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THE PEDIATRIC GAP

Why have most medications never been properly tested on kids?

by JEROME GROOPMAN

Not long ago, a three-year-old boy fell off a jungle gym in Boston and lacerated his cheek. His parents rushed him to the emergency room of a nearby hospital. A nurse restrained the screaming boy while a surgeon cleaned his cheek and injected it with a small dose of bupivacaine, a local anesthetic that is widely used in adults. When the surgeon began to suture the wound, the child had a seizure and his blood pressure suddenly dropped; he was on the verge of going into shock. He was transferred to the intensive-care unit, where doctors tried to account for his symptoms. A cat scan taken to see if the fall had caused cerebral hemorrhage showed no evidence of brain damage.

Maureen Strafford, a pediatric anesthesiologist and cardiologist, was paged to assist, and she found that the level of bupivacaine in the boy's blood was perilously high. The boy was intubated and placed on a respirator. He spent several days in intensive care before recovering from the overdose.

The package insert for bupivacaine does not provide specific dosing information for children; the E.R. surgeon had adjusted for the boy's weight by "dosing down" from the amount recommended for adults. But such extrapolations cannot account for the differences in the biology of children. Even growing teen-agers who weigh as much as adults tend to absorb and metabolize medicine more quickly than adults, since organs that break down drugs, such as the liver, or excrete chemicals, such as the kidneys, take years to mature. The rate of blood flow to the skin and lungs is also higher in children, so topical or inhaled agents may be more rapidly absorbed.

Strafford told me that the surgeon's decision to improvise with bupivacaine was not unusual. Although the Food and Drug Administration has long required that medications be screened for safety in adults, approximately seventy-five per cent of drugs approved for use in the United States have never been subjected to comprehensive pediatric studies. A physician, however, is allowed to use any F.D.A.-approved drug in whatever way he deems beneficial, and he isn't required to inform parents if it hasn't been specifically tested on children. There is no single official repository of information about how to calibrate drug dosages for children. Since pharmaceutical companies rarely collect data about the effects of their drugs on minors, there is scant information about pediatric dosing in the Physicians' Desk Reference, a compendium of guidelines and warnings supplied by drug companies; pediatric handbooks are published by private companies, but they are not comprehensive and their data are not obtained through a

consistent methodology. In the absence of reliable information, doctors are frequently forced to engage in guesswork when administering drugs. Speaking of the three-year-old boy, Strafford said, “This is a perfect example of what can happen to a healthy kid.”

I recently spoke with Ellis Neufeld, a pediatric hematologist at Children’s Hospital Boston, who has begun to document the different ways children react to Lovenox, an anticoagulant that has been safely used in adults. A teen-ager at the hospital, he said, had recently developed a severe brain hemorrhage after taking the drug; emergency neurosurgery was required to save his life. This spring, Neufeld completed a preliminary study of thirty children who had been placed on closely monitored regimens of Lovenox. The findings helped him formulate a set of target doses in pediatric patients, adjusting for variables such as kidney function. (In very young children, the renal system is not fully developed.) His results will be ready for publication in several months. In Neufeld’s view, such a study should have been required by the F.D.A. before Lovenox was approved for use in children. “The package insert from the drug company does not provide a doctor with what he needs to know,” he said. Under the rubric “Pediatric Use,” the insert merely states, “Safety and effectiveness of Lovenox Injection in pediatric patients have not been established.”

Children with certain illnesses can be especially sensitive to the side effects of a drug. For example, infants with meningitis are much more likely than adults to react poorly to chloramphenicol, an antibiotic that is a common medication for the disease; newborns, especially premature babies, do not have the necessary enzyme in the liver to metabolize the drug. Symptoms such as vomiting, refusal to suck on a breast or a bottle, and diarrhea usually appear two to nine days after the initial treatment. When chloramphenicol accumulates at toxic levels, blood pressure drops precipitately, and the lack of oxygen in the blood causes the baby’s lips and skin to take on a bluish tint. Ultimately, body temperature plummets and the baby turns ashen. “Gray-baby syndrome” can be fatal unless the infant receives a blood transfusion.

Although pediatricians have trained themselves to be particularly careful when administering drugs, the risk of grave harm is still too high. One popular drug that was discovered to be especially dangerous to children is propofol, a sedative that has consistently proved safe in adults. During the early nineteen-nineties in England, there were several reports of children who died after receiving propofol during I.C.U. sedation; in 1992, the British government recommended against using it on patients under sixteen. In the United States, however, propofol continued to be used widely in pediatric I.C.U.s. As it turned out, some children in intensive care who had been administered propofol developed a potentially lethal buildup of acid in the blood. Finally, in 2001, AstraZeneca Pharmaceuticals, the company that created the drug, sent out a letter to American physicians disclosing the results of a pediatric trial: of two hundred and twenty-two young patients in intensive care who were given propofol, twenty-one died; only four of the hundred and five patients given standard sedatives died. In other words, the death rate of children taking propofol was two and a half times higher. The F.D.A. eventually added a new warning inside packages of the drug, contraindicating its use among youths; it remains legal, however, for doctors to administer propofol to children.

