(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
11 June 2009 (11.06.2009)

(10) International Publication Number
WO 2009/072082 A1

(51) **International Patent Classification:**
A61M 5/172 **(2006.01)**

(21) **International Application Number:**
PCT/IB2008/055112

(22) International Filing Date:
5 December 2008 (05.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2007/10634 6 December 2007 (06.12.2007) ZA

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, **BR,** BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, **HR,** HU, **ID,** IL, IN, IS, **JP,** KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, **DK,** EE, ES, FI, FR, GB, GR, **HR,** HU, IE, **IS, IT,** LT, LU, LV, MC, MT, NL, NO, PL, PT, **RO,** SE, **SI,** SK, TR), OAPI (BF, **BJ,** CF, CG, CI, CM, GA, GN, GQ, GW, ML, **MR,** NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to the identity of the inventor (Rule 4.17(i))*
— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) Title: AN INSTALLATION AND METHOD FOR THE TREATMENT OF CANCER

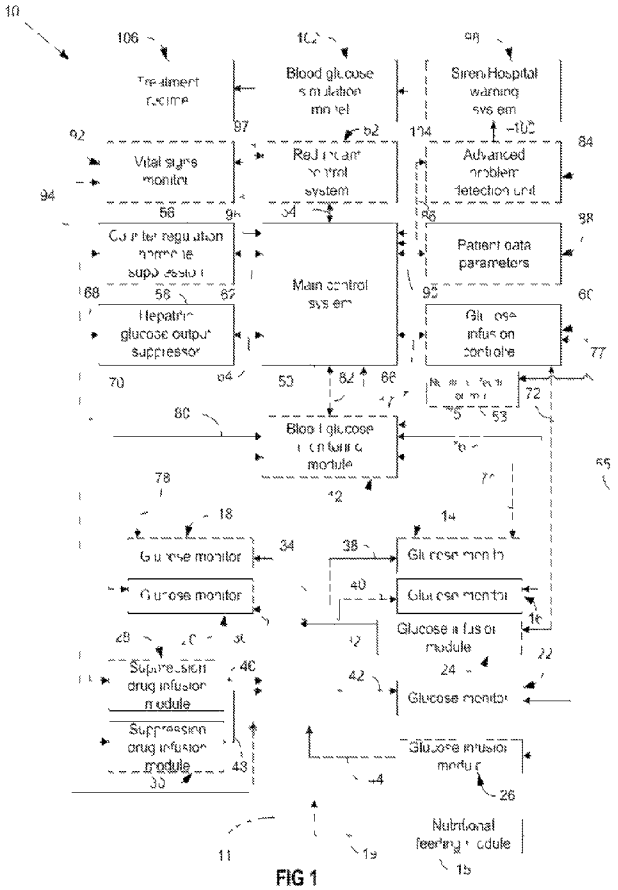

FIG 1

(57) Abstract: An installation for the treatment of cancer in a patient, the installation includes a first parenteral administration assembly for parenteral administration of glucose into a first part of the bloodstream of the patient, which part is flowing to the brain of the patient, shortly before the first part of the bloodstream reaches the brain, a first glucose monitoring assembly for monitoring the glucose level of the first part of the bloodstream after parenteral administration of the glucose, and a optionally a second part of the bloodstream, which part is flowing from the brain, a second parenteral administration assembly for parenteral administration of glucose into a third part of the bloodstream of the patient, a second glucose monitoring assembly for monitoring the glucose level in a fourth part of the bloodstream of the patient.

WO 2009/072082 A1

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

AN INSTALLATION AND METHOD FOR THE TREATMENT OF CANCER

1. FIELD OF INVENTION

THIS INVENTION relates to an installation for the treatment of cancer and to a method of treating cancer.

2. BACKGROUND

To understand this invention some background knowledge is needed. Cancer cells feed mainly on blood glucose. These fast growing cells also use much more blood glucose energy than the surrounding healthy cells. The present invention relates to a system which restricts blood glucose energy by means of primarily external glycaemic control in order to starve fast growing, highly metabolic active cancer cells.

In particular the system reduces, through correct control, the blood glucose available from feeding as well as hepatic and other counter regulation output due to : (a) stress (physiologic and/or physical) and (b) from the normal blood glucose feedback loop. As the brain is the most sensitive organ to blood glucose levels, it will be fed separately and will have a different and higher blood glucose level than the rest of the body. Both the brain and the body will be controlled to minimum acceptable levels.

As blood glucose energy from carbohydrates (CHO) was previously calculated incorrectly the relevant equations must first be derived. This is given in the equation derivation section 6 later in this specification. With the correct equations derived other factors can also be treated influencing blood glucose, namely stress (part of counter regulation) which increases blood glucose levels and thus cancer risk and exercise which decreases available blood glucose with accompanying decrease in cancer risk.

When using the new equations for calculating blood glucose energy it is seen that diet, stress and exercise (all above normal values) have a very high correlation with

cancer risk (Pearson R^2 values between 0,84 and 1,0). Higher blood glucose values raise cancer risk while a reduction in blood glucose reduces cancer risk.

This shows that control of blood glucose energy (to absolute minimum levels for healthy cells) could help with cancer treatment. Note that not all cancers have been investigated in Section 6. However, the apparatus should be effective for many cancers.

A further word of caution here. It is not believed that blood glucose is the primary cause of cancer - its prime role is to feed the cancer. The aim of this invention is to constrict this fuel to the tumours in a controlled manner. This should starve the fuel hungry cancer cells, but not the much less metabolic active healthy cells. *Inter alia* the following will be accounted for by the apparatus :

- The amount of blood glucose the brain needs is crucial. The brain will therefore be fed separately from the body and this feed will be closely controlled. The value for brain glucose feed is usually in the order of 20% of the total recommended daily allowance (RDA) energy for a patient. The apparatus will automatically find this value for a specific patient.

- The minimum allowable blood glucose level of 4[mmol/L] will be adhered to in the brain. As it is fed separately from the rest of the body, the blood glucose level may be reduced to far below 4[mmol/L] inside the rest of the body without adverse effect.

- One of the important elements of the cancer treatment apparatus is the control of blood glucose production in the body. The most prominent blood glucose producer is the liver which helps with counter regulation control of blood glucose in the body.

The initial focus will thus be to control the blood glucose (hepatic) release from the liver through pharmaceuticals and other chemicals. (This invention also foresees control of other glucose producing organs, e.g. kidneys etc. where necessary.)

The invention also includes by-passing the liver completely to ensure full external control of the blood glucose cycle. This is similar to a heart-long machine which does external pumping and oxygenation of blood. Full external blood glucose control will ensure precise blood glucose control.

Most cancers also use insulin for allowing blood glucose into the cancer cells. As an additional help to starve the cancer cells of its blood glucose fuel, anti-insulin can be delivered directly into the major tumours via injection to interfere with the blood glucose uptake in the tumour. Surrounding healthy cells should cope as they need much less blood glucose than the cancer cells. This procedure will be less traumatic than surgery.

Enhancing insulin sensitivity should also be beneficial. With insulin sensitive healthy cells which are usually more than the cancer cells, more blood glucose can be stored there, making less available for the highly metabolic active cancer cells. Better insulin sensitivity can be achieved by exercise and insulin sensitive enhancing drugs. Although exercise should be the best it is often impractical for a patient. Therefore, the relevant drugs will be used with the apparatus.

Metastasis of cancer cells should also be addressed by the apparatus as glucose fuel starvation will also affect the fast growing cancer cells which have spread to other areas of the body. However, metastasis to the brain may still present a problem as the brain is initially kept at normal blood glucose levels.

The apparatus can also be used to administer chemicals for chemo therapy. By binding a relevant cancer fighting chemical with the correct amount of glucose and administering it after blood has gone through the brain, a better targeted and less stressful cancer fighting approach should result than at present as less of the harmful cancer fighting chemicals would reach the blood glucose metabolic active brain cells.

In this case insulin sensitivity drugs (for enhancing the body's insulin sensitivity) should not be used as it will ensure that the cancer cells which are usually more insulin sensitive will take up more of the glucose.

There is another important implication of this cancer treatment apparatus. It could lead to rediscovering old pharmaceuticals that were successful in rat clinical trials but not in human clinical trials. It is believed that one reason for the difference in outcome between the rat and human studies may be the different blood glucose fuel environments for the two studies.

Humans have more psychological stress than rats when they hear about a cancer diagnosis. They therefore release more blood glucose which already means an important difference. Other differences will also be investigated in future.

With the apparatus the human blood glucose environment can be controlled to the exact level of a rat clinical trial. The rat results should then be more applicable to humans. Furthermore, older successful rat drugs, which proved unsuccessful in humans, could again be investigated.

There may be various outcomes when using this apparatus, either fully cured or cancer under control. Current thinking is often that cancer treatment is only successful when all visible cancer tumours have been removed via surgery or chemo and radio therapy. Conventional thinking may have to change to view cancer as a treatable/controllable disease e.g. diabetes. The diabetic is not cured, but his/her condition is potentially very well controllable. Similarly, for some cancer patients follow-up hospital treatment with the apparatus or the full time wearing of a mobile version of the apparatus may be advisable.

Full and safe control via this apparatus control only became practical recently with the advent of continuous glucose monitoring (CGM) systems.

3. SUMMARY OF THE INVENTION

The Applicant is aware that cancer cells to a large extent utilise glucose as an energy source and that cancer cells use more blood glucose than surrounding healthy cells (Warburg, 1927; Holm et al., 1995; Guppy et al., 2002) This effect is *inter alia* used in Positron Emission Tomograpy (PET) scans to detect tumours (Gatenby, 1995). It is accordingly an object of the present invention to provide a method and an

installation which reduces blood glucose in an externally controlled way to starve cancer cells.

According to a first aspect of the invention, there is provided a method of treating cancer, the method including the steps of

reducing the overall level of glucose in the bloodstream of a patient having cancer so that the amount of glucose available to cancer cells causing the cancer is reduced; and

parenterally introducing glucose into that part of the bloodstream of the patient flowing to the brain of the patient shortly before that part of the bloodstream reaches the brain to raise the glucose level of that part of the bloodstream to minimum acceptable levels.

Reducing the overall level of glucose in the bloodstream of the patient may be achieved by restricting the diet of the patient to cause the glucose level of the blood to fall, by feeding the patient only intravenously with feeds containing no carbohydrates.

The parenteral introduction of glucose will preferably be by introducing a glucose solution into the arteries leading to the brain. The "overall level of glucose" refers to the glucose level in the blood stream measured in other parts of the body and this level is increased shortly before the blood stream reaches the brain so that the amount of glucose in the blood stream in the brain at minimum acceptable levels, but is higher than that in the rest of the body in order to avoid any damage to the brain which would otherwise result from the low overall level of the glucose in the blood. In this way, the glucose available to cancer cells is reduced whilst the glucose level in the blood flowing to the brain is increased to minimum acceptable levels.

The overall level of glucose in the bloodstream of the patient will preferably be reduced to between about 0,5 and 5 mmol/L. It will preferably be reduced to between about 1,0 and 4,0 mmol/L, more preferably between about 1,2 and 3,0 mmol/L and more preferably between about 1,5 and 2,5 mmol/L.

The glucose level of that part of the bloodstream flowing to the brain may be controlled at between about 1,5 and4,5 mmol/L preferably between about 2,0 and 4,0

mmol/L more preferably between about 2,5 and 3,8 mmol/L and more preferably between about 3,0 and 3,5 mmol/L.

The method of the invention requires accurate monitoring of the overall level of glucose as well as the amounts of glucose being parenterally introduced into the blood flowing to the brain. The method of the invention will generally be conducted with the patient in a semi-sedated state with intravenous feed containing no carbohydrates to allow the overall glucose level in the blood to decrease to the desired value. The method may then include administering glucose parenterally into the blood stream in a part different part of the body in order to regulate the overall blood glucose level at the desired value.

The overall glucose level of the blood may thus be maintained at the reduced level by parenterally administering glucose to the patient.

When the body is deprived of nutrition so that the glucose level in the blood drops, other mechanisms come into force to produce glucose. In particular, glucose can be produced by the liver. As a further means of maintaining the low overall blood glucose level, drugs can be administered to reduce the production of glucose in this way.

Accordingly, instead or in addition the overall level of glucose in the bloodstream may be maintained by administration to the patient of a pharmaceutical formulation which suppresses glucose production by the body of the patient.

Drugs which may be used to suppress glucose production may include but are not limited to diabetic drugs (e.g. metformin), anxiety drugs, stress drugs and even alcohol. Metformin and alcohol for example suppresses the glucose output potential of the liver while anti stress and anxiety drugs suppress the activation signals of the liver.

The method may involve measuring the glucose level of the blood of the patient in the first part of the blood stream of the patient flowing to the brain of the patient shortly after parenteral introduction of glucose, a second part of the blood stream that flow from the brain, and a third part of the blood stream remote from the first

and second parts and using the measured values to control the rate of administration of the glucose, the nutrients other than glucose and the pharmaceutical formulation.

The method may include introducing small doses of glucose combined with a radio-active compound or a chemo-therapeutic compound or substance in the second part of the blood stream that flows from the brain. This will allow the glucose-radioactive compound or the glucose-chemo therapeutic compound to treat cancer cells within the body by providing, in a prioritised manner, glucose for cancer metabalisation by delivering the glucose-radioactive compound or glucose-chemo therapeutic compound to cancer targets in the body while simultaneously reducing the exposure of the brain to this potentially hazardous material by rapid absorption of the glucose by cancerous cells before reaching the brain.

The method may include maintaining the overall glucose level of the blood in the patient by parenterally administering nutrients other than glucose to the patient. These nutrients may be proteins, fats or micro-nutrients.

According to a second aspect of the invention there is provided an installation or assembly for the treatment of cancer in a patient, the installation or assembly including

a first parenteral administration assembly for parenteral administration of glucose into a first part of the bloodstream of the patient, which part is flowing to the brain of the patient, shortly before the first part of the bloodstream reaches the brain;

a first glucose monitoring assembly for monitoring the glucose level of the first part of the bloodstream after parenteral administration of the glucose, and optionally a second part of the bloodstream, which part is flowing from the brain;

a second parenteral administration assembly for parenteral administration of glucose into a third part of the bloodstream of the patient; and

a second glucose monitoring assembly for monitoring the glucose level in a fourth part of the bloodstream of the patient remote from the first and second parts.

The parenteral administration assemblies may include hypodermic needles, catheters or the like which are linked to reservoirs for infusion of glucose containing

solutions. The glucose monitoring assemblies may be Continuous Glucose Monitoring (CGM) systems of the type supplied by Medtronic or other manufacturers.

The installation or assembly may include one or more further parenteral administration assemblies for the administration of stress and anxiety relieving drugs, and drugs for controlling hepatic glucose production.

The installation or assembly may thus include one or more additional parenteral administration assemblies for parenteral administration of substances for controlling hepatic glucose production. The parenteral administration assemblies and the glucose monitoring assemblies may be linked to a central or main control system which monitors the glucose levels and controls the rate of parenteral administration of glucose and drugs.

