

Entry Level Clinical Nutrition Part XIX

Carbohydrate-protein imbalances and the impact of fructose

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Neuroscience
J Physiol 590, 10 (2012) pp 2485-2499

'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition

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Key points

- We provide novel evidence for the effects of metabolic dysfunctions on brain function using the rat model of metabolic syndrome induced by high fructose intake.
- We describe that the deleterious consequences of unhealthy dietary habits can be partially counteracted by dietary supplementation of n-3 fatty acid.
- High sugar consumption impaired cognitive abilities and disrupted insulin signalling by engaging molecules associated with energy metabolism and synaptic plasticity; in turn, the presence of docosahexaenoic acid, an n-3 fatty acid, restored metabolic homeostasis.
- These findings expand the concept of metabolic syndrome affecting the brain and provide the

Agrawal R & Gomez-Pinilla F. 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition, *J Physiology*, Vol. 590, No. 10, pp. 2485-2499, 2012.

"All parameters of metabolic dysfunction related to fructose treatment were ameliorated by the presence of dietary n-3 fatty acid. Results showed that dietary n-3 fatty acid deficiency elevates the vulnerability to metabolic dysfunction and impaired cognitive functions by modulating insulin receptor signalling and synaptic plasticity."

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60 MINUTES

60 Minutes – Sunday, April 1, 2012

Is sugar toxic?



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The new enemy

Fruit juice targeted in the war on obesity

By MONICA ENG
Chicago Tribune

Over the last decade, the nation's war on obesity has targeted some fairly obvious culprits, including fast food, pastries, fried foods and soda.

But recent scientific studies and a new government-sponsored documentary that aired last week on HBO have identified a new, less obvious enemy: fruit juice.

This might surprise the many parents and school districts that in recent years have proudly ditched soda in favor of 100 percent juice. But health experts increasingly agree that it is not juice.

"Juice is just like soda, and I'm saying it right here on camera," pediatric obesity specialist Robert Lustig said in the documentary "Weight of the Nation," produced in conjunction with the Centers for Disease Control and Prevention. "There is no difference. When you take fruit and squeeze it, you throw the fiber in the garbage. That was the good part of the fruit. The juice is nature's way of getting you to eat your fiber."

Since 2001, the American Academy of Pediatrics has advised limiting daily juice consumption to 4 to 6 ounces for children 6 and younger and 8 to 12 ounces (the size of a soda can) for children 7 to 18. The academy's head of environmental health, Jerome Paulson, took it even further when he told the Tribune in December that children do not need to drink any juice at all.

"Don't drink an apple," he said. "Eat an apple."

An important difference between fruit juice and fruit, researchers point out, is that calories and sugar delivered in liquid form don't trigger feelings of fullness and can lead to excess consumption.

Beverage-makers dispute claims that fruit juice and obesity are linked. The Juice Products Association said it supports the pediatric group's recommendations on juice but added that "current scientific evidence does not support a relationship between being overweight and juice consumption."



Daily Hampshire Gazette, May 29, 2012

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"All the News
That's Fit to Print"

The New York Times

VOL. CLXI . . . No. 55,788
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THURSDAY, MAY 31, 2012
\$2.50

New England Edition
Today, partial sunshower, breezy; less humid, high 78. Tonight, partial cloudiness, cooler, low 57. Tomorrow, partial sunshine, cool, high 71. Weather map appears on Page B16.

ISRAELI WEIGHS IMPOSED BORDERS FOR PALESTINIANS

BYPASSING PEACE TALKS

Suggestion by Defense Minister Barak Meets Mixed Reaction

By JODI RUDOREN

TEL AVIV — Defense Minister Ehud Barak said Wednesday that Israel should consider imposing the borders of a future Palestinian state, becoming the most senior government official to suggest bypassing a stagnant peace process.

Mr. Barak's statement to consider what he said many Israelis call "unilateral actions," without offering any specifics, echoed an emerging chorus of political leaders, analysts and intellectuals who have said that Israel needs to put in effect its own settlement to the Palestinian crisis. Though the Israeli government continues to call for negotiations toward a two-state solution, the drive for a one-sided approach also received a boost on Wednesday from the Institute for National Security Studies, a respected research

STRIKE A Syrian carried her injured son into Lebanon Wednesday. An American official said sectarian war could loom. Page A10.

NEW YORK PLANS A BAN ON BIG SIZES OF SUGARY DRINKS

16 FLUID OUNCES AS LIMIT

Anti-Obesity Push by the Mayor Would Affect a Range of Vendors

By MICHAEL M. GRYNBAUM

New York City plans to enact a far-reaching ban on the sale of large sodas and other sugary drinks at restaurants, movie theaters and street carts, in the most ambitious effort yet by the Bloomberg administration to combat rising obesity.

The proposed ban would affect virtually the entire menu of popular sugary drinks found in delis, fast-food franchises and even sports arenas, from energy drinks to pre-sweetened "iced teas." The sale of any cup or bottle of sweetened drink larger than 16 fluid ounces — about the size of a medium coffee, and smaller than a common soda bottle — would be prohibited under the first-of-its-kind plan, which could take effect as soon as next March.

The measure would not apply to diet sodas, fruit juices, dairy-based drinks like milkshakes, or

Ex-Liberian Leader Gets 50 Years for War Crimes

NEWS ANALYSIS

And now, a response to New York City's proposal to fight obesity by banning the sale of large sodas...

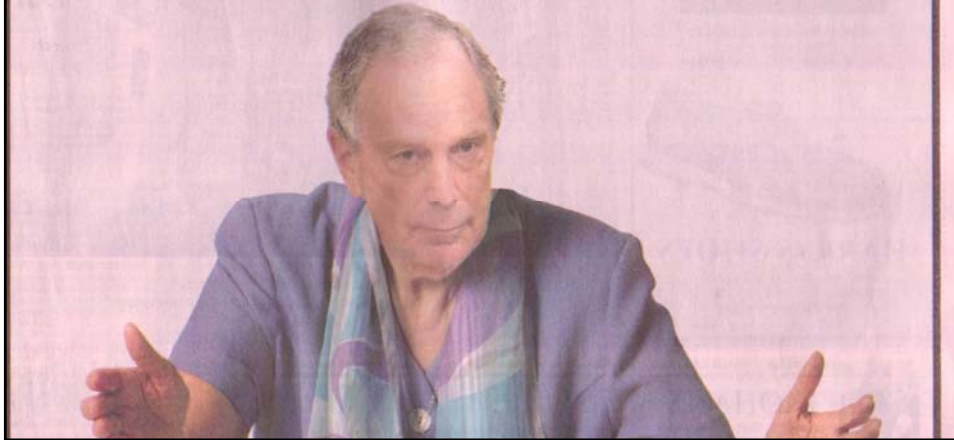
By Randy Bish, Pittsburgh Tribune-Review

USA Today, Friday, June 1, 2012

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The Nanny

You only thought you lived in the land of the free.



BA

"USA TODAY hopes to serve as a forum for better understanding and unity to help make the USA truly one nation."

—Allen H. Neuharth, Founder, Sept. 15, 1982

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Today's debate: Obesity

16 ounces of prevention is no cure for pounds

If Mayor Michael Bloomberg gets his way, which he usually does, New Yorkers will soon no longer be able to buy sugary drinks in servings larger than 16 ounces. And Bloomberg sees his idea as a national model in the fight against obesity.

