Abstract. We have carried out a series of investigations to contrast childhood fattening due to a consumption of excess calories, a severe problem in developed countries. Scheduled meals are considered to be equivalent to those demanded by the infant (null hypothesis). In adults, we have found high blood glucose (BG) before scheduled meals and low blood glucose after recognition of validated Initial Hunger (demand in infants) that we indicate as IH before a single meal and as Hunger Recognition as a trained meal pattern before meals. High preprandial BG was taken as a sign of incomplete exhaustion of a previous meal consumption and low BG as a validation of regular IH Recognition. In home week diaries of recruitment, we found low preprandial BG in a quarter of the infant and in a quarter of the adult population in association with normal weight, insulin sensitivity and no response to training IH Recognition. Instead, Hunger Recognition decreased energy intake and body weight both in adults who are overtly overweight and in those who are normal weight with insulin resistance. Below 25 Index of Body Mass (IBM) we consider hidden overweight in people with insulin resistance. In 24 clinically healthy toddlers
with chronic/recurrent diarrhea (21 months old at entry), Hunger Recognition lowered energy intake in comparison with scheduled meals. Energy intake decreased from 85.7 ± 15.3 to 70.3 ± 15.8 kcal/kg/d (P < 0.001), and hospital laboratory measurements showed an association of Hunger Recognition with lower BG before demanded meals than before scheduled meals. Weight growth was normal and height Z score increased significantly. In a subset of 14 toddlers we found a decrease of resting (sleeping) metabolic rate (RMR) four hours after lunch by respiratory analyses (indirect calorimetry) from 58.6±7.8 to 49.0±9.1 kcal/kg/d (P < 0.001). In further 10 toddlers we found a decrease of total daily energy expenditure (TEE) by doubly labeled water from 80.1±6.9 to 67.8±10.0 kcal/kg/d (P < 0.001). The decrease in energy intake was not compensated by fecal energy loss or by spared energy for less physical activity. Energy intake per kg that we estimated by home diary showed no difference from TEE at recruitment (P = 0.39), after training (P = 0.28), and on pre/post decreases (P = 0.90). This similarity validated diary reports of lower energy intake and lower BG after training. Toddlers entering the study over the median RMR decreased their RMR significantly more than those below the median RMR (P < 0.01).

**Conclusion:** By association with BG, subjects learned an objective/subjective threshold in hunger sensations (IH) although these were totally subjective. This subjective threshold that coincides with a precise low BG can be used to self-impose bearable limits in energy intake (equal to the requirement for spontaneous IH arousal at planned mealtimes) that can be maintained without any trouble for long periods. The bearable limit in BG is spontaneously maintained by a quarter of the population. A low BG is in turn associated with low metabolic rate and with insulin sensitivity that is strongly associated with an abatement of Reversible Immune Deficiency (subclinical inflammation) and better health. Hunger Recognition maintains efficiency and better health like the healthiest quarter of the population does.

**Introduction: A threshold for insufficient blood glucose**

Meal sizes and insulin releases largely determine energy availability during the inter-meal interval [1 - 12]. BG, fats and aminoacids are in correlation inside blood [13 - 15]. Healthy people on a mixed diet oxidize BG before other nutrients, except for alcohol [13, 16 - 20]. An abundance of other nutrients spares BG, but does not stop its decline because carbohydrate reserves are exhaustible and its production is limited [1 - 6, 12]. In contrast, blood fatty acids do not depend on balance in fat intake and oxidation but on acute changes in storage and emission [19, 20]. In extensive rat studies, Steffens [6] measured glucose at discrete intervals, and showed that blood glucose concentration declined before a meal, remaining at a lower plateau until another meal started, and rose sharply shortly after the initiation of a meal. Transient blood glucose drops coincided with spontaneous sensations of hunger and meal initiation in humans and rats, suggesting that these sensations correlate with exhaustion of previous intake and with development
of insufficiency of metabolic energy [7 - 12]. In humans, the condition of hunger was associated with a BG of 80 mg/dL or lower [7 - 13], and was exacerbated by injection or infusion of insulin [11]. Thus, we assumed that BG represented approximately (and RMR more thoroughly) all nutrients in blood, i.e., instant energy availability and the level of current balance between influx and eflux of energy in blood [7 - 15]. Blood glucose has long been considered a biomarker of hunger [5 - 13]. After end of absorption, fatty stores provide fatty acids to blood in limited amount. BG has a physiological decrease and reaches the set point for insufficient nutrient provision to body. Sensations (Hunger) suggest food supply to the body. At this moment, BG indicates energy balance in the last inter-meal interval [16 - 20]. Before meals, low BG reveals sufficiency until the mealtime, and very low BG reveals insufficiency of previous meal energy intake. Preprandial BG is an assessment of intake in the last meal in proportion to expenditures, it is an assessment of energy balance between subsequent meals, and may be positive, null or negative. The weekly mean of pre-meal BG indicates the habitual level of energy provision to the body in proportion to expenditures.

