The Health Benefit of The Inflammation/Insulin Resistance Connection

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Universal Defence Mechanisms in Metabolism (Figure 1)

In human evolution, genes have survived coding for responses that allowed homo sapiens (mutatis mutandis also other species), when previously healthy, to survive at least for a few weeks during fasting or famines, often even when recovering from stressful events like trauma or infection, resynthesizing damaged tissue after trauma or infection, or during breastfeeding, physical growth or pregnancy. Signals from the wound or from our gonads, stimulate the pituitary gland, producing hormones that stimulate the immune system, in turn stimulating the inflammatory response, present in all these conditions. This response is remarkably similar in trauma, disease or infection, [1-4] exhibiting an initially “pro-oxidative” response, during which damaged tissue or infection is cleared. This has priority while the GH-IGF1 axis is inhibited. Consequently, full nutritional support is not beneficial and may even be harmful. Only when damage or infection have been successfully cleared, the GH-IGF1 axis is upregulated, in turn leading to a reparative “anti-inflammatory” response, during which nutritional support becomes effective and tissue is rebuilt. [5,6] Nevertheless the inflammatory response and its unpleasant symptoms are often “treated” with anti-inflammatory drugs that may in fact interfere with successfully countering recovery from trauma, infection or during physiological growth.
Another effect of the inflammatory response is that due to increased permeability and vasodilatation, vascular, interstitial and cellular volumes increase [5], leading to dilution of substrates in these compartments, often erroneously interpreted as deficiencies (Figure 2). Other sequelae are changes in glucose metabolism (insulin resistance) that may be beneficial. [6] These findings signify that the inflammatory response includes symptoms that often are unpleasant but should not be inhibited with drugs that interfere with these underlying mechanisms.[7, 8]. We will explain that in almost all “inflammatory conditions” changes in metabolism occur that have been evolved and survived in homo sapiens, its forefathers, and other species, because being adaptive and promoting survival of the individual and the species, and which therefore should not be inhibited.

Changes in Body Composition and Function During The Inflammatory Response (Figure 2)

During the inflammatory response, vascular, interstitial and possibly cellular volumes increase due to vasodilatation and increased capillary and cell membrane permeability, if well resuscitated, which implies that cardiac output should be increased maintaining blood pressure and urine production. [9] These changes facilitate delivery of substrates to healing or growing tissues. Plasma solutes (proteins, cholesterol, glucose, amino acids, fatty acids a.o.) and cells are allowed to enter at accelerated rates the interstitial space and cells, while in turn, damaged tissue elements are phagocytosed by immune cells locally and in liver and spleen. This supports the immune response, clearing debris and stimulating...
repair in all situations diverting from adult healthy life, i.e. trauma, infection, disease or life events. The volume of the interstitial space increases, largely related to increased interstitial oncotic pressure due to escape of plasma proteins from the vascular compartment into the interstitial space. This does not only occur in diseased or traumatized states but also, although modestly during growth of children, in pregnancy and while breast feeding, and decreases haematocrit and plasma solutes, consequently not necessarily reflecting deficiencies.[5] For example, a worldwide epidemic of vit D deficiency appears to be present in chronic diseases as well as in physiological conditions like pregnancy.[10,11] This is a clear example of reversed causality. In these disease conditions the inflammatory response leads to and requires increased plasma and interstitial volumes in which consequently many solutes, including crucial binding proteins (e.g. for vitamin D), trace-elements and haematocrit, dilute.[12] Consequently, vitamin, trace-element and electrolyte levels decrease, without reflecting a deficiency and not requiring supplementation.

**Figure 2: Upper part:** normal sizes of vascular, interstitial and cellular volumes. Increased capillary permeability promotes passage of plasma solutes and fluid from the vascular space (red) to enter the interstitial space, from where solutes can enter the cellular space. There is a continuous exchange of fluids between these spaces delivering substrates from the vascular compartment to the cells supporting cellular function and via the lymphatic system back to the venous system (via the left subclavian vein). Net losses from the vascular compartment needs to be replenished from exogenous intake. Ingestion of fluids, urine production and insensible losses are not shown.

