

Reasoning on Findings to Prevent Tumors

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Abstract

Maintenance of high energy availability in blood is associated with functional disorders and vascular diseases. Much longer endurance of high energy availability, of insulin resistance and of the associated overall subclinical inflammation may increase DNA replications and constitute the main factor in the development of malignancy. Current research is mainly oriented to solve the malignancy risk by "Personalized Medicine". This approach moves away from a one size fits to the treatment and care of patients with a particular condition. The medical model of personalized Medicine separates people into different groups. Medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. The "tailoring" is mainly obtained by studying the genome. In face of a malignancy, the study of genome might predict the best intervention. We do not discourage this cumbersome and expensive way of creating a genetically individualized treatment for everyone. We made studies on conditioned intake to solve other problems. This conditioned feeding is now prevalent but is associated with overall subclinical inflammation. In tissues involved by inflammation develops an accelerated turnover of immune cells and of parenchymal cells. The increase in cellular replications increases DNA duplications and DNA mutations as in malignant tumors. Prevention of malignancy requires cessation of conditioned intake and maintenance of lower energy availability. Suppression of conditioned intake appears more effective in malignancy prevention and fruitful for general health than studying genomic differences in any individuals after malignancy arousal.

Keywords: Blood Glucose; Diabetes; Insulin resistance; Overweight; Fattening; Energy balance; Energy intake; Limit in energy intake; Hunger; Meal onset; Energy availability; Malignant diseases; Bowel disorders; Malnutrition

List of Terms and Abbreviations

*BG=Blood Glucose, an index of energy availability in blood for the whole body.

*IH=Initial Hunger consists of gastric pangs or mind or physical weakness: Inedia is the Italian word for this weakness. In sedentary adults and in children, IH corresponds to 76.6 ± 3.7 mg/dL BG. In infancy corresponds to demand before sight of food.

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

*OGTT=Oral glucose tolerance test.

*AUC=Area under curve of GTT.

*MBG=The mean of 21 BG measurements before the three main daily meals reported by a week diary. MBG measures the compliance with IHMP, MBG shows changes after training and it is negatively correlated to insulin sensitivity. Below 81.8 mg/dL (Low MBG) MBG indicates a healthy meal pattern in sedentary people. Over 81.8 mg/dL, High MBG is associated with fattening/insulin resistance.

Review

In 2005, the journal Science published an editorial by Ian T. Johnson, head of the Gastrointestinal Biology and Health Program at the Biological Sciences Research Council in the UK. The article [1] explored the microbiome, i.e., the abundant (thousands of trillions), yet largely unknown microorganisms in human intestine, their normal functions of digestion and delivery of nutrients, and the diseases to which it is prone [1]. In his editorial, "Cancers of the Gut and Western Ills," states that despite the huge progress made in understanding the molecular basis of many cancers in recent years, "most of the new knowledge has been deployed in the search for new therapies rather

than to understand the role of nutrition in their causation." Johnson says the mechanisms linking diet to cancer may be useful for both prevention and treatment, and he points to several "scientific and strategic reasons to focus such research on carcinomas of the alimentary tract." These include evidence in support of "over-nutrition" as a factor in an increased risk of bowel cancer within population of the developed world that shows overconsumption of energy, low levels of physical activity, high body mass index, and abdominal obesity. He also notes evidence for a link between obesity and esophageal cancer, once rare "but now advancing rapidly throughout North America and Western Europe. Johnson sees "little evidence" to support the view that alimentary cancers are tied to the adverse effects in the diet of food-borne carcinogens, despite the presence of mutagens in low concentrations in foods and feces. "It seems more plausible that the Western gut became vulnerable to neoplasia because of adverse metabolic factors, such as pro-inflammatory activities in precancerous tissues, and because of consumption of high energy density foods." He asserts that the role of body weight, lack of exercise, and inadequate consumption of plant foods in the etiology of gut cancers "needs to be more widely acknowledged and publicized [2,3]" also included in this issue of Science is a report from Johns Hopkins University School of Medicine, the National Institute on Aging, and Keio University School of Medicine in Tokyo, Japan, that suggests a cellular mechanism by which epigenetic alterations in normal cells may affect cancer risk. We

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completely agree on this possibility: epigenetic alterations in normal cells consist in a high metabolism, high insulin resistance, high body cell replication and increased DNA mutations [3].

