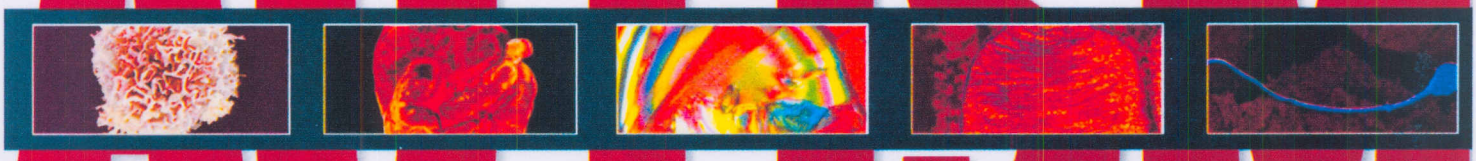
UNMASKING AUTISM



One of these **5** speculative yet provocative theories may expose the hidden culprit behind the debilitating disorder.

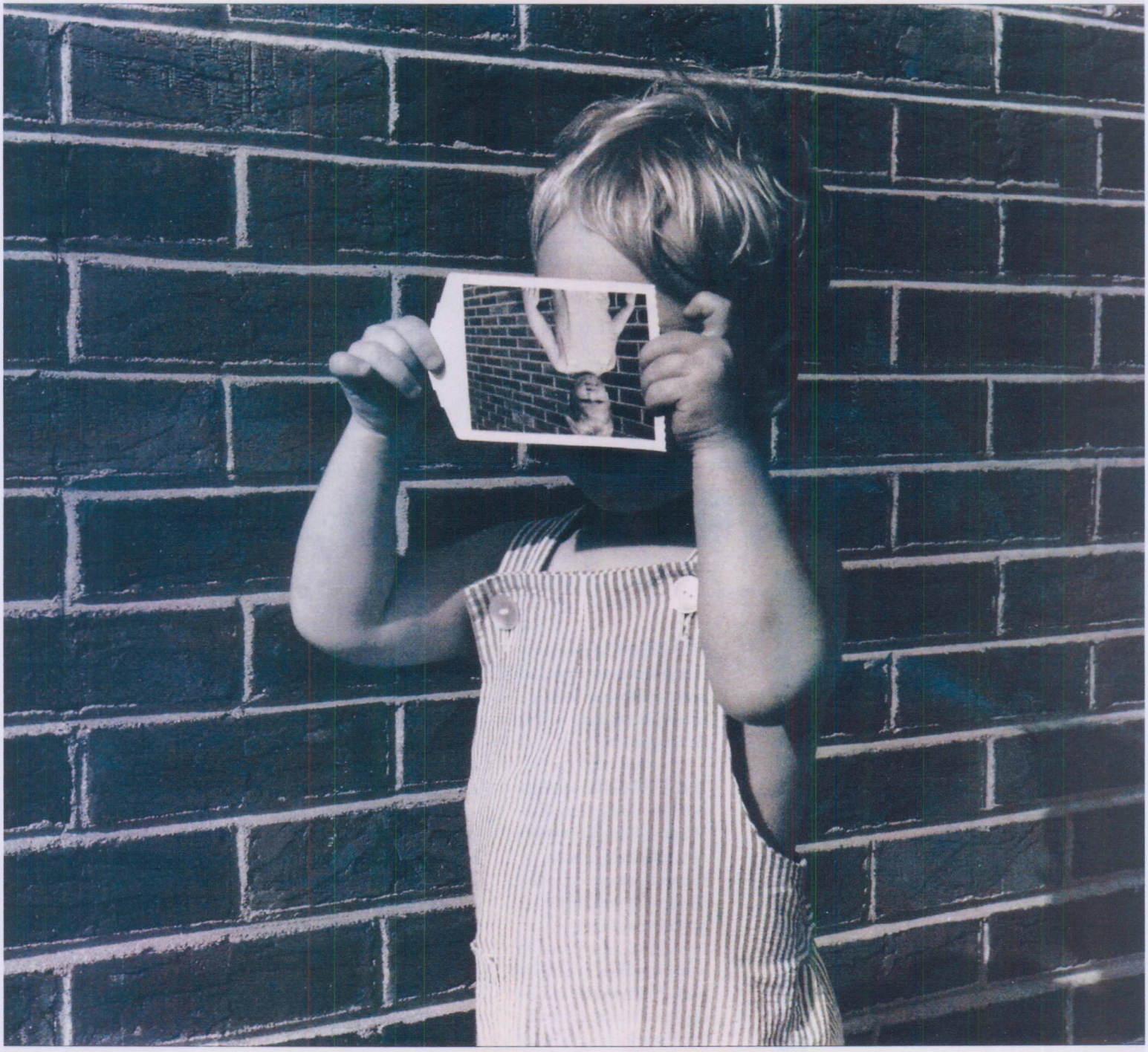
BY ADAM HADHAZY

NO PARENT WANTS TO HEAR THAT A CHILD IS SICK, but autism is a particularly difficult diagnosis to confront. Many autistic children seem perfectly normal until about 18 months, when they suddenly and drastically regress. Babies who smiled and looked their parents in the eye become distant, emotionally detached toddlers, unable to speak or listen. Many improve with medication and therapy, but autism remains a lifelong challenge. And the reported incidence keeps rising: One of every 110 children born in the United States now ends up with this mental disorder.

Perhaps because it is so mystifying, autism attracts flaky explanations. In the 1960s, many doctors blamed cold, remote "refrigerator mothers" and bad parenting; during the last decade, parents and some doctors pointed to childhood vaccines, another well-discredited idea. Parents desperate for solutions have exposed their children to fringe treatments like chelation therapy, which have not been shown to work and can even be harmful.

Science has not done much to dispel the clouds, despite decades of research and hundreds of millions of dollars in funding. In July a study of fraternal and identical twins in the journal *Archives of General Psychology* reaffirmed the conventional wisdom that both genes and environmental influences must be involved in autism, but scientists struggle to put details on that broad generalization. No one gene or set of genes has emerged as the culprit, and studies of possible toxins such as pesticides, medicines, and household chemicals have gone nowhere.

Given this stalemate, it might be time to take a second look at the unconventional wisdom—controversial but scientifically



plausible ideas that point to everything from the immune system to viruses to an overload of hormones. Many of these provocative theories shine a spotlight on the biological processes that wreak havoc on the fragile developing brain. If one of these theories pans out, it would not be the first time in medical research that a cure came from far outside the mainstream.

