A robust immunoassay for anti-interferon autoantibodies that is highly specific for patients with autoimmune polyglandular syndrome type 1

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Context: High titer antibodies to type 1 interferons have been recently reported as being highly specific for patients with autoimmune polyglandular syndrome type 1 (APS1) in patients with mutations in the AIRE gene.

Methods: This study established a competitive europium time resolved fluorescence assay for IFN-α autoantibodies and measured sera from subjects with APS1, first-degree relatives of APS1 patients, patients with Addison’s disease or type 1 diabetes.

Results: The Ab index for 6/7 APS1 patients was strongly positive and 3 standard deviations or more above that of the normal controls. Using a cutoff of 2 standard deviations above normal controls, relatives of APS1 patients were negative for type I interferon autoantibodies as were 71 patients with Addison’s disease (non-APS1) and 141 type 1 diabetes patients.

Conclusion(s): This simple high throughput competitive europium time resolved fluorescence assay had a sensitivity of ≥86% and a specificity of >99.5%.

Autoimmune polyendocrine syndrome type 1 and NALP5, a parathyroid autoantigen

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Background: Autoimmune polyendocrine syndrome type 1 (APS1) is a multi-organ autoimmune disorder caused by mutations in AIRE, the autoimmune regulator gene. Though recent studies concerning AIRE deficiency have begun to elucidate the molecular pathogenesis of organ-specific autoimmunity in patients with APS1, the autoantigen responsible for hypoparathyroidism, a hallmark of APS1 and its most common autoimmune endocrinopathy, has not yet been identified.

Methods: A human parathyroid complementary DNA library was immunoscreened using serum samples from patients with APS1 and hypoparathyroidism, to identify patients with reactivity to the NACHT leucine-rich-repeat protein 5 (NALP5). Subsequently, serum samples from 87 patients with APS1 and 293 controls, including patients with other autoimmune disorders, were used to determine the frequency and specificity of autoantibodies against NALP5. In addition, the expression of NALP5 was investigated in various tissues.

Results: NALP5-specific autoantibodies were detected in 49% of the patients with APS1 and hypoparathyroidism but were absent in all patients with APS1 but without hypoparathyroidism, in all patients with other autoimmune endocrine disorders, and in all healthy controls. NALP5 was predominantly expressed in the cytoplasm of parathyroid chief cells.
Conclusion(s): NALP5 appears to be a tissue-specific autoantigen involved in hypoparathyroidism in patients with APS1. Autoantibodies against NALP5 appear to be highly specific and may be diagnostic for this prominent component of APS1.

APS1 is characterized by lymphocytic infiltration of the target organs and by the presence of autoantibodies against a wide range of tissue-specific antigens. Mucocutaneous candidiasis occurs in all patients with APS1, and the immunological basis of the failure to eliminate Candida suggested a Candida-specific immune defect. The affected gene, named AIRE (autoimmune regulator), codes for a protein that plays a role in regulating self-antigen expression. Last year, we learned of the high titer anti-type-1 interferon antibodies [1], which occur prior to the development of other autoantibodies, and in some patients preceded any clinical features of APS1. Why do anti-interferon antibodies develop in so many patients with homozygous AIRE mutations, and what is their significance in the mechanism of APS1? After all, type-1 interferons have anti-infective properties against a wide range of opportunistic pathogens. Still, more questions than answers, but this serological test for APS1, with a sensitivity of 86% and specificity of >99.5%, was much needed in the diagnosis of this not-so-rare syndrome.

The other novel aspect this year concerns the target antigen of parathyroid destruction, one of the most frequent and early involvement of the complex autoimmune spectrum of the disease. The calcium-sensing receptor had been previously proposed as a target antigen [2] but after the initial publication, several groups have been unable to reproduce the findings and to detect antibodies to this protein. Here, the group from Uppsala has taken a systematic approach to identify new targets of autoimmunity in APS1 and have identified NALP5 as a parathyroid-specific antigen. Beyond the new ‘diagnostic tool’ that will become available (although, the diagnosis of hypoparathyroidism is relatively straightforward in the context of APS1), this findings highlights the role of an unexpected protein in the physiology of parathyroid cells. It should be remembered that the immune system selects its targets among key functional element in a given cell type: insulin in the β cell, 21-hydroxylase in the adrenal, peroxidase in the thyroid ... and it will be interesting to decipher the exact role of this protein in the parathyroid. It will also be interesting to know whether this antigen is also the target of the immune system A note of caution however, since autoimmune targets are best defined by T-cell reactivity (immune destruction is due to T cells and not to antibodies) and since APS1 is characterized by a wide spectrum of reactivity. Therefore, further work will be needed to ascertain the role of NALP5 as the ‘primary’ parathyroid autoantigen in APS1.

Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey

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Arch Intern Med 2007;167:1159–1165

Context: Results of several epidemiologic and clinical studies have suggested that there is an excess risk of hypertension and diabetes mellitus in persons with suboptimal intake of vitamin D.

Methods: This study examined the association between serum levels of 25-hydroxyvitamin D (25(OH)D) and select cardiovascular disease risk factors in US adults. A secondary analysis was performed with data from the Third National Health and Nutrition Examination Survey of 1988–1994, with oversampling of persons 60 years and older, non-Hispanic black individuals, and Mexican-American individuals.

