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They occur naturally in fish, flaxseed, canola oil, nuts and avocados. They're also extracted, packaged and sold in dozens of dietary supplements. Increasingly, they even show up on grocery shelves as the latest fortification in such popular fare as bread, eggs, dairy products, margarine, baby food and cereal.

Omega-3 fatty acids are already prized by cardiologists for protecting the heart against the inflammation that can lead to blocked arteries and for thwarting an irregular, often fatal, heartbeat. There's growing evidence that these polyunsaturated fats may also be helpful in preventing complications of diabetes and in soothing the inflamed joints of arthritis.

Now psychiatrists are also taking a closer look. Omega-3s, dubbed the "happy" fats in some quarters, are under investigation for treating depression, bipolar disease, attention-deficit hyperactivity disorder, alcoholism, Alzheimer's disease and even the so-called baby blues, or postpartum depression. Earlier this year, the American Psychiatric Association formed a committee to review the findings to make treatment recommendations for the use of omega 3s.

What makes this emerging science particularly intriguing is that the evidence for the fats' various benefits comes from several types of research: population studies, clinical trials and basic neurochemistry.

"Not only are the data consistent in those areas, but they are very robust," says Joseph R. Hibbeln, chief of the outpatient clinic at the Laboratory of Membrane Biochemistry and Biophysics at the National Institute of Alcohol Abuse and Alcoholism (NIAAA) in Bethesda.

And since there are few if any side effects to eating foods rich in omega-3 fatty acids, there's little downside to investigating these healthy fats—and a lot to be gained. Fish, and even fish oil dietary supplements, are far cheaper than most prescription medications. Plus, there's the hope that omega-3s may help bridge the treatment gap in mental disorders—up to 30 percent of people being treated for depression, for example, find drugs inadequate in controlling their symptoms.

"The main problem we have with depression is that we do not have treatment that [dependably] provides complete recovery," says David Kupfer, head of psychiatry at the University of Pittsburgh's Western Psychiatric Institute and Clinic. "We're still leaving people mildly depressed or unable to function well. It's like trying to make the last 10 yards when you're in field goal range. The same drug is not going to do it. It has to be some sort of adjunctive treatment. Whether that will come from omega-3s, St. John's wort or some other nutritional thing, we just don't know yet."

The idea that omega-3 fatty acids might help treat mental disorders dawned on Hibbeln in 1984 when he was standing in an anatomy lab. “I had cut open the brain, and it just very much struck me that it is mostly fat,” he says. “The biochemistry of fat and lipids just seemed to be very unexplored in psychiatric disorders and that seemed odd because there are many profound neurological disorders that are known to be caused by lipid problems.”

It’s well recognized, for example, that multiple sclerosis damages the fatty myelin sheaths of nerve cells. Another neurological disorder, Gaucher’s disease, results from the buildup of harmful fatty substances in cells, and a whole class of neurological disorders called leukodystrophies are caused by flawed development or maintenance of the fatty myelin in nerve cells.

The brain itself, is, in fact, about 60 percent fat, giving new meaning to the term fathead. But unlike other adipose tissue throughout the body, the brain’s fat is diverse, “as diverse as proteins in the body,” notes Hibbeln.

Essential fatty acids are fats that can’t be produced by the body but are required for good health. They play key roles in the structure of brain cells and of the eye, particularly the retina. They’re vital for each neuron’s membrane, both its outer protection and its means of accessing key nutrients. And it is these essential fats that regulate the growth of long tendrils called axons that enable neurons to communicate with each other.

Oddly enough, while the body can manufacture saturated fat, cholesterol and even some unsaturated fat—it is incapable of producing two of the fatty acids that are most vital. One is an omega-3 fatty acid called alpha linolenic acid, which is found in fish, canola oil and flaxseed. The other is an omega-6 fatty acid with the maddeningly similar name of linoleic acid, which is found in soybean, safflower and corn oils, as well as in meat, poultry, fish and such popular fare as processed foods. Omega-3s and omega-6s are close enough in chemical structure to be able to compete for the same molecular machinery that allows entry into the brain. (Omega-3 fatty acid molecules have three carbon atoms on one end; omega-6 fatty acids have six.)

