

Inside

- ❖ Coagulation Disorders Often Not Detected
- ❖ New Epilepsy Drugs Produce Fewer Side Effects in Children
- ❖ Advances in Genetics Bring New Possibilities to Pediatric Practices

Significantly more children are becoming seriously ill with community-acquired staphylococcal infections.

Antibiotic-resistant Infections On the Rise in the Community

The growing incidence of infections that are resistant to antibiotics has important implications for pediatric practice, both in the hospital and in the community.

In the past year, approximately a dozen reports have noted a dramatic increase in the number of previously healthy children infected with highly invasive and resistant community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). "This is not a subtle change; it's a dramatic change that's affecting pediatricians' practices in Southern California and across the country," says Paul Krogstad, M.D., a pediatric infectious disease specialist at Mattel Children's Hospital at UCLA. "The problem is more than just resistance to antimicrobial agents. These community-acquired staphylococcal infections are more likely

to spread to the bones and joints and to cause necrotizing pneumonia and sepsis. Moreover, these are infections acquired in the community, and not from bacteria picked up in the hospital."

A recent study involving the Centers for Disease Control and Prevention found that approximately one in five infections were being acquired in the community, with no apparent links to healthcare settings. Nearly one in four cases was serious enough to require hospitalization. Another study reports that CA-MRSA has acquired the ability to cause necrotizing fasciitis—a condition not previously associated with staphylococci. More than a dozen cases of necrotizing fasciitis caused by methicillin-resistant *Staphylococcus aureus* were reported in the Los Angeles area, all of which required surgery and most of which put patients in intensive care. "Children under the age of 2 are at particularly high risk for acquiring these dangerous infections, which can't be treated with the antibiotics pediatricians are used to prescribing for common skin infections," notes Dr. Krogstad.

A highly resistant clone of staphylococci that also expresses a toxin known as Pantone-Valentine leukocidin has emerged in the United States and is "the worst version of staphylococci we have seen in decades," says Dr. Krogstad. Pediatricians should be on the lookout for patients with recurrent skin and soft-tissue infections and consider decolonization measures in certain cases. "The organism is often harbored in the anterior nares," Dr. Krogstad

CONTINUED ON PAGE 2



CONTINUED FROM PAGE 1 notes. "Culturing can identify colonization, and then a number of steps can be taken to break this cycle of infection." Steps include determining if other family members have also had recurrent infections, potentially screening all family members; using bactericidal soaps for approximately two weeks; simultaneously washing all bedding; and employing an antibacterial ointment (mupirocin) in the anterior nares. Surgery has become an increasingly important component of treatment.

Resistant organisms cause an estimated 50 percent to 60 percent of the 2 million hospital-acquired infections each year. Bloodstream infections cause half of the deaths in infants who require hospitalization in neonatal intensive care units for more than two weeks. The leading cause of infection in hospitals is


strains of *Staphylococcus epidermidis* can trigger or enhance biofilm production, resulting in more pathogenic bacteria. "This is worrisome, because alcohol-based disinfectants are the standard in intensive care units, and their use in the community is increasing," she says.

For highly resistant staphylococci as well as highly resistant pneumococci—which, unlike the staphylococcal problem, is a development that appears to have resulted from overuse of antimicrobials—the pipeline of effective new antibiotics is limited. The problem of antimicrobial overuse has been widely publicized. "When pediatricians are treating infections that they think are caused by bacteria, it's important not to start with the big guns—the broad-spectrum antibiotics—because the more we use them, the more we allow

broader-spectrum drugs, a trend that also leads to greater resistance.

In recent years, Dr. Mangione-Smith and colleagues have sought to empirically test the assumption that parent pressure drives inappropriate antimicrobial prescription by pediatricians. Through videotaping of office visits and post-visit surveys of parents in two private pediatric practices, they explored how preferences for antibiotics were communicated by parents and whether the physicians were able to convey why the drugs were not being prescribed in a way that would leave the parents satisfied. They found that among parents whose children were not prescribed antibiotics, those who were offered a contingency plan—the possibility of antibiotics being prescribed if their child failed to get better soon—were significantly more satisfied.