**Specificity of chronic diarrheic infants**

Our Unit largely studied infants in their second year of life with chronic or recurrent diarrhea and found that they do not represent all population of the same age. These infants are slim but not weak: they have thin skinfold thickness and normal arm muscle area [21 - 25]. Skinfold thickness is on the 15th percentile of the normal reference distribution [31], and basal insulin is low at the age of 6, after four years from recovery [23]. In children, we were unable to show regression of insulin resistance after decrease of energy intake and cessation of diarrhea although we performed glucose tolerance tests [22, 25, 30]. We attribute our failure to the thinness in increase and decrease of fat tissue in these subjects that is sufficient to either produce or reduce insulin resistance. Insulin resistance consists in fattening, i.e., in volume increase of adipocytes. Adipocyte proliferation acquires a role after many months of positive energy balance. In adults, and also in normal children, adipocyte enlargement is revealed by thickening of skinfolds. Diarrheic toddlers have a low adipocyte number for a familial or genetic cause. The low number allows rapid enlargement of fatty cells, in a matter of days [23]. A transient increase in adipocyte size has little effect on the thickness of subcutaneous tissues and even a lower effect on body weight and BMI [1 - 4]. The small changes in the tiny infants’ skinfold thickness may remain within the error of measurement in the first six years of age [23 - 25]. The adipocyte enlargement increases the fatty acid flux into blood and into all the body.
This increased flux characterizes insulin resistance [32, 33]. Thus chronic diarrheic toddlers have metabolic conditions of energy accumulation that are opposite to those of overweight children [23]. Children with large production of insulin maintain a positive energy balance for long periods with progressive fattening, high insulin and no functional disorder [25]. We may thus consider chronic diarrhea as a manifestation of subclinical inflammation (proinflammatory state) that arises and disappears easily in association to transient insulin resistance [25]. For an increase in general awareness, we recently named this avoidable, unapparent, transient condition as Reversible Immune Deficiency (RID) to emphasize its association with risks. The cessation of recurrent diarrhea and the decrease in plasma BG and triglycerides [25, 30] after training suggests an overcoming the period of subclinical inflammation (Reversible Immune Deficiency, RID) associated with insulin resistance [34 - 40]. We exploited the mothers’ anxiety for this selfrecovering disease to train IH or Hunger Recognition (see later). The learned skill for Hunger Recognition may be either remembered as a skill or maintained by pancreas changes in the subject’s adulthood [41] to reduce fattening, subclinical inflammation (RID) and risks [34 - 40]. In this formation of a future adult, we had the unlimited, conscious concourse of mothers. On the other hand, infants did not show any evidence of malnutrition by enduring IH Recognition. Growth was normal in weight and was increased in height [30]. Folic acid significantly increased after training [30]. Children improved physical activity after training. Rest hours did not change.

**Insufficient exhaustion of previous meal and the physiological set point**

Excessive intake, positive balance, either unapparent or visible fattening and insulin resistance were due to a high set point in BG for intake decision. This decision develops automatically and habitually [1 - 6]. The set point is forcefully subjective. We encountered two kinds of set points in our investigations. The “automatic, scheduled set point” is scheduled on mealtimes, and may represent a cultural derangement from natural, physiological set point in mammals. The acquisition [25] begins in the first days of life, and consists on learning the habit to scheduled food administration by parents. At weaning and during adolescence, the habit may have a renewal. Changes in fat cells and in production and release of insulin and other hormones reinforce the maintenance of the automatic set point that can endure longer than a mental habit [25, 26, 41]. The automatic set point can be changed after a rationale decision and often after external suggestion. Mammals, instead, often depend...
on arousal of a physiological set point (hunger) to start a long search of food. In our investigations, subjects identified again the physiological set point after eating suspension on a mean of two hours, no more than two days. Eating suspension interrupted any automatic feeding and allowed memorizing initial hunger (IH), the physiological set point. Subjects memorized the sensation, and used it as reference sensation at hunger arousal in subsequent times. The associated BG measurement validated the actual recognition, confirming identity in the physiological condition at subsequent arousals [25, 28]. In our wide investigations, we adopted this IH as the physiological set point to start a meal. The new habit consisted in evaluating the arousal in comparison with the memorized IH before meal consumption. This newly elaborated Hunger Recognition endured months and years, and produced health improvements. Badly informed or misinformed people were afraid of excessive loss of weight or strength, in particular those who were normal-weight and insulin sensitive at recruitment. To better know the physiological role of the set point for intake decision, we are reviewing the intervention and the association between meal energy intake, BG, TEE and RMR in our findings and in those of other authors. We are also comparing our findings with the largest study on infant metabolism.

Recognition of Initial Hunger

Among various hunger sensations, we assumed the first arousal after meal suspension for less than two up to 48 hours, as the physiological set point and demonstrated that this sensation was recognized at a low BG [28]. The first arousal after meal suspension had the name of Initial Hunger (IH), and consisted in either gastric pangs (Empty Hollow Sensations, EHS) or weakness of mind or body (Inanition). The recognition of IH was reproducible in the same subject as well as in different subjects approximately at the same set point in BG during postprandial slow decline (Figure 1 and 2 and Table 1) [21 - 29]. An estimation of expenditure in the inter-meal interval was necessary at every meal onset to eat just the sufficient amount to achieve IH arousal before subsequent meals. The trained recognition of a physiological set point at low BG substituted automatic feeding at scheduled meals as a post hoc checking. This meal pattern was reproducible in the same subject as well as in different subjects (Hunger Recognition). Subsequent BG measurements served to check identity in the BG set point before any meal, and the mean in a sequence was useful to compare meal patterns in different times or in different subjects. Mean weekly BG was stable over months and years, although before any training it showed wide inter-individual variations (Table 1) [25 - 30]. Thus we were able
Figure 1. Estimated vs measured blood glucose of subjects reporting to be hungry at the final laboratory investigative session. Hollow red circles, trained subjects reporting hunger (n = 18); hollow black circles, control (untrained) subjects reporting hunger (n = 42). Linear correlation was significant for the trained data (dashed red line; r = 0.92; P = 0.0001) but not for the control data (dashed black line; r = 0.29, P = 0.06) (By courtesy of the Authors [28]).

to make a comparison on habitual provision of energy and positive or negative energy balance in blood and for all tissues. Mean BG thus assessed the individual approximation to the fundamental aim of meals, habitual energy balance, and informed on habitual intake that may be either excessive or low.