To be sure, America would be better off, not to mention thinner, if people didn't gulp down sodas from cups as big as buckets. Super-sized beverages are undoubtedly a factor in the nation's ballooning belt sizes. But Bloomberg's plan is short on logic and long on intrusion. It has so many loopholes that it's unlikely to be effective. And there are better ways to fight obesity.

The mayor's plan requires a raft of new regulations and enforces (Shiraz?) to prevent restaurants, sports venues and street carts from selling oversized beverages. Such overreach is more likely to pump up anger at government than whittle away at waistlines.

OUR VIEW

NYC 'portion cap' won't do the job

The ban — which Bloomberg protests is really a "portion cap" because you can still drink as much as you want — is just too easy to get around for precisely that reason. Fast-food joints and other soft drink sellers may well start offering two-for-one specials or perhaps bottomless cups of refills.

The city doesn't regulate grocery and convenience stores, so Bloomberg's edict wouldn't even kill off the granddaddy of super-sized drinks, 7-Eleven's Big Gulp. Introduced in 1980 at 32 ounces, it has since been left in the dust by the 64-ounce Double Gulp.

A group funded by restaurants and food companies is already running ads poking fun at the mayor, depicted in a dumpy blue dress, as "The Nanny." If the food industry is able to tame this effort as over the top, it might well set back better solutions in the future. It also gives the industry an opening to ask, what's next? Will New York, home to the towering corned beef sandwiches, soon allow them to be piled only 3 inches high?

We'll give the mayor points for this. He's think-



Hey sugar: New York Mayor Michael Bloomberg proposes a 16-ounce cap on sugary drinks.

government expenditures, estimated at \$1,300 to \$1,700 per household each year.

That's all the more reason the nation needs to find solutions that work, and others are showing more promise, including better public disclosure. Believe it or not, many people don't realize just how many calories are in that Double Quarter Pounder with Cheese (770) or 32-ounce Coke (310).

New York City, under Bloomberg, was the first to mandate calorie counts on menus, and, yes, the policy drew angry critics. But it was smart, and it spread. Empowering people with information to make choices for themselves is an effective use of government authority.

Under a recent federal law, chain restaurants across the country will have to post calories. Perhaps when people see they could eat a meal for the same number of calories as a drink, they'll think twice.

Smarter school lunch choices are helping to slow the growth in rates of child obesity. PR campaigns that promote healthier eating, or reveal the absurd number of calories in some foods, are also fair game. Already, per capita consumption of regular soda is down 16% since its peak in 1998, while bottled water and diet drinks have become more popular.

Big portions yield big waistlines

By Michael R. Bloomberg

Bold actions to protect the public's health always stir controversy at first. Smoke-free bars and restaurants, trans fat restriction and calorie posting in restaurants were all met with skepticism, but are now widely popular in New York City. They are also saving many lives each year, and life expectancy in New York City is outpacing that of the United States.

OPPOSING VIEW

Reaction follows familiar pattern

The initial reaction to our proposed portion cap on sugary beverages follows a now familiar pattern. But here are the key points. The increase in sugary drink consumption is the largest single cause of the rise in calories in the American diet in the last 40 years. Many studies show consumption of these beverages is linked to weight gain and obesity, and more recently, diabetes and heart disease.

Other studies show that people given larger portions simply consume more without noticing it or reducing calorie consumption at subsequent meals. And portion sizes of sugary drinks have ballooned drastically over the last 50 years, from

12 ounces to 32 ounces for a large beverage at a typical fast-food restaurant, not as a result of consumer demand but because of corporate decisions.

Together, these facts strongly suggest that if people are served smaller portion sizes of sugary drinks, they will consume less, gain less weight and be healthier — and we may just start to reverse the catastrophic epidemic of obesity.

Critics claim this policy restricts choice. But, currently, people almost never have the choice to purchase as small as an 8-ounce beverage, which was considered adequate for decades.

Under our proposal, people could still choose to drink as much soda as they want. If 16 ounces (promoted as enough for three people in the 1950s) is not enough, people could purchase two portions. Is that too much an inconvenience to reverse a national health catastrophe?

Rather than wringing our hands about the obesity epidemic, we in New York City are once again taking action to improve the lives of our residents. History will likely bear out that once the controversy dies down, we will look back and wonder why we did not do this sooner.

Michael R. Bloomberg is the 108th mayor of New York City.

USA Today, June 4, 2012



Daily Hampshire Gazette, June 4, 2012

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Promoting Nutrition, Disney to Restrict Junk-Food Ads

By BROOKS BARNES

LOS ANGELES — The Walt Disney Company, in an effort to address concerns about entertainment's role in childhood obesity, plans to announce on Tuesday that all

The New York Times, June 5, 2012

caused television channels, radio stations and Web sites must comply with a strict new set of nutritional standards.

The restrictions on ads extend to Saturday-morning cartoons on ABC stations owned by Disney. Under the new rules, products like Capri Sun drinks and Kraft Lunchables meals — both current Disney advertisers — along with a wide range of candy, sugared cereal and fast food, will no longer be acceptable advertising material.

The initiative, which Dis-

ney plans to detail Tuesday at a Washington news conference with the first lady, Michelle Obama, stretches into other areas. For instance, Disney will reduce the amount of sodium by 25 per-

cent at its theme parks, and create what it calls "fun" public service announcements promoting child exercise and healthy eating.

The move follows the announcement last week of a plan by New York City to ban the sale of large sodas and other sugary drinks amid increasing concern about childhood obesity in America.

Disney said that in adopting the new advertising standards it was largely following recommendations

Continued on Page 9



A fruit cart at a Disney theme park featuring fresh produce for sale. Disney's new commercial restrictions will bar some current advertisers.



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PARADE
SUNDAY, MAY 27, 2012

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WHOOPIE PIES
This treat—two circles of dark chocolate cake with a ribbon of vanilla cream in between—may have originated in 1927 in Roxbury, Mass., at the Black Cake Company, possibly as competition for Drake's Dead Dogs. Or it could have been created (and pronounced) in Pennsylvania Dutch country, where, according to lore, children were so excited to find what was known as a "huckabuck" in their lunch boxes that they shouted, "Whoopie!" The state of Maine, where

CALIFORNIA DIP
As the story goes, in 1954, two years after Lipson introduced its dry onion soup mix, a now-legendary, housewife in Southern California stirred a dry soup packet into a dry soup packet and made a creamy potato soup dip. Her recipe was reprinted in newspaper's countless times, and by the end of the 1950s, it had become a house party classic, perfectly suited for ready-to-go entertaining on the patio or in the family room. With its cornstarch, potatoes, or napkins involved, guests could hold a handful in one hand and scoop up dip with the other—a task made especially easy with the sturdy ridged

WHAT AMERICA EATS

WHOOPIE PIES
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CHEWY

HAMBURGERS
People have eaten ground beef for centuries, but a little more than 100 years ago, someone in America came up with the idea of forming it into a patty and putting it between slices of bread, turning it into a handy-to-eat meal on wheels. While it's hard to say who might have been the first, the hamburger was reportedly eaten out of paper patties at their sandwich stand at the 1895 Erie County Fair

CHILI DOGS
Historians have a hard enough time pinpointing the birthplace of the hot dog (Coney Island figures among the possibilities), and determining the chili dog's origins is just as tricky. But a prominent theory traces it to

Edy's Slow Churned
Now in Cups!
One for all
All for one
Whatever the size, Edy's Slow Churned light ice cream is always rich and creamy. Plus, it's churned slowly for all the taste with HALF THE FAT and 1/3 fewer calories.

