Anesthetic Experience in Children with Cystic Fibrosis of the Pancreas

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During the period 1945–62, 135 operations were performed on 93 children with cystic fibrosis of the pancreas. General anesthesia was given in 133 cases; two were done with spinal block. Ninety complications occurred either during anesthesia or in the postoperative period—60 were pulmonary and 30 were surgical complications. Eighteen of the pulmonary complications were related to anesthesia. One hundred and two children received a belladonna drug for pre-anesthetic medication—51 per cent had pulmonary complications; exclusion of complications due to anesthetic management reduced this figure to 36 per cent. Comparable figures for 33 children who did not receive atropine or scopolamine were 57 per cent and 50 per cent, respectively. The rate of respiratory complications was 45 per cent when diethyl ether was the primary agent, 47 per cent with cyclopropane and 53 per cent with halothane. Fifty of the 93 patients eventually died, 25 during the admission for surgery and 25 at varying periods (up to 15 years) after leaving the hospital. The overall mortality rate of this surgical group (54 per cent) fell within the range of estimated mortality of the clinical disease before children reach adulthood (50–80 per cent).

CYSTIC FIBROSIS of the pancreas is a serious disease of children, frequently affecting more than one organ system, and fatal to the majority before adulthood. The pulmonary manifestations are of particular interest to the anesthesiologist. Inhalation and antibiotic therapy have lengthened the survival period with the result that increasing numbers of them require surgery. Whether the operation is unrelated or related to the disease itself, the frequent presence of severe respiratory problems makes the anesthetic course a troublesome one. The difficulties encountered prompted us to review the accumulated anesthetic experience in the relatively large group of children with proven fibrocystic disease operated upon at the Babies Hospital of the Columbia-Presbyterian Medical Center. This report will review the present state of knowledge of the disease and present anesthetic and surgical findings.

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Material

The records of children with diagnosis of cystic fibrosis of the pancreas, a total of 702 up to January, 1963, were reviewed. Each chart involving a surgical procedure was analyzed for anesthetic and operative morbidity, degree of preoperative fibrocystic lung disease and long-term follow-up of pulmonary disease.

Our interest lay in three areas: (1) the relationship between pre-existing pulmonary disease and the anesthetic course (2) the effect of the surgical-anesthetic experience upon the subsequent course of pulmonary disease (3) the influence of the preoperative administration of a belladonna drug on the development of respiratory difficulties.

In order to evaluate these aspects, criteria were set up regarding the degree of pre-existing pulmonary disease. On the basis of roentgen-ray evidence and clinical examination, each patient was placed in one of 3 groups: (1) patients with no clinical pulmonary disease (2) patients with moderate pulmonary disease (3) patients with severe pulmonary disease. The last group included all children with chronic bilateral bronchopneumonia and emphysema.

Complications were divided into two broad categories: surgical and pulmonary. Surgical

complications were those related to surgical disease or arising from the operation, *e.g.*, wound infection, postoperative intestinal obstruction, excessive fluid and electrolyte losses from ileostomy, failure of vascular shunt, hemorrhage, and surgical error. Pulmonary complication was defined as any impairment of ventilation requiring active intervention, and included all respiratory problems, whether derived from fibrocystic lung disease or anesthetic management. The decision to combine all respiratory difficulties stemmed from the fact that it was often impossible to determine the relative contribution of the pre-existing lung disease to the onset or severity of the anesthetic difficulty. In some instances, however, the pulmonary complication was considered to be primarily anesthetic because it was believed that faulty management precipitated or aggravated the problem.

Two terms used in this report require explanation. Primary death is defined as death occurring during the hospital admission for the surgical procedure. Secondary deaths were those occurring after discharge from the hospital and were considered to be unrelated to the operation.

Clinical and Physiopathological Aspects[1,5]

Cystic fibrosis of the pancreas was not recognized as a distinct entity in the general group of malabsorption syndromes until its comprehensive description by Andersen[6] in 1938. It is a generalized, hereditary disease of the exocrine glands in which the basic defect is unknown. It is postulated that all exocrine glands are affected, even though the altered function may occur in glands which appear normal when studied with currently available histological methods. This concept explains the widespread clinical manifestations and emphasizes that organ involvement is secondary to the primary lesion of its exocrine component. The organs in which involvement give rise to the clinical picture are the pancreas, lungs, intestinal tract, liver and sweat glands. The pancreas is affected in about 80 per cent of the patients and gives rise to the classical picture of pancreatic insufficiency.

