Glycemia, starch, and sugar in context

From the original article in 2009. Author: Ray Peat.

Monosaccharide -- a simple sugar; examples, glucose, fructose, ribose, galactose (galactose is also called cerebrose, brain sugar).

Disaccharide -- two monosaccharides bound together; examples, sucrose, lactose, maltose.

Oligosaccharide -- a short chain of monosaccharides, including disaccharides and slightly longer chains.

Polysaccharide -- example, starch, cellulose, glycogen.

Glycation -- the attachment of a sugar to a protein.

Lipolysis - the liberation of free fatty acids from triglycerides, the neutral form in which fats are stored, bound to glycerine.

In the 1920s, “diabetes” was thought to be a disease of insulin deficiency. Eventually, measurements of insulin showed that “diabetics” often had normal amounts of insulin, or above-normal amounts. There are now “two kinds of diabetes,” with suggestions that “the disease” will soon be further subdivided.

The degenerative diseases that are associated with hyperglycemia and commonly called diabetes, are only indirectly related to insulin, and as an approach to understanding or treating diabetes, the “glycemic index” of foods is useless. Physiologically, it has no constructive use, and very little meaning.

Insulin is important in the regulation of blood sugar, but its importance has been exaggerated because of the diabetes/insulin industry. Insulin itself has been found to account for only about 8% of the "insulin-like activity" of the blood, with potassium being probably the largest factor. There probably isn't any process in the body that doesn't potentially affect blood sugar.

Glucagon, cortisol, adrenalin, growth hormone and thyroid tend to increase the blood sugar, but it is common to interpret hyperglycemia as "diabetes," without measuring any of these factors. Even when "insulin dependent diabetes" is diagnosed, it isn't customary to measure the insulin to see whether it is actually deficient, before writing a prescription for insulin. People resign themselves to a lifetime of insulin injections, without knowing why their blood sugar is high.

Insulin release is also stimulated by amino acids such as leucine, and insulin stimulates cells to absorb amino acids and to synthesize proteins. Since insulin lowers blood sugar as it disposes of amino acids, eating a large amount of protein without carbohydrate can cause a sharp decrease in blood sugar. This leads to the release of adrenalin and cortisol, which raise the blood sugar. Adrenalin causes fatty acids to be drawn into the blood from fat stores, especially if the liver's glycogen stores are depleted, and cortisol causes tissue protein to be broken down into amino acids, some of which are used in place of carbohydrate. Unsaturated fatty acids, adrenaline, and cortisol cause insulin resistance.

“Professional opinion” can be propagated about 10,000 times faster than research can evaluate it, or, as C. H. Spurgeon said, "A lie travels round the world while Truth is putting on her boots."

In the 1970s, dietitians began talking about the value of including "complex carbohydrates" in the diet. Many dietitians (all but one of the Registered Dietitians that I knew of) claimed that starches were more slowly absorbed than sugars, and so should be less disruptive to the blood sugar and insulin levels. People were told to eat whole grains and legumes, and to avoid fruit juices.

These recommendations, and their supporting ideology, are still rampant in the culture of the United States, fostered by the U.S. Department of Agriculture and the American Dietetic Association and the American Diabetes Association and innumerable university departments of home economics, dietetics, or nutrition.

Judging by present and past statements of the American Dietetic Association, I think some kind of institutional brain defect might account for their recommendations. Although the dietetic association now feebly acknowledges that sugars don't raise the blood sugar more quickly than starches do, they can't get away from their absurd old recommendations, which were never scientifically justified**:** “Eat more starches, such as bread, cereal, and starchy vegetables--6 servings a day or more. Start the day with cold (dry) cereal with nonfat/skim milk or a bagel with one teaspoon of jelly/jam. Put starch center stage--pasta with tomato sauce, baked potato with chili, rice and stir-fried beef and vegetables. Add cooked black beans, corn, or garbanzo beans (chickpeas) to salads or casseroles.”

The Dietetic Association's association with General Mills, the breakfast cereal empire, (and Kellog, Nabisco, and many other food industry giants) might have something to do with their starchy opinions. Starch-grain embolisms can cause brain damage, but major money can also make people say stupid things.

In an old experiment, a rat was tube-fed ten grams of corn-starch paste, and then anesthetized. Ten minutes after the massive tube feeding, the professor told the students to find how far the starch had moved along the alimentary canal. No trace of the white paste could be found, demonstrating the speed with which starch can be digested and absorbed. The very rapid rise of blood sugar stimulates massive release of insulin, and rapidly converts much of the carbohydrate into fat.

It was this sort of experiment that led to the concept of "glycemic index," that ranks foods according to their ability to raise

the blood sugar. David Jenkins, in 1981, knew enough about the old studies of starch digestion to realize that the dietitians had created a dangerous cult around the “complex carbohydrates,” and he did a series of measurements that showed that starch is more “glycemic” than sucrose. But he simply used the amount of increase in blood glucose during the first two hours after ingesting the food sample, compared to that following ingestion of pure glucose, for the comparison, neglecting the physiologically complex facts, all of the processes involved in causing a certain amount of glucose to be present in the blood during a certain time. (Even the taste of sweetness, without swallowing anything, can stimulate the release of glucagon, which raises blood sugar.)

More important than the physiological vacuity of a simple glycemic measurement was the ideology within which the whole issue developed, namely, the idea that diabetes (conceived as chronic hyperglycemia) is caused by eating too much sugar, i.e., chronic hyperglycemia the illness is caused by the recurrent hyperglycemia of sugar gluttony. The experiments of Bernardo Houssay (1947 Nobel laureate) in the 1940s, in which sugar and coconut oil protected against diabetes, followed by Randle's demonstration of the antagonism between fats and glucose assimilation, and the growing recognition that polyunsaturated fatty acids cause insulin resistance and damage the pancreas, have made it clear that the dietetic obsession with sugar in relation to diabetes has been a dangerous diversion that has retarded the understanding of degenerative metabolic diseases.

Starting with the insulin industry, a culture of diabetes and sugar has been fabulized and expanded and modified as new commercial industries found ways to profit from it. Seed oils, fish oils, breakfast cereals, soybean products, and other things that were never eaten by any animal in millions of years of evolution have become commonplace as “foods,” even as “health foods.”

Although many things condition the rate at which blood sugar rises after eating carbohydrates, and affect the way in which blood glucose is metabolized, making the idea of a “glycemic index” highly misleading, it is true that blood sugar and insulin responses to different foods have some meaningful effects on physiology and health.

Starch and glucose efficiently stimulate insulin secretion, and that accelerates the disposition of glucose, activating its conversion to glycogen and fat, as well as its oxidation. **Fructose inhibits the stimulation of insulin by glucose, so this means that eating ordinary sugar, sucrose (a disaccharide, consisting of glucose and fructose), in place of starch, will reduce the tendency to store fat.** Eating “complex carbohydrates,” rather than sugars, is a reasonable way to promote obesity. Eating starch, by increasing insulin and lowering the blood sugar, stimulates the appetite, causing a person to eat more, so the effect on fat production becomes much larger than when equal amounts of sugar and starch are eaten. The obesity itself then becomes an additional physiological factor; the fat cells create something analogous to an inflammatory state. There isn't anything wrong with a high carbohydrate diet, and even a high starch diet isn't necessarily incompatible with good health, but when better foods are available they should be used instead of starches. For example, fruits have many advantages over grains, besides the difference between sugar and starch. Bread and pasta consumption are strongly associated with the occurrence of diabetes, fruit consumption has a strong inverse association.

