Metabolic energy management and cancer

by

Suretha Potgieter

Submitted in partial fulfilment of the requirements for the degree

Philosophiae Doctor (Electronic Engineering)

in the

Faculty of Engineering

NORTH WEST UNIVERSITY

Promoter: Prof E.H. Mathews

September 2007

SUMMARY

Title: Metabolic energy management and cancer

Author: Suretha Potgieter

Promoter: Prof. E. H. Mathews

Department: CRCED (Pretoria)

Faculty: Engineering

Degree: Philosophiae Doctor

Key terms: Cancer, energy, blood glucose, insulin, diabetes, exercise, stress, fibre, diet, —ets

Abstract

This study examined the energy dependence of cancer cells. Glucose was found to be their main energy source. It seems possible to use this dependence to advantage in the fight against cancer.

A novel experiment to reduce the blood glucose supply and utilisation was proposed. It entailed caloric restriction, suppression of glucose secretion by the liver as well as suppression of stress hormones (which elevates glucose levels). This minimises the blood glucose value. As a last step, anti-insulin is provided to inhibit cancer cells to utilise the glucose. The cancer cells are thus deprived of their main energy source. This should lead to a reduction or elimination of tumours and will aid in preventing their development. Although feasible, this method turned out to be too expensive to perform the necessary clinical trials to prove the hypothesis.

Next, the focus shifted to cancer prevention. The human energy system was analysed with the goal to reduce the circulating glucose level. The main focus here was metabolised CHO energy consumption. A previously proposed unit – the **E**quivalent **T**easpoon **S**ugar, or –*ets*, was used to quantify energy with. It was shown that cancer risk increases significantly when the recommended –*ets* consumption per day is exceeded.

Furthermore, it was shown that including fibre in a meal reduces the –*ets* value of the meal. One gram of fibre leads to a reduction of around 0.6 –*ets*. The link between exercise, stress, fibre, their resulting blood glucose levels and cancer were quantified in terms of –*ets*. Exercise expends –*ets*, while stress causes the liver to secrete more –*ets*. Experimental data was analysed to confirm the relationships.

In conclusion an equation was formulated to describe the combined effect of all these elements on the energy system. One's total daily –*ets* consumption can be obtained from the equation, and it was linked to one's cancer risk. Adapting a lifestyle that ensures the correct daily –*ets* intake will lead to a significant reduction in cancer risk.

This study proved that cancer cells are very dependent on sugar and a restriction of this energy source forces them into regression. Using this knowledge to advantage may help in the combat one of the biggest killers of our time – cancer.

OPSOMMING

Titel: Metaboliese energiebestuur en kanker

Outeur: Suretha Potgieter

Studieleier: Prof. E. H. Mathews

Departement: CRCED (Pretoria)

Fakulteit: Ingenieurswese

Graad: Philosophiae Doctor

Sleutelterme: Kanker, energie, glukose, insulien, diabetes, oefening, stres, vesel, dieet, –ets, bloedsuiker

Inleiding

Hierdie studie ondersoek die energie-afhanklikheid van kankerselle. Daar is bevind dat glukose hul hoof-energiebron is. Hierdie afhanklikheid van glukose kan dalk tot voordeel gebruik word in die bestryding van kanker.

‘n Oorspronklike eksperiment om bloedsuikervlakke te verlaag is voorgestel. Dit behels beperkte kalorie-inname, onderdrukking van glukose-afskeiding deur die lewer en onderdrukking van stresshormone (wat bloedsuikervlakke verhoog). As ‘n finale stap word anti-insulien toegedien wat kankerselle verhoed om glukose te gebruik. Dit lei tot ‘n afname in die grootte en self totale uitwissing van tumors. Die koste wat aangegaan moet word om die voorgestelde metode te beproef, was egter te hoog om dit prakties uitvoerbaar te maak.

Alternatiewelik is die fokus na kankervoorkoming verskuif. Die menslike energiestelsel is ondersoek met die doel om die sirkulerende glukosevlak te verlaag. Die klem het op energie-inname geval. ’n Bestaande eenheid – die **E**kwivalente **T**eelepel **S**uiker, of —ets, is gebruik om energie mee uit te druk. Daar is bewys dat die kankerrisiko beduidend toeneem wanneer die daaglikse aanbevole —ets- inname oorskry word.

Daar is bewys dat die —ets-waarde van ’n maaltyd verlaag kan word deur vesel by te voeg. Een gram vesel lei tot ‘n verlaging van naastenby 0.6 —ets. Oefening, stres, vesel, hul resultante bloedsuikervlak en meegaande kankerrisiko is ook in terme van —ets uitgedruk. Oefening verbruik —ets, terwyl stres veroorsaak dat die lewer meer —ets uitskei. Eksperimentele data is geanaliseer om die verbande te bevestig.

Ter afsluiting is die gesamentlike effek van al die elemente van die energiestelsel deur een vergelyking voorgestel. Die vergelyking kan gebruik word om ’n persoon se totale daaglikse —ets-inname mee te bereken en sodoende ook die persoon se kankerrisiko te bepaal. ‘n Leefwyse waarin die daaglikse —ets-inname binne die voorgeskrewe perke bly, lei tot ‘n beduidende verlaging in kankerrisiko.

Hierdie studie bewys dat kankerselle uiters afhanklik van suiker is, en dat die beperking van hierdie energiebron tot hul afsterwe lei. Deur hierdie kennis tot die mens se voordeel te gebruik, kan een van die grootste oorsake van sterftes van ons tyd, naamlik kanker, bestry word.

ACKNOWLEDGEMENTS

Firstly, I would like to thank Human-Sim for the opportunity to be part of their research team.

My sincere thanks to Prof. E.H. Mathews for his guidance and advice throughout the study. His —ets concept is based on his unpublished articles (written from 2000). The implications of these articles were used in the Master's Degree of Mr. F. Pizer (2001). They, and those of Mr. J. van Rensburg, were also used in the PhD of Dr. C.P. Botha (2002). In this thesis, the updated articles (2005) were used. Prof Mathews initiated the research into the link between —ets and cancer, and the initial idea for cancer control was proposed by him.

I would like to express my gratitude to Drs. P.I. Ackermann, W.G.G. Gauché and their patients for their participation in the clinical trial.

Lastly, I would like to thank the Human-Sim team, Ruaan and Gerhard, for their input and support, my husband, Paul, for his love and encouragement throughout the study and the Creator of the wonderfully intricate human body for giving me the interest and ability to complete this study.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AUC	-	Area under the curve
CHO	-	Carbohydrates
DMBA	-	7,12-dimethylbenz(a)anthracene
ets	-	**E**quivalent **T**easpoon **S**ugar
GI	-	Glycaemic Index
GI Tract	-	Gastrointestinal Tract
GL	-	Glycaemic Load
HKD	-	Hyperketogenic Diet
IAPP	-	Islet Amyloid Polypeptide
IRs	-	Insulin Receptors
PET	-	Positive Emission Tomography
TNF	-	Tumour Necrosis Factor

GLOSSARY

Acidaemia	-	a fall below the normal pH of the blood (acid blood)
Adenocarcinoma	-	cancer of the gland cells that line the inside wall of the large intestine
Affinity constant	-	the concentration of antibody that binds 50 % of the antigen
Alloxan	-	a substance that destroys the insulin-producing pancreatic cells, used to induce diabetes in test animals
Angiogenesis	-	the formation of new blood vessels
Apoptosis	-	programmed cell death
Cachexia	-	general weight loss and wasting due to a chronic disease
Carcinogen	-	cancer-producing substance or organism
Carcinogenesis	-	the origin and development of cancer
Gluconeogenesis	-	generation of glucose from fats or protein
GLUT1	-	a protein involved in transporting glucose into most cells
Glycogenolysis	-	generation of glucose through the breakdown of glycogen in liver
Glycolysis	-	an anaerobic process in which one glucose molecule is broken down into two pyruvic acid molecules
Hydroxybutyrate	-	a ketone body, produced as a by-product when fatty acids are broken down for energy
Hyperglycaemia	-	an abnormally high concentration of glucose in the blood
Hyperinsulinaemia	-	an abnormally high concentration of insulin in the blood

Hypoglycaemia	-	an abnormally low concentration of glucose in the blood
In vitro	-	an experiment is performed in a test tube, outside a living organism or cell
In vivo	-	experimentation done in or on a living organism
Ketoacidosis	-	an increased level of hydrogen ions in the arterial blood due to elevated ketone body production, as in starvation.
Ketones	-	produced as by-products when fatty acids are broken down for energy
Ketonuria	-	enhanced urinary excretion of ketones
Ketosis	-	enhanced production of ketone bodies, as in starvation
Krebs cycle	-	an aerobic energy production process that takes place in the mitochondria of cells
Metastasis	-	the spread of cancer from its primary site to other places in the body
Metformin	-	decreases glucose uptake from the GI-tract, increases insulin sensitivity
Mitochondria	-	organelle in a cell that is responsible for the energy production of the cell
Mortality	-	the state of being dead
Neoplasms	-	an abnormal tissue that grows more rapidly than normal, may be benign or malignant
Oncogene	-	genes which normally code proteins but may cause cancer when mutated or activated
Postprandial	-	following a meal
Prognosis	-	a forecast of the probable course and/or outcome of a disease
Proliferation	-	growth and reproduction of similar cells
Regression	-	when the tumour has become smaller or the patient is in remission

CHAPTER 1 INTRODUCTION

Cancer is a disease that can affect anyone at any time and in a number of different ways. This study investigates the effect of energy management on cancer risk and prognosis. The goal is to deprive cancer cells of their energy source, thus causing them to die. This chapter gives a brief background of the literature as well as an outline of the rest of the study.

TABLE OF CONTENTS

1.1 Preamble

Cancer is a general term used to describe more than 200 different types of disease. It is characterised by cells that divide without restraint, cross boundaries they are not meant to and lose the characteristics of the cells they originated from (Varmus, 1993).

In 1855 the German pathologist, Rudolf Virchow, made the statement "*Omnis cellula a cellula*" – all cells arise from (other) cells. This fact clearly states that a cancerous cell is merely a normal cell that was stimulated, by one or more factors, to start growing uncontrollably.

Different stimulating factors have been identified, including coal tar, mine dust, tobacco, certain chemicals and radiation (American Cancer Society, 2004). In addition, new ones are still being discovered.

In the last few years a lot of attention has been called to the association between diet and cancer (Donaldson, 2004). Since a cancerous tumour consists of living cells whose survival depends on their state of nourishment, this is the starting point of the current study.

This study investigates the effect of energy management on cancer risk and prognosis (a forecast of the probable course and/or outcome of a disease). Cancer cells have a very high energy demand and sugar is the main source of this energy. It is shown that the cells rapidly die when deprived of sugar. This leads to the development of a novel therapy for the treatment of cancer patients. The therapy deprives cancer cells of their energy source without harming the rest of the organs.

Furthermore, it is shown that a lifestyle that minimises the blood glucose value leads to a reduced risk of cancer. The different elements of the energy management system are discussed and quantified in a new unit. Practical guidelines are formulated to minimise a

person's cancer risk. This includes reducing the available energy by eating less, exercising more and reducing stress levels. A method to reduce the energy absorbed from food through the use of fibre is also presented. To start off the study, the energy requirements of cancer cells are investigated.

1.2 Energy requirements of cancer cells

Because of the high growth rate of cancer cells, they have a very high energy demand (Lora, 2002). It is a generally accepted fact that cancer cells have an increased metabolic rate compared to normal cells (Chang et al., 2000; Guppy et al., 2002; Nolop et al., 1987). One of the factors influencing the energy requirements of cancer cells is their inefficient metabolism. They can't metabolize glucose through aerobic respiration as normal cells do, but rather use anaerobic fermentation.

Cancer cell metabolism

Anaerobic means "in the absence of oxygen". The first step in the metabolism of glucose in any cell is glycolysis, which takes place in the cytoplasm of cells. This is an anaerobic process in which one glucose molecule is broken down into two pyruvic acid molecules. Glycolysis is found in all living organisms and is probably the oldest way of energy production.

A cancer cell then breaks down these pyruvic acid molecules through fermentation to yield a small amount of energy and a lot of waste products (Carter, 2002). The energy-wasting behaviour of cancer cells leads to malnutrition and an undernourished state, also known as cachexia. This causes 40 % of deaths among cancer patients (Quillin, 2001).

Normal cells break down the pyruvic acid molecules through a specialized process called the Krebs cycle (or citric acid cycle). This takes place in the mitochondria of cells and is a much more efficient process. Because cancer cells have defective mitochondria, they can only metabolise glucose through fermentation. This fact may be the passport to success.

Since fermentation yields only 1/15 of the energy per glucose molecule compared to respiration, cancer cells work much harder than normal cells to produce enough energy for survival (Internet Health Library, 2001; John, 2003; Lora, 2002; Warburg, 1956). This may account for their increased glucose consumption.

Tumour growth rate

Another possible explanation for their high energy consumption is their high growth rate when compared to normal cells. As stated before, cancer is defined as unrestrained cell division. Before a cell can divide, it must grow to a certain size. Since the growth and division rate of cancer cells exceeds that of normal cells by up to eight times, they need more energy to sustain their metabolism (Lora, 2002).

Glucose as primary energy source

Cancer cells thrive on glucose. It has been proven that they use up to five times as much glucose as normal cells do (Ayre, 2003; Chung, 1999; Guppy et al., 2002; Holm et al., 1995; Kaslow, n.d.; Lora, 2002; Mazurek, 1999; Nolop et al., 1987; Nu-gen Nutrition; Quillin, 2001; Warburg, 1927). Glucose has furthermore been shown to promote tumour growth (Giovannucci, 2001; Quillin, 2001; Wang, 2003).

A further indication of the high glucose-utilisation of tumours is the use of positive emission tomography (PET) scans to detect and monitor their progress. A PET scan uses radioactively labelled glucose to detect areas of high sugar consumption (or tumours) (Gatenby, 1995). If this is the case, what will happen to cancer cells if their glucose supply is reduced or completely cut off?

Caloric restriction

Because of their high energy demand, cancer cells are not well adapted to deal with periods of low energy intake. Caloric restriction (also know as energy restriction) refers to a state where an animal is undernourished, but not malnourished (Hursting et al., 2003). The animal generally receives between 20 and 40 % less energy than it would if given free access to food. The energy is normally removed from the carbohydrate source.

Caloric restriction has been shown to reduce the formation of induced tumours, impair tumour growth, reduce the risk of cancer, enhance DNA repair and reduce oncogene expression (Carroll, 1986; Dunn, 1997; Hochman, 1988; Hsieh, 2003; Klurfeld et al., 1989; Kritchevsky, 1995; Kritchevsky, 2001; Kritchevsky, 2003; Quillin, 2001; Rogers, 1993; Thompson, 2004; Wang et al., 2003).

Energy restriction by even 30 % significantly reduces tumour formation and growth in rats (Klurfeld, 1989). Caloric restriction also inhibits the recurrence of surgically removed tumours (Kritchevsky, 1997) and reduces the number of tumours induced through radiation in rats by 77 % (Gross & Dreyfuss, 1984).

Hursting et al. (2003) describe caloric restriction as "the most potent, broadly acting cancer-prevention regimen in experimental carcinogenesis models". Animals maintained on restricted diets tend to be healthier and live longer than *ad lib* (unrestrained) fed controls (Hursting et al., 2003). On the other hand, a high-energy diet leads to an increased cancer risk (Day, 2005; Kritchevsky, 1995).

The composition of the diet also affects the cancer risk. Women who derived 57 % or more of their daily energy needs from carbohydrates had a 2.2 times higher risk of developing breast cancer compared to those following a more balanced diet (Day, 2005). The direct result of a diet where energy intake exceeds energy expenditure is obesity.

Obesity

Obesity is defined as "an excessive accumulation of energy in the form of body fat, which impairs health" (Caro, 2002). Stone artefacts exhibiting obese individuals dating back 25 000 years have been found, indicating that obesity is not a recent phenomenon. What is alarming is the marked rate at which obesity in developed countries has increased over the past two decades (Heymsfield in Calle, 2004). In 2000 nearly two thirds of adults in the USA were overweight or obese (Flegal, 2002).

Obesity is also a well-known risk factor for cancer (Calle & Kaaks, 2004; Donaldson, 2004; Kritchevsky, 2003). 15 to 20 % of cancer deaths in America are a result of overweight or obesity (Calle et al., 2003). In addition, the researchers found that overweight, cancerous subjects had death rates of 52 % (men) and 62 % (women) higher than those of cancerous subjects with normal weight. One of the negative effects of obesity is an increased blood glucose level.

Blood glucose level

The blood glucose level is used to define the concentration of glucose in the blood. Consumption of a high-energy diet (specifically high in glucose) leads to a large blood glucose response. This means that the postprandial blood glucose value shoots up very high before returning to the normal level (Rubin, 1999).

Carbohydrates are almost exclusively responsible for the rise in blood glucose. Normal fasting blood glucose levels for humans are between 5 and 6 mmol/l, while a reading of 6 to 7 mmol/l indicates impaired glucose tolerance (Rubin, 1999). One would thus expect a direct relationship between blood glucose value and cancer risk or tumour growth.

This relationship does exist, as proven by Jee et al. (2005) and Reaney (2004). From a study on 1.3 million Koreans, Jee et al. (2005) found that a blood glucose reading of 6.1 to 6.9 mM/l increased the overall cancer risk by 13 % compared to a reading of below 5 mM/l. When the glucose concentration went up to 7.8 mM/l, the cancer risk increased by 22 %.

Reaney (2004) also showed an increased risk of bowel cancer with elevated blood glucose values. Cancer patients with low blood sugar have an increased life expectancy compared to those with high blood sugar (Quillin, 2001).

Santisteban et al. (1985) also demonstrated the relationship between blood glucose value and tumour growth. They injected 68 mice with an aggressive strain of murine breast

cancer and kept them on different diets inducing either normo-, hypo- or hyperglycaemia. Decreasing the blood glucose increased the survival rate in a dose-dependent manner.

1.3 Immune system, sugar and cancer

The immune system is the first line of defence against tumour formation (Santisteban et al., 1985). An investigation was conducted to determine the influence of the blood glucose level on the immune system.

Despite the fact that a high blood glucose value means a lot of fuel for the cancer cells to consume, it has also been shown that sugar suppresses the immune system. Sachez et al. (1973) showed a decrease in the capacity of neutrophils to engulf bacteria after the consumption of 100 g of carbohydrates from glucose, sucrose, honey or orange juice for up to five hours. They concluded that maintaining the blood glucose value in the lower part of the normal range may increase a host's defence against infections.

Wasmuth et al. (2004) conducted a study to investigate the relationship between blood glucose concentrations and different immune variables. They found a reduction in tumour necrosis factor (TNF)-α production in intensive care patients with hyperglycaemia. TNF-α was named for its antitumour properties (Szlosarek, 2003).

Turina et al. (2005) did a comprehensive literature study in which they reviewed all the literature published between 1966 and 2004 on hyperglycaemia and the immune system. Their conclusion was that hyperglycaemia affects all the components of the immune system and reduces the host's ability to fight off infections.

In conclusion to their study on glycaemic modulation of tumour tolerance, Santisteban et al. (1985) stated that hyperglycaemia lowers the intracellular ascorbic acid of leukocytes, inducing tumour tolerance. They continued by stating that hypoglycaemia improves the host's defence against neoplasms.

Critically ill patients are often hyperglycaemic (> 7 mmol/l) and show insulin resistance (Van der Berghe et al., 2001). Insulin resistance refers to a situation where tissues become less responsive to insulin. Since the glucose molecules cannot be utilised, hyperglycaemia results. Circulating insulin levels are elevated in order to restore the glucose homeostasis.

Intensive insulin therapy refers to a form of treatment in which insulin is used to maintain the patient's blood glucose level between 4.4 and 6.1 mmol/l. Van der Berghe et al. (2001) applied intensive insulin therapy to critically ill patients to assess the effect it had on their prognosis. The results were very positive and included a 34 % reduction in hospital mortality, a reduction in bloodstream infections of 46 % and a reduced need for mechanical ventilation in treated patients compared to controls.

It is thus clear that a reduction in the blood glucose value will improve the host's immune system. The conclusion of a recent point-counterpoint discussion by Block et al. (2002) was that boosting the immune system may play a role in cancer prevention or assist in preventing the return of resected tumours.

1.4 Relationship between cancer and diabetes

Diabetes background

Diabetes is one of the fastest growing diseases of the Western world. In 1994 an estimated 140 million people around the world were living with diabetes. It is estimated that by 2010 that number will rise to 300 million (Rubin, 1999).

Diabetes is characterised by an excessive build-up of glucose in the blood. The body needs insulin to absorb glucose. When insulin levels drop, blood glucose concentration rises because the cells are unable to use the circulating glucose. These elevated glucose levels are known as hyperglycaemia.

Diabetes is classified as either type 1 or type 2. Type 1 diabetes occurs when the pancreas is unable to produce the required amount of insulin. The resulting abnormally low levels of circulating insulin is known as hypoinsulinaemia.

In type 2 diabetes, the pancreas produces enough insulin but the body is unable to use it effectively. This is known as insulin resistance. In response the pancreas increases its insulin production in an attempt to maintain a normal glucose metabolism. The now elevated circulating insulin levels are known as hyperinsulinaemia.

It is thus clear that type 1 and type 2 diabetes are very different conditions, the common factor being abnormal insulin and glucose concentrations (Beaser, 1995; Rubin, 1999).

Type 1 diabetics require daily insulin injections to maintain normal blood glucose levels. Before diagnosis they normally have elevated blood glucose levels (because of the insulin deficiency). After diagnosis they start injecting insulin, and depending on the accuracy of the insulin dose, they may be slightly hypo- or hyperglycaemic.

Type 2 diabetics have elevated insulin and glucose levels before diagnosis. After diagnosis, they control their blood glucose level by following a healthy diet. This leads to a decrease in insulin levels as well. If they continue leading their unhealthy lifestyle, they will remain hyperglycaemic and –insulinaemic.

Cancer and diabetes

Previous investigations into the relationship between cancer and diabetes have yielded conflicting results. Some researchers find that diabetes has an inhibiting effect on cancer, while others suggest that persons suffering from diabetes have an increased risk of developing cancer. The reason for the conflicting opinions will become clear in the rest of the section.

Very few of the studies discriminate between type 1 and type 2 diabetes. As has been shown above, the initial symptoms of type 1 and 2 diabetes are very different. Most

researchers do not take this fact into consideration, which might explain the conflicting results.

Cocca and Martin (1998) found less aggressive development of tumours in diabetic rats than in the non-diabetic group. Diabetic rats had fewer tumours per rat and a lower tumour growth rate.

Rhomberg (1975, cited in Cocco, 1998) reported that women with both breast cancer and diabetes have a longer life expectancy than women with only breast cancer. Furthermore, he found that metastasis took more time in diabetic patients. On the other hand Czyzyk (2000) and Coughlin (2004) indicated an increased risk of breast cancer in diabetic patients.

Up to 80 % of patients with pancreatic cancer also have diabetes or glucose intolerance (Pour, 1997; Wang, 2003). Glucose intolerance is basically a precursor to diabetes. The cancer is normally diagnosed within two years of the diagnosis of diabetes (Gullo, 1999; Wang, 2003).

Gullo (1999), in a study of 720 patients, did not find a single patient diagnosed with type 1 diabetes before cancer. This is one of the main proofs of the assumption in the thesis, namely that cancer needs insulin to consume energy. Since a type 1 diabetic patient has an insulin shortage, the cancer cells are deprived of their energy source.

Pour (1997) found that diabetes sometimes disappears after a tumour is removed from the pancreas. Wang (2003) and Parazzini (1999) respectively found that type 1 diabetes does not increase the risk of pancreatic or endometrial cancer. Zendehdel (2003) and Reuters Health (2003), however, found a 20 % increased risk of cancer of the stomach, cervix and endometrium for type 1 diabetics compared to the normal population.

Zendehel (2003) also cites two Swedish studies that confirm the increased risk of endometrial cancer. Reuters Health (2003), however, states that the increase in the risk of

stomach cancer only appears 15 years after diabetes hospitalization and the risk of endometrium cancer might be attributed to other factors.

Type 2 diabetes leads to an increased risk of some cancers, including that of the colon and/or rectum (colorectal) (American Cancer Society, 2004; Czyzyk, 2000; Hu, 1999; Jee, 2005; Orwant, 2004; Reany, 2004; Svacina, 2001), the pancreas (American Cancer Society, 2004; Jee, 2005; Silverman, 1999; Zendehdel, 2003), oesophagus (Jee, 2005), the kidneys (Czyzyk, 2000; Zendehdel, 2003), endometrium (Czyzyk, 2000; Parazzini, 1999; Zendehdel, 2003), breast (Czyzyk, 2000) and liver (Adami, 1996; Czyzyk, 2000; Davila, 2005; Jee, 2005; Zendehdel, 2003). One of the cancers for which no elevated risk exists in diabetic patients is lung cancer (Hall et al., 2005).

The risk of prostate cancer in men increases for the first three years after diabetes has been diagnosed. After that, it decreases to a third lower than the risk for a healthy male (Rodriguez, 2005).

Some authors speculate that cancer causes diabetes. Cancer patients have raised levels of islet amyloid polypeptide (IAPP), which leads to insulin resistivity (Permert, 1994; Pour, 1997). In the long run, this may lead to type 2 diabetes.

Clearly, it is not possible to draw a direct relationship between cancer and diabetes. This might be due to the fact that the general term “diabetes” is used to describe some very different situations.

When a type 1 diabetic is first diagnosed, he/she has very low insulin levels (due to the malfunctioning pancreas) and very high glucose levels (glucose cannot be utilised without insulin). After diagnosis, daily insulin injections start. Depending on the degree of control the individual may have a normal, high or low insulin level, directly influencing the glucose level.

Type 2 diabetics at first have high glucose levels due to an inability to utilise glucose efficiently. The body tries to compensate for this by raising the insulin level. In time, the pancreas becomes exhausted, leading to very low insulin levels. At this stage type 2 diabetes changes into type 1 diabetes. The condition progresses as described above.

The hypothesis in this thesis states that a certain glucose-insulin balance is necessary for cancer proliferation, namely high glucose levels with enough insulin to absorb the glucose. These conditions are not present in all persons classified as "diabetics", which describes the difficulty in finding a direct link between cancer and diabetes up to now. To prove this hypothesis, it is necessary to investigate cancer cells further.

1.5 Insulin and cancer cells

Insulin is necessary for the absorption of glucose into cells. The direct effect of an increased blood glucose level is an increase in the circulating insulin level (Wise, 1999). Furthermore, insulin is known to promote cell growth and division (Ish-Shalom et al., 1997; King, 2004).

Properties of insulin

Insulin is a polypeptide hormone consisting of 51 amino acids with a molecular weight of 5734 (PhatNav, 2003). A hormone can be defined as a chemical messenger secreted in one part of the body to transmit information via the bloodstream to another part. Insulin is secreted by the beta cells in the pancreas.

Every tissue in the body is affected by insulin in one way or another. More specifically, insulin is necessary for glucose absorption, its storage as fat, and the formation of proteins (Mantzoros, 2003; Pittman, 2004; Wise, 1999).

Glucose is the body's main energy source. It can be obtained from ingested food or the breakdown of glycogen in the liver (glycogenolysis), or generated from fats or protein

(gluconeogenesis). Glucose enters the bloodstream, thus increasing the blood glucose value. The increased blood glucose causes an increase in insulin secretion.

All cells that need to absorb glucose for energy are surrounded by a membrane expressing insulin receptors (IRs). Insulin from the bloodstream binds with the IRs. This notifies the cell that glucose is available for absorption. In this way insulin acts as the "key" to open cells for glucose (Beaser, 1995). Since insulin is known to promote normal cell proliferation, the question arises if the same will be true for cancer cells.

Cancer and insulin

For a cell to be influenced by a certain peptide, it needs to express surface receptors for that peptide. Insulin receptors are found on various cancer cells (up to ten times more than on normal cells), and some of these cells even secrete their own insulin (Ayre, 1986; Fisher, 1996; Fisher, 1998; Mossner, 1985; Stephen, 1990).

As stated before, cancer leads to insulin resistivity in the rest of the body, increasing insulin expression from the pancreas (Nature's healthcare, accessed 2005; Permert, 1994; Pour, 1997; Silverman, 1999). This leads to the conclusion that cancer cells make use of and may even be dependent on insulin.

It has been shown that insulin can stimulate carcinogenesis (the origin and development of cancer) of different cell lines (Adami et al., 1996; Boyd, 2003; Calle & Kaaks, 2004; Czyzyk & Szczepanik, 2000; Giovannucci, 1995; Heuson et al., 1972a; Kim, 1998; Volkers, 2000).

Fisher (1996) found that insulin increases tumour proliferation by up to 120 % compared to controls. Orwant (2004) states that mutations in the insulin signalling system can cause uncontrolled cell division. Wang et al. (2003) and Heuson et al. (1972a) found that rat, mouse, hamster and some human pancreatic cancers grew better in the presence of insulin *in vitro* and *in vivo.* Mossner et al. (1985) state that insulin stimulates both the growth and amylase synthesis of pancreatic cancer in rats.

