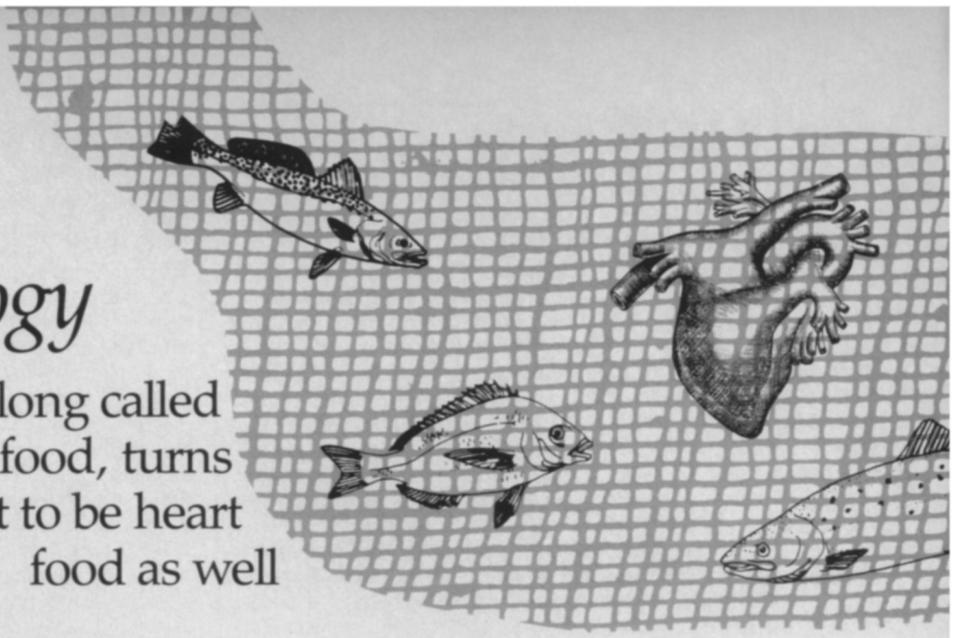
Fish, Fatty Acids and Physiology



Fish, long called brain food, turns out to be heart food as well

By JENNIE DUSHECK

Eskimos have a lower incidence of heart disease than do other populations, even though their high-fat, high-cholesterol diet ought to make them a high-risk group for heart disease. How do the Eskimos get away with it?

The answer lies in the kind of fat they eat. The Eskimo diet consists mostly of fish, seal and whale. Fat from these animals contains "omega-3 fatty acids," which are structurally distinct from the "omega-6 fatty acids" that most Westerners get from domestic meats. Epidemiologic studies of populations, such as the Eskimos and Japanese, that consume a lot of fish suggest that the omega-3 fatty acids in fish reduce the likelihood of getting heart disease, rheumatoid arthritis and other inflammatory diseases (SN: 5/11/85, p. 295).

This finding, combined with increasing knowledge about a class of compounds called eicosanoids, has brought many nutritionists and biochemists to a pitch of excitement. Eicosanoids, which are derived from fatty acids, regulate communication between cells and, consequently, inflammation and other immunological responses.

About 150 scientists convened in Washington, D.C., last June for a three-day conference on the health effects of polyunsaturated fatty acids in seafood and struggled to decide what is really known about fatty acids and eicosanoids. They focused mainly on how omega-3 fatty acids may function to reduce the incidence of heart disease, what other effects they may have on health and what quantity of omega-3 fatty acid should be recommended for a normal diet or a therapeutic dose.

"The excitement we feel about the possible uses of seafood is balanced by a rather sobering awareness of our ignorance," says William Lands, head of biological chemistry at the University of Illinois in Chicago and a cochair of the conference.