Although pure fructose and sucrose produce less glycemia than glucose and starch do, the different effects of fruits and grains on the health can't be reduced to their effects on blood sugar.

Orange juice and sucrose have a lower glycemic index than starch or whole wheat or white bread, but it is common for dietitians to argue against the use of orange juice, because its index is the same as that of Coca Cola. But, if the glycemic index is very important, to be rational they would have to argue that Coke or orange juice should be substituted for white bread.

After decades of “education” to promote eating starchy foods, obesity is a bigger problem than ever, and more people are dying of diabetes than previously. The age-specific incidence of most cancers is increasing, too, and there is evidence that starch, such as pasta, contributes to breast cancer, and possibly other types of cancer.

The epidemiology would appear to suggest that complex carbohydrates cause diabetes, heart disease, and cancer. If the glycemic index is viewed in terms of the theory that hyperglycemia, by way of “glucotoxicity,” causes the destruction of proteins by glycation, which is seen in diabetes and old age, that might seem simple and obvious.

Glycemic List	White Bread	Glucose Based
Fructose	32	22
Lactose	65	46
Honey	83	58
High fructose corn syrup	89	62
Sucrose	92	64
Glucose	137	96
Glucose tablets	146	102
Maltodextrin	150	105
Maltose	150	105
Pineapple juice	66	46
Peach, canned	67	47
Grapefruit juice	69	48
Orange juice	74	52
Barley flour bread	95	67
Wheat bread, high fiber	97	68

Wheat bread, wholemeal flour	99	69
Melba toast	100	70
Wheat bread, white	101	71
Bagel, white	103	72
Kaiser rolls	104	73
Whole-wheat snack bread	105	74
Bread stuffing	106	74
Wheat bread, Wonderwhite	112	78
Wheat bread, gluten free	129	90
French baguette	136	95
Taco shells	97	68
Cornmeal	98	69
Millet	101	71
Rice, Pelde	109	76
Rice, Sunbrown Quick	114	80
Tapioca, boiled with milk	115	81
Rice, Calrose	124	87
Rice, parboiled, low amylose Pelde	124	87
Rice, white, low amylose	126	88
Rice, instant, boiled 6 min	128	90

But there are many reasons to question that theory.

Oxidation of sugar is metabolically efficient in many ways, including sparing oxygen consumption. It produces more carbon dioxide than oxidizing fat does, and carbon dioxide has many protective functions, including increasing Krebs cycle activity and inhibiting toxic damage to proteins. The glycation of proteins occurs under stress, when less carbon dioxide is being produced, and the proteins are normally protected by carbon dioxide.

When sugar (or starch) is turned into fat, the fats will be either saturated, or in the series derived from omega -9 monounsaturated fatty acids. When sugar isn't available in the diet, stored glycogen will provide some glucose (usually for a few hours, up to a day), but as that is depleted, protein will be metabolized to provide sugar. If protein is eaten without carbohydrate, it will stimulate insulin secretion, lowering blood sugar and activating the stress response, leading to the secretion of adrenalin, cortisol, growth hormone, prolactin, and other hormones. The adrenalin will mobilize glycogen from the liver, and (along with other hormones) will mobilize fatty acids, mainly from fat cells. Cortisol will activate the conversion of protein to amino acids, and then to fat and sugar, for use as energy. (If the diet doesn't contain enough protein to maintain the essential organs, especially the heart, lungs, and brain, they are supplied with protein from the skeletal muscles. Because of the amino acid composition of the muscle proteins, their destruction stimulates the formation of additional cortisol, to accelerate the movement of amino acids from the less important tissues to the essential ones.)

The diabetic condition is similar in many ways to stress, inflammation, and aging, for example in the chronic elevation of free fatty acids, and in various mediators of inflammation, such as tumor necrosis factor (TNF).

Rather than the sustained hyperglycemia which is measured for determining the glycemic index, I think the “diabetogenic” or “carcinogenic” action of starch has to do with the stress reaction that follows the intense stimulation of insulin release. This is most easily seen after a large amount of protein is eaten. Insulin is secreted in response to the amino acids, and besides stimulating cells to take up the amino acids and convert them into protein, the insulin also lowers the blood sugar. This decrease in blood sugar stimulates the formation of many hormones, including cortisol, and under the influence of cortisol both sugar and fat are produced by the breakdown of proteins, including those already forming the tissues of the body. At the same time, adrenalin and several other hormones are causing free fatty acids to appear in the blood.

Since the work of Cushing and Houssay, it has been understood that blood sugar is controlled by antagonistic hormones**:** Remove the pituitary along with the pancreas, and the lack of insulin doesn't cause hyperglycemia. If something increases cortisol a little, the body can maintain normal blood sugar by secreting more insulin, but that tends to increase cortisol production. A certain degree of glycemia is produced by a particular balance between opposing hormones.

Tryptophan, from dietary protein or from the catabolism of muscles, is turned into serotonin which activates the pituitary stress hormones, increasing cortisol, and intensifying catabolism, which releases more tryptophan. It suppresses thyroid function, which leads to an increased need for the stress hormones. Serotonin impairs glucose oxidation, and contributes to many of the problems associated with diabetes.

“Diabetes” is often the diagnosis, when excess cortisol is the problem. The hormones have traditionally not been measured before diagnosing diabetes and prescribing insulin or other chemical to lower the blood sugar. Some of the worst effects of “diabetes,” including retinal damage, are caused or exacerbated by insulin itself.

Antiserotonin drugs can sometimes alleviate stress and normalize blood sugar. Simply eating sucrose was recently discovered to restrain the stress hormone system (“A new perspective on glucocorticoid feedback**:** relation to stress, carbohydrate

feeding and feeling better," J Neuroendocrinol 13(9), 2001, KD Laugero).

The free fatty acids released by the stress hormones serve as supplemental fuel, and increase the consumption of oxygen and the production of heat. (This increased oxygen demand is a problem for the heart when it is forced to oxidize fatty acids. [A. Grynberg, 2001]) But if the stored fats happen to be polyunsaturated, they damage the blood vessels and the mitochondria, suppress thyroid function, and cause "glycation" of proteins. They also damage the pancreas, and impair insulin secretion.

A repeated small stress, or overstimulation of insulin secretion, gradually tends to become amplified by the effects of tryptophan and the polyunsaturated fatty acids, with these fats increasing the formation of serotonin, and serotonin increasing the liberation of the fats.

The name, "glycation," indicates the addition of sugar groups to proteins, such as occurs in diabetes and old age, but when tested in a controlled experiment, **lipid peroxidation of polyunsaturated fatty acids produces the protein damage about 23 times faster than the simple sugars do** (Fu, et al., 1996). And the oxidation of fats rather than glucose means that the proteins won't have as much protective carbon dioxide combined with their reactive nitrogen atoms, so the real difference in the organism is likely to be greater than that seen by Fu, et al.