The installation or assembly may thus include a control system, linked to the parenteral administration assemblies and the glucose monitoring assemblies and operable to regulate the rate of administration of the glucose and the substances for controlling hepatic glucose production in response to the glucose levels detected by then glucose monitoring assemblies.

The installation may introduce small dosages of glucose treated with a radio active compound in the veins shortly following the brain to treat cancer cells within the body by providing in a prioritised manner glucose for cancer metabolisation therefore delivering the treated glucose to cancer targets requiring more glucose than other non-cancerous cells within the body while simultaneously reducing the distribution of the potentially hazardous treated glucose from being metabolised by the brain as glucose is rapidly absorbed by cancerous cells before reaching the brain.

The main control system accordingly firstly controls blood glucose levels, especially the level of glucose in the blood stream feeding the brain, by regulating the amount of glucose administered by the first parenteral administration assembly. The main control system secondly regulates the rate of infusion of stress suppressor drugs either to reduce the effect of stress hormones on hepatic glucose output or to suppress signalling caused by stress that triggers the increase in hepatic glucose and, thirdly, the

main control system regulates the rate of hepatic glucose output by means of drug administration or other viable means.

Blood glucose levels are accordingly measured in different locations, by using blood glucose monitors, to accurately determine the glucose available to cells in the blood and the glucose concentration of the blood feeding the brain. The main control system may comprise a set of interlinked computer based control devices or systems which determine the correct infusion rate of glucose to the brain, regulate the glucose infusion modules, and simultaneously restrict glucose levels to an absolute minimum level in order to sustain the life of the patient.

In the method of the invention, glucose is fed through the arteries immediately prior to the brain so that the brain will have access to the correct amount of glucose. The brain will then have sufficient glucose while the remainder of the cells in the body will be blood glucose starved. As glucose is the primary source of energy for cancer cells, and since cancer cells grow aggressively and required much more glucose energy that non-malignant cells, the low glucose level will affect cancer cells more severely than non-malignant cells.

The amount of blood glucose the brain needs is crucial and is carefully monitored in the method of the invention. This value is usually of the order of 20% of the recommended daily energy allowance (RDA) for a patient. The installation of the invention automatically finds this value for a specific patient after entering certain user specific parameters including but not limited to body weigh, height, gender, carbohydrate sensitivity etc.

Generally the overall minimum allowable blood glucose level will be about 4mmol/L but because glucose is administered to the brain, the overall blood glucose level can be reduced to well below 4mmol/L in the rest of the body without adverse effect. The control of glucose levels is carried out using a continuous glucose monitoring (CGM) system.

One of the important elements of the cancer treatment method and apparatus of the invention is the control of blood glucose production in the body. The most important

producer of glucose is the liver. The invention accordingly controls blood glucose (hepatic) release from the liver by administering appropriate pharmaceutical compositions or compounds. Other glucose producing organs, such as the kidneys can also be controlled in this way. The invention also makes it possible to control blood glucose by by-passing the liver completely as used in heart-long machines to ensure precise control of blood glucose.

Most cancers also use insulin for allowing blood glucose into the cancer cells. As an additional measure to starve cancer cells of blood glucose fuel, the invention provides for anti-insulin to be delivered directly into major tumours via injection to interfere with the blood glucose uptake in the tumour. This procedure will be less traumatic than surgery. The invention also addresses the problem of metastasis of cancer cells as glucose fuel starvation will also affect the fast growing cancer cells which have spread to other areas of the body.

According to a third aspect of the invention there is provided an apparatus for the treatment of cancer in a patient, the apparatus including

a first parenteral administration assembly for parenteral administration of glucose into a first part of the bloodstream of the patient, which part is flowing to the brain of the patient, shortly before the first part of the bloodstream reaches the brain;

a first glucose monitoring assembly for monitoring the glucose level of the first part of the bloodstream after parenteral administration of the glucose, and optionally a second part of the bloodstream, which part is flowing from the brain;

a second parenteral administration assembly for parenteral administration of glucose into a third part of the bloodstream of the patient; and

a second glucose monitoring assembly for monitoring the glucose level in a fourth part of the bloodstream of the patient remote from the first and second parts.

The parenteral administration assemblies may include hypodermic needles, catheters or the like which are linked to reservoirs for infusion of glucose containing solutions. The glucose monitoring assemblies may be Continuous Glucose Monitoring Systems (CGMS).

The apparatus may include one or more further parenteral administration assemblies for the administration of stress relieving drugs, and drugs for controlling hepatic glucose production and insulin sensitising drugs.

The apparatus may thus include one or more additional parenteral administration assemblies for parenteral administration of substances for controlling hepatic glucose production and insulin sensitising substances. The parenteral administration assemblies and the glucose monitoring assemblies may be linked to a central or main control system which monitors the glucose levels and controls the rate of parenteral administration of glucose and drugs.

The invention extends to a wearable treatment apparatus which can be worn by a patient, the treatment apparatus comprising an assembly including

a first parenteral administration assembly for parenteral administration of glucose into a first part of the bloodstream of the patient, which part is flowing to the brain of the patient, shortly before the first part of the bloodstream reaches the brain;

a first glucose monitoring assembly for monitoring the glucose level of the first part of the bloodstream after parenteral administration of the glucose, and optionally a second part of the bloodstream, which part is flowing from the brain;

a second parenteral administration assembly for parenteral administration of glucose into a third part of the bloodstream of the patient;

a second glucose monitoring assembly for monitoring the glucose level in a fourth part of the bloodstream of the patient remote from the first and second parts; and

an attachment arrangement for attaching the apparatus to the body of the patient.

The attachment arrangement may be a harness or the like.

DESCRIPTION OF PRIOR ART

The applicant is aware of the following patents:

- *USPTO Patent 6,815,433: COMPOSITION AND METHOD FOR THE TREATMENT OF DYSGLUCAEMIA:* This patent deals with glycaemic control through granulated corn starch administration.

- *USPTO Patent 6,703,045: COMPOSITION AND METHOD FOR MAINTAINING BLOOD GLUCOSE LEVEL:* This patent deals with glycaemic control through an oral controlled release system releasing a mixture comprising of several chemicals. It entails taking a mixture of chemicals that includes an insulin sensitivity agent.
- *WIPO Patent WO/2006/108008: A METHOD AND COMPOSITION FOR NUTRITIONALLY IMPROVING GLUCOSE CONTROL AND INSULIN ACTION:* This patent deals with glycaemic control through use of a nutritional formulation having a carbohydrate:fat:protein ratio of about 1 :1 :1.
- *WIPO Patent WO/2005/020983: COMBINATION THERAPY FOR GLYCAEMIC CONTROL:* This patent deals with glycaemic control through administration of an antidiabetic agent such as thiazolidine or pyrrolidine.

In summary: No current patent could be found which feeds and controls the brain's blood glucose need separately from the rest of the body. No current patent could be found which attempts to control the full blood glucose cycle to minimise blood glucose levels inside the body (while keeping the brain at normal levels). No patent uses a combination of drugs to suppress hormone signalling to Blood Glucose Producers (BGP) inside the body (e.g. the liver) in conjunction with drugs to suppress BGP action, in conjunction with insulin sensitizing drugs. No patent infuses chemo drugs (bound to glucose) after the brain has been fed.

5. DESCRIPTION OF DRAWINGS AND EXAMPLE EMBODIMENT

The invention is now described, by way of example with reference to the following Examples and Figures, in which

Figure 1 is a block diagram of an installation in accordance with the invention;

Figure 2 shows the relationship between mass loss and "isocloric" kcal ingested for nine different food types (kcal calculated in the conventional way);

Figure 3 shows the relationship between mass loss and ETS cal;

Figure 4 shows the relationships between daily ETS consumption and (a) the relative risk of four different cancers as well as (b) the average of the four;

Figure 5 shows the relationships between (a) fibre intake and relative risk for two cancers and (b) the average graph for the two expressed in ETS/day;

Figure 6 shows the relationship between daily exercise and (a) relative risk for four cancers and (b) the average graph for the four;

Figure 7 shows the correlation between metabolised carbohydrate energy in ETS and the risk for CHD;

Figure 8 shows the relationship between stressful life events (long-term) and breast cancer risk;

Figure 9 shows the combined effect of the average of all blood glucose contributors (in ETS) to cancer risk (for food using Δ ETS/day above 30 ETS and using for additional fibre Δ ETS/day above 4 ETS);

Figure 10 shows the relationship between stress level, CHD relative risk (RR) cancer RR and ETS secretion due to stress;

Figure 11 shows a simplified schematic layout of the major energy pathways in the human energy system; A=Absorptive Phase, B=Burning (Fasting) Phase. A and B are not mutually exclusive processes but occur simultaneously with dominance of one over the other indicated by the status letter; when both are indicated in a single text frame, the process is continuous, irrespective of the phase status;

Figure 12 shows a simplified schematic layout of the blood sugar control system in the human energy system, in which A=Adrenalin, C= Cortisol, G= Glucagon, Gh= Growth Hormone, I= Insulin, T= Thyroid Hormone, GIP= Glucose Dependent Insulinotropic Peptide, Bs=BIoOd Sugar (+ or -) and the dotted lines represent Nervous Controls .....Bio-chemical Controls _____ Nervous Measure & Control.....Bio-chemical Measure & Control ..... Blood Sugar Flow _____ ;

Figure 13 shows the relationship between stress level, CHD relative risk (RR) cancer RR and ETS secretion due to stress;

Referring to Figure 1, reference numeral 10 is a schematic diagram of an installation in accordance with the invention for the treatment of cancer in a patient 11. The installation 10 includes a blood glucose monitoring module 12 which is able to rapidly monitor glucose levels in the blood of the patient 11 which is linked to a proposed five glucose monitors 14, 16, 18, 20 and 22. The installation 10 further includes glucose infusion modules 24 and 26 and two suppressor drug infusion

modules 28 and 30. The installation 10 further includes a nutritional feeding infusion module 15.

The main function of the blood glucose monitoring module 12 is to communicate measured blood glucose values to the main control system 50 while continually checking for possible inaccuracies in measurements. This is done by using dual blood glucose monitors e.g. 18 and 20 to measure blood glucose values in close proximity. Blood glucose values are communicated as digital data via communication channels (e.g. wire or wireless communication e.g. 80, 78) between the blood glucose monitors and the blood glucose monitors monitoring module. If any two measured blood glucose readings measured in close proximity are more than marginally different, this will be reported to the main control system 50 as a possible error. It is proposed that the data validation be implemented as a software module receiving digital or analog blood glucose measurements and communicating the validated data or error signalling to the main control system 50 via a communication bus, whether via wires or wirelessly. The algorithm will be executed by an internal processing unit or may share processing power and memory with the main control system 50. The blood glucose monitors monitoring module is customisable to accommodate different continuous blood glucose measuring devices and therefore a translatory interface is included to translate signals received from a specific type of blood glucose monitor to a generalised data format that the blood glucose monitors monitoring module is able to interpret. Furthermore, the monitoring module 12 is also customisable to utilise only a single blood glucose monitor per measuring point in the case where the reliability and accuracy of the blood glucose monitor is deemed to be acceptable for the type of installation. The monitoring module 12 therefore consists of an array of dual blood glucose monitors measuring the blood glucose levels in different locations. The blood glucose monitoring module receives power from a centralised location or may be implemented to use battery power. For safety reasons, the individual blood glucose monitors are electrically isolated (e.g. optical or wireless communication) from the rest of the system and therefore the blood glucose monitors will be powered with their own battery power supplies.

The glucose infusion modules 24, 26 and the suppressor drug infusion modules 28, 30 are standard installations of the type used for intravenous infusion of drugs or the like. The modules receive input signals consisting of mainly infusion rates

from various modules such as the glucose infusion controller 60, the hepatic glucose output suppressor 58 and the counter regulation hormone suppressor 56. The main control system calculates in real-time the required infusion rates and communicates these values via the communication bus which can either wired or wirelessly to the different controllers 60, 56 and 58. Each controller is customisable for accommodating different types of infusion equipment from different manufacturers. Therefore a translationary interface is included to communicate infusion rate signals to each infusion module e.g. 26, 28 and 30. Similar to the blood glucose monitors monitoring module 12, these controllers 56, 58 and 60 may share power, processing power and memory storage with the main control system or be implemented as a separate modular unit. Communication between the infusion modules and the controllers can be either wirelessly or wired and is indicated by illustration by 68, 70 and 109 .

In use, the glucose infusion module 24 supplies glucose to the arteries leading to the brain of the patient 11 as shown by the arrow 32. In this embodiment of the invention the glucose monitors 18 and 20 function independently, the one serving as a back-up for the other while also providing two measurements per measurement point to validate data accuracy, and, in use, measure glucose in the arteries leading to the brain after infusion of glucose by the infusion module 24 (shown by the arrows 34, 36). The glucose monitors 14 and 16 are also independent monitors which, in use, measure the glucose level in the main veins leaving the brain as shown by the arrows 38, 40. The glucose monitor 22 monitors the overall glucose level in the body of the patient as shown by the arrow 42. The glucose infusion module 26 and the two suppressor drug infusion modules 28 and 30 provides glucose and one or more suppressor drugs as shown by the arrows 44, 46 and 48. The nutritional feeding module 15 feeds nutritional such as proteins, fats and micronutrients but not carbohydrates to the patient 11 as shown by the arrow 19.

All of the modules or assemblies described above are linked directly or indirectly to a central or main control system 50 which, in turn, is linked to a redundant control system 52 as shown by the arrow 54. The main control system 50 is also linked to a nutritional feeding controller 53 as shown by the arrow 17, a counter regulation hormone suppressor 56, a hepatic glucose output suppressor 58 and a glucose infusion controller 60, as shown by the arrows 62, 64, 66. The counter regulation hormone

suppressor 56, the hepatic glucose output suppressor 58 and the glucose infusion controller 60 are also linked to the suppressor drug infusion modules 30 and 28 and the glucose infusion module 24 as shown by the arrows 68, 70, 72. The blood glucose monitoring module 12 is linked to the glucose monitors 14, 16, 18, 20 as shown by the lines 74, 76, 78, 80. It is proposed that these monitors be electrically isolated from the monitoring module 12 to ensure the safety of the patient by preventing any leakage current from entering the body of the patient. The main control system 50 is also linked to the blood glucose monitoring module 12 as shown by the arrow 82. The nutritional feeding controller is shown by the arrow 55.

The main control system is implemented on a reliable computer system comprising of an input means (e.g. keyboard or keypad and pointing device), permanent storage means (e.g. hard disk drive), volatile memory, processing means (e.g. central processing unit), communication busses and interfaces, output means (e.g. monitor, speaker and printing device). The input device is used to enter patient specific data 88 into the main control system that stores this information for later use. Furthermore, a computer software program is proposed to present the treatment provider with various options and adjustable treatment parameters in order to select a suitable treatment regime 106 for the specific patient. The redundant control system 52 is of similar composition and serves as a backup safety system to ensure the system can proceed with its functions if the main control system's hardware fail. Both the main control system 50 and the redundant control system 52 are implemented on independent hardware systems able of communicating with each others' hardware and secondly able of communicating with all connected hardware (e.g. sensors etc.) via means of wired or wireless communication.