Initial Hunger (Demand) meal pattern (IHMP) in adults and infants

We asked adults (and mothers for their children) to suspend food intake for a few hours, to devote themselves to usual playing or working activity and noticing the first specific sensations of hunger (manifestations of the child’s first food demand) [21 - 29]. Adults noticed empty hollow sensations (EHS). Remembering this first sensation was the corner point in the construction
of the novel meal pattern. The memorized sensation served as a comparison reference at subsequent arousals before meals. Crying, mood changes like loss of enthusiasm for playing, gestural or verbal demand and searching for food without any ‘external’ stimulus were all considered to be signs of demand (Initial demand or Initial Hunger, IH). Mothers learned IH manifestations. The main investigator accurately phoned at the end of every first training day to ascertain the actual change made by the subject or mothers. The first adherence to this protocol resulted in a mean meal consumption after a delay of two hours (0 - 48 hours range). At subsequent mealtimes, mothers evaluated arousals according to their first experience to assess if the demands coincided with IH. Our previous studies [21 - 24] show that BG is significantly lower in children that demand food compared to those

**Figure 2.** Estimated vs measured blood glucose (BG) of trained subjects with measured BG below 87 mg/dL at the final session. Below this value, 18 subjects reported the EHS (hollow red circles) and 14 subjects reported inanition only, but not EHS (filled black squares). These 14 subjects showed an average estimation error of 4.5 ± 3.1% of the measured BG, which did not significantly differ from the estimation error of the 18 trained subjects who reported the EHS (3.2 ± 2.4%; P = 0.20). Linear regression was significant for the hungry subjects reporting EHS (dashed red line; r = 0.92; p = 0.0001) but not for those not reporting EHS (solid black line; r = 0.18; P = 0.54). (By courtesy of the Authors [28]).
Table 1. Prevalence of low mean blood glucose (LBG) either by free, spontaneous choice at recruitment (Before) or after training (After) Hunger Recognition in 8 different groups.

<table>
<thead>
<tr>
<th>Subgroups and training</th>
<th>% within subgroup</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 out of 24 NW ctrl adults,</td>
<td>38</td>
<td>77.3 ± 3.92</td>
<td>No training</td>
</tr>
<tr>
<td>26 out of 66 trained NW adults,</td>
<td>39</td>
<td>76.5 ± 3.9</td>
<td>76.7 ± 4.1</td>
</tr>
<tr>
<td>40 HBG out of 66 trained NW adults</td>
<td>91.4 ± 7.7</td>
<td>80.1 ± 6.67</td>
<td></td>
</tr>
<tr>
<td>8 out of 21 OW ctrl adults,</td>
<td>38</td>
<td>77.4 ± 3.6</td>
<td>No training</td>
</tr>
<tr>
<td>12 out of 38 trained OW adults,</td>
<td>32</td>
<td>77.1 ± 3.1</td>
<td>77.2 ±4.8</td>
</tr>
<tr>
<td>26 HBG out of 38 OW adults,</td>
<td>91.3 ± 6.5</td>
<td>79.6 ± 7.57</td>
<td></td>
</tr>
<tr>
<td>49 HBG out of 70 infants,</td>
<td>91.3 ± 7.2</td>
<td>76.9 ± 6.77</td>
<td></td>
</tr>
<tr>
<td>21 out of 70 infants,</td>
<td>30</td>
<td>76.4 ± 4.5</td>
<td>75.2 ± 6.6</td>
</tr>
</tbody>
</table>

90 normal-weight (NW), 59 overweight (OW) adults and 70 infants in the second year of life at recruitment and after 5 months [25, 29]. These three groups are each divided in two subgroups, trained and control (ctrl). The subgroups are divided in subjects beyond and below 81.8 mg/dL, and are named HBG, high blood glucose and LBG, low blood glucose. Six adult groups and two infant groups are presented. HBG ctrl subjects (NW and OW) are excluded because useless for this table. “% within subgroup” stands for the percentage with LBG of the total number at recruitment. 2 Mean ± SD of 21 pre-prandial BG from week-diary in mg/dL. 3 No training refers to subjects kept as control (ctrl).

who do not after training. We reported the validation of demand recognition [25 - 28]. After training with 42 measurements at hunger arousal, we investigated 16 toddlers not demanding food in comparison with 54 who instead demanded food in the hospital laboratory before breakfast [28]. No demand was associated with a significantly higher mean BG than the condition of food demand (96.3 ± 10.5 mg/dL vs. 74.6 ± 7.7 mg/dL; P = 0.0001). The meaning of this validation is that mothers can recognize food request as manifestations that arise at a constant (low) BG in their infants, ie corresponding to a physiological identifiable condition. Based on these studies, IH was conceived as a threshold phenomenon triggered by low energy availability in blood indicated by low BG [25, 28]; prior to IH arousal normal activity is not inhibited by low energy. The intervention may be summarized as a stop of automatic eating to practice habitually a judgment on the amount of food. At the end of the meal, subjects ceased any dependence on fullness sensations, because attainment of fullness deceives toward a prolongation of the satiety interval. Satiety is here an activity without IH sensations. Mothers received information on food energy contents, on balance factors, on recommended vegetable intake and on physical activity per day. Half kg per day for children and one kg for adults were the recommended fruit and vegetable amount. The investigators

Mario Ciampolini
promoted energy expenditure by decrease in over-heating and over-clothing, and fostering outdoor and gym activities. Absence of IH manifestation before meals was treated in subsequent meals by alternations in behavior that would enhance hunger, such as a decrease in energy-dense food in subsequent meals. Avoiding snacks was suggested, though too early IH arousal was satisfied with fruit and adequate energy-dense food. Social obligations like parties and school catering were included in planning the intake amount and timing of the previous and subsequent meals.