Pediatricians sometimes adopt extraordinary measures to insure that their patients are not harmed by treatments that have not been adequately studied in children. Ben Mizell, the former medical director of the Infant Unit at Primary Children's Medical Center, in Salt Lake City, told me that he often resorted to painful procedures—such as the placement of a catheter into the bloodstream—so that he could carefully monitor the level of a drug in an infant's blood. At other times, he used outdated drugs, because he lacked data on the pediatric safety of more modern medicines. When he did prescribe a new antibiotic, he said, "we did so with the caveat that only God knows what is going to happen." Mizell described how difficult it was to explain to families that many of the treatments their infants received were being administered without sufficient knowledge. "As soon as you admit your ignorance, parents lose faith in your ability to help," he said.

With some common pediatric illnesses, doctors have essentially no choice but to administer unscreened medication. Asthma is a particular problem. Michael Shannon, the director of the Children's Hospital Boston emergency room and an expert on pediatric toxicology, told me, "We don't know the safe limits of dose and frequency of modern inhaled asthma drugs like albuterol, and so when we give children inhalants we sometimes make them sick." Moreover, no intravenous asthma drug has been comprehensively tested on children. One such medication, intravenous terbutaline, "is fairly ineffective, and, frankly, it can be toxic," Shannon said. "It can cause a rapid heart rate as well as high blood pressure or injury to the heart. We need to be able to use better treatments on kids."

Several years ago, Shannon conducted his own pediatric trial of a common adult asthma therapy, intravenous magnesium, versus a placebo. His clinical fellow recently finished another. "They're the only placebo-controlled trials that I know of in the literature for moderate childhood asthma," he said. Shannon and his colleague donated the time they spent on the studies, and Shannon drew on discretionary funds from the hospital to pay for blood tests. Preliminary results from the studies suggest that the therapy is safe for children.

In recent years, federal legislation has sought to give pharmaceutical firms financial incentives to pay for clinical studies targeted to children. Since 1997, a company that agrees to set up a pediatric trial to screen a new drug has received a six-month extension of market exclusivity for the medication. Yet such reforms don't address the larger problem of old drugs that have never been tested on children. Children's health advocates also complain that the F.D.A. does not require manufacturers of medical devices to create variants that are designed for children; consequently, pediatric surgeons and cardiologists must perform procedures on children using equipment that was developed for adults. "It's what I call the reverse lifeboat phenomenon," Maureen Strafford told me. "In medicine, children come last."

Testing drugs on children used to be a priority. Stuart Siegel, a pediatric hematologist-oncologist and the director of the Children's Center for Cancer and Blood Diseases at Children's Hospital Los Angeles, told me that in the nineteen-fifties and sixties children with cancer were typically given experimental drugs before adults. The logic was that sick children deserved to be the first to receive the latest treatments. These days, the situation is often reversed; important new therapies—for example, Gleevec and Avastin—have been tested on adults first. Siegel attributes

this shift to “an ethical change in society.” Doctors and parents are increasingly concerned about whether children can truly give informed consent to participate in potentially harmful research. Drug companies have equally strong misgivings; they fear legal liability and negative publicity. If a child dies during a clinical study and the parents sue, jury awards can be very high.

“I’ve had discussions with some leaders in the pharmaceutical industry,” Siegel said. “The feedback is consistent. They’ll cite the cost and then they’ll also cite the risk, in terms of an adverse event and what that would do to their profits and their stock.”

Indeed, Eli Lilly and Company recently received a tremendous amount of bad press when Traci Johnson, an Indiana college student, committed suicide during a clinical trial of Cymbalta, an antidepressant. She had initially been given high doses of Cymbalta, but a few days before her death she had been switched to a placebo. Scientists have found that hallucinations and paranoid delusions can occur when a patient is in withdrawal from an antidepressant. A spokesman for Lilly has stated that it is unclear what led to the girl’s suicide; the F.D.A. officially cleared the company of wrongdoing and approved the drug.