Results: There were 7,186 male and 7,902 female adults 20 years and older with available data in the Third National Health and Nutrition Examination Survey. The mean 25(OH)D level in the overall sample was 30 ng/ml (75 nmol/l). The 25(OH)D levels were lower in women, elderly persons (≥60 years), racial/ethnic minorities, and participants with obesity, hypertension, and diabetes mellitus. The adjusted prevalence of hypertension (odds ratio (OR) 1.30), diabetes mellitus (OR 1.98), obesity (OR
2.29), and high serum triglyceride levels (OR 1.47) was significantly higher in the first than in the fourth quartile of serum 25(OH)D levels (p < 0.001 for all).

Conclusion(s): Serum 25(OH)D levels are associated with important cardiovascular disease risk factors in US adults. Prospective studies to assess a direct benefit of vitamin D supplementation on cardiovascular disease risk factors are warranted.

These results add to a growing volume of evidence that many of us have vitamin D insufficiency and that it is associated with hypertension (OR 1.3), diabetes mellitus (OR 1.98), obesity (OR 2.29) and high serum triglyceride (OR 1.47). Whereas it is the renal 1,25 dihydroxyvitamin D that is required for calcium metabolism, we need vitamin D3 as a substrate for intracrine prereceptor modification in many other body systems. Our old definition of vitamin D deficiency as serum levels of <10 and insufficiency <15 ng/ml, might have been promiscuous. It seems that to prevent the newly described consequences of vitamin D insufficiency, we may have to redefine it to levels that have been measured in non-human primates: >32 ng/ml (80 nmol/l). With this new definition, and in the UV-insufficient lifestyle we have created, D3 is again a vitamin; we all need vitamin D supplementation. Keep in mind that the often recommended 400 units will increase serum levels of an adult individual by no more that 4 ng/ml. I (Z.H.) prescribe for prevention is sub-flooded Israel 800 units in the summer and 1,200 units in the winter, but some recommend double these doses.

Food for thought: but when food is limited …

Life history tradeoffs explain the evolution of human pygmies
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Proc Natl Acad Sci USA 2007;104:20216–20219

Context: Traditional hypotheses assume that the small body size of human pygmies is an adaptation to special challenges, such as thermoregulation, locomotion in dense forests, or endurance against starvation.

Methods: This article presents an analysis of stature, growth, and individual fitness for a large population of Aeta and a smaller one of Batak from the Philippines and compare it with data on other pygmy groups.

Results: The Philippine pygmy Aeta has a life expectancy at birth of only 16.5 years. Pubertal girls stop growing at ages 12–13, and that their reproductive fitness peaks at 15 years, at a height of 140 cm.

Discussion: The authors argue that human pygmy populations and adaptations evolved independently as the result of a life history tradeoff between the fertility benefits of larger body size against the costs of late growth cessation, under circumstances of significant young and adult mortality. Human pygmies do not appear to have evolved through positive selection for small stature – this was a byproduct of selection for early onset of reproduction.

Classically, the short stature of the pygmies was believed to present a selective advantage for forest life or to provide greater resistance to starvation, but not all pygmies reside in forests or are short of food. The Philippine pygmy Aeta have a life expectancy at birth of only 16.5 years, pubertal girls reach their adult height of 140 cm at age 12–13, and their reproductive fitness peaks at 15. By comparison to a similarly nourished group, the Turkana women of East Africa start reproducing at an average age of 22 years, women can expect to survive 48 years, and by 18–19 years they have reached an average adult height of 166 cm. The spectrum of life history of various species stretch from ‘live fast, die young’ to ‘live slow, die old’. The disposable soma theory suggests that longevity is determined through the setting of longevity assurance mechanisms so as to provide an optimal compromise between investments in somatic maintenance (including growth) and in reproduction. A corollary is that species with low extrinsic mortality are predicted to invest relatively more effort in maintenance, resulting in slower intrinsic ageing, than species with high extrinsic mortality. Larger adult size has an obvious evolutionary advantage, but it appears that for a pygmy it is too risky to wait; instead, it pays off to grow up fast and have babies before disaster hits.
**Identification of xanthurenic acid 8-O-β-D-glucoside and xanthurenic acid 8-O-sulfate as human natriuretic hormones**

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Proc Natl Acad Sci USA 2007;104:17873–17878

**Context:** Hormonal regulation of salt excretion and water balance by the kidneys was widely believed to depend on glomerular filtration rate and aldosterone-controlled sodium balance.

**Results:** This paper reports the identification and natriuretic activity of two closely related small molecules isolated from human urine, xanthurenic acid 8-O-β-D-glucoside and xanthurenic acid 8-O-sulfate. The two compounds were partially purified by activity-guided fractionation and subsequently identified by using NMR spectroscopic analyses of enriched active fractions. Both compounds caused substantial and sustained (1- to 2-hour) natriuresis in rats and no or minimal concomitant potassium excretion.

**Conclusion(s):** These compounds constitute a class of kidney hormones that also could influence sodium transport in non-kidney tissues given that these tryptophan metabolites presumably represent evolutionarily old structures.