On the other hand, Takeda (1991) reports a cell line from a well-differentiated pancreatic adenocarcinoma with a very high tumour growth rate that was not influenced by insulin. Similarly, Heuson (1967) investigated the effect of insulin on cell proliferation in organ culture. Five out of twelve tumours showed increased proliferation in the presence of insulin, while the other seven did not.

It is noteworthy to state that the spontaneous cell proliferation rate of these seven tumours was already very high (in the same order as that of the other five with insulin added). The researchers concluded that some tumours might be insulin-dependent and others not, or that the insulin-dependency might occasionally disappear in the process of tumour progression. Another point to take note of is that the experiments were conducted *in vitro*, which means that exactly same conditions as found *in vivo* might not have been present.

Wang (2003) also reported some human pancreatic cell lines that did not respond to insulin stimulation. Pour (1984; 1990) even found that insulin administration inhibited tumour induction in the pancreas, gallbladder and common duct of hamsters treated with a carcinogen. This might have been due to the fact that insulin suppresses the replication of pancreatic and ductal cells.

It is speculated that the increased cancer risk with type 2 diabetes can be attributed to hyperinsulinaemia (Brunning, 1992; Calle & Kaaks, 2004; Czyzyk & Szczepanik, 2000; Giovannucci, 2001; Hu, 1999; Jee, 2005; Kaaks, 1996; Zendehdel, 2003). This is supported by the fact that the increased risk of cancer decreases with time (Czyzyk & Szczepanik, 2000; Hu, 1999). The lowering of the cancer risk might be due to the fact that insulin secretion decreases over time from the onset of type 2 diabetes owing to exhaustion of the pancreas.

Rodriguez (2005) came to the same conclusion in his study on the risk of prostate cancer in men from the United States. The researcher found that the risk of prostate cancer was increased in the first three years after diagnosis of diabetes and reduced after that. The

varying risk was attributed to the fact that insulin levels are normally elevated for the first few years of type 2 diabetes (when the body is trying to compensate for the insulin resistance), and reduced thereafter (when the pancreas become exhausted).

Contradictory to this, Silverman (1999) found that the risk of pancreatic cancer increases with years after diagnosis of diabetes. There might, however, be some other link (e.g. a virus) between diabetes and pancreatic cancer, since both originate from the same site, namely the pancreas (or insulin produced in the pancreas). He also found that insulin treatment does not influence cancer risk.

In a recent study, Soliman et al. (2006) identified insulin resistance (which is correlated with hyperinsulinaemia) as independently associated with endometrial cancer. If insulin does stimulate tumour growth, the removal of insulin should inhibit growth.

Kritchevsky (1997) did a study in which he showed that caloric restriction inhibited tumour growth. Caloric restriction reduces the blood glucose value and thus circulating insulin levels. He hypothesizes that insulin deprivation might be the cause of the inhibition of growth.

Heuson and Legros (1972b) induced alloxan diabetes in rats treated with a carcinogenic substance (7,12-dimethylbenz(a)anthracene or DMBA). Alloxan is a substance that destroys the insulin-producing pancreatic cells. The diabetes completely prevented tumour formation.

When tumour-bearing rats were made diabetic, 90 % of their tumours regressed (got smaller). Tumours did not regress in rats that failed to become diabetic or in rats receiving insulin replacement therapy (daily injections of insulin). Cohen and Hilf (1974) did a similar study on diabetes and cancer, but because of a less severe degree of induced diabetes, found that only 60 % of tumours regressed.

Kim (1998) also speculated that the link between diabetes, obesity, physical inactivity and an increased risk of colorectal cancer may be hyperinsulinaemia. The fact that energy restriction of even 30 % leads to a reduction in the plasma insulin levels might explain its protective effect against cancer (Giovannucci, 2001).

Insulin levels in cancer patients

As stated, cancer induces insulin resistivity in the cancer patient, which leads to elevated insulin levels in the blood (Permert, 1994; Pour, 1997). It is also known that cancer uses a high amount of insulin (because of its high glucose metabolism). The question arises whether cancer patients will have elevated or reduced insulin levels.

Heber and Byerly (1985) found normal insulin levels in lung cancer patients, although they had elevated glucose levels after a glucose test. This again shows the inability of the body to utilise insulin effectively.

Ogilvie (2003) and Quillin and Zablocki (2000) found that insulin levels only increase in the later stages of cancer, when cachexia sets in, both in animals and humans. Zablocki (2000) also stated that women with breast cancer and high insulin levels have an eight times greater chance of dying from the cancer compared to those with lower insulin levels. This again confirms the hypothesis that cancer cells thrive in the presence of insulin.

From the numerous studies already conducted it is clear that glucose, insulin and cancer are closely connected. This emphasizes the need for the current study, to investigate this relationship further and propose methods to use it to advantage.

1.6 Mission statement and objectives

It has been shown that cancer is a fast growing disease with an enormous appetite for blood sugar. The hypothesis is that if a tumour's sugar supply or its ability to utilise that supply is cut off, it will die. This hypothesis will be investigated. Methods to reduce the blood

glucose concentration will be provided along with a practical method to render a tumour temporarily unable to utilise glucose.

The proposed method is *inter alia* via the temporary removal of insulin from the circulation system. Without insulin, glucose utilisation is impossible, leading to the regression and even the complete disappearance of the cancerous tumour. Continuous removal of insulin from the body has not been attempted before.

Cancer prevention is investigated by reducing the circulating glucose supply and thus depriving a tumour of sugar. Without an energy source, tumour growth is impossible. Four different factors influencing the blood glucose level will be investigated along with their influence on cancer risk. No previous studies were found that quantifies the link between exercise, stress or fibre on the blood glucose level and cancer risk using one common unit. Quantifiable guidelines will be given to implement a lifestyle promoting these blood glucose lowering mechanisms and thus reducing one's cancer risk.

The mission statement can be defined as: (a) *The proposal of a novel therapy for tumour regression combining, for the first time, several methods of blood glucose control in cancer patients as well as (b) quantifiable guidelines for cancer prevention in the general public through good blood glucose management techniques using one common unit.*

The objectives can be broken down into:

- a holistic experiment on tumour regression through blood glucose control, *inter alia* using insulin removal to inhibit blood glucose usage, suppression of glucose production in the liver and administering a minimum amount of blood sugar for direct use by the brain to prevent hypoglycaemia, coma and death,
- an evaluation of the growth of a cancerous tumour in the above experiment,
- providing a practical and quantifiable relationship between cancer risk and blood glucose level due to diet,

- showing the value of an easy-to-use concept to improve the diet, leading to a reduced cancer risk,
- finding the quantifiable link between stress, the resulting blood glucose response and cancer risk,
- finding the quantifiable link between exercise, the resulting blood glucose expenditure and cancer risk, and
- combining these factors into quantifiable elements using a common unit to formulate guidelines for a lifestyle that minimises the risk of developing cancer.

1.7 Contributions of the study

This study approaches the medical science from an engineering perspective. In medicine, it is customary to take a large amount of measurements and to base conclusions thereon. In the engineering field, it is desirable to create a model of the system under observation.

If the model is complete, it is possible to predict outcomes and confirm them with measurements. If the measurements differ from the predictions, it means that the model is incomplete or incorrect. Either way, the system is thus not fully understood yet and the model needs to be updated. This iterative process cultivates a complete understanding of the system and the effect of external parameters on it.

In this study a model of the human energy management system (in terms of blood glucose) is used to investigate the effect of metabolised glucose energy on cancer. This is used to predict the effect of energy variations on cancer. The predictions made will be verified by the large amount of measurements available from the medical sciences.

The first part of the study will focus on cancer patients, their treatment and possible recovery. The second part deals with cancer prevention. Taking into account that an estimated 18 million new cancer cases have been diagnosed in America since 1990 (American Cancer Society, 2004), the whole of humanity can benefit from the study. The contributions are stated below.

- a novel metabolic therapy for the treatment of cancer patients is suggested,
- blood glucose energy consumption is linked in a quantifiable manner to cancer risk,
- a method is proposed to lower the metabolised glucose energy content of any meal,
- the effect of exercise and stress on cancer risk is quantified, and
- practical guidelines are given to implement a lifestyle that minimises the cancer risk of the man in the street through metabolic energy management.

A single unit describing the effect of various factors on the blood glucose value and the associated cancer risk has not been proposed before. This, along with the novel cancer control treatment, is an important contribution of the study.

1.8 Outline of the study

Figure 1.1 gives a brief summary of the study and also indicates in which chapter each part is addressed. The study involves the human energy system and evaluates where cancer fits into it. Chapter one describes cancer as a glucose energy-intensive disease and explains its metabolism. Methods for blood glucose control resulting in cancer regression or prevention are suggested.

These methods are then explained in more detail. A novel method for potential cancer regression in patients is proposed. Other methods for cancer prevention using blood glucose control are then discussed.

In the closure the link between cancer and blood glucose energy is quantified in one common unit. Practical, easy-to-implement guidelines are supplied, which, upon implementation, should lead to a healthier lifestyle and a significant reduction in cancer risk.

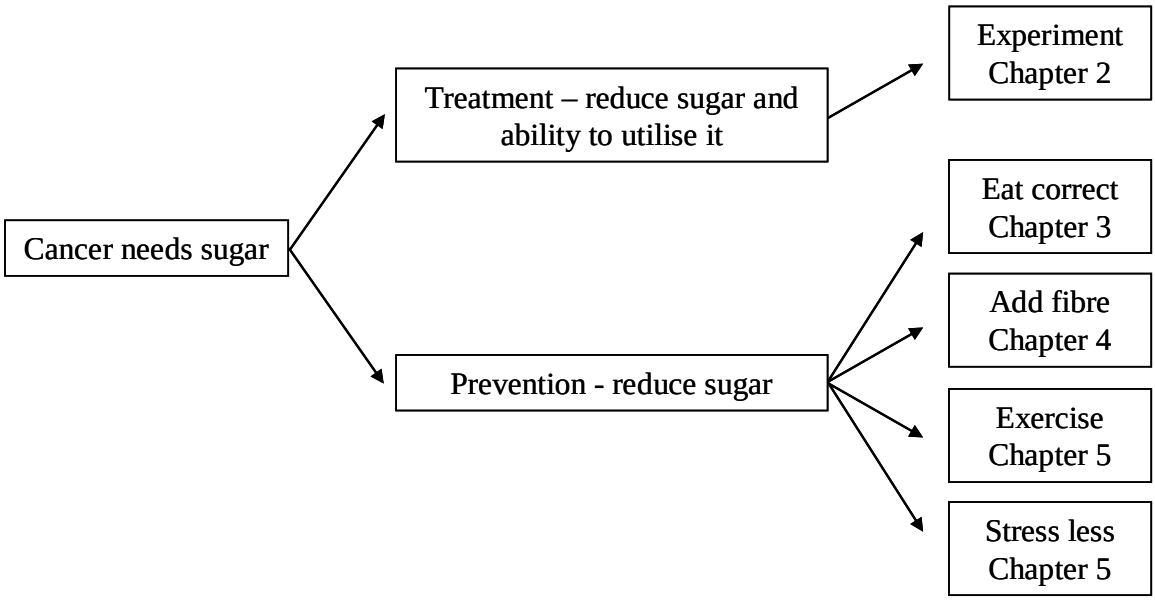

Figure 1.1. Schematic representation of the outline of the study

1.9 References:

Adami, H.O., Chow, W.H. et al. (1996), "Excess risk of primary liver cancer in patients with diabetes mellitus". *Journal of the National Cancer Institute*, 88 (20), pp.1472 - 1477.

Ayre, S.G., Garcia y Bellon, D.P.et al. (1986), "IPT: a new concept in the management of chronic degenerative diseases", *Medical Hypothesis*, 20 (2), pp.199 – 210.

Ayre, S.G. (2003, August 15 – last update), "Insulin Potentiation Therapy", (*The Cancer Cure Foundation*), Available:

http://www.cancure.org/insulin_potentiation_therapy.htm (Accessed: 2005, August 12).

American Cancer Society (2004), "Cancer Facts & Figures 2004", Available: www.cancer.org: American Cancer Society (Accessed: 2005, January 25).

Beaser, R.S. & Hill, J.V.C. (1995), *The Joslin guide to diabetes: a program for managing your treatment*, Fireside, New York.

Block, K.I., Boyd, B. et al. (2002), "The Immune System in Cancer", *Integrated Cancer Therapies*, 1 (3), pp.294 – 316.

Boyd, D.B. (2003), "Insulin and cancer", *Intergrated Cancer Therapy*, 2 (4), pp.315 - 329.

Brunning, P.F., Bonfrer, J.M. et al. (1992), "Insulin resistance and breast-cancer risk", *International Journal of Cancer*, 52 (4), pp.511 - 516.

Calle, E.E., Rodriguez, C. et al. (2003), "Overweight, obesity and mortality from cancer in a prospectively studied cohort of U.S. adults", *The New England Journal of Medicine*, 348 (17), pp.1625 – 1638.

Calle, E.E. & Kaaks, R. (2004), "Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms", *Nature Reviews. Cancer*, 4 (8), pp. 579 – 591.

Caro, J.F. (2002), "Definitions and classification of obesity". In: Caro, J.F. (ed) *Obesity*, Available: http://www.endotext.org/obesity/index.htm (Accessed: 2005, April 6).

Carroll, K.K. (1986), "Diet and carcinogenesis: historical perspectives", *Advances in experimental medicine and biology*, 206, pp.45 - 53.

Carter, J. S. (2002, September 6 – last update), "Cellular respiration and fermentation", Available: http://biology.clc.uc.edu/courses/bio104/cellresp.htm (Accessed 2005, January 25).

Chang, S.G., Lee, S.J. et al. (2000), "Expression of the human erythrocyte glucose transporter in transitional cell carcinoma of the bladder", *Urology*, 55, pp.448 – 452.

Charles River Laboratories (2003), "Oncology – Nude Rat Studies", Available: http://www.criver.com/products/dd/PDF/Oncology_NudeRat_Insert.pdf (Accessed: 2005, August 4).

Chung, J.K., Lee, Y.J. et al. (1999), "Mechanisms related to [18F]fluorodeoxyglucose uptake of human colon cancers transplanted in nude mice". *Journal of Nuclear Medicine*, 40 (2), pp.339 - 346.

Cocca, C., Martin, G. et al. (1998), "An experimental model of diabetes and cancer in rats", *European Journal of Cancer*, 34 (6), pp.889 - 894.

Cohen, N.D. & Hilf, R. (1974), "Influence of insulin on growth and metabolism of 7,12-dimethylbenz(a)anthracene-induced mammary tumours", *Cancer Research*, 34 pp.3245 - 3252.

Coughlin, S. S., Calle, E. E. et al. (2004), "Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults", *American Journal of Epidemiology*, 159 (12), pp.1160 – 1167.

Czyzyk, A. & Szczepanik, Z. (2000), "Diabetes mellitus and cancer", *European Journal of Internal Medicine*, 11, pp. 245 - 252.

Davila, J.A., Morgan, R.O. et al. (2005), "Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study", *Gut*, 54, pp.533 – 539.

Day, C. "Study links high carbohydrate diet to increased breast cancer risk", (Health & Beyond), Available: http://chetday.com/highcarbdietcancer.htm (Accessed: 2005, January 5).

Donaldson, M.S. (2004), "Nutrition and cancer: A review of the evidence for an anti-cancer diet", *Nutrition Journal*, 3 :19, October 2004.

Dunn, S.E., Kari, F.W. et al. (1997), "Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumour progression in p53-deficient mice", *Cancer Research*, 57 (21), pp.4667 – 4672.

Fisher, W.E., Laszlo, G.B. et al. (1996), "Insulin promotes pancreatic cancer: evidence for endocrine influence on exocrine pancreatic tumours", *Journal of Surgical Research*, 63, pp.310 – 313.

Fisher, W.E., Muscarella, P. et al. (1998), "Variable effect of streptozotocin-diabetes on the growth of hamster pancreatic cancer (H2T) in the Syrian hamster and nude mouse", *Surgery*, 123 (3), pp.315 – 320.

Flegal, K.M., Carroll, M.D. et al. (2002), "Prevalence and trends in obesity among US adults, 1999 - 2000", *The Journal of the American Medical Association*, 288 (14), pp.1723 – 1727.

Gatenby, R.A. (1995), "Potential role of FDG-PET imaging in understanding tumor-host interaction", *Journal of Nuclear Medicine*, 36 (5), pp.893 – 899.

Giovannucci, E. (1995), "Insulin and colon cancer", *Cancer causes control*, 6 (2), pp.164 - 179.

Giovannucci, E. (2001), "Insulin, insulin-like growth factors and colon cancer: a review of the evidence", *American Institute for Cancer Research 11th Annual Research Conference on Diet, Nutrition and Cancer*, pp.3109S - 3120S.

Gordon, S. "Blood sugar levels linked to cancer rates", (MedicineNet.com), Available: www.medicinenet.com (Accessed: 2005, January 26).

Gullo, L. (1999), "Diabetes and the risk of pancreatic cancer", *Annals of Oncology*, 10 (supplement 4), pp.79 - 81.

Guppy, M., Leedman, P. et al. (2002), "Contribution by different fuels and metabolic pathways to the total ATP turnover of proliferating MCF-7 breast cancer cells". *The Biochemical Journal*, 364, pp.309 - 315.

Gross, L. & Dreyfuss, Y. (1984), "Reduction in the incidence of radiation-induced tumors in rats after restriction of food intake", *Proceedings of the National Academy of Sciences, USA*, 81, pp.7596 – 7598.

Heber, D., Byerly, L.O. et al. (1985), "Metabolic abnormalities in the cancer patient", *Cancer*, 55 (1 Suppl), pp.225 - 229.

Heuson, J.C., Coune, A. et al. (1967), "Cell proliferation induced by insulin in organ culture of rat mammary carcinoma", *Experimental Cell Research*, 45, pp.351 – 360.

Heuson, J.C., Legros, N. et al. (1972a), "Influence of insulin administration on growth of the 7,12-dimethylbenz(a)anthracene-induced mammary carcinoma in intact, oophorectomized and hypophysectomized rats", *Cancer Research*, 32, pp.233 - 238.

Heuson, J.C. & Legros, N. (1972b), "Influence of insulin deprivation on growth of the 7,12-dimethylbenz(a)anthracene-induced mammary carcinoma in rats subjected to alloxan diabetes and food restriction", *Cancer Research*, 32, pp.226 - 232.

Hochman, G. (1988), "Prevention of cancer: restriction of nutritional energy intake (joules)", *Comparative Biochemistry and Physiology A.* 91 (2), pp.209 - 220.

Holm, E., Hagmüller, E. et al. (1995), "Substrate balances across colonic carcinomas in humans", *Cancer Research*, 55, March, pp.1373 – 1378.

Hsieh, L.J., Carter, H.B. et al. (2003), "Association of energy intake with prostate cancer in a long-term aging study: Baltimore longitudinal study of aging (United States)", *Urology*, 61, pp.297 - 301.

Hu, F.B., Manson, J.E. et al. (1999), "Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women", *Journal of the National Cancer Institute*, 91 (6), pp.542 - 547.

Hursting, S.D., Lavigne, J.A. et al. (2003), "Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans", *Annual Review of Medicine*, 54, pp.131 – 152.

Internet Health Library (2001, March 28 – last update), "Oxygen Therapy", (Therapies), Available:

http://www.internethealthlibrary.com/Therapies/OxygenTherapy.htm#top (Accessed: 2005, January 25).

Ish-Shalom, D., Christoffersen, C.T. et al. (1997), "Mitogenic properties of insulin and insulin analogues mediated by the insulin receptor", *Diabetologia*, 40 (Suppl 2), pp.S25 – 31.

Jee, S. H., Ohrr, H. et al. (2005), "Fasting serum glucose level and cancer risk in Korean men and women", *Journal of the American Medical Association*, 293, pp.194 – 202.

John, A.P. (2003), "Cancer treatments are different", (A. P. John institute for cancer research), Available: http://www.apjohncancerinstitute.org/physician-2.htm (Accessed: 2005, January 25).

Kaslow, J.E. (n.d.) "Beating cancer". Available: http://www.drkaslow.com/html/cancer.htm (Accessed: 2005, January 25).

Kim, Y.I. (1998), "Diet, lifestyle, and colorectal cancer: is hyperinsulinemia the missing link?", *Nutrition Reviews*, 56 (9), pp.275 - 279.

King, M.W. (2004, November 4 – last update), "Type 1 and 2 diabetes mellitus", (*The medical biochemistry page*), Available:

http://web.indstate.edu/thcme/mwking/home.html (Accessed: 2005, April 4).

Klurfeld, D.M., Welch, C. B. et al. (1989), "Determination of degree of energy restriction necessary to reduce DMBA-induced mammary tumourigenesis in rats during the promotion phase", *Journal of Nutrition*, 119 (2), pp.286 – 291.

Kritchevsky, D. (1995), "The effect of over- and undernutrition on cancer", *European Journal of Cancer Prevention*, 4 (6), pp. 445 – 451.

Kritchevsky, D. (1997), "Caloric restriction and experimental mammary carcinogenesis", *Breast Cancer Research and Treatment*, 46, pp.161 - 167.

Kritchevsky, D. (2001), "Caloric restriction and cancer", *Journal of Nutritional Science and Vitaminology*, 47 (1), pp.13 – 19.

Kritchevsky, D. (2003), "Diet and cancer: whats next?", *International Research Conference on Food, Nutrition and Cancer, Supplement*, pp.3827S - 3829S.

Lora (2002, Feb 22 – last update), "Cancer and sugar's role in it", (The low carb luxury newsletter), Available:

http://www.lowcarbluxury.com/newsletter/lclnewsvol03-no04-pg2.html (Accessed: 2005, January 25).

Mantzoros, C. & Sherdy, S. (2003, November 25 – last update), "Insulin action", (*UpToDate Patient Information*), Available:

http://patients.uptodate.com/topic.asp?file=diabetes/23821#2 (Accessed: 2005, April 4).

Mazurek, S., Eigenbrodt, E. et al. (1999), "Alterations in the glycolytic and glutaminolytic pathways after malignant transformation of rat liver oval cells". *Journal of Cellular Physiology*, 181 (1), pp.136 - 146.

Mossner, J., Logsdon, C.D. et al. (1985), "Insulin, via its own receptor, regulates growth and amylase synthesis in pancreatic acinar AR42J cells", *Diabetes*, 34 (9), pp.891 – 897.

Nature's healthcare, "General cancers". Available:

http://www.natureshealthcareinfo.com/diseases/general_cancers.php (Accessed:

2005, February 9).

Nolop, K.B., Rhodes, C.G. et al. (1987), "Glucose utilization in vivo by human pulmonary neoplasms", *Cancer*, 60 (11), Dec 1, pp.2682 – 2689.

Nu-gen Nutrition, "7 Cancer Facts", Available: http://www.cancerchoices.com/ (Accessed: 2005, January 25).

Ogilvie, G.K. (2003), "Nutrition and cancer: new keys for cure and control in 2003!", (*28th World Congress of the World Small Animal Veterinary Association*), Available:

http://www.vin.com/proceedings/Proceedings.plx?CID=WSAVA2003&PID=6569&O=Generic (Accessed: 2005, April 7).

Orwant, R. (2004), "Cancer unplugged", *NewScientist*, 14 August 2004, pp.34 - 37.

Parazzini, F., La Vecchia, C. et al. (1999), "Diabetes and endometrial cancer: an Italian case-control study", *International Journal of Cancer*, 81 (4), pp. 539 – 542.

Permert, J., Larsson, J. et al. (1994), "Islet amyloid polypeptide in patients with pancreatic cancer and diabetes", *The New England Journal of Medicine*, 330 (5), pp.313 - 318.

PhatNav (2003), "Insulin", (*PhatNav's Encyclopedia*), Available: http://www.phatnav.com/wiki/index.php?title=Insulin (Accessed: 2005, April 4).

Pittman, I., Philipson, L.H. et al. (2004), "Insulin biosynthesis, secretion and structure – activity relationships ". *In*: Goldfine, I.D., Rushakoff, R.J. (eds) *Diabetes and carbohydrate metabolism*, Available:

http://www.endotext.org/diabetes/index.htm (Accessed: 2005, April 4).

Pour, P.M. & Stepan, K. (1984), "Modification of pancreatic carcinogenesis in the hamster model. VIII. Inhibitory effect of exogenous insulin", *Journal of the National Cancer Institute*, 72 (5), pp.1205 - 1208.

Pour, P.M., Kazakoff, K. et al. (1990), "Inhibition of streptozotocin-induced islet cell tumours and N-nitrosobis (2-oxopropyl)amine-induced pancreatic exocrine tumours in Syrian hamsters by exogenous insulin", *Cancer Research*, 50 (5), pp.1634 - 1639.

Pour, P. M. (1997), "The role of langerhans islets in pancreatic ductal adenocarcinoma", *Frontiers in Biosciences*, 2, pp. 271 – 282.

Quillin, P. (2001), "Cancer Cells Preferentially use Sugars", (*Beating Cancer with Nutrition*), Available:

http://www.ndmnutrition.com/cancer%20loves%20sugar (Accessed: 2005, March 30).

Quillin, P. "A review of cancer therapies", *(The Fountain of Life*). Available: http://www.thefountainoflife.ws/cancer/therapies.htm (Accessed: 2005, February 9).

Reuters Health (2003), "Stomach and Uterine Cancer Risk Higher in Diabetes", (*Lifescan*), Available: www.lifescan.com/care/news (Accessed: 2005, January 13).

Reany, P. (2004), "Diabetics may have triple normal bowel cancer risk", (*Lifescan)*, Available: http://www.lifescan.com/care/news/dn060404-2/ (Accessed: 2005, April 1).

Rhomberg, W. (1975), "Metastasierendes mammakarzinom und diabetes mellitus-eine prognostisch günstige krankheitskombination", *Deutsche medizinische Wochenschrift*, 100, pp.2422 – 2427. Cited in: Cocca, C., Martin, G. et al. (1998), "An experimental model of diabetes and cancer in rats", *European Journal of Cancer*, 34 (6), pp.889 - 894.

Rodriguez, R., Patel, A.V. et al. (2005), "Diabetes and the risk of prostate cancer in a prospective cohort of US men", *American Journal of Epidemiology*, 161 (2), pp.147 – 152.

Rogers, A.E., Zeisel, S.H. et al. (1993), "Diet and carcinogenesis", *Carcinogenesis*, 14 (11), pp.2205 - 2217.

Rubin, A.L. (1999), *Diabetes for dummies*, Hungry Minds, Inc, New York.

Sanchez, A., Reeser, J.L. et al. (1973), "Role of sugar in human neutropilic phagocytosis", *The American Journal of Clinical Nutrition*, 26, Nov, pp.1180 – 1184.

Santisteban, G.A., Ely, J.T. et al. (1985), "Glycemic modulation of tumor tolerance in a mouse model of breast cancer", *Biochemical and Biophysical Research Communications*, 132 (3), pp.1174 – 1179.

Silverman, D.T., Schiffman, M. et al. (1999), "Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer", *British Journal of Cancer*, 80 (11), pp.1830 - 1837.

Soliman, P.T., Wu, D. et al. (2006), "Association between adiponectin, insulin resistance, and endometrial cancer", *Cancer*, 106, 11, Apr 25, pp. 2376 – 2381.

Szlosarek, P.W. & Balkwill, F.R. (2003), "Tumour necrosis factor alpha: a potential target for the therapy of solid tumors", *The Lancet Oncology*, 4 (9), pp.565 – 573.

Stephen, G. & Ayre, M.D. (1990), "The physiology and clinical pharmacology of insulin in relation to its application in insulin potentiation therapy", Available: http://www.iptq.com/phys&pharm.htm (Accessed: 2005, April 4).

Svacina, S., Matoulek, M. et al. (2001), "Diabetes as risk factor for incidence and location of colon cancer", *37th Annual Meeting of the EASD, Glasgow, United Kingdom, 9 September 2001*. Diabetes UK.

Takeda, Y. & Escribano, M.J. (1991), "Effects of insulin and somatostatin on the growth and the colony formation of two human pancreatic cancer cell lines", *Journal of Cancer Research and Clinical Oncology*, 117 (5), pp.416 – 420.

Thompson, H.J., Zhu, Z.et al. (2004), "Weight control and breast cancer prevention: are the effects of reduced energy intake equivalent to those of increased energy expenditure?", *The Journal of Nutrition – Supplement*, pp. 3407s - 3411s.

Turina, M., Fry, D.E. et al. (2005), "Acute hyperglycemia and the innate immune system: Clinical, cellular, and molecular aspects", *Critical Care Medicine*, 33 (7), pp.1624 – 1633.

Van der Berghe, G., Wouters, P. et al. (2001), "Intensive Insulin Therapy in Critically Ill Patients", *The New England Journal of Medicine*, 345, Nov 8, pp.1359 – 1367.

Varmus, H. & Weinberg, R. A. (1993), *Genes and the biology of cancer*. Scientific American Library, New York.

