Severe Malnutrition, Radiation Enteritis and Insulin Resistance: A Solution by Initial Hunger and Associated Low Blood Glucose

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Abstract

Background
After elimination of infections and infestations, most people remain undernourished and in poor health. Persistence of diarrhea and malnutrition are sustained by conditioned eating.

Objective
An impressive decrease of pre-prandial blood glucose (BG) was associated with a similarly impressive recovery of body weight and active life in a boy of 12 with third degree malnutrition in the Gomez classification.

Methods
Training a subjective, reproducible limit in intake (initial hunger) and to learn to estimate current blood glucose. A diary reported self-measured pre-prandial BG by validated portable device. Reports from seven days provided the mean pre-prandial BG.

Results
The boy “C” decreased mean blood glucose (MBG) from 98, 9±15, 1 mg/dL to 74.0 ± 14.2 within the first month in hospital and decreased mean blood glucose to 68, 6±12, 2 mg/dL after six months. At recruitment “C” weight was 19.5 kg, (56% of weight for age) corresponding to severe (third degree of) malnutrition in the Gomez classification. Body Mass Index was 10.7 kgs/squared height in meters at recruitment. At the end of follow-up at the age of 20, “C” was 55 kg (89% of weight for that age) and Body Mass Index had increased to 19.6. Anthropometric recovery, symptom abatement and achievement of an active life without symptoms impressively show the pathogenic role of conditioned intake, of associated pre-prandial high blood glucose and insulin resistance. “C” died at the age of 39 years for pulmonary polycystic disease.

Conclusion
Restriction of energy administration by suppression of conditioned intake (substituted by demanded meals and insulin sensitivity) rapidly allowed recovery from malnutrition and recovery of active life in a heavily malnourished boy.

Keywords
Energy Balance; Even Energy Balance; Initial Hunger; Blood Glucose; Energy Intake; Malnutrition; Insulin Resistance; Fattening; Lipoatrophy.

List of Abbreviations
BG = Blood Glucose, an index of energy availability in blood for the whole body
OGTT = Oral Glucose Tolerance Test
AUC = Area under Curve of GTT
RMR = Resting Metabolic Rate

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TEE = Total Daily Energy Expenditure


BMI = Body Mass Index = body weight in kg divided by squared height in meters

NSV = Non-Starchy Vegetables, food with lower content than 30 kcal/100 grams

List of Terms

IHMP: Initial Hunger Meal Pattern: Energy intake is adjusted to three arousals of IH per day.

IH = Initial Hunger consists of gastric pangs or mind or physical weakness. In sedentary adults and in children, it corresponds to low BG: 76.6 ± 3.7 mg/dL

High BG is over 81.8 mg/dL and Low BG is a BG below 81.8 mg/dL, respectively associated with insulin resistance and insulin sensitivity.

MBG = The mean of 21 BG measurements before the three main daily meals reported by a week diary. MBG origins as a series of BG measurements sampled at the 21 moments of formation of the will to eat before meals.

MBG shows the metabolic moments in BG levels that are becoming insufficient thus revealing the preferred energy availability. MBG also measures the compliance with IHMP, the changes after training and is negatively correlated to insulin sensitivity. Below 81.8 mg/dL, MBG is associated with fattening/insulin resistance.

HOMA = Pre-prandial BG and pre-prandial insulin are used together in the denominator of HOMA estimate (22.5/BG in mmol/L multiplied by plasma insulin in micro/mL). HOMA is considered an estimate of insulin sensitivity [19].

