Pathogenesis of adolescent idiopathic scoliosis in girls - a double neuro-osseous theory involving disharmony between two nervous systems, somatic and autonomic expressed in the spine and trunk: possible dependency on sympathetic nervous system and hormones with implications for medical therapy

R Geoffrey Burwell*1, Ranjit K Aujla1, Michael P Grevitt1, Peter H Dangerfield*2, Alan Moulton3, Tabitha L Randell4 and Susan I Anderson5

Address: 1Centre for Spinal Studies and Surgery, Nottingham University Hospitals Trust, Queen's Medical Centre Campus, Nottingham, UK, 2School of Biomedical Sciences, University of Liverpool, Liverpool, UK, 3Department of Orthopaedic Surgery, King's Mill Hospital, Mansfield, UK, 4Department of Child Health, Nottingham University Hospitals Trust, Queen's Medical Centre Campus, Nottingham, UK and 5School of Biomedical Sciences, University of Nottingham, Nottingham, UK

Email: R Geoffrey Burwell* - gburwell@tiscali.co.uk; Ranjit K Aujla - ranjit.aujla@gmail.com; Michael P Grevitt - mpg@doctors.org.uk; Peter H Dangerfield* - spine92@liverpool.ac.uk; Alan Moulton - alan.moulton@ntlworld.com; Tabitha L Randell - Tabitha.Randell@nuh.nhs.uk; Susan I Anderson - susan.anderson@nottingham.ac.uk

* Corresponding authors

Abstract

Anthropometric data from three groups of adolescent girls - preoperative adolescent idiopathic scoliosis (AIS), screened for scoliosis and normals were analysed by comparing skeletal data between higher and lower body mass index subsets. Unexpected findings for each of skeletal maturation, asymmetries and overgrowth are not explained by prevailing theories of AIS pathogenesis. A speculative pathogenetic theory for girls is formulated after surveying evidence including: (1) the thoracospinal concept for right thoracic AIS in girls; (2) the new neuroskeletal biology relating the sympathetic nervous system to bone formation/resorption and bone growth; (3) white adipose tissue storing triglycerides and the adiposity hormone leptin which functions as satiety hormone and sentinel of energy balance to the hypothalamus for long-term adiposity; and (4) central leptin resistance in obesity and possibly in healthy females. The new theory states that AIS in girls results from developmental disharmony expressed in spine and trunk between autonomic and somatic nervous systems. The autonomic component of this double neuro-osseous theory for AIS pathogenesis in girls involves selectively increased sensitivity of the hypothalamus to circulating leptin (genetically-determined up-regulation possibly involving inhibitory or sensitizing intracellular molecules, such as SOC3, PTP-1B and SH2B1 respectively), with asymmetry as an adverse response (hormesis); this asymmetry is routed bilaterally via the sympathetic nervous system to the growing axial skeleton where it may initiate the scoliosis deformity (leptin-hypothalamic-sympathetic nervous system concept = LHS concept). In some younger preoperative AIS girls, the hypothalamic up-regulation to circulating leptin also involves the somatotropic (growth hormone/IGF) axis which exaggerates the sympathetically-induced asymmetric skeletal
effects and contributes to curve progression, a concept with therapeutic implications. In the somatic nervous system, dysfunction of a postural mechanism involving the CNS body schema fails to control, or may induce, the spinal deformity of AIS in girls (escalator concept). Biomechanical factors affecting ribs and/or vertebrae and spinal cord during growth may localize AIS to the thoracic spine and contribute to sagittal spinal shape alterations. The developmental disharmony in spine and trunk is compounded by any osteopenia, biomechanical spinal growth modulation, disc degeneration and platelet calmodulin dysfunction. Methods for testing the theory are outlined. Implications are discussed for neuroendocrine dysfunctions, osteopontin, sympathoactivation, medical therapy, Rett and Prader-Willi syndromes, infantile idiopathic scoliosis, and human evolution. AIS pathogenesis in girls is predicated on two putative normal mechanisms involved in trunk growth, each acquired in evolution and unique to humans.

Introduction
The autonomic nervous system through its hypothalamic neuroendocrine control of puberty, menarche and skeletal growth [1-3] contributes importantly to the pathogenesis of AIS [4-6]. Melatonin [7-13] and its signaling pathway dysfunction [14-20] and platelet-calmodulin dysfunction [21,22] detected in AIS subjects involve the autonomic nervous system. In AIS girls, autonomic nervous system activity was reported to be higher than controls [23].

The double neuro-osseous theory for AIS pathogenesis in girls postulates developmental disharmony between somatic [24] and autonomic [25,26] nervous systems [27-29] expressed in the spine and trunk and exaggerated by hormones producing systemic skeletal overgrowth (preoperative girls) (Figure 1) [30-45]. The theory predicates AIS pathogenesis in girls on dysfunction in one or both of two putative normal mechanisms involved in trunk growth, each acquired in evolution and unique to humans, namely:

**Autonomic nervous system**

**LHS concept**
1. Selective hypothalamic up-regulation of sensitivity to leptin with asymmetry from mutation(s)
2. Sympathetic nervous system activated asymmetrically
3. Vertebral growth plates asymmetric in 1-3D
4. Other skeletal length asymmetries in ribs, upper arms and ilia

**Somatic nervous system**

**Escalator concept**
1. CNS postural maturational delay/ or asymmetry(ies) fail to control initiating scoliosis
2. Apical & periapical asymmetry(ies) can initiate scoliosis in rapidly enlarging and actively moving spine

? Primary growth plate (GP) disorder

**Figure 1**

**Double neuro-osseous theory for the pathogenesis of AIS in girls.** Disharmony in spine and trunk between the two nervous systems, autonomic (leptin-hypothalamic-sympathetic nervous system - LHS - concept) and somatic (escalator concept). The drawing of the girl shows three extraspinal sites where left-right skeletal length asymmetries have been detected in AIS subjects - ribs [30,31], upper arms [32] and iliac height [33,34]; the latter two asymmetries correlate significantly with adjacent spinal curve severity suggesting the presence of vertebral growth plate asymmetries [32,34-36]. Asymmetries are also found in tibial lengths [34,37], femoral anteversion [38,39], femoro-tibial correlations [40,41] but not tibial torsion [39,42]. There is some evidence suggesting a “primary” vertebral growth plate disorder in AIS [43,44] but this is controversial [45].
(1) Physiological trunk width skeletal growth driven hormonally and supplemented by the sympathetic nervous system acting symmetrically [25,26,46-50].

(2) Physiological trunk postural mechanisms of the somatic nervous system adapting normally to the growing and biomechanically changing skeletal framework [24,51,52].

There is preliminary evidence suggesting that the hypothalamus of some normal juvenile girls, but not boys, functions with central leptin resistance of the somatotropic (growth hormone/IGF) axis. This mechanism may limit the energy invested in female skeletal growth thereby conserving energy for reproductive development [50]. AIS in girls is viewed here as commonly resulting from increased central leptin sensitivity of hypothalamic sympathetic functions and, in some girls, of the somatotropic (growth hormone/IGF) neuroendocrine axis.

These concepts provide an evolutionary and biological perspective [53] of energy homeostasis (bioenergetics) [54], particularly involving white adipose tissue storing excess energy as triglycerides, from which the double neuro-osseous theory is formulated. At the molecular level, disharmony between genes is established [55]. Gene variants that may impact the biology of AIS pathogenesis [56] are considered here in relation to body mass index (BMI), timing of puberty, leptin, leptin-receptor deficiency, changes in hypothalamic resistance/sensitivity to leptin, some hormones thought to be related to AIS pathogenesis, and certain genetically-modified mice.

The double neuro-osseous theory accommodates evidence that AIS may not be a single condition [51,57-65]. This explains different relative contributions to the trunk deformity by the autonomic (sympathetic nervous system and hormone effects) and somatic nervous systems (postural mechanisms), which can vary between subjects.

The aims of this paper are to:

- consider an evolutionary perspective [53] for the pathogenesis of AIS in girls stemming from female fat accumulation in puberty; and
- foster new thinking and research to improve causal knowledge of AIS pathogenesis.

Background

General comments

Most experts agree that the causes of adolescent idiopathic scoliosis (AIS) are multifactorial with no generally accepted theory of pathogenesis (Appendix 1) [14,51,57,58,66-111]. This reflects shortcomings in our understanding of the complex biological and biomechanical multifactorial processes involved in AIS pathogenesis which needs innovative thinking [73], to which we add new findings not explained by prevailing theories. One recent review suggests that genetics and the unique mechanics of the fully upright human spine play a decisive role in AIS pathogenesis [75]. A genome-wide association study revealed 30 markers identified as the most useful prognostically [56].

Biomechanical spinal growth modulation

A commonly held pathogenetic theory is that initiating changes in the spine of unknown origin lead to biomechanical spinal growth modulation causing curve progression [80-82,107]. Brace treatment is based on this view of pathogenesis.

Neurological abnormalities

Studies over many years in AIS subjects have shown abnormalities of visual, vestibular, proprioceptive and postural control [67,69,70,94-96,99-104] involving the brain stem [69,95,97-99], cerebral hemispheres and corpus callosum [69,95,104,111-115], though not without controversy. Lowe et al [67] suggested that the pathogenesis of adolescent idiopathic scoliosis (AIS) results from a primary pathology in the hind brain causing a defect of central control, or processing in the central nervous system (CNS) that affects a normal growing spine [116]. Neurological abnormalities with AIS have been explained by four fairly comprehensive concepts for pathogenesis:

(1) visuo-spatial perceptual impairment producing a motor control problem [104];

(2) body-spatial orientation concept [69];

(3) neurodevelopmental concept [105,106]; and

(4) sensory integration disorder [102].

Abnormal asymmetries of brain structure and function are found in AIS girls for each of cerebral hemispheres [112-115].
115], dichotic listening [112], brain stem [97-99] and, in preliminary research for left thoracic AIS, on MR brain scans, reduced white matter density in the left internal capsule and corpus callosum [114,115].

**Origins of the double neuro-osseous theory - the escalator concept**

Summarizing concepts of AIS pathogenesis in 2008 [51], we suggested a novel neuro-osseous escalator concept for AIS in girls (Figures 1, 2 and 3). This involves interaction between the growing skeleton and postural mechanisms of the maturing somatic nervous system. The dependence of AIS progression on growth is attributed not to growth velocity, but to rapid skeletal enlargement hormonally-induced, producing skeletal sizes for age beyond the capacity of postural mechanisms of the somatic nervous system to control the initiating deformity.

**Origins of the double neuro-osseous theory - the LHS concept**

Later in 2008, from analyses of anthropometric data of adolescent girls - normal, screened and preoperative, we reported that relatively higher and lower subsets of body mass index (BMI) reveal different features of skeletal maturation [46,47,117-119] and asymmetries of spinal deformity and upper arm lengths [46,120,121] (Figure 1). Subsequently, skeletal overgrowth patterns for age were found in preoperative AIS girls compared with normal girls when analysed separately by higher and lower BMI subsets [29,122]. Then, in normal girls and boys, an excess of severe back humps was found to be associated with lower BMI subsets [123-125]. These and other findings were not explained by any of the theories surveyed (Appendix 1, items 1-15). A more comprehensive hypothesis for AIS pathogenesis in girls was needed incorporating energy homeostasis (bioenergetics) and the hypothalamus in a disorder presenting as abnormalities of trunk growth with axial and appendicular skeletal asymmetries and systemic skeletal features in preoperative girls. The components included in the new formulation are white adipose tissue, leptin, hypothalamus and sympathetic nervous system (LHS concept). Together with the escalator concept, they form the double neuro-osseous theory (Figure 1). It has common ground with the thoracospinal concept [59-63]. These findings for AIS girls and the severe trunk asymmetry of healthy adolescents [123-125] are consistent with the hypothesis that the control mechanisms of bioenergetics have relevance to the etiopathogenesis of such shape deformities/distortions.

**Scientific Basis of the Escalator Concept**

The central nervous system and the changes of the human frame during development and growth

Sporns and Edelman [126] wrote:

“There is overwhelming evidence that the emergence of coordinated movements is intimately tied to both the growth of musculoskeletal system and to the development of brain. The neural development and learning cannot be considered outside of their biomechanical context. A key theoretical issue is how the changes in brain circuitry controlling muscles and joints become matched to simultaneously occurring developmental changes at the periphery.”

**CNS body schema (‘body-in-the-brain’)**

The CNS body schema in adults is defined as a “.....system of sensory-motor processes that continually regulate posture and movement - processes that function without reflective awareness or the necessity of perpetual monitoring.” [127]. This control involves the posterior parietal cortex which participates in the dynamic representation of the body schema integrated with other cortical areas [127-130].

**SOMATIC NERVOUS SYSTEM - the escalator concept**

**Normal adolescent girls**

We postulate that during normal growth and maturation, a physiological balance is continuously renewed between two synchronous polarized processes we term neuro-osseous timing of maturation (NOTOM) escalators (Figure 2) [24,51,111], namely:
Osseous escalator. Increasing skeletal size, changing skeletal shape and relative mass of the different body segments which, through posture and motion of the body by producing developmental biomechanical and kinematic changes at the periphery, create developmentally-altering proprioceptive and visuo-spatial inputs to the neural escalator in the brain.

Neural escalator and postural control. The brain and CNS body schema are recalibrated as they continuously adjust to skeletal enlargement, shape and relative mass changes to enable them to coordinate motor actions. The posterior parietal cortex (Area 7) in human clinical and experimental studies has been shown to participate in the dynamic representation of the CNS body schema (Figure 2) [127-130]. Leptin functionally enhances NMDA receptors which are critically involved in most models of learning and memory [131,132]. Increased circulating leptin levels may explain the reduced grey matter of certain brain areas in obese subjects [133].

The term escalators are applicable only during growth. Muscles are not included in this terminology because they do not primarily drive skeletal growth, but have key roles in sensory and motor function and contribute to segmental masses. Similar mechanisms are being evaluated in robotics and specifically the learning in, and from, brain-based devices [134].

Girls with AIS

Figures 1 and 3 provide an outline of the escalator concept for AIS pathogenesis in girls. Putative abnormalities of the two polarized components of the escalators - with asynchrony and asymmetry(ies) - provide the mechanisms of the escalator concept for AIS pathogenesis before and during the curve acceleration phase [5] in:

1. spine growing rapidly with asymmetry(ies), and
2. brain and CNS body schema with -
   a) postural maturational delay, and/or
   b) brain asymmetry(ies) [113-115].