Xanthurenic acid 8-O-β-D-glucoside is known as the moiety responsible for lens color, which can act as a cataractogenic agent. Now it becomes a kidney hormone. It has been supposed for years that an unknown small molecule was acting in the kidney along with other known hormones in regulating sodium and water excretion. The two new xanthurenic acid derivative hormones may be yet other human natriuretic hormones. They were isolated from human urine, and caused sustained natriuresis in rat kidneys, but also in frog skin. The authors suggest that the closely related molecule xanthurenic acid, which is suspected to be a part of many biological processes, derivatizes to affect sodium transport in other tissues and could possess other activities.

**Watch it day and night: concept revised**

**Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study**

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Lancet 2007;370:1219–1229

**Background:** Few studies have formally compared the predictive value of blood pressure at night over and beyond the daytime value.

**Methods:** This study investigated the prognostic significance of ambulatory blood pressure during night and day and of the night-to-day blood pressure ratio by 24-hour blood pressure monitoring in 7,458 people in Denmark, Belgium, Japan, Sweden, Uruguay, and China. They calculated multivariate-adjusted hazard ratios for daytime and night-time blood pressure and the systolic night-to-day ratio, while adjusting for cohort and cardiovascular risk factors.

**Results:** The median follow-up was 9.6 years (5th to 95th percentile 2.5–13.7). Adjusted for daytime blood pressure, night-time blood pressure predicted total (n = 983; \( p < 0.0001 \)), cardiovascular (n = 387; \( p < 0.01 \)), and non-cardiovascular (n = 560; \( p < 0.001 \)) mortality. Conversely, adjusted for night-time blood pressure, daytime blood pressure predicted only non-cardiovascular mortality (\( p < 0.05 \)), with lower blood pressure levels being associated with increased risk. Both daytime and night-time blood pressure consistently predicted all cardiovascular events (n = 943; \( p < 0.05 \)) and stroke (n = 420; \( p < 0.01 \)). Adjusted for night-time blood pressure, daytime blood pressure lost prognostic significance only for cardiac events (n = 525; \( p > 0.07 \)). Adjusted for the 24-hour blood pressure, the night-to-day ratio predicted mortality, but not fatal combined with nonfatal events.
Conclusion(s): In contrast to commonly held views, daytime blood pressure adjusted for night-time blood pressure predicts fatal combined with non-fatal cardiovascular events. The increased mortality in patients with higher night-time than daytime blood pressure probably indicates reverse causality. The findings support recording the ambulatory blood pressure during the whole day.

Night-time blood pressure is a good indicator of overall mortality, but daytime has a better predictive value for all cardiovascular events. Blood pressure is best monitored for 24 h, and the authors suggest that the diagnosis of hypertension has to be based on such 24-hour monitoring. Similar results were reported by Laurent [3].

The complexity of water control: new active proteins

Dehydration-induced proteome changes in the rat hypothalamo-neurohypophyseal system

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Endocrinology 2007;148:3041–3052

Context: The hypothalamo-neurohypophyseal system (HNS) mediates neuroendocrine responses to dehydration through the action of vasopressin (VP). VP is synthesized in magnocellular neurons of the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus. The HNS undergoes a dramatic function-related plasticity during dehydration. The authors hypothesize that alterations in steady-state protein levels might be partially responsible for this remodeling.

Methods: They investigated dehydration-induced changes in the SON and pituitary neurointermediate lobe (NIL) proteomes using two-dimensional fluorescence difference gel electrophoresis.

Results: Seventy proteins were altered by dehydration, including 45 in the NIL and 25 in the SON. They identified six proteins in the NIL (four down, two up) and nine proteins in the SON (four up, five down) that are regulated as a consequence of chronic dehydration. Results for five of these proteins, namely Hsp1 (heat shock protein 1), NAP22 (neuronal axonal membrane protein 22), GRP58 (58 kDa glucose-regulated protein), calretinin, and ProSAAS (proprotein convertase subtilisin/kexin type 1 inhibitor), have been confirmed.

Conclusion(s): These proteins may play roles in regulating and effecting HNS remodeling.

Excess weight gain during the early postnatal period is associated with permanent reprogramming of brown adipose tissue adaptive thermogenesis

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Endocrinology 2007;148:4150–4159

Background: Excess weight gain during the early postnatal period increases the risk of persistent obesity into adulthood and impacts on the subsequent risk for metabolic and cardiovascular diseases.
Methods: The current study investigated the long-term effect of early excess weight gain, through reduced nursing litter size, on body weight regulation and its relation to brown adipose tissue (BAT) thermogenesis. Animals raised in a small litter (SL, 3 pups/litter) were compared with those raised in a normal litter size (NL, 8 pups/litter). BAT from young adult NL and SL rats, maintained under either ambient or cold conditions, were used for gene expression, morphological, and functional analysis.

Results: Compared with NL, SL rats showed excess weight gain, and adult SL animals had a reduced thermogenic capacity as displayed by lower levels of uncoupling protein 1 (UCP1). When exposed to cold, BAT from SL rats was less active and demonstrated reduced responsiveness to cold. Furthermore, reduction in transcript abundance of several lipid lipases and transcriptional regulators was observed in SL rats either at ambient temperature or under cold conditions. Finally, the expression of sympathetic β3-adrenergic receptor and the response to the sympathetic receptor agonist isoproterenol were decreased in SL rats.

