Research Resources Reporter

May 1985, Vol. IX, No. 5

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Serving the Division of Research Resources in Animal Resources, Biomedical Research Technology, General Clinical Research Centers, Minority Biomedical Research Support and Biomedical Research Support

This Issue:

by
Margaret Patlak

Research Indicates That Some Fats May Reduce Heart Disease and Insure Good Vision

The principal building blocks of fish fats—omega-3 fatty acids—have a number of health-enhancing properties, according to scientists at Oregon Health Sciences University in Portland, Oregon.

Dr. William Connor and his colleagues have discovered that these fatty acids, which are also prevalent in green leafy vegetables, may help prevent hardening of the arteries and heart attacks. They are also essential for good vision and may be important for normal brain development.

"We think these fatty acids are precious to the body and, unlike nonessential fatty acids, are used for many purposes besides the production of energy," says Dr. Connor, professor of medicine at Oregon Health Sciences University. Because the body cannot synthesize omega-3 fatty acids, he adds,

Fish are major sources of omega-3 fatty acids—compounds which have a number of health enhancing properties, according to scientists at the Oregon Health Sciences University in Portland, Oregon.

Photo courtesy of Giant Foods, Inc.

HEART DISEASE *continued*

they must be acquired from the diet.

Animal tests by Dr. Connor and Dr. Martha Neuringer indicate that omega-3 fatty acids affect the ability of cells in the retina to be stimulated and that deficiency of these fatty acids can reduce sharpness of vision. The possibility that there are similar effects on the stimulation of brain cells involved in learning and behavior is being tested.

In clinical studies the Oregon researchers showed that the omega-3 fatty acids may help prevent hardening of the arteries by lowering blood levels of cholesterol and triglycerides. They may also retard the formation of platelet blood clots, which frequently occur in atherosclerotic arteries and may cause heart attacks.

Omega-3 fatty acids comprise a group of highly polyunsaturated and very long-chain fatty acids that are prevalent in all marine fish and seafood, Dr. Connor explains. They are found in particularly high concentrations in salmon and mackerel, which have a lot of fat. The compounds are also prevalent in green leafy vegetables such as spinach, kale, and romaine lettuce, and a few vegetable oils like soybean. Omega-3 fatty acids are scarce in corn and safflower oils and in butter.

Studies recently completed at the Oregon Regional Primate Research Center in Beaverton show that a lack of omega-3 fatty acids during gestation and early life can impair the development of vision. Drs. Connor and Neuringer fed female monkeys a diet deficient in omega-3 fatty acids for 2 months prior to and during their pregnancies. Infants born to the monkeys were then fed the deficient diet for almost 2 years.

The infants' sharpness of vision was tested with a method based on the tendency of infant monkeys to gaze at patterns. The same method has been used to test the vision of human infants. In the tests, the infants were shown pairs of cards on a gray background. One card in each pair was covered with black and white stripes. The other card in the pair was solid gray like the background. The monkeys tended to look at the striped cards as long as the stripes were visible to them. When the stripes were too small to see, they appeared gray and did not attract the monkeys' attention. By varying the width of the stripes and observing the infants' reactions, the researchers were able to measure the sharpness of vision. The response to visual stimuli was also measured with electrodes attached to the monkeys' scalps that recorded the electrical activity of the visual centers in the brain and with special contact lenses that recorded the electrical responses of the retina.

At 12 weeks of age the sharpness of vision of the monkeys fed the deficient diet was only half that of monkeys fed a normal diet. In addition, the electrical response of the retina was slow to recover in the deficient monkeys after a flash of light. An analysis of fat content in the retina and brain cells of some animals receiving the deficient diet showed very low levels of omega-3 fatty acids. These compounds also were barely detectable in the monkeys' blood, and their liver, skin, and fat cells showed only 5 to 20 percent as much omega-3 fatty acids as did the tissues from control animals.

"The lack of omega-3 fatty acids in the retina and brain cells probably explains the monkey's loss of sharp vision," Dr. Connor says. Omega-3 fatty acids render cell membranes more fluid, possibly enabling the cells to react more quickly to electrical or chemical signals, he explains. These fatty acids are particularly concentrated in the membranes of photoreceptor cells in the retina and in the membranes of nerve synapses, where nerve impulses are conveyed from one neuron to the next.