Volkers, N. (2000), "Diabetes and cancer: scientists search for a possible link", *Journal of the National Cancer Institute*, 92 (3), pp.192 - 194.

Wang, F., Herrington, M. et al. (2003), "The relationship between diabetes and pancreatic cancer", *Molecular Cancer*, vol 2, pp. 1 – 5.

Warburg, O., Wind, F. et al. (1927), "The metabolism of tumours in the body", *The Journal of General Physiology*, vol 8 (6), pp. 519 – 530.

Warburg, O. (1956), "On the origin of cancer cells", *Science*, vol 123 (3191), pp. 309 – 314.

Wasmuth, H.E., Kunz, D. et al. (2004), "Hyperglycemia at admission to the intensive care unit is associated with elevated serum concentrations of interleukin-6 and reduced *ex vivo* secretion of tumor necrosis factor-α", *Critical Care Medicine*, 32 (5), pp.1109 – 1114.

Wise, P.H. (1999), *Understanding your diabetes – For people with insulin-dependent (type 1) diabetes*, Foulsham, The Publishing House, Berkshire, England.

Zablocki, E. (2000), “High Insulin Levels Linked to Breast Cancer Death”, (*WebMD*), Available: http://my.webmd.com/content/Article/25/1728_57897.htm?printing=true (Accessed: 2005, April 7).

Zendehdel, K., Nyren, O. et al. (2003), “Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden“, *Journal of the National Cancer Institute*, 95 (23), pp. 1797 – 1800.

CHAPTER 2 TUMOUR REGRESSION THROUGH CONTROL OF GLUCOSE SUPPLY AND UTILISATION

This chapter addresses a holistic experiment on tumour regression through blood glucose control. Removal of insulin from a living organism renders it unable to utilise glucose. While the other organs can switch to different energy sources, cancer cells cannot. They are thus left without an energy source and die. The proposed experiment examines the feasibility of using anti-insulin serum for temporary insulin removal along with other factors to minimise the blood glucose level.

TABLE OF CONTENTS

2.1 Background

In the previous chapter the background on cancer, sugar and insulin was given. It was established that blood sugar promotes cancer growth and is necessary for the proliferation of cancer cells. In this chapter a novel experiment is proposed that reduces the glucose supply and controls its utilisation in the body.

Anti-insulin serum

Monoclonal antibodies are the "identical offspring of a single, cloned antibody producing cell" (Monoclonal Antibody Production, 2005). They are produced by immunizing a host animal with the antigen (insulin, in the present case). This stimulates the host to produce antibodies against the antigen. Antibodies bind very tightly to their antigen. They are normally produced to defend the body against infections. The antibody-antigen complex is then eliminated by the body.

In monoclonal antibody production the antibody-forming cells are isolated from the host's spleen and fused with tumour cells. The resulting cell is called a hybridoma and is characterised by a high antibody production rate. By allowing the hybridoma to multiply in culture, a population of antibody-producing cells are created (Monoclonal Antibody Production, 2005). The antibodies they produce are used to form an antibody serum against the antigen.

Anti-insulin serum (which binds to insulin molecules) has been produced before. Beck et al. (1982) injected anti-insulin serum into mice to estimate their insulin secretion rates. McGarry et al. (1975) used a one hour infusion of anti-insulin serum to induce a ketogenic profile in rat livers. This caused an elevation in plasma glucose, free fatty acid and ketone bodies. The researcher proposes to use this same method of anti-insulin infusion to remove most of the host's insulin temporarily. "Most of" is used instead of "all" for a very specific reason.

As stated before, insulin is required for glucose absorption. When insulin levels are reduced, the body's main energy supply (glucose) is cut off. The body thus goes into "starvation mode" and starts using its reserves for energy. This includes burning fat or muscle tissue to produce glucose (gluconeogenesis), and the transformation of glycogen to glucose in the liver (glycogenolysis).

Without insulin to replenish it, the liver's glycogen supplies are depleted after about three to five days (VanItallie & Nufert, 2003). When fat or muscle tissue is burned, ketone bodies are formed as a by-product.

Ketones

When in starvation, the body transports free fatty acids to the liver where they are metabolised to glucose. Ketones are formed as a by-product (Cohen & Stark, 1938; King, 2004; Werk et al., 1955). The three ketone bodies are hydroxybutyrate, acetoacetate and acetone. Of these, hydroxybutyrate and acetoacetate are strong acids, with hydroxybutyrate normally being the main contributor to an elevated plasma ketone concentration.

Acetone is the smallest ketone and is present in much lower levels than the other two. It can be excreted via the lungs or, along with hydroxybutyrate and acetoacetate, via urine. A rise in blood ketone levels causes the bicarbonate level to fall drastically. Bicarbonates act as a buffer in the blood, preventing it from becoming too acidic. Their decrease thus lowers the pH of the blood, leading to acidaemia (acid blood) (Insel et al., 2003; Ketone bodies, n.d.; Veech, 2001).

In the initial stages of starvation, the muscles burn ketone bodies for energy. As the period of starvation increases, the muscles revert to fatty acids for energy, reserving the ketone bodies for the brain (Cahill, 1970). Because the brain is a critical organ to ensure the survival of any organism, it has the highest priority when it comes to the distribution of energy resources.

In their article “The selfish brain”, Peters et al. (2004) present the idea that the brain looks after itself first, before it allocates energy resources to the rest of the body. It thus ensures it own survival, even at the cost of other organs. This is necessary because the brain is more selective with respect to energy sources than the other organs.

Previously, it was believed that the brain could only utilise glucose as energy source. Cahill et al. (1966) were the first to prove that the brain uses ketone bodies as an alternate fuel source when glucose supplies are too low. If the brain could use only glucose, a starving adult would survive only two to three weeks without any food. With ketones as an alternate energy source, it is possible to survive for up to two months (Veech, 2001).

The main function of ketone bodies is thus to supply the brain with an alternate energy source during periods of starvation. As its ketone utilisation increases, that of glucose decreases, maintaining constant energy consumption (Hasselbalch, 1994).

The brain uses an exceptional amount of energy when compared to the rest of the body. Even though it only accounts for about 2 % of the body mass, it is responsible 15 to 20 % of the total daily energy consumption (South, 2004). This can be ascribed to the large number of instructions executed by the brain, its central role in survival, as well as its limited energy storage capacity (Peters et al., 2004).

There is always a small concentration of ketones in the serum and urine. Human blood ketone levels after an overnight fast rarely exceed 0.5 mM/L (VanItallie & Nufert, 2003). When in starvation or without insulin, the body starts burning fat for energy. This raises the blood ketone levels. This high rate of ketone production is known as ketosis (a concentration of between 0.2 mmol/l and 7 mmol/l) (Erochenko).

Normally, insulin ensures that excessive amounts of ketone bodies are not produced. In the absence of insulin, however, the dangerous condition of ketoacidosis might develop.

Ketoacidosis

Ketoacidosis is defined as an increased level of hydrogen ions in the arterial blood due to elevated ketone body production. This happens owing to starvation or diabetes, and is characterised by a lowering of the blood pH.

Hydroxybutyrate levels of hospitalized patients with severe ketoacidosis rise to 23 mM/l (Foster, 1991). At this stage glucose levels will also be severely elevated. The body tries to restore the normal balance by increasing urinary output. This results in dehydration and excessive loss of electrolytes (i.e. sodium and potassium) (Veech, 2001). It usually develops over a period of days, so early identification and treatment is possible. Ketoacidosis is characterised by:

- a lowering of blood pH (< 7.25), which impairs the binding of haemoglobin to oxygen,
- nausea, vomiting,
- tiredness and weakness,
- abdominal pain,
- heavy breathing with an acetone odour,
- dehydration, and
- a disturbed electrolyte concentration (Beaser, 1995; Wise, 1999; Worthly, 2003).

Treatment encompasses administration of fluids, sodium, potassium, magnesium, phosphate, bicarbonates and insulin to restore their normal concentrations (Worthly, 2003).

In the proposed experiment, the animal will be kept in a controlled state of ketosis, while preventing the development of ketoacidosis. Although ketone levels will be elevated, the

pH level will be controlled by administering the necessary electrolytes and bicarbonates. If untreated, ketoacidosis will lead to coma and eventually death.

Therapeutic uses of ketones

Ketones are not all bad. It has been shown that hydroxybutyrate is a more efficient energy source per unit of oxygen than glucose for the brain, heart and sperm cells (Veech, 2001). Furthermore, ketones have been shown to decrease cell death in models of Alzheimer's and Parkinson's disease (Veech, 2001).

Epilepsy has been treated with fasting and ketogenic diets since the early 20th century. Hugh Conklin treated epileptic children with a diet of only water for 30 days, with some positive results.

Russel Wilder was one of the first to prescribe the high fat/low carbohydrate ketogenic diet for the treatment of epilepsy. The diet consists of four parts fat and one part protein and carbohydrate combined. It has been termed a hyperketogenic diet (HKD) because of the severity of the ketosis it induces. It reduced seizures in 40 % of drug-resistant patients by 90 % and in an additional 40 % by 50 – 90 % (VanItallie & Nufert, 2003; Veech, 2001). Because of the high cholesterol content of the diet, it is seldom prescribed for patients over the age of 17.

The reason for the diet's success is not clear. One possible explanation is that some types of epilepsy are caused by a GLUT1 deficiency. GLUT1 is a membrane protein and a member of the glucose transport family. It is necessary to transport glucose into the brain. With the high ketogenic diet, the brain is supplied with an alternate energy source (ketones), reducing epileptic seizures (Veech, 2001). Serum ketone levels of 2 – 7 mM/l are necessary for the treatment of epilepsy (VanItallie & Nufert, 2003).

A diet low in carbohydrates is not necessarily a ketogenic one. Heinbecker (1928) noted that Eskimos living on Baffin Island did not show high ketonuria levels (ketones in urine)

even though their diet consisted almost exclusively of meat. The explanation for this is that a large part of proteins can be converted to glucose. If the protein intake is high enough to supply the body with the required amount of glucose, hyperketonemia will not result (VanItallie & Nufert, 2003).

A popular ketogenic diet followed by many weight losers is the Atkins diet. It is an energy restricted diet consisting of mostly protein and fat with very little carbohydrates. The subject is in a constant state of ketosis. Since the subjects are not diabetics and do not suffer from insulin deficiency, they will not develop ketoacidosis (Debunking the myths, n.d.). A typical ketogenic diet induces plasma ketone levels of 0.28 – 0.4 mM/L (VanItallie & Nufert, 2003).

Cancer and ketones

Since the brain and heart can use ketone bodies as an energy source, it was regarded as possible that cancer could also utilise ketones. An investigation showed that this is not the case. As stated before, glycolysis is the first step in the metabolism of glucose. A critical enzyme in this process is phosphofructokinase.

Ketones inhibit the activity of this enzyme, essentially stopping glycolysis. When this happens, normal cells revert to the Krebs cycle (which takes place in the mitochondria) to derive energy directly from ketones or fats. Because of their faulty mitochondria, cancer cells are unable to do this. Left without an energy source, it is impossible for them to survive (John, 2001).

A study of the effect of a ketogenic diet on paediatric cancer patients showed that it reduced the glucose uptake in the tumour by 21.8 % (Nebeling & Lerner, 1995). These results are promising, since tumours rely almost exclusively on glucose for energy (see section 1.2). Flatt et al. (1987) did a study on rats, which showed that tumour weight decreased by 50 % in rats with diet-induced ketosis compared to controls. Magee et al. (1979) confirm the inhibiting effect of ketones on cancer.

A study done by Urgoiti et al. (1963) proved that the development of ketoacidosis is dependent on lack of insulin only when a high level of stress hormones accompanies it. A suppression of the stress hormones will thus delay or prevent the onset of diabetic ketoacidosis.

Stress hormones

Cortisol, glucagon, epinephrine and growth hormone are the four main stress hormones that occur at elevated levels in stressful situations. Their function is to raise the blood glucose and they are normally released when the blood glucose is low (Schermerhorn, 2001; Sieber & Traystman, 1992).

Epinephrine is known to stimulate gluconeogenesis and glycogenolysis during insulin deficiency. Glucagon increases the efficiency of gluconeogenesis, while cortisol increases the supply of precursors (e.g. glutamine, alanine and lactate) to the liver (Goldstein et al., 1995).

When there is insufficient insulin in the body, the cells cannot use the glucose in the blood. They interpret this as a glucose deficiency, or low blood sugar. Stress hormones may thus be secreted to raise the blood glucose, which is in fact already elevated. This causes severe hyperglycaemia, which worsens the ketoacidosis. It is thus desirable to limit the excretion of stress hormones, as well as the production of glucose in the liver.

To reduce stress hormone levels, a long-acting neuroleptic drug will be used. Neuroleptic drugs are often used as tranquilizers in wildlife management to reduce stress associated with the capture and translocation of animals. They suppress the activity of neurotransmitters in the central nervous system (Read, 2002). This leads to relative indifference to surroundings.

Perphenazine enanthate (also known as Trilafon-LA) was selected because its effect lasts for seven to ten days after administration (Read, 2002). Perphenazine has been shown to reduce the production of corticosterone in rats (Wexler, 1976) and to have no influence on insulin production (Melkersson et al., 2001). Corticosterone is the main stress hormone secreted in rats and the equivalent to human cortisol (Day, 1999). Hyperglycaemia is a further aggravator of ketoacidosis. To minimise the blood glucose level, Metformin will be used.

Metformin

Metformin was developed in 1957 to reduce glucose production from the liver and to increase glucose uptake by peripheral tissues. It is used by diabetics to lower their blood sugar and to reduce diabetes-related death rates, heart attacks and strokes. Fasting blood glucose levels are lowered by an average of 25 % and insulin requirements reduced (Metformin, n.d.).

In the current study, lowering of the blood sugar is desirable to reduce dehydration and ketoacidosis. Furthermore, depletion of the glucagon supply in the liver increases stress hormone production which, along with dehydration, aggravates ketoacidosis. A recent pilot study suggests that Metformin may also reduce the risk of cancer in type 2 diabetic patients (Evans, 2005). Metformin is not metabolised, but is excreted in the urine.

2.2 Outline of the experiment

Figure 2.1 gives a schematic representation of the proposed main experiment. The rat will be placed on a CHO restricted diet. To suppress the liver from secreting glucose, Metformin will be used. Further suppression of the liver is accomplished by using a tranquilizer to prevent the secretion of stress hormones which activates glucose secretion by the liver. Lastly, the anti-insulin infusion will be supplied. This is a novel experiment that has not been proposed before.

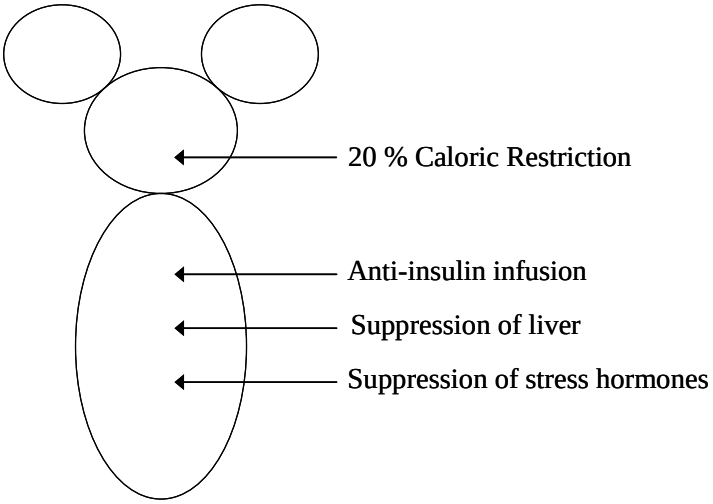

Figure 2.1. Outline of main experiment.

Phase one is the pilot study, which will investigate the feasibility of using monoclonal insulin antibodies produced in the mouse for *in vivo* insulin reduction in the rat. The toxic preservative needs to be removed before infusion, and the concentration necessary for insulin removal has to be determined.

As a starting point, the insulin level will be reduced by 90 % and the ketogenic status of the animal monitored. If this insulin level proves to be too low, the antibody infusion will be reduced to ensure the well-being of the animal.

The information gained in this study will be used to fine-tune the antibody infusion for the main experiment (phase two). Phase two will examine the growth of cancer tumours in rats in the absence of insulin.

2.3 Methods - Phase one

Implementation

Monoclonal anti-insulin antibodies produced in a mouse (I2018) will be bought from Sigma-Aldrich. To remove the preservative, sodium azide, the procedure described by Travers (1989), will be followed. It comprises the dilution of 0.5 ml of anti-insulin serum

to 5 ml with distilled water. The solution is then dialyzed for 48 hours at 4 ºC with constant agitation. This ensures removal of the sodium azide.

The concentration of antibodies required for the reduction of the insulin level can be determined from the definition of the affinity constant, K_a. K_a defines the concentration of antibody that binds 50 % of the antigen, and is computed from the equation:

$$K_a = \frac{[bound\ antibody - antigen]}{[antibody][antigen]} \tag{2.1}$$

where the square brackets denote concentration (Rule, 2003). Taking into consideration that a rat has an insulin concentration of about 312 ρM/l (McGarry, 1975), the fact that the researcher wants to reduce it by 90 %, and the affinity constant of the antibodies of $8.8 \cdot 10^9$ l/M (Monoclonal anti-insulin antibody produced in the mouse, n.d.), the desired antibody concentration in the rat is about 100 ρM/l.

The specific antibody concentration differs for each batch produced by Sigma, but it is in the order of 21 nM/ml. It is sold in 0.5 ml packages, containing about 10.5 nM per package.

The plasma half-life of insulin is around six minutes (Duckworth, et al., 1998). This means that the insulin production rate in the rat is around 50 ρM/min. To reduce this by 90 % means that an antibody infusion rate of about 17 ρM/min will be required.

One 0.5 ml package will be diluted to 8 ml with saline, yielding an antibody concentration of 1.3 μM/l. This will be infused at a rate of 11 μl/min, resulting in an antibody infusion rate of 14 pM/min. This infusion rate is similar to the one used by McGarry et al. (1975) for infusion of anti-insulin serum (10 μl/min). This should reduce the plasma insulin concentration to 10 % of the normal value. One 0.5 ml package will thus be infused in about 12 hours.

A silicon infusion catheter will be implanted into the femoral vein of the rats a few days before commencing with the experiment. After insertion, the catheter will be filled with heparin and its ends closed until such time as the infusion is started. The catheterization site will be inspected daily to ensure early detection and treatment of infections.

The main side-effect of such a severe reduction in insulin level is the development of diabetic ketoacidosis. In humans, ketoacidosis is characterised by hyperglycaemia, acidaemia and dehydration, and may lead to coma or death if left untreated (Managing diabetes, n.d.). Rats, however, display a greater capacity for destroying ketones in the liver (Cohen & Stark, 1938). It is nonetheless necessary to monitor the development of ketoacidosis and to reduce the antibody infusion if it becomes too severe.

The pH value will be used as an indication of the degree of ketoacidosis present in the animals. Bäckman (1999) did an acid-base experiment in which rats were maintained in metabolic acidosis for six weeks at a pH of 7.15 – 7.33. The rats were in good health at the end of the experiment. A pH of 7.15 will thus be used as the lower limit of safe acidosis. If the pH drops below 7.15, the antibody infusion rate will be decreased by 1 μl/min to allow the insulin level to increase.

The infusion rate should only be changed once a day, directly after the measurements have been taken. This will lower the production of ketone bodies and allow the rat to recover partially from the ketoacidosis. Ketoacidosis will further be inhibited by reducing the blood glucose and stress hormone levels.

To limit the blood glucose value, the rats will be fed a CHO restricted diet. “Caloric restriction” refers to the fact that an animal is undernourished, but not malnourished (Hursting et al., 2003). The maintenance caloric requirements of adult rats can be described by the following equation:

$$0.45 \cdot BW^{0.75} \qquad (2.2)$$

expressed in MJ, with *BW* describing the body weight of the rat in kilogram (Clarke et al., 1977). The rats will be fed a 70 % caloric restriction diet, which means that they will receive 30 % of the maintenance caloric requirements for adult rats. This drastic measure is imposed to reduce the blood glucose value to the minimum.

A similar caloric restriction was imposed by Gross and Dreyfuss (1990). Their rats received between 21 and 29 % of an ad lib diet for the whole duration of their life. The rats on the restricted diet lived longer (females 27 % and males 7 %) than the ones allowed free access to food.

The rats will be weighed prior to implantation of the catheters, and their caloric needs for the duration of the study will be calculated from this body weight. The final caloric content of the restricted diet can be computed from equation 2.3:

$$0.135 \cdot BW^{0.75} \qquad (2.3)$$

The blood glucose value will be reduced further by suppressing the production of glucose from the liver. This is accomplished with the anti-diabetic drug Metformin, which will be given at a dose of 500 mg/kg/day dissolved in the drinking water (Baret et al., 2002).

To reduce stress hormone levels, a long-acting neuroleptic drug, perphenazine, will be used. Perphenazine will be obtained from Sigma-Aldrich and it will be administered at a dose of 0.1 mg/ml in the drinking water of the rats. This dose has been used by Stringer et al. (1990) in rats, and it lies between the values used by Carter et al. (2002) in mice.

Observations

The pH, insulin and glucose levels will be determined each morning at the same time. The measurements will commence one day before the antibody infusion. The least amount of blood necessary for the measurement will be drawn daily from the saphenous vein. This is the vein of choice because it causes minimal pain to the rat and thus does not require anaesthesia. It also yields more blood than the tail or dorsal pedal veins (Hoff, 2000).

The maximum amount of blood to be drawn from a rat repeatedly is 2 % of its total blood volume (Hoff, 2000). The normal rat's circulating blood volume is 60 ml/kg (Blood Collection – Rodents [Rats, mice and guinea pigs], 2002). Since about 0.2 ml will be required for all the necessary measurements, rats weighing at least 200 g are required.

Replacement fluids of the same volume of blood removed will be given at the time the blood is collected. Warm, sterile, saline fluid will be given intravenously at a slow, steady rate (Hoff, 2000).

Table 2.1 shows the normal values of glucose, insulin and pH in the rat. The glucose value is expected to rise slightly during the course of the trial. It is, however, desirable to keep it as close to normal as possible. This is accomplished by placing the rats on an energy-restricted diet and administering Metformin to suppress glucose production in the liver.

The insulin value is expected to reduce to 10 % of the normal value in reaction to the antibody infusion. The final reduction in insulin will be used to calculate the reactivity of the insulin antibodies.

The pH value gives an indication of the degree of acidaemia present. If the pH value drops below 7.15, the antibody infusion rate should be decreased by 1 μl/min per day to allow the insulin level to rise. If the pH is greater than or equal to 7.15, the infusion rate should be

kept constant. The final infusion rate is the main outcome of the pilot study which will be used in the main experiment.

Table 2.1. Normal levels of elements in the rat

Element	Value	Units	Reference
Glucose	4 - 7	mM/l	IACUC Guidelines, 2004
Insulin	312	ρM/l	McGarry, 1975
pH	7.3 – 7.4		Bäckman, 1999

Even though the rats receive water *ad lib*, a daily assessment of their hydration status will be made. This encompasses a visual inspection of the rat's coat and skin turgor. Any dehydration should be recorded. The blood collection and catheter sites should be inspected daily for any signs of infection, inflammation or irritation. Table 2.2 shows the daily schedule to be followed.

Table 2.2. The daily schedule for the duration of the experiment

Draw blood from saphenous vein
Determine glucose, insulin and pH value from blood
Replace removed fluids
Determine hydration status of each rat by clinical examination
Inspect catheterisation site
Supply correct amount of food, as computed on day one
Add Metformin to drinking water
Add Perphenazine to drinking water

At the end of the experiment, the rats will be euthanized by an overdose of Euthanase, after which they will be incinerated at the Onderstepoort Campus, Pretoria according to the UPBRC (University of Pretoria Biomedical Research Centre) protocol.

Outcome

The outcome of the experiment will be the infusion rate at which anti-insulin antibodies should be supplied to reduce the circulating insulin level to a minimum while ensuring the safety of the rat. It is desirable to find the lowest maintainable insulin value that does not induce ketoacidosis.

2.4 Methods - Phase two

This is the main experiment in which the following will be investigated: the growth of tumours in a low blood glucose regime together with anti-insulin to prevent glucose uptake. All the rats in the study will be implanted with mammary tumours. This is the preferred tumour type because it is possible to monitor the tumour growth throughout the experiment with a Vernier calliper.

The rats will be divided into two groups – one receiving the proposed treatments (see Figure 2.1) and a control group. The anti-insulin serum will be infused as determined from the pilot study. After a period of four weeks, all the rats will be killed and the tumours removed. A comparison will be drawn between the tumour burden (weight of all tumours) of the control group and the treated group.

The expected result is that the control group will have a much larger tumour burden than the treated group. The group receiving the glucose control treatment will have just enough glucose to keep the brain functioning. Along with that, they will have very low insulin levels. If any glucose is thus not absorbed by the brain, the other cells will not be able to utilise it efficiently either. This means that the main energy source of the tumours will be cut off (Holm et al., 1995; Quillin, 2001).

Since cancer cells need a lot more glucose than normal cells (up to six times as much) to survive (Ayre, 2003; Guppy et al., 2002; Lora, 2002; Nolop et al., 1987; Warburg et al., 1927), the tumour will be affected first by this glucose deprivation.

The researcher hypothesises that this treatment will reduce the size of the tumour and may even result in its complete disappearance, while it will only temporarily and reversibly affect the rat.

2.5 Financial implications

As stated, 0.5 ml of anti-insulin serum will be infused in 12 hours. This means that 1 ml of serum will be used per rat per day. To ensure that the results obtained are statistically significant, a minimum of ten rats will be used for the pilot study. Their insulin level will be monitored for at least one week, or until it is possible to maintain a steady level for at least 48 hours. This means that a minimum of 70 ml of anti-insulin serum will be required.

At a cost of around R 5 500 per millilitre, this amounts to R 385 000. This price excludes the rats, their housing, food and the implantation of catheters for the antibody infusion. This is also just the cost of the pilot study. The main experiment will be more expensive. Since sufficient funds are not currently available, the study has had to be postponed.

2.6 Conclusion

In this chapter a novel method for the control of blood glucose supply and utilisation was proposed. It involves reducing the glucose supply by CHO restriction, suppression of glucose secretion by liver, suppression of stress hormones (which increase the blood glucose level) and an infusion of anti-insulin serum that binds to insulin molecules, thus preventing the utilisation of glucose. Since glucose is the main energy source of cancer cells to sustain their high growth rate, these cells suffer more than the rest of the body in the absence of glucose.

The hypothesis is that the cancer cells will die at a higher rate than the rest of the body's cells. If this holds true, it will be possible to reduce the size of a cancerous tumour by depriving it of glucose without harming the host. It might even be possible to eradicate the tumour completely.

The implication, were this method to work, is that a cancer patient would be admitted to the hospital, placed on this therapy for a few days and be dismissed again. Any tumours (primary or metastasis) will be affected adversely. The rest of the body's organs switch to another energy source and continue to function normally. It is thus a method that affects the cancer cells more severely than it does the normal cells.

The drawback of the study is the large cost of performing the experiment. At the moment, funds for this type of study are not available. The focus of the study shifted to cancer prevention.

2.7 References

Bäckman, T. (1999), "Acid-base balance, dentinogenesis and dental caries – Experimental studies in rats", Institute of Dentistry, University of Oulu, FIN-90401 Oulu, Finland.

Baret, G., Peyronnet, J. et al. (2002), "Increased intraabdominal adipose tissue mass in fructose fed rats: correction by metformin", *Experimental and Clinical Endocrinology & Diabetes*, 110, pp.298 – 303.

Beaser, R.S. & Hill, J.V.C. (1995), *The Joslin guide to diabetes: a program for managing your treatment*, Fireside, New York.

Beck, L.V., Basu, I. et al. (1982), "Estimation of insulin secretion using extracts of plasma from mice injected with anti-insulin serum: effects of arginine, glucose and anti-insulin serum", *Journal of Endocrinology*, 95, pp.125 – 135.

"Blood Collection – Rodents (Rats, mice and guinea pigs)" (2002 – last update), (*McGill University Animal Care Committe*), Available: upload.mcgill.ca/rgo/1blood-r.rtf (Accessed: 2005, June 20).

Cahill, G.F. Jr, Herrera G. et al. (1966), "Hormone-fuel interrelationships during fasting", *Journal of Clinical Investigation*, 45, pp.1751 – 1769.

Cahill, G.F. (1970), "Starvation in man", *The New England Journal of Medicine*, 282, pp.668 – 75.

Carter, D.B., Kennett, M.J. et al. (2002), "Use of perphenazine to control cannibalism in DBA/1 mice", *Comparative Medicine*, 52 (5), Oct, pp.452 – 455.

Clarke, H.E., Coates, M.E. et al. (1977), "Dietary standards for laboratory animals: report of the Laboratory Animal Centre Diets Advisory Committee", *Lab Animal*, 11, pp.1 – 28.

Cohen, P.P. & Stark, I.E. (1938), "Hepatic ketogenesis and ketolysis in different species", *Journal of Biological Chemistry*, 126, pp.97 – 107.