**Lower part:** When well resuscitated there is in inflammatory conditions an increase in vascular volume by vasodilatation, and there is more rapid exchange with the interstitial space due to increased capillary permeability. Proteins also enter the interstitial space, increasing oncotic pressure and consequently increasing volume. Also exchange occurs between the interstitial space and the cells which also swell, aggravated by diminished membrane potential. Consequently, the interstitium increases in volume and most solutes in these compartments dilute, decreasing their concentrations as indicated by lighter colors. Very likely in this situation also cell swell, although intracellular protein and electrolyte concentrations decrease. Decades ago it was shown that membrane potential decrease.

At present, vitamin D supplementation is prescribed to many patients suffering from chronic disease or acute trauma/illness in view of the low vitamin D levels and a large number of other vitamins and trace-elements, found in these situations. In addition, in conditions of growth (pregnancy, puberty, breast feeding) the inflammatory state is also associated with increased plasma and interstitial volume, leading to dilution of all these solutes. It is telling that e.g. after elective surgery or during acute critical illness vitamin D levels (and other plasma solutes) decrease, while they normalize after recovery without supplementation. [13-18] This signifies that no true deficiency exists, which is also confirmed by lack of benefit when supplementing vitamin D in these conditions.[19] Even in our Western world in big cohorts there will always be a small group of true patients with short or dysfunctional bowel, leading to malabsorption, or individuals that willingly ingest hypocaloric diets, containing insufficient trace-elements and vitamins. Such individuals should and can be identified and require careful nutritional assessment and support. Similarly, due to increased blood volumes in inflammatory states, haematocrit drops, while erythrocyte mass may not be decreased. Low haematocrit may even play an adaptive role [20].

**Insulin Resistance and the Warburg Effect (Figures 3 and 4)**

The inflammatory response includes metabolic pathways in which repair and tissue maintenance are prioritized even when starving or during famines, and therefore utilizing endogenous substrate sparingly, allowing to survive as long as possible, thereby increasing the chances of recovery. This implies that the modest amount of glycogen and glucose, present in the body should not be fully oxidized, but predominantly utilized for crucial pathways that require glucose as building blocks and as substrate for the production of reducing equivalents, while energy is largely furnished by fatty acids or ketone bodies. [6] Contrary to what is often suggested in the literature, Warburg did not claim that glycolysis primarily served to generate ATP at times of hypoxia/
ischemia.[21] Specifically Crabtree found that no oxygen was required for the pathway from glucose to pyruvate and lactate and that this pathway was prioritized, but that there was also respiration (i.e. utilizing oxygen), in view of the introduction of glucose derived Acetyl-coA into the Krebs-cycle, while the flux of Acetyl-coA through this pathway was smaller than the flux through the glycolytic pathway during cancer growth.[22] Importantly, if the tissue could have had access to fatty acids, glucose oxidation might have been much lower, but glycolytic rates maintained or even increased, while cancer growth rate might have been even higher, in view of increased availability of glycolytic intermediates for cataplerotic production of building blocks. Crabtree emphasized that this type of metabolism did not only support growth of cancer tissue but also infectious tissue growths like cutaneous vaccinia lesions [22].

**Warburg effect, Cori-cycling and secondary glucose cycling**

![Figure 3: Cori-cycling and secondary glucose-cycling. The right half of the figure represents the Cori-cycle. Peripheral tissues deliver substrate (alanine, other amino acids and lactate), utilized by liver or kidney, producing glucose. Glucose can also be ingested. The left half of the figure represents secondary glucose-cycling. Glucose branches off from the Cori-cycle and is taken up by all proliferating cells and growing tissues, where part of the glucose is utilized as building block and for redox regulation. Another part of the glucose carbon is released back into the circulation as lactate and alanine and in turn resynthesized to glucose in liver and kidney. Intermediates of the glycolytic pathway (Warburg effect) branch off from the secondary glucose-cycles, furnishing reducing equivalents and serving for synthesis of a number of anabolic processes (see left half figure). Importantly, pyruvate is not further oxidized to acetyl-coA but is introduced into the TCA-cycle as oxalo-acetate after carboxylation. In turn, in the TCA-cycle intermediates can branch off supporting anabolic processes.](image-url)
Exchange of metabolites in rapidly growing situations (Pregnancy, breast feeding and Cancer)

