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U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes
of Health

Cover:
Research supported by the National Heart, Lung, and Blood Institute promotes good health for all people. The photo at lower left, a heart-lung machine pump, shown pumping oxygenated blood, is the front cover illustration from the supplement to this report from the National Heart, Lung, and Blood Advisory Council.

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National Heart, Lung, and Blood Advisory Council

U.S. DEPARTMENT
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National Heart, Lung, and Blood Advisory Council

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Contents

Introduction

In this, its twelfth report to the President and the Congress of the United States, the National Heart, Lung, and Blood Advisory Council

- gives examples of recent accomplishments that have advanced the research, training, demonstration, and education programs of the National Heart, Lung, and Blood Institute;
- comments on factors that enhance or limit progress; and
- recommends a budget.

Diseases of the heart, blood vessels, lungs, and blood are major causes of illness in this country, and kill more Americans than all other diseases combined. The research, demonstration, and education programs of the Institute are directed toward prevention as well as treatment of these diseases. The Institute's approach to its mission is both multidisciplinary and varied, including basic and clinical research; clinical trials; training of young investigators; and education, prevention, and demonstration programs.

Each year brings many exciting new scientific developments stemming from a dynamic and highly successful interaction between the Institute and thousands of biomedical investigators in all parts of the country. This relationship is an exemplary model of biomedical research, and to sustain and nourish the present and past levels of achievement, it must continue to grow and prosper.

In this brief report the Council does not attempt to describe all the major accomplishments during the past year, or even a large part of them. The report does, however, present a variety of highlights focused primarily on a special group of patients—children—with diseases of the heart, blood vessels, lungs, and blood. The sections devoted to accomplishments in research on these diseases show clearly that although great progress has been made, much work remains to be done. Therefore, in the final section called Priorities, Goals, and Resources, the Council expresses its concern about the declining number of physicians entering research, and urges the support of training programs specifically intended to counter this trend. The Council also discusses the priorities and resources of the Institute, lists some possible strategies for using the available resources most effectively, and recommends specific budget levels for fiscal years 1986 through 1990.

With its programs for the support of research and research training, the National Heart, Lung, and Blood Institute—one of the cornerstones of NIH—is a national resource that must be preserved. The Council, therefore, urges the appropriation of funds sufficient to sustain the momentum created by the outstanding advances already realized.

Heart and Vascular Diseases

Introduction

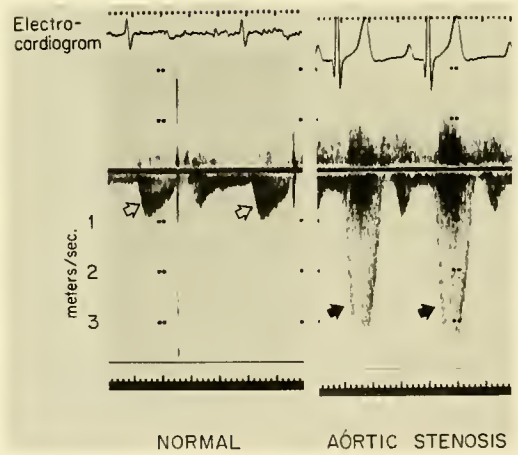
The death rate from cardiovascular disease in the United States has been steadily declining. From 1968 to 1978 the age-adjusted death rate (a calculated figure enabling comparisons free of the effects of age differences and other variables) declined 25 percent for coronary heart disease, 37 percent for stroke, 53 percent for hypertensive disease, and 38 percent for rheumatic heart disease. For the most part, these statistics describe the trends for adults with heart and vascular diseases. Another group of patients, with a different set of heart problems, consists of children with congenital heart disease. The problems in these children begin early in the prenatal period with abnormal development of the heart, which may result in underdeveloped or malformed heart chambers or in openings (that should have closed) between chambers. Although the number of U.S. children under 17 who have cardiovascular diseases of various kinds is small in comparison to the number of adults with such diseases (about 1.7 million children vs. about 47 million adults), the problems of these children should not be forgotten in the total picture of cardiovascular diseases in the United States. During the past decade, marked progress has been made in the diagnosis, treatment, and prevention of cardiovascular diseases in infants and children. This section will highlight some of the advances that have helped increase the survival of children with heart disease.

Congenital Heart Disease

In the 1950's the prognosis was virtually hopeless for many children with congenital heart disease. Almost all children with cyanotic heart disease (heart disorders in which the blood is provided with too little oxygen) died soon after birth, and many children with acyanotic heart disease (heart disorders in which the blood carries enough oxygen but other problems exist) died later in childhood. Correct diagnosis of congenital heart lesions was just becoming feasible with the advent of cardiac catheterization (passage of a small flexible tube, or catheter, through a blood vessel into the heart), which was available only to older children and adults. Surgery was primitive by today's standards and was limited to procedures on the blood vessels outside the heart.

Diagnosis. Through the years, major advances in the elucidation of cardiac malformations revealed a need for new technologies to help younger children, infants, and newborns. Research supported by the NHLBI was vital to the refinement of cardiac catheterization, making it relatively safe even for babies, and to the development of angiography (visualization of vessels or heart chambers or both by injection of contrast material during catheterization). In the last few years, attention has shifted from invasive to noninvasive methods for assessing cardiac function and anatomy. Support from NHLBI has advanced the development of two-dimensional echocardiography, a diagnostic method in which the use of ultrasound allows visualization of congenital cardiac lesions even in premature babies, and fetal echocardiography enables in utero detection of some congenital heart defects. Doppler echocardiography, which detects the velocity

A young boy being evaluated with a continuous wave Doppler technique. Using this technique, physicians can measure the velocity and direction of blood flow across the heart valves, identify obstructions or leaks, and often determine the extent of an abnormality.

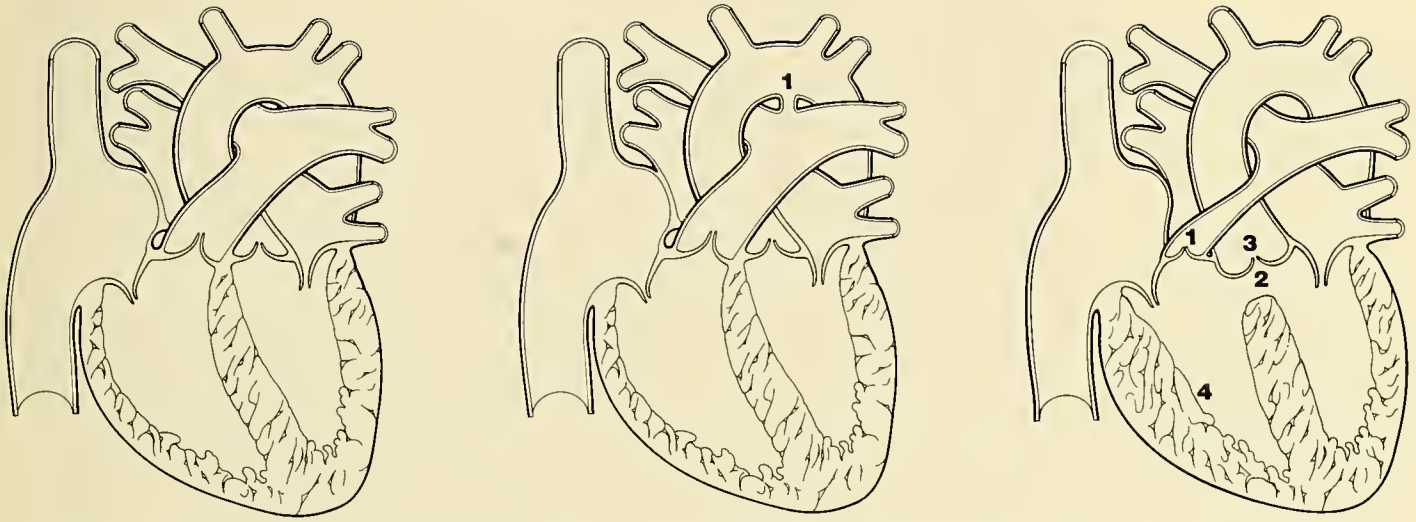


The young boy's scan, which is normal (left), compared to a patient with aortic stenosis. The blood flow through the boy's aorta has a relatively low velocity (open arrows), while the patient's blood flow is three times as high (closed arrows), which results from the narrowing of the aortic valve.

of blood flow through the heart and uses this information to evaluate the narrowing of a valve or the amount of blood the heart is pumping, is a rapidly developing technique for diagnosis in the field of cardiology. Digital subtraction angiography (a combined computer-x-ray technique) and other scanning methods involving radionuclide tracers now allow certain congenital heart defects to be evaluated without the use of an invasive technique such as cardiac catheterization.

Dramatic advances in both medical and surgical forms of therapy have been made possible by the development of diagnostic procedures that provide a very accurate assessment of the congenital lesion and can be used on quite young infants. Thousands of lives have been saved by use of nonsurgical techniques developed to create artificial defects in the wall between the two atria of the heart in newborns with certain cyanotic heart diseases.

Therapy. Some of the advances in medical therapy have stemmed in part from a better understanding of the basic effects of drugs on the heart muscle. Prostaglandins, to be mentioned again in the section on lung diseases, have a variety of effects on the heart and the rest of the body, and they have been studied intensively during the past few years. One member of this group, prostaglandin E_1, dilates the ductus arteriosus, a blood vessel that normally is open in the fetus and closes soon after birth. Thus prostaglandin E_1 can be used to treat infants with cyanotic heart disease, in which the blood flow to the lungs is inadequate; using prostaglandin E_1 to keep the ductus arteriosus open as an alternative channel eliminates the need for emergency surgery. The research that led to a better understanding of the actions of prostaglandins in the body also led to the discovery of substances that inhibit prostaglandin production, and these inhibitors have now found therapeutic application. In some premature babies the ductus arteriosus remains open (as it would if the baby were still in utero), causing high pulmonary blood flow, pulmonary hypertension, and eventually congestive heart failure. The knowledge that certain prostaglandins dilate the naturally closed ductus in newborn babies (and fetal animals) led to the hypothesis that administration of a prostaglandin inhibitor might close the ductus when it remains open in newborns. In an initial study with six premature infants, administration of the prostaglandin inhibitor indomethacin did

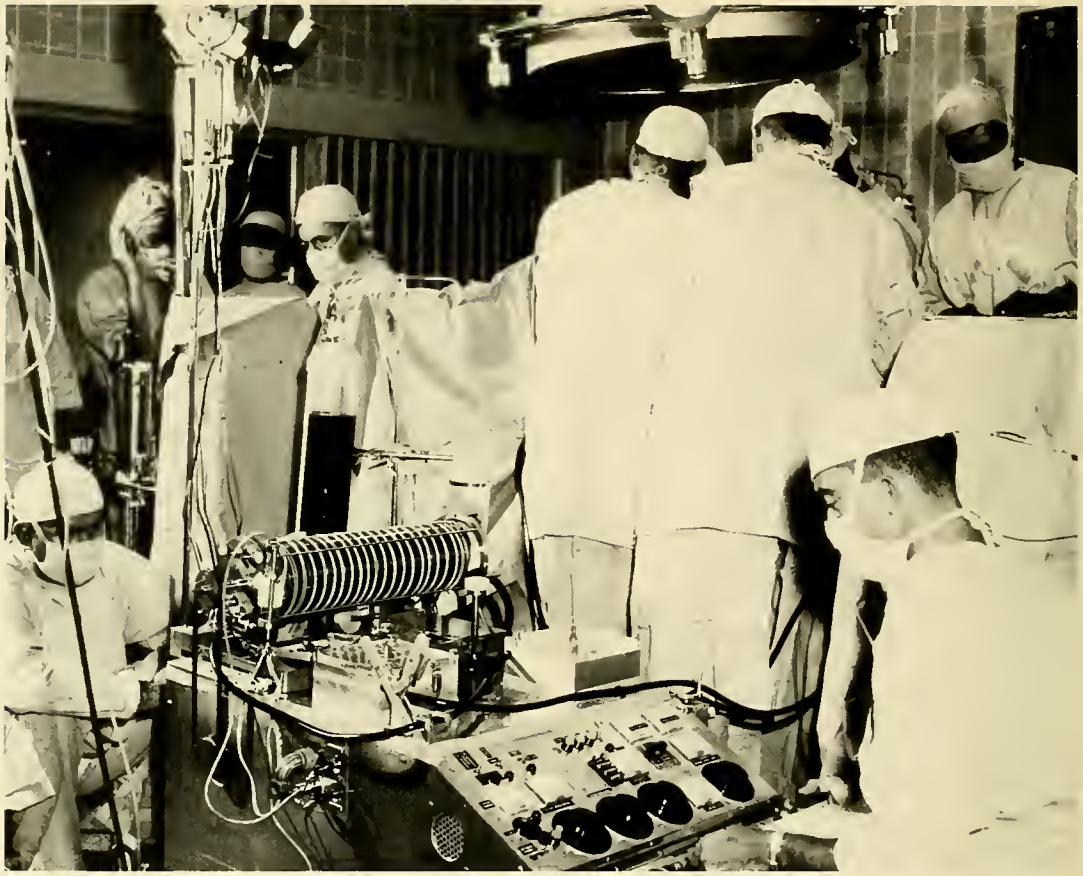


Left: A normal heart. Center: The ductus arteriosus remaining open in some premature babies (1), which can result in congestive heart failure. Right: Tetralogy of Fallot, with its four major defects: (1) a narrowing of the pulmonary artery valve; (2) a hole between the two ventricles of the heart; (3) a deviation of the aorta to the right; and (4) a thickening of the muscle of the right ventricle.

