The History of Neonatal Anesthesia

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Prelude

Operations in neonates were sometimes undertaken in the years before the introduction of anesthesia. Those procedures most frequently documented were imperforate anus and harelip (cleft lip). Harelip repair was quite often successful, whereas imperforate anus procedures were often followed by death. Many surgeons were reluctant to operate on neonates and there was controversy regarding the propriety of these procedures [1]. In 1833, Wardrop observed that "Infants are sometimes destroyed by the loss of even a small quantity of blood," although he also reported the successful repair of a double harelip in an 8-day-old child and preferred to operate on the infant at an early age [2]. At the same time, he was concerned that the emotional effects of the mother or nurse (i.e., "wet nurse") observing the infant's distress during the operation might alter the composition of her breast milk. This concern was then used to explain the cause of convulsions and death, which sometimes ensued. Indeed, he suggested that "neither the mother nor the hired nurse should be agitated by the screams of the child or that if they be at all alarmed by them the child should not be allowed to suckle until all effects of such agitation have ceased."

Considering our present knowledge of the adverse physiological effects of unmodified pain on the neonate, it is not surprising that surgery without anesthesia was often unsuccessful. It is somewhat surprising that though poppy extract (opium) had long been administered to infants who were crying with the discomforts of teething [3], there are no reports of its use to ease the pain of surgery.

The introduction of general anesthesia had the potential to render operations in neonates much more acceptable to all those who were involved (not least the patient!); however, it was to be a long time before such anesthesia was universally and effectively administered.

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Early Times

Diethyl ether was administered during operations by Crawford Long in 1842, but it was the demonstration by William G. Morton in 1846 at the Massachusetts General Hospital in Boston, Massachusetts, that led to the widespread introduction of general anesthesia. However, the benefits of anesthesia during surgery were not immediately or universally applied. "They don't feel it like we do" was a saying held to be true by physicians and surgeons long after 1846 [4]. In 1847, one-third of the surgical operations on adults at the Massachusetts General Hospital, the site of Morton's demonstrations, were performed without anesthesia [4]. Anesthesia was selectively applied to those who it was judged felt pain more severely, i.e., white, wealthy, and especially female patients. Infants, in particular, were considered incapable of perceiving pain; indeed Dr. Abel Pierson stated that "infants could sleep insensibly even while undergoing surgery" [4]. Henry J. Bigelow considered that like the lower animals, the very young lacked the mental capacity to suffer pain [5]. Indeed, in the case of the neonate, misunderstanding of their perception of pain persisted well into the twentieth century.[1]

During the second half of the nineteenth century and the early part of the twentieth century, the decision to administer anesthesia to a neonate to relieve the pain of surgery was inconsistent. This is perhaps not surprising given the primitive methods that were available to administer anesthesia, the rarity of neonatal surgery, and the fact that small infants could be quite easily restrained during an operation (in addition to the thought that they do not feel pain anyway!).

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[1]As recently as 1976, a technique of "anesthesia" for ductus arteriosus ligation in preterm infants, which was totally devoid of anesthetic or analgesic agents, was reported from a large American University Hospital in a widely respected British journal. The authors stated "No premedication was given. Just before the procedure, if necessary, a paralysing dose of suxamethonium 1 mg/kg body wt. was given. No other anaesthetic agent was used…We have avoided the use of anesthetic or analgesic agents which in our opinion are unnecessary" [6].

Reports of operations on "impervious rectum" [7], strangulated inguinal hernia, and even meningomyelocele [8] without anesthesia can be found in medical journals of this era.

However, reports from this same time period can also be found describing anesthesia that was administered to infants in the first month of life. John Snow preferred chloroform and wrote in 1855 "Chloroform may be given with propriety to patients of all ages. I have exhibited it to several infants aged from ten days to three weeks" [9]. He went on to say that "Chloroform acts very favourably on infants and children. There has, I believe, been no death from chloroform under the age of fifteen years." The most commonly described indication for elective surgery in neonates during these years was for correction of "harelip," an operation that was frequently performed "at the earliest period of life."[2] On Saturday, July 4, 1857, an entry in the case books of John Snow [10] reads "Administered Chloroform at Kings College Hospital to an infant, 8 days old, previous to Mr. Fergusson operating for hare-lip. The face piece was too large and the chloroform took very little effect." Chloroform was administered on this occasion using Snow's inhaler with a small facepiece; the latter, however, was still too large for a neonate. According to Snow, the use of the inhaler permitted "a more gradual introduction of the agent than when administered on a sponge or handkerchief" [9].

The alternative method was to administer chloroform to the infant using a sponge. "Mr. Greenhalgh preferred a sponge to every other kind of apparatus. He had employed the chloroform in a great number of cases, and with success: one of the cases was an infant, three weeks old, for an operation for hare-lip" [11].

During the second half of the nineteenth century, neonatal surgery was limited to superficial lesions. Abdominal surgery was largely confined to the emergency management of incarcerated inguinal hernia. Imperforate anus of the low type was relieved by incision, often without anesthesia. There were also reports of successful operations on neonates under chloroform anesthesia for high imperforate anus. Thoracic surgery was certainly not attempted. However, during these years, great progress was achieved in basic surgical techniques and the prevention of infection. The concepts of antisepsis and asepsis were recognized and applied. Many of the congenital lesions that would much later become the field of the neonatal surgeon were being recognized—though only as curiosities [12].

It is during this time that the first books on pediatric surgery were being published and special hospitals for children were being established. The Hospital for Sick Children at Great Ormond Street in London (GOS) in England opened in 1852; the Hospital for Sick Children, in Toronto, Canada opened in 1875; and Boston Children's Hospital, in the USA, which was modeled after GOS, opened in 1882 [12]. Other European and North American cities established children's hospitals at about this time. "Pediatric surgery" in these early years involved mainly orthopedic procedures, neonatal surgery was rarely performed, but the children's hospitals would serve as a site and a catalyst for the subsequent expansion of infant surgery.

In the late nineteenth century, progress was being made in the care of the sick neonate and preterm infant. It was recognized that the survival of small preterm infants was improved if they could be kept warm. A warm-air heated incubator was developed by a French obstetrician, Stephane Tarnier, and installed at the Paris Maternity Hospital. This was based on a device for raising poultry, which Tarnier had seen at the zoological garden [13]. The design was improved by Pierre Budin, and his incubators were shown at the Berlin World Exhibition of 1896 by his associate Martin Couney, infants being provided by Dr. Czerny, who was the Professor of Pediatrics in the city. Couney later exhibited his incubators in London and at the Pan-American Exposition in Buffalo, New York, in 1901. He also opened an exhibit at the Coney Island fairground in New York City, which ran until 1943. Infants in incubators were also displayed at various other public exhibitions and fairgrounds. The public was invited to pay 25 cents to view these infants in incubators, an unlikely start for the specialty of neonatology. Once having been used in an exhibit, many incubators were later sold to hospitals.

The Twentieth Century

In 1905, ethyl chloride was being used for brief procedures in infants as young as 5 days of age. It was administered using an inhaler [12, 14, 15]:

> A celluloid face-piece is generally preferable since it not only permits the anaesthetist to observe the patient more readily but also resists the action of the vapour better than rubber. For infants of a few days or a few weeks old I commence by spraying three cubic centimetres into the inhaler; for those of six months and upwards I give five cubic centimetres at once. The mask is then approached to the face but not pressed against it so that the baby has several breaths of air and vapour mixed; it is then more closely applied so as to exclude all air except that which is already in the bag, and in a few seconds the child becomes unconscious. When one is sure that the anaesthesia is deep and the surgeon has made his incision or begun the operation the mask should be removed from the face and a few breaths of air should be given. If it is desired to continue the period of narcosis for some time the mask should not be kept off for long but only raised occasionally for air. If the respiration indicates the lightening of the narcosis a few more cubic centimetres may be added to the bag; on these lines the anaesthesia may be indefinitely prolonged.