Introduction

The Gastroenterology Unit was created in the Pediatric Ward of Florence University in the Sixties to treat malnourished and diarrheic children [1, 4]. The Unit approached the causes and the treatment in controlled, randomized studies. Energy intake (daily mean from week diaries), Total Energy expenditure per day by doubly labelled water (TEE), Resting Metabolic Rate (RMR) by indirect calorimetry, pre-prandial Blood Glucose (BG) reported by home week diaries (mean BG, MBG), anthropometry, Glucose Tolerance Tests (GTT), HbA1c, duodenal biopsy with bacteria count (Colony Forming Units, CFUs), total and HDL cholesterol were assessed in infants and/or adults. In our observations, fasting BG was a unreliably standardized measure for variable high BG persistence after a previous, unknown dinner energy intake. Pre-prandial BG measurements were instead within mean confidence limits of ± 3.84 mg/dL around the mean of a week in diary reports at recruitment. One hundred and twenty investigated adults could be stratified in ten small strata that significantly differed by MBG (5). MBG was stable in each control subject over five months, the mean absolute change was 6.0 ± 4.6 mg/dL. This constancy suggests that MBG may be a more reliable index than fasting BG for the assessment of individual meal pattern and metabolic state. The metabolic state may be indicated in mg/dL and is the MBG in a period of time. The MBG measurements are taken at meal onset decisions, thus the metabolic state may be conceived as a personal aim to reach a desired level in availability. This am becomes the habitual level of energy availability and energy balance and is unique for the single subject and different from everybody else. Energy availability and balance include glucose, fats and amino acids that provide energy from blood to the body and are reproducible, highly reliable and stable in comparison with fasting BG. We report the contradictory coincidence of a high level metabolic state together with very thin skinfold thickness in a 12 year old boy with malnutrition of third degree (Gomez classification) at recruitment. Fat skinfold thickness, body weight and other anthropometric measures have no pathogenic role in malnutrition and intestinal disorders in contrast with the dynamic metabolic state in blood and insulin sensitivity. A low metabolic state (MBG) may be the guide in food administration during infections and enteritis.

Methods

Declarations

The study was reviewed and approved by the Departmental Human Experimentation Committee. Informed, written consent was obtained from “C”s parents at the time of recruitment. The local Hospital Ethics Committee approved the report in compliance with the Helsinki Declaration. Data are archived in the Pediatric Clinic of Florence University. The author declares that he has no competing interests. The here summarized research was supported by the Italian Ministry of University,
Research, Science and Technology grants for the years 1980–2002 and by ONLUS Nutrizione e Prevenzioni, Firenze, for the years 2003–2015. This funding amounts to about 2,500 € every year. This funding includes the government support of the ONLUS (= non-profit association) “Nutrizione e Prevenzioni”, ONLUS code 94081990486.

Author’s information: the A. directed the Gastroenterology Unit in the Pediatric Clinic of the University of Florence from 1960 to 2000 and was a member of the Italian Executive Committee for the Study of Pediatric Gastroenterology and is member emeritus of international group for the Study of Ingestive Behavior (SSIB). The A. made the first diagnoses of Celiac Disease by the Watson capsule in Florence (Tuscany) and treated Adults for this diagnosis. Doctor Cecchi Gaia contributed by collecting anamnestic data, elaborating figures and tables and collecting permissions for copyrights.

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Design

The immune background shortly consists of the sequence: 1. Conditioned intake 2. High-energy intake 3. High pre-prandial BG 4. High Metabolic State in blood, i.e. fattening/ insulin resistance 5. Absorption slowdown 6. Expansion of few immunogenic bacteria species on intestinal mucosa 7. Increased (either acute or chronic) immune stimulation 8. Overall inflammation 9. Poor body growth. The sequence is largely accepted but in our investigations the sequence starts with about 80 mg/dL BG in sedentary, ill subjects. Awareness on this BG fluctuation and on current energy and BG balances can be trained and the learning allows adequate intake restriction, to prevent this chained development. Availability and balance awareness was obtained by meal suspension and by instructions on IH and associated BG recognition. Administration of 100 g of Non-Starchy Vegetables (NSV) per meal was a modest compensation at voluntary meal energy restriction to let arise IH three times per day. After discharging from hospital, physical exercise was added. Periodically, MBG and anthropometry were assessed to demonstrate compliance with instructions and nutritional achievements.

MBG and the metabolic state

The metabolic state consists of the energy availability and balance in a person and is an important variable in individual health. MBG is closely associated with insulin resistance and is habitual [5, 6]. MBG and either the condition of insulin sensitivity (= absence of insulin resistance) or the insulin resistance degree represent important, individual, correlated indexes of the metabolic state. This state cannot be considered as a diagnosis like an infection or a pneumonia [7]. The metabolic state is a characteristic of each individual like dimensions in height, weight or fatness degree that also are stratified in the population. Most people, but not all, live in a permanent condition of high energy intake, availability and expenditure: in our findings by doubly labelled water, many maintain a RMR and a TEE 15% over the level associated with insulin sensitivity that can be obtained by implementing Initial Hunger Meal Pattern (IHMP). This high RMR corresponds to a condition of insulin resistance [5, 6] that was actually measured and found in 55 out of 89 adults at recruitment.