Conclusion(s): Postnatal excess weight gain results in abnormalities in BAT thermogenesis and sympathetic outflow, which likely increases susceptibility to obesity in adulthood.

In the rodent, one of the key structures involved in the regulation of body weight is the interscapular brown adipose tissue (BAT), the major thermogenic center. BAT is composed of primarily brown adipocytes that are characterized by multilocular lipid droplets, a large number of mitochondria, dense innervation by sympathetic nerves, and abundant uncoupling protein 1 (UCP1). Defective BAT thermogenesis has been observed in animal models of genetic obesity (ob/ob and db/db), and transgenic mice with a specific ablation of BAT develop obesity in the absence of hyperphagia. On the other hand, mice overexpressing UCP1 are obesity resistant. The hypothesis was that altered energy expenditure may be involved in the increased body weight and adiposity in these postnatal overfed (POF) animals. To address these issues, they investigated whether altered BAT thermogenesis contributes to the adult overweight phenotype in POF animals. The results show that male, but not female offspring of POF rats develop an overweight phenotype, which is maintained into adulthood even after being placed in identical conditions from the time of weaning (P23) and that POF leads to permanent changes in BAT thermogenesis through the SNS-mediated mechanism.

Evo-devo: where do you come from?

Evo-devo of child growth

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Pediatr Res 2008;64:2–7

Context: Human size is a tradeoff between the evolutionary advantages and disadvantages of being small or big.

Hypothesis: This paper proposes that adult size is determined to an important extent during transition from infancy to childhood.

Impact: This transition is marked by a growth spurt. A delayed transition has a lifelong impact on stature and is responsible for 44% of children with short stature in developed countries, and many more in developing countries.

Conclusion(s): The paper presents the data and theory of an evolutionary adaptive strategy of plasticity in the timing of transition from infancy into childhood in order to match the prevailing energy supply. It proposes that humans evolved to withstand energy crises by decreasing their body size, and that evolutionary short-term adaptations to energy crises trigger a predictive adaptive response that modifies the transition into childhood, culminating in short stature.

The Yearbooks of Pediatric Endocrinology have devoted quite a large number of its comments to evolutionary aspects, but evo-devo (evolutionary development biology) is introduced here for the first time. Evo-devo addresses the issues of how developmental systems have evolved and probes the
consequences of these historically established systems for organismal evolution. Research in evo-devo has formed around comparative embryology and morphology, evolutionary developmental genetics, and experimental epigenetics. This article takes evo-devo into the realm of clinical medicine and child growth.

Many of us have contemplated the infancy-childhood-puberty (ICP) model. This paper introduces the concept of delayed infancy-childhood transition (DICT) and suggests that final adult height is determined to a large extent during the transition from infancy to childhood, and that DICT explains as much as 44% of ISS cases. ISS may not be as idiopathic as we thought.

**New hormone: FGF21 a new kid in the insulin sensitivity arena**

**FGF21 attenuates lipolysis in human adipocytes – a possible link to improved insulin sensitivity**

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*FEBS Lett* 2008;582:1725–1730

**Context:** Fibroblast growth factor 21 (FGF21) is active in murine adipocytes and has beneficial metabolic effects in animal models of type 2 diabetes mellitus. This paper assessed whether FGF21 influences lipolysis in human adipocytes and 3T3-L1 cells.

**Results:** FGF21 had no short-term effect (h) while a 3-day incubation with FGF21 attenuated hormone-stimulated lipolysis. FGF21 did not influence the mRNA expression of genes involved in regulating lipolysis, but significantly reduced the expression of the lipid droplet-associated phosphoprotein perilipin without affecting differentiation.

**Conclusion(s):** Via reduced release of fatty acids into the circulation, the anti-lipolytic effect could be a mechanism through which FGF21 promotes insulin sensitivity in man.

**Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans**

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*Diabetes* 2008;57:1246–1253

**Context:** Fibroblast growth factor 21 (FGF21) is a metabolic regulator with multiple beneficial effects on glucose homeostasis and insulin sensitivity in animal models. This study aimed to investigate the relationship between its serum levels and various cardiometabolic parameters in humans.

**Methods:** A newly developed immunoassay was used to measure serum FGF21 levels in 232 Chinese subjects recruited from our previous cross-sectional studies. The mRNA expression levels of FGF21 in the liver and adipose tissues were quantified by real-time PCR.

**Results:** Serum FGF21 levels in overweight/obese subjects were significantly higher than in lean individuals. Serum FGF21 correlated positively with adiposity, fasting insulin, and triglycerides but negatively with HDL cholesterol, after adjusting for age and BMI. Logistic regression analysis demonstrated an independent association between serum FGF21 and the metabolic syndrome. Furthermore, the increased risk of the metabolic syndrome associated with high serum FGF21 was over and above the effects of individual components of the metabolic syndrome. Our in vitro study detected a differentiation-dependent expression of FGF21 in 3T3-L1 adipocytes and human adipocytes. In db/db obese mice, FGF21 mRNA expression was markedly increased in both the liver and adipose tissue compared with that in their lean littermates. Furthermore, FGF21 expression in subcutaneous fat correlated well with its circulating concentrations in humans.

