"Easy-to-follow" diet plans appear each year to convince overweight Americans that there is finally a way to lose weight permanently. Barry Sears and Bill Lawren's book, The Zone, is no exception; in fact, Sears' book cover advertises that it is "a dietary road map to lose weight permanently, reset your genetic code, prevent disease, achieve maximum physical performance, [and] enhance mental productivity." But is this realistic? Can a diet really accomplish all of those tasks? After numerous searches through several databases, only two journal articles analyzing this diet plan surfaced, both warning readers about the misinformation contained in the book. There are definitely problems with Sears' diet; for example, his daily caloric intake recommendation is dangerously low. Tufts University Diet and Nutrition Letter stated that they believed "[Sears was] confusing the near-euphoria he promises from following the Zone diet with lightheadedness from hunger" (3). Dr. Zamenhof, Associate Professor of Biological Chemistry at UCLA said that it was probably due to an increased release of endorphins, enkephalins, and catecholamines. In addition, the information he provides regarding carbohydrate and fat metabolism, as well as insulin and glucagon secretion, are wrong. However, Sears also says that there is a direct relationship between insulin and glucagon with the synthesis of "good" eicosanoids (prostaglandin E1 and prostaglandin I2 and "bad" eicosanoids (prostaglandin E2, thromboxanes, and leukotrienes). Coleman, the author of one of the articles critiquing The Zone, states that there is no known metabolic pathway connecting diet, insulin-glucagon, and eicosanoids (2). In fact, Sears may actually be right: there have been studies in the past demonstrating the effect of insulin on arachidonic acid (a precursor of the "bad" eicosanoids and one "good" eicosanoid, PGI2 synthesis.

Insulin, Glucagon, and Carbohydrates

According to Sears, "traditional" diet plans recommending caloric intakes of 70% carbohydrates, 15% fat, and 15% protein actually cause people to gain weight. He says that high carbohydrate meals cause an insulin surge of up to 4 hours. The presence of insulin keeps the body from being able to use any of its glucose stores. As a result, one eventually becomes hypoglycemic and hungers for more sweets. In reality, the insulin surge experienced by a normal individual after consuming carbohydrates is much shorter than 4 hours. When normal individuals took the Oral Glucose Tolerance Test, insulin levels peaked around 30 minutes after ingesting the glucose; by the end of two hours, insulin levels were reduced by over 50% (7). Sears also says that high carbohydrate meals promote fat storage; there is, however, no scientific evidence to support his claim (2).

His solution to all of this is a diet that is 40% carbohydrates, 30% fat, and 30% protein. This promotes glucagon secretion, which helps in body fat reduction by utilizing stored fat and increases one's endurance by increasing fatty acid utilization. Sears believes that this diet, alone, affects the insulin-glucagon axis. This is a gross oversimplification. Insulin and glucagon levels change second to second based on the body's demands and other hormonal influences. In addition, even after a meal of only 40% carbohydrates, there is enough insulin around to keep the glucagon levels low.

Eicosanoid Production

According to Sears, wellness is the production of more good eicosanoids (PGI2 and PGE1) than bad eicosanoids (PGE2, TXA2, leukotrienes). Below is a summary of the roles of each of the eicosanoids:

PGI2:
vasodilator
bronchodilator
decreases platelet aggregation

PGE1:
decreases platelet aggregation
reduces release of histamine
releases lymphokines
inhibits secretion of acid
vasodilator
reduces pain
bronchodilator

TXA2
increases platelet aggregation

PGE2
promotes pain
depresses immune system

leukotrienes
promotes allergic responses
promotes skin disorders
histamine like actions

The overall scheme of Sears' diet is to eat a diet low in carbohydrates (limiting insulin secretion) and high in proteins (increasing glucagon secretion). A high fat content is needed to provide the body with the essential fatty acids needed to make "good" eicosanoids. Glucagon enhances good eicosanoid production while insulin causes bad eicosanoid synthesis.

The synthesis of eicosanoids requires essential fatty acids acquired from one's food intake. Diet provides linoleic acid, which is converted to gamma linolenic acid (GLA) by delta6 desaturase. Addition of 2 carbons yields dihomo gamma linolenic acid (DHLA). DHLA may follow one of three pathways, forming either "good" prostanoids, leukotrienes, or arachidonic acid (the precursor to bad eicosanoids, with the exception of PGI2 The conversion of DHLA to arachidonic acid (AA) requires delta5 desaturase. Diet also provides another essential fatty acid, alpha linolenic acid (ALA). ALA can eventually become eicosapentaenoic acid (EPA). EPA can form another family of

prostanoids and leukotrienes which are "neutral" eicosanoids. These pathways are the accepted pathways found in standard texts (although the "good", "bad", and "neutral" commentaries about the eicosanoids are from Sears) (10). (See Figure 1.)