Figure 4: Simplified representation of net exchange of metabolites utilized for growth (in green) and coverage of energy requirements (in red) of cancer, fetal and host tissues. Contrary to earlier belief Glucose oxidation is limited in all these tissues prioritizing biosynthetic functions. Consequently tissues largely rely on oxidation of fatty acids and ketone bodies. Net fluxes are schematically shown. In reality metabolism runs in futile cycles, in which eg in one organ/host a substrate is inserted in the cycle which is transformed at other sites (placenta, cancer cells, fetus, host tissue) and exits as another substrate or as the initial substrate in fetal or cancer tissue. Examples are for instance the Glutamine/Glutamic acid, the Serine/Glycine and the Branched Chain Amino Acid/Branched Chain Keto-Acid (probably predominantly Leucine) cycles. The placenta significantly modifies the substrate mix presented to the fetus and initially provided by the mother (see work of groups led by Battaglia FC [23-25] and van Goudoever JB[26]). Recent findings suggest that stromal cells (adipose tissue, fibroblasts, immunocytes) play similar roles in modifying the substrate mix presented in the systemic circulation and providing cancer cells with suitable fuel and building stones to proliferate (see work of Lisanti MP and coauthors[27]).

The Cori’s stated that, in vivo, continuous glucose availability is ensured by a cycle in which glucose is synthesized in the liver to glycogen while, subsequently glycogenolysis yields glucose that is released again in the circulation and degraded in peripheral tissues (predominantly muscle) to lactate (and alanine), which are released and resynthesized to glycogen in the liver. [28,29] However, Cori suggested later that predominantly gluconeogenesis, not necessarily followed by glycogen synthesis, is part of the cycle. This is plausible in view of the inhibition of glycogen synthesis during insulin resistance associated with any type of repair, growth and starvation. [30] It is therefore questionable whether glycogen is a continuous and integral part of the cycle, unless glucose is liberally ingested. The views on the function have somewhat changed. The cycle is a basal cycle acting as a shuttle in which glucose is continuously and partly degraded to lactate/pyruvate/alanine in all peripheral tissues, while these in turn are released in the circulation and taken up by kidney and liver, where they are resynthesized to glucose. In these peripheral tissues glucose can be taken up when necessary to synthesize tissue or regulate the redox state, when synthesizing reducing equivalents. To attain these anabolic effects, net glucose introduction into the Cori-cycle should occur, derived from food and when fasting largely derived from glucogenic muscle amino acid carbon chains and lipolysis derived glycerol. These responses are essential for survival, which will fail if overtime, 40% of pre-existent muscle protein mass, present in the healthy state, is lost [31]. The cycle runs at low speed in non-inflammatory conditions leading to only modest levels of glucose and lactate, but runs faster in the presence of inflammation to meet glucose requirements, which requires increased glucose ingestion or formation of new glucose and will accelerate muscle losses, supporting glucose synthesis.. This increased flux leads to modestly increased plasma concentrations of glucose (< 8-10 mmol) and lactate (< 3 mmol) in otherwise healthy individuals [32].

In conclusion, this (modified) Cori-cycle is a primary cycle (gluconeogenesis in liver and kidney and lactate and alanine production in peripheral (predominantly muscle tissue). From this cycle glucose can branch off, delivering glucose for redox regulation and tissue building when and where required. This leads to secondary cycles, because part of the glucose taken up as building blocks yields lactate and pyruvate, which are partly resynthesized in liver or kidney. After trauma or infection, anabolism or maintenance of body protein can only be achieved when the anti-inflammatory stage is reached, i.e., after successful clearance of infection or posttraumatic tissue debris during the pro-inflammatory phase. See previous section (Figures 3,4) During benign tissue synthesis (e.g. pregnancy, breast feeding, other types of growth) net body protein synthesis is increased, leading to net accumulation of protein in growing tissues.