Intestinal obstruction of the newborn due to meconium ileus occurs in 10–15 per cent of all patients with cystic fibrosis. The obstruction is due to excessive and tenacious meconium. Volvulus and perforation are not uncommon. It is not clear whether the abnormal meconium is a result of deficient digestion resulting from pancreatic achylia or whether there is associated an abnormal mucoprotein secretion from the intestinal glands.

Autopsy has revealed that the liver is affected in most patients, although only a small percentage have clinically apparent hepatic symptoms. The microscopic lesion is one of biliary ductile obstruction with concretions surrounded by fibrosis, biliary proliferation and inflammatory reaction. These focal lesions give no clinical manifestations until a diffuse multi-lobular cirrhosis supervenes and the clinical picture of cirrhosis, portal hypertension, ascites, hypersplenism and esophageal bleeding becomes manifest.

Chronic pulmonary disease is present in almost all patients at some time during the course of the illness and determines the ultimate prognosis. The onset is variable and may not be apparent for years after birth. It is fatal in 50 per cent of patients before the age of 10 and possibly 80 per cent before the age of 20. The pulmonary lesion is primarily an intrabronchial one, the result of a combination of obstruction and infection. Viscid secretions in large amounts are a constant feature: they seem to be the result of hypersecretion by the mucus glands. The infectious element is secondary to the obstruction and has certain characteristic features. The initial invading organism usually is *Staphylococcus aureus*. Although the infection can often be brought under control with antibiotics, the underlying obstruction remains and sets the stage for subsequent bouts of infection. In the repetition of these cycles, any one of which can be fatal, bronchial damage becomes irreversible. The end results are: emphysema, bronchopneumonia, collapse of one or more lobes, multiple peribronchial abscesses, spontaneous pneumothorax, hemoptysis, CO_2 narcosis syndrome and usually death within 1–3 years of respiratory or cardiopulmonary failure.

The role of the sweat glands in cystic fibrosis was pointed out by Kessler and Andersen[7] in 1951 who emphasized that fibrocystic chil-

TABLE 1. Classification of operations, complications and deaths in 133 general and 2 spinal anesthetics

Group	Number of Patients	Number of Procedures	Complications		Deaths	
			Surgical	Pulmonary	Primary	Secondary
1. Meconium ileus	33	42	21	20 (6)*	21	7
2. Thoracic	12	13	3	10 (3)	0	4
3. Bronchoscopy-bronchogram	14	17	0	11 (3)	1	1†
4. Ear, nose, throat	21	25	0	6	0	5
5. Abdominal (exclusive of meconium ileus)	10	14	4	5 (1)	2	2
6. Vascular shunt	6	9	2	4 (4)	1	3
7. Miscellaneous	12	15	0	4 (1)	0	3
	93‡	135	30	60 (18)	25	25

* Number in parentheses indicates pulmonary complications considered to be primarily anesthetic.
† Four patients appear as secondary deaths in other groups.
‡ This number is less than the column total because some children had multiple operations and appear in more than one group.

dren have a low tolerance to hot weather. A subsequent study by Darling and his coworkers[8] clearly established that the sweat of fibrocystic patients had abnormally high concentrations of Na^+ and Cl^-. Since the rate of secretion remained normal, it became evident that this mechanism could account for a salt loss during hot weather. These observations were repeatedly confirmed and led to the development of the "sweat test," now the cornerstone of diagnosis and the means for the recognition of heterozygote forms of the disease.

The incidence of the fully manifested disease, *i.e.*, pancreatic insufficiency, chronic pulmonary disease and positive "sweat test," is estimated as about 1 in 1,000 live births.[9] There is a racial incidence for it is rare in Negroes and Mongolians.