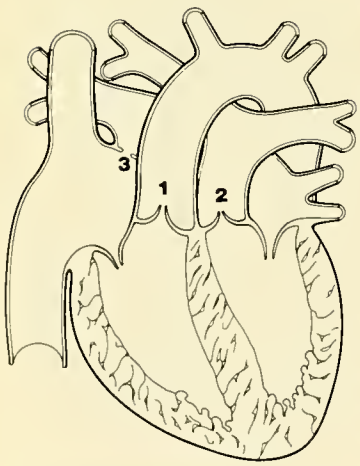
indeed close the ductus and thus eliminate the need to tie it surgically. A large, multicenter, prospective randomized trial has confirmed the value of this mode of therapy.

Tetralogy of Fallot (tetralogy) is one of the most common congenital abnormalities of the heart, and one for which the prognosis has been greatly improved by rapid advances in cardiovascular surgery during the past 25 years. The word "tetralogy," from the Greek word for "four," refers to the four major defects simultaneously present in this abnormality: (1) a narrowing of the beginning of the pulmonary artery, (2) a hole between the two ventricles (pumping chambers) of the heart, (3) a deviation of the origin of the aorta to the right, and (4) a thickening of the muscle of the right ventricle. A historic operation performed in 1944 on a severely cyanotic ("blue") child with tetralogy marked the beginning of modern cardiac surgery: the child benefited greatly from the surgical creation of an anastomosis (channel) between the pulmonary artery, which supplies blood to the lungs, and the subclavian artery, which supplies blood to the arm. The subsequent development of the heart-lung machine led to the first total correction of tetralogy in 1955. Previously, only one-half of all children with this abnormality reached age 7; one-fifth reached age 14; and fewer than one-tenth survived beyond age 21. Until recently, an initial palliative operation (such as the subclavian-pulmonary shunt mentioned above) always preceded the open-heart operation for the total correction of tetralogy. Rapid recent advances, however, have now made possible the total correction of the lesions in a single operation in infancy. Only when the malformation is very severe or the infant quite small is the two-stage approach still used.

Total correction of tetralogy by open-heart surgery is the procedure of choice, and it is made possible by the use of a machine to bypass the heart and lungs. As surgery begins, the patient's breastbone is divided and the heart sac opened. After the heart and lungs have been bypassed with a heart-lung machine, the heart is stopped and the right ventricle is opened. The thickened muscle is carefully removed, and a plastic patch is sewn in place to close the hole between the two ventricles of the heart. Great care must be taken during this maneuver to avoid



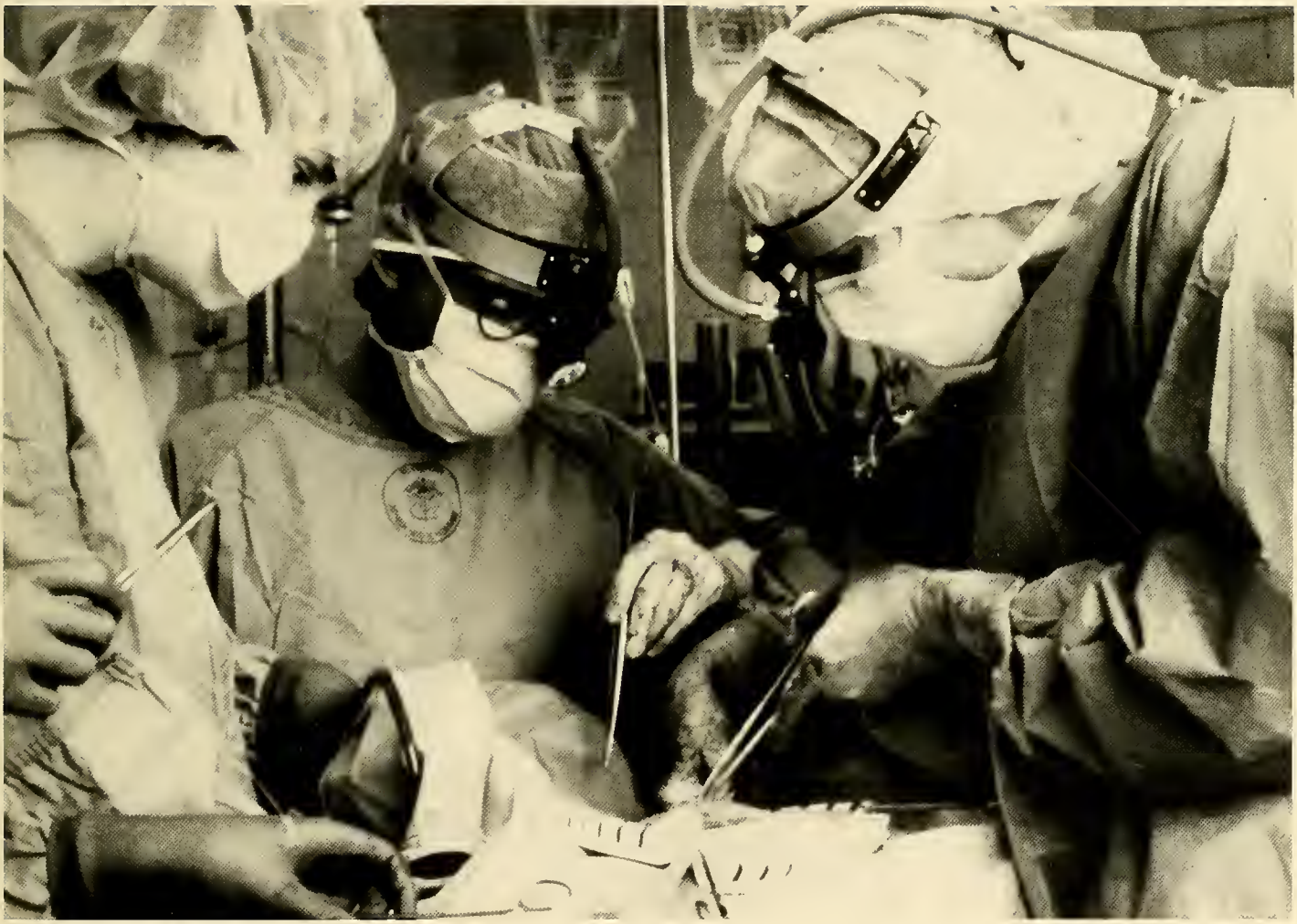
One of the early heart-lung machines, which led to the first total correction of tetralogy of Fallot.



Transposition of the great vessels, including: (1) the aorta arising from the right instead of the left ventricle; and (2) the pulmonary artery arising from the left rather than the right ventricle. The opening between the two atria of the heart is also shown (3).

damaging the electrical conduction fibers of the heart, the most important of which are found in the vicinity of the hole; interruption of these fibers may result in an immediate or late heart block (failure of the electrical impulse to be conducted through the heart). Recent improvements in heart surgery and external bypass techniques have steadily reduced morbidity and mortality from tetralogy to less than 5 percent, and good to excellent long-term results have been achieved in 90 percent of patients. Although patients with the severest varieties of tetralogy respond less well to treatment, the surgical advances of recent years are now yielding constantly improving results even with this subset of patients. Sudden death after surgical correction of tetralogy, while rare, remains a problem. Electrocardiographic evidence of a block in certain conduction fibers of the heart may portend a possibly fatal complete block, and thus should be considered an indication for insertion of a pacemaker. Recent advances in detection and surgical treatment of recurrent and sustained rapid heartbeat have resulted in a new approach to therapy—namely, excision of scar tissue—that promises to reduce this unusual but dreaded surgical complication.

Transposition of the great vessels (transposition) is a severe congenital cardiac malformation in which (1) the aorta arises from the right ventricle rather than the left, and (2) the pulmonary artery arises from the left ventricle rather than the right. For life to be sustained with such a major abnormality, a passage between the two atria (the small receiving chambers of the heart) must also be present to allow mixing of the blood between the pulmonary and systemic circulations. The physiological effects of transposition are such that without treatment, affected infants soon turn blue (that is, cyanotic), have difficulty in breathing, and die; many untreated infants die in the first week of life and few survive to 1 year of age. Survival has been extended by procedures that increase mixing between the pulmonary and systemic circulations by creating a larger passage between the atria. The first such procedure was invasive surgery, but a more recently developed procedure



Open-heart surgery.

A young boy who has had a pacemaker implanted in his chest.

involves the introduction of a dilating balloon through a peripheral vein without surgery. Although balloon septostomy (use of a balloon to enlarge the passage between the right and left atria) has increased the initial survival of infants with transposition, this technique alone will not ensure long-term survival.

A great breakthrough in the treatment of transposition occurred in 1964 with the development of the Mustard procedure, in which a plastic baffle was used to redirect (1) the blood from the right side of the heart to the lungs and (2) the blood from the left side of the heart to the systemic circulation. Similar approaches had been described, but this was the first such procedure to receive widespread acceptance and application. At first the associated mortality and morbidity were high, but over the ensuing 20 years the procedure has been used on younger and younger infants, with excellent results. The most common complication has been electrical conduction defects with heart block or even sudden death in an otherwise successful procedure, a problem similar to that mentioned in connection with surgery to correct tetralogy. Knowledge of the location of the conducting fibers in the heart and use of great care in avoiding them while placing the baffle have markedly improved the outcome. An increasingly popular variation of the baffle operation has been the Senning procedure, in which part of the patient's own atrial wall, rather than plastic, is used for the baffle. Some patients with transposition also have other abnormalities that likewise require surgical correction; the additional procedures required may add to the scope of the surgery, which may consequently be less successful.

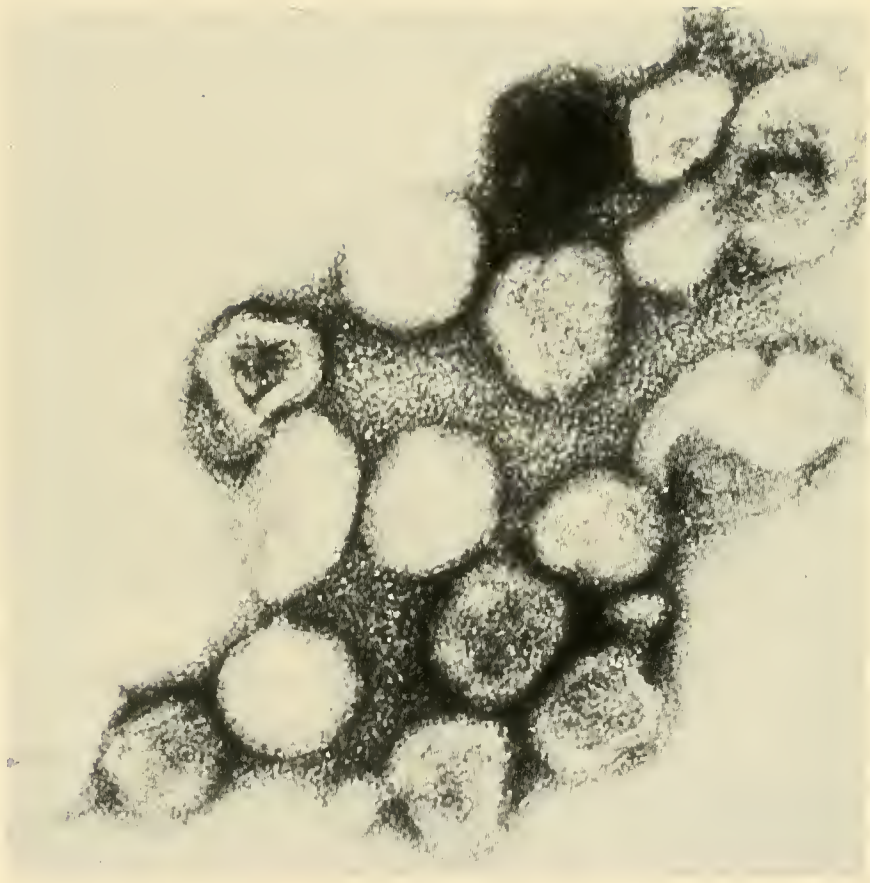
Some patients have now survived baffle operations and lived into adulthood, but it remains to determine the long-term ability of the heart valve in the left ventricle to withstand the higher systemic pressures that it undergoes during these procedures. Because both the Mustard and Senning procedures add another abnormality to the underlying one, other surgeons have sought a surgical procedure that totally corrects transposition. In a total-switch operation reported in 1975, the aorta and pulmonary arteries are divided and then reunited in their normal positions. To date, this operation has been limited to certain types of transposition, and it has been associated with a relatively high mortality. Progress, however, is being made as surgeons gain more experience with this "anatomic correction" of transposition at the arterial level, and its ultimate place in the treatment of this congenital defect is still unknown.