Postural maturational delay in the CNS may be relative to earlier skeletal maturation [135-141], or absolute arising from an abnormality in afferent [100-103,142-145], central [104,113], or motor mechanisms [104,146]. A study of stroke subjects suggests that in axial postural control, the right hemisphere undertakes higher-order spatial processing than the left hemisphere [[147], see [148]].

The fate of early AIS - to progress, become static or resolve (rarely) according to the double neuro-osseous theory generally depends on the relative contribution and outcome of the disharmony (Figure 1) between:

a) vertebral growth plate asymmetries in up to three dimensions arising wholly or in part from dysfunction in the autonomic nervous system [25-29];

b) postural control, with or without asymmetries, of a rapidly enlarging and actively moving [52,71,149] adolescent spine; and

c) postural maturity (see Discussion, Explanations for undisputed facts about AIS, (2) Predilection for females b)).

Postural scoliosis in melatonin-deficient mice

Bipedal mice and the protection by melatonin. Machida et al [150] suggested that the scoliosis development in bipedal melatonin-deficient mice and the protection from scoliosis by restoring melatonin levels, are crucial influences for a postural mechanism and bipedalism in scoliosis development. Deficiency of osteopontin or CD44 receptor also protect transgenic melatonin-deficient C57Bl/6J mice from scoliosis [19,20]. Later, we examine whether the scoliosis of these three mouse models may be markers of stress reactions involving the hypothalamus rather than crucial influences for scoliosis development (see Scientific basis of leptin-hypothalamic-sympathetic nervous system (LHS) concept, items 11 & 12).

Some Observations on Skeletal Maturation Relating to AIS not Explained by Pathogenetic Theories (Appendix 1, Items 1-15)

Prescoliotics and early skeletal maturation of AIS subjects

Little discussed features of AIS pathogenesis are:

- Prescoliotics of both sexes show body height, sitting height, and growth of sitting height greater than in non-scoliotic children [135,136].

- Early radiological maturation at 11-12 years of age in AIS subjects [137].

- Early adolescent skeletal growth attained for age by AIS girls [38,39,41,121,135-141]. In the preoperative AIS girls of the relatively higher BMI subset, all the skeletal parameters we measured when plotted as standard deviation scores against age, showed negative regressions - several statistically significant, but not for the lower BMI subset of preoperative AIS girls (unpublished observations).
Together, these observations suggest that, collectively, AIS girls have a growth pattern different from normal, involving growth factors connected to the disease [137,151], confirmed in subsequent research [64,65,89,90,152].

**Extra-spinal skeletal length asymmetries detected with AIS**

Periapical ribs longer on the concavity of right thoracic AIS in elderly scoliosis cadavers were found [30] and given pathogenetic significance, but the finding is controversial [31,63]. In thoracic idiopathic scoliosis, upper arm length asymmetry (relatively longer on convexity) is significantly associated with each of apical vertebral rotation (AVR) and Cobb angle [32]. Also in scoliosis subjects but with lower spine scoliosis (thoracolumbar and lumbar), iliac height asymmetry (relatively taller on concavity) is associated with Cobb angle and apical vertebral rotation [34], confirming an observation for subjects with lumbar scoliosis [33].

It is unknown whether these asymmetries of upper arm, iliac height and also femoral anteverision [38,39] are pathogenetically-related to any local asymmetry in the AIS spine. We speculate that they are [24,25,32,34-37,40,41,105,106,120,121]. In this connection we outlined evidence supporting a common pathogenesis of upper arm length asymmetry and thoracic AIS spinal deformity [32]. In a similar way that the extraspinal general skeletal overgrowth for age in AIS girls is associated with the relative anterior spinal overgrowth (RASO) [64,65,89,90] giving it pathogenetic significance, we view the abnormal asymmetry of paired bones as *sentinels* of vertebral and/or rib growth plate asymmetries and having pathogenetic significance. There is some evidence of a primary vertebral growth plate disorder in AIS (Figure 1) [43,44,65,90]. Extra-spinal skeletal length asymmetry is also found in ilio-femoral lengths [35]. More such asymmetries need to be sought in other bilateral bones of AIS girls - sacral alae [153-155], clavicles and scapulae.

**Body Mass Index (BMI) Relating to AIS and Causal Genes**

BMI is usually expressed as weight in kg/height in m$^2$. Standards are available for the UK in *The ‘Healthy Living’ Social Market Initiative* [156]. BMI does not distinguish between fat and muscle mass. The balance between energy intake and output determining BMI is largely controlled by powerful unconscious mechanisms within the autonomic nervous system (see Scientific basis of leptin-hypothalamic-sympathetic nervous system (LHS) concept, item 3).

**BMI and AIS**

In girls with AIS and young adults with scoliosis, lower body mass index [157-165] has been found by most but not by all workers [46,135,166,167] These findings have implications for body development, abnormal spinal development, or nutrition of patients with AIS [165]. There is some evidence of disordered eating behavior [159,168,169], but the low body-mass index of girls with AIS is said not to be the result of the eating disorder [168].

**Overweight AIS patients**

There is a trend towards increasing numbers of adolescents with AIS in the overweight category [170,171]. The hypothesis that increased BMI can influence scoliosis presentation was tested in 427 adolescents with idiopathic scoliosis [170]. Female subjects who presented with larger curves (>50 degrees) were older and had a greater BMI than those with curves less than 50 degrees (p = 0.0557). Possible curve detection difficulties, endocrine factors and an earlier puberty with increased fat mass were suggested for the association of the larger curves with obesity.

**Fat mass related to bone mass and genetic markers in normal children**

In humans, common variants at only two loci, *FTO* and *MC4R* (melanocortin-4 receptor) have been reproducibly associated with body mass index (BMI) [172,173]. Mutations of *MC4R* are the leading cause of severe childhood-onset obesity [172]. A meta-analysis of 15 genome-wide association studies for BMI identified six additional loci, including *SH2B1* [173]. Several of the likely causal genes are expressed, or known to act in the central nervous system [172-174]. Different versions of the human gene *FTO* strongly correlate with BMI [174]; the *FTO* gene with significant polymorphic variation has been identified in several papers as a candidate gene predisposing to obesity. In rats, *fto* is significantly up-regulated (41%) after food deprivation [174]. In humans, fat mass, and genetic markers for obesity genes *MC4R* and *FTO*, are strongly related to bone mineral content, total body and regional, measured by DXA [175].

*SH2B1* is a strong prior candidate for regulating body weight; it is implicated in leptin signaling; *Sh2b1*-null mice are obese; and the evidence suggests that the effects of this gene on obesity are mediated through the central nervous system [173] (see *Leptin, hypothalamus and AIS*).

Overall, these findings support the view that fat mass is on the causal pathway for bone mass in normal children [175].

**Fto gene in mice**

In mice, loss of the *Fto* gene leads to postnatal growth retardation, reduction of adipose tissue and serum leptin, increased energy expenditure, enhanced circulating levels of adrenaline and noradrenaline; these changes are attributed to sympathetic system activation (sympathoactiva-
tion) controlling energy expenditure through mitochondria and fatty acids/triglycerides [176,177]. In Fto-deficient mice the sympathoactivation associated with decreased circulating leptin levels is similar to the hypothalamic up-regulation and sympathoactivation we postulate for AIS girls, but without the skeletal overgrowth for age (see Autonomic nervous system - leptin-hypothalamic-sympathetic nervous system (LHS)-driven mechanism in health and LHS concept in AIS).

Relation of relatively higher and lower BMIs to skeletal sizes and asymmetries in AIS girls

Most previous research on AIS has evaluated BMI as a sole parameter, or in relation to a few skeletal features [163,164,167]. The genetic aspects of BMI for AIS have not been reported but it may be difficult in such research to disentangle the contributions of lower BMI from that of the AIS.

Our recent findings for AIS girls show that higher and lower BMI subsets relative to median BMI values for age have different patterns by each of (1) skeletal sizes for age, (2) bilateral skeletal length asymmetries, and (3) skeletal overgrowth for age in preoperative AIS compared with normal girls, which is systemically distributed suggesting hormonal effects.

Body Mass Index (BMI) Subsets in AIS and Normal Girls Reveal Effects of Energy Stores on Skeletal Maturation, Asymmetry and Overgrowth: Summary of Recent Findings

Three groups of adolescent girls were measured: normals (n = 274 in 1973-81); routinely screened for scoliosis using a prescribed method [178] (n = 137 in 1988-2001); and preoperative (n = 122 in 1992-99). The possibility that observed skeletal differences were due to secular changes (except for sitting height at 10 years of age) was excluded by comparing data from healthy girls measured in 1994-6 with those measured in 1973-81 [140]. The BMIs were not significantly different between groups with 4.7%, 4.6% and 5.6% respectively outside the 95% confidence intervals of the BMI values, almost entirely overweight. These percentages are lower than expected from societal changes [156].

Energy priority of trunk width growth is revealed by body mass index (BMI) subsets in adolescent girls (Figures 4 and 5) - intrinsic or extrinsic mechanisms? A contrast with vertebral length growth in melatonin-deficient mice

Figure 4 shows that preoperative girls in the higher BMI subset have larger biiliac widths for age relative to those in the lower BMI subset (p < 0.001). We reported that BMIs above and below mean (now median) levels separated girls with relatively earlier and larger trunk width at each of the pelvis, chest and shoulder girdle for each of a) preoperative, b) screened [46,117-119] (except for biaxial width in screened girls), c) normal adolescent girls [47,48], and d) normal juvenile girls at 5-10 years [49] with little or no such effect in limb segment lengths (Figure 5). We term this phenomenon energy priority of trunk width growth. Normal boys show this BMI effect on skeletal maturation in trunk widths and, unlike girls, also in the limbs during adolescence [47,48] and at 5-10 years [49].

- "Energy", is used because relatively higher BMI probably implies relatively higher circulating leptin indicating more energy available from fat.

- "Priority", is used because growth plates (GPs) contributing to the trunk width of girls, take priority over those in limbs in "tapping" available energy.

(1) How does the higher BMI subset of preoperative girls attain greater biiliac width for age than the lower
Figure 5
In the autonomic nervous system of normal adolescent girls, the leptin-hypothalamic-sympathetic nervous system (LHS)-driven mechanism (red) supplements bilaterally the blood-borne hormonal contribution (lowest oblique arrow) to trunk width growth at the pelvis, chest and shoulders (yellow box) with little or no sympathetic nervous system (SNS)-induced effect in the limbs (upper arms, forearm-with-hands, tibiae and feet) [46,117-119]. In the preoperative AIS girls, the LHS concept suggests that the GH/IGF axis (upper arrow labeled GH/IGF) and possibly estrogen [122], causes exaggeration of the SNS-induced vertebral/rib length asymmetry with both GH/IGF and sympathoactivation contributing to scoliosis curve progression (Figure 6) in an inverse pathogenetic relationship. The LHS concept suggests that both putative mechanisms, GH/IGF and SNS, provide therapeutic potential for progressive AIS in girls (GPs = growth plates, see Endocrine and Therapeutic Implications).

Energy priority of trunk length growth in leptin-deficient mice?
In leptin-deficient mice (ob/ob) altered leptin signaling has significantly different effects on bone growth in the axial and appendicular skeletons [179]. Compared with normal mice, leptin-deficient mice have significantly shorter femora, and significantly increased vertebral lengths, a trend confirmed in subsequent research [180]. Suggested reasons for this axial/appendicular skeletal growth difference in mice include: (1) decreased thigh muscle mass as a factor for the femoral shortening through mechanotransduction pathways [179]; and (2) vertebral growth plates respond to absent leptin signals in a fundamentally different manner from long bone growth plates [180]. The latter interpretation is consistent with the view that leptin-deficient mice have energy priority of vertebral linear growth relative to limb bones, in contrast to the energy priority of trunk width growth in girls (Figure 4). This apparent human/mouse difference is consistent with an evolutionary change to the trunk broadening of hominins (Figure 5) (hominins include living humans and fossil species that are ancestral to living humans, see Evolutionary Origins).

Skeletal asymmetries
Mean upper arm length asymmetries in preoperative girls
In the lower BMI subset, mean upper arm length asymmetry (7.0 mm, right minus left) is significantly greater preoperative than in screened (-0.8 mm) and normal girls (2.1 mm)(each p < 0.001 with statistically significant variance ratios). In the higher BMI subset, mean upper arm length asymmetries are respectively 3.7 mm, 1.1 mm, and 2.4 mm, greater in preoperative than screened girls (p = 0.031) (analyses of variance correcting for age) [46].

Right thoracic AIS, curve severity and upper arm length asymmetries
Figure 6[181] shows that apical vertebral rotation is significantly associated with upper arm length asymmetry for the lower, but not higher BMI subset, also for Cobb angle (p < 0.001, r = 0.510) [46,120,121]. These findings suggest that the abnormal upper arm length asymmetry of thoracic AIS [32] is not secondary to the spinal deformity but has a pathogenesis common to the spinal deformity [32].

Right thoracic AIS, upper arm length asymmetry and age
In girls with right thoracic AIS, mean upper arm length asymmetry is significantly greater than normal girls (5.6/2.2 mm, p < 0.001). The asymmetry is similar at 11-12 years of age in both higher and lower subsets. It negatively regresses on age in the higher BMI subset (p < 0.001, r = -0.486) but not significantly in the lower BMI subset (p = 0.125, r = -0.212, variance ratio of lower to higher BMI subset = 2.05, p < 0.01); and menarcheal age negatively regresses on upper arm length asymmetry in the higher
Right thoracic AIS girls from preoperative (n = 77) and screened (n = 33) girls. Linear regression analyses, Pearson correlation coefficients and scatter diagrams of apical axial vertebral rotation (AVR, Perdriolle [181]) against upper arm length asymmetries (right minus left) for higher (n = 57) and lower (n = 53) BMI subsets (mean BMIs 21.8 and 17.3 respectively, p < 0.001). Note, the statistically significant correlation for the lower (p = 0.002, r = 0.421) but not higher BMI subset (p = 0.444, r = 0.105); the difference between higher and lower BMI subsets after correcting for menarcheal age is statistically significant for AVR (p = 0.001) but not Cobb angle (p = 0.199). Mean Cobb angles 45.4/45.4 degrees of similar curve types; mean AVRs 23.9/19.7 degrees (p = 0.015) both independent of age; mean upper arm length asymmetries (right minus left) 4.7/6.7 mm (p = 0.172) both significantly different from normals (p = 0.005/p < 0.001); mean menarcheal ages 12.69 years and 13.31 years (p = 0.046, premenarcheal n = 5 & 14 respectively) (ANOVA correcting for age) [46,120,121].