Johnson’s death occurred at the same time that the F.D.A. was analyzing a large set of data compiled from multiple clinical trials. The results, which were released in October, indicated that twice as many children taking antidepressants in clinical trials considered or attempted suicide as children taking placebos. The agency will require pharmacists to include a warning, to be released later this month, that cites this study when dispensing packages of antidepressants. Although antidepressants can still be legally administered to children, the children must now be stringently monitored by doctors.

One reason the F.D.A. was slow to identify this danger, critics say, is that individual clinical trials sponsored by drug companies involved small numbers of children. (The more subjects involved in a study, the costlier it is.) Pfizer’s pediatric studies of Zoloft, for example, involved fewer than four hundred children; according to Lawrence Scahill, a researcher in pediatric psychopharmacology at the Yale Child Study Center, thousands of depressed children would need to be studied before researchers could pinpoint a subtle difference in behavior, such as increased suicidal thoughts. The F.D.A. extended Pfizer’s patent on Zoloft for six months because it conducted the trial, which will allow it to reap hundreds of millions of dollars in added revenue.

Although the precise biological differences between adult depression and childhood depression are not yet known, there is reason to believe that the maladies are not identical, and that antidepressants may work differently on a developing brain. Harold S. Koplewicz, the director of the New York University Child Study Center, told me that few children or teen-agers exhibit the classic symptoms of adult depression: insomnia, sadness, passivity, loss of libido, and loss of appetite. Rather, they often oversleep, overeat, and feel irritable and aggressive. “There are revolutionary changes in the brain that begin around age thirteen and end around twenty-five,” Koplewicz said. “In terms of neural pathways, country roads become superhighways.” He theorizes that, in some children, these tumultuous brain changes lead to depression. Koplewicz believes that some antidepressants can help teen-agers, but cautions that young people’s brains

may be more sensitive to daily fluctuations in drug levels, and that these pharmacological changes themselves may foster destructive thoughts and behavior.

In the late nineteen-eighties, Britain's medical regulatory agency began closely monitoring anecdotal reports of suicidal behavior and withdrawal symptoms related to one class of antidepressants, selective serotonin re-uptake inhibitors (S.S.R.I.s). Warnings were issued by the British government about the potential dangers of these drugs in 1993 and 2000. In June, 2003, the agency convened an emergency meeting to review pediatric trial data on Seroxat, an S.S.R.I. known in the United States as Paxil, and concluded that the drug should not be prescribed for minors. By the end of that year, the British government had banned doctors from giving five other S.S.R.I.s to children. Ten more months passed before the F.D.A. took similar action on children and antidepressants.

In 2003, Congress passed legislation that codified what is known as the Pediatric Rule. A drug company working on a new treatment for a disease that affects both adults and children is now required to conduct pediatric studies. (The rule does not slow the process of approving new drugs for adult use.) To make this regulation palatable, the F.D.A. continues to offer a six-month extension of market exclusivity for drug companies that perform pediatric studies.

Children's health advocates, who had fought for years to help pass this legislation, were dismayed to discover that there were significant loopholes in the 2003 law, as well as in other recent reforms. For example, Congress did not set a timetable for the completion of pediatric studies. Moreover, the reforms include a "sunset clause" that will cause them to expire in 2007. (This clause was added as a result of pressure from drug companies and groups that oppose government regulation.) Advocates worry that many drug companies will exploit the clause by agreeing to conduct a trial but allowing the study to languish until 2007, when a different Congress may decline to renew the reforms.

An even greater oversight of the congressional reforms is that they do not adequately address the potential dangers of generic drugs. A list of medications for which pediatric studies are urgently needed is published annually in the Federal Register. The 2004 list includes twenty-five drugs that are prescribed for children hundreds of thousands of times each year—drugs such as rifampin, an antibiotic that combats tuberculosis and staph infections, and furosemide, a common diuretic. Another drug on the list, the sedative ketamine, has sometimes caused children to stop breathing. There are insufficient data, however, to suggest why this occurs—and whether a different dosing regimen might be safer.

The National Institutes of Health has begun to commission pediatric studies of the generic drugs on the Federal Register list, but it has not been given any additional funds for this urgent task. The National Institute of Child Health and Human Development estimates that it costs, on average, five to ten million dollars to do a comprehensive pediatric study of a drug. By diverting funds from other programs, the N.I.H. has begun studies of only two of the twenty-five drugs on the Federal Register list.