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[2] Repair of cleft lip ("harelip") today conjures up thoughts of a delicate procedure with carefully planned and positioned skin flaps sutured using many fine sutures in a procedure lasting an hour or more. In the 1850s, the repair would require 3–5 sutures and be completed within 3–5 min, at most.

Abdominal surgery for infants became established around the turn of the twentieth century with the introduction of surgical procedures for the relief of pyloric stenosis. Originally managed by gastroenterostomy, the lesion was later corrected by pyloroplasty [16] and finally by Ramstedt's extramucosal pyloromyotomy [17]. Though most patients were older, some neonates were operated upon for pyloric stenosis. Chloroform was the preferred anesthetic and the need for adequate and constant levels of anesthesia was recognized. Reporting success in their cases of pyloroplasty in the Lancet in 1902, Cautley and Dent stated: "Unless the patient is deeply under the influence of chloroform (which certainly appears to be the best anaesthetic) there is risk of protrusion of the intestine and rapidity of operating becomes a matter of great difficulty. On the other hand, in abdominal operations on very young children deep anaesthesia, unless most carefully induced and maintained, may lead to very sudden and alarming symptoms. Any interruption to the operative procedure while in progress would be a very serious matter, for if the patient is not deeply anaesthetised there is every likelihood of his recovering sufficiently to cry or to struggle. If any such event happens the intestines are likely to protrude at once with the most astonishing suddenness and force. In a case recorded by Stern; both of these troubles seem to have occurred. The child's breathing stopped just after the operation had begun; the anaesthetic was so badly borne that it had to be discontinued while the operation was completed; and the result was that the intestine protruded extensively, thus prolonging the operation and enormously increasing its severity" [16]. There followed a much-deserved tribute to the skill of their own anesthetists: "The success of our cases was largely due to the extreme care and skill with which the anaesthetic was administered, in the first case by Dr. H. Menzies, and in the second by Dr. G. P. Shuter. The surgeon is too often inclined to absorb all the credit of a successful operation, when a great part of it is really due to the anaesthetist" [16]. Anesthesia for infants was already recognized as requiring special attention to detail.

Monitoring during these early years depended on observation of the patient's color, the pattern of ventilation, and in older patients perhaps a finger on the pulse! Much skill must have been needed to maintain an airway without instrumentation, ensure a constant level of anesthesia, and avoid cardiorespiratory depression. It is not at all surprising that the mortality rate for infants was very high. However, some amazing successes were reported with what must have been very challenging clinical cases. One such was the resection of an extremely large teratoma from the neck of a child 3 weeks old [18]. Anesthesia was induced and maintained with chloroform on a sponge. "The element of time was necessarily a most important point in the operation and it was hoped that as the cyst wall was well defined it might be possible to shell out the tumour throughout the greater part

of its extent. This fortunately proved to be the case and the whole operation lasted only 12 min, notwithstanding the fact that the work had to be stopped every few seconds to allow the infant to breathe. In order to diminish the duration of the operation and the amount of shock a continuous catgut suture was used and no attempt was made to remove the superfluous skin" [18].

These then were the early days of neonatal surgery. The treatment of major congenital anomalies would have to await further progress in the perioperative and anesthesia management of the infant. One major step forward was the introduction of endotracheal anesthesia and the associated potential for controlling ventilation.

Endotracheal Intubation of Neonates

MacEwen introduced the concept of passing tubes through the adult glottis into the trachea as an alternative to tracheotomy in 1880 [19]. Elsberg passed intratracheal catheters and used these to insufflate anesthetic gases describing his technique in 1909 [20]. When using an intratracheal insufflation technique, a small catheter was utilized to leave an adequate route for expired gases. Indeed, common practice was to pass a second catheter through the glottis to provide a reliable route for expiration. This prompted C Langton Hewer, who a year later was to write the first British text on pediatric anesthesia, to state in 1924: "Endo-tracheal anaesthesia is contra-indicated in the following class of case:—Babies below the age of one year. The lumen of the glottis is so small in babies that it is practically impossible to obtain a catheter of such size as will permit sufficient vapour to pass and yet leave an adequate return airway" [21]. However, also in 1924, Ivan Magill did describe an expiratory attachment for an intratracheal catheter, which was available in five sizes—the smallest of which would attach to a 9-French catheter (i.e., a 3-mm external diameter catheter) [22]. The expiratory attachment was essentially a tapered metal tube, which could be sited at the level of the glottis and connected to a second catheter. He later reported that he had used this tube attachment in children under 2 years.

In 1928, Magill was routinely using endotracheal tubes of sufficient caliber to permit *to-and-fro* ventilation, a method he preferred in small children and which he had first used in adults in 1920 [23]. Magill tubes were manufactured of red rubber and the smallest size was 00 which had an external diameter of 4 mm, similar to that of today's 3.5-mm ID plastic tube, though the internal diameter of the Magill 00 tube was only 3 mm.

In 1939, Gillespie described methods for routine tracheal intubation of infants [24]. He stressed that though the advantages of intubation were now universally accepted, the intubation itself was more difficult in infants and, in inexperienced

hands, might endanger the patient. To facilitate intubation, he favored a nitrous oxide/oxygen mixture with ether anesthetic and added 5% of carbon dioxide to induce hyperpnea and speed induction. When respiration was regular and automatic, the mandible relaxed, and no trace of glottic spasm evident, intubation could be attempted. (There were, of course, no relaxant drugs available at this time.) He had developed a modification of the smallest-size Chevalier Jackson laryngoscope, which was marketed under the name "Shadwell" laryngoscope (Fig. 1.1). It was designed to be held with the fingers rather than in the palm of the hand "to discourage the use of force" [24].

Gillespie noted that the epiglottis in the neonate was proportionally longer than in the adult and that, with each breath, the larynx tended to move anteriorly and out of the field of vision; deepening the anesthetic to prevent this movement tended to induce signs of impending cardiorespiratory failure. He stressed the need for gentleness and warned that any use of force might cause complications varying from a croupy cough to acute edema of the larynx. In his own reported series of 70 infants under the age of 2 years, he had remarkably few complications, especially in view of his statement that the largest possible tube should be passed. He was concerned to not narrow the airway, as all his patients

Fig. 1.1 The Shadwell laryngoscope

were breathing spontaneously. However, he did stress the need to attempt to pass the tube "gently" [24].

The use of endotracheal intubation in infants was not without problems, however, and cases of postoperative laryngeal edema and, more rarely, subglottic stenosis were reported. The need to use a tube, which passed easily through the glottis and subglottic space and allowed a slight leak on pressurization of the anesthesia circuit, was, in time, recognized by anesthesiologists. A classic paper by Eckenhoff [25] in 1951 described the anatomy and dimensions of the infant larynx and stressed the need to avoid injury to the mucosa in the region of the cricoid ring. The problems that sometimes followed intubation and the fear that these might adversely affect outcomes led many surgeons, particularly in the USA, to oppose this practice for their patients. Anesthesia providers were directed to manage neonates for complex repairs, e.g., tracheoesophageal fistula or coarctation of the aorta, using mask anesthesia. However, the pioneers of pediatric anesthesia persisted, perfected safer methods, and thus facilitated acceptance of the need for endotracheal intubation, essential if progress in neonatal surgery was to continue.