These products of lipid peroxidation, HNE, MDA, acrolein, glyoxal, and other highly reactive aldehydes, damage the mitochondria, reducing the ability to oxidize sugar, and to produce energy and protective carbon dioxide.

Fish oil, which is extremely unstable in the presence of oxygen and metals such as iron, produces some of these dangerous products very rapidly. The polyunsaturated "essential fatty acids" and their products, arachidonic acid and many of the prostaglandin-like materials, also produce them.

When glucose can't be oxidized, for any reason, there is a stress reaction, that mobiles free fatty acids. Drugs that oppose the hormones (such as adrenalin or growth hormone) that liberate free fatty acids have been used to treat diabetes, because lowering free fatty acids can restore glucose oxidation.

Brief exposures to polyunsaturated fatty acids can damage the insulin-secreting cells of the pancreas, and the mitochondria in which oxidative energy production takes place. Prolonged exposure causes progressive damage. Acutely, the free polyunsaturated fatty acids cause capillary permeability to increase, and this can be detected at the beginning of "insulin resistance" or "diabetes." After chronic exposure, the leakiness increases and albumin occurs in the urine, as proteins leak out of the blood vessels. The retina and brain and other organs are damaged by the leaking capillaries.

The blood vessels and other tissues are also damaged by the chronically increased cortisol, and at least in some tissues (the immune system is most sensitive to the interaction) the polyunsaturated fats increase the ability of cortisol to kill the cells.

When cells are stressed, they are likely to waste glucose in two ways, turning some of it into lactic acid, and turning some into fatty acids, even while fats are being oxidized, in place of the sugar that is available. Growth hormone and adrenalin, the stress-induced hormones, stimulate the oxidation of fatty acids, as well as their liberation from storage, so the correction of energy metabolism requires the minimization of the stress hormones, and of the free fatty acids. Prolactin, ACTH, and estrogen also cause the shift of metabolism toward the fatty acids.

Sugar and thyroid hormone (T3, triiodothyronine) correct many parts of the problem. The conversion of T4 into the active T3 requires glucose, and in diabetes, cells are deprived of glucose. Logically, all diabetics would be functionally hypothyroid. Providing T3 and sugar tends to shift energy metabolism away from the oxidation of fats, back to the oxidation of sugar.

Niacinamide, used in moderate doses, can safely help to restrain the excessive production of free fatty acids, and also helps to limit the wasteful conversion of glucose into fat. There is evidence that diabetics are chronically deficient in niacin. Excess fatty acids in the blood probably divert tryptophan from niacin synthesis into serotonin synthesis.

Sodium, which is lost in hypothyroidism and diabetes, increases cellular energy. Diuretics, that cause loss of sodium, can cause apparent diabetes, with increased glucose and fats in the blood. **Thyroid, sodium, and glucose work very closely together to maintain cellular energy and stability.**

In Houssay's experiments, sugar, protein, and coconut oil protected mice against developing diabetes. The saturated fats of coconut oil are similar to those we synthesize ourselves from sugar. Saturated fats, and the polyunsaturated fats synthesized by plants, have very different effects on many important physiological processes. In every case I know about, the vegetable polyunsaturated fats have harmful effects on our physiology.

For example, they bind to the "receptor" proteins for cortisol, progesterone, and estrogen, and to all of the major proteins related to thyroid function, and to the vesicles that take up nerve transmitter substances, such as glutamic acid.

They allow glutamic acid to injure and kill cells through excessive stimulation; this process is similar to the nerve damage done by cobra venom, and other toxins.

Excess cortisol makes nerve cells more sensitive to excitotoxicity, but the cells are protected if they are provided with an unusually large amount of glucose.

The cells of the thymus gland are very sensitive to damage by stress or cortisol, but they too can be rescued by giving them enough extra glucose to compensate for the cortisol. Polyunsaturated fatty acids have the opposite effect, sensitizing the thymus cells to cortisol. This partly accounts for the immunosuppressive effects of the polyunsaturated fats. (AIDS patients have increased cortisol and polyunsaturated fatty acids in their blood.[E.A. Nunez, 1988.])

Unsaturated fatty acids activate the stress hormones, sugar restrains them.

Simply making animals “deficient” in the unsaturated vegetable oils (which allows them to synthesize their own series of animal polyunsaturated fats, which are very stable), protects them against “autoimmune” diabetes, and against a variety of other “immunological” challenges. The “essential fatty acid” deficiency increases the oxidation of glucose, as it increases the metabolic rate generally.

Saturated fats improve the insulin-secreting response to glucose.

The protective effects of sugar, and the harmful effects of excessive fat metabolism, are now being widely recognized, in every field of physiology. The unsaturated vegetable fats, linoleic and linolenic acid and their derivatives, such as arachidonic acid and the long chain fish oils, have excitatory, stress promoting effects, that shift metabolism away from the oxidation of glucose, and finally destroy the respiratory metabolism altogether. Since cell injury and death generally involve an imbalance between excitation and the ability to produce energy, it is significant that the oxidation of unsaturated fatty acids seems to consume energy, lowering cellular ATP (Clejan, et al, 1986).

The bulk of the age-related tissue damage classified as “glycation end-products” (or “advanced glycation end-products,” AGE) is produced by decomposition of the polyunsaturated fats, rather than by sugars, and this would be minimized by the protective oxidation of glucose to carbon dioxide.

Protein of the right kind, in the right amount, is essential for reducing stress. Gelatin, with its antiinflammatory amino acid balance, helps to regulate fat metabolism.

Aspirin's antiinflammatory actions are generally important when the polyunsaturated fats are producing inflammatory and degenerative changes, and aspirin prevents many of the problems associated with diabetes, reducing vascular leakiness. It improves mitochondrial respiration (De Cristobal, et al., 2002) and helps to regulate blood sugar and lipids (Yuan, et al., 2001). Aspirin's broad range of beneficial effects is probably analogous to vitamin E's, being proportional to protection against the broad range of toxic effects of the polyunsaturated “essential” fatty acids.

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J Nutr 2000 Oct;130(10):2503-7. **A high carbohydrate versus a high monounsaturated fatty acid diet lowers the atherogenic potential of big VLDL particles in patients with type 1 diabetes.** Georgopoulos A, Bantle JP, Noutsou M, Hoover HA. "A high (25%) monounsaturated fatty acid (Mono) diet and a high (61%) carbohydrate (CHO) diet were provided for 4 wk in a randomized crossover design to 19 normolipidemic, nonobese patients with type 1 diabetes. The two diets were matched for protein, polyunsaturated/saturated fatty acids, cholesterol and fiber content." "We conclude that a high CHO diet might be preferable to a high Mono diet, on the basis of the premise that more big VLDL particles could increase the atherosclerotic risk in patients with diabetes."