**Conclusion(s):** FGF21 is a novel adipokine associated with obesity-related metabolic complications in humans. The paradoxical increase of serum FGF21 in obese individuals, which may be explained by a compensatory response or resistance to FGF21, warrants further investigation.
FGF21 was reported in 2001 to be expressed in murine liver and thymus. It became a cytokine and a hormone of interest when it was demonstrated in 2005 to stimulate non-insulin-dependent glucose uptake in adipocyte, mediated via increased expression of GLUT1. In vivo administration of FGF21 in rodent models of diabetes lowered both plasma glucose and triglyceride levels and improves insulin sensitivity and glucose clearance, and transgenic mice over expressing FGF21 from the liver displayed resistance to diet-induced obesity and improved glycemic control. In diabetic rodents, FGF21 directly affects the endocrine function of the pancreas by enhancing insulin production and β-cell survival and reduces the maladaptive glucagon release. FGF21 requires the presence of the transmembrane protein β-klotho (that was discussed in the Yearbook 2006 and 2007) for its effect.

We now learn that human FGF21 has no acute but long-term effects on lipolysis in human fat cells, and these cells express β-klotho which is a prerequisite for FGF21 responsiveness. A 3-day FGF21 treatment lowered catecholamine- and ANP-stimulated lipolysis by 50%. Since attenuated lipolysis results in reduced NEFA release it is conceivable that the anti-diabetic effect of FGF21, at least in part, may involve regulation of lipolysis. The decrease in lipolysis could also contribute to a reduced lipotoxicity on islet cells in addition to the direct effects of FGF21 recently shown in β cells.

The second of these papers shows high FGF21 levels in overweight subjects in positive correlation with adiposity, fasting insulin, and triglycerides but negatively with HDL cholesterol. The increased risk of the metabolic syndrome associated with high serum FGF21 was over and above the effects of individual components of the metabolic syndrome. The paradoxical increase of serum FGF21 in obese individual may be explained by resistance to FGF2.

**Mechanism of the year: diseaseasomics integrating social networks**

**The spread of obesity in a large social network over 32 years**

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**Background:** The prevalence of obesity has increased substantially over the past 30 years. A quantitative analysis of the nature and extent of the person-to-person spread of obesity as a possible factor contributing to the obesity epidemic was performed.

**Methods:** A densely interconnected social network of 12,067 people assessed repeatedly from 1971 to 2003 as part of the Framingham Heart Study was assessed. The body-mass index was available for all subjects. Longitudinal statistical models were used to examine whether weight gain in one person was associated with weight gain in his or her friends, siblings, spouse, and neighbors.

**Results:** Discernible clusters of obese persons (body mass index ≥30) were present in the network at all time points, and the clusters extended to three degrees of separation. These clusters did not appear to be solely attributable to the selective formation of social ties among obese persons. A person’s chances of becoming obese increased by 57% (95% confidence interval (CI) 6–123) if he or she had a friend who became obese in a given interval. Among pairs of adult siblings, if one sibling became obese, the chance that the other would become obese increased by 40% (95% CI 21–60). If one spouse became obese, the likelihood that the other spouse would become obese increased by 37% (95% CI 7–73). These effects were not seen among neighbors in the immediate geographic location. Persons of the same sex had relatively greater influence on each other than those of the opposite sex. The spread of smoking cessation did not account for the spread of obesity in the network.

**Conclusion(s):** Network phenomena appear to be relevant to the biologic and behavioral trait of obesity, and obesity appears to spread through social ties. These findings have implications for clinical and public health interventions.

The obesity epidemic has urged active research in various aspects of the epidemiology and pathophysiology of the disease. The genetic basis of the susceptibility to weight gain is one aspect that has received a lot of attention and where multifactorial traits modulating risk are well accepted. However, the same concepts have not applied so far to environmental aspects where research has...
mostly been focused on individual factors. Here the researchers from the Sociology and Health Care Policy Department at Harvard have taken advantage of the comprehensive data collection from the Framingham study to assess the role of social networks in the risk of obesity. The results are very impressive and show that being a friend of somebody who becomes obese increases your chances of becoming obese by 57%. This risk is higher than the increase in risk (40%) if a sibling becomes obese. The beauty of the paper also resides in the methodology in analyzing network interactions and in the videos showing the spread of obesity in the network mode over time. When we see an obese patient in the clinic, most of us will ask for the weight of relatives. From now on we will also have to get information on the weight of friends. An editorial is associated with the paper and predicts the role of ‘network medicine’ in medical practice. Of note, the same group published a paper on the dynamics of smoking cessation in a social network [4] and concluded that smoking behavior spreads through close and distant social ties and that smokers are increasingly marginalized socially. Altogether, these findings are important for clinical and public health interventions to modify health-related traits such as body weight or smoking. Some good news could be that not all individuals need to be targeted, as far as you target their best friends.

Concepts revised: forget about neurosecretory dysfunction?