Red rubber tubes were largely abandoned in favor of plastic tubes in the 1950s. However, early plastic tubes were also not without problems. Irritant chemical substances (organotins) within the plastic material were found to be capable of stimulating local tissue reactions that could lead to fibrosis [26]. The establishment of routines for implantation testing of plastic material led to improvements in endotracheal tube composition and manufacture and a subsequent decrease in complications.

In 1945, Cole described a new endotracheal tube for infants. This tube had a wider proximal portion and a narrower distal segment to pass through the glottis, the rationale being that the wider portion would decrease the resistance to airflow. In addition, it was claimed that the shoulder of the tube would decrease the likelihood of the tube passing too far and entering a bronchus. In fact, the resistance of the Cole tube was found to be greater than that of a similar internal diameter parallel-sided tube [27]. This was attributed to turbulent flow within the Cole tube. More seriously, the shoulder on the tube was shown to cause laryngeal damage if advanced into the glottis [28]. The Cole tube was generally abandoned for use during anesthesia but remained in use for neonatal resuscitation in some centers, the claim being that it was easier for the less expert practitioner to insert.

The concept of prolonged endotracheal intubation as an alternative to tracheostomy was presented by Bernard Brandstater at the First European Congress of Anesthesiology in 1962 [29]. He reported his experience with seven patients ranging in age from the neonate to 4 years. Until that time, it had been customary to perform a tracheostomy if infants required ventilator assistance [30]. The tracheostomy tubes
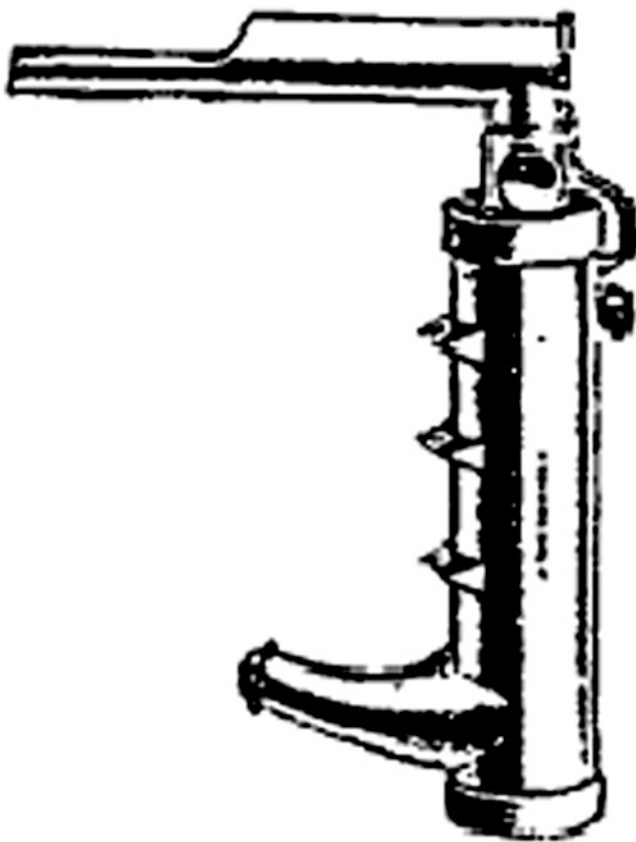
in general use were uncuffed and the variable leak that occurred via the glottis made a constant level of ventilation difficult to attain—especially in patients with reduced pulmonary compliance. Fortunately, the ventilators in common use in North America at this time were pressure cycled (the "Bird" Mark VIII) and this reduced the problem to some extent. In mid-1960s, the use of intermittent positive pressure ventilation (IPPV) in the therapy of newborn respiratory distress syndrome was becoming established as was the need to treat respiratory insufficiency in the postoperative cardiac patient [31]. In 1965 Reid and Tunstall reported a case of respiratory distress syndrome in a 1800-g preterm infant successfully treated by IPPV via a 2.5-mm ID nasotracheal tube [32]. In the same year, McDonald and Stocks from the Royal Children's Hospital in Melbourne, Australia, reported a larger series of infants treated with prolonged nasotracheal intubation [33]. They described the complications, including post-intubation subglottic stenosis, and offered suggestions to minimize the incidence of this serious outcome. By the end of the 1960s, prolonged endotracheal intubation had superseded tracheostomy as the management of choice for infants requiring ventilatory assistance.

During the 1960s and 1970s, it was a very common, almost standard, practice to intubate the trachea while the infant was awake, before induction of anesthesia. This, it was claimed, minimized the danger of regurgitation and aspiration and facilitated the rapid induction of anesthesia [34]. In addition, if attempts at intubation failed, there was little danger as the infant would usually maintain the airway and continue ventilation. Awake intubation of the neonate continued to be widely practiced until toward the end of the twentieth century when concerns about the physiological stress that might be imposed on the infant prompted further consideration [35]. In addition, it was demonstrated that intubation is much more likely to be successful with fewer attempts and less elapsed time if performed in the anesthetized infant [36].

Having intubated the airway in the neonate, the scene was set to control ventilation during anesthesia. This would facilitate procedures to correct intrathoracic congenital defects. In addition, it would allow the administration of neuromuscular blocking drugs to provide optimal conditions for abdominal surgery and reduce the need for high concentrations of inhaled anesthetics.

Neuromuscular Blocking Drugs

d-Tubocurarine was introduced into anesthesia practice in the 1940s and succinylcholine became available in the 1950s. Both drugs were used in neonates soon after their introduc-

tion, but initially, there was a lack of universal enthusiasm for using relaxant drugs in the neonate. In Europe, a pioneering neonatal anesthetist, Dr. Jackson Rees, wrote in 1950 "In the newborn, as has already been shown, control of the respiration is easily obtained at light levels of anaesthesia without the use of relaxants: muscle relaxation does not appear to be of major importance in the production of good operating conditions, and the usual untoward effects of endotracheal-tube induction are not seen.(sic) On these grounds it can be said that the use of relaxant drugs in anaesthesia is contraindicated in the newborn patient, and I have abandoned these drugs in such cases" [34].

In the USA, the study of Beecher and Todd published in 1954 [38] demonstrated an increased mortality associated with the use of relaxant drugs—especially in those in the early years of life. Postoperative respiratory difficulties were reported in infants given relaxants [39]. In 1955, Stead reported that the neonate was sensitive to the effects of nondepolarizing neuromuscular blocking drugs but was resistant to the effect of the depolarizing drug succinylcholine [40]. This further supported the impression that residual curarization was a problem in infants. However, Rackow and Salanitre in New York reported their experience with relaxant drugs [41] and suggested that postoperative respiratory depression was seen only as a result of drug overdose or with hypothermia; the latter was not uncommon at that time in the smaller infants. Warming from hypothermia had been demonstrated to potentiate any residual block [42]—hence, the infant placed in a heated isolette to rewarm after surgery was at risk! This observation encouraged efforts to maintain normothermia during neonatal surgery (see below).

In the 1960s, the use of neuromuscular blocking drugs in the neonate was widely accepted, and the use of heating blankets and overhead warmers to maintain normothermia became routine. Rees wrote "Following intubation the child may be saturated with nitrous oxide as rapidly as possible by intermittent positive pressure ventilation, and the relaxant drug may then be administered. In this way perfect operating conditions are obtainable, and the more potent and, therefore more toxic agents are eliminated from the anesthetic technique" [37]. This was the "Liverpool technique," which was widely used in Britain and elsewhere. For brief procedures, it was not uncommon to use repeated injections of succinylcholine as a relaxant.