The installation 10 further includes a problem detection unit 84 which is linked to the main control system as shown by the arrow 86. Patient data parameters, as shown schematically by the block 88, are fed to the main control system 50 as shown by the arrow 90. The installation 10 further includes vital signs monitoring devices of the usual type found in hospitals, as shown schematically by the block 92, for monitoring the vital signs of the patient 11 as shown by the arrow 94. The vital signs monitoring devices 92 are also linked to the main control system 50 as shown by the

arrow 96. The problem detection unit 84 is linked to a siren or warning system 98 as shown by the arrow 100.

The problem detection unit 84 is implemented as a software module sharing processing and storage resources with the main control system. The main control system reports any data validation errors, communication errors and internal system errors to the main problem detection unit 84. This unit 84 then signals an appropriate response that may include: generating an audible alarm on the siren or hospital warning system 98. The main objective of unit 84 is to attract immediate attention of a person responsible for caring for the patient in treatment. The siren or hospital warning system 98 receives an input signal via a communication medium from the problem detection unit 84. This unit 98 is customisable to generate various different types of alarms including audible siren, visible flashing lights or transmitting a communication signal to the hospital's or facilities warning system.

The installation 10 further includes a blood glucose simulation module 102 which is linked to the main control 50 as shown by the arrow 104. The blood glucose simulation model is included to predict the effect of a certain adjustment in infusion rates for the specific patient with specific patient data parameters 88. The main control system can therefore calculate the desired infusion rates of the glucose infusion module 32 to maintain the blood glucose levels at the different control areas at their desired blood glucose control setpoints specified by the patient treatment regime 106. A specific blood glucose simulation model is not specified as there are numerous different blood glucose simulation models available. The ETS blood glucose simulation model may be used but will not be discussed in extensive detail in this patent specification.

The installation 10 further includes a treatment regime program, shown schematically by the block 106, which forms part of the main control system 50. The input means provided for the implementation of the main control system is used to customise a patient specific treatment regime for the specific patient. The parameters for the patient specific treatment regime 106 include but are not limited to: time profiles specifying the blood glucose control setpoints for different locations at different times, nutritional feeding rate (e.g. macro and micronutrients), the types of counter regulation hormone

suppressor drugs, hepatic glucose output suppressor drugs and intravenous nutrition to be administered.

In use, the patient 11 will be kept in a semi-sedated and fasting state so that the blood glucose levels in the blood of the patient are lowered and kept at an absolute minimal level to sustain life by controlled administration of glucose via the glucose infusion module 24, reducing the hepatic glucose output and reducing the blood glucose counter regulation by administration of drugs and hormones such as metformin as well as anti stress and anti anxiety drugs.

All of the various modules are accordingly controlled by the main control system 50 and executed via software and externally linked hardware.

To provide redundancy and increase the safety of the system 10, the redundant or backup control system 52 monitors the main control system 50 hardware and is able to communicate, monitor and control all externally linked hardware modules that are linked to the main control system 50.

If the main control system 50 malfunctions, the redundant control system 52 will detect this, and immediately take over control. When this happens, the advanced problem detection unit 84 will detect the crossover action and signal an alarm and also generate an error report to be displayed to the operator of the system.

The main control system 50 uses the feedback from the blood glucose monitoring module 12 in conjunction with the treatment regime 106 program and the patient data parameters 88 to customize the treatment regime for the patient 11. It thus determines an appropriate amount (if any) of glucose to be administered to the patient 11 by the glucose infusion controllers 60 link to the external glucose infusion module 16 that supplies the two arteries leading to the brain. The infusion rate for each artery may differ.

Furthermore, as the rest of the body's blood glucose level is kept at a different level as the brain, the glucose infusion controller 60 communicates the appropriate glucose infusion rate to the secondary glucose infusion module 26. The main control system

measures the blood glucose values in real time measured by the glucose monitors and communicated and validated via the blood glucose monitors monitoring module and compares these values with the desired different glucose setpoints as specified in the patient treatment regime 106 and then uses a digital control algorithm to calculate the rate of glucose infusion.

The blood glucose simulation module 102 is also used to calculate the appropriate infusion rates by taking the historically measured glucose values and infusion rates into account. Furthermore, the main control system 50 also calculates the infusion rates of the counter regulation hormone suppressor drug, hepatic glucose output suppressor drug and the nutritional feeding and communicates these respective infusion rates to the counter regulation hormone suppressor 56, hepatic glucose output suppressor 58 and the nutritional feeding controller 107.

These controllers then translates the infusion rates to their respectively controlled infusion modules which infuses the desired rate of chemical formulation. Provision is made for backward propagating communication in order for the infusion modules to communicate information such as reservoir levels that are low or any malfunctions back to their respective controllers, which in turn communicates this to the main control system and then activates or is recognized by the problem detection unit 84.

The hepatic glucose output suppressor module 58 also uses the blood glucose levels and treatment regime program 106 to determine the rate of suppressive drug or hormone administration by the external suppressor drug infusion module 28. The counter regulation hormone suppressor module 56 also uses the blood glucose levels and treatment regime program 106 to determine the rate of suppressive drug or hormone administration by the external suppressor drug infusion module 30.

To ensure safety, the main control system 50 is complemented by a redundant control system 52 capable of taking over control from the main control system 50. The problem detection unit 84 constantly monitors the vital signs monitored by the external vital signs monitor 92. The vital signs include the various blood concentration levels in the patient's body. Safe ranges for all measured quantities are

defined in the treatment regime module 106 and the patient data parameters 88. Algorithms can be defined in the problem detection unit 84 to predict the responses of the various vital signs and measurements, thereby allowing early detection of any responses.

In the method of the invention, blood glucose levels are measured at a high frequency of at least one measurement every few minutes. Direct blood glucose measurements in the blood are preferred to measurements in other tissue, therefore reducing the lag time of measurements. The blood glucose measuring equipment does not form part of this invention's specification but utilises external measuring equipment to measure glucose levels.

Blood glucose measurements should be both accurate and precise. It is therefore preferably that two or even three independent glucose-monitoring units per measuring location be used for example 14, 16 and 18, 20 to perform glucose measurements in the same locale and then comparing the results to ensure accuracy of measurements. Blood glucose is measured in the two main arteries feeding the brain by the two independent blood glucose monitors 18, 20 to ensure accuracy and precision. The blood glucose level in the main veins leaving the brain is also measured by the two independent blood glucose monitors 14, 16.

This allows the determination of the rate of glucose energy expenditure of the brain and also ensures that the patient's brain is supplied with the minimum energy for its basal energy requirements. Blood glucose is also measured by glucose monitor 22 at a different location to provide additional information about the blood glucose levels outside the brain.

Because the installation 10 reduces and controls glucose levels in the blood at low levels, this poses an inherent risk for hypoglycaemia to the cancer patient. Accordingly adequate glucose supplies are essential for brain functioning. In this regard the brain has been called selfish in the sense that it will take all the glucose it needs from the blood irrespective of the other cells in the body's energy needs, but glucose supply to the brain cannot be reduced below the energy levels required for normal brain functioning.

The amount required is usually close to 20% of the patient's RDA energy or just above the equivalent energy in 1 ETS/h. However, the precise percentage for a patient need not be known beforehand as the apparatus will automatically increase or reduce glucose infusion via the module 24 to ensure the correct blood glucose level in the arteries and veins of the brain.

The glucose infusion rates for each artery are calculated by the main control system 50 in conjunction with the treatment regime module 106 and the patient data parameters 88 while taking the current blood glucose levels measured by the glucose monitors 14, 16, 18, 20.

The glucose monitor 22 monitors the glucose level in the rest of the body. The rate of glucose infusion by the glucose infusion model 22 for the rest of the body excluding the brain (if necessary) is calculated by the main control system 50 using the parameters 88 and the treatment regime 106.

As described above, the liver helps the body to achieve blood glucose equilibrium. When blood glucose levels fall too low, counter regulation hormones signal the liver to increase the hepatic glucose output. Figure 12 shows the signalling hormones influencing blood sugar levels while Figure 11 shows the conversion of blood glucose in the human body. Carbohydrates from meals are digested and absorbed into the blood as glucose. This excess glucose is then stored *inter alia* in the liver as glycogen as a result of the hormone insulin being secreted by the pancreas or administered by the diabetic patient.

Gradually throughout the day, glycogen is converted and released as glucose in the blood. This glucose provides energy especially to the brain, but to a lesser extent also to the cells of the body. Blood glucose is released from the liver in response to several counter regulation hormones such as glucagon, Cortisol, adrenalin and the like. The method of the invention suppresses normal hepatic glucose production.

Glucose output is also increased during periods of stress or illness when more stress hormones such as Cortisol is secreted and also especially when the brain

becomes energy starved, requiring more glucose for energy. There are several drugs which can be used to suppress or reduce hepatic glucose output. These drugs form part of a group of diabetic drugs that interact in different ways to reduce glucose output by the liver (e.g. Metformin). For many diabetics this is an effective way of reducing blood glucose levels. Alcohol also suppresses the liver output. Hepatic glucose output is thus a mechanism responsible for increasing blood glucose levels.

The invention reduces the hepatic glucose output by means of precisely controlled drug administration and finely controlling the glucose levels of the patient 11 at different locations using glucose infusion modules. The main control system 50 is responsible for calculating the rate of administration of the hepatic glucose suppression drug (HGSD) using the treatment regime 106, the blood glucose levels reported by the blood glucose monitoring module 12, patient data parameters 88 and the counter regulation hormone suppressor 56.

The hepatic glucose output suppressor module 58 communicates the desired rate of HGSD infusion to the suppressor drug infusion module 28. This in return infuses the HGSD at the required rate communicated by the hepatic glucose output suppressor module 58. The infusion module 28 is also able to communicate with the hepatic glucose output suppressor 58. HGSD infusion rate data is logged against time. The HGSD infusion module 28 uses historic infusion rate data in conjunction with the signalling of the main control system 50 to calculate an optimum dosage and infusion rate of HGSD for the specific patient at that moment.

Any problem encountered by these modules such as low levels of HGSD in the reservoir, communication problems between the units or the like will be detected by the problem detection unit 84 via the main control system 50. A warning signal will then be generated by the problem detection unit 84 and an alarm triggered by the siren / hospital warning system module 98.

The body's glucose control system uses several signalling hormones to signal glucose producers in the body (e.g. liver, kidneys etc.) to produce glucose. For example, stress results in the secretion of several stress hormones such as Cortisol, adrenalin etc. These hormones are all classified as blood glucose counter regulation

hormones. Although the rate of their actions differs, they all increase the blood glucose output especially from the liver. The different stages of hypoglycaemia also result in the secretion of these hormones. As the main goal of the invention is to reduce sources of blood glucose and control blood glucose using external sources, the invention controls the action of these hormones.

The invention uses drugs (e.g. anti-stress and anti-anxiety drugs) to suppress or reduce either the signalling, secretion or end-effect of blood glucose counter regulation hormones. A combination of a multitude of drugs may be used to achieve the desired effect. These drugs are collectively called hormone activated blood glucose counter regulation suppression drugs (CRSD).

The installation 10 of the invention reduces the hepatic glucose output by precisely controlled drug administration (CRSD) and then finely controlling the glucose levels of the patient 11 at different locations using the glucose infusion module 26. The main control system 50 is responsible for calculating the rate of the hormone activated blood glucose counter regulation suppression drugs (CRSDs). This is done by taking the treatment regime 106, the blood glucose levels reported by the blood glucose monitoring module 12, patient data parameters 88 and also the hepatic glucose output suppressor 58 into account.

The counter regulation hormone suppressor module 56 communicates the desired rate of the different CRSDs' infusion to the suppressor drug infusion module 30. This unit in return infuses the different CRSDs at the required rate communicated by the counter regulation hormone suppressor 56. Furthermore the infusion module 30 is also able to communicate to the counter regulation hormone suppressor module 56. The counter regulation hormone suppressor module 56 works in conjunction with the main control system 50. CRSDs' infusion rates data are logged against time. The CRSDs' infusion control system uses historic infusion rate data in conjunction with the signalling of the main control system 50 to calculate an optimum dosage and infusion rates of the different CRSDs for the specific patient 11 at that moment.

Any problem encountered by these modules such as low levels of the different CRSDs in the reservoir, communication problems between the units will be

detected by the problem detection unit 84 via the main control system 50. A warning signal will then be generated by the problem detection unit 84 and an alarm triggered interfaced by the siren / hospital warning system module 98.

The vital signs monitor 92 constantly monitors the patient's vital signs while the problem detection unit 84 also monitors all hardware, software and signals received from all units for potential safety problems. The increased redundancy will help to eliminate the occurrence of any adverse events.

Furthermore, although the hepatic glucose output of the liver is being suppressed, the blood glucose control is being controlled externally by the glucose infusion controllers 60 and the glucose infusion modules 24, 26 preventing the blood glucose level from falling too low, thereby preventing hypoglycaemia, especially in the brain and to a lesser extent in the body. The hepatic glucose output may be eliminated by means of temporary medical procedure to completely intercept all glucose discharge from the liver preventing it from entering the blood stream. This will make the control of blood glucose levels at a very low level more consistent.

6. DERIVATION OF EQUATIONS FOR LINK BETWEEN BLOOD GLUCOSE AND CANCER

Cancer cells prefer blood glucose as an energy source. Factors which increase or decrease the blood glucose concentration also increase or decrease the risk for cancer. The blood glucose effect on various forms of cancer of food, exercise, stress and of fibre intake is thus investigated here.

To express the influence of all four factors, a common unit for blood glucose effect had to be developed. It was called equivalent teaspoon sugar (ETS). Another reason for developing this unit is that previous energy calculations for carbohydrates (source of blood glucose) are shown to be incorrect. Furthermore, a teaspoon of sugar is easy to visualize and to understand.

The glucose hypothesis was tested using data from the clinical trials of others. The Pearson R^2 values for the analysed data of 11 studies varied between a very high 0,84 and a perfect 1,0.

Previously the links between cancer and food, exercise, stress as well as fibre were shown. However, various different reasons for the link mechanisms were given. Here we give one consistent theory leading to consistent results to quantify the effects of the four factors on various cancers.

The unifying effect is blood glucose energy which is for the first time calculated correctly with the new ETS equation. This correct calculation now leads to a better insight which makes possible control of various cancers more obvious. Control of cancer via blood glucose control is the focus of this invention.

A. Introduction

Cancer is a condition where normal cells become malignant, requiring vast amounts of energy to sustain their increased growth rate. Cancer cells usually prefer glucose as an energy source (Warburg, 1927; Holm et al., 1995; Guppy et al., 2002). This effect is *inter alia* used in Positron Emission Tomograpy (PET) scans to track tumours (Gatenby, 1995).

We know that various factors influence blood glucose, namely food intake, fibre intake in addition to a meal, exercise and stress. However, they are all measured in different units, e.g. for food intake we use grams of carbohydrates (CHO) and the Glycaemic Index (GI); for fibre we use grams; for exercise it is kcal expended and stress is usually reported as low, medium, high, etc.