For patients with transposition, the combination of earlier diagnosis, balloon septostomy, and much improved surgical techniques has changed the prognosis from hopeless to having an excellent chance for normal life expectancy without apparent physical restrictions. The medical and surgical management of

transposition is truly a story of almost unbelievable progress and a source of much satisfaction for those working in the field of cardiovascular disease.

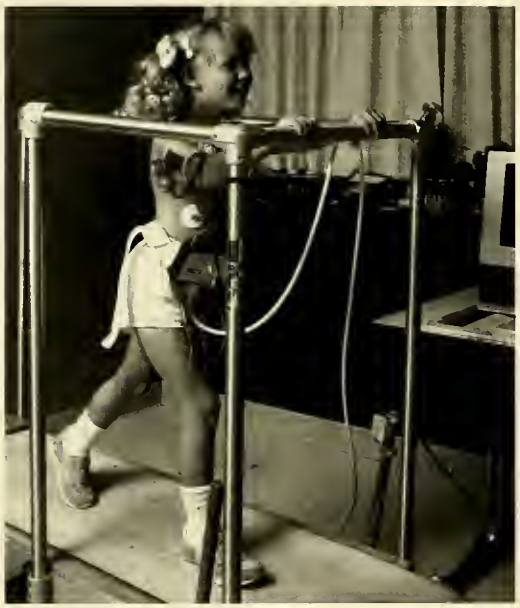
Research. Research is currently under way to discover the underlying cause of congenital heart defects, with the ultimate goal of prevention. By studying normal and abnormal flow patterns of blood through the embryo, scientists are finding possible causes for the underdevelopment of valves or chambers of the heart. Others are searching for environmental causes for congenital defects. Maternal rubella infection (German measles) is now widely recognized as the cause of certain congenital heart defects. The availability of an effective vaccine has reduced the number of children born with rubella-induced heart defects. Other congenital defects are caused by excessive maternal intake of alcohol or drugs during pregnancy; appropriate education to women likely to become pregnant should reduce the occurrence of these defects. In addition to chromosomal disorders, such as Down syndrome, single-gene mutations have been associated with congenital heart defects, and such mutations have also been associated with multisystem disease in newborns. Little is known of how these mutant genes act in the chemistry of the cell, or how they bring about the abnormal development of the heart.

Several studies now in progress are intended to provide fuller understanding of the structural development of congenital heart disease. Results of a recent study led to the hypothesis that in the developing embryo, cells from nervous tissue in a specific region at the back of the head give rise to the connective tissue involved in forming the wall between the aorta and the pulmonary artery. Lending additional support for this hypothesis, other researchers have found that abnormalities in the formation, multiplication, or migration of nerve cells from a region of the head of the embryo profoundly affect the eventual structure of the face; patients with a midfacial deformity may also have transposition, tetralogy, and an abnormal artery arising from both ventricles. Additionally, infants with fetal alcohol syndrome, a condition associated with maternal consumption of alcohol, may have both cardiovascular and midfacial defects. Thus, the association between certain facial and cardiac deformities may be a manifestation of an abnormality originating in specific nervous tissue in the head.



Rubella (German measles) virus as seen with the electron microscope.

A stress exercise test to diagnose the type of cardiac arrhythmia in a young girl with a history of arrhythmias induced by exercise.



A young boy with cardiac arrhythmia being monitored to evaluate the efficacy of drug therapy.

Cardiac Arrhythmia

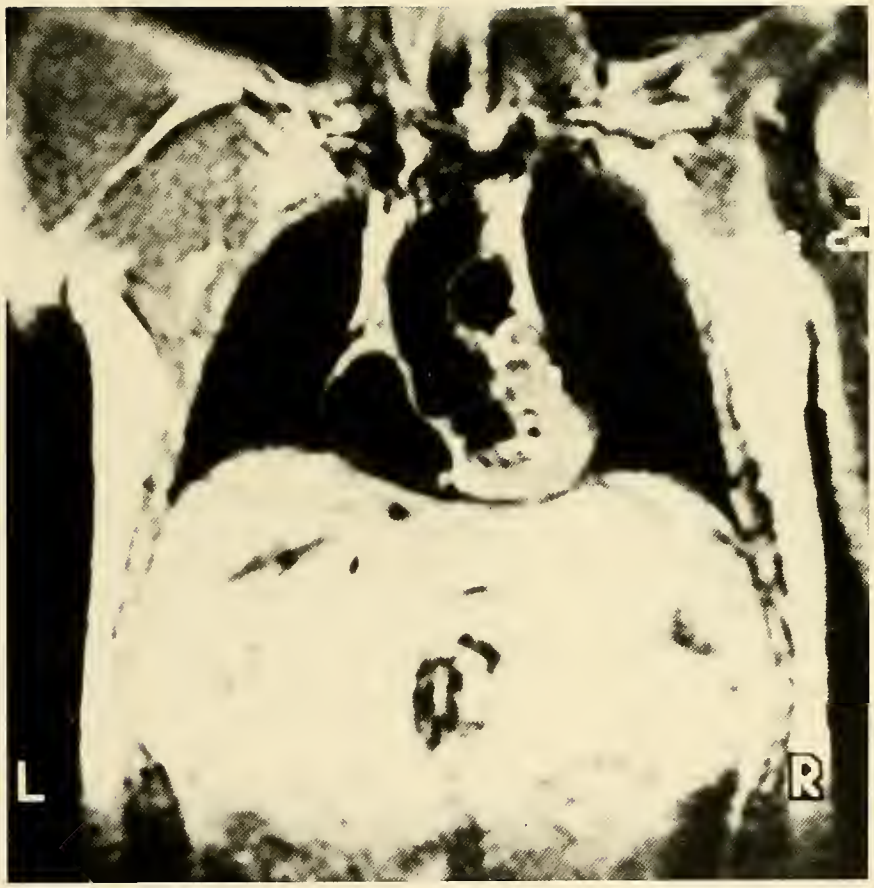
The interest of NHLBI-supported investigators in cardiac arrhythmias (irregular heartbeat) in children, as well as in adults, has increased research into the causes and treatments of these problems. In the United States about 400,000 people die suddenly every year, and most of these deaths are presumed to be from cardiac arrhythmias. About 75 percent of the group in question are known to have had heart disease. The incidence of arrhythmias in children is difficult to determine, but in one large study, 2 percent of randomly selected children had some form of arrhythmia. Use of new techniques for ambulatory monitoring of the electrocardiogram (EKG) has shown the prevalence to be greater than was previously thought. Effort has been expended to define normal values of heart rate and rhythm in children of various ages. Some pediatric as well as adult arrhythmias are benign and transient, but others are serious and even fatal. Certain forms of congenital or acquired heart disease increase the likelihood of the patient experiencing early or late postoperative arrhythmias. The percentage of children with congenital heart disease who survive corrective surgery is increasing, and with this improved survival an increasing incidence of arrhythmias has been observed.

A particular problem has been arrhythmias following the repair of the two common congenital heart lesions discussed earlier, transposition and tetralogy. Each year about 1,000 children with transposition and 5,000 children with tetralogy successfully undergo corrective surgery. The significance of the conduction or rhythm disturbances subsequently developed by many of these children, and the relationship of the disturbances to sudden death, are not yet clear. The natural history of these arrhythmias, however, suggests that as the children become adults, their arrhythmia problems will continue and perhaps worsen; there

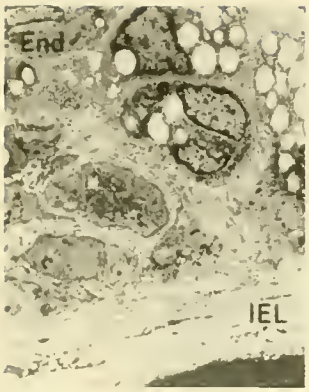
is need to develop treatment for both children and adults. New drugs are being developed, but years of research will be required to demonstrate their usefulness and safety. Research interest is increasing in the use of pacemakers and surgery to treat problems of conduction and rhythm. Despite all the questions that have been answered, understanding is limited in many areas.

Cardiac Function and Metabolism

Fundamental knowledge is needed for a better understanding of ways to protect the immature heart during periods of low oxygen and inadequate blood supply. The mammalian heart appears to continue its maturation postnatally, and the cardiac function and metabolism of the newborn and infant differ from those of the adult. The advent of fetal echocardiography has now made possible the diagnosis and transplacental therapy of heart failure in the fetus. The effectiveness of this type of therapy would be improved by a better understanding of cardiac metabolism in relation to age. For diagnosis, the development of sophisticated, only minimally invasive diagnostic procedures such as nuclear magnetic resonance (NMR) imaging and positron emission tomography (PET), means that the patient is subjected only to apparently harmless nonionizing radiation or to intravenous injection of a radiolabeled substance, respectively, and these procedures enable physicians to study cardiac metabolism in the living infant. Recently, use of an NMR procedure demonstrated that the ratio between two phosphate-containing compounds was abnormally low in an 8-month-old girl with congenital cardiomyopathy (disease of the heart muscle). The ability to evaluate the high-energy phosphate profile of the human heart, and to manipulate the diet accordingly, provides the potential to improve diagnosis and treatment of pediatric cardiomyopathies.



An NMR scan through the chest. The view looks similar to a conventional x-ray but represents only a 1 cm thick slice through the chest. The lungs are black and surround the heart and great vessel. The aorta as well as the left ventricle and left and right atria of the heart are well defined.



An electron micrograph of an early fatty streak in the aorta. Lipid droplet in the smooth muscle cells has begun to proliferate and separate the endothelium (END) from the internal elastic lamina (IEL) on which it normally lies.

Precursors of Cardiovascular Diseases

Precursors of two major chronic cardiovascular problems of adulthood, atherosclerosis (a form of hardening of the arteries) and hypertension, may already be present in childhood. In the lining of their arteries, many children have fatty changes like those of atherosclerosis; this condition is believed by some investigators to foreshadow the atherosclerosis of young adulthood. The fatty changes are the subject of current research interest, including an effort to determine whether they are associated with high risk-factor values—such as elevated blood lipids (fats), hypertension, and (in older children) smoking—as atherosclerosis is in adults. It is clear, however, that diabetes is a risk factor that promotes cardiovascular disease in youth as it does in adulthood.

Research supported by the NHLBI in the past decade has done much to delineate the distribution of levels of blood lipids and blood pressure in children. The actual levels found in young children tend to persist, or "track," so that young children with high levels continue to manifest high levels into older childhood and adolescence. Studies are under way to determine whether such tracking continues into young adulthood and beyond. For example, in two of the NHLBI's Specialized Centers of Research, several thousand children are participating in long-term studies on precursors of atherosclerosis and hypertension.

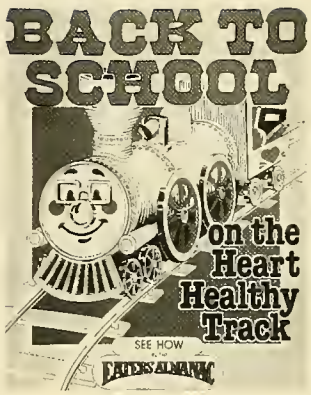
Although high values of risk factors in childhood seldom pose imminent danger, they may well persist and become chronic. Research supported by the NHLBI has shown, however, that certain drugs and changes in lifestyle can do much to return abnormal risk-factor values to normal, and thus to reduce the number of deaths from cardiovascular disease. In particular, the adoption of elements of a beneficial lifestyle—involving the avoidance of smoking; a balanced, judicious diet; exercise; and calorie balance to avoid overweight—by children and adolescents can reduce abnormally high levels of blood lipids and blood pressure. Research into behavior and behavioral change in children and their families, with the goal of promoting awareness of health and appropriate lifestyles for the young persons to carry into adulthood, is a matter of continuing interest and concern to preventive medicine.

The Past and the Future

Rheumatic fever (an acute, generalized inflammatory process that follows an infection of the upper respiratory tract with certain *Streptococcus* bacteria) and rheumatic heart disease (the scarring and deformity of heart valves that may follow one or more attacks of acute rheumatic fever) used to be the most common cause of death in school-age children. Treatment consisted of months or years of bedrest, aspirin for the joint problems, a low-salt diet and digitalis for the heart failure, and sulfonamides to prevent recurrences. Despite treatment, the prognosis for the acute heart involvement was poor: 20 percent of the patients died within 10 years after the initial attack, and about 75 percent of the survivors developed permanent valve damage. There has been a marked decline in the occurrence of acute rheumatic fever in the United States, and NHLBI-supported research on the use of penicillin for prevention of the disease was crucial to this decline.

The same noninvasive techniques used to evaluate congenital heart defects now make it possible to diagnose valve abnormalities

A young girl having her blood pressure checked. Researchers supported by NHLBI have found that in children, blood pressure levels tend to persist through adolescence.