**Diary compilation for children and adults**

Food intake written records were collected for 7 – 10 consecutive days before any intervention to assess dietary compliance, estimate energy and fiber intake. Also recorded were the time spent at playing outdoors and sleeping, and daily stool weights in infants. Subjects and caregivers were contacted by telephone at least 7 times during the seven weeks between the two evaluations to assess the child's feeding behavior and general activity levels.

Food intakes were estimated by weighing or measuring food volumes before and after cooking. Measurement utensils were provided to the subjects or caretakers by the investigators and all portions served to the child after cooking and leftovers were weighed or measured. Each caretaker (subject) was instructed in food measurement and weighing by a dietician during the first visit. Particular care was suggested for oil added to vegetables, and dietitians checked the consumed oil at diary hand over. All data were recorded on special forms provided by the investigators, checked by a dietician at handing and reported on a computer program. Energy intake was calculated according to McCance [42]. Energy taken from unavailable carbohydrates was added to the energy content of the food in the proportion of 2 kcal/g of fiber intake [21 - 30]. Intake measurements were obtained when samples were collected to estimate TEE or in the period RMR was obtained.

Training subjects in measured capillary blood by glucometer (a portable potentiometer for whole blood glucose measurement: Glucocard Memory; Menarini Diagnostics; Florence, Italy) in the quarter-of-an-hour before breakfast, lunch and dinner for a total of 21 measurements in a week or 30 measurements in ten days. We suggested this longer period of diary in RMR and TEE studies. The inter-series precision on two series of 12 different glucose (weighed) concentrations was 1.7 ± 1.4 mg/dL. We measured the same blood sample from investigated children by portable instrument and by autoanalyzer ten times and found an absolute difference of 4.0 ± 3.4 mg/dL.
The assessment of meal pattern

A huge amount of studies demonstrate that insulin sensitivity is associated with the best energy balance for health [1-5, 34-40]. We thus evaluated meal pattern based on the subject’s achievement of insulin sensitivity. Insulin sensitivity and fat decrease resulted in correlation with mean preprandial BG in a study on 89 adults. After training to an actual change in the set point, we checked the change by mean BG. The construction of the arousal of IH before meals substituted Hunger Recognition for the automatic, scheduled, habitual set point. We assumed that IH was the physiological set point. By BG, we distinguished a false from an actual compliance with IH arousal before eating. The importance of this problem has been illustrated in the last chapters of a recent publication [27]. Changes in energy intake documented a change in the group, but were insufficient to show a change in the single individual. Home diary reports of preprandial BG and energy intake closely described energy events from intake to provision of energy to body tissues, thus high-lightening the necessary adjustments, while proving the acquisition of the trained intake habit [27]. Mean BG from 89 week diaries varied between 65 mg/dL and 110 mg/dL (Figure 3). This high variability was due to inter-individual differences in intake habits and not to high intra-individual variance. The mean confidence interval (95%) of diary measurements around mean BG was ±3.84 mg/dL [25-27]. Mean BG revealed to be constant also over 5 months in a study on 31 adults without any training [25-27]. 31 control subjects maintained a stable mean BG after 5 months (from 85.2 ± 8.1 mg/dL to 85.3 ± 7.6 mg/dL). The absolute pre/post change (increase or decrease) was 6.0 ± 4.6 mg/dL. In conclusion, huge differences in balance were unrevealed by meal pattern, energy intake or body weight but were shown by preprandial BG. Subjects (mothers for infants) adapted energy intake on a written diary to provide a personal level of energy that remained constant within the diary and as a learned skill, for months [27, 29].

A different way of life

Energy intake, mean pre-prandial blood glucose concentration (BG) and resting metabolic rate (RMR) decreased together after training Hunger Recognition in recent studies on infants [21-24]. In adults, the high BG meal pattern was revealed by insulin levels, insulin resistance, HbA1c and subjectively by ignoring IH. Mean preprandial BG objectively showed decisions in intake habits that remained subjective, like a complete or an incomplete exhaustion of previous meal energy. In the same individual, mean
Figure 3. Difference of mean preprandial blood glucose after training vs blood glucose at recruitment for each trained subject. Column height shows 5-month post-less pre-training mean blood glucose difference in each trained subject. Significant increases are indicated by blue bars, significant decreases by red bars, and not significant changes by black bars. Mean blood glucose are reported in sequentially increasing order at recruitment, not in linear correlation with segment length on the x-axis scale. The range of mean blood glucose values at recruitment is indicated by the minimum and maximum values for the first and last subjects (large arrows). The vertical dashed line indicates the most significant division between subjects who showed no mean blood glucose decrease after training (low BG group, n = 34 subjects) and those who showed significant decrease of mean blood glucose (high BG group, n = 55 subjects; $\chi^2$ analysis: $P = 0.00001$). This threshold blood glucose at recruitment (demarcation point) is 81.8 mg/dL (4.5 mmol/L) at recruitment in the randomised controlled studies. Subjects above this threshold accounted for most of the improvements in weight and insulin resistance. (By courtesy of the Authors [26]).