Dr. Connor notes that other types of fatty acids replaced the omega-3 compounds in the cell membranes of the monkeys fed the deficient diet. These replacements, however, apparently hampered some of the reactions that occur within or on the membrane surface.

Because omega-3 fatty acids are prevalent in the cerebral cortex of the brain, Dr. Connor believes a nutritional deficiency of the omega-3 compounds might impair intellectual functions such as the ability to learn and reason, as well as overall intelligence. Other researchers have shown that rats fed a diet deficient in omega-3 fatty acids did not learn to run a maze as well as rats fed a control diet. Preliminary observations, by the Oregon scientists, of the monkeys deficient in omega-3 fatty acids indicate no impairment of the animals' learning ability. But the researchers plan to use more finely tuned tests of the monkeys' intellectual functions and behavior.

The proven benefits of omega-3 fatty acids in primates—and the dangers of deficiencies—underscore their importance in the human diet. According to Dr. Connor, the human brain acquires half of its fat composition before birth and most of the rest during the first year of life. "This fact combined with our findings make it vitally important that pregnant and lactating women eat a sufficient amount of omega-3 fatty acids," he says. "An adequate amount of omega-3 fatty acids in baby formulas also must be ensured."

The minimum amount of omega-3 fatty acids required in the daily diet has not yet been determined. "The balance between omega-3 and omega-6 fatty acids—the primary constituents of many vegetable oils—is probably a crucial factor in human nutrition," he says. The current recommended daily intake of omega-6 fatty acids is 1 to 2 percent of the total calories consumed, "and omega-3 fatty acids should probably represent about three- to five-tenths of a percent of the total calories," Dr. Connor adds.

More than this meager amount of omega-3 fatty acids is required for people to reap

Research Resources Reporter

Published monthly by the Research Resources Information Center (ISSN: 0160-807X)

A publication of the Division of Research Resources, National Institutes of Health

Director:
Edward Post
Assistant Director:
Gregory T. Freiherr
Science Adviser:
Donald W. McKinstry, Ph.D.

NIH Project Officer:
Jim Augustine, Information Officer, DRR
Science Correspondents:
Mark Bello
Ron Cowen
Margaret Patlak

For sale by the Superintendent of Documents U.S. Government Printing Office Washington, D.C. 20402 Charge orders telephone (202) 783-3238

Correspondence should be addressed to:
Research Resources Information Center
1601 Research Boulevard
Rockville, Maryland 20850
Telephone: (301) 984-2870

Use of funds for printing this periodical has been approved by the Office of Management and Budget through September 30, 1985.

the additional health benefits the compounds can provide. One of these health benefits was first uncovered accidentally when Dr. Connor and his colleagues at the Oregon Health Sciences University General Clinical Research Center (GCRC) were evaluating a number of foods for their ability to raise blood levels of cholesterol. The high cholesterol content of shellfish led the researchers to expect that a diet high in this food would significantly raise plasma cholesterol levels. Instead, the researchers found that the shellfish diet had negligible effects on plasma cholesterol levels.