Before we investigate the impact of these factors on cancer, we must develop a common unit to describe the blood glucose effect of all these factors. We start off by investigating food intake.

There are numerous studies linking a diet high in refined carbohydrates (CHO) to an increased risk for cancer (Franceschi et al., 1998). But why refined CHOs? Do they

metabolize more glucose energy than unrefined CHOs, thus more efficiently fuelling the cancer?

Unfortunately conventional wisdom states that all CHOs release blood sugar with energy content of 4 kcal per gram into the body. This means that the metabolized glucose energy from refined and unrefined CHOs are the same. This can thus not explain the difference in cancer risks for the two food types. But is this conventional wisdom regarding CHO energy metabolism correct? This will be investigated in more detail in the rest of this specification and then applied to cancer risk.

B. Glucose energy metabolized from carbohydrates

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 (Atwater and Bryant, 1900; Rubner, 1901). For CHO this value is approximated as 4 kilocalories (kcal) per gram of CHO.

The two conversion processes are, however, very different. Therefore, contrary to popular belief, it is suspected that vastly different amounts of energy are released by the two processes. This suspicion was investigated further.

Nine groups, each consisting of eight healthy Spraque Dawley rats, were investigated. All rats were of the same age and received the same kcal per body mass. The kcal values were determined from the energy equation from Clark et al., (1977) for recommended daily allowance (RDA) for rats:

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

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. Kellogg's Nutrific.* The energy content of the foods was measured in 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, the mass of the rats is not expected to change. If there is a small mass loss/gain due to an error in Equation 1, this loss/gain should be the same for all groups as they received the same amount of kcal per body mass.

The results in Figure 2 show that all the groups lost mass. (The experiment had to be stopped 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.

The first conclusion is that, contrary to conventional belief, a living creature cannot extract the full 4 kcal of energy per gram of CHO. A second conclusion is that the amount of glucose energy extracted differs for different types of CHO. The correct way to quantify the metabolised glucose energy from different CHOs is now investigated in more detail.

C. Derivation of equations : Metabolic efficiency of carbohydrate-glucose conversion

In the previous section it was shown that the 100 year's understanding of energy from CHO may be wrong. A better way to estimate the blood glucose energy metabolized from CHO is necessary. To accomplish this, it is first necessary to find the true metabolic efficiency of any CHO.

Only CHO in a meal is directly metabolized into blood glucose during digestion. The *"metabolic conversion efficiency (η_{CH0})* of CHO estimates the amount of energy which is converted into blood glucose by a typical person. All losses, including energy needed for digestion, incomplete digestion, gas and heat production, etc. are accounted for in η_{CH0}. This value can be measured (as discussed later) and is a property of the meal. It depends on many factors including the content of dietary fibre, fat and protein in the meal.

Energy from CHO which can be metabolized by a person (E_{CH0} [kcal]) in the form of blood glucose is a function of the mass of CHO (including fibre) in the meal (m_{CHO} [g]), the full energy content per mass of the CHO (k_{CH0} [kcal/g]) measured outside the body by means of a bomb calorimeter and the metabolic efficiency (η_{CH0}) of the meal, which accounts for how efficiently the energy can be extracted inside the body as blood glucose.

The correct equation for CHO energy in a meal which can be metabolized inside the body (E_{CH0}) is then shown by:

$$E_{CHO} = \eta_{CHO} m_{CHO} k_{CHO} . \quad (2)$$

Efficiency towards metabolizing the CHO from a meal (Equation 2) into blood glucose varies between different people. This personalised CHO efficiency is represented by the term f_{CH0}. (Remember that f_{CH0} is a function of a specific person while η_{CH0} is a function of a meal.) The total energy metabolized as blood glucose for a specific person is then given by

$$E_{Metab} = f_{CHO} E_{CHO} = f_{CHO} \eta_{CHO} m_{CHO} k_{CHO} . \quad (3)$$

As E_{Meta} Jkcal] is the CHO energy metabolized into blood glucose for a specific person, E_{Metob} can also b^{θ} found by means of blood glucose measurements for that specific person. First the response curve for blood glucose concentration has to be integrated ($\int BG(t)dt$) over a period in which the blood glucose rises above the basal level.

This period is usually in the order of 120 minutes and is the period used in Glycaemic Index (Gl) methodology (Brouns et al. (2005)). The resulting integral value is called Area Under the Curve (AUC). AUC now gives the time integrated concentration of blood glucose in [mmol/L]min.

This concentration is multiplied by the total volume of blood of the person *(VoI)* [liter] to find the total amount of extra glucose in the blood due to the meal. Finally, E_{Metab} [kcal] is found by multiplying with *e[U/mmol]* , the energy value of glucose and dividing by the integration period of 120 minutes.

$$E_{Melab} = \frac{VoLe}{120} \int_{t=t_0}^{t=t_0+120\,min} BG(t)dt = \frac{VoLe}{120} AUC = f_{CHO}\eta_{CHO}m_{CHO}k_{CHO} \quad (4)$$

The energy absorption for any CHO relative to that of glucose is given by the following equation :

$$\frac{E_{Metab\backslash CHO}}{E_{MetaUGlucose}} = \frac{VoLe.AUC_{CHO}}{VoLe.AUC_{Glucose}} = \frac{f_{CHO}\eta_{CHO}m_{CHO}k_{CHO}}{f_{Glucose}\eta_{Glucose}m_{Glucose}k_{Glucose}} \quad (5)$$

The following assumptions can be made: for the same person, $f_{CH0} = f_{Glucose}$ and $k_{CH0} = k_{Glucose} = 4[JcCaUg]$ as measured in a bomb calorimeter. Eating the same amounts of CHO and glucose (50 g), means $m_{CH0} = m_{Glucose}$. Assuming 100% metabolic efficiency for ingested glucose to blood glucose (although we know it will be slightly less) results in $\eta_{Glumse} = 1$. These assumptions lead to Equation 6:

$$\eta_{CHO} = \frac{AUC_{CHO}}{AUC_{Glucose}} \quad (6)$$

But according to the definition of GI from Brouns et al. (2005)

$$GIcH_O = 100 \times \frac{AUC_{CHO}}{AUC_{Glucose}} \quad (7)$$

By comparing Equations 6 and 7 it has been proven that the metabolic efficiency (η_{CH0}) of a CHO (times 100) is its GI value. The metabolic efficiencies of many CHOs are therefore available through their GI values. This finding also leads to the conclusion

that the current thinking on GI may be wrong including how fibre is treated. This will be explained in another article.

D. Derivation of equations : Correctly estimating glucose energy metabolized from carbohydrates

In Section C it was shown that a better method than the one used during the past century is needed to calculate the glucose energy metabolized from a CHO by a living creature. It was also shown that, contrary to popular belief the metabolized energy from different CHOs can differ vastly.

Based on these results the metabolic conversion efficiency (η) of different CHOs (as derived in Section C) has to be accounted for. The energy E_{CH0} [kcal] converted into blood glucose from a CHO with a metabolic conversion efficiency of η_{CH0} and a mass of $m_{CH0}[g]$, (including fibre), is given by Equation 8:

$$E_{CHO}[kcal] = \eta_{CH0}\, m_{CH0}[g]\, 4[kcal\ /\ g] \qquad (8)$$

It is desirable to express the energy content in any CHO in a unit that is easy to understand and visualize 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.

Implementing Equation 8 for one teaspoon of sugar (containing 5 g of CHO) results in Equation 9:

$$E_{TeaspoonSugar}[kcal] = \eta_{Sugar}\, 5[g]x4[kcal\ /\ g] \qquad (9)$$

To obtain the metabolized blood glucose energy from any CHO (E_{CHO}) in terms of an equivalent teaspoons sugar (ETS), Equation 8 is divided by Equation 9. This gives the amount of ETS in any CHO, namely ETS $_{CHO}$.

$$ETS_{CHO} = \frac{E_{CHO}}{E_{Teaspoon\ Sugar}} = \frac{\eta_{CHO}\, m_{CHO} \times 4[kcal/g]}{\eta_{Sugar}\, m_{Teaspoon} \times 4[kcal/g]} = \frac{\eta_{CHO}}{\eta_{Sugar}} \frac{m_{CHO}}{5} \quad (10)$$

In the previous section it was shown that $\eta_{CHO} \sim G_{1/100}$. Measured values for η_{CHO} for most of the important CHOs are therefore available. (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 9 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 13 kcal (see Equation 11).

$$E_{TeaspoonSugar}\,[\text{kcal}] = \text{one ETS}\,[\text{kcal}] = 0.65 \times 5 \times 4 = 13\,[\text{kcal}]. \quad (11)$$

Now that the metabolized blood glucose energy from any CHO has been established in terms of ETS (Equations 10 and 11), a new way of calculating energy available to the body is proposed.

The new energy value is called ETS cal, to avoid confusion with standard kcal. It is calculated by the following equation (note that similar efficiencies for fat and protein metabolization should exist although their effect should be smaller than that for CHO):

$$\begin{aligned} \text{ETS cal} = {} & 13[\text{kcal/ ETS}] \times \text{ETS}_{CHO} + \\ & 9[\text{kcal/g}] \times \text{mass}_{Fat}[\text{g}] + \\ & 4[\text{kcal/g}] \times \text{mass}_{protein}[\text{g}] \end{aligned} \quad (12)$$

By utilising experimental data from Section B, Figure 3 was constructed. A linear relationship is found between the ETS cal values of a food containing CHO and the percentage 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 4 kcal/g historically used, shown in Figure 2.

As we will show more detail in later papers, the correct GI values are not always correct. With more correct definition of GI, more accurate GI values and thus metabolic efficiencies will result, leading to better results than reported in Figure 2.

E. Indirect measurements in humans of the correct energy metabolized from CHO

It has been shown that the historical calculation of metabolized CHO energy can lead to large errors when using rats as test subjects. A new method for calculating metabolized blood glucose energy was therefore proposed. The next step is to test whether this method is applicable to humans.

It is more difficult to conduct an experiment as described in Section 2 on humans than on rats. An indirect approach was thus utilized. Insulin secretion is a function of the blood glucose energy metabolized from CHO (Lee and Wolever (1998)). Furthermore, insulin secretion can be measured fairly easily.

The relationship between insulin secretion and the newly proposed measure of energy will be investigated. If this relationship is more consistent than that of insulin secretion and the historical method of energy calculation, the new energy method is preferable to the old one.

Equation 4 shows the relationship between energy metabolized from any CHO (E_{Metab}) and blood glucose response. For CHO there is a direct relationship between blood glucose response $(JBG(t)dt)$ and insulin response $(JBI(t)dt)$ (Giugliano et al. (2000)).

Although this relationship is not perfectly linear, Lee and Wolever (1998) found a linear relationship with an R^2 value of 0.963 from measurements by 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. This person specific characteristic is described with the insulin blood glucose factor, f_{IBG}.

Formulating this in equation format using the same integration period of 120 minutes for the insulin as for the blood glucose response results in Equation 13:

$$\int_{t_0=start\ of\ meal}^{t=t_n+120\,\mathrm{min}} BI(t)dt = f_{IBG}\int_{t_0=start\ of\ meal}^{t=t_n+120\mathrm{min}} BG(t)dt \qquad (13)$$

Substituting Equation 13 into Equation 4 results in Equation 14, which describes the person specific insulin response to ingested food.

$$\frac{\int_{t_0=start\ of\ meal}^{t=t_0+120\,\mathrm{min}} BI(t)dt}{120} = \frac{f_{IBG} f_{CHO} I_{CHO} m_{CHO} k_{CHO}}{VoLe} \qquad (14)$$

Equation 14 can be simplified further by substituting in Equation 10 and using the fact that $\eta_{Sugar} = 0{,}65$ (as stated before). A new term is furthermore defined - the Area Under the Curve for Insulin $(AUCI)$ for the integral. Equation 14 reduces to

$$\frac{\int_{t_0=start\ of\ meal}^{t=t_0+120\mathrm{min}} BI(t)dt}{120} = \frac{AUCI}{120} = \frac{f_{IBG} f_{CHO} k_{CHO} \eta_{CHO} m_{CHO}}{VoLe} = \frac{f_{IBG} f_{CHO} k_{CHO}}{VoLe} 3{,}25\ ETSd \qquad (15)$$

By defining a new person specific factor, f_{AUCI}, Equation 15 can be simplified to the following:

$$AUCI = f_{AUCI}\ ETS \qquad (16)$$

$$\textbf{where}\ f_{AUCI} = \frac{3{,}25 f_{IBG} f_{CHO} k_{CHO} 120}{VoLe} \qquad (17)$$

Equation 17 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 18:

$$AUCI = f\ m_{CH0}, \qquad (18)$$

where m_{CH0} is the mass of the CHO ingested in grams.

The quality of the relationships given by the newly derived Equation 16 and the historical Equation 18 are evaluated using measurements from Wolever and Bolognesi (1996) and Lee and Wolever (1998).

The average R^2 and its standard deviation (S) as a percentage of the average for 15 test subjects were computed using both equations. Equation 16 resulted in R^2 = 0.807; S = 10% and Equation 18 in R^2 = 0.562; S = 32%. It is clear that the new Equation 16 gives a better approximation of metabolized blood glucose energy than the historical Equation 18 when applied to humans.

F. Cancer risk and the correct metabolized glucose energy from CHO

Now that a more correct way of calculating metabolized glucose energy has been established, its link with certain cancers can be investigated with more accuracy.

The new equation shows that refined CHOs are more efficiently metabolized into blood glucose than unrefined ones, resulting in more energy made available for cell growth.

The ETS -concept (Equation 10) was proposed to simplify the correct metabolized energy values for general use. From Equation 10, $\eta_{CH0} \sim GI_C H_O/100$ and η_{sugar} = 0,65, Equation 19 is obtained:

$$ETS_{CHO} = \frac{\eta_{CHO}}{\eta_{Sugar}} \frac{m_{CHO}}{5} = \frac{GI_{CHO}\, m_{CHO}}{325} \qquad (19)$$

where η_{CH0} and η_{sugar} are the metabolic efficiencies of the CHO under investigation and sugar, respectively. The mass of the CHO is given by m_{CH0}. All GI values are referenced to the glucose standard.

Four studies were identified which report sufficient information to enable the computation of their participants' metabolized CHO energy consumption as described by the ETS equation. The cancers which were investigated are upper aero-digestive (Augustin, Gallus et al. (2003)), ovarian (Augustin, Polesel et al. (2003)), prostate (Augustin et al. (2004)) and colorectal (Higginbotham et al. (2004)).

Participants were asked to complete a food frequency questionnaire which evaluated their average dietary intake for the year or two prior to cancer diagnosis. It was possible to analyse the resulting data in terms of ETS content.

The η_{CHO} ($\sim Glc_{H}o/100$) and m_{CH0} values were obtained from the clinical trials investigated, and the average daily ETS consumption prior to cancer diagnosis was computed using equation 19. The results in Figure 4(a) show the effect of daily ETS consumption on risk for the four cancers. The R^2 values for the cancers vary between 0,91 and 0,94.