The metabolic state (i.e. MBG, the measurable index of a metabolic state) is heavily associated in a causal relation with overall inflammation that also is stratified from a subclinical state to the development of catastrophic vascular and malignant diseases [6-26].

Blood Glucose (BG) Fluctuations

The liver delivers glucose into blood every 12 minutes with 10% changes [27]. Physical activity, one gram of bread, troubles and worries, all significantly increase BG. Measuring pre-prandial blood glucose is directly useful for the patient who assesses undesired fluctuations in energy intake and energy balance at changing foods or activity. The patient can directly notice unbalanced meals (between intake and expenditure) and so may make appropriate adjustments. Moreover, he/she can learn the effects of physical exercise, open air, climate changes and occasional stressful and untoward events on blood glucose [6-21, 27-40]. MBG characterizes the individual meal pattern better than energy intake and much better than single fasting measurements [40]. In the pre-prandial setting BG and MBG are directly associated with insulin resistance. BG summarizes the metabolic condition that follows the previous meal and shows the personal aim.
on energy availability [34, 35, 40]; the metabolic condition WcrWeated by previous meal ceases completely with the incoming meal. The glucose diary may be accurately performed by the patient under the surveillance of the family physician.

Fasting standardization of BG is ineffective. We do not know the end of the post-absorptive period, before breakfast BG is often high [5, 6]. A major factor in altering BG is energy balance that changes with ambient, activity and climate. An idea of BG levels may better be drawn by the mean of many well standardized measurements. Sampling blood glucose at meal onset appears closely linked with nutrition and metabolism: just before changes due to the meal in energy availability, metabolic rate and immune responses [22, 23, 28-32]. This metabolic moment informs us about previous intake exhaustion, i.e. if energy expenditure between meals was higher or lower than energy intake of the last meal(s). A series of pre-prandial BG measurements in a week allows calculation of MBG that is the mean of 21 BG before meals reported in a week food diary. A slight confidence interval of 3.8 mg/dL subsists around MBG and this mean is stable for months in control subjects [5, 6]. By itself, this small confidence interval suggests reliability. We could stratify the MBGs of 120 subjects in ten thin strata at recruitment. Each stratum included subjects without differences in MBG that instead were significant from all the other strata. We might say that each subject was imprisoned in his/her own stratum of habitual intake during free choices and maintained a steady meal pattern to have the same BG (energy availability) before meals and during light activity. The MBG represents also an intriguing assessment in the pathogen development toward diabetes [33]. A training intervention was able to subvert fattening/insulin resistance that otherwise would have persisted [5, 6, 34]. Here emerges the value of MBG. It shows the habitual level of energy availability of each subject. Better, MBG characterizes energy expenditure of that subject and this energy expenditure differs from other subjects. MBG may become higher than 100-110 mg/dL. These high MBG values cause unwanted, pathogen reflexes. The main pathogen reflex is the depression of gastrointestinal functions, bacteria increase in the intestine and the development of an overall state of immune activation [1-4, 10, 21]. The definition of insulin resistance implies a reduction in the passage of nutrients from circulation to body tissues [7, 8]. To show the existence of this problem, we reduced energy metabolic rate in the experimental animal and humans by elevating environmental temperatures [22, 23]. We found a correspondent decrease of intestinal absorption rate. Increasing food administration in this condition caused further absorption and progression slowdown in small intestine. Intestinal slowdown is followed by bacterial growth [1-4] and absorption decrease as well as diarrhea relapses [32-35]. In the same experiments instead, the absorption rate increased when the metabolic rate was increased by low environmental temperature. High total cholesterol, high triglycerides, low HDL cholesterol, high uric acid, high basal insulin, HOMA, and insulin responses during Glucose Tolerance Tests (GTTs) are correlated with high MBG [5, 6, 29-35] to form the metabolic syndrome. The MBG gives us the degree of abnormal elevation of energy availability, indicates the faulty meals and shows the completeness of the correction after changes in intake. Assessment of BG at the lowest points in the day (i.e., before meals) protects the subject against the fear of hypoglycemia, an important factor that promotes excess intake in overweight subjects (OW) who want body weight loss. These subjects were bizarre, sometimes they engaged in food restriction at recruitment and were incapable of any further decrease after training.