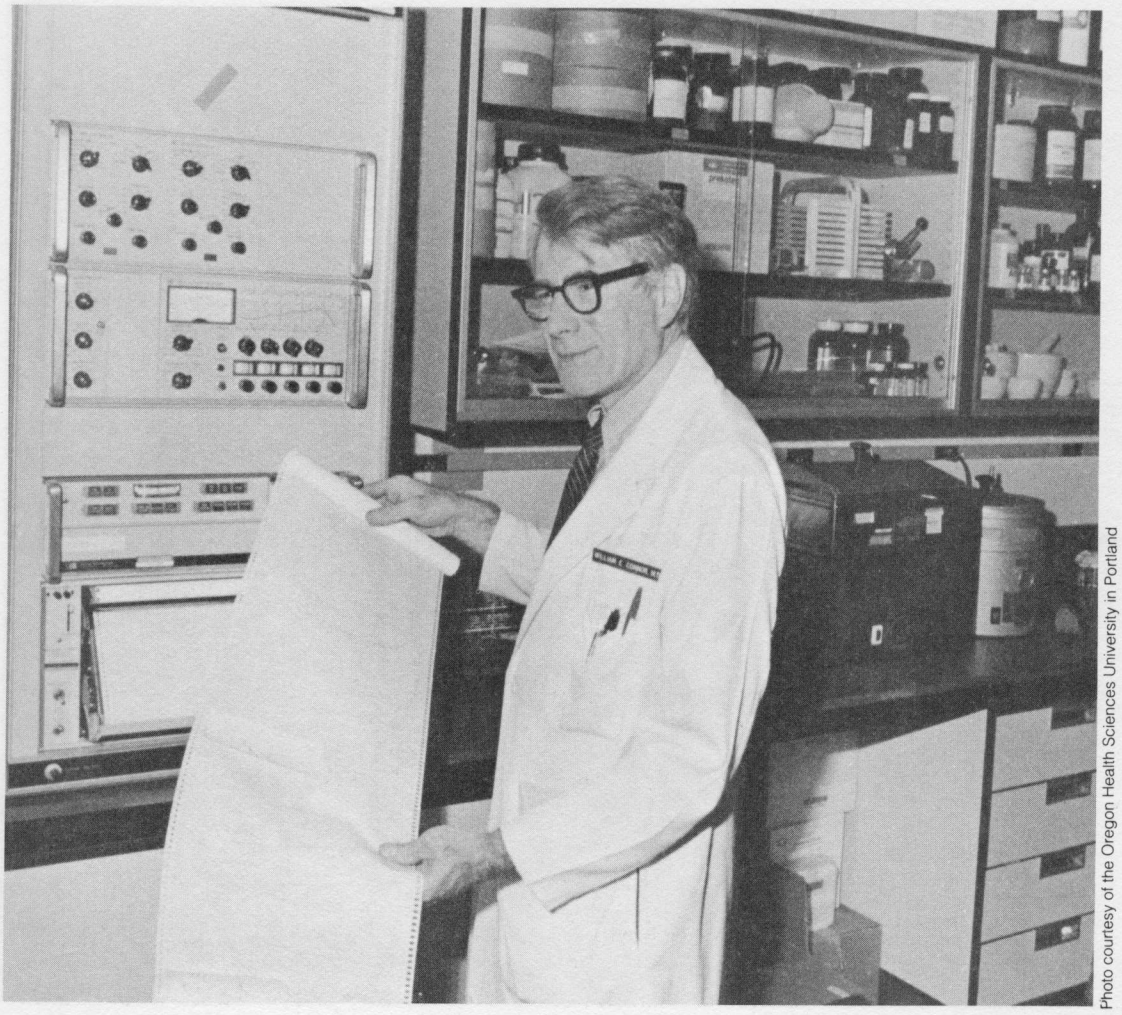
Dr. Connor then began a series of studies to see if it was the omega-3 fatty acids in the seafood that were inhibiting the increase of cholesterol in the blood. In one of Dr. Connor's most recent studies, which was also conducted at the Oregon Health Sciences University GCRC with Drs. Roger Illingworth and William S. Harris, seven volunteers followed for a month a diet with a fat content derived solely from salmon oil. In the second month of the 3-month study, the volunteers returned to their normal diets. In the last month, the subjects were fed a control diet with a fat content derived solely from vegetable oils low in omega-3 fatty acids. The cholesterol content of the experimental diet and the control diet was the same.

The fish oil diet reduced the average plasma cholesterol levels 23 percent below the levels obtained while on the control diet. The plasma triglyceride levels were 43 percent lower.

The researchers also determined the volunteers' cholesterol content in the various types of lipoproteins, all of which transport cholesterol in the body. They were particularly interested in the effects the fatty acids could exert on low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL), since high blood levels of these compounds are risk factors for atherosclerosis. Their analysis revealed that the blood levels of VLDL cholesterol were lowered most by the fish oil diet; many volunteers' VLDL cholesterol levels were half as high when they were on the fish oil diet as when they were on the control diet. The blood levels of LDL cholesterol, in addition, fell 20 percent when the volunteers were on the fish oil diet.