CHILI DOGS
Historians have a hard enough time pinpointing the birthplace of the hot dog (Coney Island figures among the possibilities), and determining the chili dog's origins is just as tricky. But a prominent theory traces it to

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Cartoon Parade®



"Your cholesterol is off the charts."



"You might as well pay the check now, I've already decided to ignore you for the rest of the evening."

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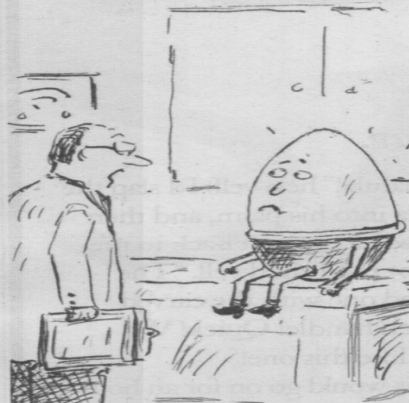
Lay's
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MESQUITE BBQ

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Happiness is simple

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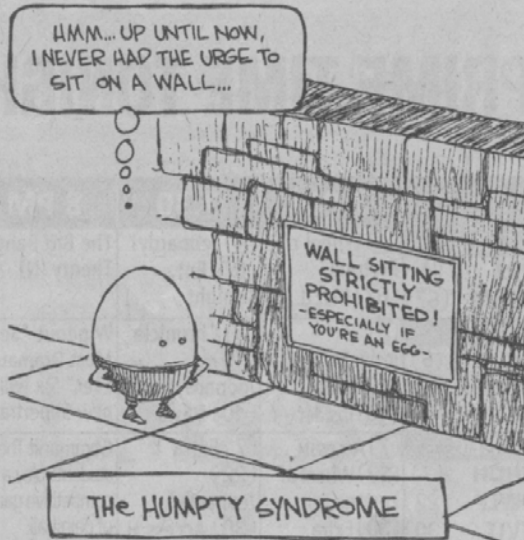
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"Your cholesterol is off the charts."

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NON SEQUITUR



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Quality of life issues are the major concerns more than ever now.

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Summer of Work Exposes Medical Students to System's Ills - NYTimes.com
Page 1 of 3

The New York Times



September 9, 2009

Summer of Work Exposes Medical Students to System's Ills

BY NEVIL ACHER

SEATTLE — This summer, medical students from the University of Washington took a long look under the hood of the health care system they are about to inherit, and many returned to campus last week with their eyes wide open and their idealism tempered.

Jacob R. Olsgaard, 26, a second-year medical student, said he was struck by the "tidal wave of chronic disease" — diabetes, hypertension, obesity, depression — that left many questioning how much any one physician could really accomplish.

"I often wondered what we were actually doing to help people," Mr. Olsgaard said.

Not surprisingly, the students learned not only to deliver babies and suture wounds, but also to order unnecessary tests as protection against lawsuits, to hector specialists into seeing Medicaid patients, to match patients with prescriptions on Wal-Mart's \$4 list. And they saw firsthand what Mr. Olsgaard called "a tidal wave of chronic disease" — diabetes, hypertension, obesity, depression — that left many questioning how much any one physician could really accomplish.

"You have to be able to deliver babies and suture wounds, but also to order unnecessary tests as protection against lawsuits, to hector specialists into seeing Medicaid patients, to match patients with prescriptions on Wal-Mart's \$4 list. And they saw firsthand what Mr. Olsgaard called "a tidal wave of chronic disease" — diabetes, hypertension, obesity, depression — that left many questioning how much any one physician could really accomplish.

For 21 years, the University of Washington School of Medicine has dispatched its rising second-year students across the Northwest to provide primary care in rural or underserved areas. The monthlong program is elective, but a record number of students took part this year — 117 from a class of 216.

The school has a cooperative agreement to train medical students from Alaska, Idaho, Montana and Wyoming, none of which has a medical college of its own. The summer program is one of several vehicles, along with loan forgiveness enticements, designed to lure students back to their home states to practice in areas with a shortage of primary care givers.

This year, the students set out as negotiations were intensifying in Washington over wholesale changes to the health care system they will soon be joining. Whether there will be improvements to the system remains to be seen, but few students returned thinking there was little to fix.

http://www.nytimes.com/2009/09/09/health/policy/09medschool.html?_r=1&th=&cmc=th&... 9/9/2009

Summer of work exposes medical students to system's ills, *The New York Times*, September 9, 2009

"...a tidal wave of chronic illness..."

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Nestlé Nutrition Workshop Series
Clinical & Performance Program, Vol. 8

Nutrition and Critical Care

Luc Cynober
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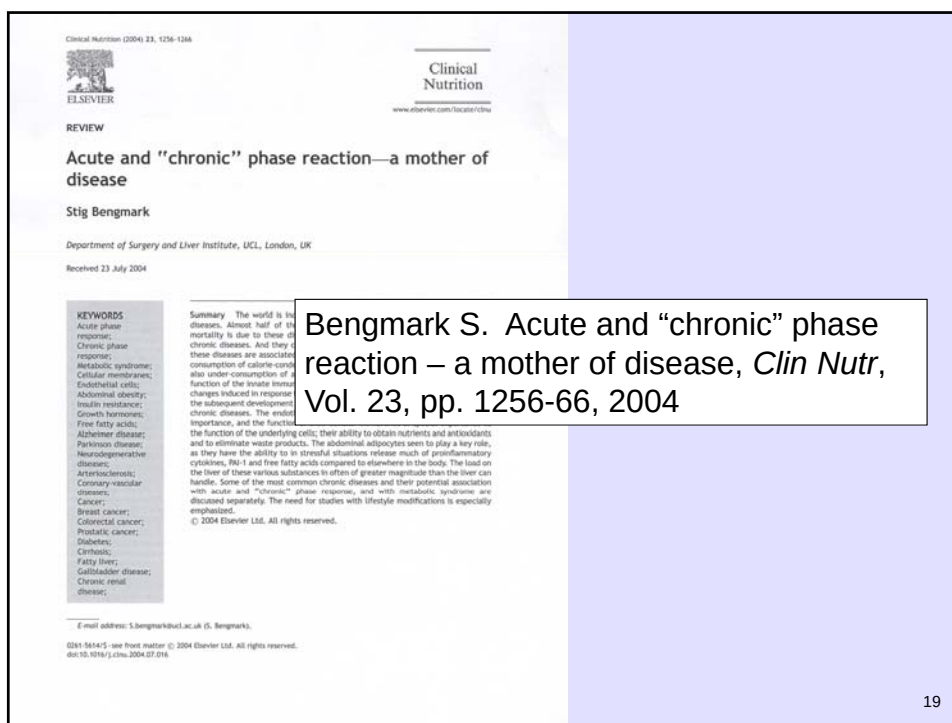


Baracos VE. Overview on metabolic adaptation to stress, pp. 1-13.