Day, H.E.W., Campeau, S. et al. (1999), "Expression of α_{1b} Adrenoceptor mRNA in Corticotropin-Releasing Hormone-Containing Cells of the Rat Hypothalamus and Its Regulation by Corticosterone", *The Journal of Neuroscience*, 19(22), 15 November, pp.10098 – 10106.

"Debunking the myths" (n.d.) (*Atkins can help*), Available:
http://atkins.com/Archive/2001/12/18-590441.html (Accessed: 2005, April 11).

Duckworth, W.C., Bennett, R.G. et al. (1998), "Insulin degradation: progress and potential", *Endocrine Reviews*, 19 (5), pp.608 – 624.

Erochenko, T., "Ketosis: mystery or misconception?" (*BellaOnline – the voice of women*), Available: http://www.bellaonline.com/articles/art18495.asp (Accessed: 2005, April 7).

Evans, J.M.M., Donnelly, L.A. et al. (2005), "Metformin and reduced risk of cancer in diabetic patients", *British Medical Journal*, BMJ, doi:10.1136/bmj.38415.708634.F7 (published 22 April 2005).

Flatt, P.R., Swanston-Flatt, S.K. et al. (1987), "Effects of diet-induced ketosis in rats with hypoglycaemia due to a serially transplantable insulinoma", *Diabete & Metabolisme*, 13 (5), pp.503 – 507.

Foster, D.W. (1991) Diabetes mellitus, in: Wilson, J.D., Braunwald, E., Isselbacher, K.J. (eds) *Harrison's Principles of Internal Medicine*, 12th edition, McGraw-Hill, New York.

Goldstein, R.E., Abumrad, N.N. et al. (1995), "Effects of an acute increase in epinephrine and cortisol on carbohydrate metabolism during insulin deficiency", *Diabetes*, 44 (6), pp.672 – 681.

Gross, L. & Dreyfuss, Y. (1990), "Prevention of spontaneous and radiation-induced tumors in rats by reduction of food intake", *Proceedings of the National Academy of Science of the United States of America*, 87, Sept, pp.6795 – 6797.

Heinbecker, P. (1928), "Studies on the metabolism of eskimos", *Journal of Biological Chemistry*, 80, pp.461 – 475.

Hoff, J. (2000), "Methods of blood collection in the mouse", *Lab Animal*, 29 (10), November, pp.47 – 53.

Hursting, S.D., Lavigne, J.A. et al. (2003), "Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans", *Annual Review of Medicine*, 54, pp.131 – 152.

"IACUC Guidelines for the care and use of live vertebrate animal", (2004 – last update) (*UNMC/UNO Institutional Animal Care and Use Committee (IACUC)*, University of Nebrasca Medical Center, Available: www.unmc.edu/iacuc/index.html (Accessed: 2005, June 28).

Insel, P., Turner, R.E. et al. (2003), "Spotlight on metabolism", (*Discovering nutrition*), Available:

nutrition.jbpub.com/discovering/disc_nut_spotlightmetabolism.pdf (Accessed: 2005, April 21).

John, A. P. (2001), "Dysfunctional mitochondria, not oxygen insufficiency, cause cancer cells to produce inordinate amounts of lactic acid: the impact of this on the treatment of cancer", *Medical Hypothesis*, 57 (4), pp.429 – 431.

"Ketone bodies", (n.d.) (*Dictionary.laborlawtalk.com*) Available:

http://encyclopedia.laborlawtalk.com/Ketone_bodies (Accessed: 2005, April 21).

King, M.W. (2004, October 6 – last update), "Fatty acid oxidation", (*The medical biochemistry page*), Available:

http://web.indstate.edu/thcme/mwking/home.html (Accessed: 2005, April 8).

Kreisberg, R. (1978), "Diabetic ketoacidosis: new concepts and trends in pathogenesis and treatment", *Annals of Internal Medicine*, 88, pp.681 – 695.

Magee, B.A., Potezny, N. et al. (1979), "The inhibition of milignant cell growth by ketone bodies", *The Australian Journal of Experimental Biology and Medical Sciences*, 57 (5), pp.529 – 539.

"Managing Diabetes" (n.d.) (*Diabetes SA*), Available:

http://www.diabetessa.co.za/main.html (Accessed: 2005, June 28).

McCrindle, C.M., Ebedes, H. et al. (1989), "The use of long-acting neuroleptics, perphenazine enanthate and pipothiazine palmitate in two horses", *Journal of the South African Veterinary Association*, 60 (4), pp.208 – 209.

McGarry, J.D., Wright, P.H. et al. (1975), "Rapid activation of hepatic ketogenic capacity in fed rats by anti-insulin serum and glucagon", *The Journal of Clinical Investigation*, 55, June, pp.1202 – 1209.

Melkersson, K., Khan, A. et al. (2001), "Different effects of antipsychotic drugs on insulin release in vitro", *European neuropsychopharmacology*, 11 (5), Oct, pp.327 – 332.

"Metformin" (n.d.) (*Diabetes Mall – Health through information*), Available:

http://www.diabetesnet.com/diabetes_treatments/metformin.php (Accessed: 2005, April 12).

"Monoclonal anti-insulin antibody produced in the mouse" (n.d.) (*Sigma Aldrich*), Available:
http://www.sigmaaldrich.com/catalog/search/ProductDetail/SIGMA/I2018
(Accessed: 2005, June 29).

"Monoclonal Antibody Production", (2005, September 26 – last update) (*National Health Museum*) Availiable: http://www.accessexcellence.org/RC/VL/GG/monoclonal.html (Accessed: 2005, September 27).

Nebeling, L.C. & Lerner, E. (1995), "Implementing a ketogenic diet based on medium-chain triglyceride oil in pediatric patients with cancer", *Journal of the American Dietetic Association*, 95, pp.693 – 967.

Peters, A., Schweiger, U. et al. (2004), "The selfish brain: competition for energy resources", *Neuroscience and Behavioural Reviews*, 28, pp.143 – 180.

Read, M.R. (2002), "Long acting neuroleptic drugs", in: Heard, D. (eds) *Zoological Restraint and Anesthesia*, International veterinary information service, Ithaca, NY.

Rule, G. (2003), "Ligand Binding", (*Biochemistry I*), Available:

http://stingray.bio.cmu.edu/~web/bc/Ligbind/ligbind.PDF (Accessed: 2005, June 29),

Schermerhorn, T. (2001), "Management of insulin overdose", *Standards of Care-Emergency and Critical Care Medicine*, 3.11, Nov/Dec, pp.1 – 14.

Sieber, F.E. & Traystman, R.J. (1992), "Special issues: glucose and the brain", *Critical Care Medicine*, 20 (1), pp.104 – 114.

South, J. (2004, July 20 – last update), "Beating attention deficit disorder", (*International antiaging systems*), Available: http://www.antiaging-systems.com/extract/add.htm (Accessed: 2005, April 21).

Stringer, B.M., Rowson, J. et al. (1990), "Effect of sustained serum prolactin elevation on breast epithelial and myoepithelial cell proliferation", *Cell and Tissue Kinetics*, 23 (1), Jan, pp.17 – 30.

Travers, J.P. (1989), "Effects of low insulin levels on rat embryonic growth and development", *Diabetes*, 38, pp.773 – 778.

Urgoiti, E.J., Houssay, B.A. et al. (1963), "Hypophyseal and adrenal factors essential for ketoacidosis of pancreatectomized dogs", Diabetes, 12, pp.301 – 307.

VanItallie, T.B. & Nufert, T.H. (2003), "Ketones: metabolism's ugly duckling", *Nutrition Reviews*, 61 (10), pp.327 – 341.

Veech, R.L., Chance, B. et al. (2001), "Ketone bodies, potential therapeutic uses", *Life*, 51, pp.241 – 247.

Warburg, O., Wind, F. et al. (1927), "The metabolism of tumours in the body", *The Journal of General Physiology*, vol 8 (6), pp. 519 – 530.

Werk, E.E., Mcpherson, H.T. et al. (1955), "Studies on ketone metabolism in man. A method for the quantitative estimation of splanchnic ketone production", *The Journal of Clinical Investigation*, 34 (8), pp.1256 – 1267.

Wexler, B,C. (1976), "Comparative effects of prolactin, perphenazine and reserpine on non-arteriosclerotic (virgin) vs arteriosclerotic (breeder) rats", *Atherosclerosis*, 24 (1-2), Jul – Aug, pp.19 – 36.

Wise, P.H. (1999), *Understanding your diabetes – For people with insulin-dependent (type 1) diabetes*, Foulsham, The Publishing House, Berkshire, England.

CHAPTER 3 THE EFFECT OF CARBOHYDRATE ENERGY CONSUMPTION ON CANCER RISK

The focus shifts to cancer prevention via glucose control. Ingested food is the main source of glucose. A quantifiable link between ingested glucose and cancer risk is proposed and guidelines are given to implement a lifestyle that promotes a reduced cancer risk.

TABLE OF CONTENTS

3.1. Preamble

In the previous two chapters it was shown that cancerous tumours are very dependent on glucose for proliferation. A procedure was proposed to reduce the blood glucose supply and utilisation. The goal is to assess tumour growth in this low-energy utilisation environment. Due to the high cost of the one part of the procedure, its feasibility could not be established.

In this chapter, the focus shifts from cancer control to cancer prevention. A method to quantify the energy-related factors contributing to cancer risk is investigated. A theoretical analysis of these energy factors is also done.

In previous articles (Mathews, as early as 2000 and updated in 2005a, see addendum C) a more correct way was derived to estimate the available energy from carbohydrates (CHO). Currently, it is assumed that one gram of CHO delivers approximately 4 kCal of energy to the body, irrespective of the source of the CHO. This method has been questioned before (Buchholz & Schoeller, 2004). Mathews proposes a new unit to quantify metabolisable energy in – the ***E****quivalent* ***T****easpoon* ***S****ugar*, or *ets*.

3.2. The *ets* concept

The amount of *ets* in any CHO can be calculated by using equation 3.1 (equation 3, Addendum C):

$$ets = \frac{E_{CHO}}{E_{Teaspoon\ Sugar}} = \frac{\eta_{CHO}\, m_{CHO} \times 4[kCal/g]}{\eta_{Sugar}\ m_{Teaspoon} \times 4[kCal/g]} = \frac{\eta_{CHO}}{\eta_{Sugar}}\ \frac{m_{CHO}}{5} \qquad (3.1)$$

Where E_{CHO} (in kCal) is the energy in any CHO described by (equation 1, Addendum C)

$$E_{CHO}[kCal] = \eta_{CHO}\, m_{CHO}[g]\ 4[kCal/g] \tag{3.2}$$

and $E_{TeaspoonSugar}$ is the energy in one teaspoon (5 g) of sugar (in kCal) as given by (equation 2, Addendum C)

$$E_{TeaspoonSugar}[kCal] = \eta_{Sugar}\ 5[g] \times 4[kCal/g] \tag{3.3}$$

In the above equations, η describes the conversion efficiency and m the mass in grams. From the earliest work of Atwater and Bryant (1900) and Rubner (1901) it is known that the metabolizable energy of CHO is 4 kcal/g.

It was furthermore proved that η_{CHO} = GI/100, with GI the glycaemic index of the CHO (Mathews, 2005b). This means that it is possible to obtain η_{CHO} for most foods. By keeping in mind that the GI of sugar is 65, thus η_{sugar} = 0.65, one can calculate the energy in one teaspoon of sugar (*ets*) as 13 kCal (equation 3.3). Equation 3.1 can be simplified to

$$ets = \frac{GI \cdot m_{CHO}}{325} \tag{3.4}$$

One now has an equation from which the effect of any ingested CHO can easily be determined. The equation takes the specific CHO source into consideration, and it gives a more accurate idea of the energy released from CHO than the previous 4 kCal/g.

To prove that $\overline{ets}$ is a more accurate measure of the energy available from food, the following analysis was done on data published by Brand-Miller et al. (2003). They gave groups of people different foods to eat and measured their plasma glucose and insulin levels at regular intervals over the next two hours.

The idea was to give the people the same amount of metabolic energy (as measured from glucose and insulin response) using different foods. The resulting glucose and insulin response curves were then plotted against the different energy measures (GI, CHO mass and $\overline{ets}$) to determine which of the three measures provided the most accurate prediction of the energy metabolised from the food.

A common measure of the glucose and insulin response is the incremental area under the curve (AUC) of the glucose or insulin response plotted against time (Le Floch et al., 1990). Figure 3.1 shows the GI, mass of CHO and $\overline{ets}$ value of five different foods plotted against the glucose AUC resulting from their consumption. It should be kept in mind that all the foods consumed are supposed to have the same energy content.

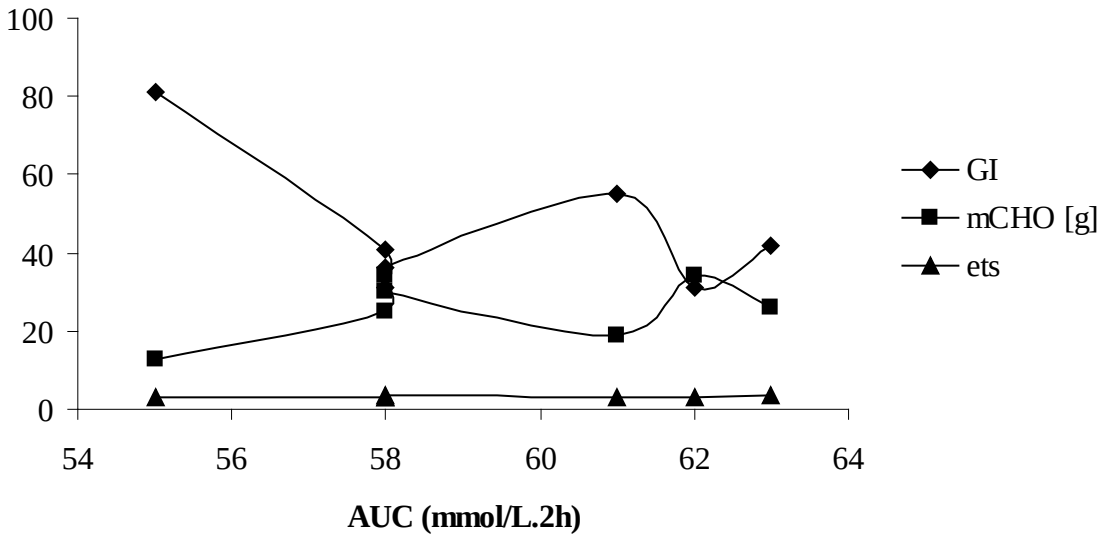

Figure 3.1. AUC plotted against $\overline{ets}$

In Figure 3.1 the AUC of the five different foods consumed (rice bubbles, porridge, apricots, apples, sweet corn and grain bread) shows a small variation (varies from 55 to 63 mmol/L.2h, 12 % difference). This is basically seen as a constant value. Similarly, the $\overline{ets}$ value of the five foods varies by only 6 %.

The $\overline{ets}$ value thus predicts that very similar amounts of energy will be available from the five foods. This is confirmed by the similar AUC values resulting from consumption of the five foods.

The variation in both GI and mCHO is in the order of 60 %. If either of these should be accurate measures of the metabolic energy available from food, it means that the energy content of the foods differs widely. The similar AUC values, however, show that this is not true. The conclusion is thus that $\overline{ets}$ is the best estimation of the metabolised energy available from food.

It is known that the blood sugar response is mainly caused by the ingestion of CHO and that this is linked to the insulin response (Holt et al., 1997). It should thus be possible to determine a link between $\overline{ets}$ and insulin.

3.3. Relationship between $\overline{ets}$ and insulin

In a previous article (Mathews, 2005c) it was shown that the link between the insulin response and blood sugar can be approximated by (equation 2, Addendum D)

$$\int_{t=ingestion}^{t=basal} BI(t)dt = f_{IBS} \int_{t=ingestion}^{t=basal} BS(t)dt \qquad (3.5)$$

where *BI* is the blood insulin level, *BS* the blood sugar level and f_{IBS} a factor used to describe the insulin/blood sugar relationship for a specific person (an abbreviation for **I**nsulin **B**lood **S**ugar relationship).

The CHO energy in a meal that can be utilised inside the body can be determined either by taking the person-specific CHO efficiency into account, or by evaluating the blood sugar response of the person. This is described by the two equations (equation 1, Addendum D)

$$E_{Absorb} = \frac{\int_{t=ingestion}^{t=basal} BS(t)dt}{\Delta t} Vol.k_{CHO} \quad = \quad f_{CHO}\,\eta_{CHO}\,m_{CHO}\,k_{CHO} \qquad (3.6)$$

The first equation describes the CHO energy converted into blood sugar for a specific person, with Δt the time over which the integral is computed, *Vol* the total blood volume of the person and k_{CHO} the energy value of the CHO. The value of k_{CHO} is determined outside the body in a bomb calorie meter. The second equation describes the person-specific CHO conversion efficiency with f_{CHO} a personalised CHO efficiency term. It should be remembered that f_{CHO} is a function of the person and η_{CHO} of the meal.

By substituting equations 3.4 and 3.6 into 3.5 and simplifying them a little, one obtains the following:

$$\frac{AUCI}{\Delta t} = \frac{325\, f_{IBS}\, f_{CHO}}{Vol} \text{ ets} \qquad (3.7)$$

where *AUCI* is the **A**rea **U**nder the **C**urve of **I**nsulin response, and replaces the insulin integral term. By grouping all the person-specific factors into one, f_{AUCI}, the final equation linking insulin and ets is obtained (equation 5, Addendum D):

$$AUCI = f_{AUCI} \text{ ets} \qquad (3.8)$$

One thus sees that $\overline{ets}$ is directly proportional to the AUCI, or the insulin response. A reduction in the $\overline{ets}$ value of a meal will thus reduce the postprandial glycaemic as well as insulinaemic response.

Following a low $\overline{ets}$ diet will have two positive effects. Firstly, it reduces one's CHO energy consumption. This means that there is less extra energy for cancer cells to use as fuel. Secondly, it also leads to a lower insulin response after a meal. Without insulin, cancer cells cannot utilise glucose. It thus further deprives them of their main energy source.

3.4. Methods

Various experiments investigating the relationship between GI, GL or CHO consumption and cancer have been performed. Some concluded that no relationship was apparent (Cho et al., 2003; Higginbotham et al., 2004a; Holmes, 2004; Jonas et al., 2003; Kalapothaki et al., 1993; Michaud et al., 2002; Silvera et al., 2005a, b, c; Terry et al., 2003), while others found a clear link (Augustin et al., 2001; Augustin et al., 2003a, b; Augustin et al., 2004a, b; Chatenoud, et al., 1999; Folsom et al., 2003; Franceschi et al., 2001; Higginbotham et al., 2004b; Levi et al., 2000; Slattery et al., 1997).

Most of the studies that found a direct link analysed the patient's diet two years prior to the diagnosis of cancer. The studies in which they seemed unrelated sometimes used a food questionnaire of 20 years prior to diagnosis. This information could obviously be outdated, and does not necessarily describe the diet just prior to the diagnosis of cancer. The focus was thus placed on the studies that analysed current data.

Four papers were identified that report sufficient results to enable the computation of their participants' $\overline{ets}$ consumption. The cancers investigated are upper aero-digestive

(Augustin et al., 2003a), ovarian (Augustin et al., 2003b), prostate (Augustin et al., 2004a) and colorectal (Higginbotham et al., 2004b).

Participants were asked to complete a food frequency questionnaire which evaluated their average dietary intake for the year or two prior to the diagnosis of cancer (for cases) or hospitalisation (for controls). The number of items on the questionnaire ranged from 78 to 131.

The average daily GI was computed in the studies and expressed by the glycaemic response elicited by a standard food (either glucose (Augustin et al.) or white bread (Higginbotham et al.)). The reported GI values were normalised to the glucose standard and substituted into the $\overline{ets}$ equation:

$$\overline{ets} = \frac{GI \cdot m_{CHO}}{325} = \frac{GL}{325} \tag{3.9}$$

It was thus possible to compute the average daily $\overline{ets}$ consumption of the subjects for a certain period prior to the diagnosis of cancer.

3.5. Results

In the first study, focussing on ovarian cancer (Augustin et al., 2003b), 1 031 cases and 2 411 controls completed a food frequency questionnaire to assess their diet. Figures 3.2 to 3.4 show the results obtained for cancer risk with increasing habitual GI, CHO mass or $\overline{ets}$ value of the diet. The regression coefficient for a linear trend line fitted to the data is also shown.

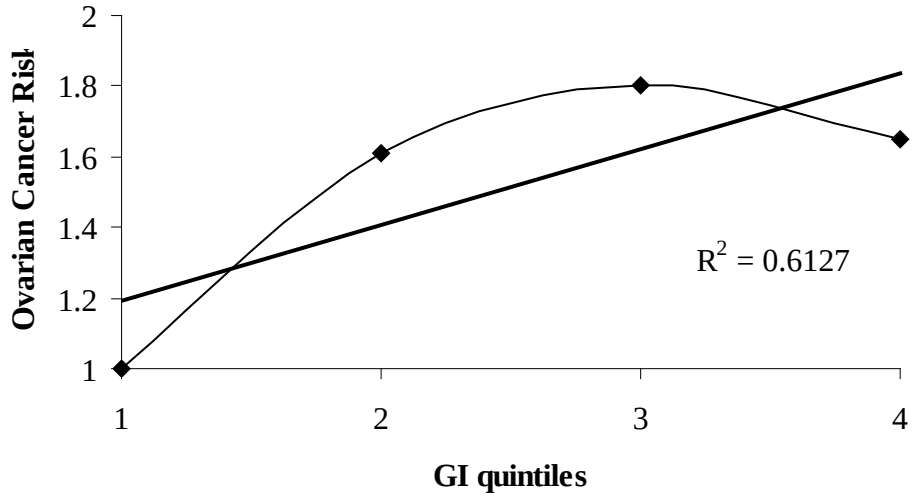

Figure 3.2. The relationship between ovarian cancer risk and increasing daily GI value of meals

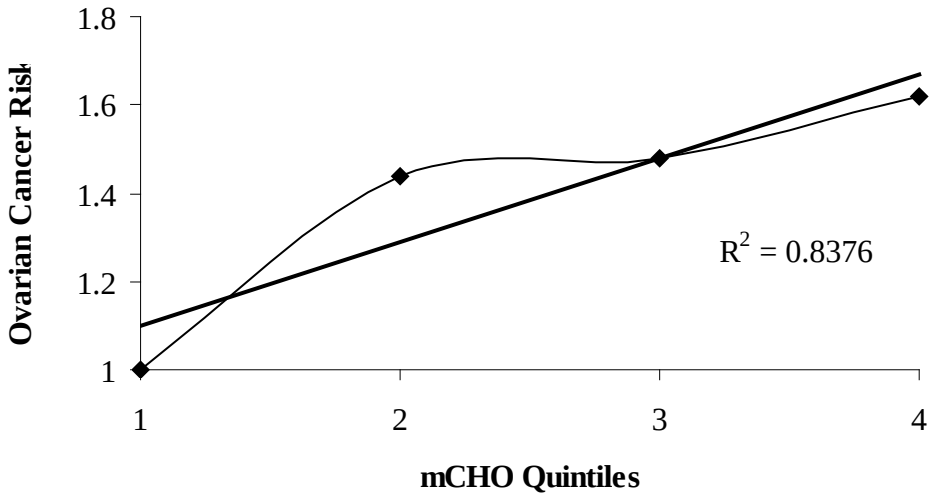

Figure 3.3. The relationship between ovarian cancer risk and increasing daily mass of CHO consumed

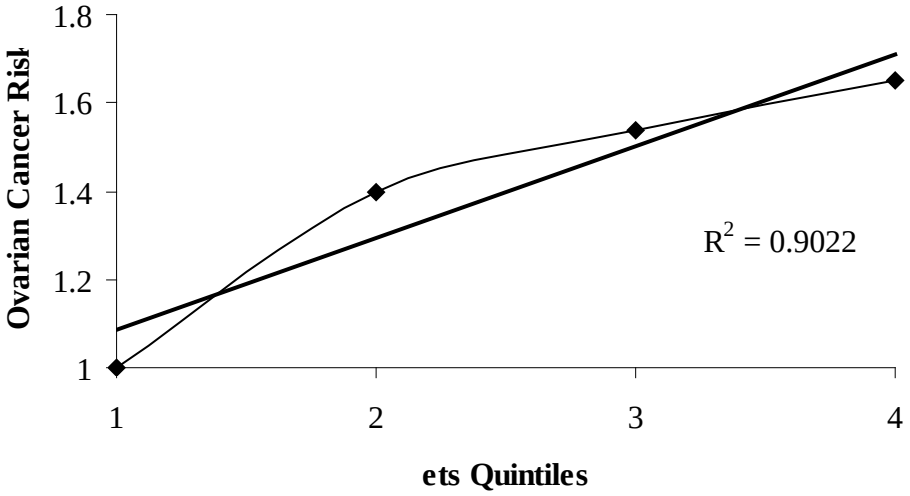

Figure 3.4. The relationship between ovarian cancer risk and increasing daily ets consumption

Comparing Figures 3.2 to 3.4 shows that the largest regression coefficient is obtained when the ovarian cancer risk is plotted against increasing ets intake. This means that ets is a better indicator of cancer risk than either GI or the mass of CHO consumed. Owing to the unavailability of data, the following graphs of cancer risk are only shown against ets consumption.

The second study investigated the risk of upper-aero digestive cancer with increasing ets consumption and included 1 362 cases and 3 322 controls. The results from Augustin et al., (2003a) were analysed and can be seen in Figure 3.5. A general increase in cancer risk can be seen with increasing ets consumption.

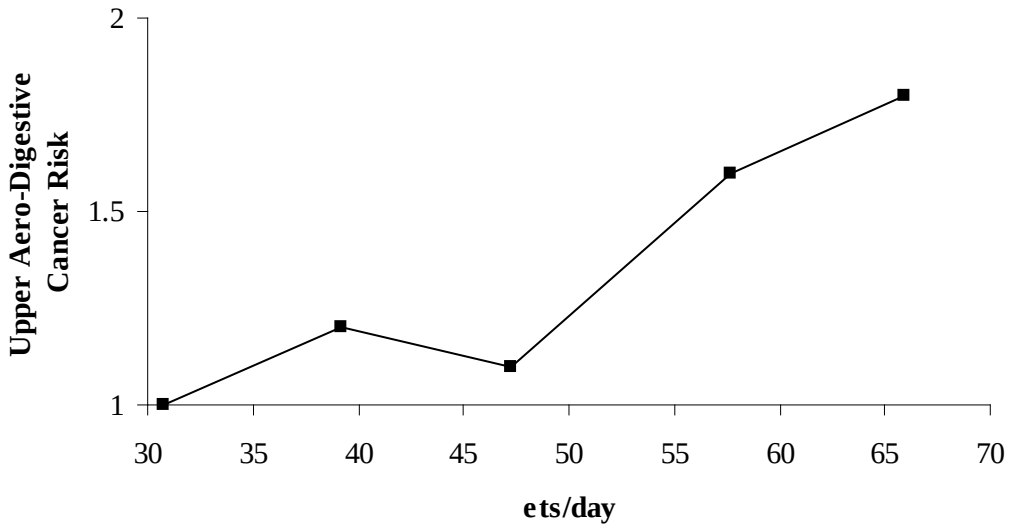

Figure 3.5. The relationship between daily ethanol consumption and risk of upper-aero-digestive cancer

Study three investigated the risk of prostate cancer (Augustin et al., 2004a). It incorporated 1 204 cases and 1 352 controls. Figure 3.6 shows the relationship between this risk and ethanol consumption. As in the previous two studies, an upward trend in cancer risk with increasing ethanol is seen.