Further studies indicated that the omega-3 fatty acids in the fish oil diet reduce plasma concentrations of cholesterol and triglycerides by lowering the rate of synthesis of LDL and VLDL by the liver and vascular tissues. Both lipoproteins are carriers of triglyceride as well as cholesterol.

The researchers determined that the reduced levels of LDL resulted from decreased synthesis of LDL rather than from an increased metabolic destruction of it—a fact they learned by measuring both processes in their subjects. When the volunteers were on the fish oil diet, the investigators removed a fraction of the LDL from the subjects' blood and radioactively labeled it. This labeled compound



Dr. William Connor of the Oregon Health Sciences University in Portland: "We think these fatty acids are precious to the body and, unlike nonessential fatty acids, are used for many purposes besides the production of energy."

Photo courtesy of the Oregon Health Sciences University in Portland

HEART DISEASE *continued*

was then reinjected into the subjects, and the researchers determined the amount of labeled and unlabeled LDL in blood samples at regular intervals over a 2-week period.

The rate of metabolic destruction of LDL, as measured by the amount of the metabolic LDL end product in the urine over time, was practically the same for both diets. In contrast, the rate of LDL synthesis, as measured by the ratio of unlabeled to labeled LDL in the blood over time, was significantly lower when the volunteers were on the fish oil diet than when they were on the control diet.

Dr. Connor and Dr. Paul Nestel of the Baker Medical Research Institute used similar techniques in a study done at the institute, which is located in Melbourne, Australia. They discovered that omega-3 fatty acids also reduced synthesis by the liver of VLDL and triglycerides.

"These findings indicate that a diet high in omega-3 fatty acids might be helpful in preventing and treating atherosclerosis," Dr. Connor says. Although research has not definitively linked high blood levels of triglycerides to atherosclerosis development, many patients with atherosclerosis have high blood levels of triglycerides, according to Dr. Connor.

A diet high in fish might also prove therapeutic for patients with a disorder characterized by abnormally high blood levels of triglycerides. In other research conducted by Dr. Connor and his colleagues at the Oregon Health Sciences University GCRC, patients with this disease, termed hypertriglyceridemia (type V), were fed a diet in which 30 percent of the calories were provided by fish oil. The diet, which was rich in omega-3 fatty acids, caused a 77 percent drop in blood triglyceride levels below the level obtained with a control diet having only 5 percent fat and no omega-3 fatty acids. Cholesterol levels also fell.

Omega-3 fatty acids might have additional benefits for patients with certain types of heart diseases, Dr. Connor says. Research he has done with Dr. Scott Goodnight has shown that a diet with a high amount of fish rich in omega-3 fatty acids can decrease the stickiness of platelets, which can clump together to form blood clots. These clots frequently form in atherosclerotic arteries, which are narrowed by calcified plaques, Dr. Connor explains. A blood clot can completely block such a narrowed artery and cause a heart attack.

The tendency of omega-3 fatty acids to prevent clots was discovered after an epidemiology study revealed that heart attacks rarely occurred in a population of Eskimos whose diets were exceptionally high in marine fish. Further studies suggested that the high concentrations of omega-3 fatty acids in the Eskimos' diet probably lowered the incidence of heart dis-