The question of the sensitivity of the neonate to d-tubocurarine (dTc) was finally resolved by Fisher in 1982 [43]. The neonatal neuromuscular junction is indeed sensitive to the effects of dTc, but this is largely compensated by the increased volume of distribution of the drug in this age group [43].

Anesthesia Circuits and Controlled Ventilation

The T-piece system was considered by many to be the anesthesia circuit of choice for the neonate. It is lightweight and simple and has low dead space and low resistance, and ventilation could be controlled simply by intermittently occluding the expiratory limb with the finger. Jackson Rees in Liverpool improved on this system by adding an open-ended bag to the end of the expiratory limb [34]. A vulcanite tap was inserted into the open end of the bag and adjusted to maintain the bag inflated but to allow escape of expired and excess gases. Manual controlled ventilation was readily applied with this system. However, a fresh gas flow of 2–2.5 times the minute ventilation was required to prevent rebreathing of expired gases. This was wasteful of anesthetic gases, which were cheap in those days, and potentially caused significant atmospheric pollution (not appreciated to be a problem until the 1970s). A modification to prevent rebreathing with lower fresh gas flows was to use a small-sized Waters soda lime canister on the expiratory limb for CO_2 absorption, but this was generally considered less easy to apply to the small infant. Indeed, Leigh and Belton writing in 1950 stated "Use of absorption technic in the first few months of life is impracticable and affords no distinct benefits to patient, surgeon and anesthesiologist" [44].

The pattern of ventilation chosen by the Liverpool group for infants is interesting. Dr. Jackson Rees always encouraged the use of rapid shallow ventilation for the neonate. He admitted that this often led to hyperventilation and hypocapnia but did not consider this to be a significant problem [37]. In later years, he would add small concentrations of carbon dioxide to the inspired gases when indicated to prevent hypocapnia (Rees GJ, personal communication). The pattern of ventilation used, however, did tend to limit the duration of expiration and maintain a constant positive pressure—both of which acted to reverse the reduction in lung volumes that occurs during anesthesia and muscle paralysis and thus improve gas exchange. Dr. Rees was quite gratified to read much later of the clinical studies that defined adverse changes in pulmonary function which accompanied infant anesthesia, changes which his technique had tended to moderate.

As neonatal surgery became more complex and longer procedures were performed, the need to provide for mechanical ventilation during surgery was apparent. Fortunately, by this time, progress in ventilator design made this possible. Quite simply, the Bird Mark VIII ventilator or the Ohio Ventimeter Ventilator could be adjusted so that they would periodically serve to occlude the expired limb of a T-piece system.

As an alternative to the T-piece system, which required a fresh gas flow 2–3 times the minute ventilation to prevent rebreathing, some anesthesiologists preferred to use non-rebreathing valves. These required only a gas flow equal to the minute ventilation. Ronald Stephen and Harry Slater described their non-rebreathing valve in 1948. It incorporated two rubber valves and was described as having very low resistance to breathing and negligible dead space. Controlled ventilation could be delivered by compressing the exhalation valve with a finger while compressing the reservoir bag, and the authors claimed to have used this method in infants of 3 weeks for up to 90 min [45]. In 1948, Digby Leigh independently described a valve of very similar design, which could be used in infants [46]. George Lewis modified the Leigh valve to permit controlled ventilation without the need to digitally compress the exhalation valve. The Lewis/Leigh valve incorporated a flap that would close the exhalation port if the reservoir bag were compressed [47].

A problem with the T-piece system and with non-rebreathing valves was that they delivered very dry gases to the airway. In the USA, this concern led to the development of circle systems modified for the neonate. The Bloomquist infant circle was marketed by the Foregger company and incorporated a soda lime canister. However, a laboratory study of the humidity output of this circuit concluded that it offered no advantage over a humidified T-piece system and was more cumbersome to use [48]. The Columbia Valve was developed to allow a modified adult circuit to be used for infants; the valve had low resistance and a very low dead space of 0.5 mL [49]. This valve was used in a circuit in which the fresh gases were passed through the soda lime canister together with the expired gases in an effort to maximize the level of humification (Rackow H, personal communication). The T-piece and its variants were almost always used for the neonate in Britain and Canada; non-rebreathing valves and various circle absorber systems were more commonly used in the USA.

In later years, pediatric anesthesiologists adapted various neonatal ventilators for operating room use. Progressive improvements in anesthesia machine design eventually allowed small infants to be successfully managed simply by changing to a smaller-diameter set of circuit tubing.

Monitoring

As has been stated previously, monitoring in the early days consisted of watching the chest movements, examining the color, and perhaps feeling the pulse. Indeed, this situation persisted well into the twentieth century. Writing on anesthesia for neonatal chest surgery in 1965, Bell stated "*A guide to the general clinical condition I find useful is this:*

baby pink and pulses palpable-condition good;
baby pale, pulses palpable or baby pink, pulses not palpable-condition satisfactory, but check ventilation and blood balance;
baby pale, pulses not palpable—condition serious.

I do not think that cardiac stethoscopes (the heart action can be seen in thoracic operations), sphygmomanometers, pulse monitors or E.C.G. tracings contribute enough additional information about a baby's condition to merit their use; they may be distracting" [50].

I cannot say that this was the general attitude to monitoring in those years, but it is a recorded opinion.

Accounts of neonatal anesthesia prior to 1960 make little or no mention of monitoring [34, 37, 39]. In fact, the technology to satisfactorily monitor blood pressure in the neonate was not generally available until the late 1950s. Palpation or auscultation distal to a blood pressure cuff was noted to be very difficult in small infants. Oscillometry had been used but was not uniformly reliable. Hence, it was not common practice to monitor the blood pressure even in larger infants. Anesthesia records from this era commonly displayed only a heart rate. In an article on anesthesia for major surgery in 1950, CR Stephen displayed an anesthesia record for pyloromyotomy on which the only vital signs recorded were the heart rate and respiratory rate [51].

The optimal width of the blood pressure cuff (one inch) that was required for accurate measurement in the neonate was determined in 1939 by direct comparison with an intra-arterial needle [52]. However, as noted above, it was uncommonly used in anesthesia practice. Detection of pulsation distal to the cuff most often depended upon oscillometry. To detect the very small deflection of the oscillometer needle was frequently highly dependent upon "the eye of faith." This could be very worrying during thoracic surgery or indeed any other major procedure; this I remember well.

In 1969, the use of the Doppler flow meter to monitor flow in the radial artery distal to a blood pressure cuff and reliably measure intraoperative blood pressure in infants was reported [53]. The battery-operated "Parks Doppler Flowmeter" became widely available and took much of the worry out of neonatal anesthesia. It could be used to measure blood pressure and also served as a continuous audible monitor of the pulse volume, serving as an early warning of adverse changes.

Direct intravascular measurement of the arterial pressure was initially measured from the umbilical artery; however, this resulted in a relatively high incidence of serious complications (e.g., bowel infarction) and was only applicable in the immediate neonatal period. Percutaneous cannulation of the radial artery in neonates was described in 1975 as a safer alternative [54, 55]. The use of the temporal artery for monitoring was also suggested [56] but was later generally abandoned when it became known that cerebral embolism was associated with this technique [57]. Femoral artery lines were also used on occasion but, in the neonatal age group, the incidence of ischemic complications exceeded that with radial lines [58].