J. Girard, "Role of free fatty acids in insulin resistance of subjects with non-insulin-dependent diabetes," Diabetes Metab. 21(2), 79-88, 1995. **"Studies performed in the rat suggest that impaired glucose-induced insulin secretion could also be related to chronic exposure of pancreatic beta cells to elevated plasma free fatty acid levels."**

Ann Intern Med 1988 May;108(5):663-8. **Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus.** Glauber H, Wallace P, Griver K, Brechtel G. "Increased interest in using omega-3 fatty acids led us to examine their metabolic effects in six men with type II (non-insulin-dependent) diabetes mellitus. After 1 month of a diet supplemented with these fatty acids, the patients' fasting glucose rose from 13.1 +/- 1.3 to 15.3 +/- 1.3 mmol/L (P = 0.03) and **glucose area during a mixed meal profile rose by 22% (P = 0.04)." "After omega-3 fatty acid withdrawal, fasting glucose returned to baseline. Omega-3 fatty acid treatment in type II diabetes leads to rapid but reversible metabolic deterioration, with elevated basal hepatic glucose output and impaired insulin secretion** but unchanged glucose disposal rates. Caution should be used when recommending omega-3 fatty acids in type II diabetic persons."

A. Golay, et al., "Effect of lipid oxidation on the regulation of glucose utilization in obese patients," Acta Diabetologica 32(1), 44-48, 1995. **[Free fatty acids strongly and quickly depress the ability to oxidize or store glucose.]**

Biol Neonate 1985;47(6):343-9. **Increased maternal-fetal transport of fat in diabetes assessed by polyunsaturated fatty acid content in fetal lipids.** Goldstein R, Levy E, Shafrir E. The distribution of fatty acids was determined by gas-liquid chromatography in total lipid and triglyceride fraction of extracts of several tissues of streptozotocin-diabetic rats and their fetuses on day 20 of pregnancy. In maternal rats, diabetes did not significantly affect fatty acid distribution apart from small changes in the relative content of linoleate in adipose tissue and liver. In the placenta, the fetal carcass and the fetal liver the **triglyceride content increased approximately 2-fold as a result of maternal diabetes, in association with the elevation in triglycerides and free fatty** acids in the maternal circulation. A pronounced increase in the relative content **of linoleate was recorded in the total lipid and triglyceride extracts of placenta (35 and 59%), fetal carcass (56 and 66%) and fetal liver (100 and 205%). Small increases in arachidonate proportion were also seen in some fetal tissues. The large increase in fetal hepatic linoleate indicates that this** tissue is an important uptake target of maternal lipids transported in excess into the fetus. The results confirm the previous observations on increased transplacental fat passage in diabetes by demonstrating that the increment in the essential fatty acid, linoleate, parallels the diabetes-induced triglyceride accumulation in the fetoplacental unit.

A. Gomes, et al., "Anti-hyperglycemic effect of black tea (Camellia sinensis) in rat," J. of Ethnopharmacology 45(3), 223-226, 1995. **It "was found to possess both preventive and curative effects on experimentally produced diabetes in rats."**

J Endocrinol 2002 Apr;173(1):73-80. **Acute effects of fatty acids on insulin secretion from rat and human islets of Langerhans.** Gravena C, Mathias PC, Ashcroft SJ. "Long-chain fatty **acids (palmitate and stearate) were more effective than medium-chain (octanoate). Saturated fatty acids (palmitate, stearate) were more effective than unsaturated (palmitoleate, linoleate, elaidate)."**

Diabetes Metab 2001 Nov;27(5 Pt 2):S12-9. **[Modifications in myocardial energy metabolism in diabetic patients]]** [Article in French] Grynberg A. "**Because FA is the main heart fuel (although the most expensive one in oxygen, and prompt to induce deleterious effects), this process is based on a balanced fatty acid (FA) metabolism.** Several pathological situations are associated with an accumulation of FA or derivatives, or with an excessive b-oxidation. The diabetic cardiomyocyte is characterised by an over consumption of FA. The control of the FA/glucose balance clearly appears as a new strategy for cytoprotection, particularly in diabetes and requires a reduced FA contribution to ATP production. Cardiac myocytes can control FA mitochondrial entry, but display weak ability to control FA uptake, thus the fate of non beta-oxidized FA appear as a new impairment for the cell." "Sudden death, hypercatecholaminemia, diabetes and heart failure have been associated with an altered PUFA content in cardiac membranes."

Diabetologia 1996 Mar;39(3):251-5. **Acceleration of experimental diabetic retinopathy in the rat by omega-3 fatty Acids.** Hammes HP, Weiss A, Fuhrer D, Kramer HJ, Papavassilis C, Grimminger F. Omega-3 fatty acids exert several important biological effects on factors that may predispose to diabetic retinopathy. Potential pathogenetic mechanisms include platelet dysfunction, altered eicosanoid production, increased blood viscosity in association with impaired cell deformability and pathologic leucocyte/endothelium interaction. Therefore, we tested whether a 6-month administration of fish oil (750 mg Maxepa, 5 times per week), containing 14% eicosapentaenoic acid (EPA) and 10% docosahexaenic acid, could inhibit the development of experimental retinopathy of the streptozotocin-diabetic rat. The efficiency of fish oil supplementation was evaluated by measuring EPA concentrations in total, plasma and membrane fatty acids and by measuring the generation of lipid mediators (leukotrienes and thromboxanes). Retinal digest preparations were quantitatively analysed for pericyte loss, and the formation of acellular capillaries. Omega-3 fatty acid administration to diabetic rats resulted in a twofold increase of EPA 20:5 in total fatty acids, and a reduction of the thromboxane ratio from 600 (untreated diabetic rats) to 50 (treated diabetic rats). Despite these biochemical changes, diabetes-associated pericyte loss remained unaffected and the formation of acellular, occluded capillaries was increased by 75% in the fish oil treated diabetic group (115.1 +/- 26.8; untreated diabetic 65.2 +/- 15.0 acellular capillary segments/mm2 of retinal area). We conclude from this study that dietary fish oil supplementation may be harmful for the diabetic microvasculature in the retina.

Y. Hattori, et al., "Phorbol esters elicit Ca++-dependent delayed contractions in diabetic rat aorta," Eur. J. Pharmacol. 279(1), 51-58, 1995. **[Diabetic tissue is more responsive to activation of protein kinase C by phorbol esters.]**

Nutr Metab 1975;18(1):41-8. **Adipose tissue metabolism in essential fatty acid deficienty. Effects of prostaglandin e1, epinephrine, and ACTH.** Hazinski TA, Barr M, Hertelendy F. In an effort to better define some of the metabolic changes that accompany essential fatty acid deficiency (EFAD), we studied glucose metabolism in adipose tissue of EFAD and normal mice under basal conditions and in the presence of prostaglandin E1 (PGE1), epinephrine, and ACTH1-18. Isolated fat cells were incubated in Krebs-Ringer bicarbonate medium containing glucose 1(-14C) or 6(-14C), and the incorporation of radioactive carbon into CO2, total fat, fatty acids, and glyceride-glycerol was determined. **It was found that EFAD increased glucose uptake over controls which could be attributed to increased oxidation to CO2 and fatty acid synthesis. The contribution of the pentose cycle to glucose oxidation was 50-80% higher in EFAD adipocytes as compared to controls. ACTH1-18** (0.1 mug/ml) suppressed this by 18 and 30% in the control and EFAD groups, respectively, while epinephrine decreased pentose cycle activity by 83 and 55% in the two groups, respectively. PGE1 alone had no significant effect, but in combination with epinephrine it abolished the inhibitory action of the catecholamine in both groups."