**Hyperinsulinemia and The Crucial Role of Hyperglycemia**

An important consequence of the type of inflammatory metabolism described in the previous section is, that to maintain or to lower glucose levels, more insulin is required than in non-inflammatory states. This is the essence of insulin resistance. When liberal amounts of glucose are ingested in inflammatory states, the type of metabolism described in the previous section, still has priority, including gluconeogenesis and utilizing glucose primarily for synthetic and redox regulating purposes. The remaining glucose can be oxidized. Sparing glucose in the fasting state is crucial because in turn, it will also spare muscle protein, the predominant deliverer of gluconeogenic amino acid carbon, the main precursor of glucose formation by liver and kidney. This prolongs survival, when starving as well as when nourished. Under these conditions, lipolysis derived glycerol can be estimated to produce 10 g of glucose/day in a normally built adult human being, which is far less than delivered by gluconeogenesis from amino acid carbon from muscle (roughly 25-35 g) (Figure 4).

Increased gluconeogenesis and glycolytic rates (as part of Cori-cycling), and inhibition of glucose oxidation are the hallmarks of Insulin resistance, that is invariably present in all the conditions requiring cell proliferation, matrix deposition and redox regulation as mentioned in the first sentences of the introduction to this paper. A consequence of this role of glucose is that due to insulin resistance, and in view of the $K_\text{m}$s of glucose transporters, higher glucose levels are required than in non-inflammatory states, to increase glucose uptake and utilization for anabolic purposes and redox regulation in inflammatory states as mentioned in the first paragraph. Consequently, endeavours to “normalize” glucose levels to between 4-6 mmol decreases the metabolic flux through healing pathways and consequently compromises clinical outcome. Therefore, depending on the degree of critical illness, glucose levels higher than 6 mmol up to an estimated 10 mmol should be maintained, tailored to the severity or extent of illness, trauma or growth rate. Insulin administration is in these conditions a more logic treatment than oral antidiabetics that lower glucose levels by interfering with the adaptive metabolism, previously described for instance by promoting glucose oxidation (Table 1). Consequently, the pathophysiology driving increased glucose levels should not be interfered with but rather supported. In previously healthy lean individuals, subject to disease or trauma, these levels will be reached and are associated with diminished glucose oxidation and increased endogenous insulin secretion.

In chronic conditions like obesity or other chronic inflammatory diseases, long term hypersecretion and the chronic inflammatory state itself, may lead to damage to the pancreatic $\beta$-cells. This leads to failure to produce sufficient amounts of insulin, in turn requiring supplementation. Oral antidiabetics are generally the first line of treatment, but have risks because with the exception of acarbose all other oral antidiabetic drugs achieve lower glucose levels by interfering with beneficial metabolism (see Table 1). Insulin administration is a more causal treatment, although considered unpleasant because requiring parenteral administration and also (like oral antidiabetics) being associated with variable plasma glucose levels including the danger of developing hypoglycemia. The inventor of a feasible method to preserve or/from promoting $\beta$-cell function in chronic insulin resistant states should receive the Nobel price.
Table 1: In this table the metabolic effects of most available antidiabetic drugs on glucose metabolism, insulin secretion and anabolic actions of glucose are summarized. Arrows indicate whether pathways are stimulated or inhibited. The colors of the arrows indicate whether the changes are beneficial or harmful. NB. Urine production, stool losses and insensible losses not shown. Ingestion of fluids not shown.