"If the child looks very sick and you're not sure whether or not it's a bacterial illness but you're uncomfortable sending him or her home without starting something, then you need to prescribe medication," says Dr. Mangione-Smith. But she recommends that pediatricians offer the contingency for other cases in which they feel strongly that the child has a viral condition.

"We found that even if antibiotics were not clinically indicated, giving a treatment plan to help relieve symptoms such as cough or ear pain and telling the parent that an antibiotic will be considered if the child is not getting any better in 48 hours results in a satisfied parent most of the time," Dr. Mangione-Smith explains. 

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Antibiotics are being over-prescribed for bacterial infections — and even for viral cases of childhood bronchitis and other infections for which they are of no use.

Staphylococcus epidermidis. "This is an organism normally present on the skin of patients and healthcare providers, but patients who are immunocompromised or who have indwelling or implanted foreign polymer bodies are at high risk for infection caused by the organism," says Vladana Milisavljevic, M.D., UCLA neonatologist. Thus, premature infants who require central catheter lines are at particularly high risk, she notes, adding that the organisms acquired during hospitalization are likely to be multi-resistant to antibiotics.

Dr. Milisavljevic is conducting research to determine what makes the organism normally habitant on the skin become a pathogen once it gets into the bloodstream of immunocompromised babies. She says that one of the most important pathogenic qualities of *Staphylococcus epidermidis* is its production of a biofilm that coats plastic polymer devices, preventing antibiotics from penetrating. Recently, she has studied the effect of alcohol on such biofilm production and has found that low percentages of alcohol added to certain

bacteria to learn how to resist them," Dr. Milisavljevic explains. Adds Dr. Krogstad: "We finished the 20th century with many antimicrobial agents but now face the possibility that a lot of them will be ineffective in the next 10 to 20 years unless we use them more judiciously."

The results of surveys and focus groups of pediatricians have suggested that over-prescription of antibiotics, particularly for upper-respiratory infections, results from their feeling pressured by parents. "We're living in a consumerist medical environment, and there is a great deal of concern that if you don't give people what they want, they will just go see someone else," says Rita Mangione-Smith, M.D., UCLA pediatrician.

Antibiotics are being over-prescribed for bacterial infections—and even for viral causes of childhood bronchitis and other infections for which they are of no use. Where antibiotics are indicated—most commonly for ear infections—first-line drugs such as amoxicillin are too often being skipped in favor of

Coagulation Disorders Often Not Detected

Advancements in the treatment and management of blood coagulation, or bleeding disorders have dramatically improved the health and quality of life for many of the 2 percent to 4 percent of the overall population who are afflicted. For many pediatric patients this means normal childhood activities such as physical play and sports are no longer forbidden, and they can look forward to a relatively normal and healthy future.

Severity of bleeding disorders can range from mild and often undetected to debilitating and crippling. Bleeding disorders manifest in prolonged—not profuse—bleeding, and carry the risk of severe internal bleeding, often into the joints. These conditions—whether inherited or not—can stem from many causes, including deficiencies in clotting factors and abnormal platelet function.

Hemophilia

The hemophilias, perhaps the most well known group of related bleeding disorders, represents a deficiency of specific coagulation proteins called factors. Usually they are X-linked recessive and typically pass from mother to son. Rarely, the daughter of a male hemophiliac and a female carrier can also inherit the disease. In up to one-third of diagnosed cases, no family history exists and the disorder arises from a spontaneous genetic mutation.

“Hemophilia is easy to diagnose by a simple laboratory test. The difficulty is to consider the diagnosis as a possibility and actually order the test,” says Guy Young, M.D., pediatric hematology and oncology specialist at the Hemophilia Treatment Center at Mattel Children’s Hospital at UCLA. The most obvious trigger is family history; if the boy’s maternal grandfather has hemophilia, a 50 percent chance exists that the child will inherit it. If the

family history is unknown, signs to watch for include prolonged bleeding after circumcision, slow trickles of blood from the umbilical stump, significant swelling with immunizations, or abnormal bruising from crawling. Any of these should prompt physicians to order a partial thromboplastin time (PTT) test. If the result is abnormal, then test for the deficient factor, usually VIII or IX.