There is some precedent. Doctors laughed at the idea that stomach bacteria could cause ulcers until Australian microbiologist Barry Marshall gave himself one in 1984 by downing a petri dish of bacteria—and then cured it with antibiotics. Even if none of these ideas turns out to be right, they may provide clues that ultimately lead to life-changing treatments.

Antibodies made by lymphocytes (right) may attack microbes, but they can also target healthy fetal tissue.

1

Attack of the Antibodies

THE IDEA The mother's immune system invades and attacks her fetus's brain, disrupting neurodevelopment.

THE EVIDENCE Immunologist Judy Van de Water of the University of California, Davis, found immune cells that recognize fetal brain proteins as foreign invaders in the blood of some mothers of autistic kids. "When the mothers have these antibodies, they have kids with autism," she says. For a follow-up study, still under way, Van de Water has identified pregnant women with these antibodies—and so far every one of them has given birth to a child later diagnosed with autism. Animal studies also support her theory: Monkeys and mice exposed to these human maternal antibodies had babies that developed behaviors resembling those of autism.

THE FLAWS Only 18 percent of autistic children have mothers with these antibodies, so even if Van de Water is right, the finding does not explain four out of every five autism cases. She also needs to figure out how the immune cells could wreak havoc in the fetal brain and cause the neurological symptoms associated with autism. "The big hole right now," Van de Water admits, "is determining whether these antibodies are truly pathologic."

POSSIBLE PAYOFF If antibodies are to blame, a quick blood test could identify mothers at high risk. Drugs could then knock out the antibodies during pregnancy.

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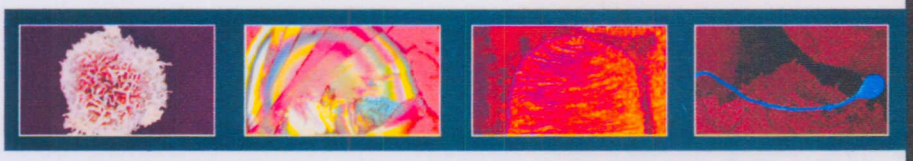


The gut harbors mysterious microbes, including some that could cause neural problems.

THE IDEA Gut bacteria secrete poisons that interfere with digestion and brain development.