In our hands, the measurements by a portable device were reliable like the whole construction around IH [34-37]. We measured BG by a portable potentiometer for whole BG measurement with the hexokinase method. The adult subject had to personally measure BG with the portable instrument against the auto analyzer in the lab as he/she did at home. The auto analyzer obtained a mean ± SD of 89.9 ± 11.3 mg/dL (N = 85). Subjects measured 89.0 ± 12.5 mg/dL. The mean difference (0.9 ± 7.1) was not significant. On absolute values, the mean difference was: 5.7 ± 4.3 mg/dL with no bias. This new parameter of 21 measurements by portable device (MBG) was much, much more consistent in repeated measurements than a single fasting BG by auto analyzer.

**Initial Hunger (IH)**

Hunger arousal might be the preferred moment for intake because the sensation corresponds to the arousal of gastric activity and to a decrease in bacterial counts in duodenum. The moment of food demand had to be well defined, to be recognized by all adults as well as by all mothers taking care of their children (reproducible). Initial Hunger (IH) emerged after meal suspension as a biophysical, subjective sensation that coincided with a recognizable, constant, physiological state of diminishing...
energy availability [28, 34]. The physiological state recurred sometimes per day and suggested spontaneously energy intake in absence of visual, smell or word food cues [5, 28, 34-37]. Blood glucose (BG) identified the energy availability at IH recognition. In ten adults, hunger training appeared to be a feasible method and was successful in 84% of pre-prandial instances over two weeks, when an individualized fasting blood glucose was used to indicate that a meal could begin [37]. In periodical assessments by home diaries, lean adults and mothers for toddlers reported IH in association of a BG that was low in 90% of occasions. This percentage decreased to 60% of breakfasts in overweight (OW) adults and to 50% in OW children.

Treatment

The treatment consisted of instructions to restrict energy intake at any meal to allow IH to arise three times per day. Consistently, the subject had to recognize low BG (IH) before any energy intake. A training with BG measurements teaches the correspondence between hunger sensations and BG. In controlled studies, a rhythm of IH arousal associated to BG lowering three times per day (IHMP), improved metabolic state and reduced insulin resistance [5, 32, 33, 35] as well as both conditions of overweight and malnutrition [5, 28, 33, 35].

Results

**Figure 1**: Height (add 100 to the reported height in cm), body weight, arm circumference and arm skinfold thickness during 100 months of follow-up.

![Figure 1: Height (add 100 to the reported height in cm), body weight, arm circumference and arm skinfold thickness during 100 months of follow-up.](image)

**Case Presentation**

The Pediatric Clinic of the University of Florence assigned “C” to the attention of the Gastroenterology Unit when “C” was 11 years and 2 months old. “C” had had a surgical operation for Kidney Wilms Tumor at the age of two. In that occasion, “C” had also X-rays treatment that left poor motility in the second half of the small intestine as an after-effect. This lesion was complicated by two intestinal perforations in the year before the recruitment. At the assignment, the child was profoundly anorectic and had vomited for 20 days, the weight was 19.5 kg and height 135.5 cm, arm and leg skinfold thicknesses 2.6 mm, arm and leg muscle areas 16.7 and 79.1 square cm. After the first week devoted to assessments of MBG and blood examination, an Initial Hunger Meal Pattern (IHMP) was implemented, i.e. the meals were administered after demand (after Initial Hunger arousal) and BG measurement that was performed by hospital auto analyzer. Pre-prandial BG measurements by hospital lab confirmed the recognition of hunger at the moment of demand (within 76.6 ± 3.7 mg/dL). When still in hospital, “C” had once vomited the full prescription of non-starchy vegetables (NSV, 300 grams). This amount would make easier the decision to stop energy intake when the meal was sufficient to have three IH arousals per day. We accepted an intake of 100 grams NSV per meal. Gluten was present in his diet and was continued, milk was suspended for no blood response in lactose tolerance test. The following month, a duodenal biopsy was performed and this showed a chronic enteritis and partial atrophy of the mucosa. In the S. Lazare Hospital de Paris, prof. Rambaud JC considered the biopsy as an enteritis that may arise even several years after X-ray therapy. Gluten was continued. IHMP was continued, attention was drawn on energy administration and hunger arousal before any meal. Energy intake was between 870 and 1100 kcal/d. The boy decreased MBG (mean of 21 measurements in a week) from 98.9±15.1 mg/dL to 74.0 ± 14.2 within the first month in hospital and decreased to 68.6±12.2 mg/dL after six months. After hospital discharge, the boy suspended measurements that had become useless: he knew the number before its appearance on the portable instrument.