BG showed an objective correspondence to subjective changes from one month to another. Mean BG also showed inter-individual differences in intake that were subjectively taken and remained ignored without measurements. Subjects with high BG were totally unaware of their situation in the scale of mean BG between 65 mg/dL and 110 mg/dL. These subjects were unconscious of the RID condition that is associated with insulin resistance, they were unaware of preparing functional disorders, deterioration, infarction, ictus and also malignancy [1 - 4].
Weight

We attribute the stop in deterioration of bodily functions and of immune defenses to a stop in fattening. We conceive this stop as a decrease in postprandial fat deposition associated with a net deficit between meals in overweight subjects and insulin resistant subjects, or with a null inter-meal balance in normal-weight insulin sensitive subjects [29].

Hunger Recognition was associated with significant decreases in body weight and BMI in overweight subjects compared to controls, after 7-weeks of training and after 3 further months of application. BMI decreased from 28.7 ± 3.5 to 26.5 ± 3.5 in the trained group. The decrease was significant in comparison to controls (P = 0.004) and in comparison with baseline values of the same group (P = 0.0001). MANOVA showed a significant association between training and both BMI and weight. Pre-meal BG emerged as the most significant predictor of variations in BMI and body weight. Normal weight subjects maintained weight overall, however trained normal weight subjects whose BG was high at recruitment also lost weight compared to controls [29].

Insulin sensitivity

Hunger Recognition was associated with significant decreases in insulin and BG peaks, insulin at 60 minutes and 90 minutes during GTT, glycated hemoglobin, and mean pre-meal BG as well as energy intake and BMI when compared to controls. Insulin sensitivity index increased from 7.1 ± 4.1 to 9.4 ± 5.2. The increase was significant in comparison to controls (P < .01) and in comparison with baseline values of the same group (P < .001) [43].

New approach to diabetes prevention and treatment

Type 2 diabetes mellitus is a devastating outcome after maintaining positive energy balance (see above: fattening). Hunger Recognition suggests an innovative approach to diabetes prevention and control. In a longitudinal investigation of 13,163 subjects, a fasting plasma glucose greater than or equal to 87 mg/dL (3.9 mmol/L) was found to be associated with an increased risk of Non-Insulin-Dependent-Diabetes-Mellitus in men compared to those whose fasting plasma glucose was less than 81 mg/dL (4.5 mmol/L) [44]. It is interesting that this latter figure corresponds closely to the demarcation point which separated our low BG and high BG groups in infants as well as in adults [25, 26]. By recognizing hunger pre-meal and
eating only when hunger is present, most of our subjects were eating at a BG of < 81 mg/dL. Our finding that the high BG control subgroup showed a decreased insulinogenic index of beta cell function whereas the high BG trained subgroup showed an increase in this index, supports the use of Hunger Recognition in diabetes prevention and treatment [26]. The difference in insulinogenic index [26] between the two groups was significant implying higher insulin production and preservation of beta cell function in the trained group. It should be noted that the IH Meal Pattern is diametrically opposite to the prevailing treatment of diabetes which calls for steady caloric intake at prescribed times during the day. Diabetes control using this rigid method is notoriously difficult. We suggest that the meal-by-meal feedback furnished by the IH Meal Pattern is a more physiologic approach to this widespread and difficult disorder.

**Implications of improved insulin sensitivity**

**Resolution of the pro-inflammatory state**

It is a clinical commonplace that healing is poor in uncontrolled diabetes. However, pre-diabetic glucose metabolism derangement is also associated with immune disruption and low-degree inflammatory activity. This has been variously termed the pro-inflammatory state or subclinical inflammation [32 - 38], and is characterised by the development of bacterial biofilms (including *Helicobacter Pylori*) inside the alimentary canal [45 - 47]. Subclinical inflammation is implicated in the gradual development of cardiovascular disease, cancer, autoimmune diseases and other disorders [32 - 38, 48 - 52]. Inefficient inflammatory reactions grow and prolong destructions in all tissues. We stressed this meaning by using a synonym: Reversible Immune Deficiency. In a randomized controlled study, we studied the direct effect of Hunger Recognition on *H. Pylori* gastrointestinal disease [24]. We trained a group of children and adults (n = 24) aged from 5 years to 25 years known to have *H. Pylori* serum antibodies to recognize hunger (recovery study). Twenty-three subjects of similar age and serum antibodies formed the control group. The outcome was assessed after about one year. We also trained another group of healthy children (n = 43) aged between 6 and 60 months in comparison with 43 healthy control subjects of the same age (prevention study). Groups in the prevention study were assessed at 4, 8 and 12 years post intervention.

The diagnosis of *H. pylori* gastrointestinal disease is supported by the presence of serum antibodies whose titer decreases after successful treatment. In the recovery study, 15 out of 24 trained subjects (62.5%) had lost
seropositivity for *H. pylori*, compared to only 3 out of 23 (13%) control subjects (p = 0.002). In the prevention study, 13 out of 43 control subjects showed seropositivity at the end of the study compared to just 2 positive (plus one transient) conversions to seropositivity among the intervention group. This difference was highly significant and corresponded to one infection every 176 years under intervention, compared to one infection every 25.6 years in control subjects.