J Neurosci Res 1989 Oct;24(2):247-50. **Brain mitochondrial swelling induced by arachidonic acid and other long chain free fatty acids.** Hillered L, Chan PH. "**Polyunsaturated fatty acids (PUFAs), arachidonic acid in particular, are well known, potent inducers of edema in the brain, while monounsaturated and saturated long chain fatty acids do not possess this quality.**" "**ATP-MgCl2 both prevented and reversed this swelling, while binding of the 20:4 by the addition of bovine serum albumin could only prevent but not reverse the swelling.**" **"Moreover, reversal of the swelling occurred without recovery of respiratory function."**

J Neurosci Res 1988 Aug;20(4):451-6. **Role of arachidonic acid and other free fatty acids in mitochondrial dysfunction in brain ischemia.** Hillered L, Chan PH.

B. A. Houssay and C. Martinez, **"Experimental diabetes and diet,"** Science 105, 548-549, 1947. **[Mortality was zero on the high coconut oil diet, 100% on the high lard diet. It was 90% on the low protein diet, and 33% on the high protein diet. With a combination of coconut oil and lard, 20%.]**

B. A. Houssay, et al., **"Accion de la administracion prolongada de glucosa sobre la diabetes de la rata,"** Rev. Soc. argent. de biol. 23, 288-293, 1947.

S. Ikemoto, et al., **"High fat diet-induced hyperglycemia: Prevention by low level expression of a glucose transporter (GLUT4) minigene in transgenic mice,"** Proc. Nat. Acad. Sci. USA 92(8), 3096-3099, 1995. **"...mice fed a high-fat (safflower oil) diet develop defective glycemic control, hyperglycemia, and obesity."**

M. Inaba, et al., **"Influence of high glucose on 1,25-dihydroxyvitamin D-3-induced effect on human osteoblast-like MG-63 cells,"** J. Bone Miner. Res. 10(7), 1050-1056, 1995.

J. S. Jensen, et al., **"Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects,"** Clin. Sci. 88(6), 629-633, 1995.

J Am Geriatr Soc 1984 May;32(5):375-9. **Low triiodothyronine and raised reverse triiodothyronine levels in patients over fifty years of age who have type II diabetes mellitus: influence of metabolic control, not age.** Kabadi UM, Premachandra BN. "Several studies have demonstrated that the uncontrolled diabetic state in both type I as well as type II diabetes mellitus is characterized by altered thyroid hormone metabolism, which results in the **lowering of serum triiodothyronine (T3) levels and a reciprocal elevation of T3 (rT3) levels."** "Serum T3 levels declined and rT3 levels rose in the diabetic patients with worsening of the metabolic control."

Metabolism 1989 Mar;38(3):278-81. **The effect of fatty acids on the vulnerability of lymphocytes to cortisol.** Klein A, Bruser B, Malkin A. "We have shown previously that cortisol-sensitive lymphocytes (thymocytes) have a much lower capacity than cortisol-resistant cells to catabolize cortisol and that **linoleic acid inhibits the catabolism of cortisol by lymphocytes and modulates the sensitivity of lymphocytes to cortisol."** "Measuring the effect of fatty acids on cortisol catabolism by lymphocytes indicated that **the polyunsaturated fatty acids, linoleate, arachidonate, and eicosapentaenoic, inhibit cortisol catabolism by lymphocytes." "Examining the effect of fatty acids on the vulnerability of lymphocytes to cortisol, we noted that saturated fatty acids had no significant effect, whereas the aforementioned polyunsaturated fatty acids make lymphocytes more sensitive to cortisol."**

Jpn J Pharmacol 1978 Apr;28(2):277-87. **Relationship between cerebral energy failure and free fatty acid accumulation following prolonged brain ischemia.** Kuwashima J, Nakamura K, Fujitani B, Kadokawa T, Yoshida K, Shimizu M. "Mitochondria isolated from the ischemic brain showed an impairment of oxidative phosphorylation. The ischemic **brain was also characterized by remarkable accumulation of free fatty acids known to have properties as an uncoupling factor." "These results indicate that cerebral energy failure in the ischemic brain is related to the accumulation of free fatty acids, which are derived from endogenous brain lipids."**

Probl Endokrinol (Mosk) 1992 Nov-Dec; 38(6):53-4. **[Effect of protein content in rat diet on water-soluble vitamin metabolism in streptozotocin-induced diabetes]** [Article in Russian] Kodentsova VM, Sadykova RE, Dreval' AV, Vrzhesinskaia OA, Sokol'nikov AA, Beketova NA. Water-soluble group B vitamins metabolism was studied over the course of streptozotocin-induced diabetes mellitus in rats fed semisynthetic isocaloric diets containing 18 and 50% of protein. A high-protein diet in diabetes mellitus does not influence riboflavin metabolism disordered in this disease but reduced 4-pyridoxyl acid excretion to the level characteristic of healthy animals. The observed trend to an increase of liver nicotinamide coenzymes levels and of 1-methylnicotinamide urinary excretion reflects increased niacin synthesis from **the diet protein tryptophan, for niacin level is reduced in diabetes.**

M. Kusunoki, et al., **"Amelioration of high fat feeding-induced insulin resistance in skeletal muscle with the antiglucocorticoid RU486,"** Diabetes 44(6), 718-720, 1995. **"These results suggest that glucocorticoids play, in a tissue-specific manner, a role in the maintenance and/or production of insulin resistance produced by high-fat feeding."**

J Neuroendocrinol 2001 Sep;13(9):827-35. **A new perspective on glucocorticoid feedback: relation to stress, carbohydrate feeding and feeling better.** Laugero KD. "In this review, I discuss findings that have led us to view glucocorticoid feedback in the HPA axis in a new light. Much of what has precipitated this view comes from a very surprising finding in our laboratory; sucrose ingestion normalizes feeding, energy balance and central corticotropin releasing factor expression in adrenalectomized (ADX) rats." "Taken together, recent findings of the well-known importance of glucocorticoids to feeding and energy balance, and the modulatory actions of carbohydrate ingestion on both basal and stress-induced activity in the HPA axis, strongly suggest that many metabolic (e.g. obesity) and psychological (e.g. depression) pathologies, which often present together and have been associated with stress and HPA dysregulation, might, in part, be understood in light of our new view of glucocorticoid feedback."