Corrected stature by age for preoperative and normal girls. Corrected standing height (by the Bjure-Nachemson formula [182]) plotted against age in years for relatively higher (n = 65) and lower (n = 57) BMI subsets (CA = Cobb angle). Graphs show best-fit quadratic regression lines for preoperative and normal girls with p values for differences between preoperatives and normals (correcting for menarcheal age p < 0.001 for each BMI subset). MN = menarcheal age of normals, M preop = menarcheal age of preoperative girls: mean menarcheal ages of preoperatives and normals in higher BMI subset 12.82 years and 12.59 years (p = 0.717); and lower BMI subset 13.43 years and 13.14 years (p = 0.825, premenarcheal for normals n = 45 & 63 respectively). Mean BMIs for preoperatives as in Figure 4, and for normals 21.0 (n = 139) and 17.3 (p < 0.001 n = 135) (ANOVA correcting for age or menarcheal age) [29,122].
BMI subset \((p = 0.027, r = -0.325)\). This 'transient' asynchronous upper arm length growth detected with abnormal systemic earlier skeletal overgrowth for age as in some younger preoperative girls (Figure 7), suggests a relation to pathogenesis. There were insufficient girls with left thoracic AIS for separate analyses \((n = 12 [46])\) (see Discussion, Upper arm length asymmetry and the higher BMI subset of right thoracic AIS, and Skeletal asymmetries and lower BMI subsets).

**Skeletal overgrowth for age in preoperative AIS/normal girls (Figure 7)**

Figure 7[182] shows that with relatively higher BMIs, the younger AIS girls, have larger corrected stature for age than do the normal girls, becoming normal sizes by 16 years of age \((p < 0.001, ANOVA with age correction)\). This pattern is found in each of 11 skeletal segments, four of them in bilateral limb segments suggesting a systemic response. Mean menarcheal ages are not significantly different. The skeletal pattern for age suggests earlier skeletal maturation with overgrowth in these younger girls probably from circulating hormones \(\text{GH/IGF-I}\) and possibly estrogen \([29,122]\). The AIS girls with relatively lower BMIs show a more complex pattern with two growth phases: earlier phase similar to normals, and later phase in most skeletal segments, mainly postmenarcheal, with larger overall skeletal growth attained for age in preoperatives relative to normals, \(\text{estrogen effect} [29,122]\). The AIS girls with relatively lower BMIs show a more complex pattern with two growth phases: earlier phase similar to normals, and later phase in most skeletal segments, mainly postmenarcheal, with larger overall skeletal growth attained for age in preoperatives relative to normals, \(\text{estrogen effect} [29,122]\). The similar mean Cobb angle and apical vertebral rotation show that while curve severity at the time of surgery appears independent from (1) skeletal growth patterns, and (2) BMI subsets, we suggest that common factors in different proportions and other common factors, determine the similar curve severities in both subsets (see Discussion Skeletal sizes for age - curve severity, sympathoactivation and hormonal stimulation).

**Back contour asymmetry in normal girls and boys**

The excess of severe back humps in girls and boys was associated with lower BMI subsets \([123-125]\).

**Considered together, the above findings are not explained by any of the prevailing theories of AIS pathogenesis (Appendix 1, items 1-15)**

A more comprehensive hypothesis for girls with AIS was required involving energy homeostasis and the hypothalamus in a disorder presenting as abnormalities of trunk growth with axial and appendicular skeletal asymmetries and in preoperative girls with systemic skeletal features.

**Scientific Basis of Leptin-Hypothalamic-Sympathetic Nervous System (LHS) Concept**

From a novel interpretation of the above findings, the leptin-hypothalamic-sympathetic nervous system (LHS) concept for AIS pathogenesis was formulated \([25,26]\) after surveying evidence relating to:

1. Thoracospinal concept.
2. New neuroskeletal biology.
3. Energy homeostasis and sympathetic nervous system.
4. White adipose tissue, leptin, hypothalamus, sympathetic nervous system and bone formation/resorption in health.
5. Leptin and bone growth in mice.
6. Leptin and bone growth in children.
7. Leptin, hypothalamus and AIS.
8. Central leptin resistance in obesity and possibly in healthy females.
9. AIS as a systemic disorder - platelet calmodulin dysfunction.
10. AIS as a systemic disorder - melatonin, melatonin signaling, osteopontin and soluble CD44 receptor.
11. Some melatonin-deficient mouse models of scoliosis - markers of developmental stress!
12. Osteopontin and bone remodeling in mice.
13. Melatonin receptor 1B (MT1B), AIS, glucose metabolism and type 2 diabetes.

**Thoraco-spinal concept**

Right thoracic, but not left thoracic AIS in girls, is considered by Sevastik and colleagues to be initiated by dysfunction of the sympathetic nervous system leading through vascular changes to relative overgrowth of concave peripheral rib lengths \([59-63]\). This section is written in collaboration with Professor JA Sevastik. Compared with right thoracic AIS, the pathogenesis of left thoracic AIS in girls remains relatively unexplored \([114,115]\). The thoracospinal concept of pathogenesis was established from anatomical and clinical evidence including left-right asymmetries of thoracic skin temperature, breast size and vascularity, and apical vertebral rib length asymmetry \([30]\). Subsequent experimental studies \([61]\) provided evidence for the correction of experimentally-induced scoliosis consistent with the pathogenetic conclusions. The thoracospinal concept is supported by recent studies on breast size \([183]\), vascular \([184,185]\) and peripheral nerve \([186]\) findings. It does not encompass evidence relating to the new neuroskeletal biology, energy homeostasis, or white adipose tissue which is central to
the regulation of energy balance by adipokines, particularly leptin, hormones of the digestive system and metabolites, particularly glucose (Figure 8).

Biomechanical mechanisms are thought to be involved in pathogenesis. Evidence [60] showed that gradual elongation of one rib affects the position of the numerically corresponding vertebra in the three cardinal planes in a way similar to the apical vertebra in idiopathic scoliosis. The disc space wedging is explained by the rotational movement of the central vertebra in the frontal plane, and the lordotic tendency of the scoliotic segment is explained by ventral vertebral translation in combination with tilt in the sagittal plane. Curve progression is attributed to biomechanical mechanisms [63,80-82].

**New neuroskeletal biology (Figure 8)**

In the last decade it was shown initially in mice, that the central nervous system regulates bone remodeling, and more recently longitudinal bone growth via the sympathetic nervous system linking leptin-responsive hypothalamic neurons to bone tissue [187-198]. In reviewing this new field of neuroskeletal biology, Patel and Elefteriou [195] summarize long-standing clinical observations relating to bone and the nervous system including reflex sympathetic dystrophy, hyperplastic callus associated with head injury and myelomeningocele, and osteo-
nia associated with stroke, spinal cord injury and peripheral neuropathy. Conflicting reports on the effect of β-blockers for risk of fractures are published, and randomized clinical trials are needed [199]. Theoretically, neuroskeletal mechanisms expressed via the sympathetic nervous system through its bilaterality (Figure 5), could create asymmetries, although from animal experiments there is no evidence for or against such asymmetries.

**Energy homeostasis and sympathetic nervous system (Figure 8)**

Bodily energy reserves are managed actively by complex systems that regulate food intake, substrate partitioning and energy expenditure thereby regulating long-term adiposity [200]. Energy homeostasis, fat and glucose metabolism are regulated by integratory centers in the central nervous system which receive, and convey information by signals from peripheral organs (such as adipocytes, gut and pancreatic islets - eg insulin and amylin both short-term satiety signals, the latter being a hind brain signal), and which send efferent neural and hormonal signals to peripheral tissues that regulate food intake, energy expenditure, metabolism and behavior (feeding) [200-203]. The obesity genes *MC4R, FTO and SH2B1* may participate in the central control of energy homeostasis [172-174,200,203]. A neuroanatomical framework explaining the effects of leptin on neuroendocrine and sympathetic nervous system function has been reported [204].

**White adipose tissue, leptin, hypothalamus, sympathetic nervous system and bone formation/resorption in health (Figure 8)**

Adipose tissue, where fatty acids are stored as triglycerides in lipid droplets, is central to the regulation of energy balance [205]. White adipose tissue constitutes separate depots that contribute with the hypothalamus as the key centre for integration and control of energy balance [200]. Leptin, best known as a satiety hormone, a signal of energy sufficiency and long-term adiposity, is one of several cytokine-like hormones secreted by adipocytes [1,2,200]. In girls there are gradual age- and BMI-related increases in circulating leptin levels [206]. Molna-Carballo et al [12] from a longitudinal study reported that the leptin concentration increases in both sexes with the progression of puberty, this value being 40% greater in girls, which correlates with the increase in body volume and fat accumulation [206,207]. Girls have higher serum leptin levels before, during, and after puberty than boys, even after accounting for the development of greater female adiposity [207]. The sexual dimorphism in leptin concentrations during puberty appears to be partly due to a stimulatory effect of estradiol on fat deposition and leptin concentration in females and a suppressive effect of testosterone on leptin concentration in males [207]. Leptin levels in men are lower than women at all decades of life [208].

Leptin, the product of the obesity gene (*ob*) circulates in both free and bound form, and targets neurons including the arcuate nucleus and other nuclei of the hypothalamus [200]. Leptin is a master hormone that acts via a specific receptor (OB-R with six types of receptor, LepRa-LepRf; the longest form, LepRb is the only receptor isoform that contains active intracellular signaling domains). The leptin receptor is present in a number of hypothalamic nuclei, where it exerts its effects. Within a complex web of signals with many regulatory functions for food intake, body weight, increasing energy expenditure through sympathetic activation, thermogenesis, other metabolic and endocrine functions, reproduction, immune/inflammatory responses, and wound healing, mainly through signaling to the hypothalamus including [1,2,200,209]:

a) appetite repression and body weight control (*anti-obesity, anorexigenic*);
b) initiation of puberty in girls as one gate with *kisspeptin* in a permissive role [1,2]; genetic variation in LIN28B on chromosome 6 is associated with the timing of puberty [210];
c) stimulation of the sympathetic nervous system, more in females than in males, possibly because of their greater fat mass [211,212];
d) in bone formation, *anti-osteogenic in mice* acting centrally through the sympathetic nervous system [187-192,194-197,213] involving the molecular clock and circadian regulation [214], possibly with an opposite direct effect on bone [190,195,196,198]. Several genes are identified having high levels of expression in the hypothalamus [192,195,196]. Mice lacking β-adrenergic receptors have increased bone mass [215]. In feedback, the skeleton exerts an endocrine regulation of energy metabolism through the *Esp* gene exclusive to osteoblasts controlling secretion of the hormone-like substance osteocalcin [216-218] (Figure 8).

Animal experimentation suggests a two-way interaction between leptin and the sympathetic nervous system, with leptin causing sympathoactivation, and the sympathetic nervous system exercising regulatory feedback inhibition over leptin release [219].

**Leptin and bone growth in mice (Figures 8 and 9)**

Leptin stimulates longitudinal bone growth in leptin-deficient (*ob/ob*) and leptin-receptor deficient (*db/db*) mice [180,194,220-222], and growth plates in culture
[180,222-224] being chondro-osteogenic and angio-genic [190]. The leptin appears to act centrally through the sympathetic nervous system (Figure 8) [190,194,213], growth hormone stimulation [180,190,220,222], and peripherally [190,222] with a direct effect on growth plate chondrocytes by its signaling receptor [180,220,222], regulating IGF-I receptor expression [190,223], and by other mechanisms (Figure 9) [180]. There is evidence for mice, that vertebral body growth plates may respond to leptin differently from long bone growth plates [179,180]. Iwanciec et al [194] propose that hypothalamic leptin plays a role in coupling energy homeostasis and bone growth, acting as an important permissive factor for normal bone growth. Leptin appeared in evolution with the bony skeleton [216].

Leptin and bone growth in children
Maor et al [223] reviewed clinical evidence that after craniopharyngioma surgery in children, circulating leptin may contribute to bone growth including normal height velocity [225], showing more advanced bone age/chronological age [227], earlier puberty and menarche [226] and no significant correlation of leptin and estradiol levels [228]. Montague et al [229] reported two severely obese consanguinous children with congenital leptin deficiency, the findings of which strongly suggested that leptin critically influences energy balance in prepubertal humans. One child developed abnormalities of growth in long bones of her legs treated by corrective surgery, an abnormality attributed to growth plate fragility [180]. Subsequently, in three children who were congenitally deficient in leptin and morbidly obese, Farooqi et al [230] reported radiological skeletal maturation was increased by 2.1 years, and that leptin therapy produced beneficial effects on the skeleton.

Severe dietary restriction, a common cause of leptin insufficiency and growth/length restriction in humans [194], is probably associated with, and explained by, decreased GH and IGF-I receptors in growth plates [231].
**Leptin, hypothalamus and AIS**

Qiu and colleagues [163,164] reported a marked decrease in circulating leptin in AIS girls compared with controls, confirmed by Dr A Moreau (personal communication). Positive correlations were found between leptin and each of age, menstrual status, weight, corrected height, BMI, Risser sign, bone mineral content and bone mineral density (lumbar spine and femoral neck) but not Cobb angle, suggesting that leptin may play an important role in the lower BMI of AIS girls [164]. Longitudinal studies are needed.

**Central leptin resistance in obesity and possibly in healthy females**

Central leptin resistance is defined as reduced ability of circulating leptin to suppress appetite and weight gain and to promote energy expenditure [232].

In obesity. Central leptin resistance is considered to be one of the main causes of obesity [232,233]. It is thought to result mostly from a state of diminished hypothalamic responsiveness to increased levels of circulating leptin [200] which may be selective [232-236].

In healthy females: normal juvenile girls and somatotropic axis. Central leptin resistance may occur normally in girls [227], and in pregnancy thereby permitting the accumulation of adipose tissue stores necessary for growth, reproduction and lactation [227,237]; leptin sensitivity returns, possibly by signaling mechanisms [232], or by altering the leptin dose-response curves [223,238]. There is preliminary evidence [50] suggesting that the hypothalamus of some normal juvenile girls, but not boys, functions with central leptin resistance of the somatotropic (growth hormone/IGF) axis. This putative mechanism, is interpreted as limiting energy invested in female skeletal growth thereby conserving energy for reproductive development [50]. It may be related to the female predisposition to AIS.