Cranial irradiation and growth hormone neurosecretory dysfunction: a critical appraisal
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J Clin Endocrinol Metab 2007;92:1666–1672

Background: It has been suggested that radiation-induced GH neurosecretory dysfunction exists in children; however, the pathophysiology is poorly understood, and it is unknown if such a phenomenon exists in adult life.

Methods: Twenty-four-hour spontaneous GH secretion was studied by 20-min sampling both in the fed state (n = 16; 6 women) and during the last 24 h of a 33-hour fast (n = 10; 3 women) in adult cancer survivors of normal GH status defined by two GH provocative tests, 13.1 ± 1.6 (range 3–28) years after cranial irradiation (18–40 Gy) for nonpituitary brain tumors (n = 12) or leukemia (n = 4) in comparison with 30 (9 women) age- and body mass index-matched normal controls (fasting, 11 men and 3 women).

Results: Using previously published diagnostic thresholds, all patients had stimulated peak GH responses in the normal range to both the insulin tolerance test and the combined GHRH plus arginine stimulation test, as well as normal individual mean profile GH levels during the fed and fasting states. However, gender-specific comparisons revealed a marked reduction (by 40%) in the overall peak GH responses to both provocative tests but similar GH secretory profiles; no differences were seen in the pulsatile attributes of GH secretion (cluster analysis) or the profile absolute and mean GH levels in the fed state or when the hypothalamic-pituitary axis was stimulated by fasting.

Conclusion(s): Radiation-induced GH neurosecretory dysfunction either does not exist or is a very rare phenomenon in irradiated adult cancer survivors. The normality of physiological GH secretion in the context of reduced maximum somatotroph reserve suggests compensatory overdrive of the partially damaged somatotroph axis and constitutes a relative argument against somatotroph dysfunction being explained purely by hypothalamic damage with secondary atrophy due to GHRH deficiency. It is therefore possible that radiation in doses less than 40 Gy causes dual damage to both the pituitary and the hypothalamus.

Neurosecretory dysfunction, was proposed as an entity with decreased spontaneous GH secretion and ‘normal’ GH secretion after conventional stimulation tests. The concept makes much sense in light of the complexity of the regulation of spontaneous GH secretion and of the crude nature and imperfections of GH stimulation tests [5]. This diagnosis became popular after its initial description [6] in 1984, at a time where GH treatment for short stature was limited to GH deficiency and when
the tendency was to widen the spectrum of GH deficiency. Thereafter, the limitations of spontaneous GH measurement became obvious and the difficulties in making this diagnosis precisely became apparent [5]. However, it remained consensual in the field that GH neurosecretory dysfunction truly existed in patients with hypothalamic irradiation. Here, Stephen Shalet and his group revisit this concept in adult patients with cranial irradiation and normal GH stimulation tests, therefore candidates for having ‘adult GH neurosecretory dysfunction’. The authors could not find evidence for such a phenomenon in the small group of 16 patients that were carefully studied. Their conclusion is as always wise and cautious and highlights once again the difficulties in assessing the somatotropic axis in practice and to finely evaluate hypothalamic from pituitary dysfunction.

Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study

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Background: Turner syndrome, one of the most common cytogenetic abnormalities, is characterized by complete or partial X-chromosome monosomy. Cancer risks in women with Turner syndrome have not been clearly established. We aimed to compare the risk of cancer in women with this syndrome with that of the general population.

Methods: A national cohort of 3,425 women who were cytogenetically diagnosed with Turner syndrome in Great Britain between 1959 and 2002 was formed. Identifying information for these patients was sent to the National Health Service Central Register (NHSCR) for England and Wales and to the NHSCR for Scotland. Individuals who were identified on this register were followed up for cancer incidence. Standardized incidence ratios (SIRs) and 95% CIs were calculated on the basis of the number of cancers observed compared with that expected based on national incidence rates. Cumulative risk estimates were obtained by use of the Kaplan-Meier method.

Results: A total of 58,299 person-years were accrued during the study, with a mean of 17.0 years (SD 8.6) follow-up per patient. 73 malignancies other than non-melanoma skin cancer occurred (SIR 0.9; 95% CI 0.7–1.2). Risks were significantly increased for tumors of the CNS (n = 13; SIR 4.3; 95% CI 2.3–7.4), especially for meningioma (n = 7; SIR 12.0; 95% CI 4.8–24.8) and childhood brain tumors (n = 3; SIR 10.3; 95% CI 2.1–30.1), and for cancers of the bladder and urethra (n = 5; SIR 4.0; 95% CI 1.3–9.2) and eye (n = 2; SIR 10.5; 95% CI 1.3–37.9), compared with the general population. However, the risk of breast cancer was significantly decreased (n = 10; SIR 0.3; 95% CI 0.2–0.6). The SIR for cutaneous melanoma was 2.2 (95% CI 1.0–4.4; n = 8), and one of the ocular cancers was a melanoma. The risk of corpus uteri cancer was significantly increased at ages 15–44 years (n = 3; SIR 8.0; 95% CI 1.6–23.2). During follow-up, 5 women, all with a Y-chromosome lineage, developed gonadoblastoma of the ovary, corresponding to a cumulative risk of 7.9% (95% CI 3.1–19.0) by age 25 years in this group.