That fact might simply still be a little quirk of nature had not a huge shift occurred in diets during the past century. In 1909, Americans got most of their fat from free-range animals, which have higher levels of omega-3s than the chicken, beef and pork commonly eaten today. They also consumed about 0.02 pounds per year of soybean oil—a number that increased gradually until about 1960, when “soybean oil took over the U.S. food chain,” says William Lands, a retired biochemist with NIAAA. “It was like a tsunami.”

By 1999, soybean oil—a major ingredient in crackers, bread, salad dressings, baked goods and processed food of all sorts—accounted for 20 percent of total calories consumed in the United States, according to the U.S. Department of Agriculture. Per capita consumption reached 25 pounds per year. “That means that there has been an 1,000-fold increase in [consumption of] omega-6 fatty acids” over 100 years, Hibbeln says. “So we have literally changed the composition of people’s bodies and their brains. A very interesting question, which we don’t know the answer to yet, is to what degree the dietary change has changed overall behavior in our society.”

Flooding brains and bodies with a diet rich in omega-6 fatty acids theoretically could give an unfair advantage to these molecules, allowing them to block omega-3s from getting inside cells and replenishing stores in the brain and elsewhere in the body.

Intrigued by this possibility, Hibbeln charted fish consumption worldwide and compared those figures to rates of depression. In a paper published in 1998 in *The Lancet*, he showed that nations with the highest fish consumption—Japan, Taiwan and Korea—also had the lowest rates of depression. Nations with the lowest fish consumption—New Zealand, Canada, West Germany, France and the United States—had the highest rates of depression. “It becomes an interesting picture across countries,” Hibbeln says.

Next, he took a look at homicide, suicide and aggression rates and compared them to seafood consumption. Similar patterns emerged. Using World Health Organization statistics, for example, Hibbeln found that men living in land-locked Hungary, Bulgaria and Austria had the lowest fish consumption and the highest rates of suicide, while their counterparts in Japan, Portugal, Hong Kong, Korea and Norway ate the most fish and had the lowest rates of suicide. Men living in the United States, Canada, Italy, Australia and Sweden fell between the two extremes on both seafood consumption and suicide rates.

Since then, Hibbeln has examined patterns of postpartum depression, which provides a particularly interesting window of opportunity for studying the psychological aspects of omega-3 fatty acids. That’s because during pregnancy, mothers are the sole source of an omega-3 fatty acid known as docosahexaenoic acid (DHA) to the fetus. So key is this substance to fetal brain development that the mother’s stores are depleted if she doesn’t consume enough DHA in her diet. In a 2002 study published in the *Journal of Affective Disorders*, Hibbeln reported that “rates of postpartum depression are 50 times higher in countries where women don’t eat fish,” he says.

Of course, results from such population studies—known as epidemiology—can at best show only associations and trends, not cause and effect or a biological mechanism. To nail down any new scientific theory requires both basic science and clinical trials.

## **A Hard Sell**

As director of the psychopharmacology research lab at McLean Hospital near Boston, psychiatrist Andrew Stoll often gets the most difficult patients to treat, the ones for whom standard therapy has failed.

In the late 1990s, research had already shown that depressed people seem to have lower levels of DHA in their brains than healthy people. Studies by Hussein Manji at the National Institute of Mental Health also found that people who respond well to antidepressants have neurons that exhibit greater plasticity, meaning that they are more receptive to changes that help them grow. Other laboratory work suggested that omega-3 fatty acids could help neurons be more plastic.