Although *H. pylori* thrives at a pH between 6 and 7 (that is, lower than most bacteria), it cannot survive in the extreme acidity commonly found, for example, in the fundus of a healthy stomach. In these conditions its acid-buffering strategies (such as the production of ammonia by urease) are overcome. *H. pylori* therefore seeks a niche in which pH and other factors are optimal for its survival. Reference has already been made to the “housekeeping” effect of Phase III contractions associated with the EHS. Gastric emptying and upper gastrointestinal secretions are known to increase with increasing insulin sensitivity and are inhibited by high glycaemic concentrations [53 - 55]. Approximately 20% of *H. pylori* in the stomach adheres to the surfaces of mucus epithelial cells partly to inflict cellular damage and inflammation but also to avoid mechanical clearance [52]. Gastric and duodenal “sweeping” combined with lowered gastric pH may account for the inhibition of *H. pylori* proliferation.

*H. pylori* is just one of a number of intestinal bacteria that may proliferate when high BG inhibits gastric motility. In an investigation on children with irritable bowel syndrome and coeliac disease, the bacteria count (mainly streptococci and staphylococci) per gram of mucosa for all subjects was 24 times higher after a 20 hour fast than after a 26 hour fast and for coeliac sufferers, 39 times higher [45]. In these subjects bacteria persisted longer than the inter-meal interval [45]. Other immunogenic bacteria are implicated in irritable bowel syndrome, colorectal cancer and obesity [46 - 48]. Avoiding long periods with positive energy balance, fosters the clearing of the bowel of the unwanted bacteria, and prevents the pro-inflammatory state.

Hunger Recognition may help prevent a wide range of disorders, including the autoimmune diseases. Fasting has long been recognised as beneficial in rheumatoid arthritis [56 - 58]. The IH Meal Pattern is, actually, a controlled fasting in which the subject fasts just long enough to allow hunger to appear. This yields the benefits of fasting without the disadvantages. The inflammatory marker C-reactive protein (CRP) is one indication of the pro-inflammatory state and shows a strong positive correlation with insulin resistance.
**Hunger Recognition may help with psychological stress**

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. During stress, IH does not emerge, suggesting a loss of one or two meals that can prevent bacterial proliferation on intestinal mucosa, and stop high immune stimulation (RID) [27, 32 – 38, 48 - 52].

**Total (daily) energy expenditure (TEE)**

Home BG measurements by portable devices and reports on food intake have been effective in adjusting intake to Hunger Recognition as a new meal pattern, but we had still doubts on the reported changes [40]. We thus investigated RMR and TEE (sleeping metabolic rate by indirect calorimetry and TEE by doubly labeled water) in infants with chronic diarrhea [30]. We found no difference in energy intake per kg versus total daily expenditure per kg at recruitment (P = 0.39), after training (P = 0.28), and on pre/post decreases (P = 0.90). The decrease in energy intake during Hunger Recognition was explained by decrease in energy expenditure and not by lower fecal energy loss or by spared energy for less physical activity. PAL (physical activity level) is the proportion between TEE and RMR [59]. The normal level is 1.4 within the same group at this age, and this level was actually maintained after training [59]. The decrease in RMR thus explains the decrease in TEE. As a corollary, reported home diaries are validated. More important, the reductions in total energy expenditure after training validate all diary reported changes after training and validate the use of subjective sensations to maintain energy balance, low mean BG, insulin sensitivity and stop RID (Reversible Immune Deficiency, subclinical inflammation or pro-inflammatory states).

**Deceiving BG measurements**

In hospital, the laboratory autoanalyzer measured BG right after patients’ BG estimation. The estimation error was the difference between estimation and measurement. During training, we observed an increase in this estimation error during 30 – 90 minutes after physical exercise, after food tasting, after intake of one – two grams of food, after indoor entry, after stop in ventilation in a closed ambient, after increase in clothing or after a stressful event, or during a feverish or not feverish infection. The listed events elevate BG from about one hour, two hours or few days, but subjects in training fail the
elevation at estimation. Subjects must omit BG measurement in all these circumstances and busy people must postpone training. A significant increase in error was unfortunately permanent after 60 years of age in comparison with younger ages (unpublished findings) [21 - 30].

**Meal pattern and blood glucose (BG)**

We assume that BG indicates current energy balance in blood [21 – 30]. In this assumption, low BG was useful to validate the Recognition of Initial Hunger by showing identity in the associated nutrient availability at arousal of the initial hunger sensation [25 - 29]. Subjects achieved an exhaustion of previous meal during the inter-meal interval or delayed intake until recognition of IH arousal before starting a meal. Mothers recognized Initial Demand (IH) as a signal for meal administration to infants [25 - 29]. Adults, and mothers for their infants, are able to distinguish accurately high from low BG after training with BG measurements during 42 arousals of hunger sensations [25 - 28]. At both ages, the most significant distinction between high and low BG is around 81 mg/dL [25 - 29]. In the laboratory, adults and infants showed an association between gastric pangs, low BG estimation and low BG measurement. The sensations for BG estimation and meal start included mind and/or body weakness. We allowed intake for weakness when BG was either measured or estimated in the range associated with gastric pangs [25 - 28]. Attaining 81 mg/dL of BG and below this, transient BG drops become frequent and are associated with hunger reports [7 – 10, 25 - 28]. Also animal experiments have shown BG drops and declines in RMR before moving to feed [44]. Maintenance of spontaneous IH arousals and low BG before each meal and taking meals at usual mealtimes require energy intake limitation at each meal to predispose meal energy exhaustion at the desired mealtimes [21 – 30]. This self-imposed restraint pertains now to common wisdom. The present report is helpful to provide an objective restraint, which is reproducible by the single subject thanks to trained association with BG, to personal experience and to the information on food labels of energy contents. Subjects renounced any aim of eating less and of decreasing weight and lost the fear for energy insufficiency in subsequent hours (low RMR). Ideal body weight and energy intake amount are arbitrary even when professionally prescribed.