**Hypothalamic mechanisms of central leptin resistance in obesity**

Several mechanisms have been revealed to explain central leptin resistance in obesity [232], namely:

1. Impaired leptin transport across the blood-brain barrier e.g. triglycerides [238-240].

2. Serum leptin interacting proteins (SLIPS) such as C-reactive protein [241], but see [200].

3. Inflammation [239,242].

4. Intracellular inhibitory molecules (negative regulators) of leptin signaling including:

   a) the suppressors of the cytokine signaling (SOCS) family [200,243,244].

   b) protein-tyrosine phosphatases (PTPs) [200,245,246]; and

   c) OB-R gene related protein (OB-RGRP) [247,248].

a) Suppressors of the cytokine signaling (SOCS). Howard et al [243] and Mori et al [244] noted that the leptin receptor is highly expressed in the hypothalamus and belongs to the cytokine-receptor superfamily that activates the Janus tyrosine kinase-signal transducers and the activators of transcription (JAK/STAT) pathway to modulate cellular responses in a negative feedback loop [249,250], for detail and other pathways see [232]. They report evidence for mice that SOCS-3 neuronal deletion enhances leptin sensitivity [244,250] as does haploinsufficiency of SOCS-3 [243]. SOCS-3 is also a human gene. SOCS-2, a genetic determinant of height growth in normal children, is involved in the regulation of IGF-I signaling [251].

b) Protein-tyrosine phosphatases (PTPs). PTP-1B also contributes to leptin resistance by inhibiting intracellular leptin receptor signaling by inhibiting JAK2 activation [232,240,252]. PTP-1B deficient mice by knockout and by an antisense (anti-DNA) oligonucleotide designed to blunt the expression of PTP-1B, showed improved leptin and insulin action [252]. PTP-1B is a major regulator of energy balance, insulin sensitivity, and body fat stores [246]. PTP-1B is also a human gene.

c) OB-R gene related protein (OB-RGRP). Couturier and colleagues [247,248,253] report that OB-RGRP negatively regulates the specific leptin receptor OB-R in the hypothalamus of mice. They comment that if the results obtained in the diet-induced obesity mouse model are transposable to humans, targeting the regulator of the leptin receptor rather than the receptor itself (either by RNA interference or by pharmacological antagonists), could be a more appropriate basis for identifying potential new therapeutic targets for a variety of diseases, including obesity.

(5) Intracellular stimulatory molecules (positive regulators) of leptin signaling. According to Morris and Rui [232], SH2B1 enhances leptin signaling. It appears to be required for the maintenance of leptin sensitivity, energy balance and body weight, ultimately through activation of the PI 3 kinase pathway. The ability of SH2B1 to enhance leptin sensitivity may be modulated by other members of the SH2B family. Cellular leptin sensitivity may be determined, at least in part, by a balance between positive (e.g. SH2B1) and negative (e.g. SOCS3 and PTP-1B) regulators.
(6) Chronic endoplasmic reticulum (ER) stress, mediated through protein tyrosine phosphatase 1B and not through suppressors of cytokine signaling-3, contributes to leptin resistance and obesity, presumably by activating various unfolding protein response signaling pathways, Inhibition of ER stress in the hypothalamus by either genetic or pharmacological means markedly improves leptin sensitivity and decreases food intake and body weight in mice.

(7) Defects in neural circuitry including impairment of MC4R signaling in the paraventricular nucleus, induce leptin resistance, hyperphagia and obesity, with genetic and environmental factors modulating the synaptic remodeling and rewiring of this circuitry.

The challenge is to develop diagnostic approaches for the different forms of central leptin resistance and design personalized healthcare programs to treat obesity.

**AIS as a systemic disorder - platelet calmodulin dysfunction**

Lowe et al. suggested that altered paraspinal muscle activity explained the relationship between platelet calmodulin level changes and Cobb angle changes in AIS with calmodulin acting as a systemic mediator of tissues having a contractile system (actin and myosin). An alternative speculative concept to explain the findings of Lowe is that in predisposed subjects, platelet activation with calmodulin changes occurs within dilated vessels of deforming vertebral bodies. The activated platelets in juxta-physeal vessels release growth factors which, after extravasation, abet the hormone-driven growth of the already mechanically-compromised vertebral endplate physes to promote the relative anterior spinal overgrowth (RASO) and curve progression of AIS.

**AIS as a systemic disorder - melatonin, melatonin-signaling, osteopontin and soluble CD44 receptor**

Machida and colleagues found lower plasma melatonin (MLT) levels through 24 hours with progressive AIS curves and concluded that MLT disturbance has a role in AIS progression more than its cause. They suggested that AIS is an inherited disorder of neurotransmitters from neuro-hormonal origin affecting MLT associated with a localized neuromuscular imbalance and torsion in the bipedal condition. The relevance of lower circulating MLT levels to AIS pathogenesis is now controversial since no significant decrease in circulating MLT levels has been observed in a majority of studies.

- MLT and leptin are said not to interact in the initiation or progression of human pubertal development.

- The relationship between MLT and GH is poorly understood.

- How MLT may interact with estrogens is discussed by Leboeuf et al.

- Melatonin-calmodulin interaction may represent a major mechanism for regulation and synchronization of cell physiology.

**Systemic melatonin-signaling dysfunction**

In progressive AIS, Moreau et al. found melatonin-signaling transduction to be impaired in osteoblasts, myoblasts and lymphocytes caused by the inactivation of Gi proteins. These findings, extended in subsequent papers, led to the conclusion that melatonin-signaling dysfunction detected in osteoblasts, myoblasts and lymphocytes is a decisive factor for the pathogenesis of AIS.

**Osteopontin and soluble CD44 receptor**

Most recently, Moreau et al. reported mean plasma osteopontin (OPN) levels to be increased in:

- patients with idiopathic scoliosis, correlating significantly with curve severity, and

- "an asymptomatic at-risk group" (offspring born from at least one scoliotic parent).

In contrast, mean plasma levels of soluble CD44 receptor (sCD44) were significantly lower in patients with Cobb angles of 45 degrees or more. Drawing on evidence from mouse models, it was concluded that OPN is essential to induce scoliosis formation and curve progression through interactions with CD44 receptors, "thus offering a first molecular concept to explain the pathomechanism leading to the asymmetrical growth of the spine in idiopathic scoliosis."

We ask whether:

(1) in mice, the scoliosis of melatonin-deficient models has another interpretation; and

(2) in the AIS subjects, the increased OPN levels are secondary to bone remodeling.

**Some melatonin-deficient mouse models of scoliosis - markers of developmental stress?**

Moreau et al. found all transgenic melatonin-deficient C57Bl/6J mice devoid of OPN or CD44 receptor were protected against scoliosis, contrasting with wild-type ones. May this be, not because OPN is essential for...
scoliosis pathogenesis, but because OPN deficiency reduces stress reactions in mice [260].

For, in mice, circulating OPN plays a significant role in the body's reaction to stress by regulating hormones of the hypothalamic-pituitary-adrenal axis (HPA) [260] modulated by leptin which activates the JAK/STAT pathway. Stressors cause less up-regulation of the stress hormone corticosterone in OPN-deficient mice [260]. This may be tested in the model used for mice: (1) rendered bipedal at 3 weeks of age, and (2) kept in tall cages to make them reach up increasingly for food and water [150]. The developmental stress hypothesis [261], if confirmed, suggests that OPN deficiency through reduced corticosterone up-regulation causes less stress-reaction damage to the neural development of posture and so protects against the scoliosis. If so, these transgenic mouse findings [19,20] may not be relevant to AIS pathogenesis.

**Osteopontin and bone remodeling in mice**

Osteopontin, a major non-collagenous bone matrix glycoprotein originally isolated from bone - sialic acid rich, phosphorylated and inhibitor of calcification - has a critical role in bone remodeling which in OPN-knockout mice was suppressed [262]. Hence, the interpretation under item 11. above, and the evidence from Fujihara et al [262], together raise caution about attributing a causal, rather than a consequential, role to increased plasma OPN in AIS pathogenesis.

**Melatonin receptor 1B (MT1B), AIS, glucose metabolism and type 2 diabetes**

Promoter polymorphisms of the gene for melatonin receptor 1B (MT1B) are associated with the occurrence of AIS, but not directly with curve severity; this supports the hypothesis of a MLT-signaling pathway dysfunction in AIS [263]. There is a lack of association between promoter polymorphism of the MTNR1A gene and AIS [264]. Genome-wide association studies have shown that melatonin receptor 1B variation is also associated with insulin and glucose concentrations; the risk genotype of this SNP predicts future type 2 diabetes suggesting that blocking the melatonin ligand-receptor system in the endocrine pancreas could be a therapeutic avenue for type 2 diabetes [265,266]. These genetic findings:

- are consistent with hormone receptors having a variety of parallel but independent downstream effects; and
- raise the question: Do post-operative AIS girls after 60 years of age have a lower prevalence of type 2 diabetes, because they are protected by being leaner and using their energy in a different way with a more efficient burn within their systemic disorder?

**AUTONOMIC NERVOUS SYSTEM - leptin-hypothalamic-sympathetic nervous system (LHS)-driven mechanism in health and LHS concept in AIS**

We postulate that in normal girls, trunk widening of the pelvis, ribcage and shoulder girdle, characteristic of humans, is contributed to by a leptin-hypothalamic-sympathetic nervous system (LHS)-driven mechanism acting bilaterally (Figure 5). Differential sympathetic innervation between axial and appendicular bones may be present [196]. The pattern of skeletal sizes for age [47-49] suggests that any differential innervation by the sympathetic nervous system may differ between girls and boys.

In normal human growth, biacromial broadening reflects widening mainly of the underlying upper thorax (Figures 10 and 11) [149,267-269], and pelvic broadening reflects iliac flaring and widening mainly of the sacral alae (Figure 12); the latter reaches its maximum in hominins to provide a firm base of support for the trunk during bipedal posture and locomotion (Figures 13, 14) [153,267,269-271]. Hominid lumbar vertebrae also exhibit a caudally progressive widening of their laminae and of the space separating their articular processes [270]. Pelvic inlet width is a predictor of pediatric chest width [272].

The evidence suggests that pelvic widening in the frontal plane [267] (which varies with climatic conditions), together with pelvic incidence in the sagittal plane...
Scoliosis 2009, 4:24

[273,274], provided hominins with conservation of energy [273] through biomechanical economy enabling -

- bipedalism with upright posture [75,153],
- modified spinal movements [275], and in the last 3 million years -
- increasing fetal brain size [270,271,276,277] with sagittal expansion of birth canal (Figure 12) [149,270,271], possibly with the bigger brain, from (1) a bigger baby,. (2) longer lumbar region, and (3) ability to conceive of tool construction and usage [276].

The evidence suggests that the medio-lateral dimension of the birth canal has been relatively (but not absolutely) ample since the australopithecine stage about 3 million years ago (mya = megaannum) with a funnel-shaped upper thorax (Figure 11) [269], as in the contemporary chimpanzee (Figure 13). A more ovoid pelvic shape with increase particularly of the sagittal dimension, then evolved in response to increasing brain size particularly from about 0.5 mya (Figure 12) [270,271] (see Evolutionary Origins).

---

**Figure 11**
The change in the ribcage from funnel-shaped to barrel-shaped in 3 million years of evolution. Reassembly of the fossil skeleton (black) of "Lucy" (Australopithecus afarensis) compared with the skeleton of a modern human female. The upper thorax is funnel-shaped with narrow shoulders, like modern-day chimpanzees (Figure 12). The blades of the ilia have turned in providing hip mechanics appropriate for erect walking. Compared with the modern adult human female, "Lucy" was much smaller with the relative brain size of a chimpanzee, chimpanzee-shaped thorax, a broad pelvis from iliac flaring and widening of sacral alae (possibly related to gut size), and totally bipedal (Diagram modified from [269] and Burwell et al [149]).

---

**Figure 12**
Pelvis of "Lucy" and modern human female separated by 3 million years of evolution. "Lucy"s" sacral alae are wide thereby increasing separation at the hips, the ilia are more flared increasing the mechanical advantage for hip function, and frontal pelvic width greater than sagittal pelvic dimension. The major change visible in this view, namely the more ovoid form of the human pelvis, is accompanied by a sagittal expansion of the birth canal needed for the increase in brain size since "Lucy". (Modified from [271] and Burwell et al [149].)
The LHS concept for girls with AIS

AIS in girls from the standpoint of the autonomic nervous system is viewed as expressing increased central leptin sensitivity of hypothalamic sympathetic functions and, in some girls, of the somatotropic axis, which subsequently develop an inverse relationship. We speculate that AIS arises from dysfunction of the normal LHS-driven mechanism (Figure 5) by genetically-determined and selectively increased hypothalamic sensitivity (up-regulation from mutations) to circulating leptin leading to hypothalamic asymmetry. The asymmetry is viewed as an adverse response to stress [25,36], with asymmetric activity mediated via the sympathetic nervous system bilaterally to vertebral and/or ribs (Figures 1 and 5), to upper arm lengths in thoracic AIS, and to iliac heights in thoracolumbar and lumbar AIS. The increased sensitivity of the hypothalamus to leptin is viewed as being enhanced by increasing circulating levels of leptin from the fat accumulation of adolescent girls [12], despite the lower leptin levels of AIS girls [163,164].

The requirements for the theory are that in dysfunction, the sympathetic nervous system (SNS)-driven effects contribute with neuroendocrine mechanisms to produce [25]:

1. Earlier skeletal maturation (hormonal).
2. Sympathoactivation expressed asymmetrically in vertebral growth plates in 1-3 dimensions - left-right, front-back and/or torsionally - and in some paired bones (Figures 5 and 6).
3. General skeletal overgrowth for age systemically distributed (hormonal)(Figure 7) [152].
4. Left-right extra-spinal skeletal length asymmetries (ribs, upper arms and ilia) (Figure 1) with upper arm length asymmetry being a signal of thoracic vertebral and/or rib length asymmetry (Figure 6).
5. Increased hypothalamic sensitivity to circulating leptin (up-regulation) involves the somatotropic (GH/IGF-I) axis [222] in some younger preoperative AIS girls (Figure 7, see Neuroendocrinology. Sympathetic nervous system and GH/IGF axis).
6. Hormonal effects of the GH/IGF axis cause exaggeration of the SNS-induced vertebral/rib length asymmetry contributing to curve progression of preoperative AIS girls in an inverse relationship (Figure 5, see Neuroendocrinology. Sympathetic nervous system and GH/IGF axis).
7. Relative osteopenia [88,278,279] which results in part from sympatthoactivation.