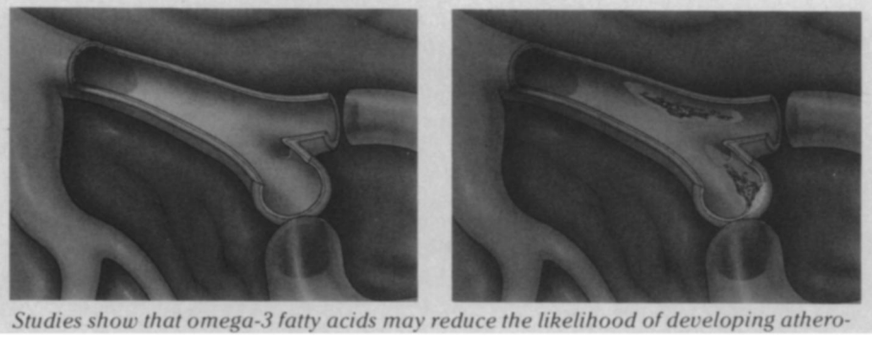
Ignorant or not, the scientists brought to the conference a wealth of information. Both epidemiologic and clinical studies suggest, they said, that the consumption of fish, fish oils or omega-3 fatty acid supplements may reduce the likelihood of developing atherosclerosis, thrombosis, rheumatoid arthritis, migraine headaches and possibly even multiple sclerosis. On the other hand, the consumption of large amounts of fish oil may have unknown detrimental effects. For example, though the Eskimos and Japanese have less heart disease than other groups, they also suffer far more strokes.

Fish oil's diverse effects appear to come about through several routes. To begin with, fatty acids, which bond to glycerol to make up fats, are broadly distributed in the body. Fats, in general, are important sources of energy; they insulate the body and certain organs; and they are a major component of nerve tissues, reproductive tissues and cell membranes. Many kinds of fatty acids are essential to the human diet. A deficiency of essential fatty acids can result in skin inflammation and impaired transport of lipids. Laboratory animals on fatty-acid-deficient diets also exhibit poor growth, infertility and susceptibility to stress. But most studies of such deficiencies have focused on omega-6 fatty acids.

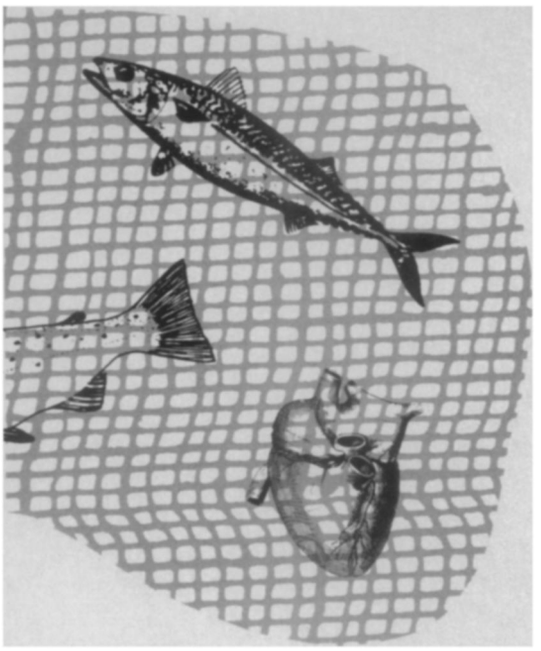
Fortunately, except in the case of people fed intravenously for long periods, fatty acid deficiencies are extremely rare in humans. Only 1 or 2 percent of the total calories in a diet need to come from essential fatty acids, said researchers at the conference, and all normal Western diets contain far more than that. In fact, fats make up about 40 percent of the calories in the average U.S. diet — about twice what is necessary. However, these fatty acids are mostly omega-6s, and we seem to need some omega-3s as well.

Though there is no proof that omega-3s are essential for human development, a number of studies suggest their importance. Rats reared on omega-3-deficient diets suffered impaired vision and reduced learning ability, according to a paper presented in 1976 by M.S. Lamptey and B.L. Walker in JOURNAL OF NUTRITION. The rats also had drastically reduced levels of omega-3 fatty acids in their brains. (Omega-3s can be synthesized by the body to some extent.) Because the learning tests involved vision, it has been suggested that the rats' impaired learning was due to impaired vision, not to an omega-3 fatty acid deficiency, says Norman Salem of the National Institute of Alcoholism and Alcohol Abuse in Bethesda, Md. "The crucial experiment — a non-visual test for the rats — remains to be done," he says.