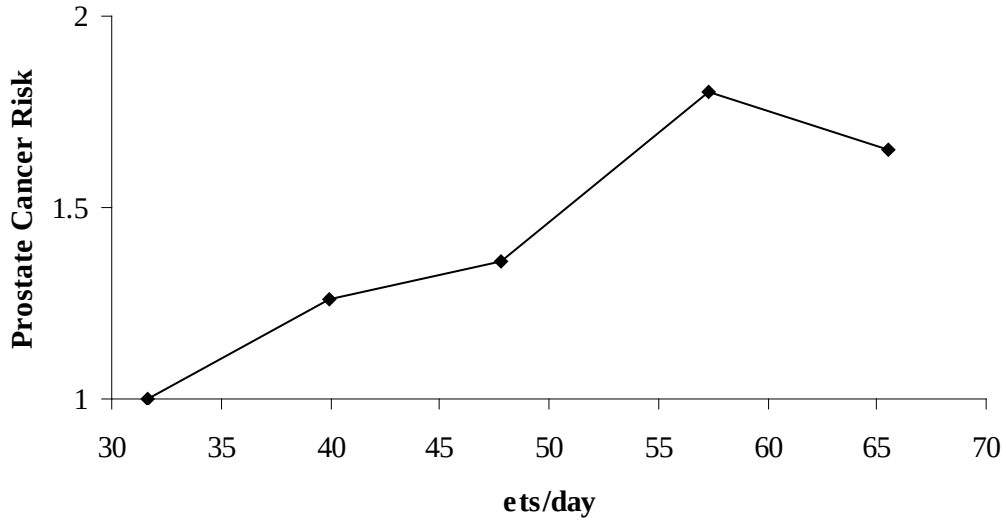

Figure 3.6. The relationship between daily ets consumption and risk of prostate cancer

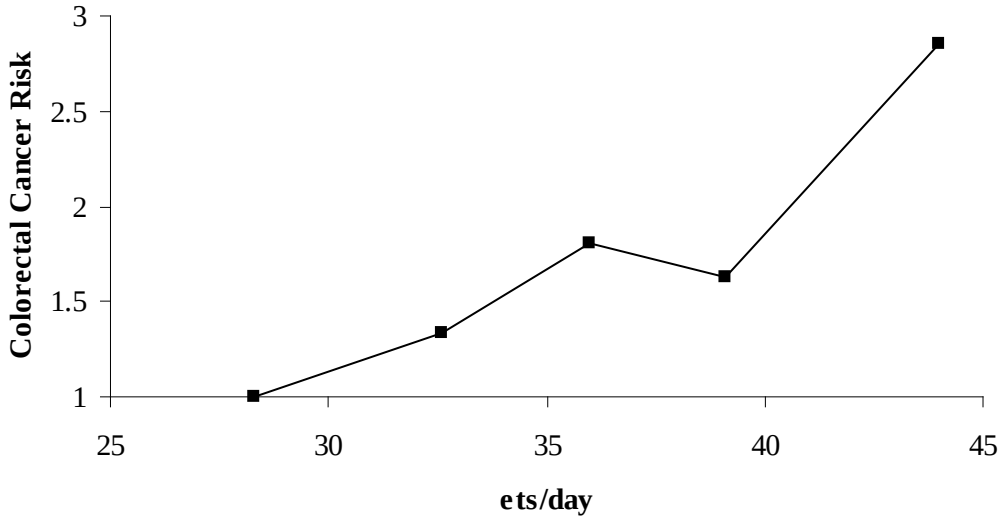

Figure 3.7. The relationship between daily ets consumption and risk of colorectal cancer

The last study looked at colorectal cancer (Higginbotham et al., 2004b). The researchers obtained a food frequency questionnaire from 38 451 women and in a follow up study 7.9 years later found 174 women with colorectal cancer. The results obtained are shown in

Figure 3.7, and again the increase in risk with increasing —ets consumption is apparent. Increasing one's —ets consumption from 28 to 41 doubles one's risk of colorectal cancer. One can thus say that Δ —ets = 13 either doubles or halves one's cancer risk.

In Figure 3.8 a summary of the results obtained is shown. Four different types of cancer were investigated, and they all show an increased risk with increasing —ets consumption.

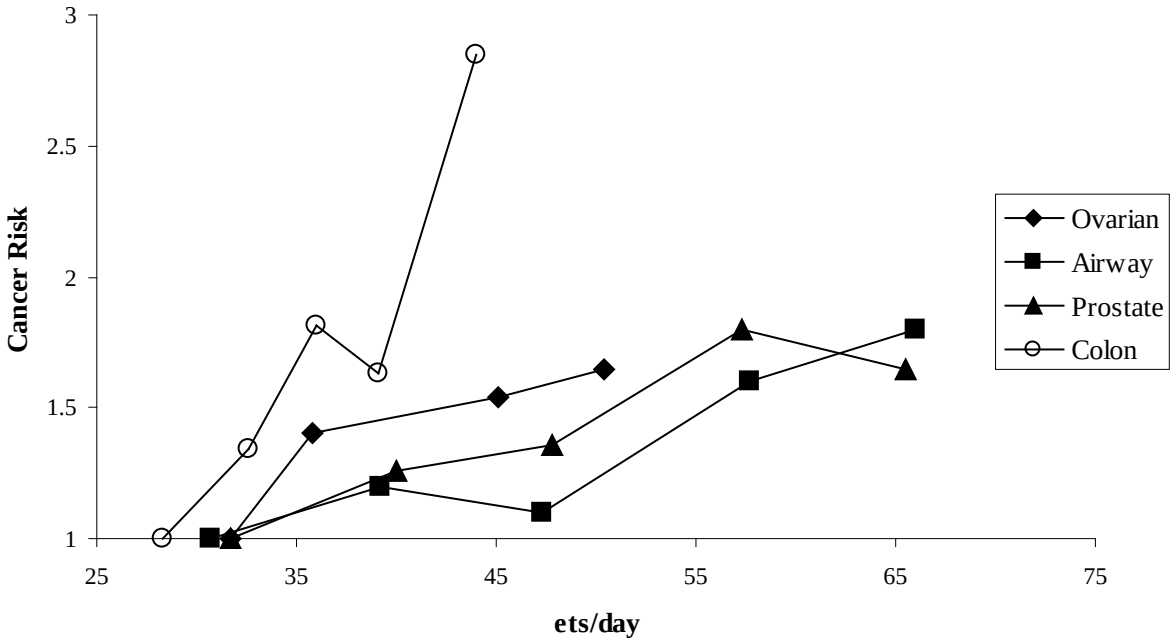

Figure 3.8. The relationship between daily —ets consumption and the risk of four different cancers

3.6. Discussion

From Figures 3.4 to 3.7 it is clear that there is a general increase in cancer risk for different cancers with increasing daily —ets consumption. The increase in risk starts from about 30 teaspoons of sugar per day. This is about the equivalent of one large portion of McDonalds french fries plus a large Coke.

The —ets values for more than 3 000 food items will be published in the book, —ets - *The missing link to an easy and scientific diet* (Mathews & Mathews, 2007). This book describes how to follow a healthy eating plan by calculating one's —ets allowance per day. The complete tables showing the —ets allowance for different people can be found in Addendum A. Table 3.1 shows the —ets values of some general foods.

A normal male, 1.8 m tall, has an allowance of 29 —ets per day (Addendum A). This correlates well to the increased cancer risk starting from around 30 —ets per day. Clearly, keeping track of one's daily —ets intake can significantly influence one's risk of contracting various cancers.

It is furthermore clear that the risk of different cancers increases at different rates. Since there are more than 200 different types of cancer, it is very difficult to generalise any results. Some cancers are more dependent on hormonal substances and others need external factors. One common factor is the fact that all cancers need energy to grow. Their energy dependence might differ (hence the different growth rates), but without energy any cell will die.

Following a healthy eating plan that limits excess energy thus restricts the cancer cells' energy source. This can be seen from the reduced cancer risk for different cancers with reduced —ets consumption.

Table 3.1. The $\overline{ets}$ values of some general foods

Description	Serving Unit	$\overline{ets}$ per serving
All-Bran	Cup	3.3
Apple	Medium Fruit	1.5
Baked potato and sour cream	Medium	4.1
Banana	Medium Fruit	3.7
Bar One	40 g Bar	3.9
Brown bread	Slice	2.8
Cheeseburger with sauce	Medium Burger	5
Choc chip cookie	Medium	1.9
Coke	Can	7.3
Corn flakes	Cup	8.5
Ham and cheese sandwich	Medium	5.8
Hotdog	Medium	3.4
McDonalds Big Mac		9.4
McDonalds hamburger		7
McDonalds large fries		16.7
McFlurry		13.5
Milkshake	300 ml	9.8
Orange	Medium Fruit	1.9
Orange juice	275 ml	4
Plain muffin	Medium	9.2
Two slices of toast, egg and sausage	Medium Serving	6.3
White bread	Slice	3.2

3.7. Conclusion

In this chapter the relationship between CHO energy consumption and cancer risk was investigated. A previously defined variable, namely $\overline{ets}$, was used to express ingested energy. The idea behind the $\overline{ets}$ concept was to develop a unit that is easy to understand, interpret and implement.

Tables exist that indicate the recommended $_{ets}$ intake for different people. From the results shown it is clear that a low $_{ets}$ diet can drastically reduce the risk of various types of cancer. As soon as the daily intake exceeds the recommended daily $_{ets}$ value, the cancer risk increases significantly.

It is thus recommended that daily energy intake be restricted to the recommended amount. Any excess energy can be utilised by cancer cells, increasing one's risk of developing one of several cancers. Controlling excess sugar and thus also insulin in the body by eating correctly is a simple, inexpensive way to prevent cancer and to starve already existing cancer cells.

Taking into account that 11 million people were diagnosed with cancer in 2002 alone (Parkin et al., 2005), a healthy eating plan may soon become a necessity rather than an optional extra.

3.8. References

Augustin, L.S.A., Dal Maso, L. et al. (2001), "Dietary glycemic index and glycemic load, and breast cancer risk: a case-control study", *Annals of Oncology*, 12 (11), pp.1533 – 1538.

Augustin, L.S.A., Gallus, S. et al. (2003a), "Glycemic index and load and risk of upper aero-digestive tract neoplasms (Italy)", *Cancer Causes and Control*, 14, pp.657 – 662.

Augustin, L.S.A., Polesel, J. et al. (2003b), "Dietary glycemic index, glycemic load and ovarian cancer risk: a case-control study in Italy", *Annals of Oncology*, 14, pp.78 – 84.

Augustin, L.S.A., Gallus, S. et al. (2003c), "Glycemic index and glycemic load in endometrial cancer", *International Journal of Cancer*, 150, pp.404 – 407.

Augustin, L.S.A., Galleone, C. et al. (2004a), "Glycemic index, glycemic load and risk of prostate cancer", *International Journal of Cancer*, 112, pp.446 – 450.

Augustin, L.S.A., Gallus, S. et al. (2004b), "Glycemic index, glycemic load and risk of gastric cancer", *Annals of Oncology*, 15, pp.581 – 584.

Atwater, W.O. & Bryant, A.P. (1900), "The availability and fuel values of food materials", *Connecticut (Storrs) Agricultural Experiment Station 12th Annual Report*, 1899.

Buchholz, A.C. & Schoeller, D.A. (2004), "Is a calorie a calorie?", *American Journal of Clinical Nutrition*, 79 (suppl), pp.899S – 906S,

Chatenoud, L., La Vecchia, C. et al. (1999), "Refined-cereal intake and risk of selected cancers in Italy", *American Journal of Clinical Nutrition*, 70, pp.1107 – 1110.

Cho, E., Spiegelman, D. et al. (2003), "Premenopausal dietary carbohydrate, glycemic index, glycemic load, and fiber in relation to risk of breast cancer", *Cancer Epidemiology Biomarkers & Prevention*, 12 (11 II) , Nov, pp.1153 – 1158.

Folsom, A.R., Demissie, Z. et al. (2003), "Glycemic index, glycemic load, and incidence of endometrial cancer: The Iowa Women's Health Study", *Nutrition and Cancer*, 46 (2), pp.119 – 124.

Foster-Powel, K., Holt, S.H.A. et al. (2002), "International table of glycemic index and glycemic load values: 2002", *American Journal of Clinical Nutrition*, 76, pp.5 – 56.

Franceschi, S., Dal Maso, L. et al. (2001), "Dietary glycemic load and colorectal cancer risk", *Annals of Oncology*, 12 (2), pp.173 – 178.

Higginbotham, S., Zhang, Z.F. et al. (2004a), "Dietary glycemic load and breast cancer risk in the Women's Health Study", *Cancer Epidemiology Biomarkers & Prevention*, 13 (1), January, pp.65 – 70.

Higginbotham, S., Zhang, Z.F. et al. (2004b), "Dietary glycemic load and risk of colorectal cancer in the Women's Health Study", *Journal of the National Cancer Institute*, 96 (3), Feb 4, pp.229 – 233.

Holmes, M.D., Liu, S. et al. (2004), "Dietary carbohydrates, fiber, and breast cancer risk", *American Journal of Epidemiology*, 159 (8), pp.732 – 739.

Holt, S.H., Miller, J.C. et al. (1997), "An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods", *American Journal of Clinical Nutrition*, 66, pp.1264 – 1276.

Jonas, C.R., McCullough, M.L. et al. (2003), "Dietary glycemic index, glycemic load, and risk of incident breast cancer in postmenopausal women", *Cancer Epidemiology, Biomarkers & Prevention*, 12, pp.573 – 577.

Kalapothaki, V., Tzonou, A. et al. (1993), "Nutrient intake and cancer of the pancreas: a case-control study in Athens, Greece", *Cancer Causes and Control*, 4 (4), July, pp.383 – 389.

Le Floch, J.P., Escuyer, P. et al. (1990), "Blood glucose area under the curve. Methodological aspects", *Diabetes Care*, 13, 2, Feb, pp. 172 – 175.

Levi, F., Pasche, C. et al. (2000), "Refined and whole grain cereals and the risk of oral, oesophageal and laryngeal cancer", *European Journal of Clinical Nutrition*, 54, pp.487 – 489.

Mathews, E.H. (2005a), "A more correct way to estimate energy metabolized from carbohydrates", Unpublished article. PO Box 2157, Faerie Glen 4, 0043, South Africa, see addendum C.

Mathews, E.H. (2005b), "Historical ideas on the Glyceamic Index are wrong", (*Scientific correspondence, Nature*), Unpublished article. PO Box 2157, Faerie Glen 4, 0043, South Africa, see addendum B.

Mathews, E.H. (2005c), "A practical relationship between insulin response and ingested carbohydrates", Unpublished article. PO Box 2157, Faerie Glen 4, 0043, South Africa.

Mathews, E.H. & Mathews, C. (2007), *—ets - The missing link to an easy and scientific diet*, In preparation for publication, PO Box 2157, Faerie Glen 4, 0043, South Africa.

Michaud, D.S., Liu, S. et al. (2002), "Dietary sugar, glycemic load and pancreatic cancer risk in a prospective study", *Journal of the National Cancer Institute*, 94 (17), Sept 4, pp.1293 – 1300.

Parkin, D.M., Bray, F. et al. (2005), "Global Cancer Statistics, 2002", CA: A Cancer Journal for Clinicians, 55, pp. 74 – 708.

Rubner, M. (1901), "Der energiewert der kost des menschen", *Zeitschrift fur Biologie*, 42, pp.261 – 308.

Silvera, S.A.N., Jain, M. et al. (2005a), "Dietary carbohydrates and breast cancer risk: A prospective study of the roles of overall glycemic index and glycemic load", *International Journal of Cancer*, 114 (4), 20 April, pp.653 – 658.

Silvera, S.A.N., Rohan, T.E. et al. (2005b), "Glycemic index, glycemic load, and pancreatic cancer risk (Canada)", *Cancer Causes and Control*, 16 (4), May, pp.431 – 436.

Slattery, M.L., Benson, J. et al. (1997), "Dietary sugar and colon cancer", *Cancer Epidemiology Biomarkers & Prevention*, 6, pp.677 – 685.

Terry, P.D., Jain, M. et al. (2003), "Glydemic load, carbohydrate intake, and risk of colorectal cancer in women: a prospective cohort study", *Journal of the National Cancer Institute*, 95 (12), June 18, pp.914 – 916.

CHAPTER 4 REDUCING THE CHO ENERGY CONTENT OF A MEAL BY ADDING SUPPLEMENTARY FIBRE

From the previous chapter it is clear that a low $\overline{ets}$ diet has various advantages, including a reduction in the risk of cancer. This chapter describes a practical method to reduce the $\overline{ets}$ value of any meal – by adding fibre. Experimental results on adding fibre to meals are also shown.

TABLE OF CONTENTS

4.1. Preamble

In the previous chapter the relationship between —ets consumption and cancer risk was determined. It was shown that the risk of various cancers increases directly with daily —ets consumption. A reduction in the —ets value of a meal will thus lead to a direct reduction in cancer risk.

It has been noted before that dietary fibre reduces the amount of energy released from ingested food and increases the amount excreted in faeces (Göranzon & Forsum, 1987). A small conversion efficiency, or low GI, and thus less energy means less —ets. This chapter addresses the concept of adding fibre to a meal to lower its —ets value and, in effect, reduce the risk of cancer.

Dietary fibre has been described as "that portion of food which is derived from the cellular walls of plants which is digested very poorly by humans" (Trowell, 1972), and later as "any dietary component that reaches the colon without being absorbed in a healthy human gut" (Ha et al., 2000).

The final definition established by the American Association of Cereal Chemists is "Dietary fiber is the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine".

"Dietary fiber includes polysaccharides, oligosaccharides, lignin and associated plant substances. Dietary fibers promote beneficial physiological effects including laxation and/or blood cholesterol attenuation and/or blood glucose attenuation" (AACC Report, 2001). Clearly, fibre plays an intrinsic role in nutrition and health, and is available from several sources. Fibre can be divided into two groups: soluble and insoluble fibre.

4.2. Soluble fibre

Soluble fibre is present in various fruits and vegetables, and also certain grains (such as oats). It undergoes some metabolism in the small and large intestine and increases stool size only moderately.

Soluble fibre dissolves in water and turns into a gel. This slows digestion and reduces the absorption of nutrients from the gut (Ha et al., 2000). It also reduces the postprandial rise in glucose and insulin levels (AACC Report, 2001; Sierra et al., 2001), which is especially helpful for diabetics (Pastors et al., 1991).

Soluble fibre is furthermore known to help lower cholesterol (AACC Report, 2001; Brown et al., 1999; Rodriguez-Moran et al., 1998; Walsh et al., 1984). Fibre binds with cholesterol molecules, and since the fibre is not absorbed, it prevents the cholesterol from being absorbed. The cholesterol is excreted from the body along with the stool without causing any harm to the body. The best known sources of soluble fibre are psyllium husk and glucomannan from the konjac plant.

4.3. Insoluble fibre

Insoluble fibre is present in bran products such as wheat bran or rice. It is not metabolised and does not dissolve in water, but increases the bulk of the gut content. This aids in "sweeping" the gut, removing harmful bacteria. Increasing the bulk also keeps the colon muscles fit. Weak muscles may lead to the formation of "pockets" in which harmful bacteria can grow.

Insoluble fibre protects against constipation and ensures that stools are large and soft, reducing the chance of haemorrhoids (Jordan, 1990; Schaefer & Cheskin, 1998). It furthermore aids in digestion and keeps the bowels healthy (Howard et al., 1995).

Both soluble and insoluble fibre increase the feeling of satiety directly after a meal. This is very helpful for people trying to lose weight (Howarth et al., 2001; Hylander & Rossner, 1983; Vita et al., 1992; Walsh et al., 1984).

Eating high-fibre food means one will eat less and still feel full. The reason for this is that cellulose and hemicellulose take up a lot of space in the stomach. Fibrous foods also take longer to chew and swallow, further reducing the eating rate (Jordan, 1990).

4.4. Fibre and cancer

Several authors have commented on the fact that fibre seems to reduce the risk of different cancers (Compher et al., 1999; Ferguson & Harris, 1999; Jansen et al., 1999; La Vecchia et al., 1997; McCann et al., 2000; Soler et al., 2001; Weisburger et al., 1993). The cancers involved range from colon, rectum and breast cancer to oral, endometrial, pharyngeal and oesophageal cancer. Different reasons are proposed for the decreased cancer risk with increasing fibre consumption.

Fibre is known to absorb harmful chemicals and increased faecal bulk dilutes carcinogens. Weisburger et al., (1993) propose this as the reason for a reduced risk of colon cancer with increased fibre intake.

In their study, Compher et al., (1999) showed that addition of wheat bran to the diet of rats induced apoptosis and reduced proliferation of cancer cells. In this way wheat bran prevents the formation of cancer tumours.

It has been shown that fibre strengthens white blood cells and makes them more effective. Fibre thus enhances the immune system, one’s first line of defence against cancer (Felippe et al., 1997).

4.5. Fibre and ets

Fibre has been shown to reduce the postprandial glucose and insulin responses. This is especially beneficial to diabetics (Jenkins et al., 1982; Pastors et al., 1991; Rodriguez-Moran, 1998; Sierra et al., 2001).

Fibre has furthermore been shown to reduce the GI of food (Jenkins et al., 1982; 2002). Jenkins et al., (2002) added fibre (β-glucan) to different foods and measured the resulting glucose response in diabetics. One gram of fibre added to 50 grams of carbohydrate reduced the GI by 4 units.

A reduction in GI and postprandial glucose response means that less energy is available in the form of blood sugar. This means that fibre reduces the blood sugar energy available from foods. In the previous chapters blood sugar energy was expressed in terms of ets. Since fibre reduces blood sugar energy, it can be translated to a reduction in the ets value of the meal.

The GI-lowering effect of fibre observed in the above study (Jenkins et al. 2002) was translated to ets. A GI of 60 was used for a typical meal. Implementing the ets equation for the first case (without fibre) results in:

$$ets = \frac{GI \cdot m_{CHO}}{325} = \frac{60 \times 50}{325} = 9.2 \qquad (4.1)$$

Adding fibre reduced the GI by four units:

$$ets = \frac{56 \times 50}{325} = 8.6 \qquad (4.2)$$

The difference seen is 0.6 ets/g.

A reduction of 0.6 $\overline{ets}$ per gram of fibre is thus obtained. It should be stated that this is an approximate value, and that it is expected to vary for different persons and different CHO sources. Munari et al., (1998) found that the addition of fibre reduced the GI of bread in type II diabetics and led to a reduced insulinic response in normal persons.

It is known that $\overline{ets}$ is directly related to the blood sugar and insulin responses. This means that fibre will have an effect on the $\overline{ets}$ value of a meal. A reduced postprandial glucose response can be translated to consuming a meal with a lower $\overline{ets}$ value. This means that fibre lowers the $\overline{ets}$ value of a meal. Since it has been shown (in chapter 3) that lower $\overline{ets}$ consumption leads to a lower cancer risk, the addition of fibre to a meal should lower the risk of cancer.

4.6. Previous experimental results

In a combined analysis of 13 previous studies, Howe et al., (1992) investigated the relationship between fibre intake and the risk of colon and rectum cancer. Their results can be seen in Figure 4.1. There is a sharp decrease in cancer risk with increasing fibre consumption.

From the figure it is clear that increasing one's fibre consumption from 10 to 31 grams per day reduces one's chance of getting cancer by a factor 2. This means that adding Δfibre = 21 g to one's daily intake halves one's cancer risk.

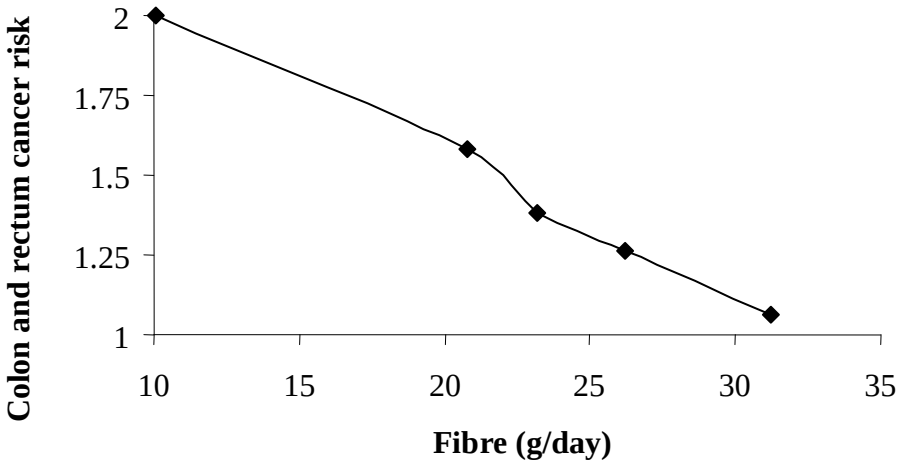

Figure 4.1. Decrease in the risk of colon or rectal cancer with increasing daily fibre intake

In their study, Goodman et al., (1997) investigated the association between endometrial cancer and fibre consumption. Their results are shown in Figure 4.2. Here, an increase in daily fibre intake from 6 to 27 g halves one's cancer risk. This results in exactly the same value of Δfibre = 21 g to halve the risk of cancer as seen in Figure 4.1.

Figure 4.3 shows the two cancer risks on one graph with trend lines added. The similarity in slope is evident. In the previous chapter the change in cancer risk due to varying one's —ets consumption was investigated. From Figure 3.4 it can be seen that Δ—ets = 13 results in the same doubling or halving of the cancer risk as in Figures 4.1 and 4.2.

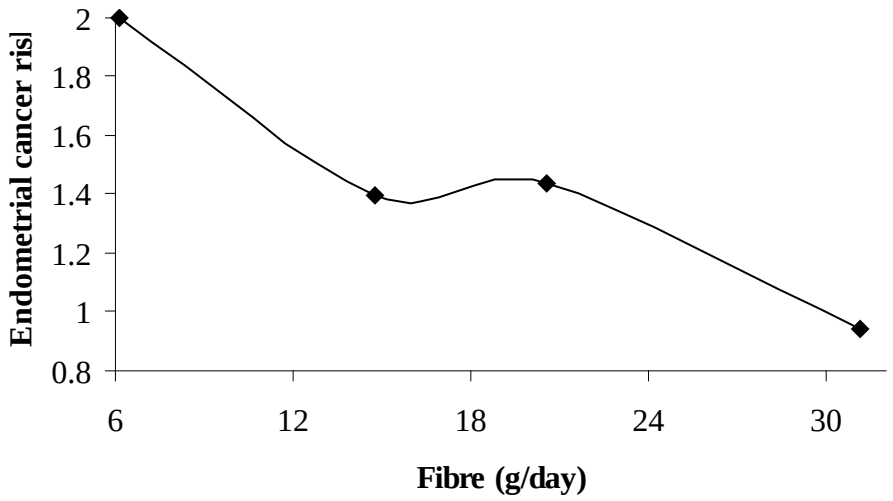

Figure 4.2. Decrease in endometrial cancer risk with increasing dietary fibre intake

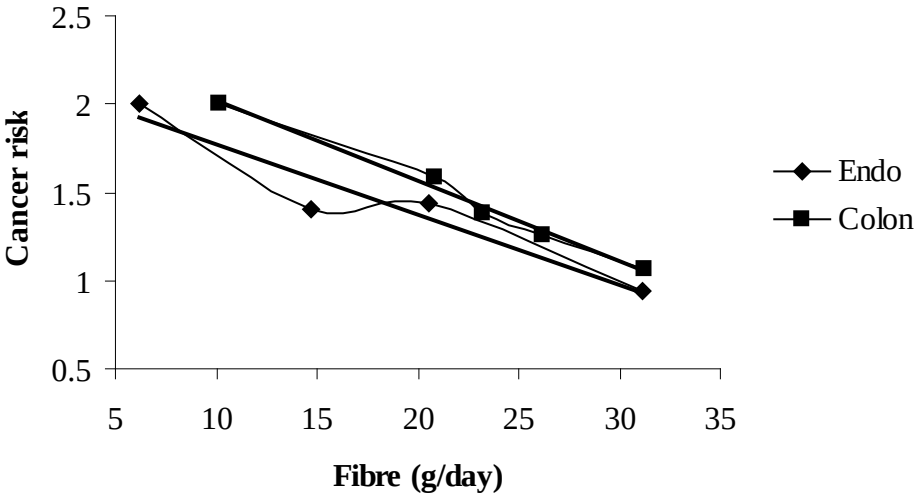

Figure 4.3. Risk of endometrial and colon cancer, as shown in Figures 4.1 and 4.2, with trend lines added

To reduce one's cancer risk by half one can thus either eat 13 ets less (Figure 3.4) or increase one's daily fibre consumption by 21 g (Figures 4.2 and 4.3). It can thus be stated that one gram of fibre results in a reduction of 13/21 = 0.6 ets. This is exactly the same value as computed earlier from the results of Jenkins et al., (2002) (equations 4.1 and 4.2). One can define a new variable, ets_{Fib}, described by the equation

$$ets_{Fib} = 0.6[ets/g] \cdot m_{Fib}[g] \tag{4.3}$$

where m_{Fib} is the mass of the fibre in grams. This value can now be subtracted from the $\overline{ets}$ value of a meal to determine the resulting effects the meal will have on one's blood sugar. The linear relationship will obviously not hold if the fibre mass is increased significantly, but it is sufficient to use as a first approximation.

It should again be stated that this reduction in cancer risk with increasing fibre intake was found by several authors (Compher et al., 1999; Ferguson & Harris, 1999; Jansen et al., 1999; La Vecchia et al., 1997; McCann et al., 2000; Soler et al., 2001; Weisburger et al., 1993). The cancers involved range from colon, rectum and breast cancer to oral, endometrial, pharyngeal and oesophageal cancer.

The above two studies are the only ones which supplied enough data to obtain the corresponding $\overline{ets}$ values. The fact that a link exists between breast, oral, pharyngeal and oesophageal cancer eliminates the possibility that it is caused the sweeping effect of fibre only.

If the above theory holds true, two isocaloric diets with different amounts of fibre should lead to different cancer risks. This was proven by Slattery et al., (1997). The conclusion from their study is that a high-caloric, high-fibre diet leads to a lower cancer risk than a diet with the same caloric but lower fibre content.

The results from the study of Honda et al., (1999) suggest that the lower limit for fibre intake is 20 g per day. They analysed data on colon cancer mortality and dietary fibre intake from both Japan and the USA. When fibre intake drops below 20 g per day, colon cancer mortality increases sharply. This can be translated to a value of ets_{Fib} = 12 $\overline{ets}$, which can be subtracted from the $\overline{ets}$ value of the meal to obtain the amount of sugar available to the body.