In 1950, the monitoring of the oxygen saturation of blood during anesthesia was described by a group from Montreal [59]. They used an earpiece, which had been developed during World War II for the purpose of studying pilots flying at various altitudes. The equipment they used was delicate, however, and required a dedicated technician to operate it. Continuous monitoring of transcutaneous oxygen tension ($TcpO_2$) in neonates was described in 1972 [60], but this was not introduced as a routine into the neonatal nursery for several years. Though $TcpO_2$ was capable of indicating trends, individual readings lacked precise accuracy especially with decreased skin blood flow [61]. Electrodes required frequent attention and had to be moved periodically to prevent burns. During anesthesia, inhaled agents were found to further interfere with the performance of the electrode and decreased its accuracy, though not to a significant degree [62].

Pulse oximetry became available for clinical use in 1983 [63] and was rapidly adopted as a routine monitor during the surgery and acute care of neonates; it was far easier to apply than the TcpO2 electrode and did not require repositioning periodically. It was now possible to continuously display the level of oxygenation throughout the perioperative period and immediately respond to any adverse changes. It was also quite possible to apply two probes: one in the preductal area and one in the postductal area. The question now arose as to the safe level of preductal oxygen saturation to maintain in the preterm infant at risk for retinopathy of prematurity (ROP). Surveys performed in recent years indicate that many units aim to maintain SpO_2 in the 85–93% range [64] and that this does indeed decrease the incidence of serious ROP changes [65].

Monitoring of end-tidal carbon dioxide as a routine procedure in anesthesia care became commonplace during the 1980s. When applied to the neonate, it became apparent that both methods for CO_2 analysis, mainstream and sidestream, are problematic [66]. The increase in dead space with mainstream analysis may lead to rebreathing in small infants. During sidestream analysis, the site of sampling, the sampling flow rate, and length of the sampling tube proved to be critical factors in obtaining accurate measurements of end-tidal CO_2.

Intraoperative Temperature Control

As more prolonged surgery was being performed in neonates, the problem of intraoperative hypothermia became recognized [67] and identified as a cause of increased morbidity and mortality [41, 68–70]. Two of five postoperative deaths in a series of 12 neonates were attributed to hypothermia [68]. In another series of 67 infants, 12 patients died; seven of these were judged due to postoperative hypothermia

[70]. It was noted that the decrease in body temperature was directly related to the duration of surgery and that smaller infants suffered a greater decrease. The vulnerability of the small infant to heat loss as a result of the large body surface area to weight ratio was noted [71]. At this time in the 1950s, little was done to keep the neonate normothermic during surgery and indeed intraoperative hypothermia was considered by some to be beneficial.

An improved understanding of the adverse physiological effects of hypothermia came in the early 1960s. It also became recognized that it was much easier to keep the patient warm during surgery than to resort to rewarming postoperatively. The adverse effects of cooling on oxygen consumption [72], catecholamine levels [73], and acid/base status [74] were identified. Oxygen consumption in the neonate was shown to correlate most closely with the skin to environment temperature gradient, hence the significance of the "neutral thermal environment." With this new understanding, efforts were made to maintain normothermia intraoperatively. Hot water bottles alongside the infant were recommended, but unfortunately, this sometimes led to burns. Heating pads for the operating room table were described by Leigh and Belton in the second edition of their book on pediatric anesthesia published in 1960 [75]. Wrapping the limbs in cotton wadding and placing the infant on a warming blanket set at 40°C were advocated by RM Smith in his textbook in 1968. It was also found that heating blankets were more effective in maintaining normothermia in smaller infants—a beneficial effect of the large surface area to body mass ratio [76]. The addition of overhead radiant heaters during preparation for surgery and humidification of anesthetic gases provided for what was considered optimal patient management in the late 1960s and 1970s [77]. In the 1990s, forced air warmers became generally available and proved very effective in maintaining normothermia [78].

Neonatal Anesthesia: Some Landmark Procedures and Their Development

Repair of Esophageal Atresia and Tracheoesophageal Fistula

The first operation for esophageal atresia was performed in London, England, by Charles Steele in 1888 [79]. The diagnosis was made when the infant became livid and had difficulty breathing "after the first nourishment"; a sound could not be passed by mouth for further than 5 inches. Surgery was performed the next day after "the infant took chloroform well." The stomach was opened via an abdominal incision and an unsuccessful attempt was made to pass a gum elastic catheter retrograde up the esophagus, in the hope that a simple membrane could be perforated. The surgery was aban-

doned and the infant died 24 h later.[79] At autopsy, the upper and lower esophagus ended blindly one and one-half inches apart. There is no mention of an associated fistula.

The first successful ligation of a tracheoesophageal fistula (TEF) with anastomosis of the associated esophageal atresia was reported by Haight in 1943 [80]. Local analgesia was used for the first part of the operation; open ether was added during the esophageal anastomosis in order to obtain optimal surgical conditions. Spontaneous ventilation was maintained throughout. In Britain, Franklin described two successful repairs of TEF with esophageal anastomosis in 1947 [81]; both of these procedures were performed using infiltration of local anesthetic (1% procaine) to the chest wall incision line and no other anesthesia. During the operation "the infant was secured prone over a rubber hot water bottle" [81].

As has been previously stated, in early days, many surgeons opposed the use of endotracheal intubation for their patients. Swenson, a much respected pioneer pediatric surgeon, reported his experiences with TEF in 1943 and advocated the administration of cyclopropane via a tightly applied face mask [82]. Kennedy and Stoelting reported a series of 86 cases of TEF operated upon at Indiana University Hospital from 1940 until 1956 [83]. Before 1948, 17 cases were managed without intubation using a combination of local analgesia and open ether; the mortality rate was 88%; two patients died during surgery. After 1948, all 69 neonates underwent tracheal intubation, none died during surgery, and the overall mortality rate was 42%. Many factors were considered responsible for these improved results, but the role of endotracheal intubation and tracheobronchial toilet was considered to be very significant. General anesthesia methods reported by Zindler and Deming in 1953 [84] employed awake endotracheal intubation to administer cyclopropane via a non-rebreathing valve and controlled ventilation. They also stressed the need for frequent suctioning of the trachea.

Progressively improving results from the surgical and anesthesia management of TEF can be followed by examining the Toronto experience. A review of the results from 1959 to 1964 [85] shows an overall mortality rate of 36.5%, with a rate of 57.5% for the infants who were under 2500 g body weight. The predictors of mortality were prematurity, the presence of associated congenital malformations (especially cardiac), and extensive pulmonary disease (i.e., delayed diagnosis). A subsequent review [86] of the years 1964–1968 noted an overall mortality rate of 22%, and the mortality rate for those under 2500 g had decreased to 40%.

The problem of gastric distension due to gases passing through the fistula into the stomach was a concern for the anesthesiologist, especially as this has been reported to cause serious ventilatory embarrassment and even cardiac arrest [87]. Some preferred to maintain spontaneous (perhaps gently assisted) ventilation until the fistula was ligated. Other suggestions to prevent this complication included perform-

ing a preliminary gastrostomy under local analgesia [88]; this was also favored by some surgeons as part of a two-stage repair, especially in critically ill infants. Passing an endotracheal tube (without a side hole) into the bronchus and withdrawing it until bilateral ventilation could be heard and then positioning the tube with the bevel facing anteriorly were also suggested [89]. This would direct ventilation to the lungs and protect the fistula with the longer side of the bevel. (However, the fistula is occasionally at the level of the carina!) Some more complicated methods to position the tube and prevent gastric distension have also been described. If a gastrostomy was present, it was suggested that placing the gastrostomy tube under water in a beaker while advancing the endotracheal tube could indicate when the ETT was below the fistula [90], i.e., no more bubbles! The significance of leaks via the fistula increased as preterm infants with respiratory distress syndrome requiring greater airway pressures presented for surgery. Karl suggested that a balloon catheter should be inserted into the lower esophagus via the gastrostomy to control the leak [91]. Others suggested that a Fogarty or pulmonary artery catheter should be advanced via a bronchoscope directly into the fistula [92]. In many units, it became a routine to perform early ligation of the fistula in preterm infants, thus largely avoiding the problem.