Anesthetic and Surgical Findings

The surgical procedures fell into two general classes. A small number were operations performed as extreme emergencies on the medical wards, very frequently on moribund children, and consisted of resuscitative measures for pulmonary or cardiopulmonary failure. These included closed thoracotomy, bronchoscopy, tracheotomy and open-chest cardiac massage. Anesthesia was required only rarely and limited to local infiltration. These cases were excluded from the study because it was thought that the presence of overwhelming, terminal disease made evaluation meaningless. The larger group consisted of 154 operations, each of which had sufficient medical, surgical and anesthetic information to allow analysis. These procedures were performed during the period 1945–62, and included 133 done with general anesthesia, 2 with subarachnoid block, 18 with local infiltration and one with thoracic paravertebral block. The last two categories consisted of children so seriously ill from either lung disease or intestinal obstruction that they were not expected to survive either tracheostomy or laparotomy; some did not, and all died within hours or days. These cases were also excluded from the reported data for the reason previously given.

The reported findings concern 135 operations, involving 93 children, 133 of which were done with general anesthesia and 2 with spinal block. Sixty-nine were performed during 1945–55 and 66 during 1956–62. This arbitrary chronological division permitted some comparison between earlier and later cases and was further justified by the fact that a permanent staff of attending anesthesiologists was assigned to the pediatric unit in 1956. Thirty-seven patients had multiple procedures.

The operations were divided into seven categories (table 1). The meconium ileus

TABLE 2. Summary of Anesthetic Agents and Methods in 135 Anesthetics

	Induction		Maintenance	
	1945–55	1956–62	1945–55	1956–62
Agents and methods				
1. Diethyl ether				
open drop and/or insufflation	10		31	7
to and fro			3	1
closed circle absorption			1	1
semiclosed circle absorption			22	17
nonrebreathing			3	5
2. Cyclopropane				
open	31	30		
closed circle absorption			8	9
3. Chloroform, ethyl chloride, divinyl ether				
open drop	15	7		
4. Nitrous oxide or ethylene				
nonrebreathing	4	1		
nonrebreathing with intravenous thiobarbiturate			1	5
5. Tribromethanol per rectum	2	1		
6. Halothane				
semiclosed circle absorption				6
nonrebreathing		3		13
7. Thiobarbiturate, intravenous	1	11		
8. Spinal block				2
9. Awake endotracheal intubations	6	11		
Total endotracheal intubations			34 (49%)	51 (80%)
Number of cases in which a muscle relaxant was used.			1	15

group comprised newborns, characteristically free of pulmonary disease, except for two patients who had aspiration pneumonia prior to operation. Multiple procedures were frequent in this group, either for recurrent intestinal obstruction or for closure of enterostomy. The thoracic, bronchoscopy-bronchogram and vascular shunt groups were heavily weighted with patients having advanced pulmonary disease. The composition of the remaining groups was heterogeneous with respect to operations and degree of fibrocystic lung disease. The otolaryngologic procedures included tonsillectomy, adenoidectomy, sinusotomy and nasal polypectomy—the latter common in children with cystic fibrosis. The abdominal group included appendicectomy, pancreatic and liver biopsy, lysis of abdominal adhesions and small bowel resection. Operations such as inguinal herniorrhaphy, dental extraction, plastic and genitourinary procedures were grouped under miscellaneous.

Management of anesthesia is summarized in table 2. Comparison of the 1945–55 and 1956–62 groups shows the following trends in the latter period: (1) introduction of halothane (2) diminished use of diethyl ether by open drop and insufflation methods (3) increased use of endotracheal anesthesia, muscle relaxants and thiobarbiturates. The drugs used for preanesthetic medication were atropine, scopolamine, secobarbital, morphine and meperidine. The kind of premedication given seemed to be based on age. The majority of newborn infants received no medication; a few were given 0.05 to 0.1 mg. of atropine or scopolamine. Almost all the older infants received a drying agent and many also received secobarbital. The majority of children above one year of age received both a belladonna drug and secobarbital; many also were given a narcotic. Atropine or scopolamine was included in the preanesthetic medication of 100 of the 133 children who were given general anesthesia and in both cases done with spinal block; morphine or meperidine was given in 57 instances.