A poster that is part of the NHLBI campaign to promote a healthier lifestyle for children.

resulting from rheumatic heart disease. Two-dimensional echocardiography allows visualization of narrow valves and enables detection of calcification and thickening of the leaflets and supporting structures; and Doppler echocardiography can accurately assess the degree of narrowing and the appropriate time for surgical replacement of the valve. Basic research on rheumatic fever is adding to knowledge of the cause and development of the disease. For example, recent findings in several laboratories provide evidence for the existence of a genetic susceptibility to rheumatic fever. Although there have been many theories about the mechanism by which the disease develops, the most attractive at present is that an abnormal response on the part of the patient to certain streptococcal antigens (substances that stimulate the production of an immune response by the body) results in an autoimmune response (an immune response directed against the body's own tissue).

What are the other current challenges? Rheumatic fever, although greatly reduced in incidence in the United States, has not yet been eliminated, and many new cases still occur each year. It is very important to gain an understanding of the fundamental mechanism of rheumatic damage to the heart. Furthermore, as children with congenital heart disease reach adulthood, a new set of problems will develop. How can the adolescent with chronic heart disease be helped into a productive life? What kind of lifestyle will promote the best health? What can we predict for the offspring of these patients? Finding the answer to all these questions, and more, will require research—research in which the scientific community will continue to look to the NHLBI for guidance and support.

Introduction

In the United States, respiratory disorders are among the most common and serious health problems of infants and children, and pediatric lung disease accounts for more than 5 percent of all lung disease. The past decade, however, has seen a marked decrease in the morbidity and mortality from these disorders—particularly the infectious diseases—in children. Unfortunately, some new, serious, and very costly problems (for example, chronic neonatal lung diseases) have emerged as a result of the same therapeutic and scientific advances that have led to benefits such as, for example, improved survival of premature and newborn infants with congenital illnesses. Before the 1970's, pediatric pulmonary research was completely fragmented and very limited in scope; suitably trained personnel were lacking. Less than 40 percent of pediatric departments included a trained pulmonologist, and training programs in pediatric lung disease were rare. Except for basic studies on neonatal respiratory distress syndrome and cystic fibrosis, research on pediatric lung disease was scanty, particularly in fields such as lung growth, structure, function, and defense mechanisms; function of the mucociliary apparatus; and other nonrespiratory lung functions. The technology needed to measure lung function in children was being developed essentially as a research tool, available to only a few investigators, not as a procedure for wide clinical use.

Recently, work in this field has expanded remarkably. More than 75 percent of pediatric departments in medical schools have already established a pulmonary division or are currently doing so, and there are more than 30 training programs in pediatric pulmonary disease. The spectrum of pediatric pulmonary disease now includes disorders not previously recognized. In addition, a growing body of compelling evidence indicates that residual damage from childhood lung injury can predispose adults to chronic pulmonary disease. The remainder of this section summarizes current NHLBI-supported research in certain key areas.

Respiratory Distress Syndrome of the Newborn and Its Sequelae

Respiratory distress syndrome (RDS) is a lung disease that mainly affects premature infants. The lungs of premature infants are only partly developed and thus cannot maintain a normal exchange of gas. Today RDS is the leading cause of respiratory failure and death in premature infants. Its onset occurs at birth, and within a few days most infants either recover or develop additional, sometimes fatal, complications. In the United States, more than 40,000 premature infants per year (or more than 1 percent of all babies born alive) are reported to develop RDS. Before the advent of modern improvements in intensive care of the newborn, mortality from RDS was higher than 50 percent, but over the past 10 years many tertiary-care centers have been able to reduce it to less than 20 percent.

The development of animal models (prematurely born subhuman primates, lambs, and rabbits) for human RDS has contributed greatly to progress with this disease. Many RDS survivors develop a chronic respiratory disorder, called bronchopulmonary dysplasia (BPD), that makes them dependent on respiratory support for prolonged periods. This problem has created a need for an animal model that undergoes pathophysiological changes in the respiratory system closely resembling

A premature infant with respiratory distress syndrome (RDS) breathing with the aid of a respirator.

A nurse checking the vital signs of a premature infant.

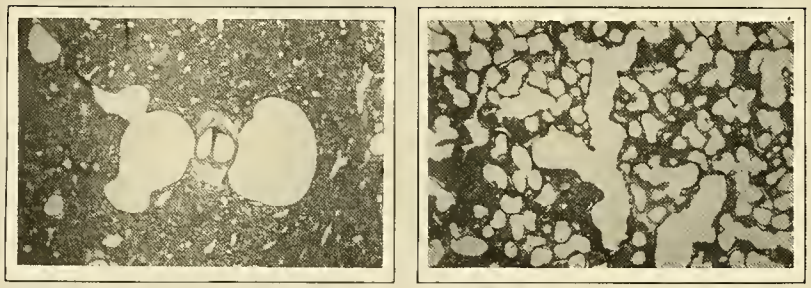
those seen in human infants who survive the acute phase of RDS. Recently such a model has been developed: infant baboons are delivered 26 to 39 days before term (at 74 to 82 percent of full-term gestation) and managed as if they were human infants. Under these circumstances the course of RDS, including both physiologic and pathologic changes, in the baboons is very similar to that in human infants. This baboon model is the first animal model with the potential to yield more definitive information on the cause of BPD than is ethically or practically possible to obtain from study of human infants. The baboon has also been valuable in studies on respiratory muscle fatigue during development; a recent series of experiments addressed the morphologic, histochemical, and functional development of respiratory muscles (diaphragm and intercostal muscle) in premature, full-term, and adult baboons up to the age of 18 years. Because infants have a highly compliant rib cage, both RDS and BPD impose tremendous workloads on their respiratory muscles; thus the clinical appraisal of respiratory muscle fatigue is critical in decisions about the treatment of respiratory failure in infants. Muscle contraction and relaxation times were found to be longer in premature baboons than in adults. It seems possible, therefore, that the rapid respiratory frequencies (more than 85 breaths per minute) frequently seen in infants with RDS may not ever allow the muscles to relax completely. Incomplete relaxation, in turn, could limit blood flow to the muscles at a time when the demand on muscle function is high.

The techniques that have reduced mortality from RDS—high concentration of inspired oxygen and intermittent positive pressure —may contribute to BPD. High frequency ventilation (HFV), however, with its lower airway pressure and smaller gas volumes, appears to have certain advantages over standard mechanical ventilation. Since newborn subhuman primates can spontaneously develop RDS, they are considered ideal for further inquiry into the relationship between ventilatory management and the occurrence of BPD, and they are used extensively in current research on HFV. Results from research at NHLBI-supported Specialized Centers of Research (SCOR's) indicate that normal newborn baboons seem to tolerate HFV for up to 8 hours without any adverse effects. Use of HFV for 6 hours or more in immature baboons with RDS, on the other hand, may cause various complications such as dilation of the distal airways. In intensive care units where HFV has been used as the last alternative for very sick newborn human infants, preliminary observations have supported the belief, mentioned above, that this therapy may offer advantages over standard mechanical ventilation. A multicenter clinical trial on HFV is currently being planned to test this hypothesis.

Pulmonary surfactant is a fatty fluid that

In studies of animals, high frequency ventilation shown to be more effective than standard mechanical ventilation for treating RDS. The lungs of animals receiving high frequency ventilation have more open air spaces.

Animal Model of RDS

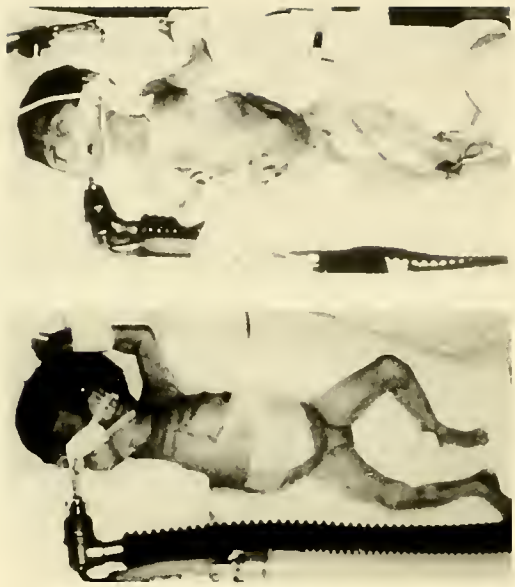


prevents collapse of the alveoli (the smallest air sacs) of the lung. Because a deficiency in surfactant production is one of the primary causes of RDS, treatment of this disorder by replacement of surfactant has for some time been the subject of intense study. Two classes of surfactant are being studied: (1) surfactant derived from mammalian sources such as lung or amniotic fluid (natural surfactant), and (2) surfactant synthesized in the laboratory (artificial surfactant). A few patients with RDS in this country have now been successfully treated with surfactant isolated from human amniotic fluid. Reactions to infections and immune reactions in a larger number of patients must be carefully evaluated, however, before firm conclusions can be drawn about this approach. The effectiveness of artificial surfactant and surfactant extracted from bovine lungs is currently under study in NHLBI-supported centers.

In 1976 the Division of Lung Diseases initiated a multicenter clinical trial on the effectiveness of antenatal steroid therapy. The major objectives were to determine whether administering a steroid (specifically, the synthetic steroid dexamethasone) to pregnant women shortly before delivery could prevent the occurrence of RDS in their infants, and whether such therapy caused any adverse reactions in the mother or child. When the trial was initiated, there was no consensus in the medicial community about the use of steroids. Some physicians believed steroids to have already been proved useful and deserving of inclusion in routine care for high-risk pregnancies; others, however, believed them to have such potential for impairing growth and development, particularly in the central nervous system, that they should never be used during pregnancy. No data were available to alleviate those fears or to provide guidance on the use of steroids during late pregnancy. Today, 8 years later, after the study of almost 700 pregnancies and more than 700 infants for up to 3 years after birth, the medical community has been assured that infants briefly exposed to steroids during late fetal life develop as well (with regard to weight, head circumference, and neurologic, mental, and psychomotor performance) as do infants not exposed to steroids.

Although its effect depends on the sex and race of the infant, dexamethasone can reduce the incidence of RDS, and no adverse short-term effects have been observed. In fact, steroid treatment appears to have an unsuspected benefit: infants exposed to dexamethasone in utero have a much lower rate of a serious disorder called necrotizing enterocolitis (NEC) than infants in the control group. The characteristic lesions of NEC are necrotic (dead) areas in the small and large intestines; sometimes these can become perforated, and the result may be peritonitis. Mortality is high (about 29 percent), and NEC is the single most common cause of surgical emergency in newborn infants. The significantly lower incidence

Surfactant being secreted from a type II, human lung alveolus cell.

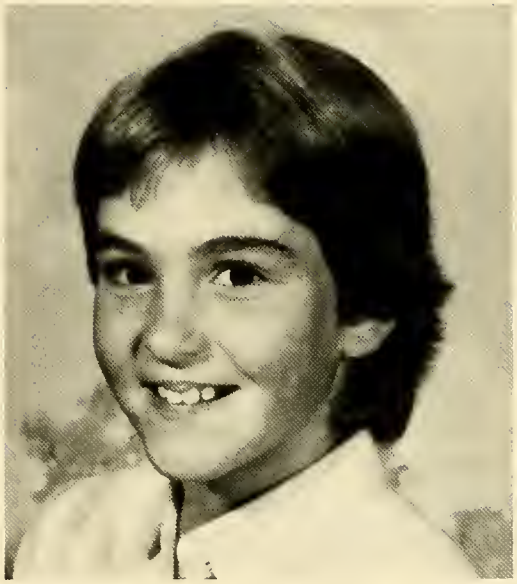


Twin girls born prematurely with RDS, the same twins two years later, and the same girls today. Research supported by NHLBI enables such children to lead normal, healthy lives.

of this disorder among infants given dexamethasone is, therefore, quite important clinically, but the reason for the reduction in incidence is not yet known. The lungs of some infants (most males and some females) exhibit a puzzling lack of response to steroids. Current studies with subhuman primates are designed to determine the conditions favoring optimal transfer of the steroid from the mother to the fetus and to characterize its action in the fetal lung.

Although advances in understanding of its pathophysiology and in its management and prevention have significantly improved the outlook for premature infants, RDS remains the leading cause of mortality and morbidity in this population. Still needed to further improve health-care delivery to infants with respiratory disorders are basic studies on developmental changes in defense functions of the respiratory system, fatigue of respiratory muscles, causes of abnormal ventilation/perfusion in the lungs, and nutritional requirements, as well as applied studies on the effectiveness of new approaches to management.

Technologic advances have yielded the instrumentation to improve management of infants with severe respiratory problems, but much of this new technology has been widely disseminated without full benefit of critical evaluation of long-term outcomes. There is serious concern that the improved survival of such infants may be accompanied by an increase in the number of permanently handicapped or damaged children, and that some of the sequelae of RDS may be partly iatrogenic (caused by treatment). As previously described, BPD occurs mostly in survivors of RDS, especially very premature infants who require ventilatory assistance. A family history of asthma is more common in RDS survivors who develop BPD than in survivors who do not; this finding suggests that BPD may be related to airway reactivity. Other probable factors are exposure to high levels of oxygen and prolonged peak ventilatory pressures.