The average daily consumption of carbohydrates ranges from 220 to 330 g for men and 180 to 230 g for women in America and Canada (Food and Nutrition Board, 2005). The average daily carbohydrate intake for an adult can thus be estimated as 255 g. When the average GI is taken as 60, one finds a daily intake of 47 —ets.

If one subtracts the 12 —ets due to fibre from this value, one ends up with 35 —ets. This is very close to the recommended 30—ets per day for an average male. Most people are involved in some kind of exercise (more negative —ets), making the approximation even better. So the 20 g of fibre per day that Honda et al., (1999) suggested could just as well have been one hour of jogging per day. All it adds up to is that an —ets consumption larger than the recommended one for a specific person increases his/her cancer risk.

4.7. New experimental results

4.7.1. Background

It has been noted before that dietary fibre reduces the amount of energy released from ingested food and increases the amount excreted in faeces (Göranzon & Forsum, 1987). This leads to the intuitive conclusion that increasing one's dietary fibre intake should lead to weight loss.

The influence of fibre on weight management is, however, a controversial topic (Burton-Freeman, 2000). Some authors report a decrease in weight with increasing fibre intake (Howarth et al., 2001), but several do not.

Baron et al. (1986) had two groups of people consuming isocaloric diets, but one consisting of a higher carbohydrate/higher fibre regime and the other a lower carbohydrate/lower fibre one. The group consuming the lower fibre diet lost 26 % more weight over three months than the higher fibre group.

Rock et al. (2004) investigated the effect of postdiagnosis dietary modification on breast cancer. They had an intervention group receiving dietary guidelines and a control group.

One year later the intervention group reported an increased intake of fibre (29 g/d vs 22 g/d), but no significant weight loss compared to the control group.

The purpose of the study is to investigate the effect of increasing the fibre content of a diet on weight loss.

4.7.2. Methods

The study was done in co-operation with a weight loss clinic. Patients attending the clinic were given a daily allowance of calories according to their body weight and the amount of weight they needed to lose. They also received a booklet showing the calories in different foods and different daily menus to choose from.

Patients could voluntarily join the fibre study. Each participating patient received a fibre supplement, which had to be taken 30 minutes prior to the three main daily meals. The supplement consisted mainly of plantago fibre husk (80 %), mixed with some sugar-free colourant and flavouring to enhance the taste. Two heaped teaspoons (approximately 3.5 g) had to be diluted in 250 ml of water before drinking.

The patients revisited the clinic about fortnightly to be weighed. A patient was allowed to resign from the study at any time without explanation. As a control, data from newly joined as well as old patients were used.

The study lasted for four months, but since some patients' records were incomplete, data from only three months were used. Data were obtained for 15 patients using the fibre supplement while on the diet and 27 patients on the diet alone.

4.7.3. Results

The results obtained are shown in Figure 4.4. From the results it is clear that the patients taking the fibre supplement while on the diet lost less weight than those on the diet alone. Both groups did, however, lose weight. The group using the fibre supplement lost an average of 2.9 kg (standard deviation of 3 kg), while those on the diet alone lost an average of 6.7 kg (standard deviation of 5.3 kg) over the three month period.

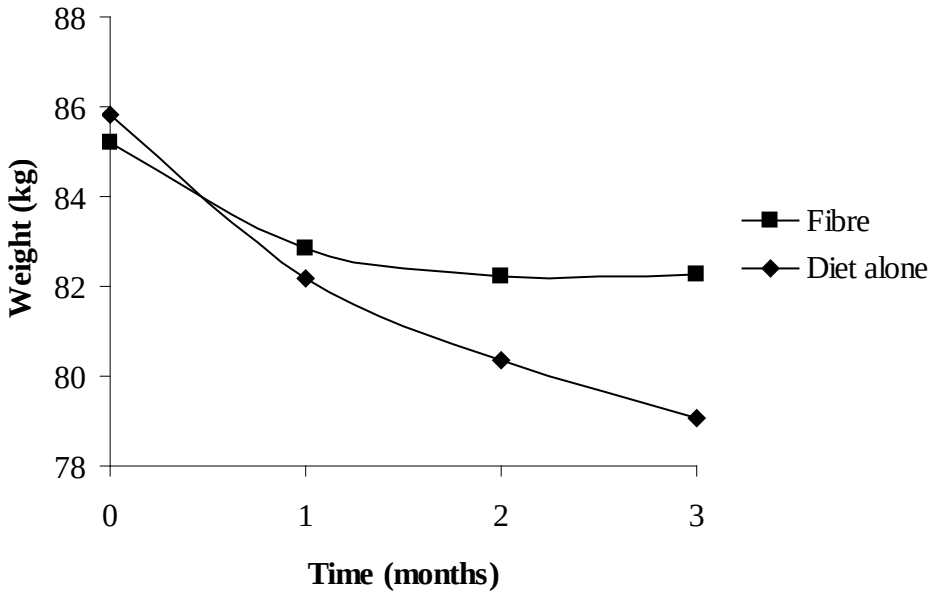

Figure 4.4. Weight loss of patients on diet alone or taking fibre supplement with the diet

4.7.4. Discussion

The results obtained from the study show that increasing the fibre content of a diet does not necessarily imply a reduction in weight. These results seem to conflict with the first comment that fibre reduces the energy released from food. If less energy is released, a person's weight is expected to decrease. This is, however, not always the case.

Aller et al. (2004) investigated two groups of people consuming either 10 or 30 g of fibre per day for a period of three months. Although both groups' calorie intake was reduced, neither group showed a change in body weight at the end of the study. Their LDL cholesterol and glucose levels did, however, improve with increased fibre intake.

This result can have two possible explanations. Either the people on the diet felt that they could "cheat" a bit, since the fibre was supposed to help them lose weight, or the fibre did not reduce the energy released from the food as expected. The last situation mentioned again leads to two possibilities. Either most of the energy from the food was released, but

over a longer period of time, or the type of fibre used was ineffective for reducing energy release.

It has been shown that foods with high fibre content (like lentils) do not cause a significant increase in the post-prandial blood glucose and insulin values (Brand-Miller, 2003; Sierra et al., 2001). Their energy is released slowly over a longer period of time. This is very desirable for diabetics, who struggle to keep their blood sugar value constant. It does, however, not necessarily mean that the total amount of energy released from the food is lower.

This points to the fact that the amount of energy released by two isocaloric foods with different fibre content may not differ, but the time over which the energy is released does. The body thus has time to absorb the energy as it is released, improving the blood glucose value.

This is very valuable information with regard to the fact that cancer cells are known to consume mainly sugar and thrive in a high blood glucose, high insulin regime. Even though fibre added to food might not reduce a person's weight, it will stabilise his blood glucose value, creating an unfavourable setting for cancer proliferation.

If this is not the explanation, it means that the fibre used was ineffective in reducing the energy released from food. From previously published results, it seems that for patients taking plantago husk, or psyllium, weight loss did not occur. Their blood glucose, insulin and even cholesterol values did improve significantly (Hylander & Rossner, 1983; Munari et al., 1998; Pastors et al., 1991; Rodriquez-Moran et al., 1998).

Another kind of fibre supplement is glucomannan, a water-soluble dietary fibre derived from konjac root. Subjects taking glucomannan before meals did show a decrease in weight along with a reduction in cholesterol (Keithley & Swanson, 2005, Vita et al., 1992; Walsh et al., 1984; Woodgate & Conquer, 2003).

There seems to be some difference between psyllium and glucomannan, causing greater weight loss when the latter is consumed. It might have something to do with the fibre density, or that a greater amount of psyllium will yield the same results as glucomannan.

Further research might lead to the introduction of a factor similar to GI or GL to describe the efficiency of certain fibres in reducing the $\overline{ets}$ value of meal.

This might be linked to the fact that in some cases where dietary fibre did cause a reduction in weight, the amount of fibre was increased by between 14 and 30 g/day (Howarth et al., 2001; Thompson et al., 2005). This fibre was derived from food, and not taken as a supplement.

It thus seems possible that a certain amount of fibre slows the release of energy from food, and any additional fibre stops it. The participants in the current study were given only 10 g of fibre per day. This is less than the 14 to 30 g which caused weight loss, as stated above. The fibre supplement might thus have been too little to have the required effect.

Another factor that might be significant is the fact that the fibre was taken 30 minutes prior to meals. In hindsight, the fibre should have been taken with the meal to ensure maximum positive effects due to the fibre.

Lastly, the possibility exists that the participants did not use the fibre as often as required. A more controlled experiment with more frequent patient contact might be considered for the future.

4.7.5. Conclusion

In this study, the effect of increasing the fibre content of a meal by using a psyllium supplement on weight loss was examined. The results show that people consuming 10.5 g more fibre per day while on a diet lost an average of 2.9 kg over three months, while those on the diet alone lost an average of 6.7 kg.

The psyllium supplement thus did not increase weight loss. This is ascribed to the fact that too little fibre supplement was prescribed to the participants. It is hypothesised that different types of fibre have a different efficiency for weight regulation.

A further hypothesis is that a certain amount of fibre is necessary to slow glucose absorption, and increasing that amount prevents it. The different fibre supplements might

thus have different fibre densities, explaining why equal amounts of different supplements do not have the same effect on weight loss.

Lastly, the fibre should be taken with the meal and not 30 minutes before (as done in the current experiment).

4.8. Conclusion

Fibre has long been known to reduce the risk of cancer, specifically colon cancer. The reason for this decreased risk is not clear, but many suggestions have been made. They include:

- reducing the postprandial blood glucose and insulin response (one of the primary suggestions),
- speeding up digestion, thus limiting the amount of time cancer-causing chemicals spend in the intestines,
- absorbing cancer-causing substances, preventing them from being absorbed by the gut,
- improving the immune system, and
- creating a feeling of satiety, thus reducing food intake. Less food means less energy for cancer cells to grow.

In this chapter it has been proven that fibre can be seen as negative –ets. The addition of fibre to any meal will thus lower the –ets value of that meal. As shown in the previous chapter less –ets means less energy for cancer cells to thrive on.

One gram of fibre leads to a reduction of roughly 0.6 –ets. If a person thus finds it difficult to stay within the recommended –ets allowance, this principle can be utilised to compensate for extra ingested –ets. It should, however, be kept in mind that this will only work for a few extra –ets per day.

Furthermore, these values are only a rough estimation. Owing to the complexities of the human body as well as inter-person variations it is impossible to determine the exact effect that fibre will have on the metabolism analytically. More experiments should be conducted to validate the use of -0.6 ets per gram of fibre.

Figure 4.5 shows the combined effect of ets ingested through food and negative ets, cancelled by fibre. The cancer risk doubles from -2 to 1 and again from 1 to 2. Clearly, the slope of the food curve is a bit steeper, but it is almost a mirror image of the fibre curve. This confirms the proposal that ingested ets can be cancelled by ets derived from the intake of fibre.

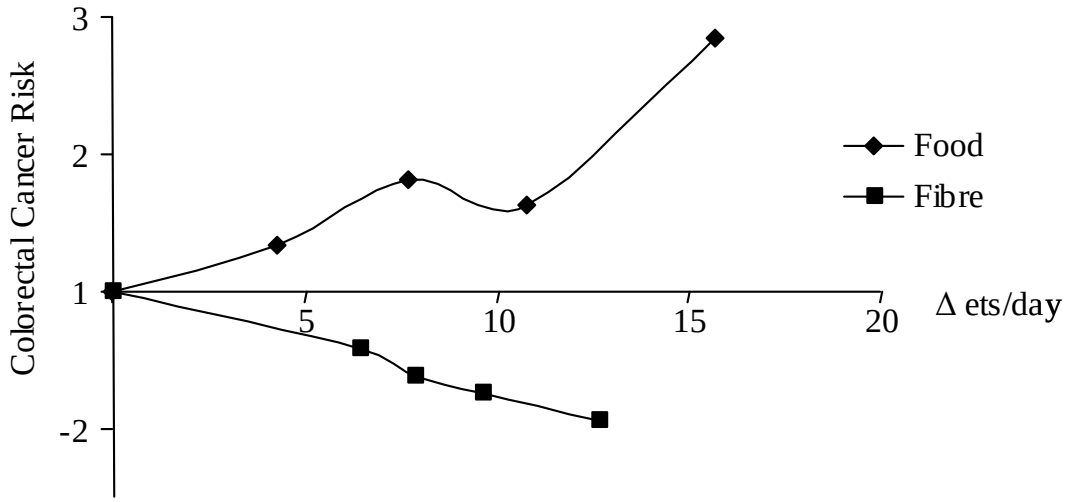

Figure 4.5. The effect of Δ ets ingested (food) and cancelled (fibre)

The experiment to determine the effect of adding fibre to a meal on weight loss showed that consuming 3.5 g of psyllium fibre before meals does not increase weight loss over a period of three months. It is hypothesised that psyllium fibre is less effective in reducing the energy released from food, and more fibre may be necessary to see an effect on weight loss. Fibre should also be taken with the meal, and not beforehand.

An addition of fibre to the daily diet is the second useful tool that can be applied for the prevention of cancer. Fibre slows the absorption of sugar from food, and thus reduces the

effective $\overline{ets}$ value of a meal. It is a very simple method and means that if a person finds it difficult to change his diet, it is still possible to change the energy content of that diet. Adding fibre to food places the low-energy diet regime within reach of everyone.

Lastly, it should be stated that the $\overline{ets}$-reducing effect of fibre only holds when fibre is added as a supplement to the meal. Foods containing natural fibre will have a lower $\overline{ets}$ value to start off with. The effect of the fibre in these foods has thus already been compensated for in the computation of the $\overline{ets}$ value. Adding fibre-rich foods to a meal will thus still increase the $\overline{ets}$ value of the meal, albeit less than adding foods containing no fibre.

4.9. References

AACC Report, (2001), "The definition of dietary fiber", *Cereal Foods World*, 46 (3), March, pp.112 – 126.

Aller, R., De Luis, D.A. et al. (2004), "Effect of soluble fiber intake in lipid and glucose levels in healthy subjects: a randomized clinical trial", *Diabetes Research and Clinical Practice*, 65, Jul, pp. 7 – 11.

Baron, J.A., Schori, A. et al. (1986), "A randomized controlled trial of low carbohydrate and low fat/high fiber diets for weight loss", *American Journal of Public Health*, 76, 11, pp. 1293 – 1296.

Brand-Miller, J. C., Thomas, M. et al. (2003), "Physiological validation of the concept of glycemic load in lean young adults", *Journal of Nutrition*, 133, pp. 2728 – 2732.

Brown, L., Rosner, B. et al. (1999), "Cholesterol-lowering effects of dietary fiber: a meta-analysis", *American Journal of Clinical Nutrition*, 69 (1), Jan, pp.30 - 42.

Burton-Freeman, B. (2000), "Dietary fiber and energy regulation", *Journal of Nutrition*, 130, pp. 272S – 275S.

Compher, C.W., Frankel, W.L. et al. (1999), "Wheat bran decreases aberrant crypt foci, preserves normal proliferation, and increases intraluminal butyrate levels in experimental colon cancer", *Journal of Parenteral and Enteral Nutrition*, 23 (5), pp.269 – 277.

Felippe, C.R., Calder, P.C. et al. (1997), "Fatty acid composition of lymphocytes and macrophages from rats fed fiber-rich diets: a comparison between oat bran and wheat bran enriched diets", *Lipids*, 32, pp.587 – 591.

Ferguson, L.R., Harris, P.J. (1999), "Protection against cancer by wheat bran: role of dietary fibre and phytochemicals", *European Journal of Cancer Prevention*, 8 (1), Feb, pp.17 – 25.

Food and Nutrition Board (2005), *Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids*, The National Academic Press, Washington DC.

Goodman, M.T., Wilkens, L.R. et al. (1997), "Association of soy and fiber consumption with the risk of endometrial cancer", *American Journal of Epidemiology*, 146, 4, pp. 294 – 306.

Göranzon, H. & Forsum, E. (1987), "Metabolizable energy in humans in two diets containing different sources of dietary fiber. Calculations and analysis", *Journal of Nutrition*, 117, pp.267 – 273.

Ha, M-A., Jarvis, M.C. et al. (2000), "A definition of dietary fibre", *European Journal of Clinical Nutrition*, 54, pp.861 – 864.

Honda, T., Kai, I. et al. (1999), "Fat and dietary fiber intake and colon cancer mortality: a chronological comparison between Japan and the United States", *Nutrition and Cancer*, 33 (1), pp.95 – 99.

Howard, M.D., Gordon, D.T. et al. (1995), "Dietary fructooligosaccharides and gum arabic have variable effects on fecal and colonic microbiota and epithelial cell proliferation in mice and rats", *Journal of Nutrition*, 125, pp.2604 – 2609.

Howarth, N.C., Saltzman, E. et al. (2001), "Dietary fiber and weight regulation", *Nutrition Reviews*, 59 (5), May, pp.129 – 139.

Howe, G.R., Benito, E. et al. (1992), "Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies", *Journal of the National Cancer Institute*, 84 (24), Dec 16, pp.1887 – 1896.

Hylander, B. & Rossner, S. (1983), "Effects of dietary fiber intake before meals on weight loss and hunger in a weight-reducing club", *Acta Medica Scandinavica*, 213 (3), pp.217 – 220.

Jansen, M.C., Bueno-de-Mesquita, H.B. et al. (1999), "Dietary fiber and plant foods in relation to colorectal cancer mortality: the Seven Countries Study", *International Journal of Cancer*, 81 (2), April 12, pp.174 – 179.

Jenkins, D.J.A., Ghafari, H. et al. (1982), "Relationship between rate of digestion of foods and post-prandial glycaemia", *Diabetologia (Historical Archive)*, 22 (6), June, pp.450 – 455.

Jenkins, A.L., Jenkins, D.J.A. et al. (2002), "Depression of the glycemic index by high levels of β-glucan fiber in two functional foods tested in type 2 diabetes", *European Journal of Clinical Nutrition*, 56, pp.622 – 628.

Jordan, P. (1990), "Neuroendocrinology – latest in weight loss. Endocrinology", *American Fitness*, May-June.

Keithley, J. & Swanson, B. (2005), "Glucomannan and obesity: a critical review", *Alternative Therapy and Health Medicine*, 11, 6, Nov – Des, pp. 30 – 34.

La Vecchia, C., Ferraroni, M. et al. (1997), "Fibers and breast cancer risk", *Nutrion and Cancer*, 28 (3), pp.264 – 269.

McCann, S.E., Freudenheim, J.L. et al. (2000), "Diet in the epidemiology of endometrial cancer in western New York (United States)", *Cancer Causes and Control*, 11 (10), Dec, pp.965 – 974.

Munari, F.A.C., Pinto, B.W. et al. (1998), "Lowering glycemic index of food by ascarbose and Plantago psyllium mucilage", *Archives of Medical Research*, 29 (2), pp.137 – 141.

Pastors, J.G., Blaisdell, P.W. et al. (1991), "Psyllium fiber reduces rise in postprandial glucose and insulin concentrations in patients with non-insulin-dependent diabetes", *American Journal of Clinical Nutrition*, 53, pp.1431 – 1435.

Rock, C.L., Flatt, S.W. et al. (2004), "Effects of a high-fiber, low-fat diet intervention on serum concentrations of reproductive steroid hormones in women with a history of breast cancer", *Journal of Clinical Oncology*, 22, Jun 15, pp. 2379 – 2387.

Rodriguez-Moran, M., Guerrero-Romero, F. et al. (1998), "Lipid- and glucose-lowering efficacy of Plantago Psyllium in type II diabetes", *Journal of Diabetes Complications*, 12 (5), Sept-Oct, pp.273 – 278.

Schaeffer, D.C. & Cheskin, L.J. (1998), "Constipation in the elderly", *American Journal of Family Physician*, 58, pp.907 – 914.

Sierra, M., Garcia, J.J. et al. (2001), "Effects of *ispaghula husk* and guar gum on postprandial glucose and insulin concentrations in healthy subjects", *European Journal of Clinical Nutrition*, 55, pp.235 – 243.

Slattery, M.L., Caan, B.J. et al. (1997), "Dietary energy sources and colon cancer risk", *American Journal of Epidemiology*, 145 (3), pp.199 – 210.

Soler, M., Bosetti, C. et al. (2001), "Fiber intake and the risk of oral, pharyngeal and esophageal cancer", *International Journal of Cancer*, 91 (3), Feb 1, pp.283 – 287.

Thompson, C.A., Rock, C.L. et al. (2005), "Longitudinal changes in body weight and body composition among women previously treated for breast cancer consuming a high-vegetable, fruit and fiber, low-fat diet", *European Journal of Nutrition*, 44, Feb, pp. 18 – 25.

Trowel, H. (1972), "Dietary fibre and coronary heart disease", *European Journal of Clinical and Biological Research*, 17, pp.345 – 349.

Vita, P.M., Restelli, A., Caspani, P. et al. (1992), "Chronic use of glucomannan in the dietary treatment of severe obesity", *Minverva Medica*, 83 (3), pp.135 – 139.

Walsh, D.E., Yaghoubian, V. et al. (1984), "Effect of glucomannan on obese patients: a clinical study", International Journal of Obesity, 8 (4), pp.289 – 293.

Weisburger, J.H., Reddy, B.S. et al. (1993), "Protective mechanisms of dietary fibers in nutritional carcinogenesis", Basic Life Science, 61, pp.45 – 63.

Woodgate, D.E. & Conquer, J.A., (2003), "Effects of a stimulant-free dietary supplement on body weight and fat loss in obese adults: a six-week exploratory study", *Current Therapeutic Research*, 64, 4, April, pp. 248 – 262.

CHAPTER 5 STRESS, EXERCISE AND CANCER

This chapter explores two more alternative methods to fight cancer. Stress and exercise are both quantified in terms of $\frac{ets}{}$ and their relationship with cancer risk is shown. Furthermore, ways in which these relationships can be used against cancer growth and proliferation are discussed.

TABLE OF CONTENTS

5.1. Introduction

The chapters up to now have all focussed on cancer, the risk of developing it and factors influencing its growth. In this chapter two more parameters to the already intricate scenario are introduced, namely stress and exercise. Both are discussed frequently – open any magazine or switch on the television and one will be told to stress less and exercise more. But can this actually have any effect on cancer?

5.2. Stress and cancer

Stress can be defined as a situation where "environmental demands exceed a person's resources to meet those demands" (Lazarus & Folkman, 1984). It has become synonymous with life in the 21st century. Doctors constantly point out the negative effects of stress – high blood pressure, increased risk of cardiovascular diseases, strokes and heart attacks. Is it possible that stress can also play a role in the development of cancer?

As stated in chapter two, there are four stress hormones, namely cortisol, glucagon, epinephrine and growth hormone. These hormones are secreted in stressful situations, and one of their functions is to raise the blood glucose by secreting glucose from the liver's store (Schermerhorn, 2001; Sieber & Traystman, 1992). This phenomenon dates back to prehistoric times when a stressful situation required either a fight or flight action. Cortisol is, however, known to suppress the immune system (Anisman & Merali, 1999).

Chronic stress suppresses the immune system and causes a decrease in natural killer cells that fight cancer (Maddock & Pariante, 2001). This is termed stress-related immune impairment (Vedhara & Nott, 1996). As stated earlier, the immune system is the first line of defence against any disease. A suppressed immune system thus means increased vulnerability to any form of infection – including cancer.

In their overview of stress, Maddock and Pariante (2001) discuss a paper that investigates 29 studies on stressful life events and the risk of breast cancer. They found no significant relationship.

In contrast, Ramirez et al. (1989) found a strong link between stress and relapse of breast cancer. The relative risk of breast cancer recurrence associated with severe life events was 5.67 and for severe difficulties it was 4.75. The relative risk is a ratio that refers to the probability of an event occurring in the exposed groups versus the control group.

Spiegel et al. (1989) found a relationship between stress reduction and improved cancer survival. Two groups of metastatic breast cancer patients were studied – one group receiving weekly group therapy and a control group. A ten year follow-up study indicated that, the survival time of patients receiving therapy was twice that of the control group. It is thus clear that stress reduction leads to a better cancer prognosis and an increased survival time.

Hassed (2002) has several theories on why an improved quality of life leads to better cancer survival. Firstly, stress leads to high levels of stress hormones, suppresses the immune system and reduces the repair capacity of DNA. Reducing stress levels thus reduces all these negative factors. Improving one's quality of life also leads to the secretion of anticancer hormones (melatonin) and a reduction in the angiogenesis of tumours.

Caregiving refers to looking after a chronically ill or disabled person. It is reported to be a stressful activity, which may have pronounced effects on the caregiver's health (Stephens & Townsend, 1997).

Kroenke et al. (2004) investigated the effect of caregiving stress on the incidence of breast cancer. They analysed data from the Nurses' Health Study, in which almost 70 000 subjects participated. There was a clear upward trend in the cancer risk with increasing daily stress.

Since it is known that stress leads to the secretion of stress hormones which, in turn, raise the blood sugar, it should be possible to establish a link between stress and —ets.

5.3. Stress and —ets

The —ets concept was explained in chapter three. It is used to express all elements affecting the human energy system in terms of an ***E**quivalent **T**easpoon **S**ugar*. The link between —ets and blood sugar, insulin and different foods has already been shown. Since stress has a direct effect on the glucose metabolism, it is possible to describe stress in terms of —ets as well.

A simulation model describing the human energy system and all the components affecting it has been developed (Mathews & Mathews, 2007). The blood sugar response from the model was compared to measurements taken from test candidates under stress to quantify the effect of stress on the blood sugar level. Stress was introduced into the model in the same way as ingested food until the correct blood sugar response was obtained. In this manner, the amount of —ets secreted by the liver in reaction to stress was estimated.

Table 5.1 shows the results obtained from the model. It describes the different types of stress encountered and the resulting blood sugar response. From the table it is clear that the effect of long-term stress is about ten times less intense than that of short-term stress.

A long-term stressful situation, like the sickness of a family member, leads to an elevated blood glucose value over a long period of time. This is a very favourable condition for cancer cells to start growing. The relapse in breast cancer found by Ramirez et al. (1989) after a stressful life event may well be explained by this phenomenon.

The liver of an averaged-sized adult can store about 30 —ets of glucose. According to Table 5.1, this means that after less than two hours of intensive fighting (like kickboxing),

the person will be exhausted, "hit the wall", and actually experience hypoglycaemia. In order to keep going, the person will have to ingest some –ets to raise the blood sugar again.

Table 5.1. Maximum amount of –ets that has to be added to the simulation model of an average sized person (70 kg male) to produce a similar blood sugar response as the stressful stimulus (Mathews & Botha, 2005)

Duration	Example	Amount of –ets
Short-term (Less than an hour)	Kickboxing	Up to 17 –ets /hour
Medium-term (More than an hour)	Writing examinations	Up to 8 –ets /hour
Long-term (More than a day)	Great illness	Up to 1.7 –ets /hour

Ginsberg et al. (1996) did a study on traumatic life events and breast cancer. It included 99 cases and 99 controls, who were asked to complete a Life Events Inventory. This is a questionnaire of 67 life events, which assigns a score to each event according to the extent of change or distress it causes.

In another study currently in progress at the institute where the researcher works, it was shown that long-term stress can be divided into low, medium and high groups (Yang, 2006). The –ets secreted by the liver in each of the groups is shown in Table 5.2. This value is multiplied by the hours per day that stress is experienced to get the increased daily –ets "intake".

Using the current information, the data published by Ginsberg et al. (1996), were analysed to determine the link between —ets due to stress and cancer risk. Figure 5.1 shows the results of their study over ten years, adjusted for potential confounders.

Table 5.2. Secreted—ets per hour for long-term stress

Stress level	ets/hour
Low	0.28
Med	0.85
High	1.82

The extra —ets secreted per day by the individuals under stress causes a rise in breast cancer risk, as seen in Figure 5.1. It shows that even low level, long-term stress leads to increased secretion of about 7—ets per day. Prolonged exposure to this level of stress leads to a doubling in breast cancer risk.

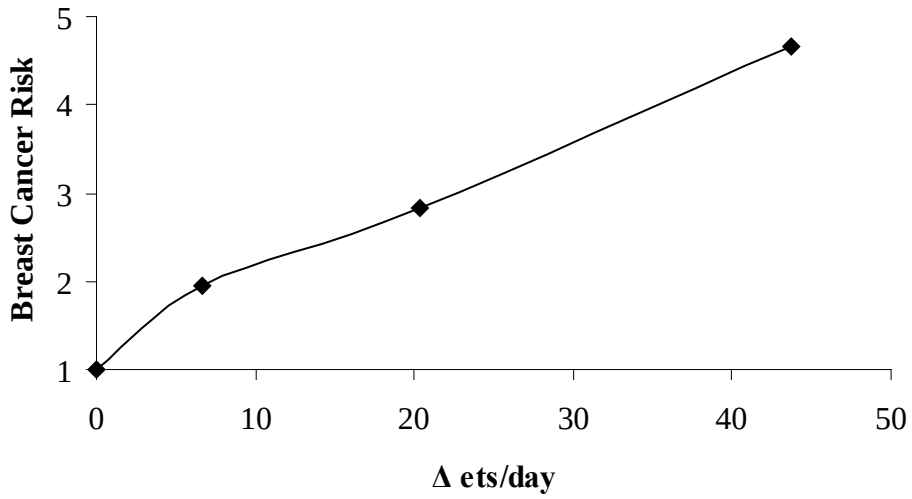

Figure 5.1. The relationship between stressful life events (long-term) and breast cancer risk

Clearly, stress can have a significant effect on the blood sugar. As seen in the previous chapters, cancer cells thrive on sugar. Stressful periods, leading to elevated blood sugar levels, thus create the perfect incubation conditions for cancer cells. When all the negative effects are considered together, stress is clearly a factor to consider in the development and growth of cancer cells. Patients suffering from cancer can definitely benefit from stress-reducing procedures.