Preoperative endoscopic examination of the fistula was introduced in the 1980s [93] and became routine in some centers [94]. It was suggested that an exact knowledge of the size and site of the fistula would improve results and in addition endoscopy permitted placement of balloon catheters to occlude the lumen. Others preferred to keep things simple and manage the airway without endoscopy [95].

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) was described in 1757 by a society of physicians in London following postmortem examination of an infant who died under 2 h of age in respiratory distress [96]. Early reports of operations for CDH are found in the medical literature of the 1930s [97] and 1940s [98], but it is significant that the neonates were all more than 20 h of age, and some patients were much older, i.e., they had adequate pulmonary function to survive the immediate neonatal period. In 1946, Robert Gross reported seven cases that came to surgery with ages ranging from 22 h to 7 years; he also recorded his preferred anesthesia technique [98]:

The choice of anesthetic agent and the method of its administration are important considerations, particularly in the cases of patients in whom cyanosis and respiratory embarrassment are pronounced. Ether can be employed, and indeed may be given with an open mask. It is preferable to use a closed system, so that a higher percentage of oxygen can be supplied to the patient and so that collapse of both lungs can be prevented in those rare cases in which there is a free communication between the two pleural cavities. In all cases of the present series, cyclopropane was used and was eminently satisfactory. It is clear, however, that this choice depended on my good fortune in having an anesthetist who is expert in handling babies and who has had enough initiative to devise a homemade apparatus which is suitable for babies of the smallest size. It must be emphasized that cyanosis should not be a deterrent to operation, since the administration of a gas containing a high percentage of oxygen will improve the baby's color, and the operative removal of the abdominal viscera from the chest will also facilitate the child's breathing efforts. It is unnecessary to use an intratracheal tube; indeed, this is apt to be followed by troublesome edema of the larynx in the ensuing twenty-four hours. Only a tightly fitting mask, without an intra-tracheal tube, was used for all of the patients reported on here. [98]

CDH was considered a surgical emergency [99] and immediate operation was recommended once the diagnosis had been made—especially if respiratory distress was present. A case report from 1950 [100] demonstrated the extent to which improvisation was employed to facilitate urgent surgery. The child was 5 days old and in considerable respiratory distress and required oxygen at all times—a decision was made to perform immediate surgery. "Ether was the anesthetic agent of choice. The equipment at hand was a small open mask, an infant-sized metal oral pharyngeal airway, a rubber infant-sized mask from a Kreiselman resuscitator, a socket elbow, a short corrugated tube section, a Peterson ether drop cup, and for a breathing bag a toy red rubber balloon." During the procedure, the two red rubber balloons that were available both disintegrated due to contact with liquid ether and were replaced by rubber condoms! To the credit of the team, the infant survived.[3]

In the 1950s, the association between pulmonary hypoplasia and CDH was reported [101]. From this time and into the 1960s, improvements in the care and transportation [102] of critically ill neonates resulted in more infants with CDH presenting for emergency surgery. Many of these who would have died without surgery now died postoperatively secondary to their pulmonary status. The high mortality rates associated with repair CDH stimulated many investigators and clinicians and attention turned to means to optimize pulmonary function postoperatively. These means included various patterns of controlled ventilation and measures to reduce pulmonary vascular resistance (PVR) [103]. The thought developed that the cause of death in some cases was not simple hypoplasia but potentially reversible changes in PVR [103]. The standard approach to anesthesia for CDH at this

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[3] The other obvious question that this case raises is whether the reporting institution was the most appropriate place to be performing this surgery. However, in 1950, the concept of regionalization of pediatric and neonatal services was undeveloped even in Europe and was largely unrecognized in North America.

time, no bag and mask ventilation, endotracheal intubation, avoidance of N_2O, and care to avoid large positive pressures, was augmented by steps to control PVR if required.

One problem that had complicated the management of the infant with CDH was that some experienced very few problems postoperatively, whereas others were desperately ill. Hence, there was great interest in identifying those prognostic factors that determined which infants would require aggressive invasive measures. Raphaely and Downs in Philadelphia developed a scoring system based on the preoperative and postreduction alveolar/arterial oxygen tension gradient [104]. Desmond Bohn and his colleagues in Toronto suggested a system to predict the extent of pulmonary hypoplasia based on the preoperative arterial CO_2 tension and a ventilatory index (mean airway pressure x ventilatory rate) [105]. Bohn et al. also suggested that consideration should be given to an initial nonsurgical approach to CDH in the expectation that impaired pulmonary function not due to hypoplasia might improve [105]. In the same year, 1987, another study from Toronto had shown that surgical repair of CDH impaired rather than improved respiratory mechanics [106]. Thus, CDH management evolved from a surgical emergency into a potential complex management problem for the neonatal intensivist, sometimes involving preoperative ECMO therapy. Surgery was now performed only when the respiratory status was improved.

Abdominal Wall Defects

Reports of exomphalos (omphalocele) are found in medical writings from the middle ages onward, but the infants generally soon died—usually of peritonitis. There are a few instances where conservative treatment using antiseptic preparations applied to the lesion resulted in granulation tissue formation and epithelialization with survival. Operative treatment before the 1940s was usually fatal [107]. Successful surgical treatment was reported in 1948 [108], and in 1951, a further successful case was reported in which the anesthetic used "was sugar and whisky administered on a small gauze nipple" [109]. The postoperative course was complicated by peritonitis; however, the patient recovered and was discharged on the 75th postoperative day. Much credit for the recovery was given to the use of prolonged intravenous fluid therapy. At this time, it was recognized that omphalocele was often associated with other significant congenital malformations. It was also noted that the immediate prognosis depended on whether the membrane covering the viscera was intact or ruptured; in the latter case, a fatal result was certain [110]. In 1953, a successful case is recorded in which open ether was administered for anesthesia: "*The bowels were returned to the abdominal cavity with difficulty, and the*

wound was closed in a single layer. The anaesthesia must be sufficiently deep to relax the abdominal muscles. This requires the services of a skilled anaesthetist" [110]. It was suggested that a stomach tube should be in place to aspirate secretions as the bowel was reduced into the abdomen—obviously a serious concern when an open technique was used.

By the 1970s, the problems of heat conservation, fluid therapy, prevention of infection, and prolonged postoperative ileus were recognized and being managed [111]. Local analgesia infiltrated by the surgeon was still quite frequently utilized "with anesthesia standby." This led to cautions in the 1979 edition of the Manual of Pediatric Anesthesia [112]: first, to monitor how much local analgesic the surgeon injected and, second, to consider intubating the airway—to protect it against aspiration of regurgitated stomach contents. The introduction of endotracheal intubation and controlled ventilation greatly facilitated general anesthesia management but introduced the problem of determining whether the infant could tolerate the increased intra-abdominal pressure (IAP) postoperatively. Controlled ventilation could be continued postoperatively, and simple closure of the skin only and delayed closure using Silon pouch were options. However, it was appreciated that increased IAP not only impaired ventilation and circulation but also severely compromised splanchnic and renal perfusion. In 1989, Yaster et al. suggested that the intragastric pressure (IGP) and/or central venous pressure (CVP) should be monitored during replacement of the viscera; IGP in excess of 20 mm/Hg or CVP increases of 4 mm/Hg are unlikely to be tolerated [113].