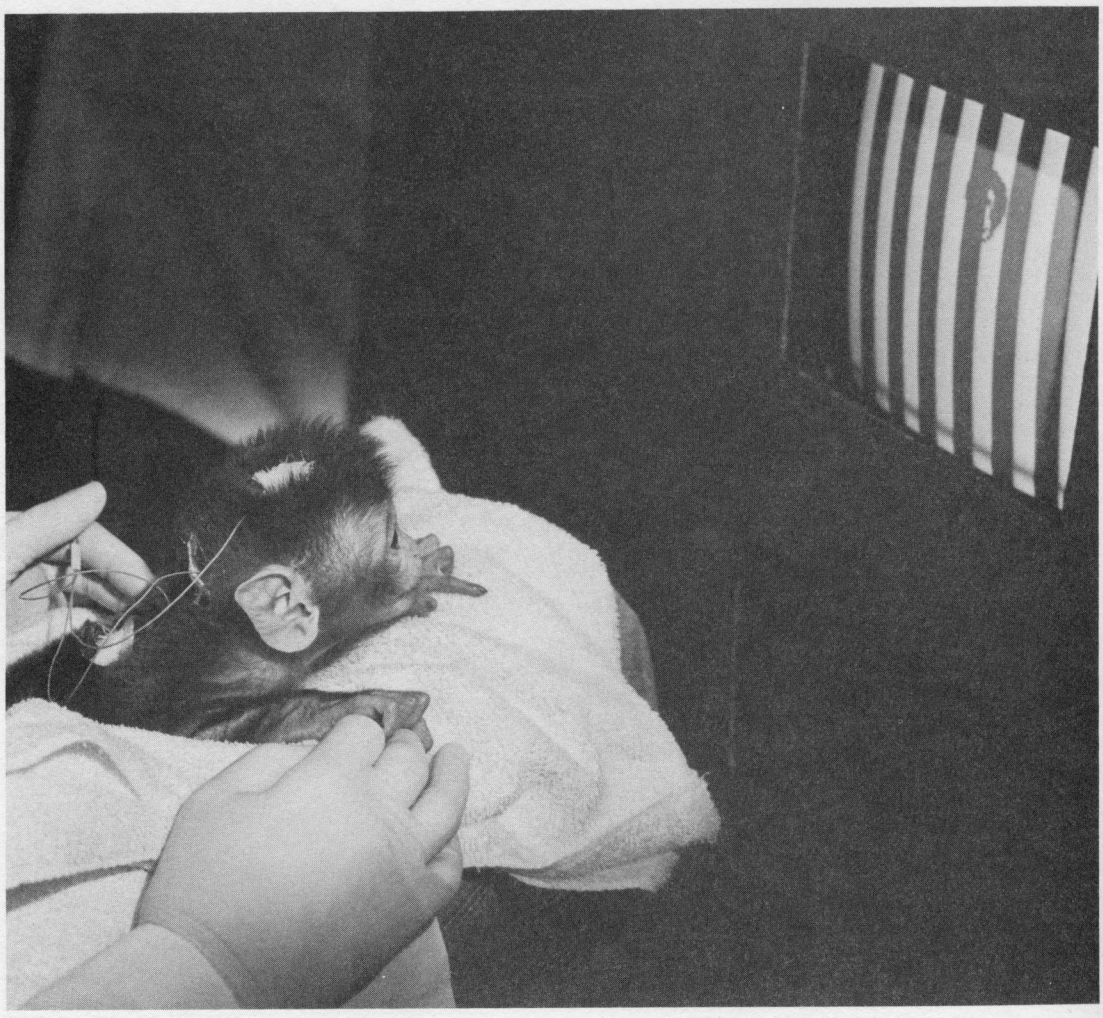


Photo courtesy of Dr. Connor

A rhesus monkey's vision is tested at the Oregon Regional Primate Research Center in Beaverton. Researchers there have shown that a type of fatty acid prevalent in fish and green leafy vegetables is essential for good vision.

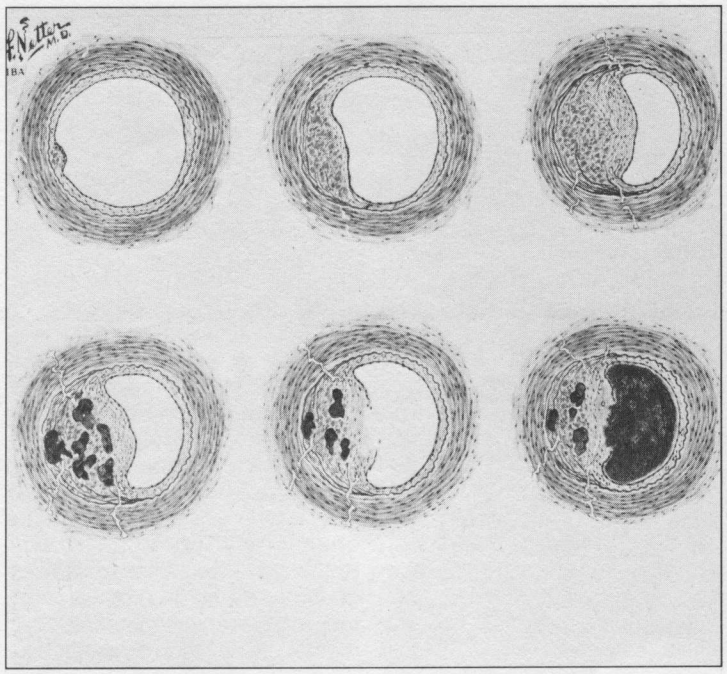
ease in the population.