Figure 4(a) suggests that the risk for various cancers increases along with blood sugar energy metabolized from CHO as expressed in ETS (which increases as the food becomes more refined). The cancer risk starts to increase from consumption of about 30 ETS per day. This is approximately the ETS - count of one upsized fast food burger meal (burger, fries and cola). It is also the amount of blood glucose the average person's brain needs. It is furthermore the amount of blood glucose the liver stores for the average person.

Colon cancer seems to be the most sensitive to excess energy intake while the other cancers have smaller sensitivities. Figure 4(a) however shows that the risk for cancer increases for all four types with increased excess energy. The average slope for the four different cancers is given in Figure 4(b).

The ideas behind the ETS concept was not only to develop a more correct metabolized CHO energy value but also to develop a unit which is easy to understand, interpret and implement. Keeping track of your daily ETS consumption is simple and assists in making smart food and portion size choices. (More than 4 000 different food stuffs have been analysed for their ETS content. This will be published in a future paper.)

The theory to calculate the correct metabolized blood glucose values is now in place. The effect of fibre on metabolized energy and its impact on certain cancers can thus be investigated in the next section.

G. Fibre : Effect on blood glucose metabolism and its impact on cancer

Several authors have shown that fibre reduces the risk for breast, colon, endometrial, rectum, oral, pharyngeal and oesophageal cancers (Weisburger et al., 1993; La Vecchia et al., 1997; Compher et al., 1999; Ferguson and Harris, 1999; Jansen et al., 1999; McCann et al., 2000; Soler et al., 2001). Different reasons are proposed for this phenomenon.

Our hypothesis is that the link between glucose energy metabolized from CHO and cancer is probably the most important contributor to the phenomenon. It has been shown that the metabolized glucose energy is dependant on the metabolic efficiency of the CHO. This efficiency is *inter alia* dependant on the GI value of the food, which is reduced when fibre is added to the CHO (Jenkins et al. (2002)). (Remember that fibre is not treated 100% correctly in the current GI formulation).

In the previous section it has been shown that a lower metabolized energy from CHO leads to a lower cancer risk. Therefore, the addition of fibre to any meal should lower the risk for cancer. In a combined analysis of 13 previous studies, Howe et al. (1992) proves this for colon and rectum cancer. Figure 5(a) shows a summary of his results. Note that a RR of -2 corresponds to a two fold decrease in the normal cancer risk (RR=1). Pearson R^2 values for the two cancers varied between 0,96 and 1,0.

Jenkins et al. (2002) added fibre to different foods and measured the resulting glucose response in type 2 diabetics. One gram of fibre added to 50 grams of CHO reduced the

GI of a typical meal by 4 units. This can be translated to a reduction of 0.6 ETS per gram of extra fibre added to a meal.

This value can also be deduced from two other studies, although it is not the purpose to discuss them here. A new variable, $ETS_{Fib\ added}$, can now be defined. It is described by the following equation :

$$ETS_{Fib\ added} = -0.6 \cdot m_{Fib\ added} \quad (20)$$

where $m_{Flb\ added}$ is the mass of the fibre added in grams. Using equation 20 and the data in Figure 5(a), Figure 5(b) can be constructed for the average of the two cancers.

This average value can now be subtracted from the ETS value of a meal. This will account for the resulting effect on metabolized energy of fibre added to the meal and thus the cancer risk (Figure 5(b)).

An important implication from our hypothesis is that additional fibre must be eaten with the meal to reduce the meal's metabolic efficiency. Fibre eaten on its own at other times of the day will have little effect according to our hypothesis.

H. The effect of exercise on blood glucose and cancer

Our hypothesis regarding exercise is that it decreases your available blood glucose energy. Less blood glucose energy, means less of the preferred energy for cancer cells to thrive on. Since cancer cells usually have an exceptional high energy demand, they should be of the first cells in the body to die of energy starvation. Let us investigate this hypothesis.

It has been shown that the energy effect on blood glucose can be described in terms of ETS. This relationship is utilized to investigate the effect on cancer risks of energy expended through exercise.

Approximately 20% of the energy expended during exercise comes from blood glucose released from the liver (Noakes, 2001). The blood glucosed energy expressed in ETS

expended by a test subject can then be calculated using the energy expended in kcal and the conversion between kcal and ETS (Equation 11), resulting in Equation 21.

$$\mathrm{ETS}_{Exercise} = 0{,}2 \times kCal_{Exercise} \times \frac{ets}{kCal} = 0{,}2 kCal_{Exercise} \times \frac{1}{13} = \frac{kCal_{Exercise}}{65} \qquad (21)$$

With the blood glucose effect of exercise quantified by Equation (21) we can now investigate published clinical trials. Slattery et al. (2003) did a study which investigated the relationship between energy expenditure and rectal 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.

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 used to determine the average daily ETS expenditure.

The results from these studies are given in Figure 6(a). Again note that a RR of -2 corresponds to a two fold decrease in normal cancer risk (RR=1). The R^2 values varied between 0,84 and 0,98. Rectal cancer seems to be the most sensitive to blood glucose energy expended. The average slope for the four cancers is given in Figure 6(b).

As expected, a favourable link between cancer risk and blood glucose energy expended (in ETS units) emerges from the figures. Daily exercise of about 13 ETS halves the risk for rectal cancer. This is the equivalent of approximately 60 minutes of jogging at 12 km/h per day for an average person.

I. Glucose energy released by counter regulation due to stress

It is known that stress causes the liver to secrete glucose. Since this is another factor influencing the blood glucose value, it is desirable to express stress in terms of ETS and then to correlate this with cancer risk. To achieve this, we have to use available

clinical trials on stress. For coronary heart disease (CHD) clinical trials were carried out for the effects of stress and also for food (ETS) intake.

Liu et al. (2000) investigated the effect of CHO ETS intake on coronary heart disease (CHD). In their study 75,521 women aged between 38 and 63 years with no previous diagnosis of myocardial infarction, angina, stroke, other cardiovascular diseases, or diabetes mellitus were followed for 10 years, starting in 1984.

Expressing their metabolized CHO energy in terms of ETS, the relationship between ETS consumption and relative risk (RR) for CHD was found. This is shown in Figure 7.

In other studies (Chen) the relationship between stress level and RR for CHD was investigated. The results are shown in the first two columns of Table 1. The relationship between stress and RR for CHD is thus known, as well as the relationship between RR for CHD and ETS consumption from Figure 7. From this, the relationship between ETS and stress levels could be derived (Table 1, columns 1 and 3).

These results were confirmed through measurements and simulations in another study (Mathews and Pelzer). Now that stress can be expressed in terms of ETS, it is possible to investigate the link between stress and cancer in a quantified manner.

Ginsberg et al. (1996) did a study on traumatic life events and breast cancer. It included 99 cases and 99 controls. They 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.

Using the aforementioned relationship between stress level and extra ETS per day due to stress, the data published by Ginsberg et al. (1996), were analysed to determine the link between ETS due to long-term stress and cancer risk. Figure 8 shows the results of their study over ten years, adjusted for potential confounders. The R^2 value was 0,99.

As expected the extra ETS secreted per day by the individuals as a result of stress causes a rise in breast cancer risk (Figure 8). From Table 1 it is known that low-level

stress leads to increased secretion of about 7 ETS per day. Prolonged exposure to this level of stress leads to almost a doubling in breast cancer risk. Higher stress levels increase cancer risk by up to five-fold.

The clinical results confirm the hypothesis that ETS secreted due to stress increases the cancer risk just as ETS ingested through food would have done. Now that stress has been quantified in terms of ETS, it is easier to make quantitative predictions about the negative effects of stress.

J. Combining all the blood glucose effects and cancer risk :

In this specification, correct unit for blood sugar energy expression of ingested CHO has been presented, namely an equivalent teaspoon sugar, or ETS. Furthermore, exercise, stress and fibre have also been expressed in terms of ETS.

The link between net ETS effect and cancer risk can now be better understood. Figure 9 shows the results of "average" cancer risk versus the four blood sugar contributors for the average person. The graphs start at a normal relative risk (RR=1) and show the positive and negative influences of the relevant contributors. The cancer risk is halved at -2 on the y-axis and doubled at +2.

Figure 9 shows that excess food intake and stress have a similar, worsening effect on cancer risk. In a nearly mirror image to that, is the positive effect of exercise and additional fibre. The absolute values of the slopes of the curves are not exactly the same, but are similar.

The ideal situation would be to have clinical trials for each type of cancer where the effects of food, fibre, exercise and stress are addressed. A graph similar to Figure 9 can then be developed for each cancer. We believe that the absolute slopes of the blood sugar contributions for each specific cancer will then be the same.

With the aid of similar graphs as Figure 9 for the average person a specific person could form an idea of his/her net ETS intake (taking into account food, stress, exercise and fibre). If the net ETS intake exceeds zero, the risk of developing cancer starts to

increase. Tables for the ETS values of foodstuffs, exercise, stress and fibre have been developed and is available on request. It will also be published in due course.

K. APPLICATION OF LINK BETWEEN BLOOD GLUCOSE AND CANCER

It was shown that current calculations for blood glucose energy from carbohydrates are wrong. It was further shown that the ETS equation gives better results than the previous used equation. With this we could show, with a very high degree of accuracy, the effect that more or less blood glucose energy, resulting from feeding, stress, exercise and fibre has on and the risk of cancer.

Previously the links between cancer and food, exercise, stress as well as fibre were shown by other researchers. However, various different reasons for the link mechanisms were given. Here we give one consistent theory, leading to consistent results to quantify the effects of these factors on various cancers. The unifying effect is blood glucose energy, calculated correctly with the new ETS equation. (With previous energy calculations this single link was not shown.) It now becomes obvious that to effectively control cancer we must control the blood glucose levels in the body.

The brain is the most important organ needing blood glucose. It usually needs approximately 20% of the total energy of the recommended daily allowance (RDA). If we feed the brain separately from the rest of the body and keep its blood glucose level at approximately 4 mmol/L we could ensure that the brain is functioning normally. We feed the body separately to ensure a much lower than normal blood glucose level in the rest of the blood cycle. in order to starve the cancer cells.

If the brain is fed the correct amounts of glucose, there will be less counter regulation that influences the glucose production by primarily the liver. Any extra signal to the liver to produce blood glucose e.g. through adrenalin, Cortisol, etc. must therefore be suppressed by *inter alia* stress and anxiety drugs. To inhibit the performance of the liver, diabetic drugs can also be used such as metformin.

The information in this section is used in the present invention.

Acknowledgements :

The original idea for taking on a century old scientific wisdom regarding energy released from different CHOs came from Corlia Mathews in 1998. This insight made the current research possible. The underlying concepts described in this text were conceived in 2000.

Many people helped with the research. Johann Holm and Corlia Mathews were always willing to listen to new ideas. The clinical trials on the rats were managed by Gerhard Bolt. Cor Botha and Francois Taljaard helped with the exercise model. Fernando Pizer and Cor Botha helped with the blood sugar simulation model. Fikkie Geyser did the computer simulation model.

Jeniffer Chen, Ruaan Pelzer and Paul Taylor helped with the stress research. Kobus Laubscher did the literature review for cardiovascular disease. Information from this was used in the stress equations.

The cancer literature survey was primarily done by Suretha Potgieter. Suretha Potgieter, Ruaan Pelzer and George Mathews helped with writing this document. Fred Keet helped with literature review, data analyses and writing of section I.

Oncological advice were given by Dr Susan Fourie. Detail on the PET scan were shared by Dr Arnold van Dyk.

As the theory is relevant to other problems, it will also be reported elsewhere for better understanding of these other problem areas.

9. EXTENSIONS AND ALTERNATIVES

In the foregoing specifications, the invention has been described with reference to specific embodiments thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention. The specification and drawings are, accordingly, to be regarded in an illustrative rather than a restrictive sense.

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CLAIMS

1. An installation for the treatment of cancer in a patient, the installation including

a first parenteral administration assembly for parenteral administration of glucose into a first part of the bloodstream of the patient, which part is flowing to the brain of the patient, shortly before the first part of the bloodstream reaches the brain;

a first glucose monitoring assembly for monitoring the glucose level of the first part of the bloodstream after parenteral administration of the glucose, and a optionally a second part of the bloodstream, which part is flowing from the brain;

a second parenteral administration assembly for parenteral administration of glucose into a third part of the bloodstream of the patient; and

a second glucose monitoring assembly for monitoring the glucose level in a fourth part of the bloodstream of the patient.

2. An installation as claimed in Claim 1, in which each parenteral administration assembly is selected from hypodermic needles and catheters.

3. An installation as claimed in Claim 1 or Claim 2, which includes one or more additional parenteral administration assemblies for parenteral administration of substances for controlling the rate hepatic glucose production and suppression of blood glucose counter regulation hormones.

4. An installation as claimed in any one of Claims 1 to 3 which includes one or more additional parenteral administration assemblies for parenteral administration of nutrients other than glucose.

5. An installation as claimed in any one of Claims 1 to 4 inclusive, which includes a control system, linked to the parenteral administration assemblies and the glucose monitoring assemblies and operable to regulate the rate of administration of glucose and the substances for controlling hepatic glucose production in response to the glucose levels detected by the glucose monitoring assemblies.

6. An apparatus for the treatment of cancer in a patient, the apparatus including

a first parenteral administration assembly for parenteral administration of glucose into a first part of the bloodstream of the patient, which part is flowing to the brain of the patient, shortly before the first part of the bloodstream reaches the brain;

a first glucose monitoring assembly for monitoring the glucose level of the first part of the bloodstream after parenteral administration of the glucose, and a optionally a second part of the bloodstream, which part is flowing from the brain;

a second parenteral administration assembly for parenteral administration of glucose into a third part of the bloodstream of the patient; and

a second glucose monitoring assembly for monitoring the glucose level in a fourth part of the bloodstream of the patient.

7. An apparatus as claimed in Claim 6, in which the parenteral administration assemblies include hypodermic needles or catheters.

8. An apparatus as claimed in Claim 6 or Claim 7, which includes one or more additional parenteral administration assemblies for parenteral administration of substances for controlling hepatic glucose production.

9. An apparatus as claimed in Claim 6, which includes a control system, linked to the parenteral administration assemblies and the glucose monitoring assemblies and operable to regulate the rate of administration of the glucose and the substances for controlling hepatic glucose production in response to the glucose levels detected by the glucose monitoring assemblies.

10. A wearable treatment apparatus which can be worn by a patient, the treatment apparatus comprising an assembly including

a first parenteral administration assembly for parenteral administration of glucose into a first part of the bloodstream of the patient, which part is flowing to the brain of the patient, shortly before the first part of the bloodstream reaches the brain;

a first glucose monitoring assembly for monitoring the glucose level of the first part of the bloodstream after parenteral administration of the glucose, and optionally a second part of the bloodstream, which part is flowing from the brain;

a second parenteral administration assembly for parenteral administration of glucose into a third part of the bloodstream of the patient;

a second glucose monitoring assembly for monitoring the glucose level in a fourth part of the bloodstream of the patient remote from the first and second parts; and

an attachment arrangement for attaching the apparatus to the body of the patient.