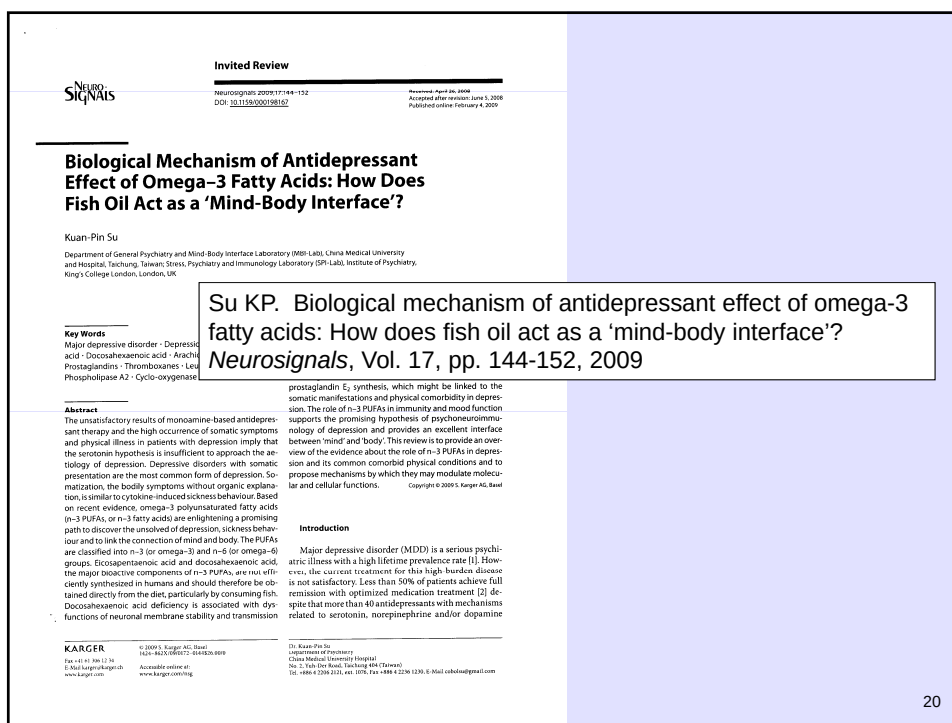
"An understanding of the nature of stress is fundamental to the rational design of nutrient mixtures to feed patients whose homeostasis has been altered by one or more stressors."

"All stresses may be presumed to be associated with characteristic modifications in the metabolism of lipids, carbohydrates, amino acids, and micronutrients."

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Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

Symptoms	Prevalence in IFN- α therapy ^a , %	Prevalence in MDD ^b , %
Fatigue/asthenia	39–90	73
Headache	27–67	33 ^e
Gastrointestinal symptoms	50 ^{c, 1}	34–47 ^f
Psychomotor slowing	40 ^c	59–65 ^f
Insomnia	20–39 ^d	63
Irritability	35 ^d	50
Arthralgia	9–36	31 ^e
Musculoskeletal pain	26–32	62–80 ^{g, 2}
Abdominal pain	15–20	21 ^e
Anorexia	13–19	40
Anxiety	13–18 ^d	57
Poor concentration	14 ^d	51

^a [46], unless otherwise specified; ^b [99], unless otherwise specified; ^c [100]; ^d [101]; ^e [102]; ^f [103]; ^g [104].

¹ Nausea, vomiting, bowel problems.

² Result from depressed inpatient population.

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Key metabolic imbalances seen with the acute phase response

- Metabolic acidosis
- Loss of lean body mass (sarcopenia)
- Insulin resistance
- Inflamm-aging (Increased innate immunity and decreased adaptive immunity)
- Suboptimal caloric intake and carbohydrate:protein ratio (Refeeding syndrome)
- Gastrointestinal dysfunction/gut atrophy
- Deficiencies of key micronutrients such as zinc, selenium, and vitamin D

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Underlying hypotheses of Entry Level Clinical Nutrition:

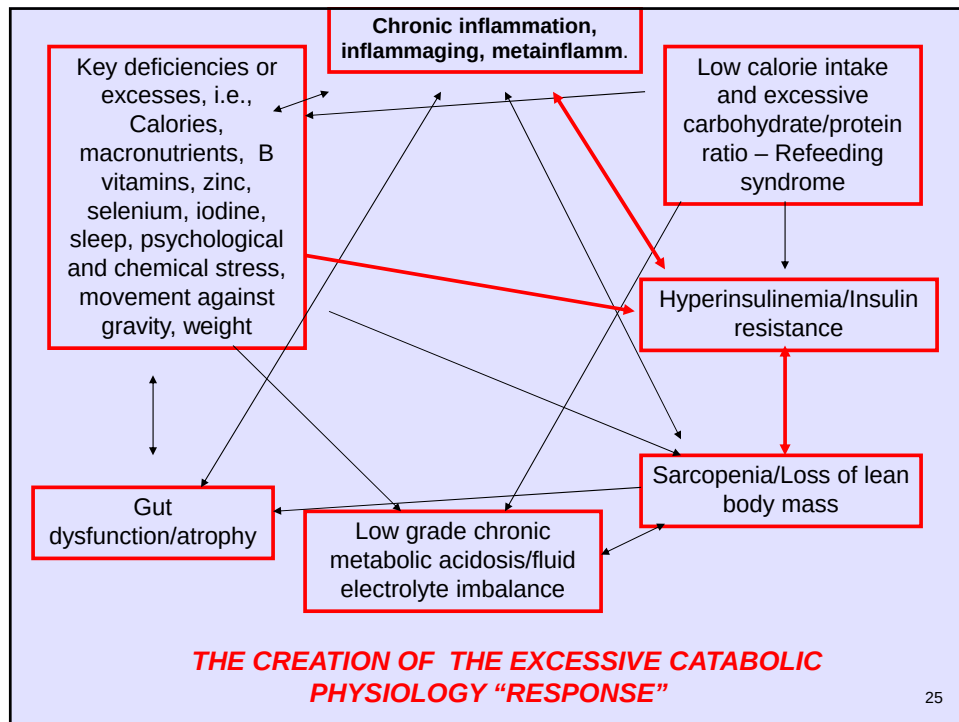
- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

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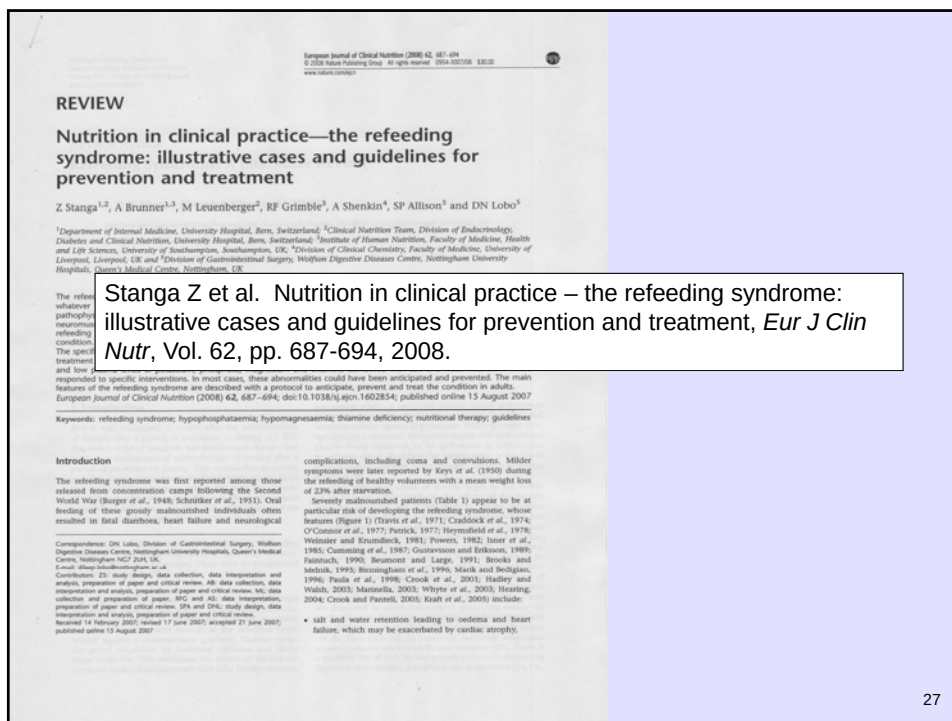
Entry Level Clinical Nutrition:

