FOOD for MIND and MOOD

Can diet affect brain function? If so, nutrients might one day be prescribed in the treatment of a number of illnesses including Alzheimer's disease and hypertension.

By STEFI WEISBURD

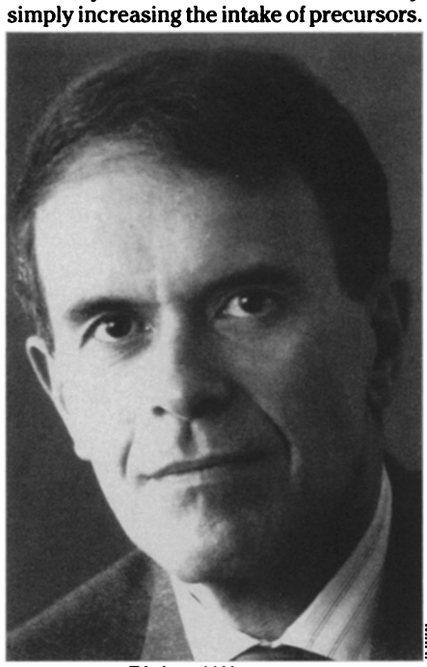
Go to any health food store today and you will find a tapestry of foods bearing claims of medicinal wonders. Tell your grandmother you cannot sleep and she will prescribe a nice cup of warm milk to make you drowsy.

The idea that foods can affect our physiology and mental state has lurked in the uncertain mists of folk wisdom for centuries. Only recently, as the biochemical microcosm of the brain is slowly unveiled, have researchers been able to scientifically link some of the nutrients found in foods to brain chemistry, and hence to brain function.

The hope of many neuroscientists is that by better understanding this relationship, nutrients, which are more easily metabolized and more specifically targeted in their actions than drugs, might one day be used in the treatment of a variety of physical and mental disorders including Parkinson's disease, memory loss and hypertension.

The man who has pioneered the idea that dietary nutrients influence brain function is Richard Wurtman, a physician and neuroendocrinologist at the Massachusetts Institute of Technology (MIT) in Cambridge. For the past 15 years, Wurtman has studied the role of certain nutrients in the synthesis of neurotransmitters, the brain's chemical messengers. Each neurotransmitter molecule is manufactured in the termi .als of a nerve cell, or neuron, that uses a specific nutrient as the raw material, or precursor. Transmitters, released by the firing of a neuron, shuttle information across a synapse to other neurons or to muscle and secretory cells. Neuroscientists believe many disorders may be caused by defects in the mechanisms that create, liberate and regulate neurotransmitters.

Wurtman and his colleagues discovered that the production rate of several neurotransmitters can be dictated by diet. Specifically, levels of serotonin, the catecholamines and acetylcholine are strongly linked to the amounts of their respective nutrient precursors — tryptophan (an amino acid found in proteins), tyrosine (another amino acid) and choline (found in lecithin) — available in the brain (see table). The fact that any of the thirty or so known transmitters are subject to precursor control was quite surprising. The prevailing wisdom when Wurtman began his work was that the production of substances needed by all of the important systems of the body was kept at equilibrium; neuroscientists did not expect that transmitter synthesis could be enhanced by simply increasing the intake of precursors.



M.I.T.

Richard Wurtman

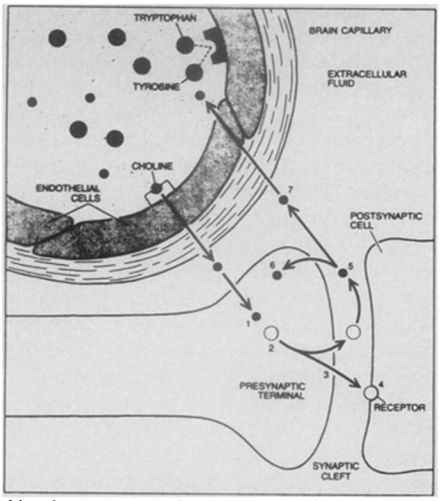
"It remains peculiar to me," says Wurtman, "that the brain should have evolved in such a way that it is subject to having its function and chemistry depend on whether you had lunch and what you ate. I would not have designed the brain that way myself."