Endocrinology 2001 Jul;142(7):2796-804. **Sucrose ingestion normalizes central expression of corticotropin-releasing-factor messenger ribonucleic acid and energy balance in adrenalectomized rats: a glucocorticoid-metabolic-brain axis?** Laugero KD, Bell ME, Bhatnagar S, Soriano L, Dallman MF. "Both CRF and norepinephrine (NE) inhibit food intake and stimulate ACTH secretion and sympathetic outflow. CRF also increases anxiety; NE increases attention and cortical arousal. Adrenalectomy (ADX) changes CRF and NE activity in brain, increases ACTH secretion and sympathetic outflow and reduces food intake and weight gain; all of these effects are corrected by administration of adrenal steroids. Unexpectedly, we recently found that ADX rats drinking sucrose, but not saccharin, also have normal caloric intake, metabolism, and ACTH." **"Voluntary ingestion of sucrose restores CRF and dopamine-beta-hydroxylase messenger RNA expression in brain, food intake, and caloric efficiency and fat deposition, circulating triglyceride, leptin, and insulin to normal."**

A. Lazarow, "Protection against alloxan diabetes," Anat. Rec. 97, 353, 1947.

A. Lazarow, "Protective effect of glutathione and cysteine against alloxan diabetes in the rat," Proc. Soc. Exp. Biol. & Med. 61, 441-447, 1946. **[While certain doses of cysteine, glutathione, and thioglycolic acid completely prevented alloxan diabetes, it was interesting that all of the rats receiving ascorbic acid became diabetic. To me, this argues for the free radical cause of diabetes, rather than just the sulfhydryl oxidation. Lazarow suggested that succinic dehydrogenase, and various other sulfhydryl enzymes, including those involved in fatty acid oxidation, might be involved.]**

Minerva Endocrinol 1990 Oct-Dec;15(4):273-7. **[Postprandial thermogenesis and obesity: effects of glucose and fructose].** [Article in Italian] Macor C, De Palo C, Vettor R, Sicolo N, De Palo E, Federspil G. "Energy expenditure was calculated both in basal conditions and during the test (resting metabolic rate: RMR) using indirect calorimetry expressed per kg of lean weight, as assessed using bioimpedance measurement techniques. Blood samples were collected to assay glycemia and insulinemia. Results show that increased RMR induced by glucose was significantly reduced in the group of obese subjects compared to controls. **In the same group of obese subjects, RMR was found to be significantly higher following fructose in comparison to the glucose response but did not differ from that in controls.** Data confirm the existence of reduced thermogenesis in obese subjects induced by glucose. The fact that this phenomenon was not recorded in the same subjects following the fructose tolerance test, whose metabolism is insulin-independent, supports the hypothesis that reduced glucose-induced thermogenesis in obese subjects may depend on insulin resistance."

Diabetes Care 2000 Oct;23(10):1472-7. **Dietary unsaturated fatty acids in type 2 diabetes: higher levels of postprandial lipoprotein on a linoleic acid-rich sunflower oil diet compared with an oleic acid-rich olive oil diet.** Madigan C, Ryan M, Owens D, Collins P, Tomkin GH.

Proc Natl Acad Sci U S A 1990 Nov;87(22):8845-9. **Incorporation of marine lipids into mitochondrial membranes increases susceptibility to damage by calcium and reactive oxygen species: evidence for enhanced activation of phospholipase A2 in mitochondria enriched with n-3 fatty Acids.** Malis CD, Weber PC, Leaf A, Bonventre JV. "Mitochondrial site 1 (NADH coenzyme Q reductase) activity was reduced to 45 and 85% of control values in fish-oil- and beef-tallow-fed groups, respectively. **Exposure to Ca2+ and reactive oxygen species enhance the release of polyunsaturated fatty acids enriched at the sn-2 position of phospholipids from mitochondria of fish-oil-fed rats when compared with similarly treated mitochondria of beef-tallow-fed rats."**

"**Phospholipase A2 activity and mitochondrial damage are enhanced when mitochondrial membranes are enriched with n-3 fatty acids."**

FEBS Lett 1998 Oct 16;437(1-2):24-8. **Generation of protein carbonyls by glycoxidation and lipoxidation reactions with autoxidation products of ascorbic acid and polyunsaturated fatty acids.** Miyata T, Inagi R, Asahi K, Yamada Y, Horie K, Sakai H, Uchida K, Kurokawa K. "In vitro incubation of proteins with ascorbic acid accelerated the production of protein carbonyls as well as CML and pentosidine, and incubation with arachidonate accelerated the production of protein carbonyls as well as CML, MDA, and HNE. By contrast, incubation of proteins with glucose resulted in the production of CML and pentosidine, but not protein carbonyls." **"The present study suggests that ascorbate and polyunsaturated fatty acids, but not glucose, represent potential sources of protein carbonyls, and that both the glycoxidation and lipoxidation reactions contribute to protein carbonyl formation in aging and various diseases."**

Chem Phys Lipids 1996 Jan 25;79(1):47-53. **Previously unknown aldehydic lipid peroxidation compounds of arachidonic acid.** Mlakar A, Spiteller G. Lehrstuhl fr Organische Chemie I, "Arachidonic acid was oxidized by iron ascorbate." "**The main aldehydic lipid peroxidation product was found to be the well-known 4-hydroxy-2-nonenal (HNE), but 2-hydroxy heptanal (HH) -- a previously unknown lipid peroxidation product of arachidonic acid -- was detected to be nearly equally abundant. Malondialdehyde (MDA), glyoxal and 2-hydroxy-4-decenal (HDE) were detected to be produced in up to 100 times lower amounts compared to HNE.". . . .** "Since this and analogous hydroxy acids (LOHs) are the main biological degradation **products of hydroperoxides of unsaturated acids (LOOHs) their further peroxidation seems to be a main source of toxic aldehydes."**

J Clin Endocrinol Metab 2000 Dec;85(12):4515-9. **Acute fructose administration decreases the glycemic response to an oral glucose tolerance test in normal adults.** Moore MC, Cherrington AD, Mann SL, Davis SN. "In animal models, a small (catalytic) dose of fructose administered with glucose decreases the glycemic response to the glucose load." "**In conclusion, low dose fructose improves the glycemic response to an oral glucose load in normal adults without significantly enhancing the insulin or triglyceride response. Fructose appears most effective in those normal individuals who have the poorest glucose tolerance."**

Tumour Biol 1988;9(5):225-32. **Modulation of cell-mediated immune response by steroids and free fatty acids in AIDS patients: a critical survey.** Nunez EA. "The overall data presented in this review show that cortisol and free fatty acids, **in particular long-chain polyunsaturated fatty acids, each have immunoinhibitory properties** on lymphoblastic transformation of certain T lymphocytes. This effect is enhanced when the two factors are associated. These data could explain in part the immunosuppression observed in acquired immunodeficiency syndrome (AIDS) patients **where enhanced concentrations of cortisol and polyunsaturated fatty acids have been observed**." "These new weapons could be the administration of diets or treatments (liposomes) modifying the lipid profile of circulating cells and/or viruses and the utilization of hormonal therapy in AIDS and in some types of cancer which often present a biologic picture similar to that of AIDS."