Factors Affecting Lung Growth and Development

The course of the normal structural development of the fetal and neonatal lung is rather well established; less clearly understood, however, are its functional development and the factors or disturbances that may modify or injure the respiratory system during development. Recent detailed morphometric (anatomical measurement) studies of postnatal lung development and pulmonary vasculature have revealed a rather complex relationship between multiplication of alveoli and changes in the number and thickness of pulmonary arteries. This finding suggests that the lung is particularly susceptible to external stimuli during certain phases of early development. There is little information on how maternal response to low oxygen levels at high altitude is related to subsequent fetal outcomes. Babies born at high altitude, however, are often retarded in growth. A recent study of pregnant women living at an altitude of 3,100 meters in Colorado showed that the smallest babies were born to those whose ventilation rate (volume inhaled per minute) was initially lowest and failed to increase during gestation. A striking finding of this study was that hemoglobin concentration during pregnancy was lower in mothers of small babies than in mothers of larger babies. Furthermore, the reduction of birth weight associated with maternal smoking was two to three times greater at 3,100 meters than at sea level. Although additional studies are needed to elucidate the mechanisms causing differences in maternal characteristics of oxygen transport, the oxygenation level in maternal arteries during pregnancy may be critical at high altitudes (or under other low-oxygen conditions such as some cardiopulmonary diseases) and may be important in predicting retardation of fetal growth.

It has been suggested that fetal breathing movements stimulate fetal lung growth, and

recent studies with chronically catheterized fetal sheep showed that fetal breathing movements were associated with significant increases in volume of lung fluid. This observation suggests that fetal lung growth is stimulated by intermittent increases in the volume of fluid. Preliminary findings in rat fetuses indicate that a decreased volume of amniotic fluid, on the other hand, significantly retards growth of the lung. It is not known whether lung growth can catch up when the intrauterine environment is returned to normal. Preliminary analysis of human fetal breathing movements has suggested that premature rupture of the fetal membranes reduces fetal breathing activity below its level in age-matched normal controls.

In about 1 of 5,000 live births, a defect or hole in the diaphragm (diaphragmatic hernia) is associated with congenital malformation of the lungs. More than 60 percent of infants born with this abnormality die soon after birth despite aggressive attempts to provide oxygenation or control the pulmonary hypertension that so often portends death. Because diaphragmatic hernia can now be diagnosed in utero, the concept of repairing this lesion also in utero is very attractive; attempts at doing so, however, must await extensive research with animal models. Recently, in a large series of experiments, diaphragmatic hernias have been created *and* repaired in lamb fetuses. After delivery at term, lambs whose hernias had been repaired lived as long as 123 days, whereas lambs whose hernias had not been repaired—like human infants with the same condition—died soon after birth. Diaphragmatic hernia markedly altered normal lung development, resulting in underdeveloped lungs morphologically similar to those seen after a shortage in the volume of amniotic fluid.

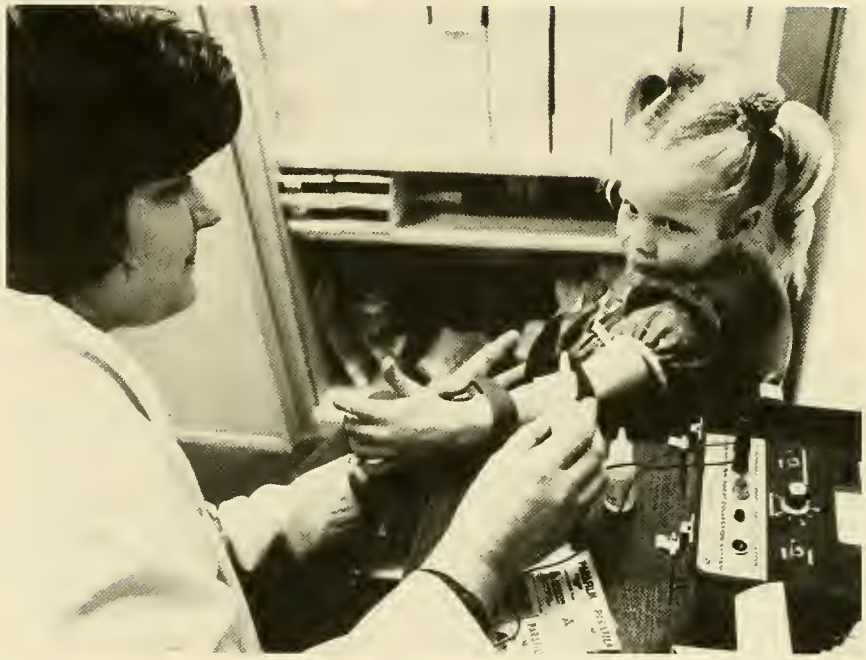
Functional Development of the Lung

Before birth, mammalian fetuses make breathing movements only intermittently; at birth, however, control of breathing changes, and breathing movements begin to occur continuously. The physiologic factors controlling fetal breathing movements are not known, but research on several fronts is beginning to give some leads. Infusing biologically potent hormonelike substances called prostaglandins (PG's) directly into fetal sheep greatly reduces the frequency of breathing movements, and conversely, infusing substances that inhibit PG synthesis markedly stimulates breathing movements. In contrast to their effect on fetal sheep, PG's stimulate breathing in adult animals and humans. Current research is addressing the complex relationship between breathing and sleep, and the way in which sensory inputs from thermal and chemical receptors are integrated into this relationship; results to date suggest that some central inhibitory process continuously suppresses fetal breathing movements and that this inhibition can periodically be overridden by abrupt environmental changes. Such changes may be relevant to the onset of breathing at birth and to the "resetting" of respiratory sensitivity in the newborn to a lower threshold than that prevailing in utero.

Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disease that begins at birth as a nutritional disorder and develops into a fatal obstructive lung disease. In the United States it affects nearly 1 in 1,500 Caucasian babies. The only diagnostic criterion now available is an elevated salt level in the sweat, but CF is also characterized by abnormalities in the balance of fluids and dissolved substances across the epithelium of several organs. The lung is the critical organ, because thickened airway secretions seem to contribute to recurrent infections and progressive loss of ventilatory functions. Death from CF is almost always caused by the pulmonary complications. Much of the research on the pulmonary-disease aspect of CF so far has centered on biological and physicochemical characterization of the abnormal mucus, means for its removal, and causes and possible cures for the pulmonary infections with specific bacteria (*Pseudomonas aeruginosa* and *Staphylococcus aureus*). The basic defect in CF is still undefined, but recent findings have suggested that this genetic disease may be characterized by functional abnormalities in the airway epithelium. In normal persons the airway epithelium regulates the volume and composition of the airway secretions by promoting active transport of certain salts and ions. The airway secretions become thicker or thinner depending on the direction in which water and ions flow across the epithelium: the secretions thicken when epithelial cells absorb water and ions, and thin out when the cells release water and ions.

The continuing search for the basic defect in CF has yielded evidence implicating a functional abnormality in the airway epithelium; specifically, defective permeability to the chloride ion. In studies on the bioelectric properties of nasal epithelium, the difference in voltage across the epithelium was twice as high in CF patients as in normal persons. These studies point to excessive transport of sodium ions and water and possibly to a defect in permeability to chloride across the airway surfaces in CF. Both of these abnormalities could lead to decreased water content in airway secretions and to thickened mucus, a characteristic of CF and a harbinger of pulmonary infections. By itself, however, the poor clearance of the thickened mucus from the lung cannot explain the specificity of pulmonary infections in CF; the explanation for this intriguing clinical observation remains elusive. Despite these remaining gaps in basic knowledge of the pulmonary aspect of CF, the evaluation of drugs and other agents with regard to efficacy, toxicity, and mode of delivery promises to be a rewarding area of research on this disease in the coming years.



Children being treated for cystic fibrosis. Research has increased the life expectancy for young people suffering from this fatal obstructive lung disease.

Blood Diseases and Resources

Introduction

Many blood diseases are a result of genetic abnormalities that manifest themselves early in childhood. Among the more common genetic blood diseases of concern to NHLBI are hemophilia, sickle cell anemia, and Cooley's anemia. Manifestation of these diseases in early childhood often presents difficult problems in clinical management, and the growing child faces special hazards while trying to cope with the complexities of life with a serious illness. Methods now available, however, enable the physician to make a diagnosis in the prenatal period, so that therapy can be started early in infancy. Therapy for all three diseases mentioned above includes infusion of blood or blood products and may also include other treatment for associated problems. With pediatric as well as adult patients, the safety of blood products used for infusion is an important consideration in choosing treatment for these blood diseases. Diseases transmissible by transfusion such as hepatitis, cytomegalovirus, and acquired immune deficiency syndrome (AIDS) present problems as serious for infants and children as for adults.

Hemophilia

The primary risk for hemophilia patients is uncontrolled bleeding, which can be life threatening. Concern about controlling hemorrhage may cause postponement of elective dental or surgical procedures, which in turn may lead to other, secondary problems. The development of clotting factor concentrates has enabled hemophilia patients to lead relatively normal lives without risk of hemorrhage. Young boys themselves, and members of their families, are taught how to infuse the concentrates, so that routine care can be done at home. Some hemophilia patients, however, develop antibodies to the infused clotting factors and are thus at risk for hemorrhage until their antibody levels can be controlled. Medical scientists are studying the mechanism by which such antibodies develop and looking for better ways to treat the patients at risk.

A hemophilic child injecting himself with clotting factor concentrate at home.

New hope for patients with bleeding disorders stems from the finding that some drugs, including certain hormones, promote the natural synthesis of the clotting factors and thus could decrease the need for infusions. The substitution of hormones for blood products is beneficial for patients with relatively mild hemophilia as well as for some patients with chronic renal disease who have prolonged bleeding times. Danazol, a modified male hormone, has been reported to increase plasma levels of factor VIII and factor IX in hemophilia A and hemophilia B. Another hormone, 1-desamino-8-D-arginine vasopressin (DDAVP), already used by some investigators in the treatment of milder forms of hemophilia A and von Willebrand's disease, is being studied more extensively to determine its mode of action. Since DDAVP increases plasma levels of factor VIII and von Willebrand

Staff at a blood center preparing reagents used to inactivate viruses in anti-hemophilic factor concentrate.

factor and decreases the prolonged bleeding time associated with chronic renal failure, it presents an alternative to plasma therapy for selected patients with bleeding disorders. Use of these hormones instead of plasma derivatives avoids both the risks (exposure to viral hepatitis and other plasma-transmitted diseases, and the potential for immunologic alterations caused by plasma proteins) and the disadvantages (nonuniformity, high cost, and inroads on the Nation's blood supply) of plasma therapy. Studies on the relative merits of these therapies are still in the early stages, however, and need to be continued and expanded.

In recent months much attention has been focused on diseases transmissible by plasma and plasma products. Because hemophilia patients depend on blood products, they have become particularly concerned about the transmissibility of diseases such as hepatitis and AIDS. During the past year several preparations of heat-treated antihemophilic factor (AHF) have been licensed. Heat treatment of AHF is designed to reduce the risk of its transmitting hepatitis virus, but no procedure has yet been found totally effective in removing the hepatitis virus from this preparation. Nevertheless, heat treatment reduces virus infectivity in plasma fractions tested in chimpanzees, and clinical studies now under way are testing the effectiveness of the new heat-treated products in therapy for hemophilia patients.

Current technological advances should enable the production of human clotting factors by genetic engineering methods rather than by isolation from blood. Proteins prepared by such methods are likely to be free of infectious agents and probably would not transmit diseases such as hepatitis or AIDS. Factor VIII, the clotting substance lacking in persons with hemophilia A, is currently derived from blood products. The recently announced partial cloning of the factor VIII gene strongly suggests that genetically engineered factor VIII will soon be available.

Cooley's Anemia

During fetal development, the major component of hemoglobin is fetal hemoglobin (Hb F). At birth, synthesis of Hb F almost ceases and synthesis of adult hemoglobin begins; patients with Cooley's anemia, however, cannot synthesize enough adult hemoglobin. The ability to synthesize Hb F is retained in adulthood, but the amount actually produced (in normal persons as well as in Cooley's anemia patients) is too small by itself to meet the oxygen-transport requirements of the body.

