

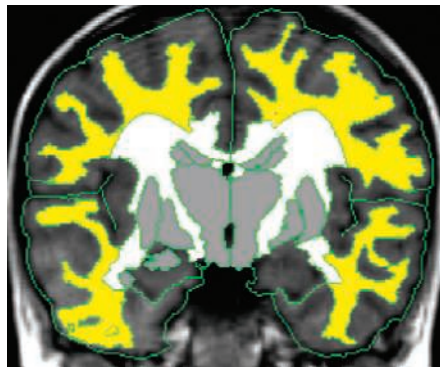
long ones, perhaps accounting for the disproportionate increase in white matter relative to gray matter in autistic brains.

And in unpublished findings from seven autistic and seven control brains, Casanova and Christoph Schmitz of the University of Maastricht in the Netherlands and their colleagues found that the autistic brains also had smaller cells in their minicolumns. Smaller cells carry shorter axons, bolstering the hypothesis that autism results from too many short-range connections and not enough long ones.

Even if a neuronal imbalance is to blame, no one knows how it arises. Courchesne and others hypothesize that it might result from a problem in the pruning, or elimination, of neurons and synapses early in life. Work from Courchesne's lab from 2003 suggests that most of the abnormal brain growth in autism occurs from birth to age 3. This may leave an unruly excess of neurons and circuitry in certain brain regions.

More questions than answers

Despite the converging evidence, not everyone is convinced that faulty connections lie at



Not too deep. Autistic brains contain an excess of surface white matter (yellow), which contains relatively short neuronal fibers, but do not show an enlargement of deeper white matter (white), where the longest fibers reside.

the heart of autism. Geraldine Dawson, an autism researcher at the University of Washington, Seattle, suggests that connectivity problems in autism might be an effect—rather than a cause—of an earlier dysfunction in the brain, such as a defect in brain systems that govern social reward and affect an infant's attention to faces and speech. Such a

defect, Dawson says, “will influence the development of speech and face perception, which ultimately will affect the development of the complex, integrated brain circuitry that underlies language and social development.”

Even if connectivity problems are at the root of autism, the theory needs fleshing out. Abnormalities in brain connectivity have also shown up in attention deficit hyperactivity disorder (ADHD), schizophrenia, and dyslexia. To get to the heart of autism, researchers now need to pinpoint which particular white matter—or gray matter—abnormalities are the problem in autism versus, say, dyslexia or ADHD, skeptics point out.


Even so, proponents argue that the theory at least points researchers in the right direction. “It's a much more valid way of looking at impairments in autism. It's where the field of autism has to go,” Müller says. And no matter where connectivity theory leads, the autism field is energized by the concept. Says Courchesne: “People smell something really exciting. They are seeing that there is a very interesting, if complex, story emerging.”

—INGRID WICKELGREN

Pharmacogenomics

Going From Genome to Pill

A new medicine for African Americans with heart failure hints at what the drug industry sees as the enormous payoff from pharmacogenomics



Last week an advisory panel to the U.S. Food and Drug Administration (FDA) took an unprecedented step in recommending approval of a drug for a single racial group. The drug, a combination pill called BiDil that contains two heart-failure medications, had failed to help patients in the general population live longer. But in a clinical trial last year, BiDil decreased the risk of death among African Americans by 43%. That was sufficient evidence to convince the panel that BiDil should be approved to treat African-American patients with heart failure. FDA was widely expected to follow the recommendation this week.

By backing BiDil, the FDA panel gave another push to pharmacogenomics, an approach that promises to revolutionize both drug discovery and patient care. African Americans have a higher likelihood of developing hypertension and other condi-

tions related to heart failure. However, whether that's due to genes, the environment, or some complex interplay isn't yet known. Still, BiDil represents the latest example of the industry's push to target drugs to subgroups of patients who, based largely on their genetic makeup, are most likely to benefit (*Science*, 24 October 2003, p. 594). In recent months studies have shown potential benefits of medicines targeted to patients with specific genotypes for treating cancer and heart disease. Other studies have helped doctors properly dose a wide variety of compounds already on the market. “I think that the use of pharmacogenomics will have a profound effect,” says Gary Peltz, head of genetics and genomics research at Roche's Palo Alto, California, lab. “It hasn't hit yet. [But] we're clearly on the road.”

To date, pharmacogenomic therapies represent a trifling portion of pharmaceutical sales, some \$3.65 billion in a \$550 billion market. That won't change unless scientists overcome an array of challenges, from untangling the genetics behind complex diseases such as diabetes to altering

practices that could disqualify patients for health insurance based on their genes. There are also concerns that approval of drugs based on race, a sociological trait, will increase racial stereotypes and bolster the discredited notion that there are fundamental genetic differences between races. But those problems, say drug industry officials, pale in comparison to the projected benefits to patients—and to the industry. “Every major pharmaceutical company is reorganizing or has reorganized their clinical paradigm” to test drugs in conjunction with tracking genes or other molecular markers of disease, says Ronald Salerno, who directs regulatory affairs for Wyeth Pharmaceuticals in Collegeville, Pennsylvania. “This is the way drugs will be developed in the future.”

Improving the odds

Although pharmacogenomics only recently entered the lexicon, the notion of treating populations based on the genes involved in health and disease dates from the 1950s. That's when researchers caught an initial glimpse that the speed at which different people metabolized drugs in their system was linked to genetics. But it took another 40 years to progress from those hints to medicines. In 1997, Genentech's Herceptin was approved to fight a form of breast cancer in which cancer cells overexpressed a protein

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