Diabetes Care 1984 Sep-Oct;7(5):465-70. **Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load.** Nuttall FQ, Mooradian AD, Gannon MC, Billington C, Krezowski P. "The plasma glucose area above the baseline following a glucose meal was reduced 34% when protein was given with the glucose." "The insulin area following glucose was only modestly greater than with a protein meal (97 +/- 35, 83 +/- 19 microU X h/ml, respectively)." "When various amounts of protein were given with 50 g glucose, the insulin area response was essentially first order. Subsequently, subjects were given 50 g glucose or 50 g glucose with 50 g protein as two meals 4 h apart in random sequence. The insulin areas were not significantly different for each meal but were higher when protein + glucose was given. After the second glucose meal the plasma glucose area was 33% less than after the first meal. Following the second glucose + protein meal the plasma glucose area was markedly reduced, being only 7% as large as after the first meal. **These data indicate that protein given with glucose will increase insulin secretion and reduce the plasma glucose rise in at least some type II diabetic persons."** Randomized Controlled Trial

Biochem J 1985 Sep 1;230(2):329-37. **Inhibitory effects of some long-chain unsaturated fatty acids on mitochondrial beta-oxidation. Effects of streptozotocin-induced diabetes on mitochondrial beta-oxidation of polyunsaturated fatty acids.** Osmundsen H, Bjornstad K. **"Evidence showing that some unsaturated fatty acids, and in particular docosahexaenoic acid, can be powerful inhibitors of mitochondrial beta-oxidation is presented. This inhibitory property is, however, also observed with the cis- and trans-isomers of the C18:1(16) acid. Hence it is probably the position of the double bond(s), and not the degree of unsaturation, which confers the inhibitory property. It is suggested that the inhibitory effect is caused by accumulation of 2,4-di- or 2,4,7-tri-enoyl-CoA esters in the mitochondrial matrix."**

Free Radic Biol Med 1999 Oct;27(7-8):901-10. **Thyroid status modulates glycoxidative and lipoxidative modification of tissue Proteins.** Pamplona R, Portero-Otin M, Ruiz C, Bellmunt MJ, Requena JR, Thorpe SR, Baynes JW, Romero M, Lopez-Torres M, Barja G. Steady state protein modification by carbonyl compounds is related to the rate of carbonyl adduct formation and the half-life of the protein. **Thyroid hormones are physiologic modulators of both tissue oxidative stress and protein degradation. The levels of the glycation product** N(epsilon)-fructoselysine (FL) and those of the **oxidation products,** N(epsilon)-(carboxymethyl)lysine (CML) and **malondialdehyde-lysine** (MDA-lys), identified by GC/MS in liver proteins, **decreased significantly in hyperthyroid rats,** as well as (less acutely) in hypothyroid animals. Immunoblotting of liver proteins for advanced glycation end-products (AGE) is in agreement with the results obtained by GC/MS. Cytosolic proteolytic activity against carboxymethylated foreign proteins measured in vitro was significantly increased in hypo- and hyperthyroidism. Oxidative damage to DNA, estimated as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8oxodG), did not show significant differences between groups. The results suggests that the steady state levels of these markers depend on the levels of thyroid hormones, presumably through their **combined effects on the rates of protein degradation and oxidative stress,** whereas DNA is more protected from oxidative damage.

Metabolism 1999 Mar;48(3):406-9. **The blood vessel, linchpin of diabetic lesions.** Plante GE, Alfred J, Chakir M. "The morbidity and mortality associated with diabetes mellitus are essentially related to the vascular lesions that develop over time in this condition. Both the macrocirculation and microcirculation are involved, and as a consequence, vital organs such as the brain, retina, heart, and kidney and the limbs become damaged." "Changes in the structure of conduit arteries, partly responsible for the alteration in compliance characteristics, could well be related to the way these arteries are fed by the vasa vasorum system." "Preliminary results indicate that the size of terminal arterioles of the vasa vasorum (increased diameter) and the capillary permeability to albumin (markedly enhanced) in this specialized network are profoundly affected in the thoracic aorta obtained from diabetic animals. Albumin extravasation into the interstitial fluid compartment of the aorta is likely to lead to structural and physicochemical changes: in fact, removal of interstitial macromolecules via lymphatic drainage is poor in the blood vessel wall of large arteries."

Metabolism 2001 Dec;50(12):1472-8. **Serum phospholipid fatty acid composition and insulin action in type 2 diabetic patients.** Pelikanova T, Kazdova L, Chvojkova S, Base J. **"Increased contents of highly unsaturated n-6 family FA (P <.01), arachidonic acid in particular . . . were found in all groups of diabetics compared with HS [healthy subjects],** while lower levels of linoleic acid were seen in DMN (P <.001) and DMH (P <.05). The contents of saturated FA and monounsaturated FA were comparable in HS, DMN, and DMD."

J Clin Invest 2002 Mar;109(6):805-15. **Acute intensive insulin therapy exacerbates diabetic blood-retinal barrier breakdown via hypoxia-inducible factor-1alpha and VEGF.** Poulaki V, Qin W, Joussen AM, Hurlbut P, Wiegand SJ, Rudge J, Yancopoulos GD, Adamis AP. "Here we demonstrate that acute intensive insulin therapy markedly increases VEGF mRNA and protein levels in the retinae of diabetic rats." "Blood-retinal barrier breakdown is markedly increased with acute intensive insulin therapy. . . ." **"To our knowledge, these data are the first to identify a specific mechanism for the transient worsening of diabetic retinopathy, specifically blood-retinal barrier breakdown, that follows the institution of intensive insulin therapy."**

Acta Endocrinol (Copenh) 1992 Apr;126(4):378-80. **Lipid peroxidation in early experimental diabetes in rats: effects of diabetes and insulin.** Rungby J, Flyvbjerg A, Andersen HB, Nyborg K. "In the kidney, lipid **peroxidation was increased after one week of diabetes; insulin treatment reduced the level of lipid peroxidation to levels lower than seen in controls. In the liver, diabetes caused an increased lipid peroxidation, which could be reversed by insulin; no additional effect of insulin was found. In heart and pancreas no effects of diabetes or insulin were demonstrated. The present paper provides** evidence that lipid peroxidation is increased in the early stages of **experimental diabetes and is reversible by insulin treatment. Hyperinsulinaemia may, in itself, counteract lipid peroxidation in kidney."**

Br J Nutr 1997 Sep;78(3):459-67. **Influence of dietary protein and fat on serum lipids and metabolism of essential fatty acids in rats.** Ratnayake WM, Sarwar G, Laffey P. A "In general, the concentrations of serum triacylglycerols and **total cholesterol and liver phospholipid levels of arachidonic acid (AA) and docosahexaenoic acid (DHA) were higher in rats fed on casein diets compared with those fed on the gelatin diets. These effects were more pronounced in rats fed** on the high-casein (300 g/kg)-high-fat (150 g/kg) diet. **Gelatin was hypocholesterolaemic and also suppressed the liver phospholipid levels of AA and DHA (reported for the first time).** The difference in the amino acid composition between casein and gelatin may be responsible for the observed effects. Casein contains higher levels of glutamic acid, methionine, phenylalanine and tyrosine, while gelatin contains higher levels of arginine, glycine and hydroxyproline."

Br Med J 1979 Jun 30;1(6180):1753-6. **Improved glucose control in maturity-onset diabetes treated with high-carbohydrate-modified fat diet.** Simpson RW, Mann JI, Eaton J, Moore RA, Carter R, Hockaday TD. "Fourteen patients with established maturity-onset diabetes were treated as outpatients with a high-carbohydrate-(about 60% of total daily energy requirements)-modified fat diet (ratio of polyunsaturated fatty acids to other fatty acids greater than or equal to 1:1) for six weeks." **"The findings suggest that it is no longer justifiable to prescribe a low-carbohydrate diet for maturity-onset diabetes."**

Postgrad Med J 1981 Aug;57(670):511-5. **Severe hypertriglyceridaemia responding to insulin and nicotinic acid therapy.** Smith SR. "Treatment with insulin and restriction of dietary carbohydrate led to a 50% reduction in the triglyceride concentration, and the addition of nicotinic acid in modest doses led ultimately to a complete normalization of the patient's lipid values. A close correlation **was noted between the falling triglyceride concentration and the rising serum sodium concentration during the course of successful therapy. Overall, it is felt likely that this patient's severe and reversible hypertriglyceridaemia was on the basis of excessively rapid lipolysis** leading to high concentrations of very low density lipoprotein production."