For many years investigators have sought ways to stimulate Hb F production. If they succeed, the technique might be useful therapeutically to enable patients with defective hemoglobin formation to synthesize enough Hb F to meet their bodies' oxygen-transport requirements. Molecular biologists have shown that the antineoplastic (anticell proliferation) drug 5-azacytidine (5-azaC) inhibits the methylation (specific chemical modification) of DNA and therefore induces the expression of otherwise dormant genes. These findings led to the demonstration that Hb F synthesis in baboons can be increased by administration of 5-azaC. Several studies involving use of this drug in humans have also been successful: scientists working at NIH observed a striking effect on Hb F production in a Cooley's anemia patient, and two other groups of investigators observed similar results in a total of three patients with sickle cell disease. Additional studies on this approach are under way in several medical centers. More recently, two other antineoplastic drugs, hydroxyurea and cytosine arabino-

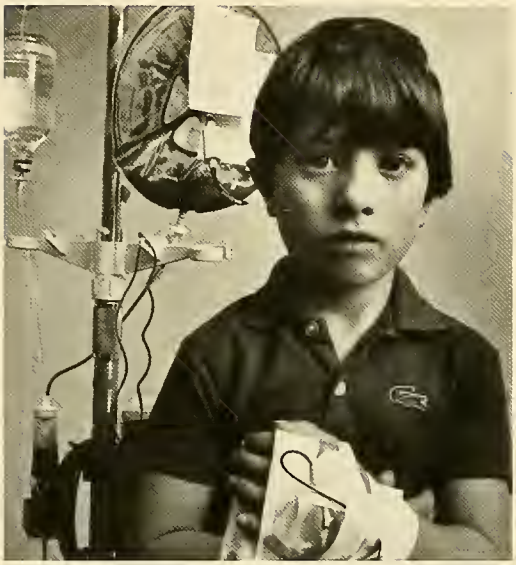
Researcher in a laboratory isolating factor VIII.

A young boy with Cooley's anemia receiving a transfusion of red cells.

side, have been used experimentally to increase Hb F production in monkeys and baboons, respectively. These drugs act by inhibiting the growth of dividing cells, so the observed increase in Hb F production may result not from unmasking of the genes via changes in the methylation of DNA, but rather from selection or recruitment of particular cell types. Some investigators believe that very primitive red blood cells can be made to develop quickly, skip some normal stages of development, and reach the circulation while still producing Hb F.

The results already obtained in animals and humans given antineoplastic drugs are extremely important for understanding gene expression. The initial studies offer a strong basis for hope that scientists will find methods to stimulate Hb F production in patients with Cooley's anemia, sickle cell disease, and other types of anemias caused by defective hemoglobin formation.

Cooley's anemia is usually treated by frequent transfusion of red cells. For most patients, maintaining an adequate hematocrit (volume of red cells per volume of whole blood) requires transfusions every 3 to 5 weeks with two to three units of packed red cells. These red cells break down after a time in the recipient and liberate their contents—including iron—into the circulation. Since the body lacks a mechanism for eliminating iron efficiently, the frequent transfusions result in iron overload, and the excess iron is deposited in the tissues. Iron overload may cause abnormalities in the heart, spleen, liver, and pancreas that can produce serious medical problems for Cooley's anemia patients who require frequent transfusions. Several years ago, however, a drug was developed that can chelate (tie up) iron and lower the rate of its deposition in the tissues. This drug, deferoxamine, must be administered subcu-



A minipump delivering the drug deferoxamine to a Cooley's anemia patient.

taneously. Children with Cooley's anemia can be fitted with an external minipump that delivers the drug over a 12-hour period daily. Studies suggest that deferoxamine can slow the development of serious cardiac problems if it is administered in early childhood, but it cannot reverse the heart muscle impairment that is often seen in children over the age of 10. Scientists are searching for chelators that are at least as effective as deferoxamine and can be taken orally.

In another approach to treating Cooley's anemia, several research centers are studying methods of isolating "neocytes" (young red cells) for transfusion, with the hope that such cells will remain in the circulation longer than red cells not selected for age. The use of neocytes would thus increase the interval between transfusions, which in turn would slow the buildup of iron overload. Results from one center indicate that transfusion of neocytes can reduce the total transfusion requirement by 16 percent. New techniques for improving the isolation of neocytes are now being developed.

A child who has sickle cell anemia. We need a better understanding of this disease, which is an important cause of illness and death in black infants and children.

Sickle Cell Disease

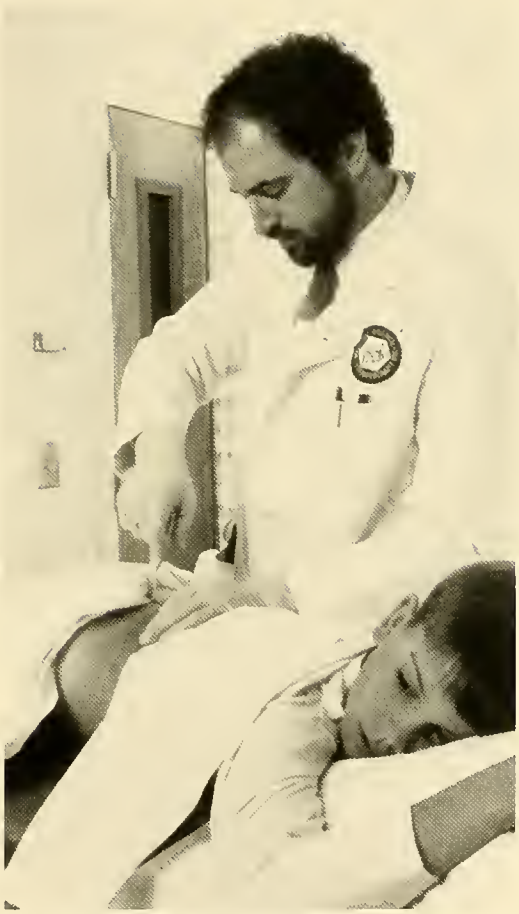
Techniques for diagnosing sickle cell disease and related hemoglobin disorders have improved dramatically over the past 10 years, and the ability to make the diagnosis at birth or even in the prenatal period now allows early initiation of prophylactic or therapeutic measures. First, in the mid-1970's, came prenatal diagnosis from fetal blood obtained either by placental sampling or by fetoscopy. This approach is useful, but because of the risk to the fetus from the obstetrical manipulation, it has not been widely adopted.

The advent of recombinant DNA techniques led the way to prenatal diagnosis by analysis of the gene structure of fetal cells. The ability to make the diagnosis from examination of fetal cells represents a major technological advance in that it eliminates the need to risk sampling fetal blood. In the new procedure, amniocentesis (surgical perforation of the uterus to withdraw amniotic fluid) is used to obtain fetal cells that have been shed into the amniotic fluid. The cells' gene structure is then analyzed by enzymatic mapping techniques, still under development, that can be used to identify missing or alternate DNA sequences. Currently, the diagnosis of sickle cell disease can be made in the second trimester, when enough fetal cells are available. Recent studies have promoted the analysis of DNA from chorionic villi (threadlike projections on the membrane that gives rise to the placenta). This technique, if it proves to be safe, might allow prenatal diagnosis during the first trimester. These techniques for prenatal diagnosis increase the number of options available to couples at risk of producing children with sickle cell disease and other genetic diseases.

Much information is available about the molecular defect that causes sickle cell disease, its mode of inheritance, and its clinical manifestations, but notable gaps still remain in knowledge of the basic mechanisms leading to the progressive damage to various organs, the increased susceptibility to infection, and the wide variety of clinical manifestations seen in patients with this disease. Most important for both patient and clinician, however, is the clinician's inability to completely control the progress of the disease. Important questions on the manifestations and treatment of sickle cell disease are under investigation through the multicenter Cooperative Study of the Clinical Course of Sickle Cell Disease (CSSCD). Unanticipated findings of chronic damage to the lungs, gallbladder, and bones in young children have underscored the need for better understanding of the natural history of the disease. Sickle cell disease is a particularly important underlying cause of illness and death in black infants and children. In children less than 3 years old, infection is the

leading cause of death, and early recognition and treatment can save lives. Pneumonia and meningitis are more common in children with sickle cell disease than in children with normal hemoglobin; in the sickle cell patients, the incidence of fulminant pneumococcal septicemia (bloodborne infection) is 10 to 12 percent, and the mortality rate for these children with septicemia is 30 percent. The CSSCD has initiated a clinical trial to evaluate the effectiveness of daily doses of penicillin in preventing severe bacterial infections in young patients with sickle cell disease.

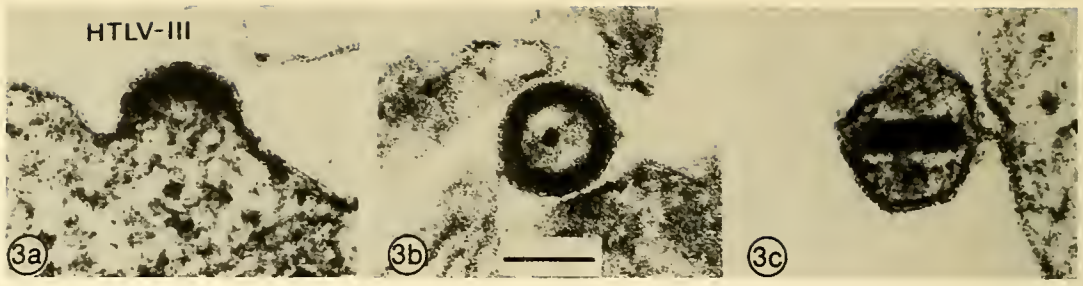
The increased susceptibility to overwhelming infection that accompanies sickle cell disease is largely related to the loss of splenic function during the first 3 years of life. The primary technique for assessing splenic function has been the spleen scan involving use of the radioactive material ^{99m}technetium colloid. From study of many pediatric patients, the CSSCD has defined the developmental patterns of splenic function via an economical, noninvasive technique: counting "pitted cells." This technique is sensitive, gives results that correlate with results of spleen scans, and enables clinicians to implement programs of protective intervention without exposing the patients to technetium scans.



Obtaining a sample of bone marrow, a procedure widely used in the study and treatment of blood diseases.

Other Aspects of Pediatric Blood Diseases

Bone Marrow Transplantation. Bone marrow transplantation is widely used in treating several serious blood diseases, including aplastic anemia, leukemia, and severe combined immunodeficiency. At present, however, marrow transplants are reserved almost exclusively for patients having a sibling with identical HLA (histocompatibility) antigens. Encouraging results have recently been obtained, however, with patients receiving transplants from parents or siblings who are genotypically nonidentical but phenotypically similar with regard to HLA antigens. A serious potential consequence of marrow transplantation is graft vs. host disease, caused by graft cells mounting an immunologic attack on host tissues. Recent advances in immunologic methods—including the development of new immunosuppressive drugs and methods to remove lymphocytes, which may provoke the graft vs. host response—have improved the survival of transplanted marrow and have led to an



An electron micrograph showing the stages of maturation of the HTLV-III virus isolated from AIDS and pre-AIDS patients.

increase in the use of marrow transplantation.

In 1972 about 750 bone marrow transplants were performed at 15 transplant centers across the United States, and it is estimated that in 1983 more than 1,000 were performed at 30 centers. Blood banks are becoming increasingly involved in providing special hematologic support for transplant patients. The average recipient of bone marrow requires about 26 units of whole blood or packed red cells and 171 units of platelet concentrates.

Aplastic anemia has a mortality rate of more than 75 percent. For the past decade, marrow transplantation has been the treatment of choice for younger patients with this disease, but at first the rate of graft rejection in these patients was high. Early transplantation, before the patient has been sensitized by blood transfusions, has almost completely eliminated the problem of rejection. Today, more than 80 percent of young patients with aplastic anemia are alive up to 10 years after receiving a marrow transplant.

Bone marrow transplantation has also become an important part of therapy for some patients with leukemia. After the leukemic cells in the patient's bone marrow are killed by irradiation, they are replaced with normal cells from the marrow transplant. About 75 percent of the leukemia patients who receive a marrow transplant, however, can be expected to have a recurrence of their leukemia 2 years later. Relapse usually results from leukemic host cells that survive chemotherapy and radiotherapy. Current research, therefore, is designed to find ways to increase the kill of leukemic cells.

Bone marrow transplantation has also been applied to several other lethal blood disorders, many of which occur in children. Marrow transplantation has long been the treatment of choice for all forms of severe combined immunodeficiency disease (SCID). In a 1981 review of the international literature, the survival of SCID patients receiving marrow transplants was found to be 55 percent. Marrow transplantation has also been used in treating several congenital aregenerative anemias (anemias characterized by failure to renew production of blood cells).

Recent reports describe complete engraftment (establishment) of bone marrow in young patients with thalassemia major (Cooley's anemia), with subsequent correction of the disorder. Furthermore, in a patient with sickle cell disease who had received a marrow transplant, hemoglobin synthesis returned to normal. These studies show that a durably engrafted transplant may replace host erythroid cells affected by thalassemia major or severe sickle cell disease and thus ensure normal hemoglobin synthesis.