The experimental results confirm the prediction that —ets due to stress increases the cancer risk just as —ets ingested through food would have done.

Because stress is such a difficult phenomenon to quantify, there are very few studies on it that give figures and results. Now that stress has been quantified in terms of —ets, it should be easier to take measurements and compare different situations.

To obtain one's final daily —ets intake, one should thus add one's stress —ets to one's ingested food —ets. If this total value is not within one's recommended daily limit, one will be at an increased risk of developing cancer.

5.4. Exercise and cancer

Research into the role of physical activity in the prevention of coronary heart disease was one of the first instances in which the scientific value of exercise was discovered. Several large studies in the United States confirmed that people with more active lifestyles had a reduced risk of developing a number of different heart conditions (McTiernan et al., 1999). This led to the question whether exercise can affect cancer risk or prognosis.

Three studies showed that occupational activity reduces the risk of colon cancer in men. Garabrant et al. (1984) found a 1.6 times increased risk of men with sedentary jobs compared to those with active jobs. From their study of 16 447 subjects, Gerhardsson et al. (1988) estimated a relative risk of 3.6 for colon cancer in low activity level candidates

compared to those with a high activity level, while Vena et al. (1985) confirmed the results with their study. Furthermore, Giovanucci (2001), Kritchevsky (2003) and Slattery et al. (2003) also showed that cancer risk reduces with increasing physical activity.

Physical activity also has an inhibiting effect on cancer growth. It has been shown that exercise prevents induction of tumours in 50 % of mice and rats, and that it furthermore reduces the growth of spontaneous and implanted tumours by up to 50 % (Kritchevsky, 2001; 2003).

In the study by Thompson et al. (2004) they showed that the intensity of exercise, rather than its duration, has an inhibiting effect on cancer. There is a certain threshold that has to be exceeded for the inhibiting effect to start. When this threshold is exceeded, an inverse relationship exists between the intensity of exercise and cancer inhibition (Thompson et al., 2004). Just as blood sugar, insulin and stress were all quantified in terms of —ets, the same is possible for exercise.

5.5. Exercise and —ets

Exercise is known to lower the blood glucose value by forcing the muscles to use glucose (Wise, 1999). It also reduces the excretion of stress hormones, which in the previous section has been shown to increase the cancer risk.

The third positive effect of exercise is that it increases the body's sensitivity to insulin. This means that less insulin has to be secreted to do the same job. One exercise session can increase insulin sensitivity for up to 16 hours (Borghouts & Keizer, 2000). It has, however, been shown that excessively high exercise levels suppress the immune system (Mackinnon, 2000).

Since exercise reduces the blood glucose value, it can be expressed as negative —ets and can be subtracted from the ingested —ets. Compensating for extra —ets ingested with

exercise means that it is possible to stay within the recommended daily limits even when enjoying special treats.

The —ets expended per hour by an average (60 kg) male for various activities is shown in Table 5.3. These values were derived from the fact that 1 —ets = 13 kCal and using available data on energy expended through exercise.

It has been have shown that cancer risk is directly related to the effective ingested —ets. Since exercise can now also be quantified in term of —ets, it should be possible to establish a link between cancer risk and exercise as well. It is known that exercise acts as negative —ets, reducing the blood glucose value. One would thus expect an inverse relationship between exercise and cancer risk.

Table 5.3. The equivalent —ets expended per hour by a 60 kg male performing different activities (Mathews & Mathews, 2005)

Activity	Equivalent ets
Cycling (9 km/h)	5.2
Cycling (21 km/h)	11.1
Golfing	4.3
Running (9 km/h)	11.1
Running (11 km/h)	14.5
Running (19 km/h)	20.4
Squash	9
Tennis	7.2
Walking (3 km/h)	3.6
Walking (6 km/h)	6.4

5.6. Experimental results

All the —ets computations in this section use a 60 kg male as reference. Slattery et al. (2003) did a study that investigated the relationship between energy expenditure and cancer risk. They interviewed more than 2 000 subjects (cases and controls) and determined the average time per day spent doing moderate to vigorous physical exercise. The —ets expended by the subjects in their experiment was computed (using an average expenditure of 13 —ets per hour), and the results are shown in Figure 5.2.

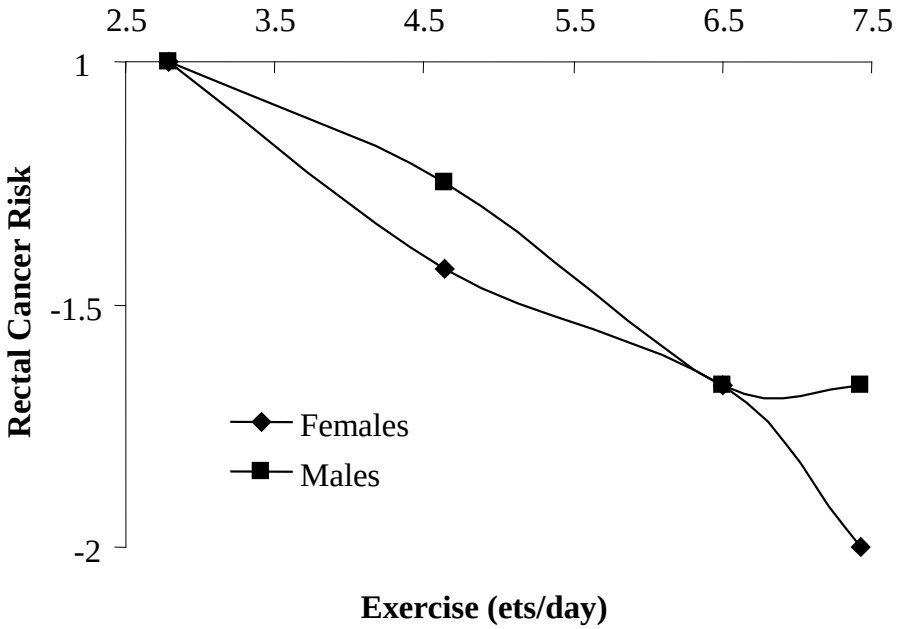

Figure 5.2. The reduction in rectal cancer risk with increased daily exercise as measured in —ets

As expected, a link between cancer risk and —ets exercised emerges from the figure. It is clear that the risk of rectal cancer decreases with increasing —ets expenditure. Daily exercise of 7.5 —ets reduces the risk of cancer by a factor of almost two. This is about the equivalent of 30 minutes of jogging at 11 km/h per day, which seems like a small price to pay for halving one's cancer risk.

In another study Friedenreich et al. (2001) investigated the relationship between breast cancer risk and the intensity of physical exercise. Subjects were interviewed to determine the hours per week they were involved in different levels of physical activities. Their results were interpreted to determine the average daily —ets expenditure. The self-reported, postmenopausal data were used. Figure 5.3 shows the results obtained.

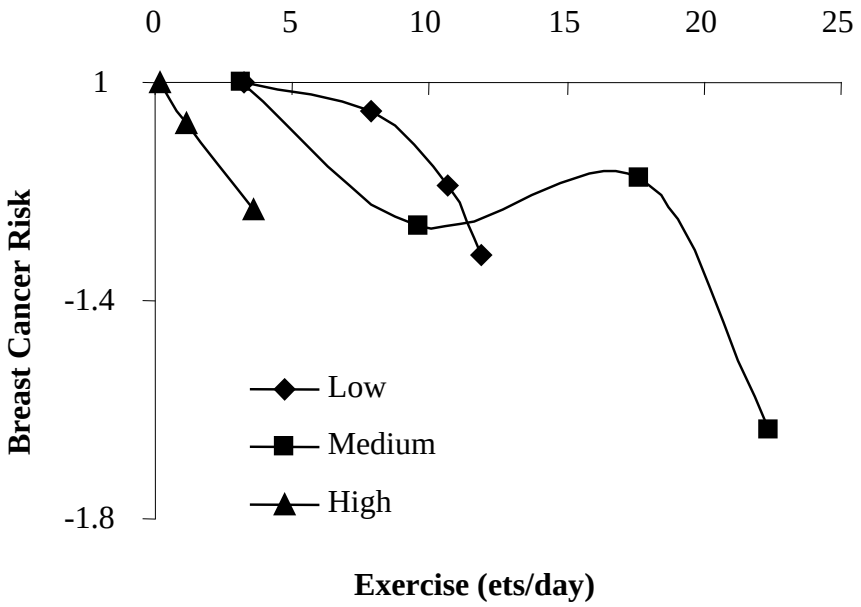

Figure 5.3. Relationship between breast cancer risk and intensity of physical exercise (Friedenreich et al., 2001)

Low intensity activity was estimated to consume 3 —ets per hour, medium intensity 9 —ets per hour and high intensity 15—ets per hour. From the figure it is clear that there is a general decrease in cancer risk with increasing —ets expenditure through exercise, irrespective of its intensity.

The gradient of decrease, however, seems to be influenced by the intensity of the exercise. High intensity exercise leads to the steepest decline in cancer risk, followed by medium and lastly low intensity. As the intensity decreases, more exercise (in —ets) is needed to cause the decrease in cancer risk.

The reason for this decrease in cancer risk with increasing exercise is moot, but one hypothesis is that of increased gastrointestinal motility (Slattery et al., 2003). This means that there is less contact time between food by-products and the gastrointestinal lumen and thus also less contact with harmful bacteria. This is especially relevant for colon and rectal cancer.

Other suggested reasons include the effect of exercise on the immune system, hormones and body fat (Lee, 1995; Mezzetti et al., 1998; Oliveria & Christos, 1997). It might even be just the mood-elevating effect of a good workout.

The above-mentioned hypothesis is noted. It was, however, shown that blood sugar response gives a constant picture of cancer risk for the factors investigated, namely diet, fibre, stress and exercise.

5.7. Conclusion

This chapter investigated two more factors that influence the risk of cancer, namely stress and exercise. Both factors were quantified in terms of —*ets*. This means that one's daily stress can be added and one's exercise subtracted from one's ingested —*ets* to determine one's net —*ets* intake.

From chapter 3 it is clear that cancer risk increases rather sharply when the daily consumption exceeds about 30 —*ets*. This chapter showed that about 7.5 —*ets* of exercise per day halved one's cancer risk. It was furthermore shown that high intensity exercise is necessary to reduce the cancer risk effectively.

Taken together, a healthy diet (of slightly more than 30 —*ets*) together with some exercise (around 7.5—*ets*) means a drastic reduction in cancer risk. Including a stress reduction mechanism in one's daily routine will reduce this risk even more. It should be stated that

the values are approximations and will differ from person to person. They do, however, show trends that exist in spite of the inter-person variability.

Figure 5.4 shows the effects of food and exercise on the same graph. The cancer risk doubles as it increases from -2 to 1 or from 1 to 2. The x-axis scale is Δ—ets/day, meaning ingested —ets in addition to the daily allowance.

It is clear that the effect of —ets consumption is almost an exact mirror image of —ets expenditure. This confirms the proposal that consumed —ets can be "cancelled" by exercised —ets. Implementation of this proposal is a very effective and convenient method to keep one's daily —ets consumption within the recommended limits.

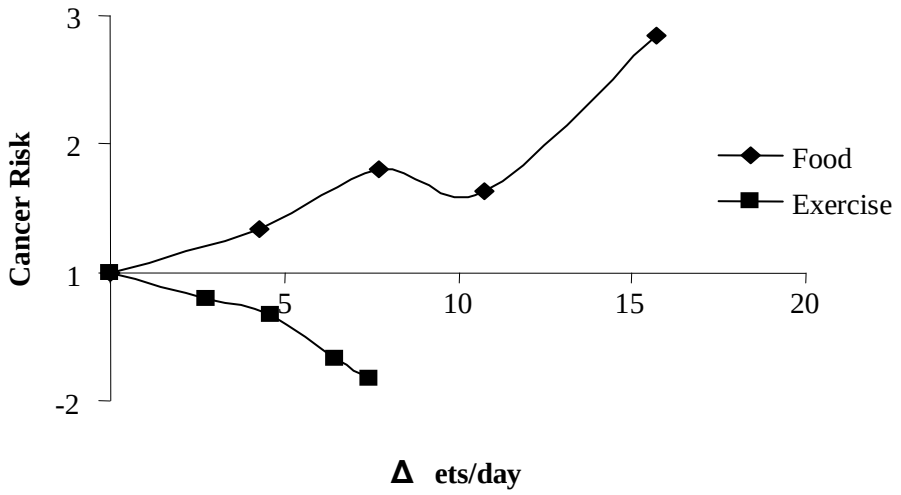

Figure 5.4. The effect of ingested —ets (food) and expended —ets (exercise)

Figure 5.5 shows the effect of food and stress in terms of —ets. Clearly, both increased energy intake and increased stress levels increase one's daily —ets intake, and thus increases one's risk of cancer. The opposite is also true – reducing one's CHO energy consumption or one's stress levels reduces one's risk of cancer.

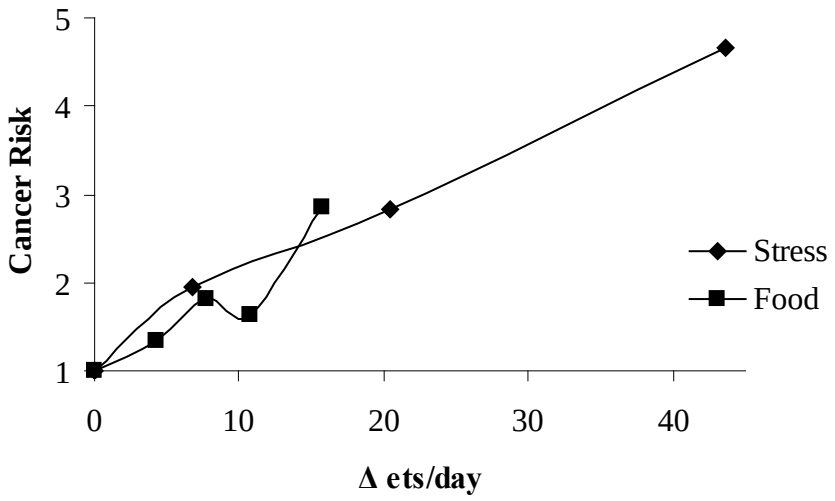

Figure 5.5. The effect of ingested ets (food) and secreted ets due to stress

Without any major alterations to one's lifestyle it is thus possible to reduce one's risk of developing one of the leading killers of the 21st century – cancer.

5.8. References

Anisman, H. & Merali, Z. (1999), "Understanding stress: Characteristics and caveats", *Alcohol research & Health*, 23 (4), pp.241 – 249.

Borghouts, L.B. & Keizer, H.A. (2000), "Exercise and insulin sensitivity: a review", *International Journal of Sports Medicine*, 21, pp. 1 – 12.

Friedenreich, C.M., Courneya, K.S. et al. (2001), "Relation between intensity of physical activity and breast cancer risk reduction", *Medicine & Science in Sports & Exercise*, 33 (9), pp.1538 – 1545.

Garabrant, D.H., Peters, J.M. et al. (1984), "Job activity and colon cancer risk", *Cancer Research*, 4, pp.116 – 118.

Gerhardsson, M., Floderus, B. et al. (1988), "Physical activity and colon cancer risk", *International Journal of Epidemiology*, 17, pp.743 – 746.

Ginsberg, A., Price, S. et al. (1996), "Life events and the risk of breast cancer: a case-control study", *European Journal of Cancer*, 32A, 12, pp. 2049 – 2052.

Giovanucci, E. (2001), "Insulin, insulin-like growth factors and colon cancer: a review of the evidence", *American Institute for Cancer Research, 11th Annual Research Conference on Food, Nutrition and Cancer, Supplement,* 3109S – 3120S.

Hassed, C. (2002), "Does living better also mean living longer? Quality of life and cancer", *Australian Family Physician*, 31 (8), Aug.

Kritchevsky, D. (2001), "Caloric restriction and cancer" *Journal of Nutritional Science and Vitaminology (Tokyo)*, 47 (1), Feb, pp.13 – 19.

Kritchevsky, D. (2003), "Diet and cancer: what's next?" *International Research Conference on Food, Nutrition and Cancer, Supplement,* 3827S – 3829S.

Kroenke, C.H., Hankinson, S.E. et al. (2004), "Caregiving stress, endogenous sex steroid hormone levels, and breast cancer incidence", *American Journal of Epidemiology*, 159 (11), pp.1019 – 1027.

Lazarus, R.S. & Folkman, S. (1984), *Stress, Appraisal, and Coping*, Springer, New York.

Lee, I.M. (1995), "Exercise and physical health: cancer and immune function", *Research Quarterly for Exercise and Sport*, 66 (4), Des, pp.286 – 291.

Mackinnon, L.T. (2000), "Chronic exercise training effects on immune function", *Medicine & Science in Sports & Exercise*, 32, 7, July, Supplement, pp. S369 – S376.

Maddock, C. & Pariante, C.M. (2001), "How does stress affect you? An overview of stress, immunity, depression and disease", *Epidemiologia e Psichiatria Sociale*, 10 (3), pp.82 – 92.

Mathews, E.H. & Botha, C.P. (2005), "Insulin requirement for stress and illness", Unpublished article. PO Box 2157, Faerie Glen 4, 0043, South Africa.

Mathews, E.H. & Mathews, C. (2007), *ets - The missing link to an easy and scientific diet*, In preparation for publication, PO Box 2157, Faerie Glen 4, 0043, South Africa.

McTiernan, A, Schwartz, R.S. et al. (1999), "Exercise clinical trials in cancer prevention research: a call to action", *Cancer Epidemiology, Biomarkers & Prevention*, 8, March, pp.201 – 207.

Mezzetti, M., La Vecchia, C. et al. (1998), "Population attributable risk for breast cancer: diet, nutrition, and physical exercise", *Journal of the National Cancer Institute*, 90 (5), pp.389 – 394.

Oliveria, S.A. & Christos, P.J. (1997), "The epidemiology of physical activity and cancer", *Annals of the New York Academy of Sciences*, 833 (1), pp.79 – 90.

Ramirez, A.J., Craig, T.K. et al. (1989), "Stress and relapse of breast cancer", *British Medical Journal*, 298 (6669), Feb 4, pp.291 – 293.

Schermerhorn, T. (2001), "Management of insulin overdose", *Standards of Care-Emergency and Critical Care Medicine*, 3.11, Nov/Dec, pp.1 – 14.

Sieber, F.E. & Traystman, R.J. (1992), "Special issues: glucose and the brain", *Critical Care Medicine*, 20 (1), pp.104 – 114.

Slattery, M.L., Caan, B.J. et al. (2003), "Energy balance and rectal cancer: an evaluation of energy intake, energy expenditure, and body mass index", *Nutrition and Cancer*, 46 (2), pp.166 – 171.

Spiegel, D., Bloom, J.R. et al. (1989), "Effects of psychosocial treatment on survival of patients with metastatic breast cancer", *Lancet*, 2, pp.888 – 891.

Stephens, M.A. & Townsend, A.L. (1997), "Stress of parent care: positive and negative effects of women's other roles", *Psychology and Aging*, 12 (2), Jun, pp.376 – 386.

Vedhara, K. & Nott, K. (1996), "The assessment of the emotional and immunological consequences of examination stress", *Journal of Behavioral Medicine (Historical Archive)*, 19 (5), Oct, pp.467 – 478.

Vena, J.E., Graham, D. et al. (1985), "Lifetime occupational exercise and colon cancer", *American Journal of Epidemiology*, 122, pp.357 – 365.

Wise, P.H. (1999), *Understanding your diabetes – For people with insulin-dependent (type 1) diabetes*, Foulsham, The Publishing House, Berkshire, England.

Yang, J. (2006), *ets and stress* (title to be confirmed), Unpublished PhD, University of North West, South Africa.

CHAPTER 6 CLOSURE

This study investigated the influence of blood glucose control on the growth and proliferation of cancer cells. The different factors that play a role in this process were identified and their cancer risk was linked to ETS. The final chapter brings it all together into practical guidelines for a lifestyle that promotes a reduced cancer risk.

TABLE OF CONTENTS

6.1. Summary

Different aspects influencing the risk of developing cancer as well as the growth of cancer have been discussed throughout this document. The conclusion was reached that cancer cells need sugar to survive. The more sugar there is available, the higher the risk of developing cancer. Extra sugar also means extra fuel for existing cancers. Sugar is furthermore known to suppress the immune system, which elevates the cancer risk and weakens the defence against cancer.

Extra sugar is obtained from ingested food or an inability of the normal cells to utilise sugar (due to insulin resistance), or it is secreted from the liver in response to stressful situations. Figure 6.1 is a graphical representation of this energy system.

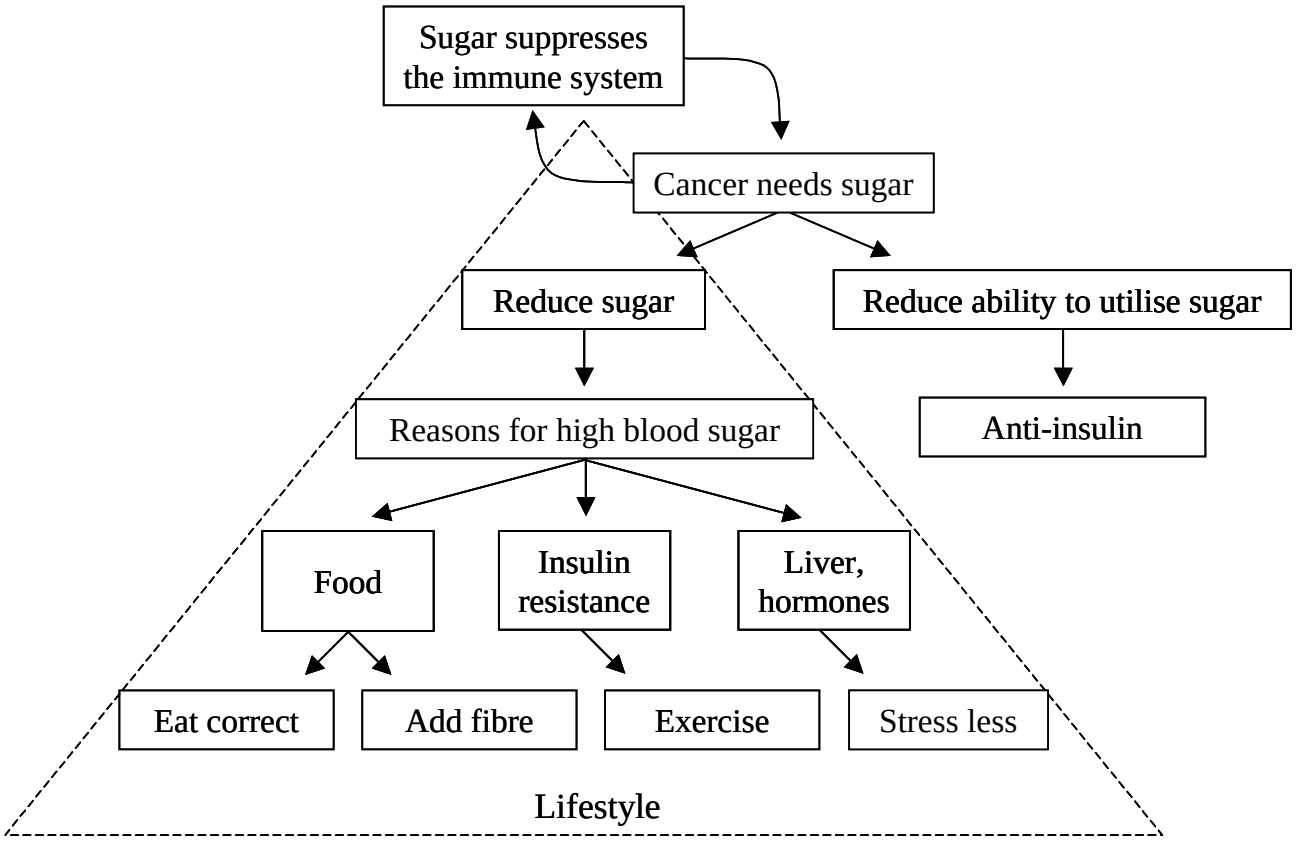

Figure 6.1. Metabolic energy management to reduce cancer risk and suppress cancer growth

The left-hand side of Figure 6.1 deals more with cancer prevention and a little treatment, while the complete figure shows a possible treatment for cancer patients. Throughout this document it was shown that the cancer risk introduced by certain factors can be quantified in terms of —*ets*.

Each person has a recommended daily —*ets* allowance (Addendum A). This defines the amount of energy one needs to sustain one's basic metabolism and ensure one's general health. To minimise your cancer risk, one's daily —*ets* intake should not exceed this allowance. Any extra —*ets* acts as fuel for cancer cells.

The first step in regulating one's —*ets* intake is developing a healthy diet. Although other steps will be discussed shortly, the diet is the main source of daily —*ets*. It is thus the easiest and most direct method to reduce one's —*ets* intake and thus one's cancer risk.

If a person has difficulty in restricting his diet to the recommended —*ets* limit, step two is to add fibre to meals. It was shown that fibre reduces the available energy from a meal and thus lowers the —*ets* value. A good approximation is to subtract 0.6 —*ets* for each gram of extra fibre added to a meal.

Step three is to reduce one's stress levels. It was shown that stress leads to the secretion of stress hormones, which, in turn, prompts the liver to secrete glucose. This high glucose environment creates the perfect conditions for cancer cells to grow in. Long-term stress leads to an increase of up to two —*ets* per day, while short-term stress increases it even more.

Lastly, including exercise in one's daily routine was shown to reduce one's cancer risk drastically. High intensity exercise is especially protective. The —*ets* expended by different types of exercise was shown. Exercise increases one's insulin sensitivity, which means that less insulin needs to be secreted before the cells start using glucose. In the

long-term, this leads to a lower glucose concentration in the body. Clearly, this is not a very suitable environment for cancer proliferation.

The final —ets intake is thus computed from the following equation:

$$ets_{Final} = ets_{Food} + ets_{Stress} - ets_{Fib} - ets_{Exercise} \quad (6.1)$$

This equation summarises the results from this study. Keeping the value of ets_{Final} equal to or lower than one's recommended daily —ets intake means minimising one's cancer risk.

Clearly, this is a simple and intuitive equation to implement. The typical values inserted into the equation are lower than ten, making computation easy. The proposed lifestyle changes are relatively easy to implement.

Figure 6.2 shows the combined effect of —ets ingested through food and that secreted owing to stress, as well as negative —ets from fibre and exercise. The cancer risk doubles from -2 to -1 and again from 1 to 2.

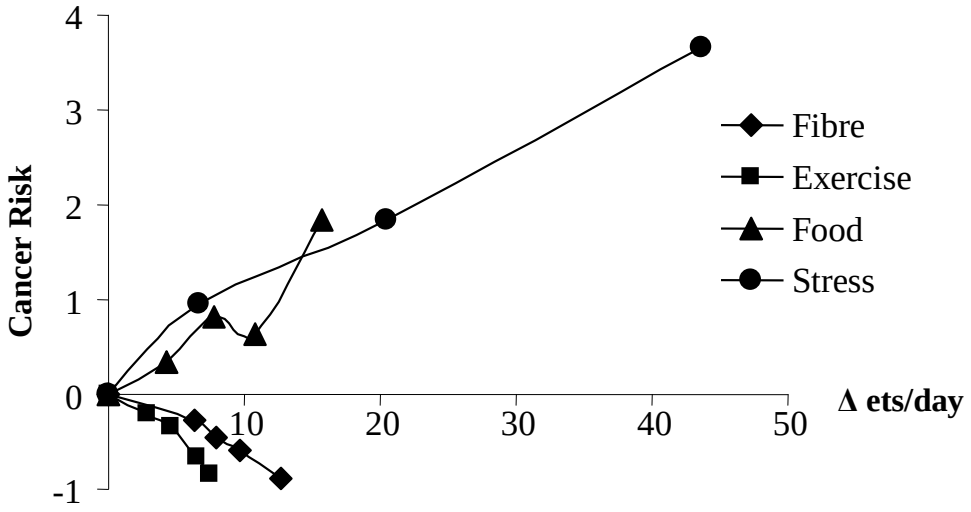

Figure 6.2. Combined effect of ingested —ets (food), negative —ets (fibre), and expended —ets (exercise)

The researcher's assumption that the combined effect of exercise and fibre is a mirror image of food seems correct. The results obtained when subtracting the negative –ets from the ingested –ets thus gives a good indication of the total daily –ets consumption.