Conclusion(s): This study shows that, in addition to having an increased risk of gonadoblastoma, women with Turner syndrome seem to be at an increased risk for meningioma and childhood brain tumors, and possibly bladder cancer, melanoma, and corpus uteri cancer, but are at a decreased risk for breast cancer. Reasons for these risks might relate to genetic and hormonal factors or to the effects of hormonal treatments given to women with Turner syndrome.

Long-term risks of common conditions such as cancer or cardiovascular events are difficult to assess in rare conditions such as Turner syndrome or others that we care for in pediatric endocrinology. The methodological difficulties are tremendous and include the need for a high number, account for a number of biases (recruitment, completion, follow-up, etc.) and use an appropriate comparator. This UK group retrospectively constituted a population-based cohort of women with Turner syndrome, by combining the registries of all but two regional cytogenetic centers in the country. This cohort was
then evaluated for cancer incidence to calculate standardized incidence ratios. Probably the most striking (but expected) result is the decrease in breast cancer incidence, highlighting the influence of estrogen deficiency (10 observed for 29 expected). In addition, unexpectedly increased risks of other tumors (mainly meningioma) were detected, in addition to the expected risk of Y chromosome-associated risk of gonadoblastoma. Although the standardized incidence ratios look impressive (12, 10, ...), the absolute risks are small (7 meningioma observed for 0.6 expected). Since GH has been associated with increased risk of meningioma in combination with cranial irradiation in cancer survivors [7], it will be particularly important to assess patients with Turner syndrome in the long-term after GH treatment.

Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study

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Background: To describe independent predictors for the development of microalbuminuria and progression to macroalbuminuria in those with childhood onset type 1 diabetes.

Methods: Prospective observational study with follow-up for 9.8 (SD 3.8) years as part of the Oxford regional prospective study. 527 participants with a diagnosis of type 1 diabetes at mean age 8.8 (SD 4.0) years. Annual measurement of glycated hemoglobin (HbA1c) and assessment of urinary albumin:creatinine ratio.

Results: Cumulative prevalence of microalbuminuria was 25.7% (95% confidence interval 21.3–30.1) after 10 years of diabetes and 50.7% (95% CI 40.5–60.9) after 19 years of diabetes and 5,182 patient years of follow-up. The only modifiable adjusted predictor for microalbuminuria was high HbA1c concentrations (hazard ratio per 1% rise in HbA1c 1.39, 1.27–1.52). Blood pressure and history of smoking were not predictors. Microalbuminuria was persistent in 48% of patients. Cumulative prevalence of progression from microalbuminuria to macroalbuminuria was 13.9% (12.9–14.9%); progression occurred at a mean age of 18.5 (5.8) years. Although the sample size was small, modifiable predictors of macroalbuminuria were higher HbA1c levels and both persistent and intermittent microalbuminuria (hazard ratios 1.42 (1.22–1.78), 27.72 (7.99–96.12), and 8.76 (2.44–31.44), respectively).

Conclusion(s): In childhood onset type 1 diabetes, the only modifiable predictors were poor glycemic control for the development of microalbuminuria and poor control and microalbuminuria (both persistent and intermittent) for progression to macroalbuminuria. Risk for macroalbuminuria is similar to that observed in cohorts with adult onset disease but as it occurs in young adult life early intervention in normotensive adolescents might be needed to improve prognosis.

The risk of nephropathy associated with poor type 1 diabetes control is well known and has been best established by the DCCT study [8]. Several other papers discussed in the Yearbook of Pediatric Endocrinology 2008 deal with diabetic nephropathy [9–12] but this paper seems particularly important [13]. The Oxford regional prospective study being the only true population-based follow-up study of children and adolescents with type 1 diabetes, its results are more generalized than those of other clinic-based studies. In addition to the expected results of increased risk of nephropathy with increased HbA1c levels, the study gives a lot of important information. The most striking result is that in the long-term, poor metabolic control in early childhood conveys the same risk of nephropathy as poor control occurring later in life. Therefore, children with early onset diabetes have an increased long-term risk of diabetic nephropathy due to longer duration of the disease with no or little protection from poor metabolic control occurring in childhood years. This finding is in contrast to a Finnish study which found a decreased risk associated with childhood years of diabetes [14]. In addition, the mean HbA1c level of 9.8% in the cohort is higher than in other large clinic-based cohorts where results range between 8.6 and 9%. This is most likely due to the fact that the Oxford study is
population-based and avoids the recruitment bias that occur in clinic-based studies. The last point illustrated by this study is the lack of high quality data on the use of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists in children and adolescent and therefore there is need for a large prospective collaborative study on the subject.

**New mechanism: epimutations and imprinting of chromosome 14**

**Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes**


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**Background:** Human chromosome 14q32.2 carries a cluster of imprinted genes including paternally expressed genes such as DLK1 and RTL1 and maternally expressed genes (MEGs) such as MEG3 (also known as GTL2), RTL1as (RTL1 antisense) and MEG8, together with the intergenic differentially methylated region (IG-DMR) and the MEG3-DMR. Consistent with this, paternal and maternal uniparental disomy for chromosome 14 (upd(14)pat and upd(14)mat) cause distinct phenotypes.