Complications and deaths in each of the categories are shown in table 1. Sixty of the 90 complications were pulmonary and included 18 which were attributed to anesthetic management. The 18 anesthetic pulmonary complications were as follows: Two infants developed postoperative respiratory obstruction, presumably due to endotracheal intubation; both died, one after tracheostomy. One child aspirated gastric contents during administration of open drop diethyl ether. Four infants required prolonged artificial ventilation after operation; none received a muscle relaxant; body temperatures were not recorded. Three children developed cyanosis and bradycardia during emergency laryngoscopy for removal of tracheal secretions. Two children developed postoperative atelectasis. One child had severe respiratory and circulatory depression following rectal tribromethanol. Two patients had obstructed endotracheal tubes from which secretions could not be suctioned; in both cases the tubes had to be removed during pulmonary lobectomy. One child, also during lobectomy, had flooding of the "down lung" and cardiac arrest; cardiac massage and defibrillation were successful and recovery was without neurological damage. The lungs of 2 children could not be ventilated after insertion of endotracheal tubes: both were treated successfully, one with intravenous succinylcholine, the other with administration of diethyl ether.

Pulmonary complications occurred in 43 (42 per cent) of 102 anesthetics in which a belladonna drug was given and in 17 (51 per cent) of 33 cases in which it was omitted; exclusion of complications due to anesthetic management reduced the incidence to 36 per cent and 50 per cent, respectively. The group of children who received morphine or demerol had a respiratory complication rate of 51 per cent as compared to a rate of 40 per cent in those who were not given a narcotic in their preanesthetic medication.

There were 41 respiratory complications in 91 anesthetics in which diethyl ether was the primary agent, 8 in 17 cyclopropane anesthetics, 10 with 19 halothane anesthetics, 1 in 2 spinal blocks and none in 6 cases in which nitrous oxide-thiobarbiturate was used.

Fifty of the 93 patients eventually died, 25 during the hospital admission in which operation was performed and 25 at varying periods of time after leaving the hospital. Eighteen of the 25 primary deaths were a result of surgical disease. Seven children died of respiratory failure: 2 were infants previously mentioned who had postoperative airway obstruction; 4 were infants with no preoperative pulmonary disease, who developed typical fibrocystic lung disease in the first weeks of life and died within the first month; one was an older child with severe preoperative lung disease who died within two weeks after bronchography.

All secondary deaths were due to classical fibrocystic pulmonary disease, often associated with cardiac failure. These occurred from 3 months to 15 years following operation. Eight patients had no clinical evidence of respiratory disease prior to operation.

Discussion

None of the questions which prompted the study could be answered with statistical validity. The reasons for were as follows: absence of a control group of patients, lack of homogeneity of groups, inadequate criteria for determining subtle progression of pulmonary disease. Nevertheless, the data yielded previously undocumented information and brought into focus some observations of clinical importance.

There is no question that pre-existing fibrocystic lung disease made the anesthetic course troublesome and postoperative management difficult. Induction of anesthesia was often stormy with episodes of cyanosis. The necessity for repeated removal of tracheobronchial secretions interfered with smooth maintenance of anesthesia and sometimes required constant and prolonged nursing care in the postoperative period. It can not be concluded, however, that the problems seen were peculiar to fibrocystic lung disease. The difficulties encountered, and their high incidence, could be expected in any group of patients with comparable amounts of secretions, whatever the etiology.

Choice of anesthetic drugs did not appear to be critical to the conduct of anesthesia.

Objection has been raised theoretically to the administration of belladonna drugs, because they are presumed to increase the already altered viscosity of tracheobronchial secretions. In this group of children, most of whom received atropine or scopolamine, the tenacious character of the secretions was not the predominant feature; the secretions were most frequently described as copious. The data did not reveal a significant difference between pulmonary complication rates of children who did or did not receive either a belladonna drug or a narcotic for preanesthetic medication. Nor was there any suggestion that the anesthetic agent played an important role. Respiratory problems were equally prominent with the three most commonly employed primary agents. Absence of difficulties with nitrous oxide-thiobarbiturate anesthesia cannot be evaluated because of the small number of cases. The spinal anesthetics are too few for comment.