11. The treatment apparatus of claim 10, in which the attachment arrangement is a harness.

12. An installation as claimed in claim 1, or an apparatus as claimed in claim 6 or an apparatus as claimed in claim 10 in which the first parenteral assembly is for administration of glucose into the first part of the blood stream to produce a glucose level of between 0,5 and 5 mmol/L.

13. An installation as claimed in claim 12, or an apparatus as claimed in claim 6 or an apparatus as claimed in claim 10 in which the first parenteral assembly is for administration of glucose into the first part of the blood stream to produce a glucose level of between 1,5 and 4,5 mmol/L.

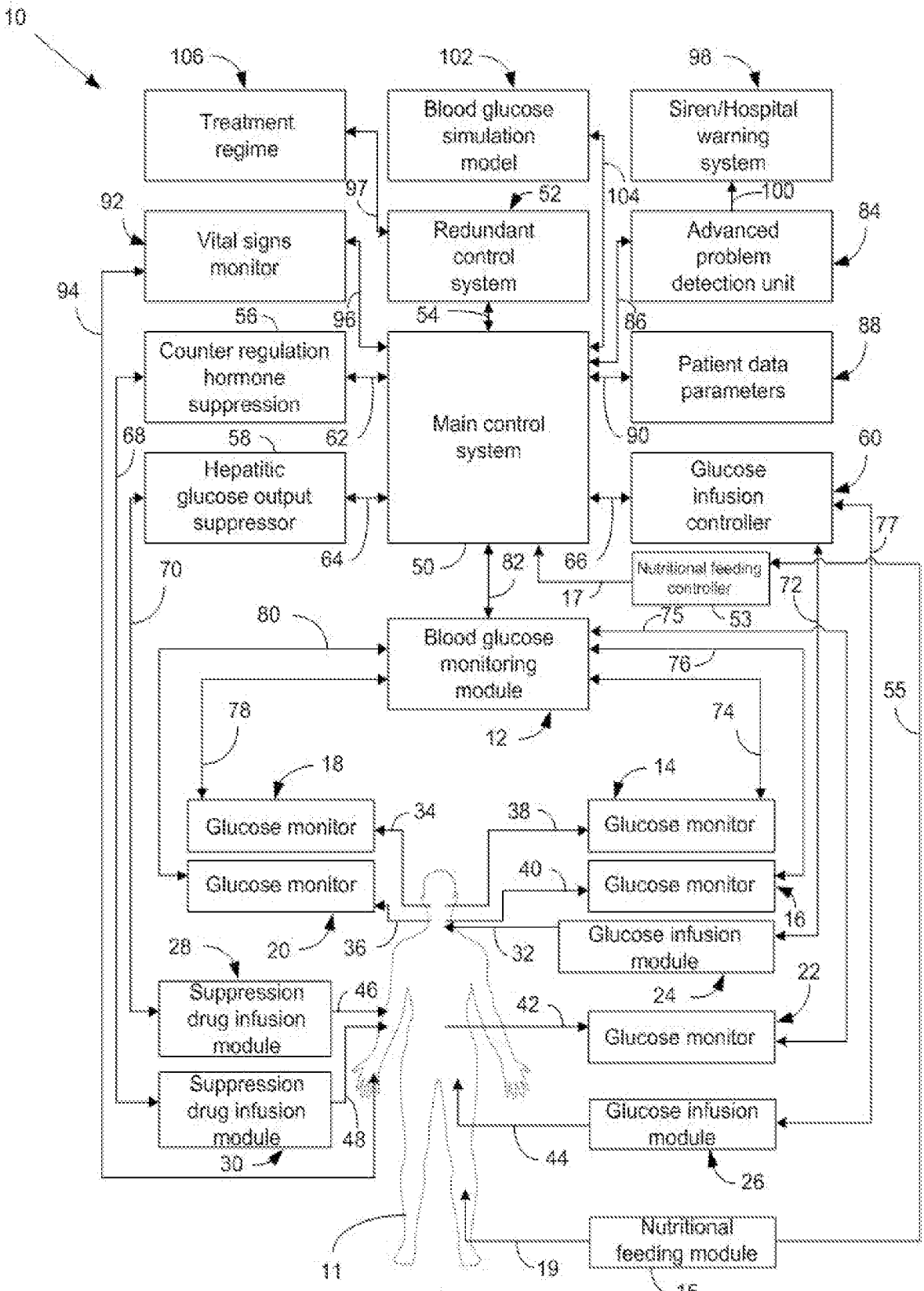

10
106
Treatment regime
102
Blood glucose simulation model
98
Siren/Hospital warning system
97
52
104
100
92
Vital signs monitor
Redundant control system
Advanced problem detection unit
84
94
56
96
54
86
88
Counter regulation hormone suppression
Main control system
Patient data parameters
68
58
62
90
60
Hepatitic glucose output suppressor
Glucose infusion controller
64
50
82
66
77
70
Nutritional feeding controller
72
17
75
53
80
Blood glucose monitoring module
76
55
78
74
12
18
14
Glucose monitor
34
38
Glucose monitor
Glucose monitor
40
Glucose monitor
16
28
20
36
32
Glucose infusion module
22
24
Suppression drug infusion module
46
42
Glucose monitor
Suppression drug infusion module
Glucose infusion module
48
44
30
26
11
Nutritional feeding module
19
15

FIG 1

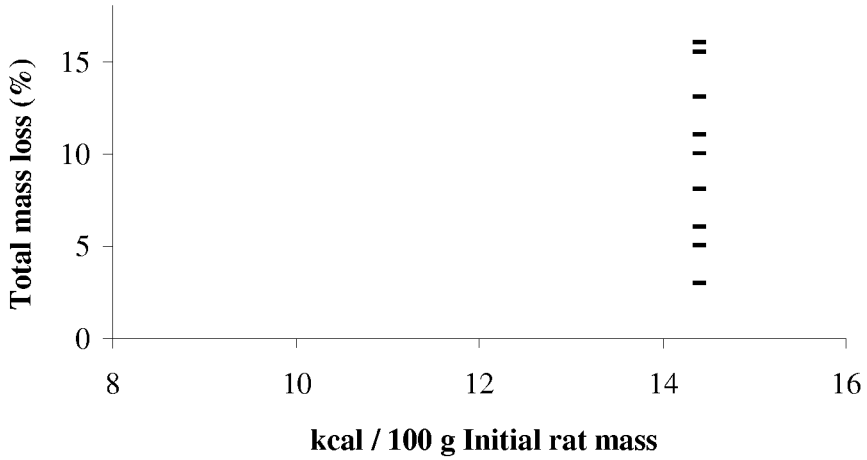

Total mass loss (%)
15
10
5
0
8
10
12
14
16
kcal / 100 g Initial rat mass

FIG 2

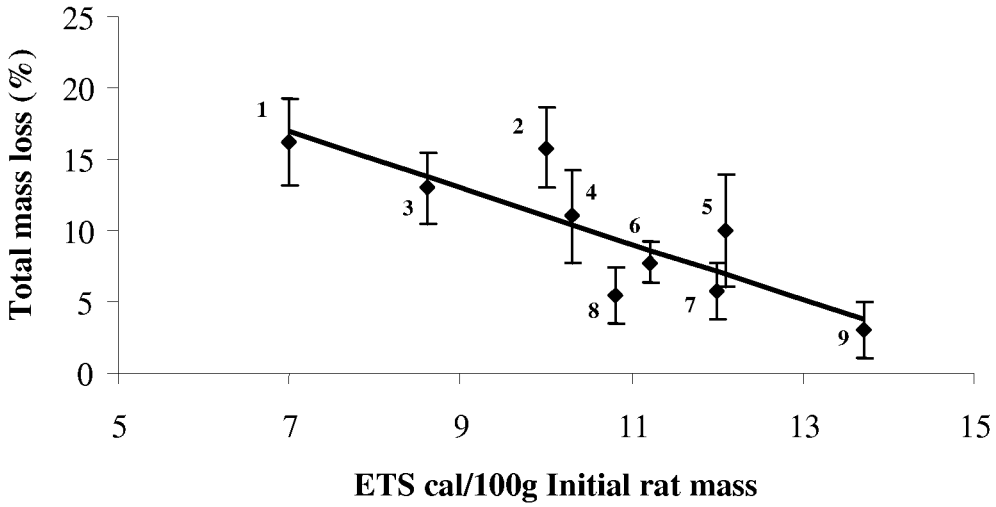

Total mass loss (%)
25
20
15
10
5
0
5
7
9
11
13
15
1
2
3
4
5
6
7
8
9
ETS cal/100g Initial rat mass

FIG 3

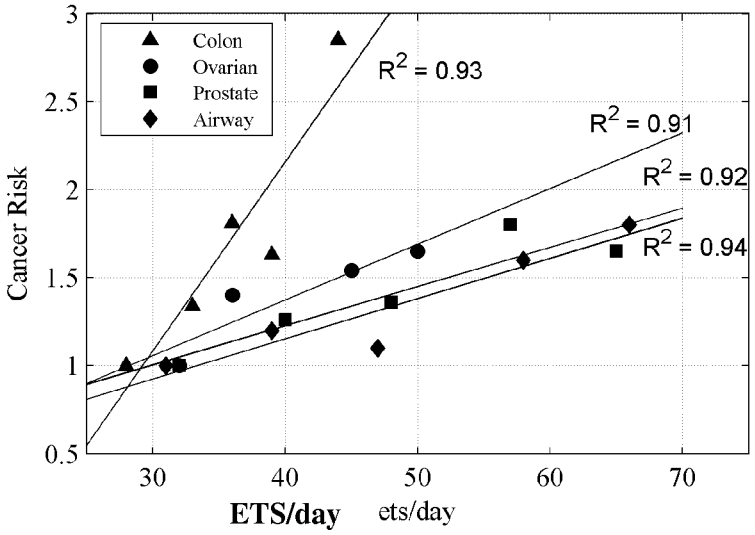

Colon
Ovarian
Prostate
Airway
R^2 = 0.93
R^2 = 0.91
R^2 = 0.92
R^2 = 0.94
Cancer Risk
ETS/day
ets/day
3
2.5
2
1.5
1
0.5
30
40
50
60
70

FIG 4a

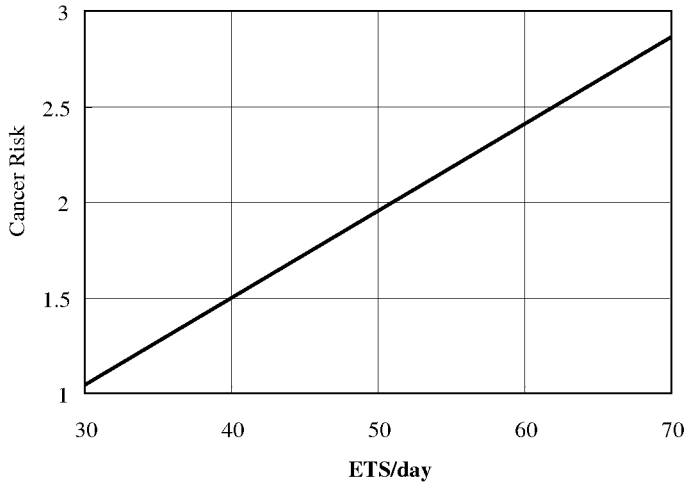

Cancer Risk
ETS/day
3
2.5
2
1.5
1
30
40
50
60
70

FIG 4b

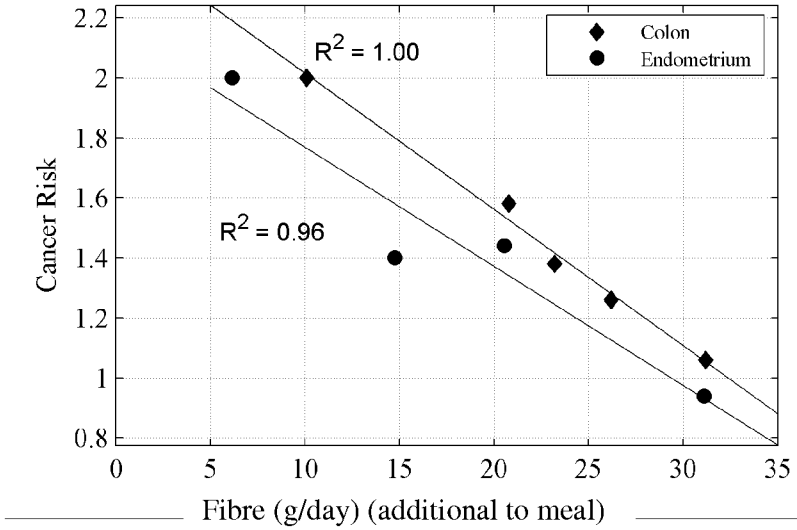

Colon
Endometrium
R^2 = 1.00
R^2 = 0.96
Cancer Risk
2.2
2
1.8
1.6
1.4
1.2
1
0.8
0
5
10
15
20
25
30
35
Fibre (g/day) (additional to meal)

FIG 5a

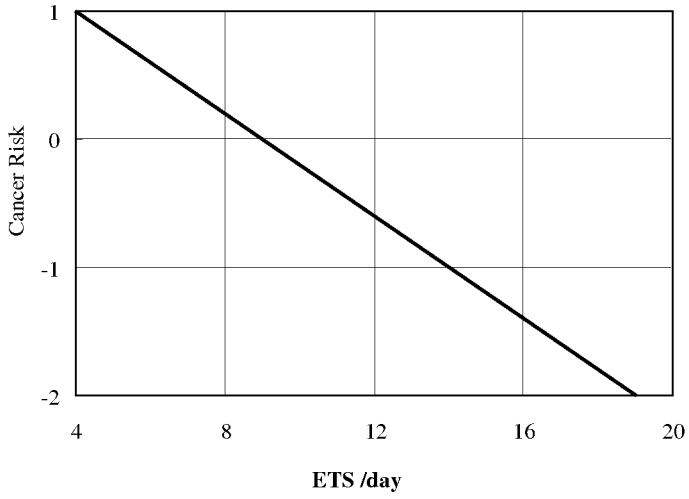
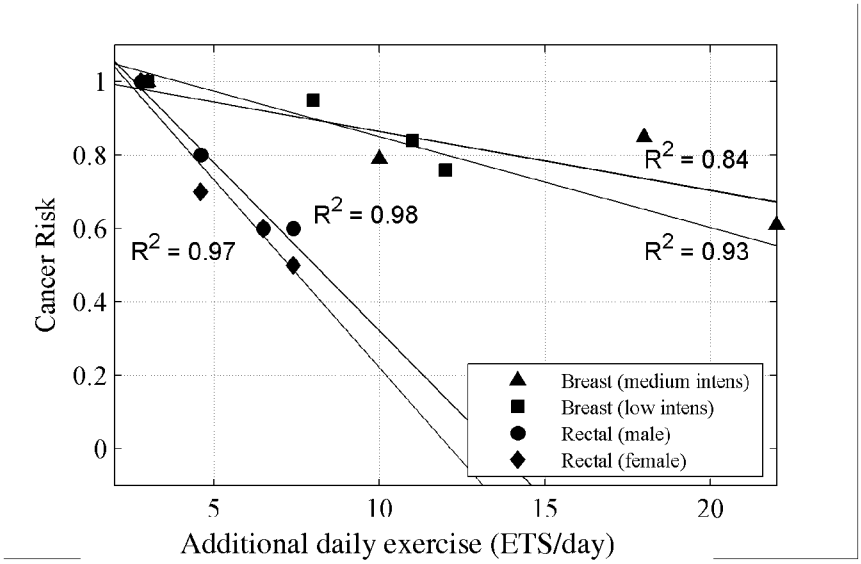