Wurtman's laboratory established the relationship between precursors and transmitters in the brain by injecting rats with isolated nutrients. Trying to control transmitter synthesis by feeding rats food containing a mixture of nutrients, however, proved to be more difficult and at times perplexing. The investigators thought, for example, that they could raise the levels of serotonin and its precursor tryptophan in the brain by giving rats dietary proteins since these are rich in amino acids, including tryptophan. To their surprise, serotonin and tryptophan levels actually fell.

The researchers discovered that tryptophan, which is the scarcest of the 22 amino acids, could not just waltz its way from the stomach into the brain. It has to compete with the hordes of other amino acids (found in much greater abundance in proteins) for a ride on special transport carriers designed to take selected molecules into the brain.

Paradoxically, says Wurtman, "the meal which most enhances brain tryptophan and hence increases the synthesis of serotonin is the meal that lacks tryptophan entirely because it lacks protein entirely." For example, carbohydrates when digested induce the secretion of insulin, which in turn coerces all other amino acids from the bloodsteam, but leaves tryptophan unscathed (since it binds to protein albumin in the bloodsteam). This increases the ratio of tryptophan to other amino acids and therefore improves the chance that tryptophan will get into the brain. Milk, high in protein, will therefore not increase the production of sleep-inducing serotonin because it contains a small amount of tryptophan relative to other amino acids.

Wurtman's earliest laboratory experiments on rats, along with the work of other neuroscientists, helped to demonstrate the complex biochemistry of serotonin, catecholamines and acetylcholine synthesis by quantifying changes in transmitter and precursor concentrations in the brain due to increased nutrient levels in the blood. This basic research has stimu-



Nutrients cross the blood-brain barrier into the brain where they are converted into neurotransmitters. Shown here is the uptake of choline in the terminal of a neuron (1) and its subsequent conversion (2) into acetylcholine (ACh), which is released into the synapse when the neuron fires (3). The ACh may interact with a receptor of another neuron, thereby transmitting a signal (4). Alternately, the ACh may be converted back into choline (5), which may then be taken up again in the terminal (6) or may be returned to the bloodstream (7).

lated a myriad of clinical investigations aimed at exploring the possible effects of biochemical changes in the physical brain on the human mind.

Neurologist John Growdon at the Massachusetts General Hospital in Boston says, "We're now looking for neurotransmitter abnormalities in the brains of patients with the same care that a generation ago was taken to look at [tissue structure] under a microscope." The jump from understanding brain biochemistry to explaining or controlling human behavior and mental disorders is extremely difficult. Neuroscientists stress that much more research — at both the clinical and laboratory levels — is required before nutrients can even be considered for treatment. Some of the most interesting current clinical work includes:

• Carbohydrate craving. Wurtman believes that in the clinical area he has had the greatest success relating serotonin to eating disorders, especially carbohydrate craving. In his model, the brain uses the production of serotonin to monitor and in turn regulate the relative proportions of proteins and carbohydrates being consumed.

Wurtman believes that this mechanism may have evolved as a result of the need for nutritionally balanced meals. It may be possible, he says, that defects in this regulatory mechanism are responsible for cravings among some people for sweet or starchy snacks, especially late in the day. In recent studies at the MIT Clinical Research Center, Wurtman and Judith Wurtman, a nutrition scientist at MIT, found that this snacking tendency was suppressed in many of their subjects by giving them low doses of a drug called fenfluramine, which increases serotonin levels. Wurtman is also interested in the effects of standard weight loss diets that are high in protein and low in carbohydrates, and hence, low in tryptophan.

• Depression. Neuroscientists speculate that depression is related to deficiencies in the production of serotonin and the catecholamines. Studies conducted by Alan Gelenberg, a psychiatrist at Massachusetts General Hospital, in conjunction with Wurtman provided the first clinical evidence that tyrosine can work as an antidepressant probably, researchers believe, by enhancing the synthesis of norepinephrine in certain regions of the brain. Gelenberg is presently engaged in a three-year study comparing the effects of tyrosine to both a standard antidepressant drug and a placebo.