Sears states that glucagon and insulin directly affect these pathways; this is Coleman's objection: "The metabolic pathways presented in The Zone that supposedly connect diet, insulin-glucagon, and eicosanoids are not currently known" (2). In Chapter 12 of this book, Sears describes how he believes glucagon and insulin to play a role in eicosanoid production. He says that insulin activates delta5 desaturase. As a result, levels of AA would increase, which has a direct effect on the amount of eicosanoid produced (1). In fact, several studies have been published showing that there is indeed a connection between insulin levels and delta5 desaturase activity. In 1989, researchers showed that DHLA becomes AA. Normal subjects and diabetic patients before and after treatment with insulin were given labeled DHLA. After a few hours, labeled AA was detected in plasma phospholipids. The researchers also believed that the study suggested an insulin dependence of delta5 desaturase in humans (5). Another study in 1991 on diabetic rats showed that delta5 desaturase and delta6 desaturase activities could be restored by injecting insulin (8).(An earlier study had suggested that impairment of platelet delta5 desaturase and delta6 desaturase is present in diabetes (9).) One year later, Mimouni and Poisson showed once again showed that treating diabetic rats with insulin could restore enzyme activity (12). More recently, a study on obese women revealed that insulin, not estrogen, increased delta5 desaturase and delta6 desaturase activity in serum, increasesd delta5 desaturase activity in platelets, but did not increase delta6 desaturase activity in platelets. In addition, platelets of obese women aggregated more and faster than of lean women (11). (Obese women were characterized by having higher insulin levels than lean women.)

Although current research supports Sears' statement that insulin plays a role in delta5 desaturase activity, no information could be found on the relationship between glucagon and delta5 desaturase suppression on Medline since 1966. Because none of the above articles hypothesized the specific mechanism by which insulin affects delta5 desaturase, it is unclear whether or not glucagon would logically inhibit delta5 desaturase. (If insulin stimulates delta5 desaturase by promoting protein dephosphorylation, it would follow that glucagon inhibits the enzyme by increasing cAMP and protein kinase A activity.) The lack of information regarding glucagon's role in the current literature is a weakness to the theory behind Sears' diet.

A fatty acid that Sears recommends is eicosapentaenoic acid (EPA). The benefits of a diet high in EPA have been documented; Greenland Eskimos, who consume large amounts of EPA., have low incidences of heart disease, diminished platelet aggregation, and prolonged clotting times. EPA increases the synthesis of thromboxane TX3 and the series 3 prostaglandins, which inhibit the release of AA from phospholipids, thereby reducing the amounts of PG2 and TX2, Sears' "bad" eicosanoids (10). He says that EPA inhibits delta desaturase. A recent study showed that both delta5 desaturase and delta6 desaturase activities in the human intestine could be inhibited after exposure to EPA (4).

The theory behind Sears' diet definitely has some problems: his daily caloric intake recommendation is too low. High carbohydrate meals do not promote greater body fat storage (Coleman)— it is a combination of the total number of calories consumed versus expended that influences body fat storage. Sears' claim that one can preferentially burn fat instead of carbohydrates when one is in "the zone" is also unfounded. Nonetheless, he has captured an interesting idea: that high levels of insulin lead to an activation of delta5 desaturase, thus increasing the amount of AA and therefore producing more eicosanoids that cause platelet aggregation, vasoconstriction, and histamine-like reactions. There is evidence that mixtures of leukotrienes (LKC4, LKD4, and LKE4) are "regulators in many diseases involving inflammatory or immediate hypersensitivity reactions, such as asthma" (10). Present day therapies for many diseases, including asthma, GI ulcers, and prevention of myocardial infarction, all involve eicosanoids (6).

Eicosanoids are definitely an important class of compounds in the human body. If glucagon truly inhibits delta5 desaturase, then perhaps modifying Sears' diet to include more calories and a lower percentage of fat (still high in linoleic acid, ALA, and EPA; low in AA) could indeed lead to better health.

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