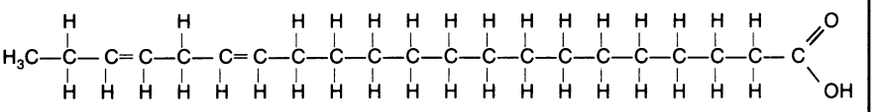
Monkeys reared on an omega-3-deficient diet suffered from blurred vision and longer response times for nerve signals from the eyes, reports William Connor of Oregon Health Science University in Portland, who adds that he has not seen



Studies show that omega-3 fatty acids may reduce the likelihood of developing athero-



Anatomy of a Fatty Acid



Fatty acids are long straight chains of carbon atoms with a carboxyl group at the end. When bonded to a glycerol, they form fats. Each carbon atom in a fatty acid can be attached to another carbon atom by either a double bond or a single bond. But a double bond between two carbon atoms in a chain reduces the number of hydrogen atoms that can attach to each of the carbons from two to only one.

If the carbons of a fatty acid each have a full complement of hydrogen atoms and no double bonds, the fatty acid is said to be completely hydrogenated, or *saturated* with hydrogen. If the fatty acid has one carbon-carbon double bond, it is *monosaturated*. If it has two or more double bonds, it is *polyunsaturated*.

The first carbon atom in the chain, the carboxyl carbon, is called the number one carbon, and the last one is known either by its number or as the "omega" carbon, omega being the last letter of the Greek alphabet. If the last double bond in the chain is on the third-to-last carbon, the fatty acid is called an "omega minus 3," or "omega-3." Fats consumed by Westerners consist mostly of omega-6 fatty acids.

impaired learning in the monkeys.

The human brain acquires half of its fat content before birth and most of the rest in the first year, says Connor. Omega-3 fatty acids accumulate in the brain, retinas and testes of a developing fetus. Because they are retained tenaciously into adulthood — even in the face of general fatty acid deficiencies — some researchers say that omega-3s may be essential in early development, if not in adulthood. Omega-3s also occur in high levels in the liver, heart and muscles.

Researchers still do not know whether consuming more omega-3s increases the omega-3 fatty acid content in human organs. But increased consumption of omega-3 fatty acids is known to increase the ratio of omega-3s to omega-6s in all the components of human blood, says Salem. Many of the beneficial effects of fish oils are attributed to this change in composition.

Of fish oil's many effects on human physiology, perhaps the greatest number result secondarily from omega-3 fatty acids' modulating effect on certain eicosanoids. Biochemists think that eicosanoids synthesized from omega-3 fatty acids are distinct from eicosanoids synthesized from omega-6 fatty acids.

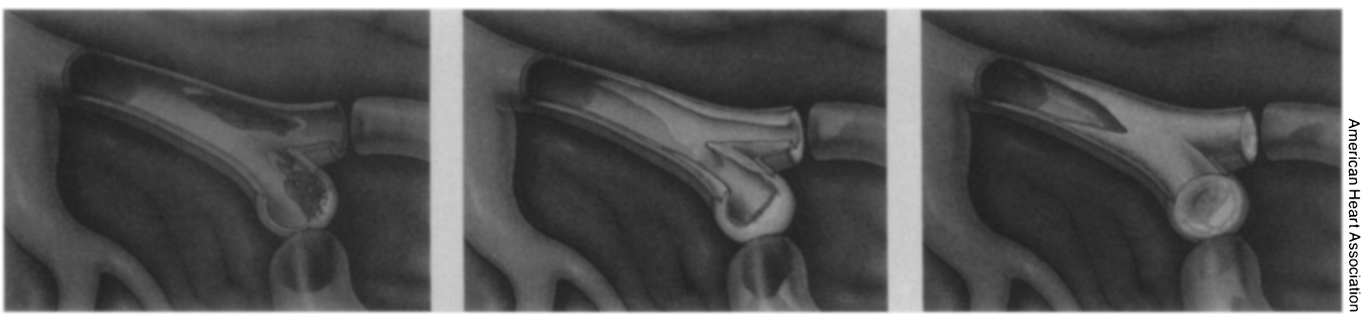
Eicosanoids are a class of about a dozen compounds whose importance has been discovered only in the last 15 years. "Eicosanoids are how the cells chatter back and forth with each other," says Lands, the University of Illinois biochemist. "We have to understand the significance of all these voices when they whisper or shout, why or what it means.