Stoll put all these elements together in a study of 30 people suffering from bipolar disorder, also known as manic depression. During the four-month study, which was published in 1999 in the *Archives of General Psychiatry*, he randomly assigned participants to receive either fish oil capsules containing omega-3 fatty acids along with their standard treatment or a placebo of olive oil plus the standard treatment. The study found that the omega-3s significantly lengthened the period of remission for those who received them.

Since then, a handful of other small, short-term studies have also found benefits to omega-3s. In England, Malcolm Peet and his colleagues at the Swallownest Court Hospital in Sheffield gave another type of omega-3 -- eicosapentaenoic acid (EPA) -- in varying doses to people with ongoing depression that was not well controlled with antidepressants. Peet found in this 12-week study that one gram per day of EPA was significantly better than placebo in improving mood. (Both groups also received standard antidepressant medication.) Other studies found that omega-3s were helpful in controlling postpartum depression, impulsivity and even antisocial behavior in prisoners.

To Stoll and other proponents of the benefits of omega-3 fatty acids in treating mental disorders, the results have been a kind of vindication. "We were laughed at five years ago and teased by our colleagues," says Stoll, an associate professor of psychiatry at Harvard Medical School. "Now this is in textbooks."

But the story is still unfolding. Exactly how omega-3s may work is not yet known. Scientists know that these fats break down into EPA and DHA in the body, while omega-6 fatty acids break down to a substance called arachidonic acid. Nothing is static in the body. So these products just continue a cascade of other biochemical reactions that produce more substances—chemicals that act like a thermostat to raise and lower production of other key substances that in turn control blood clot formation, immune responses, bone health, smooth muscles and so on and so on.

Which dosages of omega-3s may be most effective is also not certain, "although it's probably going to be in the range of one to three grams per day," says Marlene Freeman, director of the Women's Mental Health Program at the University of Arizona Health Science Center in Tucson and lead investigator of two studies examining the use of omega-3s in pregnant women at high risk for postpartum depression. "It's all kind of theoretical, but then we don't truly know how antidepressants work, either."

Nor are omega-3s a panacea for mental disorders. In schizophrenia, for instance, there have been two studies showing benefit and one showing no effect. Studies of DHA "didn't do anything for people with attention-deficit disorder," Stoll notes. "But no one has tested EPA yet, and there's lots of evidence that kids with ADD are deficient in EPA."

Alcoholism is known to deplete the brain of omega-3 fatty acids. But whether supplementation might help reverse some of the ill effects is also not yet known. Omega-3s are also under investigation for treating Parkinson's and Alzheimer's diseases.

And at least one trial, published earlier this year in the *American Journal of Psychiatry* by researchers at Baylor College of Medicine, found no significant effect of adding DHA to treatment for major depression.

Such findings explain why plenty of people—even experts in the field—are cautious about overbilling the benefits of omega-3 fatty acids.

“The biggest risk is for someone to try to treat themselves with these over the counter when what they really need is an evaluation,” says Freeman. “It scares me a little to have this in the media.”

A National Academy of Sciences panel spent months reviewing the scientific literature on omega-3 fatty acids and other fats in the diet and concluded that there was not enough evidence to set a recommended dietary allowance.

“Is the evidence strong enough to use [omega-3s] for depression?” asks Alice H. Lichtenstein, professor of nutrition at Tufts University “It’s sufficient evidence to do human trials, but not to make dietary recommendations.”

In the meantime, research continues to point to the cardiovascular benefits of eating a diet rich in omega-3 fatty acids. Some of the latest findings, published earlier this month in the journal *Circulation*, found that men who ate at least two servings of fish per week had lower heart rates, meaning their hearts beat were stronger and more efficient, beating fewer times per minute than men who ate fish less than once per week. And the twice-weekly fish eaters also had a significantly reduced risk of heart disease compared with those who ate fish less than once per week.

Some of the omega-3 researchers are so convinced of the benefits of these essential fats that they are making sure their families eat foods rich in them.

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