Hemophilias classify as mild, moderate or severe and can lead to significant pathology, especially joint disease. Major advances in the treatment of hemophilia revolve around correcting clotting deficiencies with factor concentrates as well as managing the complications of joint disease, Dr. Young adds. With proper intervention from an early age, children with hemophilia can develop normally without crippling pain, lead normal adult lives and remain mobile, a vast improvement from the average 30-year lifespan of yesterday’s sufferer.

Von Willebrand Disease

Although hemophilia is the most widely known bleeding disorder, von Willebrand disease is the most common hereditary coagulation disorder, affecting both males and females. “Von Willebrand disease, caused by a deficiency in von Willebrand clotting factor and platelet abnormalities due to defective platelet function, accounts for approximately 80 percent of all pediatric coagulation disorders,” notes Dr. Young. Blood tests can diagnose both von Willebrand disease and platelet abnormalities. Afflicted children who experience bleeding episodes may require desmopressin to temporarily increase the level of von Willebrand factor or improve platelet function, and those with von Willebrand disease may need injections of clotting factor concentrates with von Willebrand factor.

Bleeding problems are common, yet greatly underdiagnosed. Left undetected—even in their mildest forms—they can lead to significant problems. Routine medical procedures can swiftly escalate into emergencies necessitating unexpected transfusions and special care. Children with any kind of bleeding disorder, regardless of

severity, often require high doses of clotting factor before and after medical procedures, such as tonsillectomy or tooth extraction, to prevent dangerous complications.

Although pediatricians may first suspect that their patient has a bleeding disorder, subspecialists are best equipped to prescribe a regimen for optimal management of the disease. Despite the name, federally designated Hemophilia Treatment Centers (HTC) located throughout the United States provide state-of-the-art care for patients with any type of coagulation disorder. To date, the most effective treatment includes clotting factors, although the frequency of the infusions and the relatively high rate of inhibitor development are common drawbacks. “Our foremost goal is to cure these diseases, especially hemophilia, with gene therapy,” says Dr. Young. “Since that is likely many years away, our near-future goals include improved treatment, especially for patients who develop inhibitor, and novel adjunctive therapies for joint disease management.”



Further reading

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In addition to family history, warning signs of clotting disorders include:

- ❖ palpable and easy bruising, particularly in unusual locations
- ❖ frequent and recurring nosebleeds, especially if the bleeding temporarily stops then resumes again or bleeds for a prolonged period of time
- ❖ bleeding from the mouth and gums
- ❖ prolonged bleeding after circumcision
- ❖ severe bleeding after surgeries such as tonsillectomies or adenoidectomies
- ❖ heavy menstrual bleeding
- ❖ joint swelling and pain

Newer Epilepsy Drugs Produce Fewer Side Effects in Children

While traditional antiepileptic drugs (AEDs) have been relatively successful at controlling seizures, there have been long-standing concerns about their neurobehavioral effects as well as effects on various organ systems such as the liver and blood-forming organs. Selection of a medication should take into account such effects, as well as co-morbidities that are increasingly being appreciated among children with epilepsy, notes Raman Sankar, M.D., Ph.D., professor of pediatric neurology at Mattel Children's Hospital at UCLA. The new generation of AEDs that have received Food and Drug Administration (FDA) approval since the mid-1990s—including gabapentin, lamotrigine, topiramate, oxcarbazepine, levetiracetam and zonisamide—seem to be better tolerated by many children, he adds.

"There is a certain comfort level with the drugs that we have used for a long time, but there are some significant side effect issues that weren't discussed much when those were the only drugs we had," says Dr. Sankar. "The new class of AEDs is much less toxic and easier, in some cases, to combine."

With the advent of the new-generation AEDs, there is a much larger choice of drugs with comparable efficacy data for most seizure disorders, Dr. Sankar notes. Although data on the efficacy of AEDs for many infant and childhood epilepsy syndromes remains sparse, the wider selection makes accurate diagnosis more important than ever before, to ensure that the best possible decision can be made based on existing data. "A common cause of failure of the first AED is erroneous diagnosis," Dr. Sankar notes. "Assessing the child's risk factors and co-morbidities is a key to successful therapy." Development-sensitive factors that need to be taken into account when selecting an AED include age-specific organ toxicities, the drug's effect on

behavior and learning, and the patient's co-morbidities, Dr. Sankar adds.