We saw again “C” six months after recruitment. His energy intake was 39.2±5.0 kcal/kg body weight (950 kcal/24 kg body weight per day). We followed “C” up to the age of 38 years old (Table 1, Figure 1). The meantime “C” did not miss a day of school or work and he paid the yearly dues for the membership of a no-profit association (Nutrizione e Preventions, Firenze). At the age of 39, “C” died from pulmonary cystic disease.
Discussion

At recruitment, “C” was in a state of heavy malnutrition although he had a mean BG of 98, 9±15, 1 mg/dL. Also plasma triglycerides confirmed the insulin resistance. The MBG measurement before treatment and during first weeks of treatment was made by hospital auto analyzer (Table 1). His intake was increased to 950 kcal per day in three days. Mean BG dropped to: 74.0 ± 14.2 mg/dL during the first month of treatment. High MBG is associated with insulin resistance in our studies [5]. In adults, IHMP decreases MBG in association with recovery of insulin sensitivity [5, 6]. The time necessary for a complete decrease is in negative correlation to skinfold thickness [29-35]. The insulin resistance was due to previous energy intake and to enteritis. The relation between energy intake, insulin resistance and IHMP has been studied in 9 undernourished infants [36] and the association between BG and insulin resistance has been largely studied in adults and children with bowel disorders [5, 6, 28, 32]. Subsequent MBG measurements were obtained by portable instrument. BG is closely regulated and studies with GTT on adults [5, 6] show that high MBG, even beyond 85 mg/dL, may be associated with partial or clear insulin sensitivity in subjects engaged in hard manual work and exposed to open air in winter climate. Yet the association between MBG and insulin sensitivity becomes close even in sedentary people when MBG decreases to 76.6 ± 3.7 mg/dL [5]. Animal and human experiments were performed to see the effects of high energy availability. This state of abundance was achieved by permanence in a warm environment and by maintenance of constant intake [22, 23]. The abundance was associated with decreased absorption rate that was measured by xylose absorption tests. Slow absorption increases bacterial growth and provokes an inflammatory state in the intestinal mucosa [1-4]. The elimination of this state, by permanence in a cold ambient, reduced the inhibitory reflexes and the slow absorption rate [22, 23]. After IHMP implementation, the restricted energy intake and lower BG improved intestinal absorption and slowly corrected the state of malnutrition. The curative intervention consisted of the addition of nutrients to this precarious intestine only after accurate emptying of the previous meal [IHMP, 34, 36-38]. Food instructions were directed to an even energy balance as indicated by Low BG achievement before meals. Thus we decreased energy administration when IH aroused too late. The general strategy was to achieve three IH arousals per day. In this restriction, Non-Starchy Vegetable (NSV) and fruit were given in the amount of up to one kg per day and helped stop energy intake at each meal [35]. Proteins, vitamins and minerals were provided by 100 – 150 grams of meat and 300 grams of NSV and two teaspoons of olive oil, energy were given on a basis of three demands per day. We thus intended to cover minimum requirements. The actual effectiveness of this strategy was shown by pre-prandial BG measurements that dropped from 98,9±15,1 to 74.0±14.2 mg/dL after an interval of one week and to 68.2±12.2 mg/dL after three months. In adults and children, an MBG of 99 mg/dL is closely associated with insulin resistance whereas an MBG of 74 mg/dL is associated with sensitivity. A regression of enteritis slowly improved the nutritional state of “C”: a healthy, aseptic intestinal mucosa is associated with more efficient absorption than a high caloric administration to an inflamed mucosa by plenty of bacteria.