Inflammation and Damages to Body Cells

Casually, the Florence University Unit of Gastroenterology approached the energy balance issue. The casual motivation consisted in diarrhea relapses in infants with low fattening capacity in the second year of life. Meal suspension stopped diarrhea. The suspension gave place to gradual increase in energy administration. The increase often produced relapses. The best energy administration had to be found to cover needs in the time interval between meals and preventing relapses. The energy issue might consist in either a high mean or in a high SD of energy administration.

In animal experiments and in humans, we varied the energy availability for the body by changes in environmental temperature and maintaining constant energy intake. Low temperature decreased energy availability in blood by higher metabolic rate. High environmental temperature instead increased availability and this high availability provoked reflexes that decreased absorption [4-6]. At that time, xylose was commonly used to estimate absorption rate. Experiments in animals and in adults confirmed the hypotheses (Figure 1). This finding may be seen as a proof that high energy availability is associated with unwanted reflexes that may be harmful. Prolonging a slow absorption for hours produced damage by bacteria proliferation during increased energy availability [7-9]. In animal experiments, an increase of thousand times has been seen in duodenal bacteria number three hours after a meal [7]. We had to administer a little less food than the maximal amount that the infant was capable of absorption. Only after exhaustion of the previous meal from small intestine, we allowed the caregiver to administer a new meal. We hypothesized that demand by the infant, crying often, signaled the emptiness of the small intestine after (two) – three hours without food. We elaborated a subjective limit in feeding: the arousal of Initial Hunger (IH). Meals taken after three arousals per day allowed normal growth in infants and body weight maintenance in lean, insulin sensitive adults. The decrease in energy intake allowed significant improvement of insulin resistance and significant decrease of body weight in normal weight and overweight adults. Infants adopted this pattern, lost diarrhea relapses and grew normally like controls. The intake decrease was compensated by reduced resting metabolic rate and lower fecal energy emission (Tables 1 and 2) [10-13]. We named this way of eating as initial hunger meal pattern (IHMP).

Inflammation and cancer

Chronic inflammation caused by infections or autoimmune diseases is clearly associated with an increased cancer risk in a number of instances. For example, it has long been known that patients with persistent hepatitis B, Helicobacter pylori infections, or an immune disorder such as ulcerative colitis have a higher risk for the development of liver or gastrointestinal tract cancer [14-18]. It has been estimated that chronic inflammation contributes to the development of approximately 15% of malignancies worldwide. The connection between inflammation and cancer is also in agreement with the concept that anti-inflammatory drugs, NSAIDs, have antineoplastic activity. Widespread inflammatory developments closely follow insulin resistance and diabetes. Western societies promote diabetes since the first newborn meals by food offering, by scheduled and conditioned meals that are considered normal educational acquisitions [3,11-13]. Infant/mother pairs recognize easily IH without BG measurements [3,11-13]. Adults can learn the recognition in few days, and meals allowing three IH arousals per day are associated with an even energy balance and diabetes prevention [3,11-13]. This meal pattern may become the reference for normal energy intake and for normal/ideal bodyweight.

The infants recruited for these experiments differed from the normal anthropometric reference (USA, NIH). Recruited infants had a thin arm skinfold up to the seventh year of age and did not increase the skinfold thickness by increased energy intake [3-6]. The increase in energy administration increased BG, insulin resistance, overall inflammation, fecal energy emission and Resting Metabolic Rate but not weight or skinfold thickness in children with relapsing diarrhea. The children were examined at the age of 6-7 years, when they were well [8,9]. Differences in body weight and in height growth in dependence of high energy intake, emerged after the seventh year of life [8,9].