A new model of functional
medicine that incorporates
allostatic load and the “chronic”
acute phase response

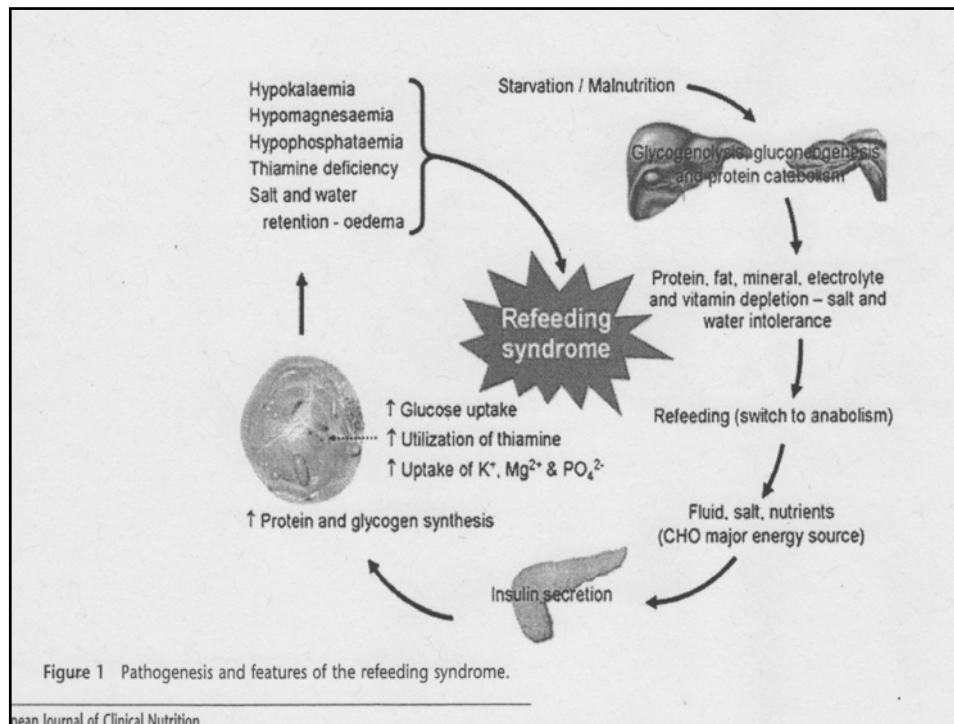
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Refeeding syndrome



- “The refeeding syndrome was first reported among those released from concentration camps following the Second World War.”
- “Oral feeding of these grossly malnourished individuals often resulted in fatal diarrhoea, heart failure and neurological complications, including coma and convulsions.”
- “Milder symptoms were later reported by Keys *et al.* during the refeeding of healthy volunteers with a mean weight loss of 23% after starvation.”



Journal of Clinical Nutrition

Table 1 Some groups of malnourished patients at particular risk of developing the refeeding syndrome

Unintentional weight loss

- Loss of > 5% of body weight in 1 month
- Loss of > 7.5% of body weight in 3 months
- Loss of > 10% of body weight in 6 months

Low nutrient intake

- Patients starved for > 7 days
- Prolonged hypocaloric feeding or fasting
- Chronic swallowing problems and other neurological disorders
- Anorexia nervosa
- Chronic alcoholism
- Depression in the elderly
- Patients with cancer
- Chronic infectious diseases (AIDS, tuberculosis)
- During convalescence from catabolic illness
- Postoperative patients
- Diabetic hyperosmolar states
- Morbid obesity with profound weight loss
- Homelessness, social deprivation
- Idiosyncratic/eccentric diets
- Hunger strikers

Increased nutrient losses/decreased nutrient absorption

- Significant vomiting and/or diarrhoea
- Dysfunction or inflammation of the gastrointestinal tract
- Chronic pancreatitis
- Chronic antacid users (these bind minerals)
- Chronic high-dose diuretic users
- After bariatric surgery

Skipping meals and then binging on fructose-laden refined foods: Is it more fuel on the fire?

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Review

Fructose and metabolic diseases: New findings, new questions

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ABSTRACT

There has been much concern regarding the role of dietary fructose in the development of metabolic diseases. This concern arises from the continuous increase in fructose (and total added caloric sweetener consumption) in recent decades, and from the increased use of high-fructose corn syrup (HFCS) as a sweetener. A large body of evidence shows that a high-fructose diet leads to the development of obesity, diabetes, and dyslipidemia in rodents, in humans, fructose has

Fructose in our diet is with sweetened beverages (soft drinks) and in some cereals (sweetened cereals). The progressive replacement of sucrose by HFCS is however unlikely to be directly involved in the epidemic of metabolic diseases, because HFCS appears to have basically the same metabolic effects as sucrose. Consumption of sweetened beverages is however clearly associated with excess caloric intake, and an increased risk of diabetes and cardiovascular diseases through an increase in body weight. This has led to the recommendation to limit the daily intake of sugar calories.

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Pure, white, and deadly: the dark side of sugar was suspected many years ago, when an association between sugar consumption and coronary heart diseases was suggested and emphasized by John Yudkin [1]. Sugar, a natural sweetener obtained from either sugar cane or beet, is a disaccharide composed of one glucose molecule linked through an α-1,4 glycoside bond to a fructose molecule. Fructose, besides contributing to half the total caloric content of sugar, can also be fructose as a fructose in fruit and honey. More recently, sweeteners started to be produced from corn through starch isolation and hydrolysis to glucose, followed by enzymatic isomerization of part of the glucose into fructose [2,3]. The resulting mixture, known as high-fructose corn syrup (HFCS), has several industrial advantages over sugar. The most important being its low price, and has progressively replaced sugar consumption in North America over the past 30 years.

Fructose metabolism has been reviewed extensively elsewhere [4–6] and will be only briefly outlined here. In the gut, fructose is transported by specific transporters, GLUT5 [7,8]. In some subjects, fructose absorption is quantitatively limited, and some malabsorption occurs when large amounts of fructose are ingested. This can cause abdominal discomfort and diarrhea, and production of volatile fatty acids from colonic fructose fermentation [9,10]. Fructose absorbed from the gut into the portal vein is nearly completely metabolized in the liver through metabolic pathways distinct from those of glucose. Furthermore, the initial steps of its metabolism are insulin-independent, and hence, fructose is largely metabolized without requiring insulin secretion and without increasing plasma glucose. This is due to the fact that 1) part of the fructose appears to be directly metabolized in enterocytes, where it is converted and into lactate and glucose, and 2) the bulk of absorbed fructose is taken up by liver cells, where it is rapidly converted into fructose 1-phosphate and triose-phosphates through the sequential actions of fructokinase

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E-mail address: luc.tappy@chuv.ch (L. Tappy).