The lower BMI [163,164] and body fat of AIS girls may be determined genetically [172-174] and contributed to by sympatthoactivation [176,219] from the putative hypothalamic up-regulation to leptin (LHS concept) [25].

Figure 13
Trunk skeletons of female primates reduced to the same total length. Widening of the trunk - chest, shoulder and pelvis, is characteristic of all higher primates. Chimpanzees have an inverted funnel-shaped upper thorax with narrow shoulders. The human pelvis has increased in width mainly through great enlargement of its sacral portions but it is short as in monkeys [267] (Diagram modified from Schultz [267] and Burwell et al [149]).

Figure 14
Top views of thorax and left shoulder girdle in adult macaque and human. In the macaque, the ribcage is narrow laterally and deep sagittally, while in truncally-erect forms it is expanded laterally and shallow from front to back, to keep the center of gravity over the feet. This trunk widening shifts the scapulae from the side to the back of the ribcage with clavicular lengthening, and the shoulder joints facing laterally rather than forward (Diagram modified from Schultz [267]).
weight girls with AIS [170,171] probably reflect changes from genetic (leptin resistance in relation to satiety) and societal factors.

Central leptin resistance/sensitivity and the LHS concept for AIS pathogenesis in girls
The LHS concept for AIS pathogenesis of girls, views the increased hypothalamic sensitivity to leptin as being at the opposite end of the spectrum to the central leptin resistance of obesity. This increased sensitivity to circulating leptin affects the hypothalamic sympathetic nervous system and, in some AIS girls, the somatotropic neuroendocrine axis. The effects produced in growing bones by these neural and endocrine mechanisms are influenced by the availability of energy, allocated by the hypothalamic through hormones and the nervous system, modulated by circulating leptin levels that measure long-term adiposity.

Autonomic Nervous System - Possible Factors Causing Selective Hypothalamic Up-Regulation in AIS
We suggest five molecular mechanisms that might contribute to the selective up-regulation of some hypothalamic neurons to leptin in the LHS concept for AIS pathogenesis.

G-protein coupled receptors
The putative dysfunction of hypothalamic neurons in AIS - increased and asymmetric sensitivity to leptin, may result from an abnormality of a G-protein-coupled receptor, or G protein, to leptin [25]. The melatonin-signaling dysfunction caused by the inactivation of Gi proteins so far detected is peripheral [14-20], and it is unknown whether any hypothalamic mechanism of etiopathogenesis is involved [Dr A Moreau personal communication]. Melanocortin-3 (MC3R) and MC4R are G-protein coupled receptors highly expressed in the hypothalamus [232].

Circulating osteopontin (OPN)
Subject to the caveat expressed for circulating OPN levels having a causal role in AIS, increased levels of circulating OPN [19,20] may act as a gate for AIS in the hypothalamus as does kisspeptin for puberty through its G-protein-coupled membrane receptor GPR54 [2,280,281].

Inhibitory molecules in the JAK/STAT pathway
Subject to the demonstration of a significant functional variation in human populations, inhibitory molecules such as SOCS-3 [232,243,244,250], PTB-1B [232,240,252]and possibly the regulator of the leptin receptor (OB-RGRP) [247,248,253] - all as negative regulators of leptin sensitivity, by their decreasing action, are candidates to increase hypothalamic sensitivity to leptin in the LHS-driven concept for AIS pathogenesis.

Stimulatory molecules in the PI 3 kinase pathway
As positive regulators of leptin sensitivity, members of the SH2B family by their increasing action [232], are candidates to increase hypothalamic sensitivity to leptin in the LHS-driven concept for AIS pathogenesis.

Hormesis - the putative cause of asymmetry in the LHS concept for AIS
Hormesis is a bimodal dose response to drugs and toxins, first stimulation and then an adverse response, usually inhibition [282-284]. There is evidence that this normal hormetic process applies to leptin [223]. The dose effect will be influenced by the combined effects of 1) increased hypothalamic sensitivity to leptin, and 2) raised circulating leptin levels from adolescent female fat accumulation. We speculate that in the hypothalamus the hormesis of leptin, in adversity leads not to inhibition but to increased sensitivity and asymmetry [36]. The concept is considered plausible by Dr EJ Calabrese [personal communication]. In rats, infused leptin increases sympathetic nervous system activity in a dose-dependent manner suggesting that leptin may act hormetically on the normal rat hypothalamus [285].

Autonomic Nervous System - Rett and Prader-Willi Syndromes
Rett syndrome
Rett syndrome is a genetic neuro-osseous developmental disorder much more prevalent in girls than boys, characterized by profound and progressive loss of intellectual functioning and growth failure [286,287]. Raised circulating leptin levels and overactivity of the sympathetic nervous system [288] are associated with its pathophysiology [286,287]. The skin sympathetic responses are related to the side of the scoliosis, on the foot ipsilateral to the convex side of the scoliosis where it shows a relatively lower amplitude [286]. These findings are consistent with the view that leptin and sympathetic nervous system dysfunction, under certain conditions, may be associated with scoliosis expression and curve laterality.

Prader-Willi syndrome (PWS)
PWS, a rare multisystem genetic disorder, is thought to result from a central hypothalamic-pituitary dysfunction [289,290]. It is associated with failure to thrive in infancy and progressive hyperphagia and obesity in childhood; there is short stature with growth hormone (GH) deficiency, obesity, eating disorders, decreased muscle mass, hypotonia, hypogonadism, and a high prevalence of scoliosis in infants, juveniles and adolescents (15-86%) with 67% affected at skeletal maturity [289,291,292]. The pathogenesis of the scoliosis is unknown [293]; it is unrelated to gender and BMI [292] and may be related to decreased muscle mass, hypotonia, and hypo-excitability of motor cortical areas with defective neurogenesis of cor-
tical tissue [294]. The contribution of the autonomic nervous system, if any, to the scoliosis appears to be unknown. PWS is not accompanied by deranged leptin concentrations and there was no evidence of an interaction of the GH/IGF axis with leptin metabolism in GH-deficient children [295]. While infants with PWS, have higher leptin levels than controls, suggesting a relative excess of fat to lean body mass [296], adults with PWS have leptin assessment corresponding to their degree of obesity [297] (see Endocrine and Therapeutic Implications, GH treatment and the Prader-Willi syndrome (PWS)).

Evolutionary Origins
From the initial chimpanzee-human divergence about 5-7 mya, hominins may have evolved their loss of body hair by about 3.3 to 1.2 mya and its replacement with increased subcutaneous white adipose tissue (80% of all fat) for insulation and energy stores, more in maturing females than males [267,298-302]. About 2 mya, these changes were associated with the decoupling of head and trunk movements required for endurance running to hunt down prey [303], since when the hominid lineage leading to modern humans evolved significantly larger, and more sophisticated brains, than other primates [299-302].

Melatonin decrease - the turning point of human evolution?
Explanations of "what makes us human" often include a bridge between culture and biology [51]. Recently, it has been suggested that decreased circulating melatonin levels due to light from campfires extending the day, "changed the timetable of growth, development and reproduction, because sitting by the fire altered the night's flow of melatonin and the cascade of hormones that follow it." [304].

Fat - Brain Growth and Nutritional Stresses
Power and Schulkin [301] in their book, 'The Evolution of Obesity', outline an evolutionary hypothesis in relation to fat and hominin brain growth [299,300]. The book is one of the first to use an evolutionary framework to analyse a major body of neuroendocrine knowledge about a specific condition [53]. Power and Schulkin write:

"Human beings have evolved to become very good at storing fat; fat appears to have been very important in our evolution. For example, human babies are among the fattest of all mammals... "The importance of fat, both in our diet and on our bodies, appears to have increased in human beings compared to our nonhuman primate relatives. We suggest that this change in nutritional biology was linked to the seminal evolutionary event in our lineage: our larger brain." [301].

Nutritionally, human brain growth is said not to be costly [299], but it does require docosahexaenoic acid (DXA), present in body fat more at birth than at any other time in life [300]. The functioning human brain enlarging particularly in the first two years of postnatal life, imposes a burden on metabolism by -

- increasing energy demands, and
- restricting flexibility in energy allocation when nutritional supply is disrupted - as in the nutritional stresses of weaning and childhood infections [299,301,302].

The relation of leptin to brain growth is not considered here [133].

Fat - Trunk Width Growth and the LHS Normal Mechanism
We suggest that another 'seminal evolutionary event' - earlier in our lineage than brain growth, was trunk width growth which has increased more in human beings compared with our nonhuman primate relatives; the latter lack the extended childhood and rapid and large acceleration of growth velocity at adolescence in humans (Figures 11, 12, 13, 14) [153,267,270,271,303].

- Pelvic width. In hominins, increased pelvic as iliac and sacral width for habitual erect walking was established by about 3 mya (Figure 12).

- Thorax and shoulder girdle width. Ribcage widening, particularly of the upper thorax (Figure 11) happened in the last 3 million years. The wide shoulders characteristic of Homo [303] evidently resulted from upper ribcage widening relative to depth (Figures 10 and 11), with clavicular lengthening (Figure 14). This trunk widening at the shoulder girdles is likely to have been selected by:

  a) the evolution of upright posture giving an enhanced respiratory importance to the upper thorax [see 268]; and
  b) counter-rotations of upper thorax and arms (but not the head) providing counter-balancing torques generated by shoulder girdles and arm-swinging needed to oppose torques created by the pelvic rotations of hominin bipedalism [71,149,268,303].

- Brain and pelvic depth. The large fetal brain size enabling a dramatic jump of adult brain size from about 0.5 mya, was made possible by further expansion of the birth canal, particularly sagittally (pelvic depth) (Figure 12) [75,267,299-303].
The *LHS mechanism* suggests that the fatness of hominins, starting over 3 mya, raised circulating leptin levels which, through the hypothalamus and sympathetic nervous system, supplemented the hormonally-driven growth in width of pelvis and ribcage [26] (Figures 10, 11, 12), and not in nonhuman primates [153,267] (Figures 5, 13 and 14). This mechanism, we suggest, provided a process in evolution that contributed to:

- pelvic widening mainly from sacral widening, enabling bipedalism with upright posture, later
- upper thorax with shoulder widening, and still later
- increased pelvic depth of *Homo sapiens* (Figure 12).

The *LHS mechanism* is interpreted as being evident today in normal human development as ‘*energy priority of trunk width growth*’ in girls (Figures 4 and 5) [47-49].

We speculate:

- In evolution, to reduce toxicity to the hypothalamus of the raised circulating leptin levels - signaling greater adipose tissue stores particularly in females, hypothalamic sensitivity to circulating leptin became diminished (desensitized, or down-regulated, i.e. central leptin resistance), possibly involving increased action of inhibitory molecules such as SOCS-3 and PTP-1B, or decreased action of stimulatory molecules such as SH2B1. It needs to be established whether humans deal with SOCS-3, PTP-1B, and SH2B1 differently from other apes.

- In evolution, the development of human bipedalism and upright posture necessitated adaptations of postural control by the somatic nervous system [51].

- The *putative central leptin resistance in the somatotropic (GH/IGF) axis* of normal juvenile girls [50], see [227,237]] is linked to a greater evolutionary down-regulation of leptin in the female than the male hominin hypothalamus.

**Fat - AIS in Girls and the LHS Concept of Pathogenesis**

The *LHS concept for AIS pathogenesis* suggests that the putative genetically-determined selectively increased hypothalamic sensitivity (*up-regulation from mutations*) to leptin leading to hypothalamic sympathetic asymmetry is rooted in the evolutionary origins of hominin fat deposition providing the energy needed for trunk width growth and later, brain growth and metabolism. We posit that increasing levels of circulating leptin associated with fat accumulation of adolescent girls [12], enhance the putative increased hypothalamic sensitivity (sympathetic and somatotropic) to leptin of AIS girls. This raises the question: Is the societal fat accumulation of normal adolescent girls [156] associated with increasing severity [170,171] and/or prevalence of AIS?

Left-right asymmetries of the neuroendocrine system and of hypothalamic structure and sex-linked function are reported in normal animals [305].

**Endocrine and Therapeutic Implications**

Within the somatic nervous system the *escalator concept*, at present, does not provide any new therapy to improve postural control for early AIS. In contrast, in the autonomic nervous system, the *LHS concept* for AIS pathogenesis suggests two broad therapeutic strategies: through the hypothalamus, and neuroendocrinology.

**Hypothalamus**

Badman and Flier [200] state that the *improvement in central leptin signaling by PTP-1B may provide a target for pharmacological intervention for weight-loss therapies* [306]. Similarly, the *LHS concept for AIS pathogenesis suggests that impairment of central leptin signaling may ultimately provide a target for pharmacological intervention for progressive AIS in girls, if this can be done selectively.

**Neuroendocrinology**

*Sympathetic nervous system and GH/IGF axis*

The *LHS concept* suggests manipulatable causes for therapy (Figure 5) relate to:

1. sympathetic nervous system causing asymmetries in spine, trunk, upper arms; and
2. increased levels of circulating growth hormone (GH)136,307,308 for age in AIS girls notably from 7-12 years, and in pubertal stage 2, and/or IGF-I formerly known as somatomedin C [5,309].

Item (2) may exaggerate the putative sympathetic nervous system-induced vertebral asymmetry particularly in prepubertal and early pubertal growth and thereby contribute to curve progression (Figure 5). Hormonal involvement in AIS progression is supported by the finding that the initiation of the curve acceleration phase correlates with the timing of peak height velocity and simultaneously with digital changes in bone aging (400-425 of the Tanner-Whitehouse RUS III method, stage F covered phalangeal epiphysis to G capped phalangeal epiphysis [5]).