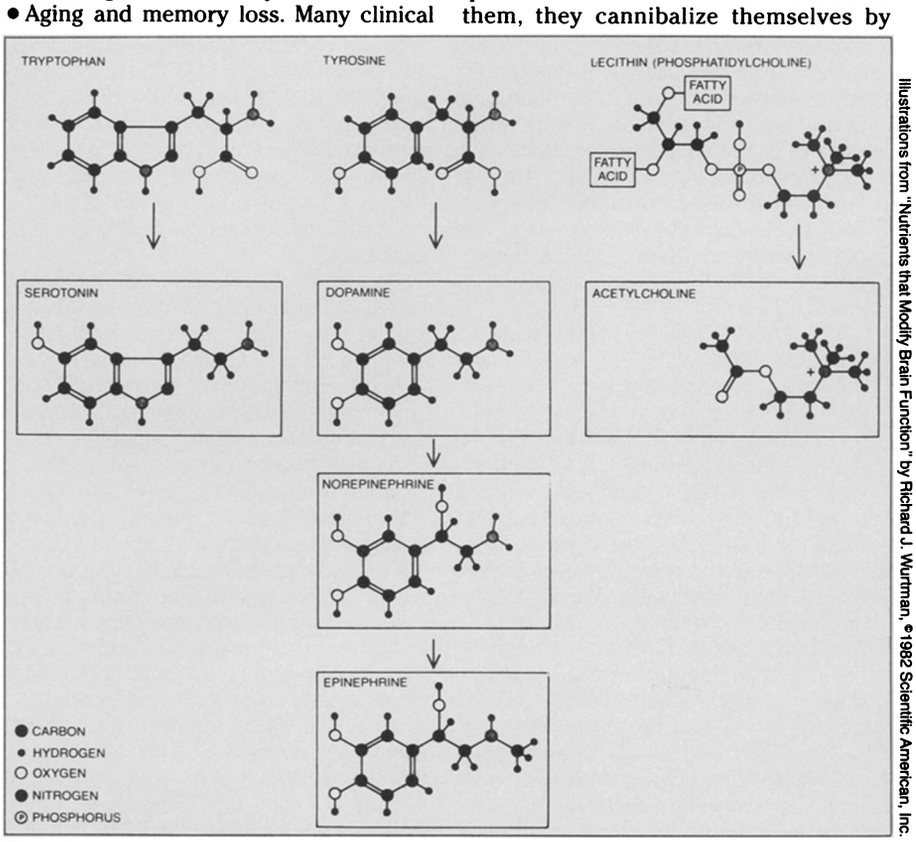
Norman Rosenthal, a psychiatrist at the National Institute of Mental Health (NIMH) in Bethesda, Md., has noticed in his studies of seasonal depression that many of his patients crave carbohydrates, especially in the winter. He believes that tryptophan may hold some promise in the treatment of some forms of depression. Herman van Praag, a psychiatrist at the Albert Einstein College of Medicine in New York agrees, noting that a number of clinical researchers including himself have developed precursor strategies based partly on Wurtman's work. "We really feel it has something to offer," he says.

• Aging and memory loss. Many clinical researchers are turning their attention to diseases associated with aging, such as senile dementia and Alzheimer's disease. Growdon is conducting two clinical investigations into the effects of choline (in the form of lecithin) given in combination with other drugs to patients with memory disorders. He thinks that lecithin treatments have the highest probablity of success of all the approaches currently being tried. While his study is not yet completed, he does see trends of beneficial effects in some patients.

This is consistent with a six-month study recently done by Raymond Levy at the Maudsley Hospital in London, in which half of the Alzheimer's disease patients given large doses of lecithin showed an improvement in cognitive function and self-care.

Many of the diseases related to aging have been linked to faulty transmission of acetylcholine. Researchers hope neurotransmission can be improved by increasing concentrations of choline in the brain.

In particular, Alzheimer's disease, like the normal aging process, is thought to be characterized by the loss of acetylcholine neurons. (Catecholamine and serotonin levels are also diminished in aging, but to a lesser degree.) Wurtman has a theory to explain Alzheimer's disease that he gives about a 5 percent chance of being correct. All cells in the body use lecithin to build up their membranes. Choline neurons are different in that they will use this membrane as a reservoir when their external supply of choline is low. When these neurons require more choline than is available to them, they cannibalize themselves by



The chemical structure of neurotransmitters and their three nutrient precursors.