**Association of BG and RMR in our investigation**

We have recently trained the passage from scheduled to demanded meals in mother/infant pairs and in adults, and reported effects on BG [25, 29] in
both ages and on RMR in infants [30]. The training was associated with a decrease in mean BG and in RMR that were significantly and positively correlated with the value at recruitment. The most significant difference in RMR was between 7 low RMR and 7 high RMR (P < 0.01). The 7 low RMR infants showed a RMR response (decrease) to Hunger Recognition that was significantly lower in comparison with the 7 infants with high RMR at recruitment (P < 0.01, Figure 4). The responses in RMR and mean BG to Hunger Recognition were (positively) correlated. Mean BG is an index of provision of energy to body and suggests that RMR depends on nutrients in blood indexed by BG. The training to Hunger Recognition significantly decreased also energy intake and TEE, but we did not find any correlation between the value at recruitment and the decrease after training. We searched further evidence for the association between Mean BG and RMR in scientific reports.

Figure 4. Resting metabolic rate (RMR) decreases (P = 0.01) in seven infants with low RMR at recruitment in comparison with seven infants with high RMR at recruitment (P = 0.01). Note: White columns show RMR values and black columns show respective decreases after training in the initial demand meal pattern. (By courtesy of the Authors [30]).

A positive correlation between energy intake, blood glucose, insulin resistance and RMR

We investigated metabolic condition in infants and adults by implementing (training) Hunger Recognition. We found no difference in BG between the two ages. Mean BG was similar at recruitment and after training and also at the BG
cut point between subjects who did decrease mean BG and those who did not. We thus assumed that most metabolic results were interchangeable, suggesting similar effects of Hunger Recognition on insulin resistance and RMR in the two ages [25, 26]. Many authors found a positive correlation of meal size [13 - 18, 20, 60 - 67], blood fatty acids [60 - 68], BG [68 - 70] versus RMR. High sensitivity allows rapid passage of BG and nutrients into body cells [1 - 4, 17, 69]. This assimilation is impaired by insulin resistance. Insulin resistance is a condition of fattening that does not coincide with being overweight. Both beyond and below the arbitrary limit of 25 IBM, adults and children may endure fattening as well as fat decrease [29]. The condition of insulin resistance is characterized by a replenishment of body cells by fatty acids that are discharged by enlarged adipocytes [70]. OW and insulin resistant people provide two - three times energy as fatty acids to metabolism in the post-absorptive hours [32 – 33]. Fattening produces this condition. People with high insulin production may endure fattening for months and years, whereas other people have inborn conditions that do not allow such rapid adipocyte proliferation (see paragraphs on diarrheic toddlers). In these conditions, increase in volume of fatty cells produces insulin resistance although the increase of skinfold thickness may be limited like in chronic diarrhea toddlers. Consistently, many AA found a positive association between body weight and RMR in overweight subjects who do not restrain energy intake [60 – 64, 66, 69, 72 - 74]. Whole body insulin resistance, a condition associated with high BG [1 - 4] and high blood fatty acids [32, 33, 60], is also associated with high RMR [1, 64, 72 - 75]. A decrease in body weight reduces RMR [72 – 75]. Changes in energy expenses to carry a different body weight contribute only in part [73 - 76]. The association between body weight change and RMR emerged after only 48 hours of overfeeding and persisted after adjustment for lean body mass [76].

In the first hours after a meal, BG and RMR increase above preprandial levels and this RMR increase has the name of thermic effect of food (TEF). The TEF (RMR increase) depends on energy expenses for energy storage of carbohydrates as fat and even more for storage of proteins [66]. Actually, increase in meal size produces high postprandial BG [25 – 29, 61, 76] and affects TEF by a significant, positive dose-response manner [61, 62, 76 - 78]. TEF increases more when insulin sensitivity is high than when low [66 - 69, 76]. High insulin sensitivity is associated with lower RMR than insulin resistance before meals. A low premeal RMR (characteristic of sensitivity) increases the difference from preprandial to postprandial RMR, and this difference is just TEF [69, 76]. Thus among scientific authors, exists a consensus on the associations of the increases in energy intake, BG, RMR and body weight.
In adults, Hunger Recognition (IHMP being a synonymous) has decreased intake and mean BG by week diaries, and body weight in association with reverting insulin resistance to sensitivity [26 - 29]. Only normal-weight adults who were insulin sensitive lost no weight in response to Hunger Recognition [26 - 29]. Infants who demand meals (after training of mothers) show a decrease in energy intake and mean BG by week diaries, but no decrease of body weight and no impairment of growth [21 - 25]. We have above discussed this seeming discrepancy.