The *GH/IGF axis* is the pivotal system [310] with estrogen [311] for regulating axial growth during puberty. Evidence from normal juvenile girls with relatively higher BMIs suggests there is *central leptin resistance in the somatotropic axis*
Scoliosis 2009, 4:24
http://www.scoliosisjournal.com/content/4/1/24

[[50], see [227,237]] which, through mutations causing central leptin sensitivity, may predispose some girls to AIS. Several papers suggest that the GH/IGF axis has a role in the pathogenesis of AIS [310,312,313], with IGF-I polymorphism affecting curve severity of AIS but not its onset [314]. Growth hormone treatment may increase the risk of progression of scoliosis [315-318].

We suggest that in preoperative AIS girls with relatively higher BMIs, the skeletal overgrowth for age (Figure 7) [38,39,41,135-141,152] results from earlier and increased hypothalamic sensitivity of the GH/IGF axis to leptin for age leading to increased GH/IGF secretions, and possibly estrogen through other neuroendocrine axes. In the lower BMI subset of preoperative AIS girls, there is no early and systemic skeletal evidence to suggest increased secretion of GH/IGF-I (Figure 7) According to the LHS concept, more sympatohoactivation in the lower BMI subset is needed to account for curve magnitudes which are similar to those of the higher BMI subset (Figure 7). This interpretation implies that in AIS girls, GH/IGF axis secretion and sympatohoactivation may have an inverse pathogenetic relationship (Figure 5, see Discussion, Medical conditions showing inverse relation of GH/IGF axis secretion and sympatohoactivation).

The therapeutic implication for AIS girls is that, whatever the BMI, consideration be given, early in curve evolution, to decreasing -

- growth hormone and IGF synthesis by a somatostatin analogue as used in tall children [319] (Figure 9), and/or
- sympathetic nervous system activity by β-blockers (as being evaluated for fractures [199]) (Figures 5 and 8).

Either medication, separately or together, might decrease vertebral and/or rib asymmetry and limit scoliosis curve progression, possibly by also affecting bone remodeling [199]. This strategy ignores a possible role for sex hormones in pathogenesis.

GH treatment and the Prader-Willi syndrome (PWS)

That GH may increase the risk of scoliosis progression is currently being evaluated in PWS patients having GH treatment for the short stature [290,292,320,321]. In the first study of a large population of children with PWS treated with GH, beneficial effects were found with no adverse effects on the progression of scoliosis [321]. In the light of the LHS concept for AIS, the latter finding suggests that in PWS, vertebral growth asymmetries are not primarily involved in the cause of its scoliosis, which may reside in musculature and somatic nervous system.

Sex hormones

Estrogen and testosterone

A third potentially manipulatable cause of AIS pathogenesis in girls relates to sex hormones in pubertal growth [17,258,311,322,323]. The relation of age at menarche to peak height velocity in AIS girls [5,6,258] and genetic findings [324-326] suggest a role for estrogens in susceptibility and/or curve progression. In the LHS concept, estrogens like GH, may exaggerate vertebral growth plate asymmetry and curve severity particularly in girls with relatively lower BMIs (Figure 7). Circulating levels of estrogen are reported to be normal or lower, and of testosterone raised, in AIS girls [307,327-329].

Gonadorhelin analogues

The NOTOM concept (Figure 15) [71,330-332] suggests a medical treatment for AIS, by administering a gonadorhelin analogue (Figure 8) to delay menarche and slow bone growth in early AIS [333] - as practised for children with idiopathic precocious puberty. This is not an ideal option, as delaying the timing of normal puberty adversely affects

---

**Figure 15**

**Neuro-osseous timing of maturation (NOTOM) concept to explain the female susceptibility to progressive AIS in relation to the somatic nervous system.**

Height velocity (cm/year) is plotted against age in relation to putative postural maturation at 12 years of age in both sexes. The postural immaturity of girls due to their earlier growth spurt makes them more susceptible to curve progression than boys. A curve initiating factor is not identified in this concept. The age and sex effect of postural sway in healthy children needs further evaluation [71]. (Diagram modified from Burwell and Dangerfield [330-332]).
bone mineralisation, and potentially could increase the risk of osteopenia long-term.

**Ballet dancers, hypoestrogenism and leptin**

The increased prevalence of mild right thoracic scoliosis in ballet dancers is associated with delayed menarche, secondary amenorrhea, anorectic behavior, osteopenia, fractures and prolonged hypoestrogenism [334]. The LHS concept for AIS pathogenesis applied to the scolioses of ballet dancers suggests that presumed low leptin levels [335] are associated with:

1. increased selective hypothalamic sensitivity to leptin;
2. increased sympathoactivation with asymmetry expressed in the spine as scoliosis;
3. limited energy being diverted away from the gonado-troph-gonadal axis [334] and GH/IGF (somatotropic) axis; and
4. osteopenia and fractures.

Treatment for the menarcheal delay includes oral contraceptive therapy [335].

**Melatonin-signaling dysfunction [12-17]**

Other manipulatable causes of AIS pathogenesis are suggested by the melatonin-signaling dysfunction detected in osteoblasts and chondrocytes.

1. **Osteoblasts.** *In vitro*, MLT significantly stimulates osteoblast proliferation, differentiation and mineralization from controls [336], but not in osteoblasts from AIS subjects [337,338]; this defect is suggested to play a role in the low bone mineral density of AIS patients and contribute to pathogenesis [338]. MLT-signaling dysfunction in AIS subjects has been revealed mainly using bone tissue because (a) osteoblasts respond to MLT, and (b) relative osteopenia is often observed in patients with AIS [14,15,88,278,279]. In some girls with AIS, a particular MLT-signaling defect is evident [17,256,258,337]. Correction of this defect *in vitro* by estradiol suggested that "the lack of estrogen that results in late menarche may be corrected by estrogen agonists having a positive effect on bone tissue remodeling" [256]. Leboeuf et al [258] suggest estrogens as important pharmacological targets to consider in AIS therapy directed to patients selected on their tissue response to MLT. This is in contradistinction to the suggestion of delaying the adolescent growth spurt for subjects in the lower BMI subset using a gonadorelin analogue [330-333] (see Sex hormones).

2. **Chondrocytes.** In cartilage from controls, MLT significantly inhibits chondrocytes proliferation *in vitro* but not from AIS subjects [339]. According to Wang and colleagues [339], the non-responsiveness (i.e. lack of inhibition) of AIS chondrocytes to MLT might play a role in the abnormally increased bone growth of AIS girls from dysfunction of the MLT-signaling pathway. In this connection, there is a decreasing expression of MT1 and MT2 mRNA in chondrocytes from AIS patients which may be related to the molecular pathogenesis of AIS [340].

**Research needs**

Rather than a clinical trial of a somatostatin analogue and β-blockers, we suggest that currently there is a need to evaluate circulating hormones and sympathoactivation in AIS girls by relatively higher and lower BMI subsets.

In addition to using *cellular dielectric spectroscopy* for AIS diagnosis based on G-protein coupled receptor detection [18], Moreau et al [19,20] suggest OPN and sCD44 as useful markers for diagnosis and prognosis of idiopathic scoliosis. Subject to further study, as already mentioned, OPN may be a potential target for therapeutic intervention in AIS subjects as suggested for psoriatic patients [341] (see Some melatonin-deficient mouse models of scoliosis - markers of developmental stress?).

**Discussion**

**Abnormalities revealed by higher and lower BMI subsets for AIS girls**

The analysis of our skeletal data by relatively higher and lower BMI subsets distinguishes two types of effect: skeletal sizes for age (Figures 4 and 7), and skeletal asymmetries (Figure 6).

**Skeletal sizes for age - energy priority of trunk width in girls.**

The skeletal size for age effect in the girls is shown as differences between:

1. higher and lower BMI subsets in each of preoperative, screened and normal girls (Figures 4 and 5) restricted mainly to the trunk [46,117-119]; and
2. preoperative and normal girls in higher and lower BMI subsets (Figure 7).

The trunk width growth priority of girls is seemingly a human characteristic. It is not explained by any of the prevailing theories of AIS pathogenesis (Appendix 1, items 1-15) each of which solely addresses pathogenesis. The trunk width features are accommodated by the LHS mechanism which invokes the sympathetic nervous system and hormones (Figure 5).
Skeletal sizes for age - curve severity, sympatoactivation and hormonal stimulation

In both higher and lower BMI subsets of preoperative AIS girls, mean Cobb angles are similar (Figures 4, and 7) with similar mean ages and curve types. It could then be argued that BMI is irrelevant to AIS pathogenesis. But the earlier systemic skeletal overgrowth for age of the higher BMI subset of younger preoperative girls (Figure 7), suggests that abnormally increased hormonal stimulation ?GH/IGF secretions, is associated with AIS pathogenesis. This led to the hypothesis that GH/IGF secretions exaggerate the sympatico-induced vertebral and/or rib asymmetry and increase scoliosis severity.

The lower BMI subset lacks evidence of earlier systemic skeletal overgrowth for age (Figure 7). In this subset, we postulate that less GH/IGF axis secretions are associated with more sympatoactivation in an inverse relationship (Figure 5). The combined sympatho-hormonally-induced effects in the lower BMI subset produce mean Cobb angle and mean upper arm length asymmetry similar to, and mean AVR less than, the higher BMI subset (Figure 6) [46]. This postulate of an inverse relationship ignores other possible mechanisms that may contribute to curve progression common to each BMI subset, including osteopenia [88,278,279], biomechanical spinal growth modulation [80-82], intervertebral disc degeneration [45,342-351], and platelet calmodulin dysfunction [21,22,107].

Medical conditions showing inverse relation of GH/IGF axis secretion and sympatoactivation

Several conditions in health and disorder show an inverse relationship of GH/IGF secretion and sympatoactivation. GH/IGF (somatotropic) axis secretions are associated with central sympathetic outflow [352,353] in an inverse relationship, though not for physical exercise [354]. In well-nourished subjects under basal conditions, evidence for an inverse relationship of GH secretion and sympatoactivation includes: acromegaly [355,356], GH-deficiency in adults [352,353,357], GH treatment of GH-deficient adults [353], idiopathic cardiomyopathy [358], middle-aged men with high waist-hip circumference ratios with reduced GH peak size concentrations [359], ageing men, with declining GH and IGF-I secretions [360], and growth hormone transgenic mice [356].

The need for this inverse relationship under basal conditions is shown by the following:

(1) In well-nourished subjects, GH stimulation of IGF and insulin is important for the anabolic storage and growth of adipose tissue, glycogen reserves and lean body mass [361]. In fasting, other catabolic states and stress, GH is lipolytic, liberating free fatty acids as an energy source.

(2) The sympathetic nervous system and catecholamines are key components of lipid mobilization in stress [362,363].

Skeletal asymmetries and lower BMI subsets

In the lower BMI subsets skeletal asymmetries are found in:

(1) preoperative girls upper arm length asymmetry is significantly greater than in screened and normal girls (each p < 0.001) [46]; and

(2) right thoracic AIS, wherein Cobb angle and apical vertebral rotation are each significantly associated with upper arm length asymmetry but only in the lower BMI subset (Figure 6) [46,120,121].

The abnormally increased upper arm length asymmetry with right thoracic AIS is explained by the LHS concept as resulting from the sympatho- and hormonally-induced asymmetric effect on humeral linear growth. This asymmetry is not significantly different in magnitude between lower and higher BMI subsets. It is limited to proximal upper limbs (bra-chium), putatively to ribs and vertebrae, all putatively influenced by hormonal effects ?GH/IGF.

Upper arm length asymmetry and the higher BMI subset of right thoracic AIS

In the higher BMI subset of girls with right thoracic AIS, upper arm length asymmetry decreased significantly with age. The LHS concept explains this resolution as sympatho- and hormonally-induced asynchronous upper arm growth affecting either:

(1) younger more than older adolescent girls; or

(2) all girls transiently, with the asymmetry starting in late juvenility with vertebral and/or rib length asymmetry that triggers the scoliosis.

Any associated vertebral osteopenia, possibly sympatho- and/or hormonally-induced, may then predispose to curve progression. Any transience of the upper arm length asymmetry may result from the neuroprotective action [132] of rising circulating leptin levels during the early stages of puberty [206-208]. This could reduce the breadth of hypothalamic asymmetric dysfunction, which may not occur in the lower BMI subset with presumptively lower circulating levels of leptin producing less neuroprotection with a tendency to more asymmetry.
Explanations for undisputed facts about AIS

Theories about the pathogenesis of AIS have to explain several undisputed facts [91,110,364].

1. Dependence of the deformity upon growth and growth rate. The relation of skeletal growth velocity to curve progression in AIS is established [4,5,137,365,366], but its mechanism of action is unclear - causative, conditional, amplifying, or coincidental [91]. In the escalator concept, the dependence of AIS progression on growth is explained not by velocity of growth, but by rapid spinal lengthening and trunk enlargement beyond the capacity of the postural mechanisms to control the deformity [24,51,111].

2. Predilection for females. Two putative mechanisms explain the greater susceptibility of girls than boys to progressive AIS:

   a) In the autonomic nervous system, the increased sensitivity (up-regulation) of the hypothalamus (sympathetic NS and somatotropic axis) to leptin by mutations with its asymmetries contributing to AIS, greater in females than in males [25], is attributed to: i) diminished sensitivity (down-regulation, i.e. resistance) to leptin of the female hypothalamus established by mutations in hominin evolution; and ii) central leptin resistance in the somatotropic axis of normal juvenile girls [50] which, through mutations causing central leptin sensitivity, may predispose some girls to AIS.

   b) In the somatic nervous system, girls may enter their adolescent skeletal growth spurt in postural immaturity, compared with boys who may enter their adolescent growth spurt in postural maturity so they are protected from developing a scoliosis curve (Figure 15) [330-332].

3. Involvement of members in involved families. This is determined by genetic factors operating in the autonomic and somatic nervous systems [56,77-79] and other mechanisms.

4. Curve types and laterality patterns. Biomechanical factors involving ribs [59-63] and/or vertebrae [64,65,91-93] and spinal cord [64,65,92,93], acting during growth may localize AIS to the thoracic spine and cause the sagittal spinal shape alterations [83-90]. The non-random laterality of thoracic AIS curves has been explained by several factors including handedness, aorta, lungs, diaphragm, pre-existing lateral curve, axial rotation and embryology [367-371]. We suggest that the laterality and site of thoracic, thoracolumbar and lumbar curves is determined, in part, by the location of the putative abnormalities of the LHS-driven mechanism in the hypothalamus and sympathetic nervous system.