Production of A Substrate Mix for Cell/Matrix Synthesis and Redox Regulation

Sparing muscle protein is not only crucial for movement, but in collaboration with the liver and kidney, also required for the synthesis of a substrate mix, suitable for repair, tissue growth and redox regulation. This mix contains glucose and all 20 different amino acids present in muscle protein but with lower amounts of branched chain amino acids than are present in muscle, because these last ones substantially supporting the synthesis of extra non-essential amino acids higher than present in muscle protein: Glutamine, Glutamic acid, Alanine, Serine, Glycine and Proline. Simultaneously, muscle furnishes pyruvate/lactate and alanine, that are part of the Cori-cycle and act as substrate for glucose formation, while in situations of growth etc, the only amino acid produced by the liver in a net fashion is Glutamic acid, which in turn supports Glutamine synthesis in peripheral predominantly muscle tissue. This type of metabolism is accelerated during growth and is facilitated by SGOT (AST) and SGPT (ALT), and explains their increased plasma concentrations Figure. This mixture is well suited for the immune response, redox regulation and cell and matrix synthesis.
Interestingly, in this situation cholesterol synthesis is enhanced (a crucial building block for cell proliferation and substrate for hormone production) while in the first two steps of the degradation of Leucine, the most abundant essential amino acid in muscle, 3-Hydroxy-Methyl-Glutaryl-coA is produced, from which in one step cholesterol can be produced. Whether this pathway is active, is not established as far as we know. Consequently, in starvation with or without ongoing disease activity or other types of tissue growth, the macronutrient determining survival is the amount of muscle (protein), unless the individual is extremely lean, with only 5-7% of body weight consisting of adipose tissue. In that situation endogenous fatty acid delivery and oxidation will be failing first, leading to the King Penguin syndrome and death. [33] When adipose tissue amounts to a normally 15-30% of body weight (higher in women than in men), sufficient adipose tissue is present not limiting survival, covering most of the caloric requirements and, to a much lesser degree than muscle protein, also furnishing modest amounts of lipid, required for tissue synthesis and other functions (cholesterol, phospholipids, sphingolipids and others). Only some important fatty acids (omega-3-fatty acids) cannot be synthesized and need to be provided in food.

The stronger the pro-inflammatory response, (for instance required during major traumatic damage or severe infection, not yet adequately dealt with), the more glucose and amino acids are required in the pro-inflammatory phase to clear damage, leading to a more rapid loss of muscle mass, which cannot be inhibited by nutritional support. This situation leads to mortality after 2-3 weeks in unrelenting sepsis or in severe and persisting traumatic damage and debris in previously well-nourished individuals, when approximately 40% of muscle mass has been lost. The world has witnessed enormous muscle losses in especially elderly patients generally already having less muscle mass, barely recovering from Covid after 2 weeks of sepsis. Recovery is heralded when urine production increases, oedema diminishes and Haemoglobin, haematocrit, albumin and other plasma solutes increase due to a decrease in plasma and interstitial volume and probably cellular volume (see section on the inflammatory response). (Figure 1) At this stage, true loss of muscle mass becomes visible due to loss of oedema. It has been demonstrated in persisting critical illness that hypocaloric nutritional support, covering approximately 50% of requirements at the height of the proinflammatory response, achieves similar or even better outcome than administering 100% of estimated caloric requirements. Similarly, in large cohorts in children or adults suffering from critical illness, full parenteral nutritional support has been shown to be associated with increased mortality. [7,34,35].

In pure starvation without coinciding stresses, or after successful clearance of damage or infection, daily muscle losses may amount to one third of the amount during severe disease, because far less amino acid carbon and nitrogen is required for maintenance than during the immune response in diseased or otherwise stressed states. Consequently, In pure starvation survival may amount to six weeks if previously healthy and well nourished.

The Quality of Food Protein and Nutritional Benefit During The Inflammatory Response?