**RMR and sensing weakness**

How far can we decrease energy intake and the associated decreases in BG, RMR and body weight? Each of the three decreases provokes justified alarm. Ignoring this problem implies an acceptance of current errors in energy intake like anorexia nervosa, overweight and insulin resistance. The answer can only be searched on a meal by meal basis [27]. Empty hollow sensations (EHS), an epigastric sensation threshold, is universally accepted by humans as hunger and an indication for meal start. Subjects were able to remember this sensation and recognize its arousal at the same BG (Table 1). This association rendered IH objective. Subjects used this subjective/objective target sensation to give start for intake, allowed maintenance of usual activity and prevented any body weight loss in lean, insulin sensitive subjects after months and years. We suggested meal consumption also after progressive development of inanition (mind or body weakness) because arousals of (mind or muscles) weakness sensations (Inanition) allow current BG estimation as accurately as gastric pangs (EHS) [28]. In clinically healthy children and adults, this weakness sensation is gradual and unspecific. The gradual arousal was easily identified and used to take a meal, although patients with anorexia nervosa, chronic disease and old age have not been adequately investigated. Patients with anorexia nervosa require training in Hunger Recognition to show their capability in BG estimation by the inanition state. Also these patients report EHS arousal sometimes. In these circumstances, patients with anorexia do not have any validated, subjective limit in the meal. These patients need to learn to calculate the energy intake to barely suppress IH arousals, a validated limit, in the inter-meal interval. The construction of a habit to match intake with expenditure when hungry may be difficult in poorly ordered people. The difficulty vanishes after verification of no hunger sufferance when getting near to subsequent meal. We found that subjects with low BG and low RMR at recruitment decreased less BG and RMR during Hunger Recognition than subjects with high BG and RMR at recruitment [25 - 28]. BG is an index of energy availability in blood; nutrients availability in blood determinates RMR value, and BG is an index of nutrient amount in blood. We believe that an
accurate estimation of current BG by weakness in absence of EHS arousal [28] depends on sensing lowering RMR. Taking food at RMR lowering has been reported in experimental animals [78]. Some people sense only weakness as an index for taking meals. In our limited investigation [26], subjects with this reference sensation for intake start, have no EHS arousal by delaying intake and enduring weakness for hours.

**Comparison with the largest study on energy expenditure**

A study of 1984 by Butte reported normal growth and lower energy intake in breast fed than formula fed infants [79]. She and other AA independently confirmed these findings [59, 80]. In the study of the year 2000 [59], Butte reported, “the infants were either exclusively breast fed (n = 40) or formula fed (n = 36) from birth to 4 months of age; thereafter feeding was at the discretion of the infant’s parents.” Yet, infants differed intake amount between breast and formula feedings up to the 9th month of life, and no more showed the difference at the age of two years. The two-year old infants investigated by Butte may be comparable to the here investigated infants at recruitment although being heavier (11.8 – 12.7 kg). Their requirements for energy intake were calculated to be between 78.8 kcal/kg/d and 81.2 kcal/kg/d. This value was a little lower than the energy intake per kg body weight in present investigation that at recruitment was 86.3±17.0 kcal/kg/d (14 infants) in RMR study and that in TEE (total daily energy expenditure) study was 84.8±13.2 kcal/kg/d (10 infants). We attribute the small difference from Butte to differences in body composition, although presence of diarrhea or different historical trends might have contributed. In Butte’s report, the RMR ranged between 55.0 ± 4.8 kcal/kg/d and 59.7 ± 4.8 kcal/kg/d that is similar to the value during scheduled meals in 14 infants of the present investigation (58.6±7.8). The TEE ranged between 78.8 ± 7.2 kcal/kg/d and 81.2 ± 14.33 kcal/kg/d in Butte’s report that is similar to the value during scheduled meals at recruitment (80.1±6.9). At recruitment, the infants investigated in our Unit were similar to those investigated by Butte, except for having less body fat and higher energy intake per kg body weight. In our investigation, infants during demanded meals lowered their RMR to 49.0±9.1 kcal/kg/d and their TEE to 67.8±10.0 kcal/kg/d. The significant (P < 0.001) decreases during demanded meals reject the null hypothesis, i.e. the equivalence between demanded and scheduled meals.

**Last remarks**

We have no measurement of energy expenditure during the three post-prandial hours that is the thermic effect of food (TEF). At recruitment (during
scheduled meals) TEF may have been low given the condition of high pre-prandial RMR, and presumably [25, 26] high BG and insulin resistance. This low value during scheduled meals was possibly compensated by the unrestrained meal sizes. When a subject is in energy balance, TEF is 10% of daily energy expenditure [66]. TEF increase during demanded meals might have been part of this amount, unable at cancelling the significant decrease of TEE.

RMR (largely determined by fat-free mass) was a marker of energy intake and represented a physiologic signal for hunger in a recent paper [81]. This report confirmed thus our last paper [30]. Coming from an independent laboratory, represents the necessary confirmation of all our work [27].

**Conclusion**

Hunger sensations can be focused as other sensations, even enjoyed, learned, recognized, reliably employed and even compared with those of others after an association with BG. Hunger Recognition is a different way of living like a travel in a far unknown land with different climate, different problems and sensations, with a safety awareness that sustains every engagement. The new habit significantly reduced meal energy intake, mean blood glucose, skinfold thickness, body weight, insulin resistance, HbA1c, RMR, TEE and increased the insulinogenic index in children and adults [25 - 30]. A single unbalanced meal has no consequences but meal patterns are maintained for years and decades, in association with immune deficiency and increasing incidence and seriousness of all illnesses. We know that men can have different socioeconomic, cultural, physical ways of life. Well, men can even have a different biological life. Young people may develop a perfect body that also works for sex attraction and better children. Unbelievable? Well, take the general progression of mankind toward diabetes as an alternative. A different, preventable biological life! 20% - 30% of current population achieves the mean BG of Hunger Recognition by free choice, before any instruction. Is the majority really unable at accomplishing the same goal?

**References**


47. Hecht G. In the beginning was Helicobacter pylori: roles for microbes in other intestinal disorders. Gastroenterology. Feb 2007;132(2):481-483.