Cancer Risk
1
0
-1
-2
4
8
12
16
20
ETS /day

FIG 5b



(a)

FIG 6a

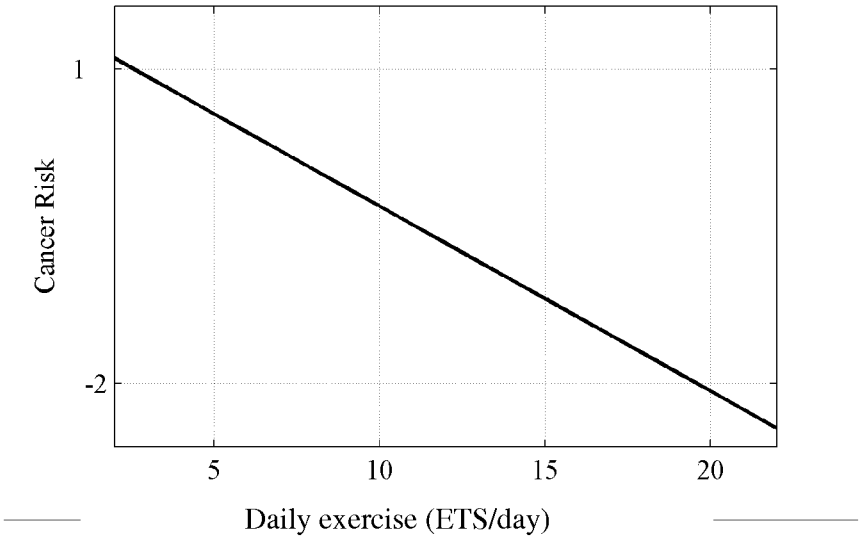


FIG 6b

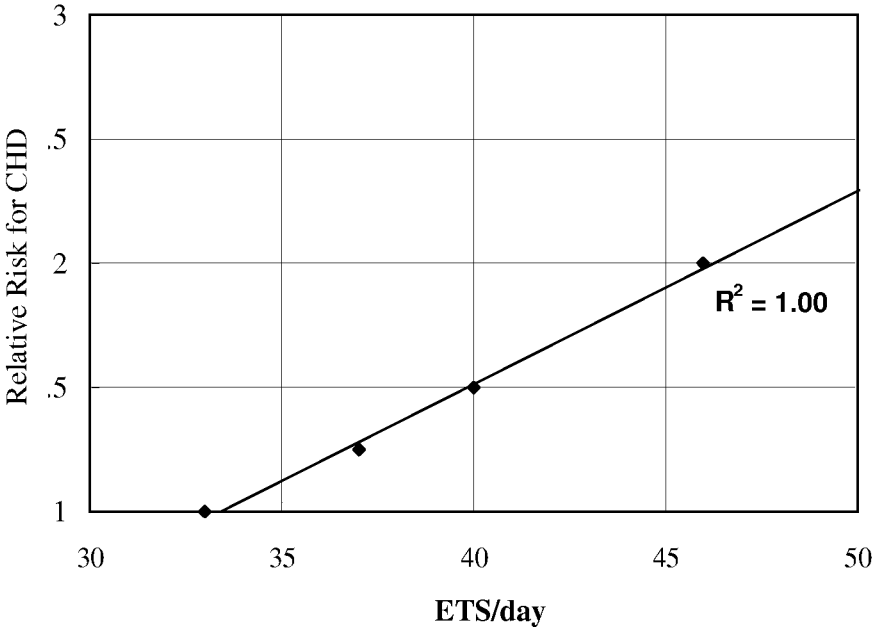

Relative Risk for CHD
3
.5
2
.5
1
30
35
40
45
50
ETS/day
R^2 = 1.00

FIG 7

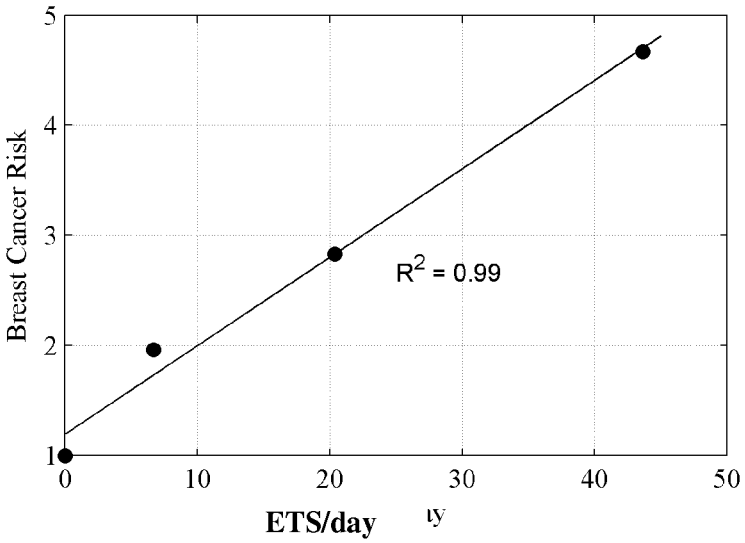

Breast Cancer Risk
5
4
3
2
1
0
10
20
30
40
50
ETS/day
R^2 = 0.99

FIG 8

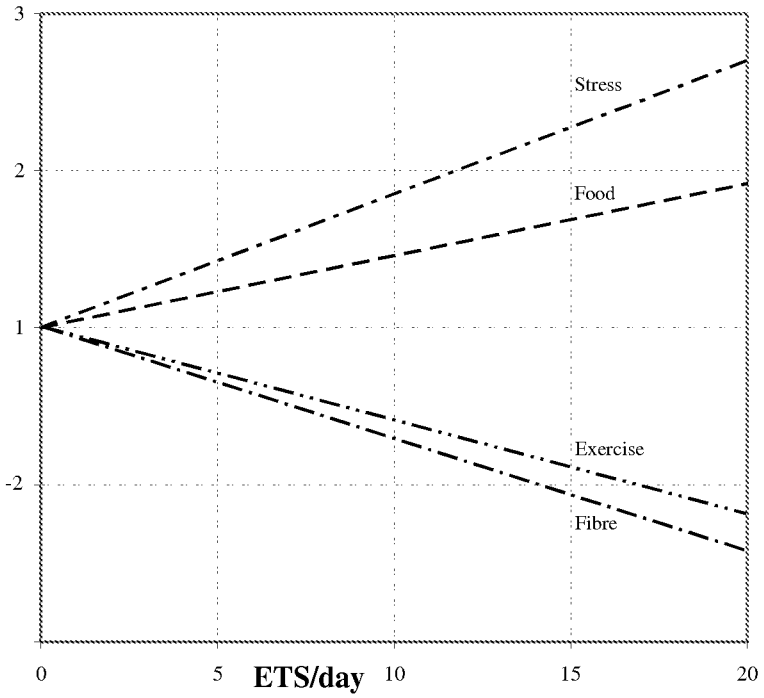


FIG 9

Stress level	Relative Risk (RR) CHD	ETS /day	Cancer RR
Low	1,4	7,2	2
Medium	2,4	21,6	2,9
High	4,1	50,4	4,8

FIG 10

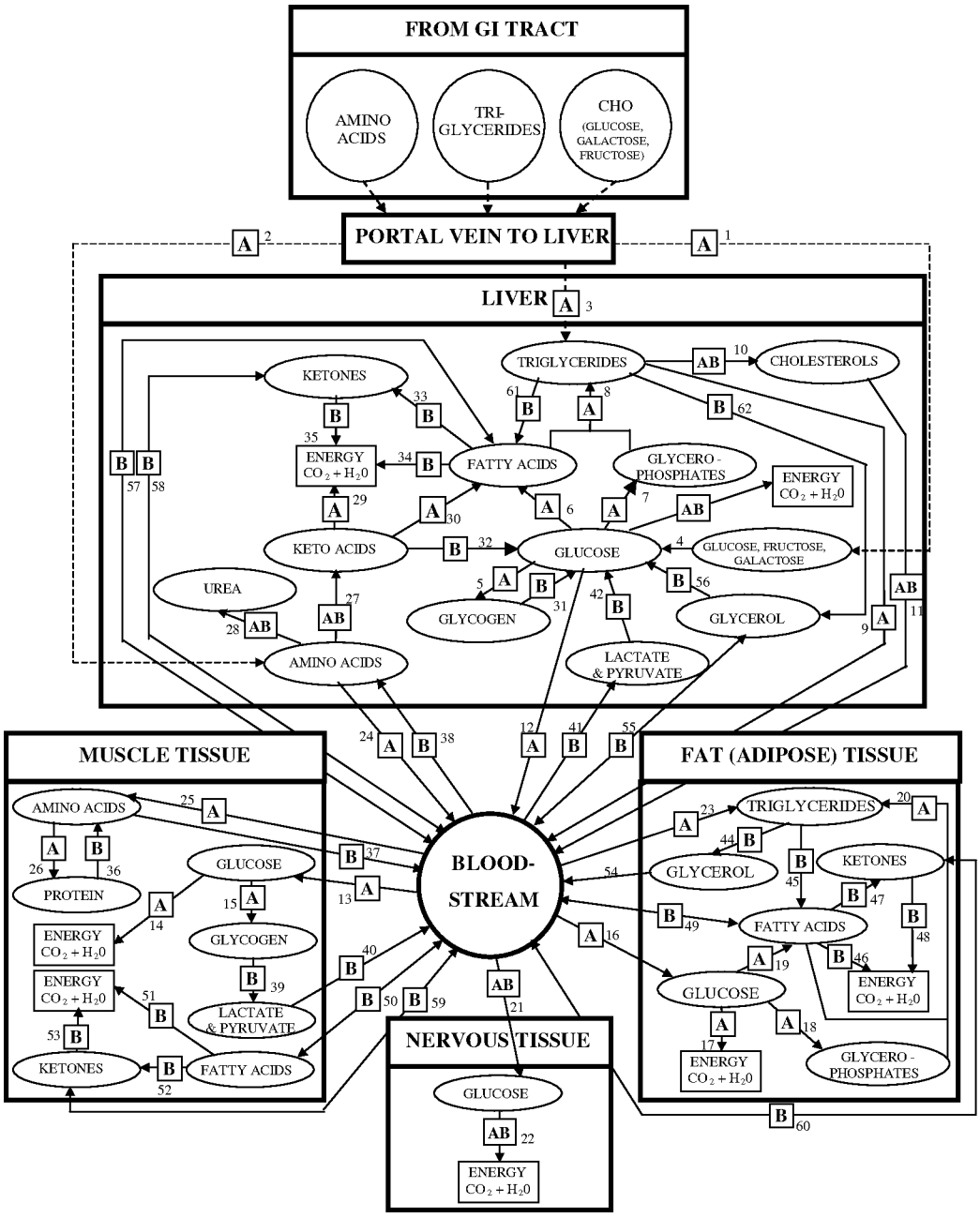

FROM GI TRACT
AMINO ACIDS
TRI-GLYCERIDES
CHO (GLUCOSE, GALACTOSE, FRUCTOSE)
PORTAL VEIN TO LIVER
LIVER
TRIGLYCERIDES
CHOLESTEROLS
KETONES
FATTY ACIDS
GLYCERO - PHOSPHATES
ENERGY $CO_2 + H_2O$
KETO ACIDS
GLUCOSE
GLUCOSE, FRUCTOSE, GALACTOSE
UREA
GLYCOGEN
GLYCEROL
AMINO ACIDS
LACTATE & PYRUVATE
MUSCLE TISSUE
AMINO ACIDS
PROTEIN
GLUCOSE
GLYCOGEN
ENERGY $CO_2 + H_2O$
LACTATE & PYRUVATE
KETONES
FATTY ACIDS
BLOOD-STREAM
FAT (ADIPOSE) TISSUE
TRIGLYCERIDES
GLYCEROL
KETONES
FATTY ACIDS
GLUCOSE
ENERGY $CO_2 + H_2O$
GLYCERO - PHOSPHATES
NERVOUS TISSUE
GLUCOSE
ENERGY $CO_2 + H_2O$

FIG 11

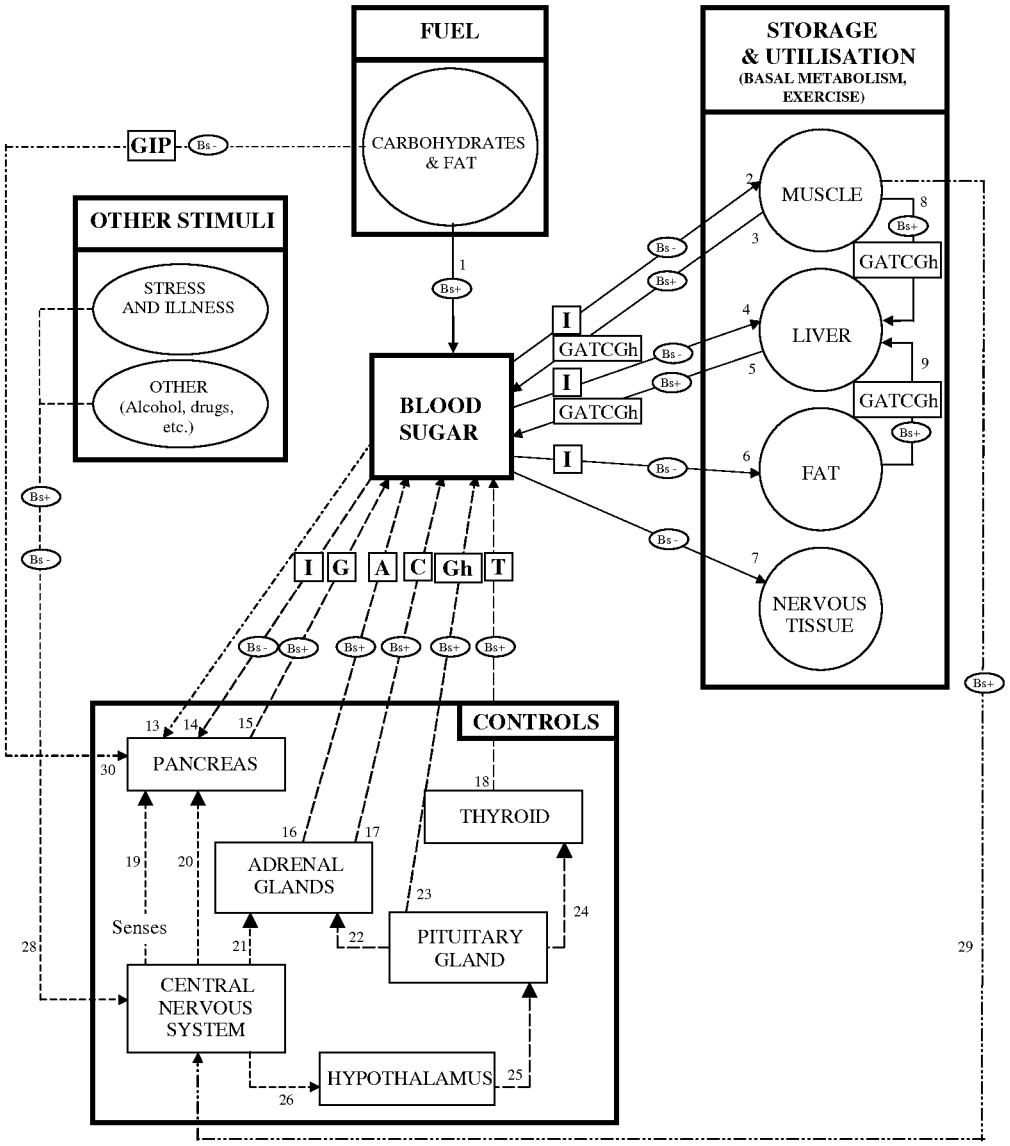

FUEL
CARBOHYDRATES & FAT
STORAGE & UTILISATION (BASAL METABOLISM, EXERCISE)
GIP
Bs -
OTHER STIMULI
STRESS AND ILLNESS
OTHER (Alcohol, drugs, etc.)
BLOOD SUGAR
MUSCLE
LIVER
FAT
NERVOUS TISSUE
GATCGh
I
Bs+
I G A C Gh T
CONTROLS
PANCREAS
THYROID
ADRENAL GLANDS
PITUITARY GLAND
CENTRAL NERVOUS SYSTEM
HYPOTHALAMUS
Senses
1
2
3
4
5
6
7
8
9
13
14
15
16
17
18
19
20
21
22
23
24
25
26
28
29
30