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Basic information on fructose

- “Sugar, a natural sweetener obtained from either sugar cane or beets, is a disaccharide composed of one glucose molecule linked through an α 1-4 glycoside bond to a fructose molecule.”
- “Fructose besides contributing to half the total content of sugar, can also be found as a hexose in fruits and honey.”

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- “More recently, sweeteners started to be produced from corn through starch isolation and hydrolysis to glucose, followed by enzymatic isomerization of part of the glucose into fructose.”
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Intestinal metabolism of fructose

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- “This can cause abdominal discomfort and diarrhea, and production of volatile fatty acids from colonic fructose fermentation.”

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- “Fructose absorbed from the gut into the portal vein is nearly completely metabolized in the liver through metabolic pathways distinct from those of glucose; furthermore, the initial steps of its metabolism are insulin-independent, and hence, fructose is largely metabolized without requiring insulin secretion and without increasing plasma glucose.”

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- “This is due to the fact that 1) part of the fructose appears to be directly metabolized in enterocytes, where it is converted into lactate and glucose, and 2) the bulk of absorbed fructose is taken up by liver cells, where it is rapidly converted into fructose 1-phosphate and triose-phosphates through the sequential actions of fructokinase and aldolase B and triokinase.”

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- “Fructokinase and aldolase B are not inhibited by ADP and citrate and hence are not regulated by the cellular energy status.”
- “In fact, fructose differs from glucose, because the ADP and citrate concentrations exert a negative feedback control of the initial steps of glycolysis.”

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- “Because fructose metabolism is not dependent on insulin secretion, at least in its initial steps, and because fructose ingestion causes only a limited rise in glycemia, fructose was initially proposed as a natural substitute of sucrose for diabetic patients.”
- “It however became rapidly apparent that an increased dietary intake of fructose had serious adverse metabolic effects in both rodents and humans.”

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“Thus it was recognized that a high-fructose intake is associated with increased plasma triglyceride concentrations, hepatic steatosis, impaired glucose tolerance and insulin resistance, and even high blood pressure.”

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Dietary fructose vs. HFCS

- “In our everyday diet, naturally occurring, free fructose (essentially with fruits and honey) is a modest component of energy intake.”
- “Furthermore, there is some evidence that consumption of fructose with fruits or honey does not produce the same adverse metabolic effects as added fructose.”

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- “This may be due to the presence of natural antioxidants and/or dietary fibers with fruits and honey.”
- “The vast majority of fructose in our diet corresponds to added sugars, the two main sources being sucrose (containing 50% fructose) and HFCS (containing 42%-55% fructose).”
- “As a consequence, the intakes of fructose and glucose always vary simultaneously, and therefore, high-fructose consumers are also high-glucose consumers.”

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Overall conclusions

- “There is compelling evidence that a hypercaloric, high fructose diet can induce, not only in animal models, but also in humans, a whole range of metabolic alterations, the most prominent being a disturbance of hepatic lipid metabolism and of plasma lipid profile.”
- “It appears therefore sound at this stage to advise limiting consumption of sugar calories to less than 140 kcal/d for men and 100 kcal/d for women (corresponding to about one can of sweetened beverage/d), as recently proposed by the American Heart Association.”

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Fructose and systemic health: The work of Robert Lustig, MD

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Arguments against Lustig

- “Most of the data Lustig presents are from rodent studies.”
- ***“The development of obesity is caused by an energy imbalance such that energy intake exceeds energy expenditure from the body.”***

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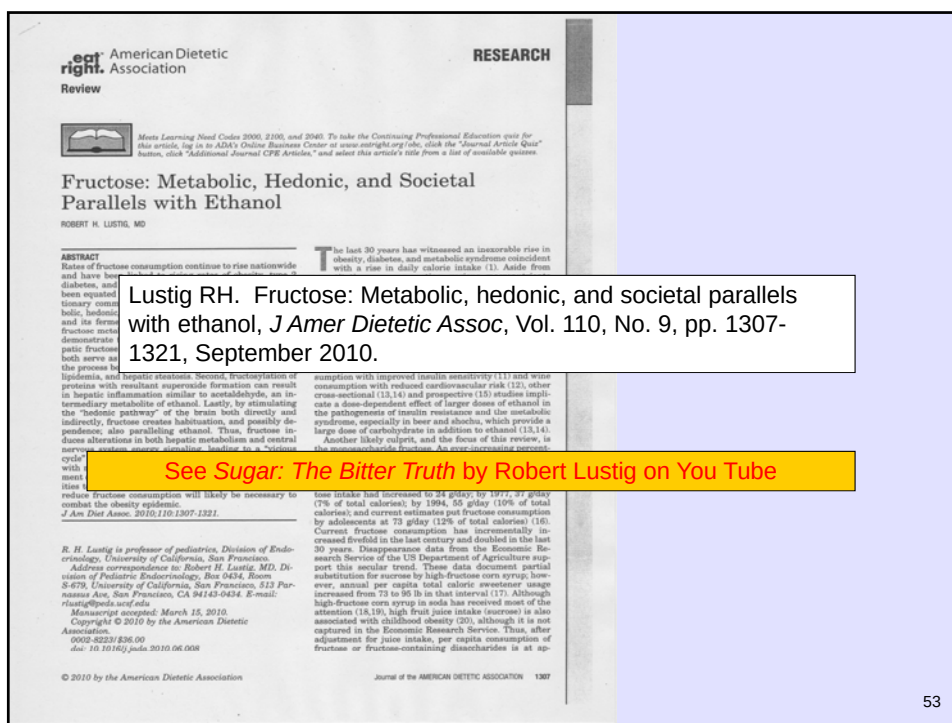
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- “Whereas the majority of studies document a relationship of visceral fat to insulin resistance, ectopic liver fat correlates better with dysfunctional insulin dynamics from which the rest of metabolic syndrome derives.”
- “In contrast to the systemic metabolism of glucose, the liver is the primary metabolic clearinghouse for 4 specific foodstuffs that have been associated with the development of metabolic syndrome: trans-fats, branched-chain amino acids, ethanol, and fructose.”

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“These 4 substrates (1) are not insulin regulated and (2) deliver metabolic intermediates to hepatic mitochondria with an appropriate ‘pop-off’ mechanism for excess substrate, enhancing lipogenesis and ectopic adipose storage.”

52



- “Elucidation of fructose metabolism in liver and fructose action in brain demonstrate three parallelisms with ethanol.”
- “First, hepatic fructose metabolism is similar to ethanol, as they both serve as substrates for de novo lipogenesis, and in the process both promote hepatic insulin resistance, dyslipidemia, and hepatic steatosis.”
- “Second, fructosylation of proteins with resultant superoxide formation can result in hepatic inflammation similar to acetaldehyde, and intermediary metabolite of ethanol.”