While children's advocates are working to fill the gaps in the congressional reforms, Sam Kazman, the general counsel for the Competitive Enterprise Institute, a Washington-based libertarian group that lobbied against the Pediatric Rule, would like to see the laws overturned. (Five per cent of the institute's annual budget comes from donations from pharmaceutical companies.) Kazman worries that requiring pediatric clinical trials on drugs will open the door to other "special groups"—such as pregnant women, the elderly, and immune-compromised patients. Each group may experience different effects from a particular drug, and requiring safety and efficacy data on each one, he told me, would further increase the costs of drug discovery and discourage new research. "These factors can tip against going forward with new drug development," he said. "It can take more than ten years and hundreds of millions of dollars to develop a drug. Placing unnecessary regulatory burdens on pharmaceutical companies only adds to their costs."

Dr. Charles Coté, a pediatric anesthesiologist and an expert on pediatric drug trials, said that some pharmaceutical companies had gone to great lengths to lower the costs of studies in children. Typically, in clinical trials on adults, a company first studies how different doses of a drug are absorbed and metabolized. The company then performs a second set of studies to determine if the drug is effective. In many recent pediatric studies, these two steps have been combined in order to cut costs. This approach requires each child involved in the study to participate for a long period of time—but, because few children have extended stays in the hospital, enrollment is often poor. "A drug company can satisfy the law without generating meaningful data about how to prescribe its drug for children," Coté said. In his view, the congressional reforms did not go far enough. "We need to require more rigorous studies, to make sure that these drugs are safe for children."

The F.D.A.'s method of monitoring drugs after they appear on the market is also flawed. Dianne Murphy, who is in charge of the F.D.A.'s Office of Pediatric Therapeutics, recently told me that the agency's approach is essentially "a passive process." Once a drug is approved for use, the F.D.A. tracks adverse reactions to medications by culling voluntary reports from patients and doctors, through a program known as MedWatch. Pediatricians, however, are often overwhelmed with paperwork for insurance companies and must carry large patient loads in order to sustain their practices; few find the time to fill out MedWatch forms. France and Britain, by contrast, have aggressive post-market surveillance programs that are more effective at getting hospitals to report drug mishaps. In the wake of the recent scandal surrounding Vioxx—a painkiller that was approved by the F.D.A. in 1999, yet turned out to cause serious heart problems—the F.D.A. is under pressure to revamp its method for tracking adverse reactions. Reform of this system will especially benefit children. Since the number of children taking a certain drug is small (relative to the adult population), it is particularly hard to detect a pattern of adverse reactions; without proper vigilance, the dangers of a drug like Paxil, for instance, can go unnoticed for years.

Last March, a woman in her twenty-fourth week of pregnancy came to Boston in the hope that a cardiac procedure would allow her fetus, which had a malformed heart, to survive after birth. The organ was about twenty millimetres wide. Owing to problems during gestation, the blood flow between the left atrium and the right atrium was poor; if the problem was left unattended, the baby would likely die soon after being born. The aim of the operation was to enlarge a one-

millimetre hole that connected the two chambers, allowing for free blood flow. The best way to do this would be to insert a catheter with an inflatable balloon into the hole at a ninety-degree angle. But no company had ever designed a catheter for children—let alone fetuses—so the team would have to use an adult catheter, which is large and cumbersome.

Two monitors in the room projected ultrasound images of the fetus. James Lock, the chief of cardiology at Children's Hospital Boston, stood by the table. A fuzzy gray-and-black outline of limbs and torso filled the screen. Wayne Tworetzky, a pediatric cardiologist, focussed the ultrasound probe on the fetal heart. It appeared as a delicate, pulsing circle. Bursts of red and blue indicated the distorted path of blood circulation through the heart and lungs.

Louise Wilkins-Haug, an obstetrician, began to press the left side of the mother's abdomen.

"That looks good," Tworetzky said. "The baby's chest is now facing outward."

"How big is the right atrium?" Lock, the cardiologist, asked.

"Six millimetres," Tworetzky answered.

A sharp white line appeared on the screen. Wilkins-Haug was advancing a metal cannula, or tube, with a needle at its tip toward the baby's heart. "The needle tip is too high," Lock warned her. "You'll blow up the back wall of the heart! Readjust." Wilkins-Haug moved the cannula; a deviation of even a few millimetres could tear the tissue of the cardiac chambers and kill the fetus.

There was a flash of white light on the screen as the needle punctured the heart wall with a tiny hole. Lock then inserted a catheter through the cannula. "Blow up the balloon," Lock instructed. The balloon would expand the hole, increasing blood flow.

Suddenly, Lock yelled, "Shit!" The balloon had ruptured in the left atrium, which meant that they could not inflate it twice, to maximize the size of the hole. The balloon, too, had been designed for an adult. Moreover, the catheter was so unwieldy and inflexible that the physicians' approach to the septum was thirty degrees short of the optimal angle. Despite the problems, bursts of red and blue appeared on the screen to indicate that blood circulation had been increased. There was a better chance that the baby would live.