FIG 12

	Height (m)	Weight (kg)	ETS Cal	ETS
Men	1.2 - 1.25	33 - 38	73	12
	1.25 - 1.3	36 - 41	79	13
	1.3 - 1.35	38 - 44	85	14
	1.35 - 1.4	42 - 48	93	15
	1.4 - 1.45	44 - 50	98	16
	1.45 - 1.5	47 - 54	104	17
	1.5 - 1.55	50 - 58	112	18
	1.55 - 1.6	54 - 62	120	19
	1.6 - 1.65	56 - 65	125	20
	1.65 - 1.7	59 - 68	131	21
	1.7 - 1.75	63 - 73	141	22
	1.75 - 1.8	66 - 77	147	24
	1.8 - 1.85	70 - 82	158	25
	1.85 - 1.9	74 - 86	166	26
	1.9 - 1.95	77 - 90	172	28
	1.95 - 2	81 - 94	181	29
	2 - 2.05	85 - 100	191	30
	2.05 - 2.1	89 - 104	201	32
	2.1 - 2.15	93 - 109	210	34
	2.15 - 2.2	96 - 114	218	35
	2.2 - 2.25	100 - 120	228	36
Women	1.2 - 1.25	33 - 38	73	12
	1.25 - 1.3	35 - 41	79	13
	1.3 - 1.35	37 - 44	83	13
	1.35 - 1.4	40 - 46	89	14
	1.4 - 1.45	43 - 50	98	16
	1.45 - 1.5	45 - 53	102	16
	1.5 - 1.55	47 - 55	106	17
	1.55 - 1.6	50 - 59	114	18
	1.6 - 1.65	53 - 63	120	19
	1.65 - 1.7	56 - 67	127	20
	1.7 - 1.75	60 - 70	135	22
	1.75 - 1.8	63 - 73	141	22
	1.8 - 1.85	66 - 77	147	24
	1.85 - 1.9	68 - 81	156	25
	1.9 - 1.95	72 - 85	162	26
	1.95 - 2	76 - 89	170	27
	2 - 2.05	79 - 93	179	28
	2.05 - 2.1	82 - 97	185	30

Fig 13

	ETS Cal expended by activities of a 40kg person			ETS expended by activities of a 40kg person		
TIME	30min	45min	60min	30min	45min	60min
Badminton	9.0	13.6	18.1	2.0	2.9	3.9
Baseball	7.5	11.3	15.0	1.6	2.4	3.3
Basketball	11.3	16.9	22.5	2.4	3.7	4.9
Bowling (non-stop)	10.7	16.0	21.3	2.3	3.5	4.6
Canoeing at 6.5 km/h	17.5	26.3	35.0	3.8	5.7	7.6
Cycling at 9 km/h	8.0	12.0	16.0	1.7	2.6	3.5
Cycling at 21 km/h	17.1	25.7	34.2	3.7	5.6	7.4
Dancing (moderate)	6.3	9.5	12.7	1.4	2.1	2.8
Dancing (vigorous)	9.5	14.3	19.0	2.1	3.1	4.1
Football	13.2	19.8	26.3	2.9	4.3	5.7
Golfing	6.5	9.8	13.1	1.4	2.1	2.8
Horseback Riding	10.8	16.2	21.5	2.3	3.5	4.7
Ping-Pong	6.2	9.2	12.3	1.3	2.0	2.7
Racquetball	13.8	20.8	27.7	3.0	4.5	6.0
Running at 9 km/h	17.1	25.7	34.2	3.7	5.6	7.4
Running at 11 km/h	22.3	33.5	44.6	4.8	7.3	9.7
Running at 19 km/h	31.3	47.0	62.7	6.8	10.2	13.6
Skiing (Alpine)	15.4	23.1	30.8	3.3	5.0	6.7
Skiing (Cross-Country)	18.7	28.0	37.3	4.0	6.1	8.1
Skiing (Water)	12.5	18.8	25.0	2.7	4.1	5.4
Skipping rope	23.1	34.6	46.2	5.0	7.5	10.0
Squash	13.8	20.8	27.7	3.0	4.5	6.0
Swimming (backstroke)	6.2	9.2	12.3	1.3	2.0	2.7
Swimming (crawl)	7.7	11.5	15.4	1.7	2.5	3.3
Tennis	11.1	16.6	22.1	2.4	3.6	4.8
Volleyball	9.0	13.6	18.1	2.0	2.9	3.9
Walking at 3 km/h	5.6	8.4	11.2	1.2	1.8	2.4
Walking at 6 km/h	9.8	14.7	19.6	2.1	3.2	4.3

FIG 14

	ETS Cal expended by activities of a 60kg person			ETS expended by activities of a 60kg person		
TIME	30min	45min	60min	30min	45min	60min
Badminton	13.6	20.3	27.1	2.9	4.4	5.9
Baseball	11.3	16.9	22.5	2.4	3.7	4.9
Basketball	16.9	25.3	33.8	3.7	5.5	7.3
Bowling (non-stop)	16.0	24.0	32.0	3.5	5.2	6.9
Canoeing at 6.5 km/h	26.3	39.4	52.5	5.7	8.5	11.4
Cycling at 9 km/h	12.0	18.0	23.9	2.6	3.9	5.2
Cycling at 21 km/h	25.7	38.5	51.3	5.6	8.3	11.1
Dancing (moderate)	9.5	14.3	19.0	2.1	3.1	4.1
Dancing (vigorous)	14.3	21.4	28.6	3.1	4.6	6.2
Football	19.8	29.6	39.5	4.3	6.4	8.6
Golfing	9.8	14.7	19.6	2.1	3.2	4.3
Horseback Riding	16.2	24.2	32.3	3.5	5.3	7.0
Ping-Pong	9.2	13.8	18.5	2.0	3.0	4.0
Racquetball	20.8	31.2	41.5	4.5	6.8	9.0
Running at 9 km/h	25.7	38.5	51.3	5.6	8.3	11.1
Running at 11 km/h	33.5	50.2	66.9	7.3	10.9	14.5
Running at 19 km/h	47.0	70.5	94.0	10.2	15.3	20.4
Skiing (Alpine)	23.1	34.6	46.2	5.0	7.5	10.0
Skiing (Cross-Country)	28.0	42.0	56.0	6.1	9.1	12.1
Skiing (Water)	18.8	28.1	37.5	4.1	6.1	8.1
Skipping rope	34.6	51.9	69.2	7.5	11.3	15.0
Squash	20.8	31.2	41.5	4.5	6.8	9.0
Swimming (backstroke)	9.2	13.8	18.5	2.0	3.0	4.0
Swimming (crawl)	11.5	17.3	23.1	2.5	3.8	5.0
Tennis	16.6	24.9	33.2	3.6	5.4	7.2
Volleyball	13.6	20.3	27.1	2.9	4.4	5.9
Walking at 3 km/h	8.4	12.5	16.7	1.8	2.7	3.6
Walking at 6 km/h	14.7	22.1	29.4	3.2	4.8	6.4

FIG 15

	ETS Cal expended by activities of a 80kg person			ETS expended by activities of a 80kg person		
TIME	30min	45min	60min	30min	45min	60min
Badminton	18.1	27.1	36.2	3.9	5.9	7.8
Baseball	15.0	22.5	30.0	3.3	4.9	6.5
Basketball	22.5	33.8	45.0	4.9	7.3	9.8
Bowling (non-stop)	21.3	32.0	42.7	4.6	6.9	9.3
Canoeing at 6.5 km/h	35.0	52.5	70.0	7.6	11.4	15.2
Cycling at 9 km/h	16.0	23.9	31.9	3.5	5.2	6.9
Cycling at 21 km/h	34.2	51.3	68.5	7.4	11.1	14.8
Dancing (moderate)	12.7	19.0	25.4	2.8	4.1	5.5
Dancing (vigorous)	19.0	28.6	38.1	4.1	6.2	8.3
Football	26.3	39.5	52.7	5.7	8.6	11.4
Golfing	13.1	19.6	26.2	2.8	4.3	5.7
Horseback Riding	21.5	32.3	43.1	4.7	7.0	9.3
Ping-Pong	12.3	18.5	24.6	2.7	4.0	5.3
Racquetball	27.7	41.5	55.4	6.0	9.0	12.0
Running at 9 km/h	34.2	51.3	68.5	7.4	11.1	14.8
Running at 11 km/h	44.6	66.9	89.2	9.7	14.5	19.3
Running at 19 km/h	62.7	94.0	125.4	13.6	20.4	27.2
Skiing (Alpine)	30.8	46.2	61.5	6.7	10.0	13.3
Skiing (Cross-Country)	37.3	56.0	74.6	8.1	12.1	16.2
Skiing (Water)	25.0	37.5	50.0	5.4	8.1	10.8
Skipping rope	46.2	69.2	92.3	10.0	15.0	20.0
Squash	27.7	41.5	55.4	6.0	9.0	12.0
Swimming (backstroke)	12.3	18.5	24.6	2.7	4.0	5.3
Swimming (crawl)	15.4	23.1	30.8	3.3	5.0	6.7
Tennis	22.1	33.2	44.2	4.8	7.2	9.6
Volleyball	18.1	27.1	36.2	3.9	5.9	7.8
Walking at 3 km/h	11.2	16.7	22.3	2.4	3.6	4.8
Walking at 6 km/h	19.6	29.4	39.2	4.3	6.4	8.5

FIG 16

	ETS Cal expended by activities of a 100kg person			ETS expended by activities of a 100kg person		
TIME	30min	45min	60min	30min	45min	60min
Badminton	22.6	33.9	45.2	4.9	7.3	9.8
Baseball	18.8	28.1	37.5	4.1	6.1	8.1
Basketball	28.1	42.2	56.3	6.1	9.1	12.2
Bowling (non-stop)	26.7	40.0	53.4	5.8	8.7	11.6
Canoeing at 6.5 km/h	43.8	65.6	87.5	9.5	14.2	19.0
Cycling at 9 km/h	20.0	29.9	39.9	4.3	6.5	8.6
Cycling at 21 km/h	42.8	64.2	85.6	9.3	13.9	18.5
Dancing (moderate)	15.9	23.8	31.7	3.4	5.2	6.9
Dancing (vigorous)	23.8	35.7	47.6	5.2	7.7	10.3
Football	32.9	49.4	65.9	7.1	10.7	14.3
Golfing	16.3	24.5	32.7	3.5	5.3	7.1
Horseback Riding	26.9	40.4	53.8	5.8	8.8	11.7
Ping-Pong	15.4	23.1	30.8	3.3	5.0	6.7
Racquetball	34.6	51.9	69.2	7.5	11.3	15.0
Running at 9 km/h	42.8	64.2	85.6	9.3	13.9	18.5
Running at 11 km/h	55.8	83.7	111.5	12.1	18.1	24.2
Running at 19 km/h	78.4	117.5	156.7	17.0	25.5	34.0
Skiing (Alpine)	38.5	57.7	76.9	8.3	12.5	16.7
Skiing (Cross-Country)	46.6	70.0	93.3	10.1	15.2	20.2
Skiing (Water)	31.3	46.9	62.5	6.8	10.2	13.5
Skipping rope	57.7	86.5	115.4	12.5	18.8	25.0
Squash	34.6	51.9	69.2	7.5	11.3	15.0
Swimming (backstroke)	15.4	23.1	30.8	3.3	5.0	6.7
Swimming (crawl)	19.2	28.8	38.5	4.2	6.3	8.3
Tennis	27.6	41.5	55.3	6.0	9.0	12.0
Volleyball	22.6	33.9	45.2	4.9	7.3	9.8
Walking at 3 km/h	13.9	20.9	27.9	3.0	4.5	6.0
Walking at 6 km/h	24.5	36.8	49.0	5.3	8.0	10.6

FIG 17

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/055112

A. CLASSIFICATION OF SUBJECT MATTER
INV . A61M5/172

According to International Patent Classification (IPC) orto both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO **BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 2005/007223 A (JOHN SASHA [CA]) 27 January 2005 (2005-01-27) paragraph [0035] - paragraph [0174]	1-13
X	WO 95/28878 A (MINIMED INC [US]) 2 November 1995 (1995-11-02) page 5 , line 7 - page 9 , line 7 ; figure 1	1-13
X	WO 2007/051139 A (INSULET CORP [US]) 3 May 2007 (2007-05-03) the whole document	1-13
X	US 2005/261660 Al (CHOI SOO B [KR]) 24 November 2005 (2005-11-24) the whole document	1-13
X	US 5 364 346 A (SCHREZENMEIR JUERGEN [FR]) 15 November 1994 (1994-11-15) the whole document	1-13

D Further documents are listed in the continuation of Box C

[X] See patent family annex

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[1]L" document which may throw doubts on pπoπty claιm(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

[1]P[1] document published prior to the international filing date but later than the priority date claimed

[1]T" later document published after the international filing date or pπonty date and not in conflict with the application but cited to understand the principle or theory underlying the invention

[1]X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed Invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu¬ments, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2009	13/05/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV RiJSWIJk Tel (+31-70) 340-2040, Fax (+31-70) 340-3016	Neilier, Frederic

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2008/055112

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US 5364346 A	15-11-1994	NONE	