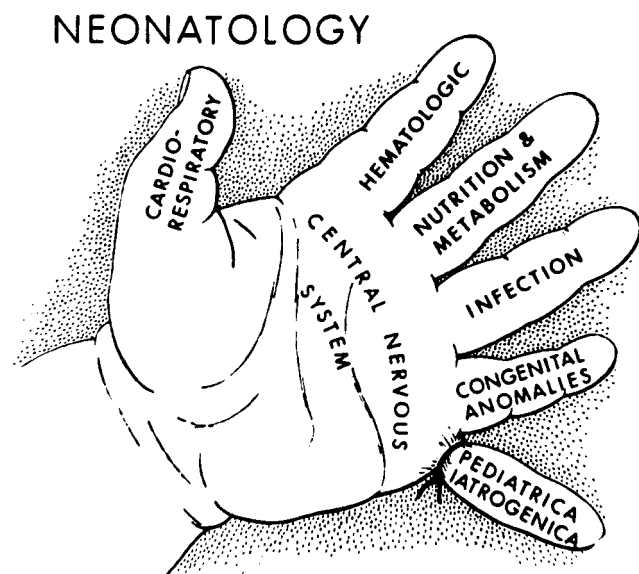
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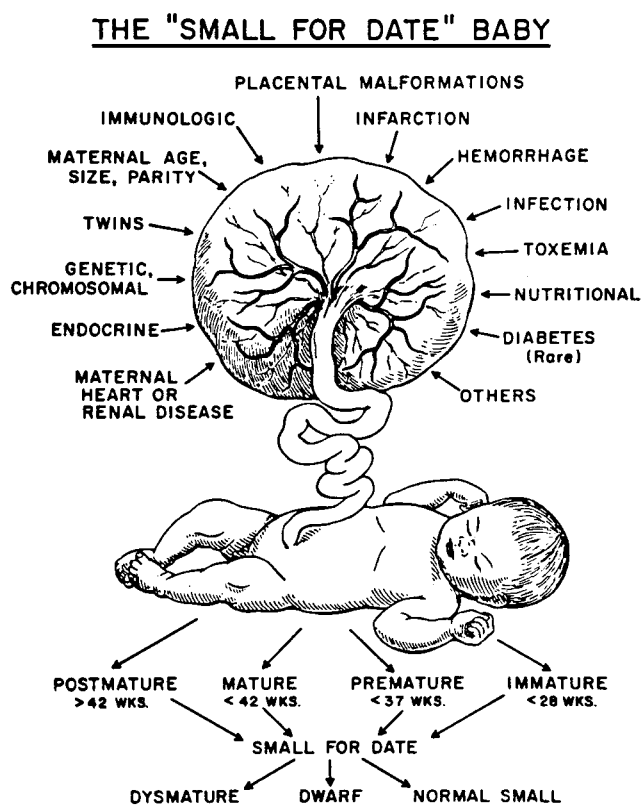
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