Ingested protein is after absorption and digestion to amino-acids not immediately fully offered to the liver,[36, 37] but is initially at least partly utilized for the synthesis of protein in the gut wall, which is thereafter slowly degraded and released into the portal vein. This protein may partly consist of rapidly turning over intestinal mucosa cells but very likely to a greater degree of exocrine digestive enzymes, rapidly synthesized to digest ingested protein and other food components. These rapidly synthesized digestive exocrine enzymes may be this temporary reservoir of protein although definitive proof of this suggestion is missing. Subsequently, the amino acids derived from digestion of food protein and from the digestive enzymes themselves are slowly presented to the liver, which “has enough time” to utilize these amino acids for anabolic purposes, while, when a meal of sufficient size and balanced composition, in health another portion is released by the liver into the systemic circulation for anabolic purposes elsewhere in the body. Three different mechanisms support the art and extent of this protein sparing type of metabolism. Firstly, absorption in the stomach, duodenum and jejunum should be slow. In this respect casein is a suitable protein because flocculating in the stomach and consequently only slowly appearing in the duodenum and jejunum and their output. Secondly, the amino acid composition of the protein should be balanced and at least contain a substantial amount of all essential amino acids. An example consists of the toxic effects (increased urea production) of bleeding in oesophagus and stomach, presenting the liver with an unbalanced amino acid composition because Haemoglobin lacks one essential amino acid i.e. Isoleucine, so that ingestion of Haemoglobin yields after breakdown an amino acid mix, unsuitable for protein synthesis.

A third factor ameliorating anabolism consists of the composition of meals, which crucially determines whether food ingested will have optimal anabolic effects. Lipids, carbohydrates (allowing to provide glucose) and protein should always be ingested together while the way and rapidity with which food is ingested and digested crucially determines its benefit. The faster absorption and digestion occur, the more rapid free amino acids will appear in the portal vein and offered to the liver, which will in this situation produce more urea than when amino acids are offered to the liver slowly, allowing synthesis of protein and other products. Consequently, passage and absorption of a bolus meal should preferably be slow, allowing the intestine to absorb
balanced food fully, in turn leading to slow degradation of protein to amino acids, in turn allowing to resynthesize protein in the gut wall itself, which thereafter is degraded again and slowly offered to the liver, promoting protein synthesis. Consequently, three factors determine this: an unbalanced amino acid composition, precluding, after digestion and absorption, resynthesis of protein in the gut, in addition bolus feeding or more protracted ingestion of food, and finally addition of glucose, promoting protein synthesis in the gut wall. Another question is which factors determine the benefit of nutrition. First, during the pro-inflammatory state full nutritional support is not effective and may even be harmful. (see previous section). “No anabolic effect (positive muscle protein balance) of nutritional support in the pro-inflammatory phase” requires a nuance, in the sense that, while during this phase debris, damage or infection need to be cleared, which requires a metabolic action utilizing substrate specifically supporting the production of immune cells to clear damage. However, during this phase, protein kinetics are such that muscle mass will be lost. Previously severely malnourished individuals will fail to clear damage, implying that at least sufficient nutrition should be ingested allowing to successfully achieve this, while vitamins, trace-elements and electrolytes should also be included. Some data suggest that in this respect, in the pro-inflammatory phase limited amounts (50% of requirements) execute this process better than when full nutritional support is applied [7,8,38-40].

**Drug Related Interference with and Misconceptions Regarding the Inflammatory Response.**

**Anti-inflammatory Drugs (NSAIDs)**

Genes have persisted, coding for a type of metabolism, allowing to protect the organism long enough to allow procreation and protect and raise children to independency. In the presence of chronic illnesses or unhealthy lifestyle, the inflammatory response leads to repair, which is also associated with scar formation as shown for instance by skin wrinkling, cardiac and muscle stiffening and early atherosclerosis and may be considered to be “the best the body can do”. Nevertheless, we actively try to inhibit the sometimes-unpleasant accompanying symptoms of these chronic inflammatory responses, despite also inhibiting their benefit. These abnormalities are generally accompanied by fatty liver and are part of the metabolic syndrome. During aging without suffering from associated illness or maintaining an unhealthy lifestyle, these abnormalities do not evolve or at least to a much lesser degree and decades later. The universal growth promoting and redox regulating effects of the inflammatory response imply that anti-inflammatory drugs interfere with these health promoting responses. Proof for this is abundant as evidenced by NSAIDs induced intestinal damage, bleeding and perforations [41-44], premature birth and cryptorchism in pregnancy,[44-46] aggravating cardiac and renal failure, [47,48] worsening of wound and bone healing,[49-51] increasing the risk of anastomotic intestinal failure and post-operative sepsis and others.[52] Possibly in auto-immune diseases like Crohn’s disease, NSAIDs may be beneficial because dealing with the disease despite also interfering with maintenance of fat free mass. Crohn’s disease is a disease, in which the normal defensive responses against bacterial toxins and nutritional antigens, are stuck in the pro-inflammatory phase of the inflammatory response, causing damage (inflammation and ultimately scarring) to the bowel wall.[53] Along a similar line of reasoning, it is logic that for instance Ketorolac (an NSAID) has been found in a large cohort of women that had been treated for breast cancer, to diminish the incidence of recurrent breast cancer after breast surgery [54,55].