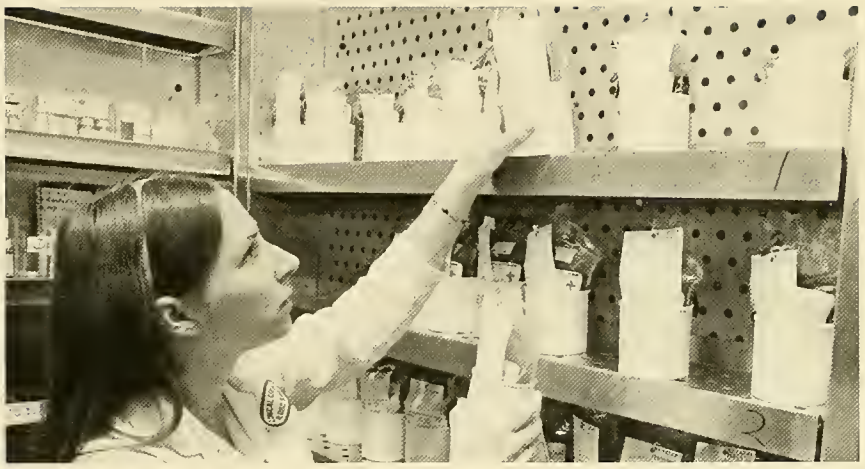
Transfusion-Transmitted Diseases. Of considerable concern is the transmission of serious diseases to children as a result of their receiving transfusions. Newborns, especially premature ones, are particularly at risk of acquiring transfusion-transmitted diseases.

Premature newborns who require multiple blood transfusions are especially vulnerable to infection with cytomegalovirus (CMV), the leading cause of both intrauterine and perinatal infections in the United States. Such premature newborns may develop a distinct syndrome of respiratory deterioration, pneumonia, liver and spleen enlargement, grey pallor, and atypical and increased lymphocytes in the blood. The mortality rate for newborns with this syndrome is about 20 percent. Although CMV may also be transmitted prenatally through the placenta, during birth, or postnatally by infected breast milk, transfusions are responsible for the vast majority of infections in newborns. Several investigators are studying the transmission of CMV and its

expression in the blood donor population. Some studies suggest that the virus infects, and is transmitted by, leukocytes (white blood cells). An association has been observed between the use of leukocyte-depleted blood and a reduction in transmission of CMV.

Acquired immune deficiency syndrome (AIDS), some cases of which have been reported in multiply-transfused persons, consists of a constellation of severe, life-threatening infections associated with a profound deficiency of the immune system. Immunodeficiency and opportunistic infections suggestive of AIDS have been reported in infants. Many of the infants whose cases have been reported to the Centers for Disease Control were born to parents belonging to a group with an increased incidence of AIDS. Three half-siblings who developed clinical and laboratory evidence of AIDS appeared to have acquired the disease via maternal transmission. Not all infants with AIDS, however, belong to high-risk families: some have received multiple transfusions as newborns for various medical problems, while in others no cause for the syndrome has been identified. Current intensive studies are designed to clarify the distinction between pediatric AIDS and other immunodeficiency syndromes in the newborn and to identify the mode of transmission during the perinatal period, with emphasis on defining the role of blood transfusion in the development of the disease.

The isolation early in 1984 of a virus that appears to be the causative agent of AIDS was a significant development in the effort to combat the disease. This virus belongs to the group known as retroviruses, which are unusual in that they replicate via RNA rather than DNA. The retroviruses previously identified in humans are designated human T-cell leukemia (or lymphoma) viruses, or HTLV types I and II. A third type, thought to be the cause of AIDS, has recently been isolated by investigators at the National Cancer Institute; it is designated HTLV-III. Unlike HTLV types I and II, HTLV-III kills most infected lymphocytes, so its propagation in quantities sufficient for study had to await the finding of a lymphocyte cell line that could survive the infection. Although absolute proof that HTLV-III is the causative agent of AIDS may never be available, the growing body of data on the isolation of HTLV-III from persons of various AIDS status and on the detection of HTLV-III antibodies in their serum suggests very strongly that this hypothesis is correct. French investigators have made similar observations with a virus designated lymphadenopathy-associated virus, which is probably the same virus as HTLV-III. When AIDS specimens from the United States are tested by the French workers' techniques, results are similar to those obtained in this country. Although estimated development periods vary, experts agree that these discoveries should enable investigators to develop a test to screen out prospective blood donors who are infected with HTLV-III and, eventually, a vaccine against this insidious and lethal virus.



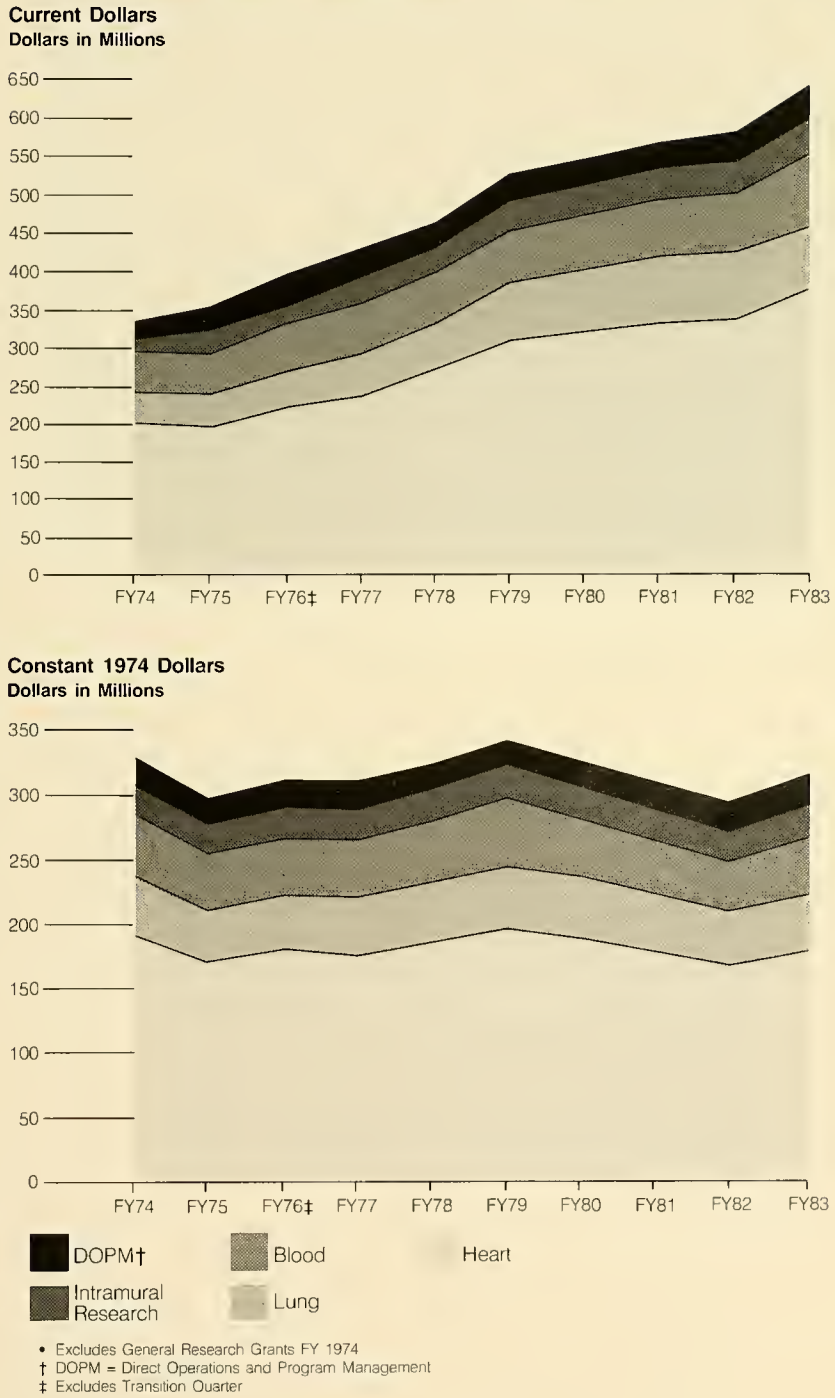
Careful blood storage and monitoring procedures, helping to reduce the risk of infections in newborns requiring blood transfusions.

The National Heart, Lung, and Blood Advisory Council celebrated its 35th anniversary in September 1983. Research supported by the National Heart, Lung, and Blood Institute during the 35 years of the Council's existence has contributed to such achievements as open-heart surgery, greatly-improved treatment of hypertension and coronary heart disease, cardiac resuscitation and cardiac pacemakers, cardiovascular and respiratory intensive-care units, diagnostic instruments (including the fiberoptic bronchoscope and the spirometer) for use in lung disease, use of factor VIII concentrates to treat hemophilia, and elimination of hepatitis B as a transfusion hazard. Significant advances in pediatrics during this period include much more effective treatment of neonatal respiratory distress syndrome, surgical correction of congenital and rheumatic heart disease, fetal electrocardiography, and use of indomethacin to treat patent ductus arteriosus.

Because the level of real resources available to the NHLBI is declining and, as a result, program balance is increasingly difficult to maintain, the scientific advances of the future may not match those of the past. In addition, because the research environment is so unstable, the difficulty of attracting and retaining young clinical investigators is becoming a major obstacle to progress. The figure "NHLBI Obligations: Fiscal Years 1974-1983" shows an increase of $298.0 million in current-year dollars, from $326.3 million in 1974 to $624.3 million in 1983. In constant dollars, however, this increase amounted to a *decrease* of $17.1 million. In 1972, of 777 approved grant applications, 492 were funded, for a funding rate of 63 percent. In 1983, however, only 748 of 2,114 approved grant applications were funded, for a funding rate of only 35 percent.

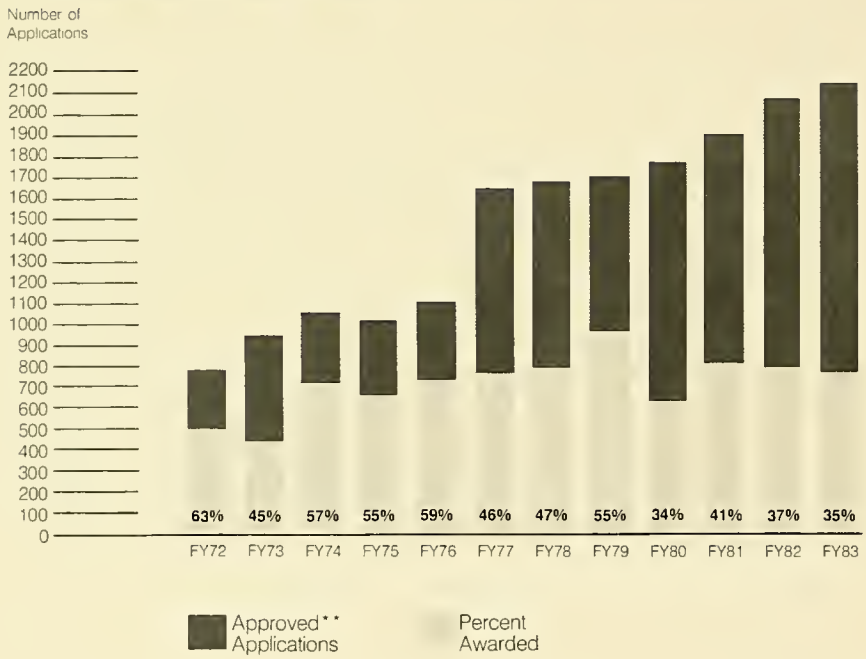
To respond to these concerns, the Council held four regional public briefings in the first half of 1983. The purpose of these briefings

NHLBI Obligations:* Fiscal Years 1974-1983



* Excludes General Research Grants FY 1974
† DOPM = Direct Operations and Program Management
‡ Excludes Transition Quarter

NHLBI Competing Research Project Grant* Applications: Approval and Award Rates



* Includes RO1, R23, and P01 grants and competing supplements.
** Includes approved but unfunded approvals carried over from previous year that were funded in year indicated.
‡ Reflects release of fiscal year 1973 impounded funds

was to inform the biomedical community, the voluntary health organizations, and the public about fiscal trends in NHLBI-supported research and training, and to enable the Council and the Institute staff to hear in person the participants' interests in, and concerns about, the NHLBI extramural programs. Various short-term and longer-term funding strategies proposed by the Council were discussed. The two short-term strategies for determining the amount of an an award were (1) a "sliding-scale" method, in which the amount recommended is reduced by a specific percentage that is determined individually for each application according to its priority score; and (2) an "overall-percentage" method, in which the amount recommended is reduced by a uniform percentage for all applications. There were 98 respondents to the strategies proposed by the Council. The "sliding-scale" method was addressed by 33 respondents, about 60 percent of whom opposed it. The "overall-percentage" method was addressed by 36 respondents, 25 (about 69 percent) of whom supported it, but only as a temporary measure. The major themes voiced by the biomedical community were that a balanced program is needed to meet research objectives and that more resources are needed to capitalize on existing opportunities for research.

Also discussed at the briefings were several specific longer-term strategies, including limiting the number or size of awards to principal investigators, limiting the number or size of awards to organizational entities, and imposing a ceiling on large grants. Although no clear consensus developed, it became apparent that the research community is expressing two (not necessarily conflicting) objectives. The objective of the first and larger group of respondents is to keep the highest possible number of laboratories in operation and to fund the highest possible number of qualified scientists

working in them. This group believes that continuing the support for all high-quality resources, but at a reduced level, is more productive than continuing full-scale support for most and interrupting support for a few. In fact, the threat of interruptions in support might deflect many prospective investigators away from research careers; as a result, the Nation's research enterprise might be damaged severely enough that the cost of rebuilding it to its present status of international preeminence would be prohibitive. In contrast, the second group prefers to use existing and improved funding processes to continue full support for projects of the highest scientific merit, at the risk of delaying or eliminating some other excellent projects. Some persons in this group believe that the risks to the less meritorious projects could be reduced by development of programs funded jointly by NHLBI and by industry, foundations, and health organizations. Such joint funding would require the implementation of controls adequate to ensure objectivity and prevent exploitation by vested interest groups.