"All these inflammatory diseases are the consequence of exaggerated eicosanoid signals. As in communication between individual humans, one mistake can be blown all out of proportion by positive feedback mechanisms."

Eicosanoids are made in the body from polyunsaturated fatty acids derived from the diet. Eicosanoids are all local regulators — that is, they are produced in short explosive bursts and then rapidly metabolized before they can travel to other parts of the body. Because these compounds are in the tissues so briefly, they are difficult to study.

Eicosanoids are divided into two families: the prostaglandins, which are made by an enzyme called cyclooxygenase; and the leukotrienes, which are made by an enzyme called lipoxygenase. Both families stimulate inflammation and smooth-muscle contraction. One difference between the two is that prostaglandin synthesis is blocked by aspirin — hence the drug's anti-inflammatory properties — while leukotriene synthesis is not. Diuretics, antihypertensives and anticlotting drugs also work by blocking the synthesis of various eicosanoids.

Several studies have shown that one of the crucial effects of omega-3 fatty acids is to reduce the rate of eicosanoid synthesis, says Lands. Normally, eicosanoids are synthesized in the body at about one-ten-thousandth the rate at which the cells are capable; in other words, synthesis is heavily suppressed and controlled. When eicosanoid production is stimulated — for example, by injury — those synthesized from omega-6 fatty acids rise "explosively" by a positive feedback mechanism to very high concentrations — much higher than concentrations of eicosanoids synthesized from omega-3 fatty acids, says Lands. Moreover, he says, the very presence of omega-3 fatty acids seems to interfere with omega-6 eicosanoid production. For example, the omega-3s compete with the omega-6s for access to the enzymes that drive eicosanoid synthesis by inactivating them. Omega-3s also form alternates to the omega-6 eicosanoids. These alternates, says Lands, are less inflammatory than omega-6 eicosanoids, but they occupy eicosanoid receptor sites and so keep the omega-6 eicosanoids from acting.



American Heart Association

sclerosis, the gradual buildup of fat deposits in arteries, as shown here.

Because eicosanoids have such broad inflammatory effects, omega-3 fatty acids also have broad effects. A case in point is atherosclerosis, one of the most closely examined inflammatory diseases.

Atherosclerosis, or hardening of the arteries, is believed to be the result of many factors; there is no single event that either initiates the disease or furthers its development. Family history, maleness and increasing age inevitably increase one's risk of developing cardiovascular disease. But some risk factors are modifiable if not controllable. These include elevated serum cholesterol and low-density lipoproteins (LDLs), depressed serum high-density lipoproteins (HDLs), hypertension, cigarette smoking, diabetes mellitus, physical inactivity, obesity and stress. The development of atherosclerosis is usually a gradual, step-by-step process, although it can be initiated in a matter of months in monkeys on a high-cholesterol diet.

Anything that interferes with the sequence of steps can halt the progress of the disease — and fatty acids seem to play a role at every level. Connors and his colleagues showed that a diet high in omega-3 fatty acids decreases serum cholesterol and LDL levels, reducing the risk that fatty streaks will form in the arteries.