Many hypotheses exist on why certain factors (like exercise or stress) have a certain influence on cancer risk. It is noteworthy that the proposed method of using blood glucose level to explain cancer risk holds for all the investigated factors (food, exercise, stress and fibre). It thus provides a single mechanism which explains the effect of vastly different factors rather accurately.

6.2. Conclusion

This study investigated the effect of blood glucose control on cancer risk. A previously proposed method to quantify all elements of the human energy system was used. It was shown that cancer risk increases directly proportionate to increasing total daily CHO consumption.

The total daily CHO consumption is a factor of the ingested food, fibre content of the food, exercise done and stress experienced. In conclusion, recommendations are made on how to decrease one's cancer risk significantly through a few simple lifestyle adaptations.

6.3. Recommendations for further work

In this study it was shown that fibre reduces the risk of developing cancer. The assumption was made that one gram of fibre leads to a reduction of 0.6–ets. This is a good first approximation, and was sufficient to prove the hypothesis. It is, however, recommended that this aspect be explored further. More experiments should be conducted to validate the use of -0.6–ets per gram of fibre.

There will be some saturation value where the addition of more fibre will not lead to a further reduction in the —ets value of the meal. This value should be obtained and a more accurate description of the relationship between fibre and energy release should be developed.

The relationship between different fibre supplements and weight loss should be investigated further. This will enable accurate recommendations on the type and amount of fibre to add to a meal to achieve weight loss or to minimise one's cancer risk.

Since the tools to quantify stress have been developed, experiments should be undertaken to verify these proposed models. Once they have been fine-tuned, the concept of stress and its effect on cancer can be explored on a new level.

The hours per day that one experiences stress should also be investigated using the —ets principles. This should lead to a better estimate of the value to multiply the "—ets due to stress per hour" values with.

The guidelines given in this document should be verified through clinical trials. If the researcher's hypothesis holds true, it should be possible to reduce the size of cancerous tumours by depriving them of sugar.

Patients with cancer in an advanced stage could be placed on the —ets diet and their progress compared with controls. A long-term study could be undertaken to compare the number of subjects developing cancer while implementing the guidelines proposed here with controls.

ADDENDUM A

RECOMMENDED DAILY ets ALLOWANCE

The tables to obtain the daily ets allowance for different persons with activity levels are supplied in this addendum.

For active people:

	Height (m)	Weight (kg)	ets
Men	1.2 - 1.25	33 - 38	16
	1.25 - 1.3	36 - 41	17
	1.3 - 1.35	38 - 44	18
	1.35 - 1.4	42 - 48	20
	1.4 - 1.45	44 - 50	21
	1.45 - 1.5	47 - 54	22
	1.5 - 1.55	50 - 58	24
	1.55 - 1.6	54 - 62	26
	1.6 - 1.65	56 – 65	26
	1.65 - 1.7	59 – 68	28
	1.7 - 1.75	63 – 73	30
	1.75 - 1.8	66 – 77	32
	1.8 - 1.85	70 – 82	34
	1.85 - 1.9	74 – 86	36
	1.9 - 1.95	77 – 90	37
	1.95 - 2	81 – 94	38
	2 - 2.05	85 - 100	41
	2.05 - 2.1	89 - 104	43
	2.1 - 2.15	93 - 109	45
	2.15 - 2.2	96 - 114	46
	2.2 - 2.25	100 - 120	49
Women	1.2 - 1.25	33 - 38	16
	1.25 - 1.3	35 - 41	17
	1.3 - 1.35	37 - 44	18
	1.35 - 1.4	40 - 46	19
	1.4 - 1.45	43 - 50	21
	1.45 - 1.5	45 - 53	22
	1.5 - 1.55	47 - 55	22
	1.55 - 1.6	50 - 59	24
	1.6 - 1.65	53 - 63	26
	1.65 - 1.7	56 - 67	27
	1.7 - 1.75	60 - 70	29
	1.75 - 1.8	63 - 73	30
	1.8 - 1.85	66 - 77	32
	1.85 - 1.9	68 - 81	33
	1.9 - 1.95	72 - 85	34
	1.95 - 2	76 - 89	36
	2 - 2.05	79 - 93	38
	2.05 - 2.1	82 - 97	40

For normal activity levels:

	Height (m)	Weight (kg)	ets
Men	1.2 - 1.25	33 - 38	13
	1.25 - 1.3	36 - 41	14
	1.3 - 1.35	38 - 44	16
	1.35 - 1.4	42 - 48	17
	1.4 - 1.45	44 - 50	18
	1.45 - 1.5	47 - 54	19
	1.5 - 1.55	50 - 58	21
	1.55 - 1.6	54 - 62	22
	1.6 - 1.65	56 - 65	23
	1.65 - 1.7	59 - 68	24
	1.7 - 1.75	63 - 73	26
	1.75 - 1.8	66 - 77	27
	1.8 - 1.85	70 - 82	29
	1.85 - 1.9	74 - 86	30
	1.9 - 1.95	77 - 90	32
	1.95 - 2	81 - 94	33
	2 - 2.05	85 - 100	35
	2.05 - 2.1	89 - 104	37
	2.1 - 2.15	93 - 109	38
	2.15 - 2.2	96 - 114	40
	2.2 - 2.25	100 - 120	42
Women	1.2 - 1.25	33 - 38	13
	1.25 - 1.3	35 - 41	14
	1.3 - 1.35	37 - 44	15
	1.35 - 1.4	40 - 46	16
	1.4 - 1.45	43 - 50	18
	1.45 - 1.5	45 - 53	19
	1.5 - 1.55	47 - 55	20
	1.55 - 1.6	50 - 59	21
	1.6 - 1.65	53 - 63	22
	1.65 - 1.7	56 - 67	23
	1.7 - 1.75	60 - 70	25
	1.75 - 1.8	63 - 73	26
	1.8 - 1.85	66 - 77	27
	1.85 - 1.9	68 - 81	29
	1.9 - 1.95	72 - 85	30
	1.95 - 2	76 - 89	31
	2 - 2.05	79 - 93	33
	2.05 - 2.1	82 - 97	34

For light activity levels:

	Height (m)	Weight (kg)	ets
Men	1.2 - 1.25	33 - 38	12
	1.25 - 1.3	36 - 41	13
	1.3 - 1.35	38 - 44	14
	1.35 - 1.4	42 - 48	15
	1.4 - 1.45	44 - 50	16
	1.45 - 1.5	47 - 54	17
	1.5 - 1.55	50 - 58	18
	1.55 - 1.6	54 - 62	19
	1.6 - 1.65	56 - 65	20
	1.65 - 1.7	59 - 68	21
	1.7 - 1.75	63 - 73	22
	1.75 - 1.8	66 - 77	24
	1.8 - 1.85	70 - 82	25
	1.85 - 1.9	74 - 86	26
	1.9 - 1.95	77 - 90	28
	1.95 - 2	81 - 94	29
	2 - 2.05	85 - 100	30
	2.05 - 2.1	89 - 104	32
	2.1 - 2.15	93 - 109	34
	2.15 - 2.2	96 - 114	35
	2.2 - 2.25	100 - 120	36
Women	1.2 - 1.25	33 - 38	12
	1.25 - 1.3	35 - 41	13
	1.3 - 1.35	37 - 44	13
	1.35 - 1.4	40 - 46	14
	1.4 - 1.45	43 - 50	16
	1.45 - 1.5	45 - 53	16
	1.5 - 1.55	47 - 55	17
	1.55 - 1.6	50 - 59	18
	1.6 - 1.65	53 - 63	19
	1.65 - 1.7	56 - 67	20
	1.7 - 1.75	60 - 70	22
	1.75 - 1.8	63 - 73	22
	1.8 - 1.85	66 - 77	24
	1.85 - 1.9	68 - 81	25
	1.9 - 1.95	72 - 85	26
	1.95 - 2	76 - 89	27
	2 - 2.05	79 - 93	28
	2.05 - 2.1	82 - 97	30

For weight losers:

	Height (m)	Weight (kg)	ets
Men	1.2 - 1.25	33 - 38	10
	1.25 - 1.3	36 - 41	10
	1.3 - 1.35	38 - 44	11
	1.35 - 1.4	42 - 48	12
	1.4 - 1.45	44 - 50	13
	1.45 - 1.5	47 - 54	14
	1.5 - 1.55	50 - 58	15
	1.55 - 1.6	54 - 62	16
	1.6 - 1.65	56 - 65	16
	1.65 - 1.7	59 - 68	17
	1.7 - 1.75	63 - 73	18
	1.75 - 1.8	66 - 77	19
	1.8 - 1.85	70 - 82	20
	1.85 - 1.9	74 - 86	22
	1.9 - 1.95	77 - 90	22
	1.95 - 2	81 - 94	24
	2 - 2.05	85 - 100	25
	2.05 - 2.1	89 - 104	26
	2.1 - 2.15	93 - 109	27
	2.15 - 2.2	96 - 114	28
	2.2 - 2.25	100 - 120	30
Women	1.2 - 1.25	33 - 38	10
	1.25 - 1.3	35 - 41	10
	1.3 - 1.35	37 - 44	11
	1.35 - 1.4	40 - 46	12
	1.4 - 1.45	43 - 50	13
	1.45 - 1.5	45 - 53	13
	1.5 - 1.55	47 - 55	14
	1.55 - 1.6	50 - 59	15
	1.6 - 1.65	53 - 63	16
	1.65 - 1.7	56 - 67	16
	1.7 - 1.75	60 - 70	18
	1.75 - 1.8	63 - 73	18
	1.8 - 1.85	66 - 77	19
	1.85 - 1.9	68 - 81	20
	1.9 - 1.95	72 - 85	21
	1.95 - 2	76 - 89	22
	2 - 2.05	79 - 93	23
	2.05 - 2.1	82 - 97	24

ADDENDUM B

ARE HISTORICAL IDEAS ON ENERGY METABOLIZED FROM CARBOHYDRATES WRONG?

An unpublished article showing that the historical method of estimating the energy available from carbohydrates is incorrect.

ARE HISTORICAL IDEAS ON ENERGY METABOLIZED FROM CARBOHYDRATES WRONG?

Over the past 100 years it was assumed that similar amounts of energy is made available by the body's energy conversion process as that made available by the conversion process in a bomb calorie meter[1,2]. For carbohydrates (CHO) this value is approximated as 4 kilocalories per gram of CHO.

However, we know that the two conversion processes are very different. Therefore, contrary to popular believe, we suspect that vastly different amounts of energy will be released by the two processes. Here we investigate our suspicion.

Nine groups, each consisting of eight healthy Spraque Dawley rats, were investigated. All rats were of the same age and received the same kilocalories (kcal) per body mass. The kcal values were determined by the following energy equation[3] for recommended daily allowance (RDA) for rats :

$$\text{RDA[kcal]} = 0.45 \times \text{body mass}^{0.75} \qquad (1)$$

Each of the groups received different foods containing a high percentage of CHO, namely: *1. Barley, 2. Provita, 3. Strawberry Pops, 4. Chickpeas, 5. Toasted Muesli, 6. Pronutro Flakes, 7. Special K, 8. All Bran Flakes and 9. Nutrific.* The energy content of the foods was measured with a bomb calorie meter. The mass loss/gain for each group was measured weekly for three weeks.

As the energy supplied to the rats (calculated in the conventional way) is their RDA, we expect that the mass of the rats should not change. However, if there is a small mass loss/gain due to an error in equation (1), this loss/gain should be the same for each group as they all received the same amount of kcal per body mass.

Our results in Figure 1 however show that all the groups actually lost mass. (We had to stop the experiment after three weeks as the ethical allowable loss limit of 15% was exceeded very quickly.) The results also show that these losses were not the same for the different groups consuming different types of "isocaloric" food.

Our first conclusion is that contrary to conventional believe, a living creature cannot extract the full 4kcal of energy per gram of CHO. A second conclusion is that the amount of energy extracted differs for different types of CHO.

An equation to address these problems and bring order to our understanding of CHO metabolisation is derived and verified in another publication[4] using the mass loss data from this paper. (We also speculate that similar equations can be derived for fat and protein but that the effects will be less pronounced than for CHO.) The concept is further verified in reference 5 in an experiment using 15 healthy people.

The implications of the findings in this paper are far reaching. Incorrect CHO energy estimation means that all our food are incorrectly labelled. It also raises questions about historical diets which are based on percentage energy from macro nutrients CHO, fat and protein. The poor is further underfed when aid of usually CHO rich food does not account for the inefficiencies of CHO conversion[4].

In other articles[6,7] we show the correct effect of CHO intake on coronary heart disease and cancer. This is not possible when using the historical constant 4kcal/g for all CHOs. We also show how this incorrect assumption leads to difficulty for diabetics in controlling their blood glucose levels[8] while the new energy equation vastly enhances control.

Edward H Mathews[+]*, Corlia Mathews*

Contracted to North West University[+], PO Box 2157 Faerie Glen 0043 RSA and consultants to Human-Sim (Pty) Ltd. E-mail: ehmathews@human-sim.com*

1. Atwater, W.O and Bryant, A.P., The availability and fuel values of food materials, Connecticut Agricultural Experiment Sation, 12th Annual Report, 1900, pp. 73-110.

2. Rubner, M., (1901), Der Energiewet der Kost des Menschen", Z. Biol, 42:261-308.

3. Clark, H E., Coates, M E., Eva, J K., Ford, D J., Miller, C K., O'Donoghue, P N., Soctt, P P., Ward, R J. (1977), Dietary standards for laboratory animals: report of the Laboratory Animals Centre Diets Advisory Committee, Lab Anim, 11: 1-28.

4. Mathews, E.H., A more correct way to estimate energy from carbohydrates (Scientific correspondence, Nature), presented for publication.

5. Mathews, E.H., Indirect measurement in humans of energy converted from carbohydrates, (Letter to Nature) presented for publication.

6. Mathews, E.H., Carbohydrate intake and the risk for coronary heart disease (CHD).

7. Mathews, E.H., Carbohydrate intake and the risk for certain cancers, (Scientific correspondence, Nature), presented for publication.

8. Mathews, E.H., Carbohydrate intake and insulin requirements.

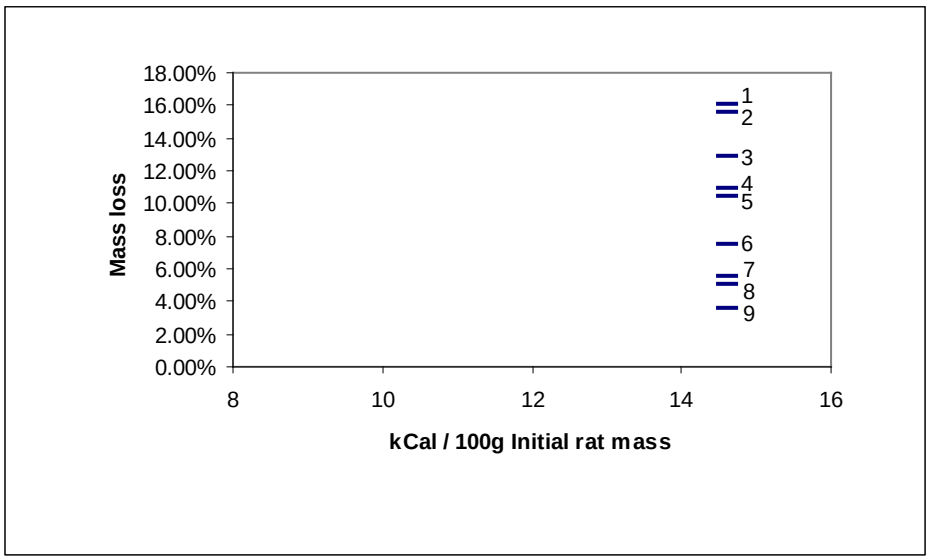

Figure B-1. Relationship between mass loss and "isocaloric" kCal ingested for 9 different foods (kCal calculated in the conventional way).

ADDENDUM C A MORE CORRECT WAY TO ESTIMATE ENERGY METABOLIZED FROM CARBOHYDRATES

An unpublished article showing a more correct way to estimate the energy available from carbohydrates.

A MORE CORRECT WAY TO ESTIMATE AVAILABLE ENERGY FROM CARBOHYDRATES

In a previous article[1] we have shown that a better method than the one used during the past century is needed to calculate the carbohydrate (CHO) energy metabolized by a living creature. It was also shown that, contrary to popular believe, the metabolized energy from different CHOs can differ vastly. Based on these results we suspect that we have to account for the metabolic conversion efficiencies (η) of the body for each different CHO. Here we derive the necessary equations and verify them.

The energy E_{CHO} [kcal] converted into blood glucose from a CHO with a metabolic conversion efficiency of η_{CHO} and a mass of m_{CHO}[g], (including fibre), can be given by equation (1). All losses, including energy needed for digestion, as well as incomplete digestion, gas and heat production etc. are accounted for in η_{CHO}.

$$E_{CHO}[kcal] = \eta_{CHO}\, m_{CHO}[g]\; 4[kcal/g] \qquad (1)$$

We want to express the energy content in any CHO with a unit which is easy to understand and visualise for the lay person, say a teaspoon of sugar. There are many other advantages for choosing this unit which will be described in more detail in future papers.

When we now use equation (1) for one teaspoon of sugar containing 5[g] of CHO, it will result in the following :

$$E_{TeaspoonSugar}[kcal] = \eta_{Sugar}\; 5[g] \times 4[kcal/g] \qquad (2)$$

Let us now relate the metabolized blood glucose energy from each different CHO (E_{CHO}) to equivalent teaspoons sugar (*ets*). We can achieve this by dividing equation (1) with equation (2) for sugar to find the amount of *ets* in any CHO, namely ets_{CHO}.

$$\text{ets}_{CHO} = \frac{E_{CHO}}{E_{Teaspoon\,Sugar}} = \frac{\eta_{CHO}\, m_{CHO} \times 4[kcal/g]}{\eta_{Sugar}\; m_{Teaspoon} \times 4[kcal/g]} = \frac{\eta_{CHO}}{\eta_{Sugar}} \;\; \frac{m_{CHO}}{5} \quad (3)$$

In another article[3] we prove that $\eta_{CHO} \approx$ GI/100, where GI is the Glyceamic Index of a foodstuff[4]. We therefore have measured values for η_{CHO} for most of the important CHOs. (It must be remembered that η_{CHO} will become even smaller than these measured values in a meal high in fat and/or protein.)

Using equation (2) and keeping in mind that GI_{sugar} = 65, thus having a metabolic conversion efficiency (η) of 0,65, the equivalent energy in one teaspoon sugar (ets) is 13kcal as calculated using equation (2)).

$$E_{Teaspoon\,Sugar}\,[\text{kcal}] = \text{one ets}\,[\text{kcal}] = 0{,}65 \text{ x } 5 \text{ x } 4 = 13\,[\text{kcal}] \quad (4)$$

Now that we have established the metabolized blood glucose energy from any CHO expressed in terms of ets (equations (3) and (4)), we can propose a new way of calculating energy available to the body. We call the new energy value ets cal, to avoid confusion with standard kcal. It is calculated by the following equation:

$$\begin{aligned} \text{ets cal} = \quad & 13[\text{kcal/ets}] \text{ x } \text{ets}_{CHO} + \\ & 9[\text{kcal/g}] \text{ x } \text{mass}_{\text{Fat}}[\text{g}] + \\ & 4[\text{kcal/g}] \text{ x } \text{mass}_{\text{Protein}}[\text{g}] \end{aligned} \quad (5)$$

By utilising experimental data from a previous article[1], Figure 1 was constructed. A linear relationship is found between the ets cal values of a food containing CHO and the % mass loss with a resulting Pearson's R^2 value of 0.68. This shows that the ets cal equation is more representative of the metabolized energy of CHO in a body than the constant 4kcal/g historically used.

Edward H Mathews

Contracted to North West University, PO Box 2157 Faerie Glen 4, 0043 RSA, and consultant to Human-Sim (Pty) Ltd. E-mail: ehmathews@human-sim.com

1. *Mathews, E.H., Historical ideas on energy from carbohydrates are wrong (Scientific correspondence, Nature), presented for publication.*
2. *Mathews, E.H., A practical relationship between insulin response and ingested carbohydrates, (Letter to Nature) presented for publication.*
3. *Leeds, A. & Miller, JB. (1996), The GI Factor: The Glycaemic Index Solutions, Hodder & Stroughton, Australia.*
4. *Mathews, E.H., Historical ideas on the Glyceamic Index are wrong, (Scientific correspondence, Nature), presented for publication.*

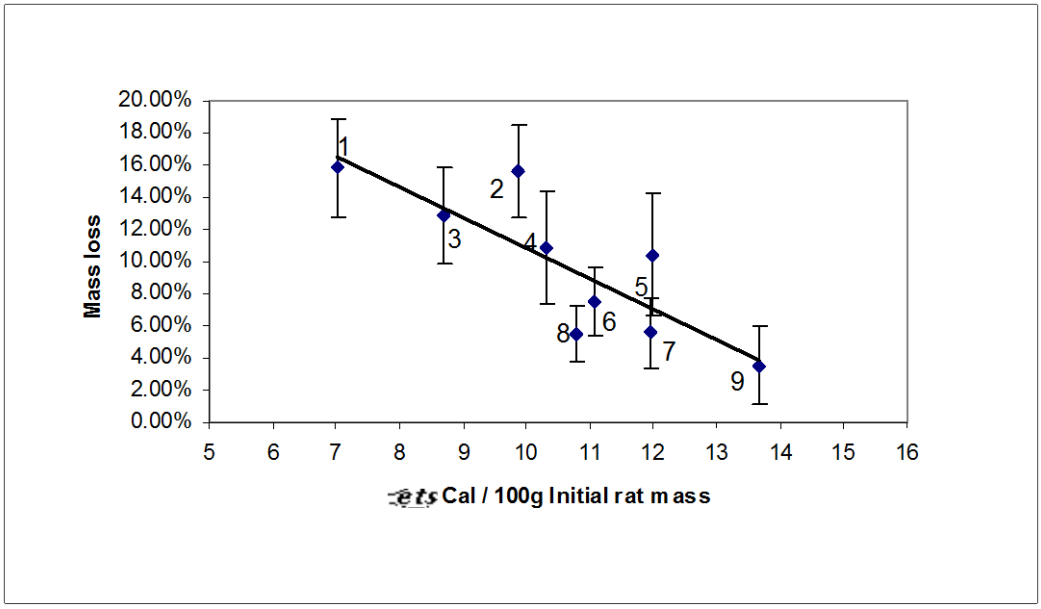

Figure C-1. Relationship between mass loss and ets Cal.

ADDENDUM D

INDIRECT MEASUREMENTS IN HUMANS OF THE CORRECT ENERGY METABOLIZED FROM CARBOHYDRATES

An unpublished article showing a more correct way to estimate the energy available from carbohydrates.

INDIRECT MEASUREMENTS IN HUMANS OF THE CORRECT ENERGY METABOLIZED FROM CARBOHYDRATES (CHO)

We have shown that the historical calculation of metabolized CHO energy can lead to large errors[1] when using rats as test subjects. A new method was therefore proposed[2]. We now want to test if this new method also applies to humans.

However, it is more difficult to control a similar experiment with humans than the one used with rats in references [1] and [2]. We therefore chose to use an indirect approach. Insulin secretion is a function of the blood glucose energy metabolized from CHO. Furthermore, insulin secretion can also be measured fairly easily.

Therefore, if the relationship between the newly proposed energy values and measured insulin secretion is more consistent than the relationship for historically calculated energy values, we know that the new method is preferable to the historical one.

From equation (3) in reference [3] the following equation is given for the metabolized energy (E_{Metab}) from a CHO :

$$E_{Metab} = \frac{Vol.e}{120} \int_{t_0 = start\ of\ meal}^{t = t_0 + 120\ \min} BG(t)dt = f_{CHO}\eta_{CHO}m_{CHO}k_{CHO,} \qquad (1)$$

where *Vol* is the blood volume, *e* the energy value of glucose, *BG(t)* the blood glucose response, f_{CHO} the person's CHO metabolic efficiency, η_{CHO} the metabolic efficiency of the CHO, m_{CHO} the mass of the CHO and k_{CHO} the CHO energy content per mass.

For CHO there is a direct relationship[4] between blood glucose response ($\int BG(t)dt$) and insulin response ($\int BI(t)dt$). Although we acknowledge that this relationship is not perfectly linear, a linear relationship with an R^2-value of 0.963 was found through measurements by Lee and Wolever[6] using meals consisting of mostly CHO. A linear relationship is thus deemed acceptable for the purposes of this study.

The insulin / blood glucose relationship further varies from one person to the next. We describe this person specific characteristic with the insulin blood glucose factor, f_{IBS}. Let us now write the above facts in equation format using the same integration period of 120 minutes for the insulin as for the blood glucose response :

$$\int_{t_0=start\ of\ meal}^{t=t_0+120\ \min} BI(t)dt = f_{IBS}\int_{t_0=start\ of\ meal}^{t=t_0+120\ \min} BG(t)dt \qquad (2)$$

If we substitute Equation (2) into Equation (1) we find Equation (3) which describes the person specific insulin response to ingested food.

$$\frac{\int_{t_0=start\ of\ meal}^{t=t_0+120\ \min} BI(t)dt}{120} = \frac{f_{IBS}\, f_{CHO}\eta_{CHO}m_{CHO}k_{CHO}}{Vol.e} \qquad (3)$$

Let us further simplify Equation (3). If we substitute Equation (3) from reference [2], namely $ets_{CHO} = \frac{\eta_{CHO}}{\eta_{Sugar}}\ \frac{m_{CHO}}{5}$ and $\eta_{Sugar} = 0{,}65$ from reference [3] into Equation (3) above and substitute the term **A**rea **U**nder the **C**urve for **I**nsulin (*AUCI*) for the integral, we find

$$\frac{\int_{t_0=start\ of\ meal}^{t=t_0+120\ \min} BI(t)dt}{120} = \frac{AUCI}{120} = \frac{f_{IBS}\, f_{CHO}k_{CHO}\eta_{CHO}m_{CHO}}{Vol.e} = \frac{f_{IBS}\, f_{CHO}k_{CHO}}{Vol.e}3{,}25\, ets \qquad (4)$$

By defining a new person specific factor, f_{AUCI}, we can further simplify Equation (4) to the following:

$$AUCI = f_{AUCI}\, ets, \qquad (5)$$

where $f_{AUCI} = \frac{3{,}25\, f_{IBS}\, f_{CHO}k_{CHO}120}{Vol.e}$ (6)

Equation (5) now yields the relationship between measured insulin response (*AUCI*) and the newly calculated blood glucose energy metabolized from ingested CHO represented by *ets*.

The relationship between insulin secretion and the historically calculated metabolized energy can be derived in a similar fashion and is given by equation (7)

$$AUCI = f\ m_{CHO}, \qquad (7)$$

where m_{CHO} is the mass of the CHO ingested in [g].

In this study we compare the quality of relationships given by the new equation (5) and the old equation (7) using measurements by Lee, Wolever and Bolognesi[5,6]. The average R^2 and its standard deviation for 15 test subjects for the new ets equation (5) are $R^2 = 0.807$; S = 10% and for the old equation (7) are $R^2 = 0.562$; S = 32%. Figure 1 gives typical results for one test subject. ets (equation (5)) gives a $R^2 = 0.929$ and the conventional method in equation (7) a $R^2 = 0.602$. It is clear that the new equation (5) gives a better approximation of metabolized blood glucose energy that the historical equation (7) when applied to humans.

Edward H Mathews

Contracted to North West University[+], PO Box 2157 Faerie Glen 0043 RSA and consultants* to Human-Sim (Pty) Ltd. E-mail: ehmathews@human-sim.com

Mathews, E.H., Are historical ideas on energy from carbohydrates wrong?, (Letter to Nature) presented for publication.

Mathews, E.H., A more correct way of estimating available energy from carbohydrates, (Letter to Nature) presented for publication.

Mathews, E.H., How to find the correct metabolic efficiency of carbohydrates, (Letter to Nature) presented for publication.

Giugliano, M., Bove, M. & Grattarola, M. Insulin release at the molecular level: metabolic-electrophysiological modelling of the pancreatic beta-cells. IEEE Trans. Biomed. Eng. ***47****, 611-623 (2000).*

Lee, B. M. & Wolever, T. M. S. Effects of glucose, sucrose and fructose on plasma glucose and insulin responses in normal human: comparison with white bread. Eur. J. Clin. Nutr. ***52****, 924-928 (1998).*

Wolever, T. M. S. & Bolognesi C. Source and amount of carbohydrate affect postprandial glucose and insulin in normal subjects. J. Nutr. ***126****, 2798-2806 (1996).*

Wolever, T. M. S. The Glycemic Index: Flogging a dead horse?. Diabetes Care ***20****, 452-456 (1997).*

Figure 1 : *Comparison between results for equation (5) (ets) and equation (7) (mass of CHO).*