- “Lastly, by stimulating the ‘hedonic pathway’ of the brain both directly and indirectly, fructose creates habituation, and possibly dependence; also paralleling ethanol.”
- “Thus, fructose induces alterations in both hepatic metabolism and central nervous system energy signaling, leading to a ‘vicious cycle’ of excessive consumption and disease consistent with metabolic syndrome.”

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Epidemiologic data

- “...our absolute consumption of dietary fat has not changed in these last 30 years, and high-fat, low-carbohydrate diets appear to be protective against the metabolic syndrome.”
- “Before 1900, Americans consumed approximately 15g/day fructose (4% of total calories, mainly through fruits and vegetables.”

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- “Before World War II, fructose intake had increased to 24 g/day; by 1977, 37 g/day (7% of total calories); by 1994, 55 g/day (10% of total calories); and current estimates put fructose consumption by adolescents at 73 g/day (12% of total calories).”
- “Although high-fructose corn syrup in soda has received most of the attention, high fruit juice intake (sucrose) is also associated with childhood obesity, although it is not captured in the Economic Research Service.”

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- “Thus, after adjustment for juice intake, per capita consumption of fructose or fructose-containing disaccharides is at approximately 156 lb/year or 0.4 lb/day for the average American.”

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“To explain the dichotomy of selective insulin resistance in the pathogenesis of metabolic syndrome, it is essential to delineate the hepatic metabolism of three energy substrates: glucose, ethanol, and fructose.”

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Hepatic glucose metabolism

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- “Upon ingestion of 120 kcal of glucose (eg, two slices of white bread), plasma glucose levels rise and insulin is released by the pancreas through glucose stimulation of β -cell depolarization via the Glut2 transporter.”
- “Ninety-six kilocalories (80%) of the glucose bolus are utilized by other organs immediately.”
- “Only 24 kcal (20%) enter the liver through the Glut2 transporter.”

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- “The liver can store large amounts of glycogen without experiencing dysfunction or damage, as demonstrated by the continued normal hepatic function into adulthood of patients with glycogen storage diseases.”
- “Only a small amount of glucose-6-phosphate (the exact amount is dependent on quantity of other substrates, and magnitude of insulin action) is broken down by the Embden-Meyerhoff glycolytic pathway to pyruvate.”

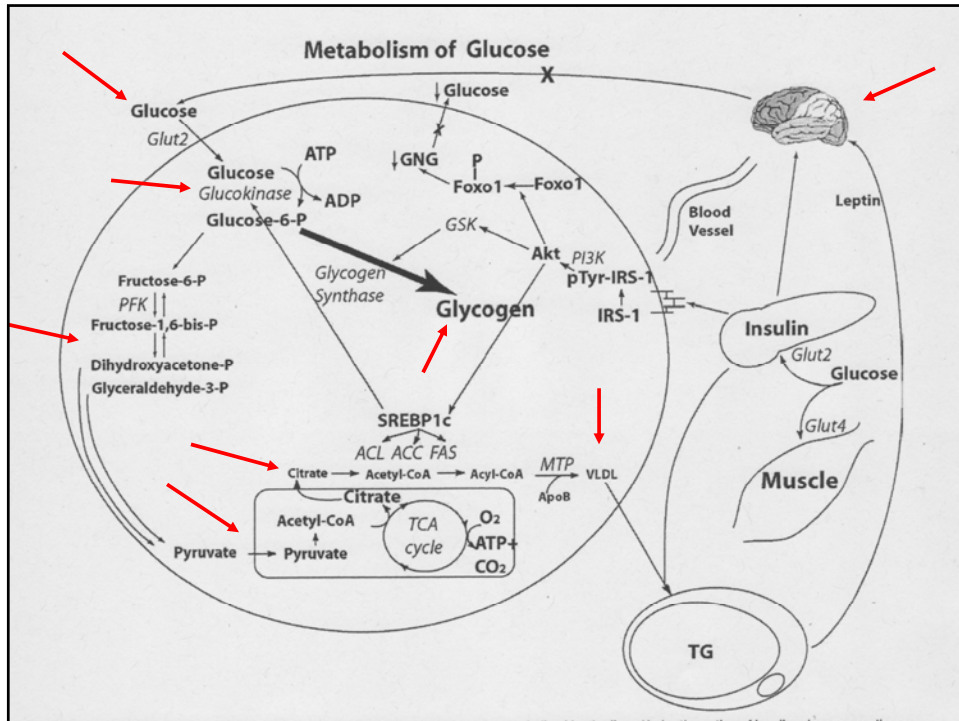
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- “Pyruvate enters the mitochondria, where it is converted to acetyl-CoA, which then participates in the Krebs tricarboxylic acid (TCA) cycle to generate adenosine triphosphate, the chemical storage form of energy, carbon dioxide, and water.”
- “The hepatic TCA cycle has a relatively fixed maximum velocity, modulated only by thyroid status, cold exposure, altitude, and exercise.”

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- “Thus, whatever tiny fraction of pyruvate is not metabolized by the mitochondria exits back into the cytoplasm as citrate through the ‘citrate shuttle’.
- “This small amount of cytoplasmic citrate can serve as substrate for the process of de novo lipogenesis (DNL).”
- “...only a tiny fraction of glucose can be hepatically metabolized to VLDL, which could contribute slowly to cardiovascular disease during a lifetime.”

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Hepatic ethanol metabolism

- “Upon oral ingestion of 120 kcal of ethanol (eg, 1.5 oz hard spirits at 80 proof, or 40%), approximately 10% is metabolized by the stomach and stomach and intestine in a ‘first-pass’ effect before entry into the portal circulation.”
- “Another 10% are metabolized by muscle and kidney.”
- “So approximately 96 calories reach the liver accounting for four times the substrate as for glucose.”

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- “Ethanol enters the hepatocyte through osmosis and does not stimulate insulin secretion.”
- “Once inside the liver, ethanol bypasses glycolysis and is converted by alcohol dehydrogenase 1B to form acetaldehyde, which, because of its free aldehyde, can generate reactive oxygen species (ROS) formation and toxic damage if not quenched by hepatic antioxidants such as glutathione or ascorbic acid.”

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- “Acetaldehyde is then quickly metabolized by the enzyme aldehyde dehydrogenase 2 to the intermediary acetic acid.”
- “From there, acetic acid is metabolized by the enzyme acyl-CoA synthetase short-chain family member 2 to form acetyl-CoA, which can then enter the mitochondrial TCA cycle; or, in the presence of other caloric substrate, it is more likely to participate in synthesis of fatty acids through DNL.”