5. Varied progression patterns. These are explained by the interaction of autonomic and somatic nervous systems in the spine and trunk compounded by any relative osteopenia of vertebrae [88,278,279], biomechanical spinal growth modulation [80-82], accelerated disc degeneration [45,342-351], and platelet calmodulin dysfunction [21,22,107]. Circulating leptin levels in AIS girls did not correlate significantly with Cobb angle [163,164]. This finding does not preclude circulating leptin levels acting with increased hypothalamic sensitivity to leptin to contribute to the magnitude of the hypothalamic asymmetry, and from that to the sympathetic nervous system-induced skeletal asymmetry(ies).

6. 3-D rotatory deformity of the spine. In thoracic AIS, Davids et al [372] found that the most valuable single MRI indicator for abnormal central nervous system findings was the absence of an apical segment lordosis. This and other evidence [91,373] suggests that in thoracic AIS, apical lordosis [83-87] is determined by processes either intrinsic to the spine ("primary", i.e. relative anterior spinal overgrowth = RASO [51,76]), and/or extrinsically by the sympathetic nervous system acting on vertebrae in 3D - left-right, front-back, and/or torsionally. Recent evidence shows that while right thoracic AIS has a reduced thoracic kyphosis (T5-12), increased pelvic incidence and sacral slope consistent with the RASO theory of pathogenesis [374], left thoracic AIS [374] has a normal thoracic kyphosis and pelvic incidence, not consistent with the RASO theory. This may signify that left thoracic AIS has a pathogenesis different from right thoracic AIS [374], possibly involving reduced white matter density of the central nervous system [114,115]. We suggest that right and left thoracic AIS in girls may be driven separately by the two nervous system components of the double neuro-osseous theory: right thoracic AIS mainly by the autonomic/sympathetic nervous system and left thoracic AIS, mainly by the somatic nervous system.

7. Vertebral bodies grow faster than the posterior vertebral elements [64,65,83-90]. This is explained in part by a greater enhancing effect of the sympathetic nervous system on vertebral bodies and their growth plates than on posterior vertebral growth leading to asymmetry in the sagittal plane and the relative anterior spinal overgrowth (RASO) of progressive AIS.

8. AIS is exclusive to humans. We suggest that AIS in girls is a consequence of abnormalities occurring in the putative physiological LHS-driven (Figure 5) and escalator (Figure 2) mechanisms of the theory, both of which are unique to humans [24,25,50] and emanating from these and other features of their evolution [298-303].
Testing the Theory

The double neuro-osseous theory (Figure 1) cannot be tested as a singularity, but many of its components, framed as hypotheses, can be tested by refutation within ethical restraints. In the multidisciplinary approach needed, some problems to be addressed include the following.

1. Genetic factors operating in somatic and autonomic nervous systems may be investigated in members of families with AIS girls, by genome-wide association studies in relation to postural control data [94] and objective evidence of autonomic dysfunction respectively (see below item (12)).

2. Studies of brain imaging, function and asymmetries of AIS subjects compared with normals during adolescence need to be extended [113-115,375]. A basic question to be addressed is: Is the spinal and trunk deformity of AIS in girls the solitary expression in the spine and trunk of a brain that is the seat of several abnormalities of symmetry control?

3. By relatively higher and lower BMI subsets, confirmation is needed for energy priority of trunk width size for age in normal and AIS girls (Figures 4 and 5), skeletal asymmetry growth patterns in girls with thoracic AIS (Figure 6), and skeletal overgrowth patterns for age in preoperative/normal girls (Figure 7). In normal babies, evaluate skull size and trunk width by relatively higher and lower BMI at each of birth, one and two years of age [376,377].

4. By relatively higher and lower BMI subsets confirmation is needed of evidence suggesting central leptin resistance in the somatotropic (GH/IGF) axis of normal juvenile girls [50] which, through mutations causing central leptin sensitivity, may predispose some girls to AIS. The possibility of other mechanisms explaining the findings needs to be evaluated by studies of leptin, soluble leptin receptor and free leptin index [378,379].

5. Since bilateral skeletal asymmetry in humans and skeletal overgrowth for age may be the key factors for the development of AIS [76], etiopathogenetic research needs to focus on skeletal length asymmetries of normal and AIS girls (Figure 1), and their relation to each of skeletal size for age, and osteopenia. The evolution of upper arm length asymmetry in girls with right thoracic AIS [135] and normal right thoracic trunk asymmetry [123-125] needs to be established in longitudinal studies of higher and lower BMI subsets.

6. In leptin-deficient ob/ob mice, evaluate whether vertebral growth plates respond to absent leptin signals in a fundamentally different manner from limb bone growth plates [179,180].

7. The energy sources of growth plates (GPs) in the trunk and limbs of humans and quadrupeds need studying [179,180,380]. Are there metabolic differences in GPs related to the anthropometric findings for girls [47-49], and in trunk width GPs of human babies compared with nonhuman primate babies? (see above, Evolutionary Origins).

8. Evaluation of receptors to hormones in growth plates and intervertebral discs including growth hormone, IGF-I, leptin, estrogens and melatonin by relatively higher and lower BMI subsets [180,220,222,382-384].

9. In AIS spinal curves, correlation studies between MRI and histomorphology of spinal growth plates obtained at surgery [43-45] need extending.

10. Sensory and sympathetic innervation of vertebral endplates in patients with idiopathic scoliosis needs more evaluation [385]. In this connection, sympathectomy as a possible prophylactic procedure for AIS in girls, and as a test of the LHS concept, needs consideration.

11. Search for extra-spinal skeletal length asymmetries in AIS girls in other bilateral bones - sacral alae [153-155], clavicles and scapulae (Figure 1).

12. Assessment of autonomic nervous system function in AIS girls [25,211,286,287,352,353,358,363,386,387]. In lower BMI subset AIS girls, is sympatheoactivation stronger without any increase in GH/IGF secretion, and vice versa in higher BMI subset AIS girls?

13. Estimates of body fat [386,388] including brown adipose tissue [205,299,389-395], BMI [161-171] and relation of the latter to calcium intake [396] and genetics [172-175] in AIS girls.

14. The suggestion that the putative hypothalamic dysfunction of AIS in girls is enhanced by raised circulating leptin levels associated with fat accumulation of female puberty suggests that, where appropriate, lowering circu-
lating leptin levels from BMI reduction may diminish scoliosis curve progression in some girls. In this connection, besides dieting, increasing calcium intake [396] and manipulating the function of brown adipose tissue [299,389-395] need consideration.

(16) As in the Rett syndrome [286,287] skin sympathetic responses need studying in AIS girls, separately for higher and lower BMIs, and subjects with the Prader-Willi syndrome, with the recording electrodes placed on both sides of the trunk and at other sites.

(17) The hypothalamus, neuropharmacology and neuropsychology, all need evaluation by neuroscientists in relation to the LHS concept of the double neuro-osseous theory particularly of a) negative regulators of leptin transduction, including SOCS-3 [243,244,250], PTP-1B [240,252], and OB-RGRP [247,248,253], and b) the positive regulator SH2B1 [232]

(18) Whether SOCS-3, PTP-1B and SH2B1 are significant contributors to AIS pathogenesis has to start with an examination of genetic association between phenotype and variation at each of these genes.

(19) According to Mattson [282], interventions that activate hormetic signaling pathways in neurons is a promising new approach for the prevention and treatment of a range of neurological disorders. Hormesis and the dose-response of leptin/bone growth in AIS girls [283-285] need more study [36] (Calabrese EJ, personal communication).

(20) The studies of girls with right thoracic AIS (Figure 6) need evaluating in girls with left thoracic and other types of AIS, and include hormonal and sympathoactivation comparisons.

(21) The above studies in girls, AIS and normals, need similar evaluation in boys [47-50,117-122] to establish gender similarities and differences [397]. Do adolescent boys with societally-increased fat accumulation have a raised prevalence of progressive AIS?

(22) Infantile idiopathic scoliosis (IIS, early onset scoliosis) occurs at the younger period of life when the human body is growing rapidly and both boys and girls accumulate fat transiently. Curve resolution/progression in boys and girls with IIS is established in relation to rib-vertebra angles [398,399]. The natural history of IIS, resolving and progressive, needs further study in relation to other variables including trunk widths, adipose tissue, and epidemiological findings that may be explained by the functions of white and brown adipose tissue (WAT and BAT). The variables are:

- the funnel-shaped upper chest in progressive IIS [400];
- biacromial and biiliac widths are narrow relative to sub-ischial height (SIH) in older IIS boys and girls (Figure 16), while SIH is not abnormal [401,402];
- in infants developing IIS under 6 months, there was an excess of curve onset in the two winter quarters and of premature low birth weight males [403];
- the declining prevalence of IIS [404] in lower socioeconomic groups in the UK [403] in relation to a) the interscapular pad of BAT, its sympathetic innervation and non-shivering thermogenesis [389,391,395,401,405,406], and b) the central heating of homes over the period of study;
- the loss of subcutaneous fat in subjects with malignant progressive IIS about 4-6 years of age [407]; and
- in normal boys and girls, the dramatic decline from chubbiness to a comparably lean condition by 5 years of age with greater interscapular BAT in premature than mature infants [299-302].
Overall, these findings suggest the hypothesis that white and brown adipose tissue, leptin, hypothalamus and the sympathetic nervous system may, collectively, play a role in the pathogenesis of IIS.

(23) In addition to the historical reductionist approach, a systems-biology approach [408] is needed to evaluate the pathogenesis of AIS, as for obesity [301]. This approach involves multidisciplinary research leading to new theories and new experiments.

**Conclusion**

(1) The double neuro-osseous theory for AIS pathogenesis in girls postulates developmental disharmony between autonomic and somatic nervous systems expressed in the spine and trunk and exaggerated by hormones producing systemic skeletal overgrowth (preoperative girls) (Figures 1 and 7).

(2) The theory predicates AIS pathogenesis in girls on dysfunction in one or both of two putative normal mechanisms involved in trunk growth, each acquired in evolution and unique to humans.

(3) The autonomic component of the double neuro-osseous theory for AIS pathogenesis in girls usually involves selectively increased sensitivity of the hypothalamus to the circulating adipokine leptin, with asymmetry routed bilaterally via the sympathetic nervous system to the growing axial skeleton where it initiates the scoliosis deformity. We speculate that increasing levels of circulating leptin [12] with the fat accumulation of adolescent girls [299,301], enhance the increased hypothalamic sensitivity to leptin.

(4) In the autonomic nervous system, the putative dysfunction - selectively increased hypothalamic sensitivity to leptin as up-regulation from mutation(s), may be regulated by one or more of five possible molecular mechanisms. The abnormal hypothalamic asymmetry is attributed to hormesis [36,124,282-284].

(5) In the somatic nervous system, dysfunction of a putative postural escalator mechanism involving the central body schema fails to control, or may induce the spinal deformity of AIS girls (escalator concept) (Figures 1 and 3).

(6) The developmental disharmony in the trunk is compounded by any relative osteopenia of vertebra, biomechanical spinal growth modulation, accelerated disc degeneration, and platelet calmodulin dysfunction.

(7) Biomechanical factors acting during growth may localize thoracic AIS and contribute to its sagittal spinal shape alterations [83-90]; these include ribs [59-63] and/or vertebrae [64,65,91-93], and spinal cord [64,65].

(8) The hypothalamic dysfunction of the double neuro-osseous theory is expressed as:

- Sympathoactivation expressed asymmetrically in vertebral plates - left-right, front-back and/or torsionally - and in some paired bones.

- Increased hypothalamic sensitivity to circulating leptin (up-regulation) in some younger AIS girls with larger curves also involves the GH/IGF-I axis [222] (Figures 5, 7 and 9).

- Hormonal effects cause exaggeration of the sympathetic-induced vertebral/rib asymmetry(ies) contributing to progression of larger (preoperative) AIS curves in girls.

- Curve progression is postulated to involve an inverse relation of sympathoactivation and GH/IGF secretions (Figure 5). An inverse relation of these functions is found in several medical conditions.

(9) Progress towards these interpretations started in 2008, when theories were summarized which led us to propose a novel neuro-osseous escalator concept for AIS pathogenesis in girls affecting the somatic nervous system (Figures 1, 2 and 3) [51,111].

(10) Subsequently, anthropometric data from three groups of adolescent girls - preoperative AIS, screened for scoliosis and normals, were analysed by an original method for scoliosis of comparing data between subsets of relatively higher and lower body mass index (BMI).

(11) New findings revealed: energy priority of trunk width growth (Figures 4 and 5) [46,117-119], skeletal asymmetries (Figure 6) [46,120,121], and skeletal overgrowth patterns for age (Figure 7) [29,122]. The contrasting skeletal features were not explained by any of the theories of AIS pathogenesis surveyed [51] including the escalator concept [51,111].

(12) The autonomic nervous system component of the theory (LHS concept) [25] draws evidence from several fields including:

- thoracospinal concept for the pathogenesis of right thoracic AIS in girls [59-63];

- new neuroskeletal biology relating the sympathetic nervous system to bone formation/resorption and bone growth [187-198];

- white adipose tissue, the adiposity hormone leptin secreted by adipose tissue which functions as a sentinel
of energy balance and long-term adiposity to the hypothalamus; and

- central leptin resistance in obesity and possibly in healthy females.

(13) A new hypothesis for AIS pathogenesis in girls is formulated incorporating white adipose tissue, energy homeostasis (bioenergetics), the hypothalamus and sympathetic nervous system, in a disorder presenting as asymmetric abnormalities of trunk growth, and, as suspected in preoperative girls, with systemic skeletal overgrowth.

(14) The endocrine and therapeutic implications of the LHS concept are discussed. An immediate need is to evaluate circulating hormone levels in AIS girls by relatively higher and lower BMI subsets; and later a possible clinical trial of medical treatment by a somatostatin analogue and β-blockers.

(15) Some methods for testing the theory’s hypotheses are outlined.

(16) The putative hypothalamic dysfunction is thought to have an evolutionary origin in hominid fat deposition which in more than 3 million years, may have provided energy needed sequentially for each of:

- trunk width growth at the pelvis (mainly sacral alae), (Figures 5 and 12);
- trunk width growth of upper thorax and shoulders (Figures 10 and 11); and
- brain growth with
- pelvic depth increase (Figure 12).

We postulate that white adipose tissue still provides for skeletal growth processes in fetal and post-natal normal human development [299-302].