By the end of the twentieth century, prenatal diagnosis and progress in anesthesia management, critical care, and intravenous alimentation resulted in significantly reduced mortality and morbidity. The mortality rate for gastroschisis was under 10% and the mortality in cases of omphalocele was largely dictated by the presence or absence of associated malformations.

Neonatal Cardiovascular Surgery

Surgery of the heart and great vessels was introduced in the 1940s and 1950s, but initially, very few of the patients were neonates. Robert Gross ligated a persistent ductus arteriosus in a child in 1939 and launched pediatric cardiovascular surgery. Most of his early patients were older but he did describe division of vascular ring in patients that included a 3-week-old infant in 1951 [114]:

Anesthesia in all these subjects has been with a closed system, using ether or cyclopropane. In all cases, an intratracheal tube, preferably of soft polyethylene, has been employed. Such a tube is essential for the maintenance of an adequate airway, particu-

larly in the first four types of anomalies just described, in each of which the trachea is markedly narrowed and an adequate exchange might not be obtained until a tube is passed down beyond the obstructed point. [114]

William Mustard in Toronto operated on neonates with preductal coarctation of the aorta in 1953 [115] with long-term success. The anesthetic regimen was: "*Induction is with pentothal 5 mg per pound and syncurine 0.01 mg per pound mixed together in the same syringe. Orotracheal intubation is performed after succinylcholine 1 mg per 5 pounds. The patient is maintained on a 50–75% nitrous oxide with oxygen mixture, and control of ventilation is maintained by means of frequent small doses of succinylcholine*" [115]. The anesthetics were all administered by Dr. Code Smith who first described the esophageal stethoscope [116], developed in order to monitor heart and breath sounds reliably during thoracic surgery in small infants.

Open Heart Surgery

The use of open heart surgery with cardiopulmonary bypass (CPB) in neonates was initially associated with very high mortality rates. In 1963, it was stated "It is apparent that perfusion can be performed on even the smallest infants. It is equally certain that present methods of perfusion in small infants are hazardous and should be applied only in extraordinary circumstances" [117]. The authors reported a mortality rate of 66% for infants of 0.2 square meters body surface area. The mortality was considered related to the severity of the CHD and to postoperative complications related to the "marginal status of the infant's cardiopulmonary system" [117] There were, however, also frequent technical problems related to the small size of the patients. The problems of applying CPB to the smaller infants stimulated an interest in performing surgery under deep hypothermic circulatory arrest (18–20 °C) using only surface cooling and rewarming [118]. The technique originated in Japan but was adopted by several centers in North America. Anesthesia was maintained using diethyl ether, which was thought to protect against ventricular fibrillation during the cooling phase [118]. Using this technique, an overall mortality rate of 42% was reported [118]. As techniques for CPB rapidly evolved, and as flammable ether was considered an unacceptable hazard by many groups, cooling of neonates on bypass became more common.

Profoundly hypothermic circulatory arrest (PHCA) was first used in neonates in the 1960s and became widely used thereafter. Intra-atrial repair was simplified in the absence of venous cannulae. However, controversy soon emerged concerning the long-term safety of PHCA versus continued perfusion [119]. There was also much debate concerning the optimal management of the pH status and other variables (e.g., hematocrit) during cooling bypass [120].

Regional Analgesia

Bier popularized spinal analgesia in 1898, though Corning had successfully used the method 15 years earlier. The use of spinal analgesia in a neonate 24 h old with acute intestinal obstruction due to congenital hernia of the umbilical cord was described in 1912 [121]. The method used was that of Dr. Tyrell Gray, at that time medical superintendent at the Hospital for Sick Children, Great Ormond Street, who had written extensively on the subject of spinal anesthesia in infants and children [122]. The drug used was Stovaine (0.012G) with glucose. Stovaine (amylocaine) was the first synthesized local anesthetic and was widely used for spinal anesthesia being less toxic than cocaine. The dose used would produce anesthesia for up to 1 h. Reports of the use of spinal analgesia for abdominal and perineal surgery in infants are found from several centers during the first half of the twentieth century.

In the 1960s, an interesting series of neonates with open myelomeningocele underwent corrective surgery after direct injection of local analgesic into the lesion by the surgeon [123]. A solution of 1% lidocaine was used and produced anesthesia very adequate for the repair—which was always completed in less than one hour. No complications were noted and the decrease in blood pressure after the injection was small. The rationale for the use of this technique was that it was less hazardous than general anesthesia administered by an inexperienced anesthetist.

Spinal anesthesia for preterm neonates with inguinal hernia became popular late in the twentieth century when it was suggested that postoperative respiratory complications were less common than after general anesthesia [124]. Studies also confirmed that the effect of a spinal block on the blood pressure is relatively minor in small infants [125]. There was also renewed interest in some centers for the use of spinal anesthesia for abdominal and even thoracic surgery.

As has been mentioned throughout this chapter, infiltration of local anesthetics was often employed for the neonate. In 1930, Denis Browne, the surgeon at Great Ormond Street Hospital, described a restraint for the small infant that could be used during local or general anesthesia (Fig. 1.2) [126]. This was widely used in Britain for many years, and he wrote of it: "In operating on babies there are certain special difficulties. Owing to their light weight and powers of contortion
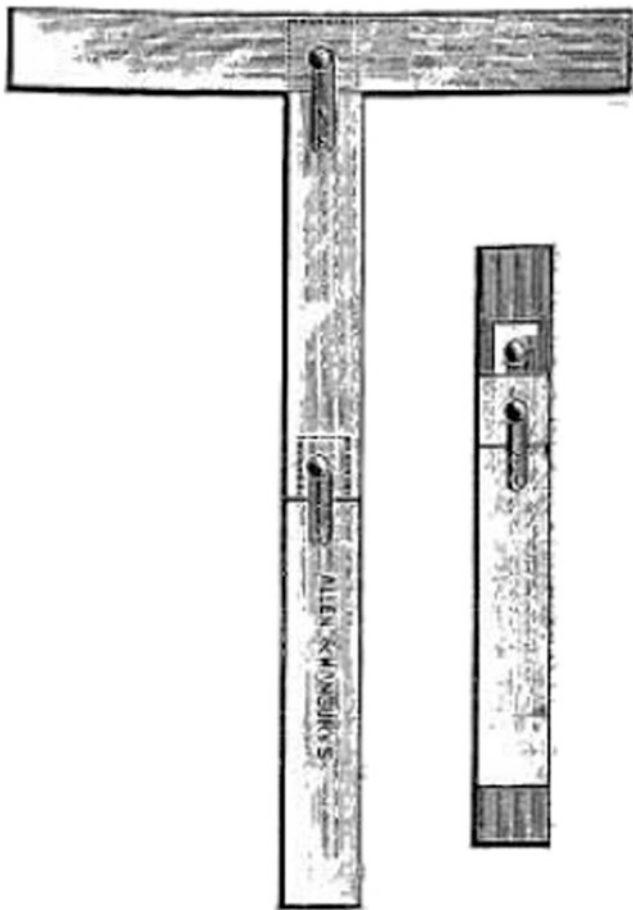
Fig. 1.2 The Denis Browne crucifix

they need careful holding for greater or less time, according to the type of anaesthetic, and their small size makes it difficult for the holder to avoid the operators. In work on these cases, both as operator and anaesthetist, I have found great help in a simple device which holds the child firmly, prevents chilling, and permits the use of local anaesthesia or the minimum of general. It is a 'crucifix,' the original model of which was a simple T of 2-inch wood, the cross limb 18 inches long and the main one 24 inches. As this was awkward to carry and had an inauspicious look about it when taken into a private house, I devised a collapsible model in duralumin, with a sponge rubber padding, and this has been very satisfactory" [126].

