tients, families, and scientists, public health researchers and other investigators must reconsider their methods of doing research and obtaining consent before publication of results. The risk to public health caused by a loss of trust in the scientific community is surely one of the greatest plagues we face.

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Brain Serotonin Neurotoxicity and Fenfluramine and Dexfenfluramine

To the Editor.—Recently the serotonin-enhancing diet drugs, fenfluramine and dexfenfluramine, were withdrawn from the market in the United States. These drugs appear to deplete the brain of serotonin, suggesting that normal physiology during treatment may require constant replenishment of serotonin.[1] Brain serotonin is synthesized from tryptophan. The rate-limiting step in brain serotonin synthesis is entry of tryptophan into the brain. Such entry is proportionate to the ratio of plasma tryptophan to other large neutral amino acids (Trp/LNNA) that compete with tryptophan for passage past the blood-brain barrier. A higher Trp/LNAA ratio corresponds to a greater capacity to synthesize brain serotonin.

In women, but not in men, dieting has been repeatedly demonstrated to decrease plasma tryptophan levels and Trp/LNAA ratios by Cowen and colleagues (see reference for citations).[2] Four other laboratories have confirmed lower Trp/LNAA ratios in dieting women.[3-6]

Long-term dexfenfluramine treatment is accompanied by alteration in brain tryptophan levels and Trp/LNAA ratios. At first, dexfenfluramine prevents the tryptophan level and Trp/LNAA ratio declines commonly seen in dieting women. After 3 months, dexfenfluramine no longer effectively prevents such declines and dexfenfluramine simultaneously loses its ability to accelerate weight loss. The causal relationship between these 2 events is unknown. Dr McCann and colleagues[1] suggest that such losses of anorectic activity may reflect damage to serotonin neurons. If this is the case, it is not known if decreases in the Trp/LNAA ratio reflect or help precipitate such damage.

In contrast to dexfenfluramine, fenfluramine may magnify the decreases in tryptophan levels and Trp/LNAA ratios commonly seen in dieting women. A single 30-mg dose of fenfluramine lowers total plasma tryptophan levels of dieting women by 23%, but does not affect the tryptophan levels of dieting men.[2] Studies in rats have confirmed that female brain serotonin, but not male, is decreased by fenfluramine. The implications of decreased serotonin synthetic capacity should be considered when the safety of any serotonin-enhancing drug is considered.

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To the Editor.—In the article by Dr McCann and colleagues,[1] the differences between fenfluramine and more standard psychostimulants, eg, dextroamphetamine, were not discussed in detail.

Some of the mechanisms that the authors suggest might explain the serious adverse events from fenfluramine might also apply to standard psychostimulants, but is there evidence that standard psychostimulants (such as those prescribed for attention-deficit/hyperactivity disorder) can cause the same serious adverse events? If standard stimulants do not produce the same serious adverse events, the search for possible mechanisms could be narrowed to pharmacologic effects of fenfluramine that standard stimulants do not share.

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1. McCann UD, Seiden LS, Rubin LJ, Ricaurte GA. Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine: a systematic review of the evidence. *JAMA.* 1997;278:666-672.

To the Editor.—In their review, Dr McCann and colleagues[1] conclude that fenfluramines damage brain serotonin neurons. They define serotonin neurotoxicity as "axotomy (ie, preterminal axon loss) of serotonin neurons in the central nervous system." Nowhere in their review do they provide evidence that fenfluramines do in fact cause axotomy; rather, they cite studies documenting what already is widely known: administration of high dosages of fenfluramines to experimental animals reduces forebrain serotonin and associated markers.

Decrements in serotonin markers cannot be equated with damage to serotonin neurons in the absence of evidence for underlying neuropathology. The presence of gliosis constitutes 1 such index of neuropathology. In our studies,[2,3] in which we observed 15% to 70% decrements in brain serotonin following high-dose dexfenfluramine regimens, we did not observe increases in the content of glial fibrillary acidic protein (GFAP), a biomarker of gliosis. Contrary to the suggestions of McCann et al, our failure to observe an effect of dexfenfluramine on GFAP does not reflect a lack of sensitivity of this measure to "small serotonin lesions." Decrements in serotonin in discrete areas of the brain that result from administration of the known serotonin neurotoxicant, 5,7-dihydroxytryptamine (5,7-DHT), are associated with large increases (40%-100%) in GFAP,[4] findings that indicate the sensitivity of GFAP as an index of gliosis and of chemical-induced damage to serotonin neurons. Thus, a hallmark of brain damage, gliosis, does occur following damage to serotonin neurons but is absent following exposure to fenfluramines.

The available preclinical data do not support the conclusion that fenfluramines damage brain serotonin neurons. We conclude that the contention of McCann et al that "serotonin neurotoxicity would be expected to occur in almost everyone taking a dose sufficient to achieve weight loss" is unwarranted.

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