We obtained meal-by-meal fasting nutrient levels (low BG measurements) prior to the next meal and suppressed fattening/insulin resistance [10-13]. This pattern has been termed the Initial Hunger Meal Pattern (IHMP). The alternative consists in conditioned meals. Limits are arbitrary and rely on a definite amount of energy intake. Ignoring Initial Hunger contributes to increase obesity and diabetes in adults and in children [10-13]. In the last half century, not only obesity and diabetes have increased in children but also asthma, autism, birth defects, dyslexia, attention deficit-hyperactivity disorder, schizophrenia [19]. IHMP and minimal bacteria growth in the alimentary canal

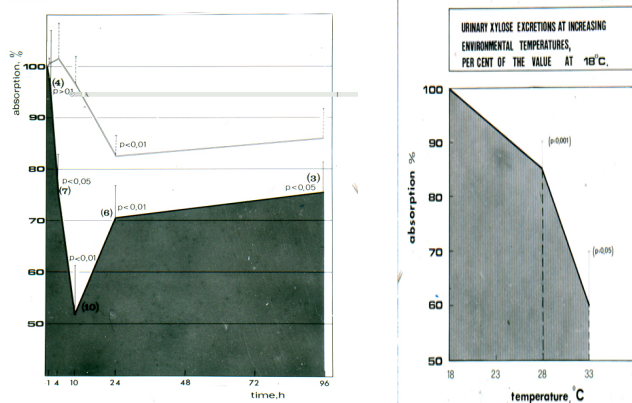


Figure 1: Percentage of increased absorption in cold environment (6°C) over absorption in warm environment (31°C) of intragastric xylose in rats. (Courtesy of Ciampolini, IRSC 1974 Copyright Clearance Center's Rights Link® service).

Training	Before	After	Before	After
	Energy intake		M B G	
38 OW adults	1756 ± 585	1069 ± 487	86.8 ± 8.7	78.8 ± 6.8
40 NW adults	1852 ± 697	1270 ± 457	91.4 ± 7.7	80.1 ± 6.6
70 Toddlers	946 ± 230	749 ± 187	86.9 ± 9.4	76.4 ± 6.7
	R M R			
14 Toddlers	58.6 ± 7.8	49.0 ± 9.1		

Note: Assessments before and after 5 months training. All differences are significant [10-13].

Table 1: Initial Hunger Meal Pattern, effects on energy metabolism.

Either before or after 5 months	26 trained OW		13 control OW	
	before	after	before	after
OW adults with High MBG BMI	29.0 ± 4.1	26.5 ± 4.0	29.2 ± 3.9	27.8 ± 4.2
	40 NW		15 control NW	
NW adults with High MBG BMI	21.8 ± 2.4	20.7 ± 1.9	20.2 ± 2.3	21.4 ± 2.1
(High MBG)	55 High MBG		19 High MBG control	
Insulin area under curve at GTT	244 ± 138	164 ± 92	222 ± 81	214 ± 98
(Low MBG)	34 trained		12 control	
Insulin area under curve at GTT	180 ± 98	183 ± 83	192 ± 106	243 ± 133

Note: Assessments before and after 5 months either training. IHMP and MBG were the most significant predictors of BMI in multivariate analysis of variance. High MBG OW subjects are here reported [10-13].

Table 2: Initial Hunger Meal Pattern and effects on insulin curve and BMI.

might become a strategy for health, to reduce these increases, as well as reversible, functional disorders vascular and malignant diseases, diabetes and Alzheimer disease [20].

About an important issue as that how orienting research on cancer, we agree with all concerns listed by Johnson. Moreover we add our findings on the importance of IH arousal. We taught infants and adults to eat after restriction of intake to the amount of energy that allowed three events of Initial Hunger (IH) per day. Clearly, eating on this condition limits intake to the energy amount barely sufficient for survival. Further limitation would mean an intolerable survival and an ethical problem in suggesting investigation. Implementing a subjective limit produces a significant decrease in energy intake, Mean Blood Glucose insulin resistance and in body weight (Tables 1 and 2). These lower energy metabolic parameters are associated with suppression of overall subclinical inflammation and of suppression of associated increase in cell proliferation and of DNA instances of mutation. Man can accept fatal illnesses and tolerate vascular sequelae but cannot accept coexistence with malignancies. Their presence cannot be ameliorated even by effective drug support. Malignancies require exclusion from human life.

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Conflict of Interests

No conflicts of interest.

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