Illustrations from "Nutrients that Modify Brain Function" by Richard J. Wurtman, ©1982 Scientific American, Inc.

From Nutrients in the Stomach to Neurotransmitters in the Brain

NUTRIENT PRECURSOR	ABUNDANCE/ SOURCE	NEURO-TRANSMITTER*	RELATED EFFECTS
Tryptophan (amino acid)	1 percent of all dietary proteins	**Serotonin**	In normal people: • Decreases alertness • Hastens sleep onset • Decreases appetite (especially for carbohydrates) • Diminishes pain sensitivity In disease states: • Adjunct in treating depression, obesity, insomnia
Tyrosine (amino acid)	5 percent of all dietary proteins	Catecholamines • norepinephrine • epinephrine • dopamine	In normal people: • Anti-stress • Subjective vigor in aged In disease states: • Normalizes blood pressure • Early Parkinson's disease • Adjunct in depression
Choline	Component of lecithin (phosphatidylcholine) found in egg yolks, soy products, and liver	Acetylcholine	In disease states: • Under experimental evaluation in tardive dyskinesia, long-term treatment of Alzheimer's disease, mania, ataxias.

*The transmitters histamine and glycine may also be subject to precursor control. There is no evidence that precursor availability regulates the production of other neurotransmitters, peptides or the so-called nonessential amino acids.

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chewing up their own membrane lecithin. This would explain why cholinergic neurons seem more vulnerable than their compatriots. One supporting bit of evidence is that plasma choline levels are considerably higher in newborns, who are probably synthesizing new membranes very rapidly, than in adults.

• Blood pressure abnormalities. No clinical studies have been performed yet, but Wurtman is enthusiastic about the potential use of tyrosine in the treatment of blood pressure abnormalities. He and co-workers have shown in the laboratory that one and the same dose of tyrosine will lower blood pressure in hypertensive rats and raise it in animals with low blood pressure (hypotensive).

This is because the brain has the ability to change the frequency at which a neuron fires as well as alter the sensitivity of certain neurons to increases in precursor supply. Since the number of transmitter molecules actually jettisonned across the synapse depends both on the number produced and the firing frequency, nutrients can be used to selectively amplify neurotransmission by increasing the release of molecules where neurons are busy firing.

In hypertensive animals, the brain calls upon norepinephrine (NE)-releasing neurons in the brain stem to fire frequently because at this site NE acts to lower blood pressure. Increasing the intake of tyrosine will then boost the brain's attempt to lower the body's blood pressure.

The same principle applies in hypotensive rats except that the neurons that are busy firing — and hence the neurons that will produce the most NE in response to more tyrosine — are located outside the brain in the sympathetic nervous system where NE acts to raise pressure. Wurtman

Regulating Medical Foods

While the potential for using nutrients either in combination with drugs or alone excites many researchers and clinicians, it also worries them. Precursors, when separated from other nutrients and given in large doses for the treatment of diseases, act like drugs. Should they then be treated as drugs or are they really foods? The question has important ramifications for the regulation and public access to these "medical foods," not only in the future, but as research is conducted today.