**Methods and Results:** Eight individuals (cases 1–8) with a uniparental disomy (14)pat-like phenotype and 3 individuals (cases 9–11) with a uniparental disomy (14)mat-like phenotype in the absence of upd(14) were studied and led to the identification of various deletions and epimutations affecting the imprinted region.

**Conclusion(s):** The results, together with recent mouse data, imply that the intergenic differentially methylated region has an important cis-acting regulatory function on the maternally inherited chromosome and that excessive RTL1 expression and decreased DLK1 and RTL1 expression are relevant to upd(14)pat-like and upd(14)mat-like phenotypes, respectively.

Chromosome 14 uniparental disomies produce well-recognized developmental abnormalities. Paternal chromosome 14 disomy results in a unique phenotype characterized by facial abnormality, a small, bell-shaped thorax, abdominal wall defects and polyhydramnion. Maternal chromosome 14 disomy is of interest to pediatric endocrinologists and leads to pre- and postnatal growth failure and early onset of puberty, associated with joint laxity, motor delay, and minor dysmorphic features of the face, hands, and feet [15]. These chromosomal abnormalities are generally identified through loss of genetic polymorphism along a chromosome or a chromosomal region. Here, the authors identified cases that had features similar to these chromosomal abnormalities but where no uniparental disomy had been identified. They examined the methylation status of several genes in the 14q32.2 imprinted differentially methylated region found that these regions were severely hypermethylated in cases with features of paternal disomy, to an extent comparable to that found in the uniparental disomy (14)-paternal case. Similarly these regions were grossly hypomethylated in that they had features of maternal disomy to a degree similar to that identified in the uniparental disomy (14)-maternal case. In addition, a deletion of the so-called intergenic differentially methylated region was identified in several cases explaining the familial nature of the disease. Altogether, these findings are consistent with the parental genomes conflict theory [16]. They indicate that patients who have short stature starting in utero and additional features, such as early or precocious puberty, should be analyzed more carefully. Last, it will be important to dissect this group of patients out of the large and heterogeneous group of short patients ‘born SGA’ to assess their clinical characteristics and response to GH treatment.
Childhood conditions influence adult progesterone levels
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Background: Average profiles of salivary progesterone in women vary significantly at the inter- and intra-population level as a function of age and acute energetic conditions related to energy intake, energy expenditure, or a combination of both. In addition to acute stressors, baseline progesterone levels differ among populations. The causes of such chronic differences are not well understood, but it has been hypothesized that they may result from varying tempos of growth and maturation and, by implication, from diverse environmental conditions encountered during childhood and adolescence.

Methods: Migrant study among first- and second-generation Bangladeshi women aged 19–39 years who migrated to London, UK, at different points in their life-course, women still resident in Bangladesh, and women of European descent living in neighborhoods similar to those of the migrants in London (total n = 227). Data collected included saliva samples for radioimmunoassay of progesterone, anthropometrics, and information from questionnaires on diet, lifestyle, and health. Multiple linear regression, controlled for anthropometric and reproductive variables.

Results: Women who spend their childhood in conditions of low energy expenditure, stable energy intake, good sanitation, low immune challenges, and good healthcare in the UK have up to 103% higher levels of salivary progesterone and an earlier maturation than women who develop in less optimal conditions in Sylhet, Bangladesh (F9, 178 = 5.05, p < 0.001, standard error of the mean = 0.32; adjusted R2 = 0.16). The results point to the period prior to puberty as a sensitive phase when changes in environmental conditions positively impact developmental tempos such as menarcheal age (F2, 81 = 3.21, p = 0.03) and patterns of ovarian function as measured using salivary progesterone (F2, 81 = 3.14, p = 0.04).

Conclusion(s): This research demonstrates that human females use an extended period of the life cycle prior to reproductive maturation to monitor their environment and to modulate reproductive steroid levels in accordance with projected conditions they might encounter as adults. Given the prolonged investment of human pregnancy and lactation, such plasticity (extending beyond any intrauterine programming) enables a more flexible and finely tuned adjustment to the potential constraints or opportunities of the later adult environment. This research is the first, to our knowledge, to demonstrate a post-uterine developmental component to variation in reproductive steroid levels in women.

This paper extends the concept of endocrine programming to ovarian function and has used the opportunity of a migrant study to dissect the influences of current vs. former environmental influences on ovarian function. They find that salivary progesterone is twice as high in women who have lived all their life in an affluent environment, as compared with those who were raised in a restricted environment. The findings themselves are questionable due to the retrospective and cross-sectional design of the study (but how could it be different in humans?). However, the study was carefully performed and adjusted on relevant parameters, such as current BMI and age at menarche. The findings are reminiscent of the influence of intrauterine growth restriction on age at menarche age and once again indicate that the gonadotropic axis programmed by energy intake. The findings have important theoretical implications that are well developed in an accompanying editorial [17] where the evolutionary implications of the findings are discussed. It is suggested that individuals who are raised in an energy deficient environment are programmed to have less progesterone, i.e. less reproductive efficiency to protect themselves from starvation during pregnancy. From a clinical standpoint, the authors suggest that the findings could relate to the increased incidence in breast cancer observed in women migrating from South East Asia to occidental environments.

References