Peter Weber and his colleagues at the University of Munich showed that a diet high in omega-3s also increases "bleeding time" — the period of time during which a wound continues to bleed. One cause of increased bleeding time may be less reactive blood platelets — the cell-like structures in the blood that initiate clots. Weber reports that platelets in the blood of persons on high-omega-3 diets are less sticky and aggregate less easily than platelets in "normal" blood. They also produce less thromboxane, a molecule that promotes platelet aggregation and blood vessel constriction. Fewer clots and more relaxed blood vessels mean less chance that the arteries will be blocked.

Omega-3 fatty acids do not seem to affect monocytes, the white blood cells that collect in arterial walls in the early stages of atherosclerosis, reports Frank Austen, who chairs the department of rheumatology and immunology at Brigham and Women's Hospital in Boston. They do, however, affect the biochemistry of neutrophils, another kind of white blood cell. Austen and his colleagues found that the neutrophils of volunteers on a six- to-eight-week, high-omega-3 diet released less 5-lipoxygenase (an eicosanoid-synthesizing enzyme) than did neutrophils of volunteers on a control diet.

Some studies have also shown a reduction in blood pressure in response to a diet high in omega-3 fatty acids, says Weber. But this change probably does not account for the reduced heart disease, he says, noting that the Japanese, whose diet is salty as well as fishy, have lower rates of heart disease in spite of more hypertension. In general, though, omega-3 fatty acids do seem to reduce the reactivity of the circulatory system.

National Fisheries Institute

Salmon steaks provide omega-3 fatty acids in the diet.

But omega-3s have been shown to have negative effects as well as positive ones. Dwight Robinson of Harvard Medical School showed that in mice fed with fish oil the incidence of glomerulitis, one kind of kidney disease, was reduced, while necrotizing vasculitis, another kind of kidney disease, seemed to be aggravated by the supplement.

Because so much about the effects of fish oils is unknown, some researchers are reluctant to make specific recommendations to the public. For example, although there is no evidence that fish oils are toxic, some researchers note that no evidence of toxicity is not the same as evidence of no toxicity. And although omega-3 fatty acids are presumed to be the beneficial ingredient in fish oils, no one is certain what positive or negative effects other components may have.

To accommodate this gap in knowledge, Austen suggests using purified fish oil extracts for research — to better understand what effects each constituent has — but whole fish oils for patient therapy. Fish oil "prescriptions" of the doctors at the conference range from several salmon meals a week to purified omega-3 fatty acid supplements for heart patients and those with abnormal blood lipid levels. "We owe it to the patient to make sure that there is an effect," says Austen.

Some researchers express doubts about accepting omega-3 fatty acids uncritically. "The Eskimo data," says Leaf, "seem to show a firm connection between omega-3 fatty acids and [reduced incidence of] coronary artery disease. But a review of other studies revealed how little fish oil might be necessary to affect the rate of heart disease, which amazed us and raised the question of whether other factors might be involved." Leaf says that large clinical studies are not yet warranted. "We need to wait for the knowledge of which constituents [of fish oils] to use for larger long-term trials," he says.

In spite of sometimes heated controversy over the issues of the essentiality, safety and recommended levels of omega-3 fatty acid consumption, most of the researchers at the meeting seemed to agree that the public ought to eat more fish. The U.S. Department of Health and Human Services and the Department of Agriculture currently recommend as many as four fish meals a week, notes Artemis Simopoulous of Health and Human Services, who chaired the conference. But, she says, the average American eats only one. A paper in the May 9 New England Journal of Medicine showed that two fish meals a week could have a beneficial effect on health, and several researchers at the conference testified that they themselves were taking fish oil supplements. No one contested that we would all do well to eat two fish meals a week.

Yet even this advice isn't as simple as it might seem. Salem and his colleagues measured the omega-3 fatty acid content of an assortment of fast foods, including fried fishwiches, fried chicken, hamburgers and pepperoni pizza. Omega-3 levels were extremely low in all of them. Surprisingly, however, the pizza had slightly more than the fishwich. Salem suggests that the sought-after fatty acids may be destroyed in the process of frying. Fast food junkies, it seems, may be better off developing a taste for poached salmon. □

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