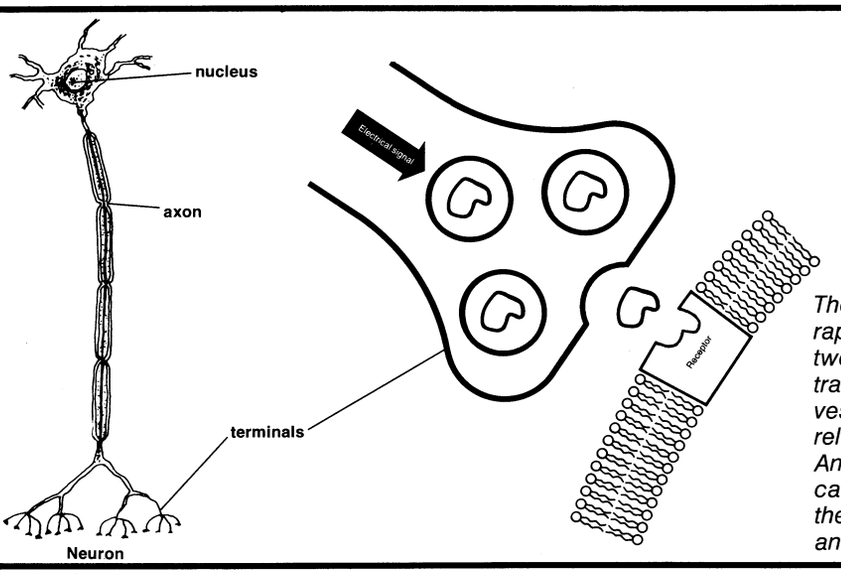
If nutrients are legally considered drugs then they must undergo rigorous testing to demonstrate safety and efficacy. This might be an overly stringent requirement, says Richard Wurtman of the Massachusetts Institute of Technology, since these nutrients have been naturally metabolized for as long as there have been animals in the world. In addition, tough requirements might dissuade food and pharmaceutical companies from investing in research on these substances. On the other hand, he says, if nutrients are treated as foods, overly lenient standards would enable anyone to use them without supervision.

The Food and Drug Administration (FDA) does not currently have regulations dealing with substances like tryptophan, although it has been aware of the need for a consistent set of guidelines for some time as the number of these compounds has increased. "It's not an easy legal issue to tangle with," explains Sanford A. Miller, director of FDA's Bureau of Foods. "Every time you open the door a little bit this way you also open the door for every quack who comes along claiming he's going to cure failing hair or impotency." According to Miller, a proposal for the regulation of medical foods should be out by the end of the year.

For the time being, scientists will have to live without clear controls over the nutrients they use in their research. But they are none too happy. Wurtman calls the present status of tryptophan "an unmitigated disaster" where no physician can prescribe it but people can buy it, self-medicate and perhaps get into trouble. Alan Gelenberg of the Massachusetts General Hospital wishes tyrosine was regulated as an experimental drug so that he wouldn't have to worry about anyone taking it prematurely. He says that instead "on the basis of one case report . . . health food publications pick it up and say that some doctor has found an effective treatment for depression. Then some health food stores stock something they call tyrosine — who knows what's in it — and people are writing from all over wanting to know how much they should take."

The situation is just as bad, if not worse, for choline which is best taken as phosphatidylcholine (PC) or lecithin, since pure choline reacts with bacteria in the intestine producing an unpleasant odor reminiscent of rotting fish. According to Wurtman, in 1938 the FDA allowed the definition of lecithin to include any number of phospholipids used as emulsifiers in mayonnaise, chocolate and other foods. Therefore what is sold in stores today contains only a small percentage of pure PC. People don't realize, says Wurtman, that in order to get a therapeutic effect they must consume enormous, and highly caloric, amounts of the lecithin available in stores.

Clinicians are fortunate not to have to rely on health food store stocks since the Thomas J. Lipton Company recently made available to qualified clinical researchers a soup containing noodles enriched with lecithin. (To avoid potential legal complications, Lipton requires researchers to file with the FDA for use of an investigative new drug.) "We are trying to provide them with a convenient and palatable method of administrating lecithin," says Harold Graham, vice president of research and development. According to Graham, the company hopes that a commercial market will some day develop for what is now an experimental product. —*S. Weisburd*



The nervous system depends on the rapid transmission of nerve impulses between neurons. Here, an electrical signal travels down a neuron's axon, causing vesicles containing neurotransmitters to release their contents into the synapse. An expelled transmitter molecule then carries a message from the terminal of the excited neuron to the receptor site of another.

says that in theory, as soon as normal pressure is obtained the firing frequencies will change so that the neurons become insensitive to additional tyrosine.

By exploiting the selectivity afforded by the brain's control over the sensitivity and firing frequency of some neurons, researchers may be able to use nutrients in the treatment of many disorders in addition to blood pressure abnormalities. For example, clinicians have used choline in the experimental treatment of tardive dyskinesia, a motor disturbance often brought on by the imprecise actions of antipsychotic drugs (which aim to block dopamine receptors, but inadvertently inhibit the release of acetylcholine in some regions of the brain).