The inhibition of blood clotting by the omega-3 fatty acids will not cause bleeding problems, Dr. Connor says, unless a person eats very large amounts of fish and has an imbalance of other dietary factors that help control bleeding.

"The practical implication of our research," Dr. Connor says, "is that omega-3 fatty acids, by lowering the level of fats in the blood and decreasing the stickiness of the platelets, may be useful in preventing and treating patients with certain types of heart disease." The findings indicate that it might be beneficial for these types of cardiac patients to substitute high fat fish in their diets for high fat meats, such as beef and pork.

Research has shown that most fats in vegetable oils also lower blood levels of cholesterol but, unlike fish fats, do not lower triglyceride levels or slow the formation of blood clots.

"Our findings reinforce the idea that it's not simply the amount of fat in the diet," Dr. Connor says, "but the type of fat that affects plasma cholesterol and triglyceride levels. We suggest that people shift a considerable portion of their meat consumption to fish and eat a 4- to 6-ounce serving of fish three or four times a week."



Drawing courtesy of CIBA

Fat and cholesterol in the diet and blood cause the progressive buildup of plaque in arteries (top row) of patients with atherosclerosis. In the later stages of the disease, the deposits calcify (bottom row) and blood clots can clog the narrow artery channel (bottom right). A diet high in fish might help prevent these blood clots from forming.

Additional reading:

1. Neuringer, M., Connor, W. E., Van Petten, C., and Barstad, L., Dietary omega-3 fatty acid deficiency and visual loss in infant rhesus monkeys. *Journal of Clinical Investigation* 73:272-276, 1984.

2. Illingworth, D. R., Harris, W. S., and Connor, W. E., Inhibition of low-density lipoprotein synthesis by dietary omega-3 fatty acids in humans. *Arteriosclerosis* 4:270-275, 1984.

3. Nestel, P. J., Connor, W. E., Reardon, M. F., Connor, S., Wong, S., and Boston, R., Suppression by diets rich in fish oil of very-low-density lipoprotein production in man. *Journal of Clinical Investigation* 74:82-89, 1984.

4. Harris, W. S., Connor, W. E., and McMurry, M. P., The comparative reductions of the plasma lipids and lipoproteins by dietary polyunsaturated fats: Salmon oil versus vegetable oils. *Metabolism* 32:179-184, 1983.

5. Goodnight, S. H., Jr., Harris, W. S., Connor, W. E., and Illingworth, D. R., Polyunsaturated fatty acids, hyperlipidemia, and thrombosis. *Arteriosclerosis* 2:87-113, 1982.

6. Connor, W. E., Neuringer, M., Barstad, L., and Lin, D. S., Dietary deprivation of linolenic acid in rhesus monkeys: effects on plasma and tissue fatty acid composition and on visual function. *Transactions of the Association of American Physicians*. In press.

7. Goodnight, S. H. Jr., Harris, W. S., and Connor, W. E., The effects of dietary omega-3 fatty acids upon platelet composition and function in man: a prospective, controlled study. *Blood* 58:880-885, 1981.

Research described in this article was supported by the National Heart, Lung, and Blood Institute; the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; the General Clinical Research Centers Program and the Animal Resources Program of the NIH Division of Research Resources; the National Heart Foundation of Australia; the National Health and Medical Research Council of Australia; and the Medical Research Foundation of Oregon.