**Oral Antidiabetics and Levels of Plasma Glucose to Aim for**

In the section on Insulin resistance, an explanation is proposed, why aiming for normal glucose levels in health amounting to between 4-6 mmol is not effective in inflammatory states, because decreasing the amount of glucose available for the organism as substrate for anabolic and redox regulating pathways. [56] In hyperinsulinemic clamp studies glucose flux through non-oxidative and thus anabolic pathways has been found to increase when aiming for higher glucose levels or when more glucose administration was required when clamping insulin at a higher level. [57,58] Outcome in critically ill patients has been found to improve when aiming for higher glucose levels although providing full nutritional support does not seem beneficial in the pro-inflammatory phase. It seems advisable in this stage to maintain cardio-respiratory stability with fluids and electrolytes and, when stable but still in the proinflammatory phase to administer hypocaloric nutrition containing glucose, protein/ amino acids, electrolytes and trace-elements/vitamins [59]. Oral antidiabetic drugs are in general the first line of treatment in patients with type II diabetes. Type II diabetes results when chronic inflammatory illnesses like obesity, COPD, rheumatoid arthritis and others, also requiring hypersecretion of insulin, lead to atrophy of pancreatic islets and inability to produce sufficient insulin to maintain normal (in this situation slightly increased) plasma glucose levels.[60] The working mechanism of oral antidiabetic drugs relies on changing metabolism among others by promoting glucose excretion in the urine, inhibiting gluconeogenesis or promoting glucose oxidation. Not only are these treatment modalities fraught with risks of hypoglycaemia, they also interfere with the anabolic and defensive actions, of insulin resistance, leading to deficient healing and failing anabolic effects and, among others cardiovascular disease. Parenteral insulin administration is a more causal treatment, although being unpleasant because requiring parenteral administration and also being associated with variable plasma
Interestingly, in truly old age for instance in frailty and cachexia, also occurring during aging without pre-existent chronic diseases.

ischemia of affected organs or structures. This is almost always continue leading to hypertension, stricturing of vessel walls and inadequately dealt with or cannot be healed, atherogenesis will rather is required for repair of damage to the arterial wall, in which case the body needs to raise an inflammatory response in health and disease. However, in chronic disease, metabolic syndrome develops, increasing ectopic lipid deposition in and around a number of organs including the arterial wall, leading to the development of atherosclerosis. Present views are that cholesterol is not causing atherosclerosis but rather is required for repair of damage to the arterial wall, in fact occurring at an accelerated rate in every disease or situation of growth (pregnancy, puberty etc). When the disease is not adequately dealt with or cannot be healed, atherogenesis will continue leading to hypertension, stricturing of vessel walls and ischemia of affected organs or structures. This is almost always also occurring during aging without pre-existing chronic diseases. Interestingly, in truly old age for instance in frailty and cachexia, the organism cannot raise cholesterol levels anymore, which is a bad prognostic sign and is called the aging cholesterol paradox. The view that hypercholesterolemia is an adaptive response, ensuring cell wall building and hormone production, should urge the medical and nutritional community to question the widespread prescription of Statins.