The respondents also discussed issues other than those originally addressed in the announcement of the briefings: indirect costs, peer review, faculty salaries, and communication between the Institute and its constituents.

As a result of these briefings, the Council members concluded that the Council and the research community agree on the following aspects of program balance:

- The full range of NHLBI funding and support programs should be preserved, with increased support for investigator-initiated grants.
- In addition to investigator-initiated grants, training and career development programs should be encouraged.
- The peer review system should be maintained.
- Indirect costs are problematical, and a strong effort should be made to examine and revise their structure.
- Minimum and maximum commitments of time should be required of federally supported investigators.
- The stability of the biomedical enterprise is threatened by the instability of funding.

Council public briefing.

Training

The Council has expressed concern about the declining number of physicians entering research. It believes that opportunities for training should be provided early in the career of persons interested in making a lifetime commitment to research. The NIH has recently created the Physician Scientist Award to provide research training for clinically trained physicians. This award will enable trainees to undertake up to 5 years of special study in basic science, with supervised research. The NHLBI has recently completed an evaluation of its Clinical Investigator Award (CIA) program. Development of the program was stimulated by a yearly decline, between fiscal year (FY) 1972 and FY 1976, in the number of M.D.'s in NHLBI research training and career development programs. The program was initiated in FY 1980 to encourage newly trained clinicians to develop interests and skills in clinical and basic research in cardiovascular, pulmonary, or blood diseases, and blood banking sciences, and to enlarge the pool of physician-investigators in these fields. Later data (for FY 1977 and FY 1982), however, show that the decline was reversed in FY 1976: since then, the number of M.D.'s in NHLBI research training and career development programs (other than the CIA) has steadily increased. The CIA program appears to have reinforced a preexisting, independent trend. Evaluation of the CIA program revealed that the number of applications has decreased markedly from the inception of the program in FY 1980 until FY 1983, but award rates, based on either the number of applications or the number of approved applications, have remained constant.

Overall, most CIA applicants have completed at least 3 years of clinical training. They generally also have more than 6 years of postdoctoral experience or its equivalent. Compared with unsuccessful applicants, successful applicants (awardees) not only tend to have had more research experience, but also are more likely to have had prior NIH research training support. Up to and including the year of their CIA application, successful applicants produce more publications than unsuccessful applicants do.

After 3 full years of program funding and four award competitions, the applicants who were approved but not paid compare favorably with the awardees on three measures of program outcome: average number of publications in the years following the application year, percentage occupying positions in academic medicine, and success as applicants for regular research grants. A more extensive evaluation of the CIA program will be conducted after at least the first cohort of awardees has completed the award terms.

Clinical Trials

Clinical trials are designed to test, in a carefully controlled setting, the efficacy and safety of preventive and therapeutic regimens before these regimens are introduced into practice. Since 1978, because of competing priorities, NHLBI has had difficulty in initiating large-scale clinical trials, but this trend is being reversed.

In FY 1983 the Institute implemented two large-scale clinical trials. One of these, Thrombolysis in Myocardial Infarction (TIMI), is designed to determine whether administration of drugs that dissolve blood clots in the coronary arteries of heart-attack patients will reduce the amount of heart muscle injury resulting from the attack. The other, Diagnosis of Pulmonary Embolism, will compare two x-ray

techniques—ventilation-perfusion scans and pulmonary angiography—for the diagnosis of pulmonary embolism.

The Institute plans to fund four new clinical trials in FY 1984: (1) The Systolic Hypertension in the Elderly Program (SHEP) which is designed to determine whether drug treatment of isolated systolic hypertension (high blood pressure occurring only during the beats of the heart) in patients 60 years old or older will reduce the incidence of fatal or nonfatal stroke. A pilot study for this trial showed that such drug treatment is effective in lowering blood pressure and merits investigation on a larger scale to assess its total clinical effect; (2) Prevention and Treatment of Congestive Heart Failure which will test the effectiveness of several drugs in reducing illness and death from heart failure; (3) High Frequency Ventilation in Premature Infants which will compare high frequency ventilation with standard mechanical ventilation for use with premature infants of low birth weight; (4) Prevention of Chronic Obstructive Lung Disease which is designed to determine, in a group of smokers, whether special care (counseling for smoking cessation and administration of drugs that dilate the air passages of the lung) is more effective than usual care in halting the decline in pulmonary function.

Results of the recently completed Coronary Artery Surgery Study (CASS) have just been published. This trial, initiated in 1973, compared coronary-artery bypass surgery with medical management for reducing mortality in 780 patients with symptomatically mild coronary artery disease. For the patient groups studied, there was no significant difference in survival between medically and surgically assigned patients: 7 years after the first patient was randomized and 4 years after the last patient was randomized, 90 percent of the medical patients and 92 percent of the surgical patients were still alive. Compared with the medical patients, the surgical patients had greater relief from angina during followup, were able to exercise longer, and took fewer drugs; but recreational activity and return to work did not differ between the two groups.

Institute Staffing

Adequate staffing is indispensable to the proper administration of programs as large and complex as those of the National Heart, Lung, and Blood Institute. Yet the Institute continues to have vacancies in high-level positions. These are a result of factors including a restriction on personnel recruitment, an unrealistic salary ceiling, and (in some instances) uncomfortable work facilities.

Budget Recommendations

The Council wishes to express to the leadership at NIH and to the Department of Health and Human Services its firm commitment to a balanced and diverse program of biomedical research and training in the best interest of the public health. The Council is convinced that a properly balanced program must offer an array of research-support mechanisms that includes contracts, program project and center grants, and solicited research proposals, in addition to a continuing strong commitment to investigator-initiated grants. The Council reaffirms its strong belief that an optimal program must encompass basic as well as applied and clinical research, laboratory studies and clinical trials, fundamental investigations of biologic phenomena, and demonstration and education activities.

In recommending the budgets for FY 1986 through FY 1990, the Council reaffirms its

principles for the determination of funding levels:

- Budgets must grow at least as fast as the increasing costs of doing research. The long-term effect of the decline in real resources available to the Institute and generally to the NIH must be evaluated.
- At least one-third of all uncommitted funds each year should be used for the centers, contracts, training, career awards, and other research mechanisms that make up a balanced Institute program, with the remaining two-thirds available for regular grants and program project grants.
- Resources should be sufficient to fund 50 percent of all approved research-grant applications.
- In FY 1984, contract-supported activity should be within 10 to 12 percent of the Institute's budget.

Using these principles and assuming 5-percent inflation in 1986 through 1990, the Advisory Council recommends the following levels of funding for maintaining the NHLBI research grants and other programs at their current levels:

FY 1986	FY 1987	FY 1988	FY 1989	FY 1990
905.0M	950.3M	997.8M	1,047.7M	1,100.0M

To continue a balanced program by adequately funding priority areas in addition to research project grants, the Council recommends the following levels:

FY 1986	FY 1987	FY 1988	FY 1989	FY 1990
1,002.0M	1,052.1M	1,104.7M	1,159.9M	1,217.9M

For comparison, the following funds would be necessary to prevent a decline in future funding from the current (FY 1984) level:

FY 1984	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990
704.9M	740.1M	777.1M	816.0M	856.8M	899.6M	944.6M

Credits

The photograph of the young boy being evaluated with a continuous wave Doppler technique and the resulting scan on page 4 were provided by Dr. Ernest Craige, University of North Carolina at Chapel Hill.

Photograph of the child with an implanted pacemaker on page 8 is by Adam Gillum.

The electron micrograph of the rubella virus on page 9 was provided by the Centers for Disease Control.

The NMR scan of the chest on page 11 was provided by Dr. Gerald M. Pohost, University of Alabama at Birmingham School of Medicine.

The photograph of the premature infant with RDS on page 15 was provided by the University of Washington, Seattle.

Photograph of the nurse checking premature infant's vital signs on page 16 is by Bruce Fritz.

The electron micrograph of animal lung tissue shows high frequency ventilation to be more effective than standard mechanical ventilation for treating RDS on page 17 was provided by the United States Air Force.

The electron micrograph of surfactant being secreted from a type II lung cell on page 17 was provided by the *American Review of Respiratory Diseases.*

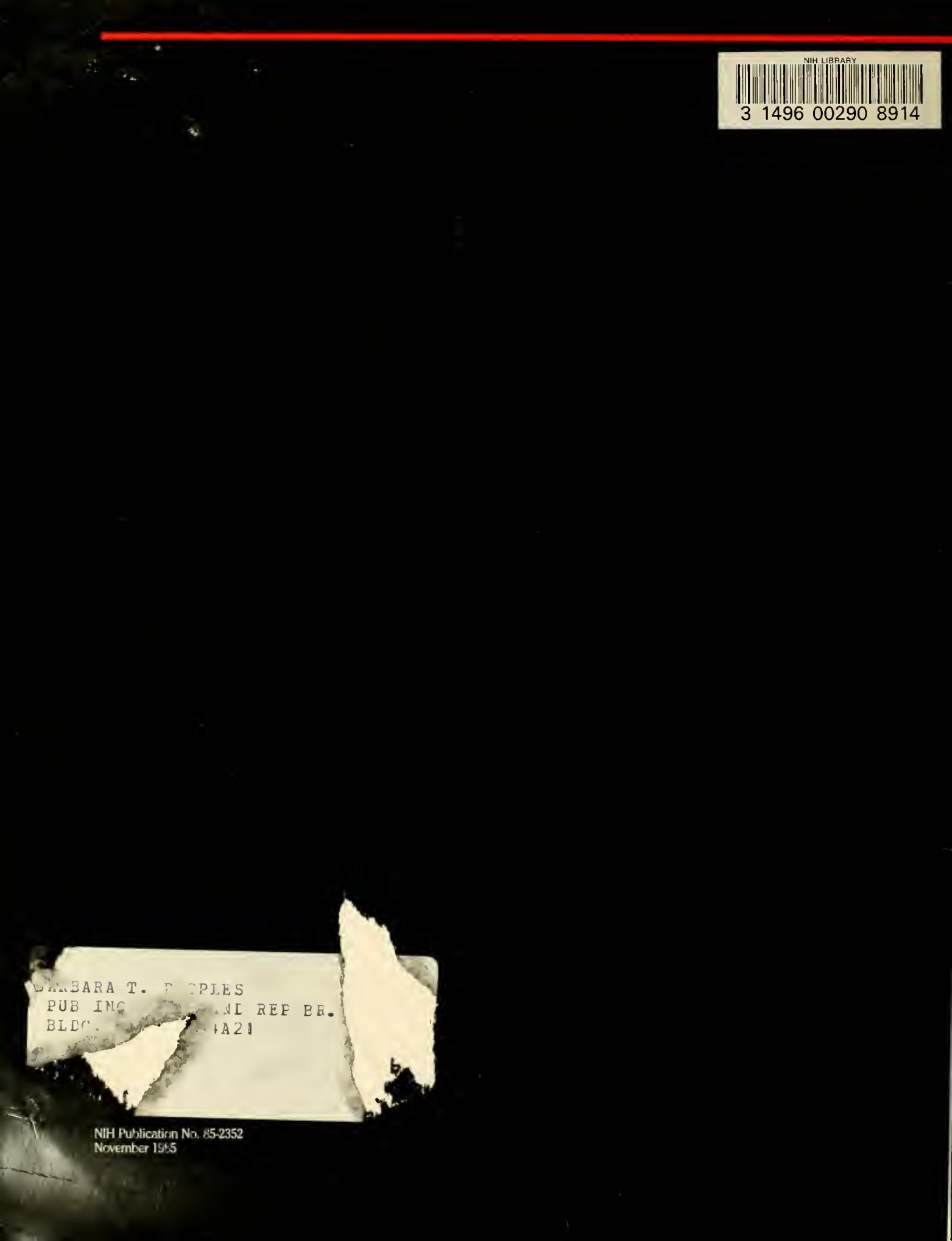
The three photographs of children being treated for cystic fibrosis on page 21 was provided by the Cystic Fibrosis Foundation.

The photograph of the hemophilic child injecting himself with clotting factor concentrate at home on page 23 was provided by Hyland Therapeutics.

The photograph of blood center staff preparing reagents used to inactivate viruses in antihemophilic factor concentrate on page 24 was provided by Dr. Bernard Horowitz, New York Blood Center.

The photograph of a researcher isolating factor VIII on page 24 was provided by the American Red Cross.

The photographs of the two Cooley's anemia patients, one receiving a red blood cell transfusion and the other receiving the drug deferoxamine via the minipump attached at the waist, on page 25 were provided by the Cooley's Anemia Foundation, Inc.



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