Am J Clin Nutr 1993 Nov;58(5 Suppl):766S-770S. **Fructose and dietary thermogenesis.** Tappy L, Jequier E. "**Fructose ingestion induces a greater thermogenesis than does glucose. This can be explained by the hydrolysis of 3.5-4.5 mol ATP/mol fructose stored as glycogen, vs 2.5 mol ATP/mol glucose stored. Therefore the large thermogenesis of fructose corresponds essentially to an increase in obligatory thermogenesis.** Obese individuals and obese patients with non-insulin-dependent diabetes mellitus commonly have a decrease in glucose-induced thermogenesis. **These individuals in contrast display a normal thermogenesis after ingestion of fructose.** This may be explained by the fact that the initial hepatic fructose metabolism is independent of insulin."

Diabetes 2002 Jun;51(6):1772-8. **Inhibition of interleukin-1beta-induced COX-2 and EP3 gene expression by sodium salicylate enhances pancreatic islet beta-cell function.** Tran PO, Gleason CE, Robertson RP.

Proc Natl Acad Sci U S A 1998 Apr 28;95(9):4882-7. **Protein-bound acrolein: potential markers for oxidative stress.** Uchida K, Kanematsu M, Sakai K, Matsuda T, Hattori N, Mizuno Y, Suzuki D, Miyata T, Noguchi N, Niki E, Osawa T. "Acrolein (CH2==CH---CHO) is known as a ubiquitous pollutant in the environment. **Here we show that this notorious aldehyde is not just a pollutant, but also a lipid peroxidation product that could be ubiquitously generated in biological systems. Upon incubation with BSA, acrolein was rapidly incorporated into the protein and generated the protein-linked carbonyl derivative, a putative marker of oxidatively modified proteins under oxidative stress." "**Immunohistochemical analysis of atherosclerotic lesions from a human aorta demonstrated that antigenic materials recognized by mAb5F6 indeed constituted the lesions, in which intense positivity was associated primarily with macrophage-derived foam cells and the thickening neointima of arterial walls. **The observations that (i) oxidative modification of low-density lipoprotein with Cu2+ generated the acrolein-low-density lipoprotein adducts and (ii) the iron-catalyzed oxidation of arachidonate in the presence of protein** resulted in the formation of antigenic materials suggested that **polyunsaturated fatty acids are sources of acrolein that cause the production of protein-bound acrolein. These data suggest that the protein-bound acrolein represents potential markers of oxidative stress and long-term damage to protein in aging, atherosclerosis, and diabetes."**

J Intern Med 1990 Aug;228(2):165-71. **Dietary supplementation with n-3 fatty acids may impair glucose homeostasis in patients with non-insulin-dependent diabetes mellitus.** Vessby B, Boberg M. "The blood glucose concentration **tended to increase during MaxEPA treatment, and to decrease during the placebo period, the changes under the two regimes being significantly different (P less than 0.01). In addition, the rate constant for glucose disappearance (k value) for the intravenous insulin-tolerance test, which reflected the peripheral insulin sensitivity, tended to decrease during MaxEPA treatment and increase** during administration of the placebo, there being a significant difference (P less than 0.03) between the changes during the two treatments. The reason for the observed changes in blood glucose concentration and peripheral insulin sensitivity is still unclear."

Diabet Med 1992 Mar;9(2):126-33. **Polyunsaturated fatty acids may impair blood glucose control in type 2 diabetic Patients.** Vessby B, Karlstrom B, Boberg M, Lithell H, Berne C. "**Average blood glucose concentrations during the third week were significantly higher fasting (+15%, p less than 0.01), and during the day at 1100 h (+18%, p less than 0.001) and 1500 h (+17%, p = 0.002) on PUFA than on the saturated fat diet."**

Drugs 1999;58 Suppl 1:31-9; discussion 75-82. **The antihyperglycaemic effect of metformin: therapeutic and cellular mechanisms.** Wiernsperger NF, Bailey CJ "Other effects involved in the blood **glucose-lowering effect of metformin include an insulin-independent suppression of fatty acid oxidation and a reduction in hypertriglyceridaemia. These effects reduce the energy supply for gluconeogenesis and serve to balance the glucose-fatty acid (Randle) cycle."**

J Biol Chem 2001 Mar 30;276(13):9800-7. **Polyunsaturated fatty acids suppress hepatic sterol regulatory element-binding protein-1 expression by accelerating transcript decay.** Xu J, Teran-Garcia M, Park JH, Nakamura MT, Clarke SD. "Our initial studies

indicated that the induction of SREBP-1 expression by insulin and glucose was blocked by PUFA. Nuclear run-on assays suggested PUFA reduced SREBP-1 mRNA by post-transcriptional mechanisms." "**Although the mechanism by which PUFA accelerate SREBP-1 mRNA decay** remains to be determined, cloning and sequencing of the 3'-untranslated region for the rat SREBP-1 transcript revealed the presence of an A-U-rich region that is characteristic of a destablizing element."

Recent Adv Stud Cardiac Struct Metab 1976 May 26-29;12:271-7. **Arrhythmogenic effects of acute free fatty acid mobilization on ischemic heart.** Yamazaki N, Suzuki Y, Kamikawa T, Ogawa K, Mizutani K, Kakizawa N, Yamamoto M.

Science 1978 Jul 28;201(4353):358-60. **Brain edema: induction in cortical slices by polyunsaturated fatty acids.** Chan PH, Fishman RA The presence of polyunsaturated and saturated fatty acids in leukocytic membranes prompted study of their possible role in the induction of brain edema. Polyunsaturated fatty acids including sodium arachidonate, sodium linoleate, sodium linolenate, and docasahexaenoic acids induced edma in slices of rat brain cortex. **This cellular edema was specific, since neither saturated fatty acids nor a fatty acid containing a single double bond had such effect.**

J Neurochem 1986 Oct;47(4):1181-9. **Effects of arachidonic acid on glutamate and gamma-aminobutyric acid uptake in primary cultures of rat cerebral cortical astrocytes and neurons.** Yu AC, Chan PH, Fishman RA. "Arachidonic acid inhibited glutamate uptake in both astrocytes and neurons. The inhibitory effect was observed within 10 min of incubation with arachidonic acid and reached approximately 80% within 120 min in both types of culture. The arachidonic acid effect was not only time-dependent, but also dose-related. Arachidonic acid, at concentrations of 0.015 and 0.03 mumol/mg protein, significantly inhibited glutamate uptake in neurons, whereas 20 times higher concentrations were required for astrocytes. The effects of arachidonic acid were not as deleterious on GABA uptake as on glutamate uptake in both astrocytes and neurons." "**Other polyunsaturated fatty acids, such as docosahexaenoic acid, affected amino acid uptake in a manner similar to arachidonic acid in both astrocytes and neurons. However, saturated fatty acids, such as palmitic acid, exerted no such effect."**