THE EVIDENCE Many autistic children have gastrointestinal problems like diarrhea and constipation in addition to neurological symptoms. Gut bacteria could explain both types of illness. "Just because autism ends up in the brain doesn't mean it starts in the brain," says Jeremy Nicholson, head of the department of surgery and cancer at Imperial College London. In 2002 a team of American and British researchers identified a distinct population of bacteria in the guts of autistic children. More recently, Nicholson's group found that the urine of autistic children has a unique chemical signature related to those abnormal intestinal germs. Another finding: a much higher than normal concentration of *Clostridium* bacteria. The microbe is known to cause diarrhea and intense abdominal pain, but recently Derrick MacFabe at the University of Western Ontario found that its products can also affect the brain. Injecting propionic acid, a chemical secreted by *Clostridium,* into the brains of rats caused symptoms such as frenetic, repetitive, and antisocial behavior, reminiscent of autism.

THE FLAWS Many autistic children show signs of the disorder before their first birthday, yet the numbers and types of gut bacteria usually remain in flux until age 2, when a permanent population establishes residence. "The cases in which children are autistic from birth clearly do not have to do with gut microbes," Nicholson says. Many studies also point to a strong genetic component in autism, which gut microbes could not explain. Even if he is right, Nicholson warns that it will take years to identify the specific bacteria and neurotoxins responsible: The human gut contains hundreds of species of microbes that produce hundreds of thousands of chemicals.

POSSIBLE PAYOFF Doctors could be more conservative in their use of antibiotics, which can wipe out beneficial gut bacteria and leave kids vulnerable to colonization by malevolent bugs. Next-generation versions of Nicholson's recent urine study might offer a simple test for early signs of autism.

2 Neurotoxic Gut Invaders

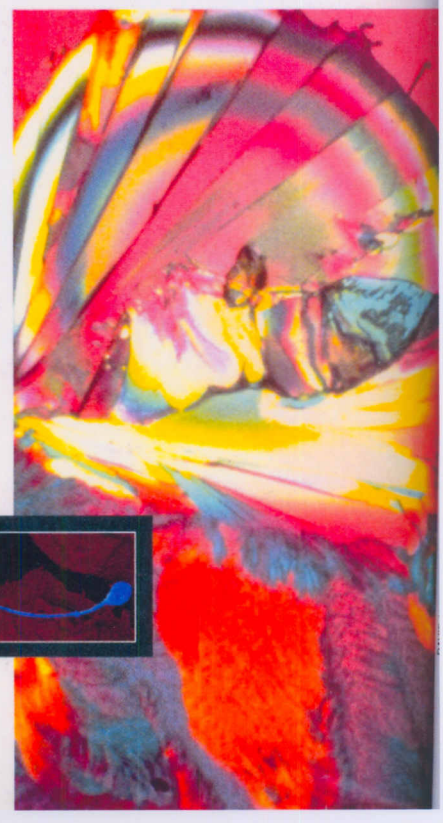
3 Hormones on the Brain

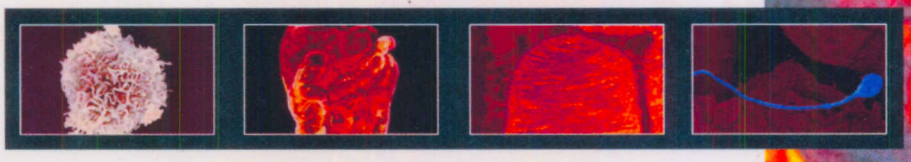
THE IDEA Excessive testosterone in the womb causes an "extreme male brain" that overamplifies typically male mental abilities.

THE EVIDENCE Boys are four times as likely as girls to develop autism, and the neurological symptoms of the disorder fit the profile of a mind skewed too far into maleness. According to Simon Baron-Cohen, director of the Autism Research Centre at the University of Cambridge, on average men are better than women at finding detail and worse at reading emotional states and detecting faux pas. These characteristics are extreme in autistics, who tend to focus on narrow interests and struggle with social relationships. In 2009 Baron-Cohen reported that fetuses with higher-than-normal testosterone levels in the womb tended years later to score lower on tests of social communication, just as autistic children do. Recent genetic studies also dovetail with Baron-Cohen's theory. Extra testosterone suppresses a gene called *RORA,* which makes proteins critical for neurodevelopment; autistic brains contain markedly less *RORA* proteins than usual.