Infants and children appear to be more susceptible than adults to toxic reactions that can affect their health, including negative effects on body weight, insulin sensitivity, lipid profile, and bone density. The older, enzyme-inducing AEDs—carbamazepine and phenobarbital—have been associated with significant increases in total cholesterol and LDL cholesterol levels in children. Carbamazepine has also been shown to significantly reduce the impact of the statin class of drugs used to lower

cholesterol—and phenobarbital and phenytoin may as well—Dr. Sankar adds. Certain AEDs have been found to cause weight gain and higher insulin levels; new-generation AEDs, on the other hand, appear to be either weight-neutral or to cause potentially beneficial weight loss. The older enzyme-inducing AEDs, including phenytoin and primidone as well as phenobarbital and carbamazepine, have been associated with lower bone mineral density. Systematic study of newer AEDs on bone mineral density is lacking.

The neurobehavioral effects of AEDs on children must also be considered, Dr. Sankar says. Specific AEDs can either improve or exacerbate co-morbidities such as attention deficit/hyperactivity disorder, autism spectrum disorders, depression and anxiety, and thought disorders.

"There is a certain comfort level with the drugs that we have used for a long time, but there are some significant side effect issues that weren't discussed much when those were the only drugs we had. The new class of AEDs is much less toxic and easier, in some cases, to combine."

—RAMAN SANKAR, M.D., PH.D.



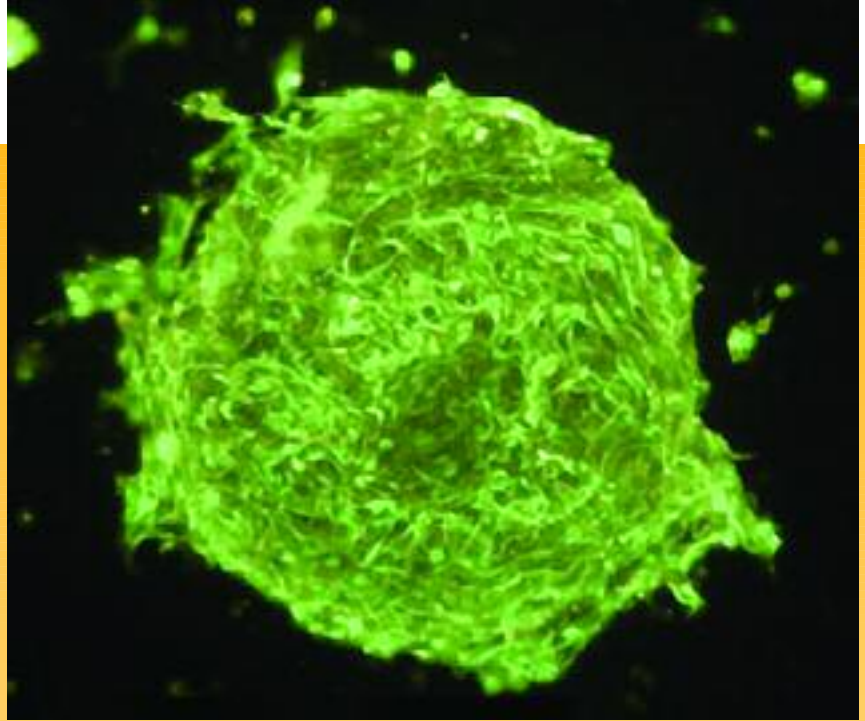
Phenobarbital is associated with increased risk of hyperactivity, impulsivity and inattention in children, and was found to result in more adverse effects on neurocognitive performance than valproic acid in a study of children with easy-to-treat epilepsy. Use of phenobarbital has also been associated with treatment-emergent depression. Topiramate has been associated with decreased verbal function. Although the cognitive effects of new-generation AEDs have not been well studied in children, data in adults indicates a strong neurocognitive profile for lamotrigine, which also appears to protect against the adverse psychiatric effects associated with topiramate and levetiracetam.

Co-morbidities to consider in selecting an AED include depression, which affects one in four adolescents with epilepsy; and disruptive, mood and anxiety disorders. The newer AEDs, particularly gabapentin, lamotrigine, and oxcarbazepine, have mood-leveling effects that can be beneficial for children with affective disorders, Dr. Sankar notes, adding that AEDs such as valproic acid and topiramate also appear to offer benefits to children with co-morbid migraine.