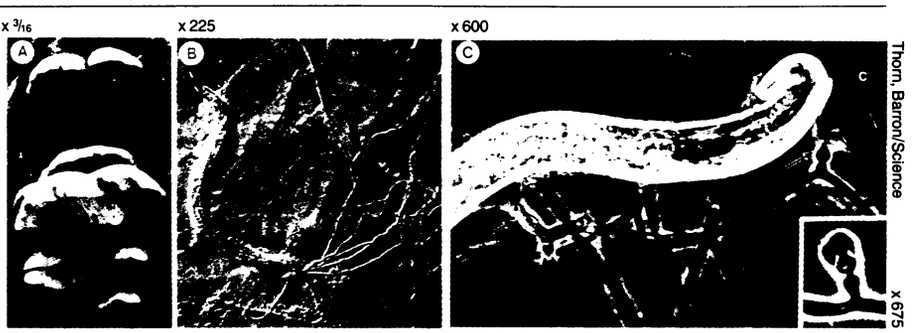
Because nutrients seem to act so precisely and are so easily metabolized, they make an attractive option for a remarkably broad range of disorders. In addition to the studies already mentioned, scientists are considering the use of tyrosine in the treatment of stress, tryptophan for pain and choline for Parkinson's disease.

"It [precursor treatment] has great appeal," says Growdon, "because it is using the body's own mechanisms, but you're making it work in your favor... and it's unlikely to have toxic side effects or long term deleterious effects that some synthetic drugs have."

Growdon adds: "The potential utility of dietary precursor treatment is quite open." □

News of the week continued from p. 215

Attack of the worm-eating mushrooms



Diverse ways to snare a nematode: The oyster mushroom grows on a living tree (A). A small piece of this fungus, put on a laboratory gel, releases a potent toxin, which immobilizes a nematode (B). Filaments of the mushroom converge on the unlucky nematode's mouth. Another fungus, called Hohenbuehelia *(C), traps nematodes with its adhesive spheres (marked with arrows and magnified in inset). The nematode's struggles pulled its cuticle (c) away from its body.*

Mushrooms growing on rotting wood can supplement their carbohydrate diets with high-protein snacks of microscopic animals. At least eleven species of gilled fungi attack and consume tiny worms called nematodes, report biologists at the University of Guelph in Ontario, Canada. Some of the fungi use sticky protuberances to catch these refreshments. But the oyster mushroom and four related fungi employ a more unusual strategy. They release a potent toxin that stops nematodes in their tracks.

The taste for meat is widespread outside the animal kingdom among organisms that grow in nitrogen-poor conditions such as swamps, bogs or decaying wood. Approximately 450 species of flowering plants digest small-animal prey. In addition, many types of microscopic, asexual fungi parasitize nematodes or other microscopic animals.

Carnivorous consumption has now been reported among the types of fungi noticeable to a hiker in the woods. "These fruiting bodies are massive, bigger than your hand," says George L. Barron of Guelph. The oyster mushroom, an edible species, and its kin are most commonly found around the world on live and recently dead hardwood trees. They are grown commercially in Europe, Israel, Asia and the United States.

Fragments of oyster mushrooms, transferred to a laboratory gel and allowed to spread filaments into a thin weave, rapidly inactivate but do not kill nematodes. "Some knock out a nematode in half a minute," Barron says. "We have no idea what the toxin is."

After the nematode is inactivated, fungal filaments called hyphae grow rapidly toward and eventually penetrate a body orifice. Within a day the nematode body is filled with hyphae and its contents digested. "This method of attacking nematodes has not been reported previously," Barron and R. G. Thorn say in the April 6 SCIENCE.

Other mushrooms examined by Thorn and Barron immobilize nematodes on adhesive knobs and some nematode-trapping microscopic fungi also use adhesive cells.

How often are nematodes on the menu? A sample of a standing maple's rotting core produced more than 900 nematodes per 100 milliliters. "Nematodes are only 200 to 1,000 microns long, but if you can catch a lot of them, that's OK. They're very high in protein," Barron says.

The scientists conclude, "In habitats such as rotting wood where nitrogen is limiting because of scarcity or intense microbial competition, the ability of fungi to feed on nematodes may be a significant advantage." — *J.A. Miller*