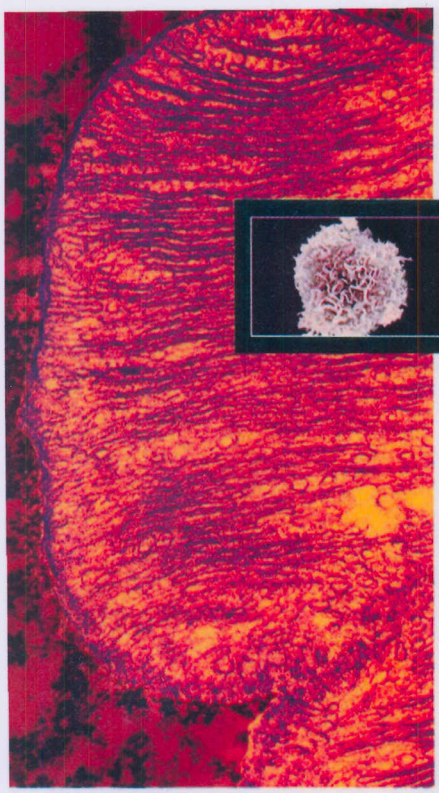
THE FLAWS Other developmental problems, from dyslexia to attention-deficit hyperactivity disorder, also seem to affect boys more than girls. "It's an open question whether male bias is special to autism or just a general point of vulnerability," says Yale Child Study Center director Fred Volkmar, who has followed Baron-Cohen's work. A direct link between high fetal testosterone and autism has never been shown, but that could soon change. Baron-Cohen is studying tens of thousands of frozen samples of amniotic fluid from Danish mothers to see if fetal testosterone correlates with autism diagnoses later in life. "This will be the strongest test," Baron-Cohen says of the study, which is due out by year's end. "But we still have quite a long way to go before we know how the autistic brain may be related to typical sex differences."

POSSIBLE PAYOFF Tinkering with testosterone in a developing fetus is potentially dangerous—the hormone shapes male genitals as well as brains. But a test for high testosterone could serve as a warning sign.





Testosterone crystal (far right), magnified 130 times. The hormone shapes the fetal brain.



Mitochondria, magnified by 110,000. These are the cells' crucial energy generators.