Dr. Sankar stresses that the new-generation AEDs are not necessarily more effective than the older ones, although for certain diagnoses they are (the best example being Lennox-Gastaut syndrome, where topiramate and lamotrigine have been shown to be most effective, and may also function very well in combination). Levetiracetam and zonisamide also appear to possess relative broad-spectrum efficacy, though there is less data in that regard, he adds. "The new-generation AEDs represent an advance because of their lower toxicity," says Dr. Sankar. "But overall, we still could use better drugs in terms of efficacy. In particular, we need drugs aimed at the developing brain to improve the efficacy and tolerability of treatment of childhood seizure disorders." ★

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Ball of brain stem cells stained with an antibody for a stem cell marker

Stem Cell Research: Potential for Treating Brain Injury and Epilepsy

Does stem cell research hold the key to future repair of pediatric brain injury? While no clinical studies are yet addressing the use of stem cells for brain injuries in children, investigators at UCLA and elsewhere are conducting basic research with potential applications. UCLA's Neural Stem Cell Research Center (<http://stemcell.crump.ucla.edu>), for example, has approximately 10 principal investigators looking into how the brain responds to injury such as stroke or trauma—and how stem cells might be used to repair such injury.

"Until a little more than a decade ago, we thought that brain and spinal cord cells were irreplaceable," says Harley Kornblum, M.D., Ph.D., the center's director. "But it has become apparent that there are stem cells that exist in the brain and spinal cord that we might be able to use to replace lost brain cells and spinal cord cells. As a result, a lot of the basic science is directed at fundamental understanding of these cells and how we can manipulate them to do the things we want them to do." Some of that research has progressed to the point where the cells are being tested in certain model systems, with promising results in certain areas such as Parkinson's disease and stroke, Dr. Kornblum says.

Researchers are optimistic about the potential use of stem cells to replace molecules missing in genetic disorders. "There are certain genetic diseases in which a key enzyme is missing in the brain," Dr. Kornblum notes. "Although it's very difficult to replace those enzymes, it's believed that we might be able to do so with stem cells." Clinical trials are being launched to address the question.

For seizure disorder, preliminary strategies are being tested in model systems that insert stem cells aimed at inhibiting seizure activity. Laboratory studies are also looking at using stem cells to replace lost cells in developmental brain injuries or disorders that cause the seizures.

Although there is much work to be done, researchers are hopeful that the developing brain will more easily be able to accept stem cells than the adult brain. "We don't know yet, but we hypothesize that the greater plasticity of the child's brain will make it more amenable to the use of stem cells from the outside being transplanted in, as well as to the mobilization of a child's own stem cells to address a problem such as brain injury," Dr. Kornblum says.

Advances in Genetics Bring New Possibilities to Pediatric Practices

“The 13-year effort to sequence the 3.2 billion base pairs of DNA in the human genome was indeed a scientific tour de force. The true challenge of genetics and genomics will be to understand the potential impact of the science on us as individuals and as members of social groups.”

— EDWARD R.B. McCABE, M.D., PH.D
co-director, UCLA Center for Society and Genetics, executive chair, UCLA Department of Pediatrics and physician-in-chief of Mattel Children’s Hospital at UCLA

The sequencing of the human genome and the wealth of information yielded about the hereditary material in our cells opens up new possibilities in pediatric practices—some clear and some controversial. When is genetic testing appropriate? Do treatments exist for detected diseases? Is the cost of a DNA test fiscally responsible?

While those and other questions will continue in medical debates, some genetic advances are already clearly impacting pediatric and family medicine practices.

Newborn Screening

California joins ranks this summer with the majority of states by mandating expanded newborn screening for 30 genetic diseases using a simple blood test. The test helps identify the one child in roughly 5,000 who may have some inherited metabolic disorder.

“With proper diagnosis, parents and physicians can often put these children on special diets or otherwise treat the condition,” notes Stephen Cederbaum, M.D., UCLA professor of psychiatry, pediatrics and human genetics, who was legislative sponsor for California’s pilot program. Undetected and untreated, these diseases can quickly prove fatal or lead to mental retardation.

