

# Positive energy imbalance and microflora overgrowth

## Abstract

At meals, people aim to maintain their usual energy level and balance in blood and all tissues. People have subjectively formed this aim through months and years poorly consciously, i.e., outside any comparison with other people, other times or feeding conditions. The aim can be assessed as the weekly mean BG,  $\pm 3.8$  mg/dL (confidence interval) and may be evaluated in the overall stratification. After 2-48 hours of meal suspension, the aim spontaneously arises as Initial Hunger (IH). Recognition of three IH arousals per day produces an even energy balance and eliminates any conditioned intake at 20% lower energy intake, 20% lower Mean BG, 20% lower RMR and 30% lower insulin resistance than automatic, conditioned feeding.

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## Immunogenic bacteria

Minimal bacteria growth on small intestinal mucosa is associated with prompt absorption of food, as happens during insulin sensitivity.<sup>1-68</sup> Any meal by meal excess intake over expenditure (insulin resistance) fosters microflora growth and reversible immune deficiency (RID: subclinical inflammation, overall inflammatory state, or pro-inflammatory state).<sup>1,2,66-71</sup> Overweight is the cumulative result of meal by meal positive balance for a period of time. Weight increase and fattening produce an increase in insulin resistance and RID. A weight stable is poorly effective on subclinical inflammation, and weight decreases diminish the overall inflammation. In the small intestine, unabsorbed food becomes harmful to mucosa and all the body for the existence of bacteria in the intestinal lumen and the possibility of an active proliferation inside the lumen until food is available.<sup>68</sup> On the contrary, rearing experimental animals without bacteria reduced to 10% cellular infiltration and immunoglobulin production in small intestine mucosa.<sup>70</sup> Tropical enteropathy exhibits a denser infiltrate than normal mucosa in dependence on absorption slowdown in a warm and humid climate.

The conception of intestinal saprophytes was rather naïve. Bacteria grow in the colon and everywhere in dependence of water and available nutrients and temperature. Water is freely available on mucosal surfaces, and nutrients (carbohydrates, proteins) depend on eating and more precisely on current energy balance. We compared the xylose absorption rate in two groups of experimental animals, one at the environmental temperature of 30 °C and the other at 6 °C environmental temperature.<sup>59</sup> At high environmental temperature, the absorption rate halved in comparison to animals kept at low temperature. We obtained similar results in humans.<sup>60</sup> A slowdown of metabolic and absorption rates explain unexpected microflora growth.<sup>59-64</sup> Bacteria in the colon double every day, very slowly in comparison with growth in the small intestine, where bacteria can double every 15 minutes.<sup>68</sup> Bacteria obtain little energy from non-absorbable, indigestible fibers in absence of oxygen. All meat, bread and every good meal component do not arrive to the colon. These highly energetic foods would promote an explosive growth. The rumen is similar to the human colon in hosting bacteria in an ambient that has poor nutrients and is absolutely devoid of oxygen. Energy rich nutrients let develop one-two liters of carbodioxid per minute in the rumen. The small intestine is also anaerobic, and oxygen

absence increases toward the end of the intestine. 60% of bacteria do not stimulate any immune response.<sup>69</sup> 10%-15% evoke a response by IgG lymphocytes and neutrophils that are destructive on invading bacteria, mucosa and overall in the body by subclinical inflammation. Minimal bacteria growth requires minimal persistence of nutrients in the small intestine lumen like on teeth. This depends on intake amount and rhythm. Amounts and intervals can be externally decided by doctors, who apply standard international averages from healthy people. Any decision about eating start, the amount and any stop may better be taken by the subject's estimation of personal cues on the personal energy balance. The suspension of food administration to a healthy baby with functional bowel disorders provoked crying for hunger (Initial Hunger, IH) within 48 hours of time.<sup>39,40</sup> This cue was subjective although being more certain than any laboratory measure. As pediatricians, we provisionally assumed that crying for hunger corresponded to initial emptiness of stomach and small intestine and to the time of most active absorption.<sup>39,40</sup> The administration amount might correspond to expenditure in the interval between subsequent similar meal demands. This correspondence is exact in the long (monthly) period. Insulin resistance may sometimes arise independently from eating, like during psychological stress and fever. A transient break in eating is useful in these events that are associated with insulin resistance. Although the energy expenditure increases and body energy balance is negative during fever, preprandial BG remains high, and the balance in blood is positive for energy influx from fat stores.<sup>71-73</sup> We consider this divergence as acceptable and normal. Hormones that allow the body to meet stress such as cortisol, cortisol releasing factor, and serotonin together raise blood glucose concentration, activate mast cells, monocytes, and macrophages, increase intestinal permeability, and contribute to subclinical inflammation-essentially the same effects as eating in the absence of IH. Suspension of meals for one three days is accepted. Yet the balance problem becomes difficult when a stressful condition persists for weeks.<sup>1,2</sup>