Minimally Invasive Neonatal Surgery

During the final decades of the twentieth century, advances in techniques and technology made it possible to apply minimally invasive/endoscopic surgery to very small infants. Closure of persistent ductus arteriosus by inserting an intravascular balloon was performed in an infant in 1979 [127]

and by thoracoscopic clipping of the ductus in a preterm infant in 1993 [128]. Regarding endoscopic abdominal surgery, extramucosal pyloromyotomy was described in 1991 in a series of 70 infants [129]. Peritoneoscopy of infants for diagnostic purposes had been performed since 1972 [130]. The physiological effects on the neonate of abdominal distension by carbon dioxide and the problems of facilitating intrathoracic endoscopic procedures were soon described and discussed [131]. Very early in the twenty-first century, thoracoscopic repair of tracheoesophageal fistula was reported [132]. By 2014, it could be stated that many surgical procedures for the neonate could be performed by minimally invasive techniques [133]. Significantly, these techniques reduce the stress of the surgical procedure and short-term morbidity [133] and eliminate the risk of some delayed complications, for example, post-thoracotomy scoliosis [134].

Ex Utero Intrapartum Treatment: "The EXIT Procedure"

The "EXIT Procedure" was described in 1997 as a means to maintain the newly delivered infant on the placental circulation until pulmonary ventilation could be established. The first indication for this was to provide time for the surgical removal of tracheal clips which had been placed to stimulate lung growth in cases of diaphragmatic hernia [135]. Subsequently, the technique has been applied to manage infants with various congenital airway obstructive lesions. Anesthesia management for the mother and infant was developed to ensure continued placental blood flow to the infant, maximize placental gas exchange, and provide uterine relaxation [136]. Most recently, the technique has been applied to permit EXIT to ECMO management of infants with potentially disastrous congenital cardiac anomalies.[137]

Regionalization of Neonatal Services

Real progress in modern neonatal surgery commenced in 1945 after World War II. In 1949, there were 58 neonatal operations at the Hospital for Sick Children in London and 27 (46%) of these infants died [138]. These results and similar figures from the Alder Hey Hospital in Liverpool led Peter Rickham to write "If in this country we are to improve the chances of survival of children born with congenital malformations an efficient neonatal surgical service must be organized" [138]. At this time, congenital malformations were listed as the third most common cause of neonatal death in the USA, but there were three centers (Boston, Philadelphia, Chicago) where Rickham observed very good results for neonatal surgery: "Surgical management and technique differed very little. American neonatal anesthesia was definitely

inferior to that in Liverpool, many operations being done under local or ether anesthesia. The important difference was the postoperative management. There were more highly trained medical personnel and nurses in the American Hospitals providing a highly efficient round the clock service….”

Mr. Rickham went on to act as a prime mover in the establishment of the “first neonatal unit in the world” which opened in 1953 at the Alder Hey Children's Hospital [139]. In the last half of the twentieth century, regionalization of neonatal services progressed steadily in Great Britain and in other European countries. The standards for the staffing and equipping of neonatal units and the organization for the transport of patients to these units are rigidly controlled. The concentration of patients in a few units ensured that the medical and nursing staff could gather the experience necessary to ensure optimal outcomes for their patients while providing training for the next generation of care providers. In Canada, complex neonatal surgery has been largely concentrated within the children's hospitals which are situated in most provinces, and thus, a similar regionalization has been achieved.

In the USA, regionalization of neonatal services and the establishment of units to serve all regions with an associated high volume of patients has been less consistent. There are many geographic problems involved, and there has also been a desire by many smaller hospitals to have a neonatal unit and to provide pediatric surgical services. This has sometimes led to problems with providing an adequate pediatric case load for credentialing purposes [140] and might indeed sometimes compromise results. In many states, however, neonatal emergency transport systems have been effective in directing a high volume of patients to regional neonatal surgical units [141]. The American Academy of Pediatrics in 2002 formulated and published general guidelines for referral of patients with major congenital anomalies to pediatric surgical specialists [142].

Research in Neonatal Anesthesia

Before 1960 very little research was conducted, those anesthetizing infants were busy with their clinical work [143], and anesthesia methods were largely based on what had worked in the experience of practitioners and their teachers. However, early investigations into the pharmacology of the anesthetic drugs in the neonate were commencing. Stead in 1955 reported the effects of neuromuscular blocking agents in the neonate [144]. Rackow and Salanitre studied the pharmacokinetics of the inhaled anesthetics in infants and reported these in 1969 [145]. The volatile anesthetic dose requirements for the neonate were the subject of some confusion until more precise studies in tightly controlled age groups were carried out in the 1980s [146]. Similar studies in preterm infants were conducted by Ledez and Lerman shortly thereafter [147]. As the numbers of pediatric anesthesia subspecialists swelled in the last decades of the twentieth century, there was a corresponding increase in research output and a more scientific approach to neonatal anesthesia became a reality. This did, however, require a closer evaluation of the ethics of performing studies in infants [148] and indeed the ethics of providing anesthesia for infants.

Ethical Considerations and Infant Anesthesia

The suggestion that the administration of anesthesia to infants might have long-term adverse consequences has been raised. In the 1970s, it was suggested that the incidence of asthma and respiratory allergies might be increased in children who were administered anesthesia in infancy [149]. A subsequent study failed to corroborate this association [150]. Late in the twentieth century, learning disabilities were described in children who had general anesthesia in infancy [151]. However, a study in more than 1100 identical twins in the Netherlands demonstrated that in discordant twins (i.e., one had an anesthetic and the other did not), the IQ values in each pair were identical in a 10-year follow-up [152]. Concerns were also raised by numerous neonatal animal studies that suggested that most general anesthetic agents are toxic to the developing brain [153]. Despite many studies [154–156], it has not been proven that exposure of human neonates to a well-conducted general anesthetic has significant adverse effects [157]. It has, however, been demonstrated that inadequately treated pain during infancy results in both short-term and long-term adverse effects [158]. Repeated anesthesia may be associated with adverse neurocognitive outcomes but many perioperative factors other than the use of an anesthetic drug are present in such patients [157]. Currently, the preponderance of evidence supports the ethical path of administering anesthesia to prevent pain and modulate the physiological responses to surgery in neonates. The problem for the anesthesiologist is to communicate these thoughts clearly to anxious parents who may have been exposed to less reliable information in the media. Indeed, parents have every right to be confused. In the 1980s, newspaper headlines screamed about newborn infants being subjected to surgery without effective anesthesia [159]; more recently, these same newspapers now warn that anesthesia drugs may harm those same patients [160].

The future path for pediatric anesthesiology is to pursue the ideal of perfecting agents and techniques that will cause the least harm and ensure the greatest benefits for our precious neonatal patients. Progressively, we have been able to practice evidence-based neonatal anesthesia management. The full history of neonatal anesthesia cannot yet be written—but the future may be just as exciting as was the past.

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