Babies born in California have routinely been tested for PKU, galactosemia, primary congenital hypothyroidism and sickle cell anemia. Using tandem mass spectrometry technology on the heel-stick blood sample, scientists can now detect up to 30 more inherited conditions.

Cystic fibrosis, a recessive disease with completely normal carriers, can also be detected at the DNA level. Wayne Grody, M.D., Ph.D., director of UCLA’s Molecular Diagnostic Laboratories, has led the way in developing a nationwide screening program to identify cystic fibrosis carriers. “Some states are proposing this screen for all newborns, and I think California will soon be one of those,” Dr. Grody notes. “Currently, obstetricians and family medicine physicians should offer the test to all pregnant couples to identify those at risk; if two parents carry the mutant gene, a one in four chance exists that their child will inherit cystic fibrosis.”

Although early treatment for cystic fibrosis is not as dramatic as for metabolic diseases—and therefore screening for the condition is still controversial—Dr. Grody notes that some newborns with the disease fail to thrive and these children can be put on special diets and enzyme supplements. The current testing guidelines are similar to those used to identify Tay-Sachs carriers in pregnant couples, the only difference is that Tay-Sachs testing is aimed at a specific ethnic group (Ashkenazi Jews), while cystic fibrosis carrier screening applies universally.

“Preferably this screening—now considered standard of care—should be offered at the first prenatal visit, so that if the parents elect to have prenatal diagnosis it can be done early enough to still offer options, such as pregnancy termination, or to allow time to plan for postnatal care,” Dr. Grody explains.

UCLA is also participating in a National Institutes of Health (NIH) study to test DNA in newborns and toddlers

for the most common genetic cause of hearing loss: the gene connexin 26 (cx26), which causes approximately 50 percent of nonsyndromic autosomal recessive sensorineural deafness. The presence or absence of cx26 mutations will play an important role in determining the medical follow-up for children with hearing loss, notes Dr. Grody. He is working with Christina Palmer, Ph.D., medical geneticist and assistant professor in the UCLA Center for Neurobehavioral Genetics, to study the feasibility of a DNA test to back up the current mandated newborn hearing screening in California.

Current California guidelines dictate that a newborn needs to fail the hearing screening three consecutive times before being referred to an audiologist for diagnostic hearing tests. Ideally, these follow-up tests occur within a month, but compliance by parents is not always ideal. In the NIH pilot program, newborns and toddlers are eligible to be tested for cx26 anytime between failing the hearing screening the first time while in the hospital and being diagnosed with hearing loss. “So far about one-third of the infants have tested positive for cx26,” Dr. Grody observes.

Testing for fragile X syndrome, a mental retardation syndrome that mostly affects males, has been proposed for all pregnant women, or even school-aged children, so that special stimulation programs can be initiated early. “This screening is a bit complicated since ‘premutations’ can be detected,” Dr. Grody notes. “The accepted application currently is to test for fragile X to make a diagnosis of a symptomatic child, or test a pregnant woman if there is a family history of the disorder.”

Predictive Genetic Testing

Dominant diseases in which a 50 percent chance exists that a mutant gene will be transmitted from parent to child can be detected through DNA testing years or even decades before the first symptoms appear. “Huntington’s disease, a degenerative neurologic disorder, usually becomes evident in middle age, and rarely affects

children. In general, this would be a disease for which we would *not* offer predictive testing to a child because of ethical considerations,” Dr. Grody says. Testing for a familial breast cancer caused by a mutation in the BRCA 1 and 2 genes would also *not* be offered to girls of mothers with this disease until they are 18 years old. “Just because a test is available does not mean it is the best thing to do,” he says.

However, some dominant disorders do start in childhood and prophylactic therapies can be offered, including familial adenomatous polyposis (FAP) and multiple endocrine neoplasia (MEN2). In both these cases, children can be tested early to see if they carry the gene

diagnosis for adult-onset genetic diseases becomes more controversial, since many of these diseases may not show up for decades, and cures may actually be found in the meantime.

“Right now these are personal choices best left to the discretion of the patient, physician and DNA lab director,” Dr. Grody notes.