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The maintenance of inflammation is much more pronounced in the mucosa of the small intestine than in that of the colon. The more intense conflict against the luminal content may depend on the surface area that has been estimated as high as 10 000 square meters in the

small intestine. The colon surface is devoid of villi and microvilli and may be about one square meter. One-two percent of big molecules in the lumen cross the small intestine epithelium, and exercises an immune stimulation inside the mucosa. For unknown reasons, bacteria exert immune stimulation more than food.<sup>70</sup> We insist that bacteria multiply in dependence on nutrients availability, mainly on energy and iron. The host gives ammonium for bacterial proteins. Minimal bacteria growth on the mucosa is a necessary step to achieve health, like on the periodontal mucosa. During positive energy imbalance, the small intestinal absorption slows down; intestinal microflora grows and produces an increase in the inflammatory infiltrate in the small intestine and reversible functional derangements.<sup>65-70</sup> In experimental animals, we have described an increase of inflammatory cells in the mucosa after administration of broth culture containing *Escherichia coli*.<sup>75-77</sup> This bacterium was not a pathogen, but elicited an inflammatory response, as an immunogenic component of intestinal microflora. We showed an increase in bacteria number in biopsies of children during absorption and a decrease in bacteria number after the last meal.<sup>70-72</sup> Subjects with irritable bowel syndrome (in infancy, chronic nonspecific diarrhea) actually show an increase in mucosal inflammatory cells.<sup>78-84</sup> Suppression and a decrease in intake cured these diarrheic toddlers by subtracting nutrients to mucosal microflora. Decrease in insulin resistance and in overall inflammation might have influenced the recovery.

## Immune involvement

In our laboratory hypothesis, each meal carries on a battle. Every meal renews or reignites the never ending conflict between bacteria growing on mucosa and immune reaction. Sometimes the conflict is acute, symptomatic; more often damages all body although progressing without any awareness (overall subclinical inflammation). Bacteria double every 10-20 minutes in the small intestinal nutrients.<sup>60-64,78-96</sup> The mucosa of the small intestine hosts half the body production of immune cells and sustains a permanent moderate local inflammation, consisting of IgA and phagocytic responses, “tolerant” inflammation.<sup>97-99</sup> About one hundred commensal bacteria are immunogenic in the human intestine.<sup>69</sup> An increase in this bacterial growth to about one billion per gram of mucosa provokes increase in production of lymphocyte and of IgG antibodies and reactions with mucosal damages.<sup>75-89</sup> The local inflammation discharges antigens and activated monocytes in circulation, producing a subclinical inflammation throughout the body.<sup>1-25</sup> This inflammation has received many names: overall inflammation, proinflammatory state and Reversible Immune Deficiency (RID).<sup>2</sup> We preferred these two last names to emphasize the detrimental, immune involvement of the entire body from meal energy intakes that are unbalanced by correspondent high energy expenditure. This immune involvement increases and prolongs all localized inflammations and worsens general diseases.<sup>1-25</sup> The suppression of the immune stimulation of intestinal mucosa was the strategy for a new life, for recovery from infection, from immune illnesses and from malnutrition as well as from obesity and to prevent risks and deterioration for everybody. Short absorption times (two-three hours) alternated with periods of emptiness may achieve this goal.

## Overall subclinical inflammation

“Insulin resistance” is associated with a “pro-inflammatory state” or “subclinical inflammation”, and the association is supported by a huge amount of research.<sup>1-25,97-99</sup> The findings of this association represent a high achievement in understanding human nutrition and health. The general acceptance of this association took unfortunately 80 years.<sup>22-25</sup> Persistent unbalanced energy intake and/or psychophysical stresses

modify the activity of monocytes, macrophages and mast cells, and together alter the neuro-endocrine system.<sup>1-25</sup> These disorders increase intestinal permeability.<sup>95</sup> Bacterial biofilms may develop inside the alimentary canal and produce endotoxins that invade blood and all tissues. Immunogenic bacteria induce a huge biological pressure on human immune system and deep functional alterations. The invasion of body tissues by bacterial products and endotoxins sustains subclinical inflammation and causes the slow progression of many chronic diseases, like asthma and rheumatoid arthritis. Thus, body tissues develop a pro-inflammatory state (subclinical inflammation, a synonym) that is sterile, ineffective and dangerous for body tissues in the intestine and elsewhere.

## Health as minimal immune stimulation

The antibiotic treatment of pneumonia and consequent recovery shows the potential harm of some of the 30-100 bacterial species that may spread from the alimentary canal and superimpose on a viral infection. An abundance of nutrients, slowdown of absorption and microflora overgrowth begin the causal chain between intake and subclinical inflammation, functional disorders, deterioration and risks. The nutrient abundance just coincides with insulin resistance and progression in fattening, two events that are associated even when appear alone. Also the absorption slowdown coincides with the condition of insulin resistance, although the evidence is poorer. In animal experiments, insulin infusion into portal vein increased intestinal absorption rate.<sup>80</sup> After a similar intake, we found a decrease in the absorption rate in a warm environment in comparison with a cold environment in both animal and human experiments.<sup>59,60,72</sup> The cold environment is associated with higher energy expenditure than the warm one.<sup>6</sup> The increase in energy expenditure decreases insulin resistance.<sup>62-64</sup> We may mention also the absorption slowdown that is well known and accepted during infection and inflammation.<sup>71</sup> We conclude that healthy nutrition, at least provisionally, coincides with insulin sensitivity, whereas slow absorption and subclinical inflammation (Reversible Immune Deficiency, RID) develop during an increase in insulin resistance. In our studies, disordered bacteria growth on intestinal mucosa and overall subclinical inflammation are due to a unifying pathogenic factor, insulin resistance.

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## Conflicts of interest

The authors declare no conflicts of interest.

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