Lack of suitable criteria for determining acceleration or premature onset of pulmonary disease precluded any conclusions regarding effects of anesthetic experience on the immediate or subsequent course of the clinical disease. The high morbidity rate suggests an overall increase in anesthetic risk, but this could not be related to increased mortality, either primary or secondary. The cardiac arrest rate of 1:135 seems to compare unfavorably with a previously established cardiac arrest rate of 1:1,381 in 34,500 operations performed on infants and children at Babies Hospital.[10] The small number of cases in the present series, however, does not justify a comparison. Equally unwarranted is a comparison of the overall mortality rates of the surgical and nonsurgical segments of the 702 patient records reviewed. The death of most of these children before adulthood gives little validity to comparisons based on long-term survival.

Failure to demonstrate a relationship between anesthetic drug and either immediate or subsequent pulmonary complications does not diminish the importance of selection of anesthetic agent and method. Increased understanding of the disease and better knowledge of anesthetic behavior should be reflected in better current management of these children. The following principles and considerations guide our own present management.

(1) Preoperative preparation, when indicated, with antibiotics, aerosolized bronchodilators and postural drainage.

(2) Prevention of dehydration. It has been established that mucus secretions in cystic fibrosis carry a reduced water content.[11] Intravenous infusions must be given. Isotonic saline should be a part of fluid therapy because of the known susceptibility of these patients to salt loss and because the reduced water content of mucus secretions is associated with low Na^+ and Cl^- content.[11] A solution containing one-third isotonic saline and two-thirds 5 per cent dextrose is commonly used.

(3) Preanesthetic medication should include atropine or scopolamine. We believe the advantages of reduced airway secretions outweigh other theoretical considerations.

(4) The inhalation agent chosen is probably not critical. Ideally, a suitable agent should have high potency, low blood solubility for rapid induction and emergence, and bronchodilator activity. None of the commonly used agents possesses all of these properties. The presence of clinically silent hepatic lesions in most patients raises questions regarding the possible hepatotoxic properties of divinyl ether, tribromethanol and halothane. These drugs were used in this study either before the hepatic effects of the drug were questioned or before the hepatic component of the disease was recognized.

(5) Endotracheal anesthesia is considered essential when secretions are present.

(6) Humidification of inhaled gases is desirable to minimize inspissation of secretions. Rebreathing methods help retain some of the exhaled water vapor.

Summary

A review of the more important features of cystic fibrosis of the pancreas has been presented. Examination of the records of 702 children with fibrocystic disease revealed that about 15 per cent had surgical procedures. In 135 operations performed on 93 patients, there were 30 surgical and 60 pulmonary

complications. Eighteen of the pulmonary complications were attributed to anesthetic management. The presence of abundant airway secretions was the most important single factor in the etiology and severity of the respiratory problems.

The data failed to show that either the use of diethyl ether, cyclopropane and halothane, or the preanesthetic administration of a belladonna drug, materially affected the incidence of pulmonary complications. The selection of any of these drugs for anesthetic management must be based on considerations other than those pertaining to the disease.

It did not appear that children with fibrocystic lung disease presented problems basically different from patients with retained secretions of other pulmonary etiology. Management, therefore, should follow the same general principles.

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UTERINE BLOOD FLOW Pregnant ewes were infused with vasopressor solutions while the aortic blood pressure and uterine artery flow were measured. Equipotent vasopressor doses of levarterenol, phenylephrine, methoxamine, and angiotensin markedly reduced uterine artery flow. Uterine artery resistance increased to a greater degree than did the blood pressure. Unlike the brain and heart, vascular resistance in the uterus is increased by sympathomimetic stimulation. The fetus is as sensitive to hypoxia as are the maternal vital organs, but the uterine circulation is not similarly adapted to the maintenance of blood flow during stress. Due to their potential deleterious effect on the fetal environment, vasopressor drugs should be used only when essential for maternal survival. (*Greiss, F. C., and Van Wilkes, D.: Effects of Sympathomimetic Drugs and Angiotensin on the Uterine Vascular Bed, Obstet. Gynec. 23: 925 (June) 1964.*)