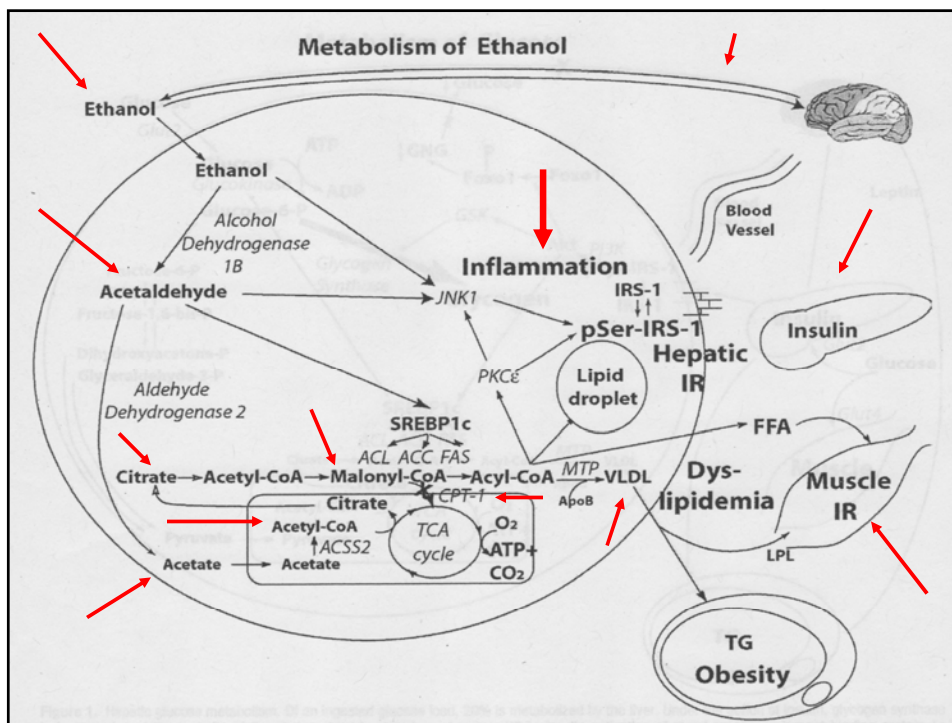
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- “In the process of DNL, the intermediary malonyl-CoA is formed in excess.”
- “However, malonyl-CoA is a steric inhibitor of the mitochondrial enzyme carnitine palmitoyl transferase-1.”
- “Carnitine palmitoyl transferase-1 is the key rate-limiting and regulatory step in mitochondrial β -oxidation; the fatty acid transporter carnitine must be regenerated for transesterification and import of fatty acids into the mitochondrial matrix to generate two-carbon fragments for ketone formation.”

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- ***“Thus, increased DNL inhibits intrahepatic lipid β -oxidation, resulting in further intrahepatic lipid buildup.”***
- ***“Lastly, ethanol is a known contributor to hepatic insulin resistance.”***

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Hepatic fructose metabolism

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- “Upon ingestion of 120 kcal of sucrose (eg, 8 oz of orange juice; composed of 60 kcal fructose and 60 kcal glucose), the overwhelming majority of the 60-kcal fructose bolus reaches the liver, along with 20% of the glucose bolus (12 kcal), for a total of 72 kcal; thus, the liver must handle triple the substrate as it did for glucose alone.”
- “In the liver, fructose is converted to fructose 1-phosphate by the enzyme fructokinase.”

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- “This is an adenosine triphosphate-requiring reaction, depleting available intracellular phosphate.”
- “Phosphorylation of this large substrate load leads to activation of the scavenger enzyme adenosine monophosphate deaminase-1, which...[leads] to the cellular waste product uric acid.”
- “Buildup of urate in the circulation inhibits endothelial nitric oxide synthase, resulting in decreased nitric oxide in the vasculature.”

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- “In contrast to glucose’s conversion to glycogen, the fructose-1-phosphate load enters the Embden-Meyerhoff glycolytic cascade.”
- “The majority of fructose-1-phosphate is metabolized directly to pyruvate, with the resultant large volume of acetyl-CoA entering the mitochondrial TCA cycle.”
- “The liver mitochondria cannot metabolize the entire fructose-derived pyruvate/acetyl-CoA substrate excess; any extra will exit the mitochondria into the cytoplasm as citrate via the ‘citrate shuttle.’”

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Fructose and de novo lipogenesis (DNL)

- “DNL is markedly increased by excess dietary CHO, rather than excess dietary fat.”
- “For example, if total CHO energy intake exceeds total energy expenditure, hepatic DNL is incremented 10-fold.”
- “Similarly, on a high-CHO diet, DNL synthesis is 27 times increased in the fasting state as compared with a low-CHO diet, and 4 times increased in the fed state.”

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- “Fructose is a primary driver of DNL.”
- “Human studies demonstrate a rate of fractional DNL of 2% with glucose and 10% after 6 days of high-fructose feeding.”
- “A recent human study demonstrated that fructose feeding increased fractional DNL to 17%.”
- “Elevated circulating VLDL in animal models of high-fructose feeding may be a result of overproduction driven by insulin resistance; increased triglyceride flux and hepatic inflammation; and decreased clearance.”

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- “Animal studies demonstrate increased hepatic lipid deposition in response to high-fructose feeding.”
- “In human studies, eucaloric replacement of glucose with fructose increased intrahepatic lipid levels by 38% within 8 days, as measured by magnetic resonance spectroscopy.”
- “Our group also has found a correlation between soft drink consumption and alanine aminotransferase levels in obese children.”

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Fructose and insulin resistance

- “Numerous human studies demonstrate the induction of hepatic insulin resistance in response to increased fructose feeding and, in particular, peripheral markers of inflammation.”
- “Excessive FFA exported from the liver leads to increased uptake into skeletal muscle.”
- “There, diacylglycerides reassembled from FFA, reduces glucose transport, resulting in skeletal muscle resistance.”

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Fructose and hyperinsulinemia

- “Hepatic and skeletal muscle insulin resistance, through increases FFA levels, promotes reciprocal hyperinsulinemia.”
- “Thus, fructose’s action on the liver is unique among carbohydrates and appears independent of insulin.”
- “Fructose metabolism gives rise to the phenotype of ‘selective hepatic insulin resistance’ typical of metabolic syndrome...”

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Fructose vs. ethanol

- “Thus, hepatic metabolism of either fructose or ethanol results in energy substrate conversion to acetyl-CoA, with any insulin regulation and with limited diversion to nontoxic intermediaries such as glycogen.”
- “The overwhelming majority of the acetyl-CoA produced will find its way into DNL, generating intrahepatic lipid, inflammation, and insulin resistance.”

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Some final thoughts from Lustig

- “Ethanol is manufactured by fermentation of fructose; the only difference is that for fructose, humans perform the glycolysis, while for ethanol, yeast have already performed the glycolysis.”

83

- “Aside from restriction of intake there are two ‘antidotes’ to the hepatic effects of fructose.”
- Exercise – “By increasing hepatic TCA cycle maximal velocity, less acetyl-CoA will be converted to citrate, providing less substrate for DNL and reducing fructose’s downstream effects.”
- “Fiber...enjoys two benefits. By reducing glycemic load and rate of carbohydrate absorption, fiber reduces the bolus of energy substrate the liver has to metabolize acutely, thereby reducing the rate of DNL and improving insulin sensitivity. Fiber also increases satiety, reducing further consumption.”

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- “Fructose consumption may also contribute to bacterial overgrowth and increased intestinal permeability.”
- “Animal and human studies suggest that non-alcoholic fatty liver disease (NAFLD) is associated with small intestinal bacterial overgrowth, which is linked to circulating endotoxemia and inflammatory cytokines.”
- “The presence of these factors in the blood has also been reported in patients with alcoholic fatty liver disease.”
- “Translocation of bacterial endotoxins through a leaky gut lumen to the portal blood increases the exposure of the liver to inflammation and injury.”

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- “The gut microflora, therefore, may be a key link between fructose feeding, plasma endotoxin levels, and systemic and hepatic inflammation associated with the metabolic syndrome.”

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Parting word

HORMESIS

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Thank you!!

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