Present findings inform on another human debated issue. “C” recovered efficient activity that may be considered as an index of good nutritional state, although he maintained a thin skinfold thickness, 4 mm. The absence of illnesses and the good school and work performances suggest that skinfold thickness are no sign of good nutrition, i.e., thin skinfolds may be accepted as normal. In nutritionally deprived subjects, the increase of skinfold thickness may be an error in strategy. A good metabolic (by BG) state may improve functions providing an adequate level of essential nutrients, but thick skinfolds by no means contribute to physiological, relational, intellectual and gym activities, although sexual attraction may improve. Thick skinfolds release higher amounts of fatty acids and this increases glucose, but BG was not defective in “C” as well as in most people in Western Countries: BG was even excessive in “C” before intervention.

The strategy applied to “C” has its “ubi consistam” on intestinal mucosa histology: Half-immune cells of the body are in the small intestine [15, 24-26]. Meal absorption develops in a conflict between mucosa and bacteria [1-4]. These assertions can be checked again and again. In the circumstance that the two assertions cannot be rejected, we must believe that a narrow range in BG (76.6 ± 3.7 mg/dL = Low BG, correspondent to IH arousal) is protective against unwanted reflexes that slow down absorption and generate bacterial growth. Obesity, diabetes, asthma, autism, birth defects, dyslexia, attention deficit-hyperactivity disorder, and schizophrenia have
increased in children in the Western Countries in the last half century [39]. Mothers often raise newborn babies to regularly eat when previous energy intake has been incompletely exhausted [29-35]. In infants, the will to eat develops habitually after stimuli (often external) that do not correlate with energy availability in blood [29-35]. Training newborns to meals on demand (Initial Hunger, IH) allows an IH Meal Pattern that is associated with low mean preprandial BG and with high insulin sensitivity [29-35]. A meal by meal even energy balance in blood [40] may prevent insulin resistance and overall sterile inflammation. This inexpensive protection has prevented malnutrition in the presently described case, has ameliorated some of increased illnesses in the Western Countries. At least, IHMP has cured and prevented fattening/insulin resistance [5, 6, 28-38]. Sadly, these unhealthy habits are so widespread to be considered as “normal”.

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References

Table 1: Changes in anthropometry and metabolism after IHMP implementation at the age of 12 in a malnourished boy.

<table>
<thead>
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<th>133</th>
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<th>140</th>
<th>154</th>
<th>172</th>
<th>179</th>
<th>189</th>
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<td>71%</td>
<td>74%</td>
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<td>18</td>
<td>18</td>
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<td>26</td>
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<td>32.2</td>
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<td>758</td>
<td>927</td>
<td>1358</td>
<td>778</td>
<td>251</td>
<td>172</td>
<td>184</td>
<td>42</td>
<td>256</td>
<td>124</td>
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<tr>
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<td>75</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum IgA (mg/dL)</td>
<td>299</td>
<td>244</td>
<td>193</td>
<td>234</td>
<td>263</td>
<td>194</td>
<td>239</td>
<td>259</td>
<td>387</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum IgG (mg/dL)</td>
<td>1290 *</td>
<td>1140</td>
<td>986</td>
<td>998</td>
<td>1620*</td>
<td>754</td>
<td>969</td>
<td>913</td>
<td>1297</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (1000/mm³)</td>
<td>990 *</td>
<td>527</td>
<td>480</td>
<td>551</td>
<td>310</td>
<td>494</td>
<td>416</td>
<td>329</td>
<td>395</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>133</td>
<td>136</td>
<td>140</td>
<td>154</td>
<td>172</td>
<td>179</td>
<td>189</td>
<td>190</td>
<td>194</td>
<td>214</td>
<td>232</td>
<td>239</td>
<td>250</td>
</tr>
</tbody>
</table>

• In our interpretation, high IgG and high platelet count show a condition of overall immune stimulation.
• Weight/adult weight of same height, reproduced by courtesy of HV Meredith, Iowa Child Welfare Res Station, The State University of Iowa.

* Data in Bold


34. Ciampolini M, Bianchi R (2006) Training to estimate blood glucose and to form associations with initial hunger Nutr Metab (Lond) 3: 42.


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