Genetic Counselors

“The most powerful tool available to any physician is the family history,” stresses Michelle Fox, M.S., C.G.C., UCLA genetics counselor. “By asking specific questions about your patient’s family history, valuable

UCLA is participating in a National Institutes of Health study to test DNA in newborns and toddlers for the most common genetic cause of hearing loss: the gene connexin 26 (cx26), which causes approximately 50 percent of nonsyndromic autosomal recessive sensorineural deafness. The presence or absence of cx26 mutations will play an important role in determining the medical follow-up for children with hearing loss.

and then watched carefully or have a prophylactic colectomy (to prevent colon cancer) or thyroidectomy (to prevent thyroid cancer), if necessary. Conversely, if the mutant gene is not present, the child can be spared unnecessary colonoscopies and surgery.

Prenatal Diagnosis

Choices for prenatal diagnoses are expanding. Down’s syndrome can be picked up in the first trimester by routine ultrasound examination based on nuchal skin fold thickness, Dr. Cederbaum notes.

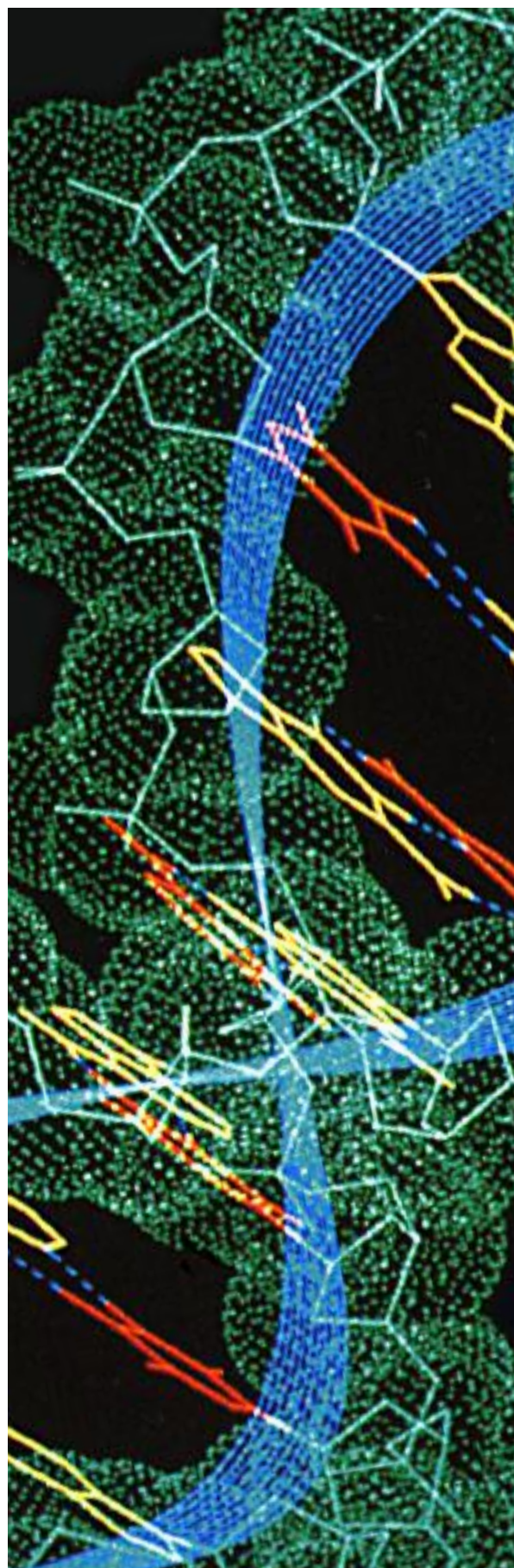
Prenatal testing for cystic fibrosis should be offered to couples at risk since amniocentesis or CVS can test DNA for inherited mutations. Offering prenatal

information can be gathered and specific testing recommendations can be made. If the physician does uncover a pattern of retinal disease, heart disease, cancer or developmental problems, a primary physician may discuss options for testing, refer to a geneticist, or suggest speaking to a genetic counselor.” ★

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June Myers

Design

The Doyle/Logan Company

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Theodore Moore, M.D.

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Inquiries about *UCLA Pediatric Update* should be directed to UCLA Medical Center, Marketing Communications, 10920 Wilshire Blvd., Suite 1010, Los Angeles, California 90095-6923.

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