A few days after the operation, I met with Lock, who is an expert in interventional cardiology—the use of devices to fix heart problems. "We have to show we can make this work with the wrong equipment, and then convince someone to make us the right equipment," Lock explained. He told me that the first device he tried to create for children was an instrument to open a stenosis, or closure, of two portals to the heart: the aortic and the mitral valves. If Lock could dilate these valves using a tiny catheter, a child with the condition could avoid open-heart surgery. He went to Boston Scientific Corporation, a prominent medical-device manufacturer. The company suggested that he use a catheter designed to open a small artery in the abdomen of an adult. "They told me there wasn't a market," he recalled. So, for three years, Lock used the abdominal catheter to open the aortic and mitral valves of adults. This was relatively successful,

and Boston Scientific, convinced that there was an adult market, agreed to make an aortic-and-mitral-valve catheter—for adults. “As an act of charity only, they made a few pediatric-shaped catheters,” Lock said. “It’s unlikely that we would ever have got the pediatric catheters built if there hadn’t been an adult market—which we had to invent.”

The operation I had witnessed, Lock said, would be much safer if he had the right equipment. “What do I need?” he asked rhetorically. “It’s not very complicated. I need somebody to put a bend on this catheter. You want it to be shaped like a hockey stick on the tip so if I’m at the wrong angle I can just rotate it.” He showed me a prototype of the specialized catheter, which he had made himself. “You see, I can turn it,” he said.

Although only fifty to a hundred babies a year require the surgery that I had observed, Lock said, he and his colleagues at the hospital believe that the hockey-stick cannula could be used in a variety of pediatric procedures. An obstruction in a baby’s bile duct could be readily opened using such an instrument. Anesthesia could be delivered to a hard-to-reach part of a child’s body, like the nerves in the shoulder. Rusty Jennings, a fetal surgeon at the hospital, told me that hundreds of babies are born each year with a malformation at the base of the bladder which results in kidney failure. If this bladder abnormality could be repaired before birth—a procedure for which Lock’s cannula might be an ideal tool—the kidneys would be spared. “Many thousands of children could benefit from this invention,” Lock told me. Still, he had great difficulty convincing a company to take on the project and devote its own resources to manufacturing the device. As a last resort, Lock gave away the patent for his device to a small start-up company, ATC, and Children’s Hospital Boston is paying ATC for much of the research and development costs.

It seems unlikely that either private industry or the government will ever take the initiative in creating therapies specifically designed for children. As a result, some hospitals are trying to help close the pediatric gap by setting up their own research-and-development divisions. In 2003, Children’s Hospital Boston started the Pediatric Product Development Initiative. First, the hospital interviews the clinical staff about medical gaps that need to be filled. If a pediatrician says, for example, that he needs a certain drug reformulated into a liquid palatable to babies, the hospital funds research to determine how this might be accomplished. If a specific device is needed, the hospital brings in engineers to determine the feasibility of producing it; once it is deemed practical, the hospital offers the idea to a private company.

One prototype that the program has developed is that of a milk bottle designed for premature infants who are unable to coördinate sucking and swallowing, causing food to enter their lungs. This “active bottle” has a series of sensors that can detect whether the infant has learned the necessary skills. Children’s Hospital also has prototypes for a pillow for babies with misshapen heads, to keep them from sleeping always on one side.

In the meantime, pediatricians are faced with urgent clinical problems. Recently, at Children’s Hospital Boston, there was an outbreak of an unusual bacterium called B. dolosa among patients with cystic fibrosis. Thirty-six of the four hundred and fifty patients with cystic fibrosis are known to be infected with the microbe. Craig Gerard, who is the chief of pulmonary medicine

and a professor of pediatrics at Harvard Medical School, and who oversees these young patients, told me that lung function gradually declines in patients who suffer from cystic fibrosis, but in those carrying B. dolosa breathing can become severely impaired. There is no clearly effective therapy for the microbe, which does not appear to be a threat to healthy children or adults. One death has already been attributed to sepsis, and there are six other cases in which Gerard believes the microbe may have been a contributing factor. Yet there is little chance that a pharmaceutical company would develop a drug to target an unusual microbe like B. dolosa, which is not widespread enough to make such a drug profitable.

Acknowledging that this problem is outside “the great maw of the pharmaceutical industry,” Gerard has decided that the only solution is for Children’s Hospital to develop its own pediatric drugs. “We are going to try to make a designer antibiotic,” he said. Gerard and his collaborators at Harvard are using charitable funds to decode the genome of B. dolosa. “We can’t wait for the economics to drive this,” he said.