Elements, Underlying The Beneficial Role Played by the Inflammatory Response

Why do we not appreciate the beneficial role of the metabolic changes mentioned in the previous pages or alternatively, if we do appreciate them, why do we try to inhibit them in an effort to “normalize” the symptoms of these changes? Is it still pure ignorance, arising from the type of teaching in medicine and nutrition, that has become popular in recent decades? This is in the medical and nutritional sciences increasingly based on algorithms or protocols, and often focuses on dealing with physical symptomatology and plasma parameters, deviating from the normal adult healthy state, by prescribing anti-inflammatory drugs. An additional and equally worrying factor may be that efforts to “normalize” physical symptoms or deviating plasma and other parameters lead to a revenue model from which Big Pharma and the medical and nutritional professions benefit financially. An underlying cause of these two reasons is that present day teaching medicine in general precludes a holistic insight in the reactions of the body to inflammatory states as mentioned in the previous sections of this paper. Hospital doctors in particular (are required to) specialize in continuously shrinking areas, which makes it difficult to understand the pathophysiologic behaviour of the organism when challenged and its benefit. General practitioners and intensivists have a more holistic perspective but are also obliged to follow algorithms agreed upon during consensus meetings of international scientific organisations, often supported by industry. Consequently, physicians and nutritionists do not know, whether to stimulate or to inhibit the inflammatory response, and when to divert from the protocols or consensus reports.

Conclusion

The inflammatory response is a universal metabolic mechanism, supporting growth, defence and redox regulation during pregnancy, child’s growth into adulthood, breast feeding, trauma, chronic disease, infection and cancer. After trauma and infection there is first a pro-inflammatory phase, during which debris or damaged tissues should be cleared and infection healed. An anti-inflammatory phase follows in which tissue is rebuilt and oxidative stress neutralized, while only in this phase nutritional support is beneficial, leading to anabolism. There is much confusion regarding the true messages of Warburg and Crabtree, which have explained that in cancer and during growth of benign
tissue, glycolytic flux is higher than respiratory flux (TCA-cycle) implying that glucose is glycolytically degraded at a higher rate than introduced as acetyl-coA (for oxidation) into the TCA-cycle. In glycolysis, intermediates branch off for anaplerosis, while part of the pyruvate, produced in glycolysis, is anaplerotically introduced into the TCA-cycle forming oxaloacetate. While doing this, glucose supports the cataplerotic production of intermediates in the glycolytic pathway and in the TCA-cycle, supporting delivery of substrates/building blocks for the synthesis of a large number of other substrates like nucleic acids, non-essential amino acid carbon and reducing equivalents, supporting the inflammatory response including tissue synthesis and redox regulation.

In inflammatory states, without exception the body is insulin resistant, implying that more insulin is required to lower glucose levels than in healthy non-stressed states, but also that higher glucose levels are required to provide glucose for anabolic and redox regulating actions. The response includes inhibition of glucose oxidation, in this way sparing the little glucose that is available in the body for those pathways that can only run on glucose. Limiting the utilization of glucose spares muscle mass, which is the main supplier of substrate for the production of glucose in many situations where nutrition is not ingested or the body is subject to an inflammatory response. This arrangement promotes long-term survival during famines or fasting with or without trauma, infection and during pregnancy and other situations e.g. when growth or countering stress are required. With the exception of cancer growth or auto-immune disease, the inflammatory response and insulin resistance are beneficial survival mechanisms, which should not be inhibited, while in inflammatory conditions modest hyperglycemia should be aimed for (8-10 mmol) to stimulate flux through the beneficial pathways mentioned. This explains the harm afflicted by NSAIDs, oral antidiabetic drugs, and the absence of by far the majority of the claimed deficiencies of vitamins and trace-elements, which are during the inflammatory response diluted in a larger plasma and interstitial volume, while the concentration of some proteins (like e.g. albumin), to which they are partly bind, decrease. As a consequence, we stress the importance to study and teach intermediary metabolism to basic scientists and medics or nutritionists to appreciate whether their findings play a positive or negative survival role in intermediate metabolism, and consequently, whether drugs are supportive or inhibitory and should be prescribed or omitted. [63,64].

References