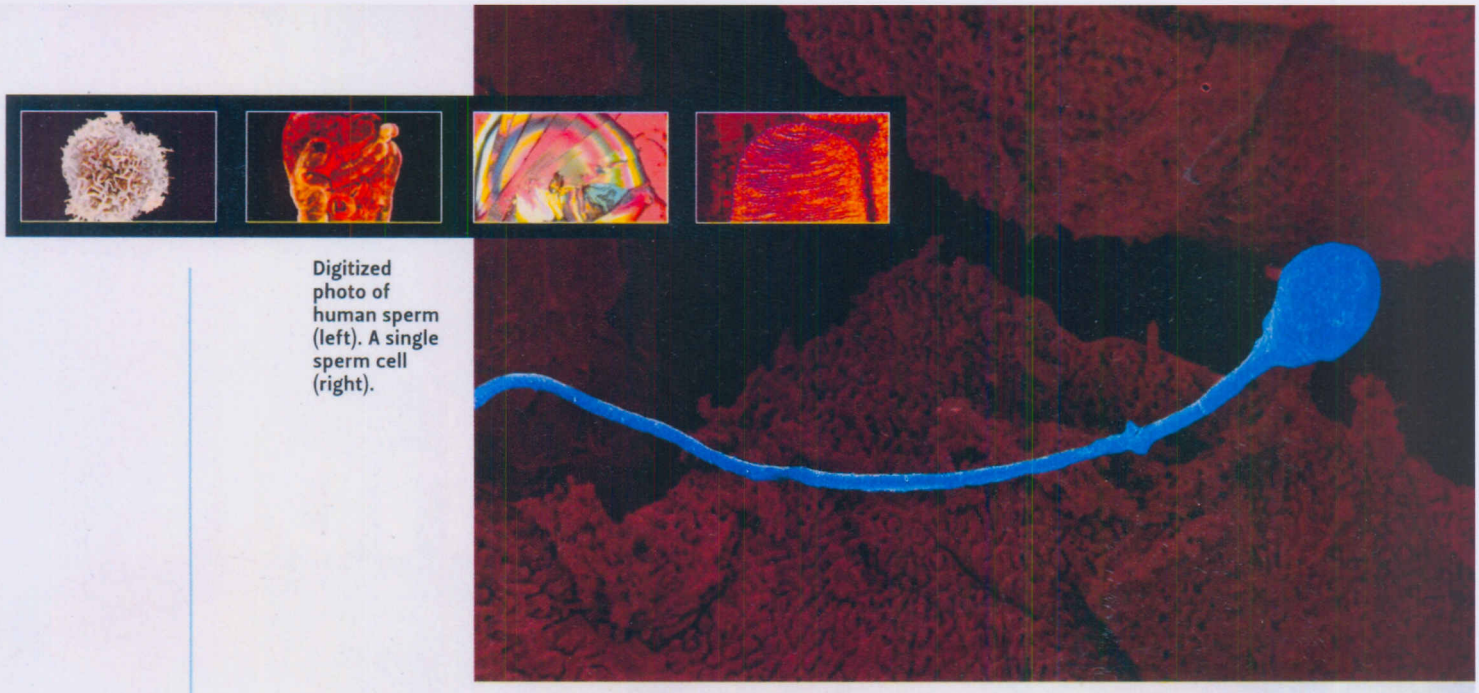
4 Power Failure

THE IDEA The developing brain is starved for energy because of sickly mitochondria, the tiny power stations of our cells.

THE EVIDENCE Although only 5 percent of autistic children are diagnosed with a disease of the mitochondria, a study published last year in the *Journal of the American Medical Association* found that up to 80 percent could have defects in the vital cellular power plants that convert sugar and oxygen into useful energy. Researchers like Richard Frye think it is worth examining how a cellular brownout might hamper neurological development. "During the early years of life, the brain is making connections, molding itself and changing, all at the same time," says Frye, who leads the Medically-Based Autism Clinic and the Laboratory for the Biological Basis of Neurodevelopmental Disorders at the University of Texas. "If you do not have the energy to do that, you're going to stall." Mitochondria are essential for neuronal communication and metabolism, so the theory might explain why autistic patients often suffer from seizures and fatigue. "The symptoms we see in children with autism are right along the lines of what we would expect in kids with mitochondrial disease," Frye says.

THE FLAWS Many children who have a diagnosed mitochondrial disorder are not autistic. As a result, some researchers believe mitochondrial dysfunction is a symptom of autism rather than a cause, a case of cells' getting overtaxed in responding to the body's snowballing metabolic and neurological problems. The mitochondria may be "trying to compensate to keep something worse from happening," Frye says.

POSSIBLE PAYOFF Proving the link might not provide much relief, since there are no treatments to repair defective mitochondria, but Frye says that researchers are investigating drugs that could prod cells to produce new, healthy mitochondria and ditch the weaklings.



Digitized photo of human sperm (left). A single sperm cell (right).

5 The Bad Seed

THE IDEA A virus hidden in sperm infects the embryo at conception, stunting fetal development.

THE EVIDENCE Maybe the genes for autism are hard to find because they are viral, not human, suggests neuroscientist Antonio Persico of Campus Bio-Medico University in Rome. A virus that infects a fetus right at the start would explain researchers' inability to locate causative genes in human DNA even though, about 90 percent of the time, if one identical twin has autism, so does the other. In a small study of postmortem brain tissue last year, Persico's group found that autistic subjects' brains were three times as likely as those of healthy individuals to harbor a microbe called a polyomavirus. Although scientists do not think this virus can cross into the placenta from the mother's bloodstream and infect the fetus, previous studies provide evidence that viruses can hitch rides with sperm. Persico recently began a study analyzing the virus-shuttling potential of sperm. Early results suggest that the fathers of autistic children are more likely to have polyomavirus-infected sperm than fathers of healthy kids.

THE FLAWS Just because a virus infects an embryo does not mean it causes an illness. Polyomaviruses are linked to respiratory distress and tumors, but researchers have never found connections to anything remotely like autism. In other words, Persico has a lot to prove before his theory gets serious attention.

POSSIBLE PAYOFF The idea of autism as an infectious disease sounds promising, since it seems to imply it might be curable. Unfortunately, viruses can be difficult to thwart. The few antiviral medications on the market, for major diseases such as flu, herpes, and HIV, took years to develop. But if autism is a response to the germ, doctors might be able to treat it by stifling the effects of the body's immune response, Persico suggests—just as cold medicine helps a sore throat and stuffy nose without actually killing the bug. "I know that parents of autistic children are desperate for a treatment," he says, echoing other autism pioneers. "All of this is pretty far down the line, but I think this has a reasonable shot."

DR. GARY GAUGLER/VISUALS UNLIMITED, OPPOSITE: MEHAU KULYK/PHOTO RESEARCHERS