(17) In some normal juvenile girls, but not boys, the hypothalamus may function with central (hypothalamic) leptin resistance of the somatotropic (GH/IGF) axis to prevent too much energy being invested in female skeletal growth, thereby conserving energy for reproductive development. AIS is viewed as expressing central leptin sensitivity of hypothalamic sympathetic function and, in some younger preoperative girls, of the somatotropic neuroendocrine axis (Figure 7).

(18) A new interpretation involving the hypothalamus for some melatonin-deficient mouse models of scoliosis is presented.

(19) Evidence for infantile idiopathic scoliosis is outlined suggesting a need to evaluate the hypothesis that white and brown adipose tissue, leptin, hypothalamus and the sympathetic nervous system may play a role in its pathogenesis.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
RGB and RKA undertook the day-to-day research producing results which RGB interpreted theoretically in relation AIS pathogenesis in discussion with MPG, PHD, AM, TLR and SIA. MPG has expert clinical knowledge of scoliosis, PHD in human growth studies including scoliosis, AM in research relating to pediatric orthopedics, TLR expert clinical knowledge of pediatric endocrinology and diabetes, and SIA special knowledge of bone biology.

Appendix I
Some theories of AIS pathogenesis [51]

(1) Genetics [75-79].
(2) Biomechanical spinal growth modulation [80-82].
(3) Relative anterior spinal overgrowth (RASO) [83-90].
(4) Dorsal shear forces and axial rotation instability [75,91].
(5) Asynchronous spinal neuro-osseous growth [64,65,92,93].
(6) Postural abnormalities and hind brain dysfunction [69,94-103].
(7) Motor control problem [104].
(8) Body-spatial orientation concept [69].
(9) Neurodevelopmental concept [105,106].
(10) Thoracospinal concept [59-63].
(11) Systemic melatonin deficiency [7-9].
(12) Systemic melatonin-signaling pathway dysfunction [14-20].
(13) Systemic platelet calmodulin dysfunction [21,22,107].
(14) Symmetry control dysfunction - developmental instability [108-110].
(15) Collective and escalator models [51,111].

(16) Leptin-hypothalamic-sympathic nervous system (LHS) dysfunction with disharmony between somatic and autonomic nervous systems in the spine and trunk [24-29].

Acknowledgements

We are grateful for discussion and advice to Professor T Paus, Director, Brain and Body Centre, Department of Psychology, Dr Kirsten J McKenzie, Institute of Neuroscience, Professor FJP Ebling, Professor of Neuroendocrinology, School of Biomedical Sciences, and Professor J Armour, Professor of Human Genetics and Head of School of Biology, all the University of Nottingham, UK. Dr Alain Moreau generously discussed his research with Professor RG Burwell on 24th April 2009 and subsequently by e-mail for which we thank him. We thank: Professor JA Sevastik for reading the text, contributing to the section on the thoraco-spinal concept and making other suggestions; Dr TB Grivas who read the text and made suggestions; and Mr Lyndon Cochrane for the artwork. We thank the Director of Education of Nottinghamshire for giving his permission for the schools to be approached, the Head Teachers for permitting access to the schools, the late-Dr Eleanor More, formerly Specialist in Community Medicine (Child Health), Nottinghamshire, The Nottingham School Nursing Service routinely screening students for scoliosis, Mr JK Webb FRCS referring patients, DCR, MSc. In previous years the research was funded by Action Medical Research on preoperative girls, Mrs FJ Polak MCSP, MSc, PhD and Mrs AS Kirby Health), Nottinghamshire, The Nottingham School Nursing Service routinely screening students for scoliosis, Mr JK Webb FRCS referring patients, DCR, MSc. In previous years the research was funded by Action Medical Research, AO and Arthritis and Rheumatism Council.

References

1. Ebling FJP: The neuroendoctrine timing of puberty. Reproduction 2005, 129:675-83.

2. Kaplowitz PB: Link between body fat and the timing of puberty. Pediatrics 2008, 121(Supplement):S208-S217.

3. Bandini L, Plaut A, Naumova E, Anderson S,Caprio S, Spadano-Gasbarro J, Dietz W: Change in leptin, body composition and other hormones around menarche - a visual representation. Acta Paediatr 2008, 97(10):1454-9.

4. Goldberg CJ: Adolescent idiopathic scoliosis: is rising growth rate the triggering factor in progression? Eur Spine J 1993, 2:29-36.

5. Sanders JO, Browne RH, McConnell SJ, Margraf SA, Cooney TE, Finegold DN: Maturity assessment and curve progression in girls with idiopathic scoliosis. J Bone Joint Surg Am 2007, 89(1):64-73.

6. Grivas TB, Vasiliades E, Mouzakis Y, Mihas C, Koufopoulos G: Association between adolescent idiopathic scoliosis prevalence and age at menarche in different geographic latitudes. Scoliosis 2006, 1:9.

7. Machida M, Dubousset J, Imamura Y, Miyashita Y, Yamada T, Kimura J: Melatonin. A possible role in pathogenesis of adolescent idiopathic scoliosis. Spine 1996, 21(10):1475-2.

8. Machida M: Cause of idiopathic scoliosis. Spine 1999, 24(24):2576-2583.

9. Dubousset J, Machida M: Possible role of the pineal gland in pathogenesis of idiopathic scoliosis: experimental and clinical studies. Bull de l’Acad Nat de Med 2001, 185:593-602, discussion 602-604.(French)

10. Macchi MM, Bruce JN: Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol 2004, 25(3-4):177-95.

11. Karasek M, Winczyk K: Melatonin in humans. J Physiol Pharmacol 2006, 57(Suppl 5):19-39.

12. Molina-Carballo A, Fernández-Tardaguila E, Uheros-Fernández J, Seiquer I, Contereras-Chova F, Muñoz-Hoyos A: Longitudinal study of the simultaneous secretion of melatonin and leptin during normal puberty. Horm Res 2007, 68(1):1-9.

13. Grivas TB, Savvidou OD: Melatonin the "light of night" in human biology and adolescent idiopathic scoliosis. Scoliosis 2007, 2:5.

14. Moreau A, Wang DS, Forget S, Azeddine B, Angeloni D, Fraschini F, Labelle H, Poitras B, Rivard C-H, Grimard G: Melatonin signaling dysfunction in adolescent idiopathic scoliosis. Spine 2004, 29(16):1772-1781.

15. Azeddine B, Letellier K, Wang DS, Moldovan F, Moreau A: Molecular determinants of melatonin signaling dysfunction in adolescent idiopathic scoliosis. Clin Orthop Rel Res 2007, 462:45-52.

16. Letellier K, Azeddine B, Blain S, Turgeon I, Wang D, Bagnall KM, Poitras B, Labelle H, Labelle H, Rivard C-H, Grimard G, Parent S, Ouellet J, Parent S, Moldovan F. Molecular and genetic aspects of idiopathic scoliosis: Blood test for idiopathic scoliosis. Orthopade 2009, 38(2):114-21. (German)

17. Moreau A, Turgeon I, Samba Boiro M, Azeddine B, Franco A, Labelle H, Poitras B, Rivard C-H, Grimard G, Ouellet J, Parent S, Cheng JC, Bratya-Bruno M: Clinical validation of a biochemical test for adolescent idiopathic scoliosis: an International Collaborative 19. Consortium [Abstract]. Eur Spine J 2008, 17:768-769.

18. Moreau A, Franco A, Azeddine B, Rompré PH, Bagnall KM, Poitras B, Labelle H, Rivard C-H, Grimard G, Ouellet J, Parent S. High circulating levels of osteopontin are associated with idiopathic scoliosis onset and spinal deformity [Abstract]. Proceedings of British Scoliosis Society 33rd Annual Meeting 23rd-24th April 2009, in The Curve, Rutland Street, Leicester, LE1 1SB UK: Bone Joint Surg Br, Suppl in press 2009.

19. Azeddine B, Franco A, Rompré PH, Roy-Gagnon MH, Turgeon I, Wang D, Bagnall KM, Poitras B, Labelle H, Rivard C-H, Grimard G, Ouellet J, Parent S. High circulating levels of osteopontin are associated with idiopathic scoliosis onset and spinal deformity progress [Abstract]. Proceedings of Pediatric Orthopaedic Society of North America 25th Anniversary 2009 Annual Meeting Boston, Massachusetts, April 30-May 2 2009, Boston Marriott Copley Place, p128, and In Scoliosis Research Society 44th Annual Meeting and Course, San Antonio, Texas, September 23-26 2009.

20. Lowe TG, Lawellin D, Smith D, Price C, Hafer T, Merola A, O'Brien M: Platelet calmodulin levels in adolescent idiopathic scoliosis. Do the levels correlate with curve progression and severity? Spine 2002, 27(7):768-775.

21. Lowe TG, Burwell RG, Dangerfield PH: Platelet calmodulin levels in adolescent idiopathic scoliosis: can they predict curve progression and severity? Summary of an electronic focus group debate of the IBSE. Eur Spine J 2004, 13:257-265.

22. Ensslin K, Chan DPK: Multiparameter pilot study of adolescent idiopathic scoliosis. Spine 1997, 22(10):978-83.

23. Burwell RG, Dangerfield PH, Freeman BJ: Etiologic theories of idiopathic scoliosis. Somatic nervous system and the NOTOM escalator concept as one component in the pathogenesis of adolescent idiopathic scoliosis. Spine 1997, 22(10):978-83.

24. Burwell RG, Dangerfield PH, Moulton A, Anderson SI: Etiologic theories of idiopathic scoliosis: autonomic nervous system and the left-sympathetic nervous system concept for the pathogenesis of adolescent idiopathic scoliosis. Spine 1997, 22(10):978-83.

25. Burwell RG, Dangerfield PH, Moulton A, Anderson SI: Etiologic theories of idiopathic scoliosis: autonomic nervous system and the left-sympathetic nervous system concept for the pathogenesis of adolescent idiopathic scoliosis. Spine 1997, 22(10):978-83.

26. Burwell RG, Aujla RK, Kirby AS, Dangerfield PH, Moulton A, Cole AA, Polak FJ, Pratt RK, Webb JK: Etiologic theories of idiopathic scoliosis: the left-nociceptor-sympathetic nervous system (LNS) mechanism of normal trunk width growth in girls - evolutionary origin, energy allocation, motor pathways, dysfunction and pathogenesis [Abstract]. Proceedings of the International Research Society of Spinal Deformities, 9-12th July 2008, Hope University, Everton Campus, Liverpool, UK. Abstract Book.21.

27. Burwell RG, Aujla RK, Dangerfield PH, Moulton A, Anderson SI: Pathogenesis of adolescent idiopathic scoliosis in girls: A battle between two nervous systems, autonomic and somatic, fought out in the spine and trunk? [Abstract]. Clin Anat 2008, 21(7):746.
28. Burwell RG, Aujla RK, Grevitt MP, Dangerfield PH, Moulton A, Anderson SI: Pathogenesis of adolescent idiopathic scoliosis in girls: a battle between two nervous systems, autonomic and somatic fought out in the spine and trunk - a theory [Abstract]. Proceedings of British Scoliosis Society Annual Meeting in conjunction with the British Scoliosis Research Foundation, 26th September 2008, Institute of Child Health, London WC1N 1EH, J Bone Joint Surg Br, Suppl in press 2009.

29. Burwell RG: Aetiopathogenesis of adolescent idiopathic scoliosis in girls. Disharmony between two nervous systems, somatic and autonomic, expressed in the spine and trunk. A double neuro-ooseous theory [Abstract]. Magistral Lecture, ISICO Proceedings of Rachele & Rehabilitation multidisciplinary Quinto Evidence-Based Meeting, 21st March 2009, Jolly Hotel, Assago, Milan, Italy, in press 2009.

30. Normelli H, Sevastik J, Akrivos J: The length and ash weight of the ribs of normal and scoliotic persons. Spine 1985, 20(6):590-2.

31. Giampietro P, Ghebranious N, Raggio CL, Ivacic L, Staablj J, McPherson E, Glurich I, Burmeister J, Pauli RM, Jacobsen FS, Rasmussen KJ, Faciszewski T, Boschie-Adjeli O, Blank RD: Rib length discrepancy in adolescent with idiopathic scoliosis. Scoliosis Research Society 41st Annual Meeting and Course, Salt Lake City, Utah, USA, September 10-13 2008:273.

32. Burwell RG, BJ Freeman, Dangerfield PH, Aujla RK, Cole AA, Kirby AS, Pratt RK, Webb JK, Moulton A: Left-right upper arm length asymmetry associated with apical vertebral rotation in subjects with the thoracic scoliotic anomaly of bilateral asymmetry affecting vertebral, costal and upper arm physis? Stud Health Technol Inform 2006, 123:66-71. and J Bone Joint Surg Br 2008, 90-B:Suppl III, 476.

33. Schwender JD, Denis F: Coronal plane imbalance in adolescent idiopathic scoliosis with left lumbar curves exceeding 40°. Spine 2000, 25(18):2358-63.

34. Burwell RG, Aujla RK, Freeman BJ, Dangerfield PH, Cole AA, Kirby AS, Pratt RK, Webb JK, Moulton A: Patterns of extra-spatial left-right skeletal asymmetries in adolescent girls with lower spine scoliosis: relative lengthening of the ilium on the curve concavity and of right lower limb segments. Stud Health Technol Inform 2006, 123:57-65. and J Bone Joint Surg Br 2008, 90-B:Suppl II, 445.

35. Burwell RG, Aujla RK, Freeman BJ, Dangerfield PH, Cole AA, Kirby AS, Pratt RK, Webb JK, Moulton A: Patterns of extra-spatial left-right skeletal asymmetries and proximo-distal disproportion in adolescent girls with lower spine scoliosis: illo-femoral length asymmetry and bilateral tibial/foot length disproportions. Stud Health Technol Inform 2006, 123:101-108. and J Bone Joint Surg Br 2008, 90-B:Suppl II, 445.

36. Burwell RG, Aujla RK, Grevitt MP, Dangerfield PH, Cole AA, Kirby AS, Polak F, Pratt RK, Moulton A, Webb JK, Anderson SI: Leptin, asymmetric bone growth, pathogenesis of adolescent idiopathic scoliosis (AIS) and hormesis: lower spine scoliosis [Abstract]. Clin Anat 2009, 22(3):411.

37. Burwell RG, Aujla RK, Freeman BJ, Cole AA, Dangerfield PH, Kirby AS, Pratt RK, Webb JK, Moulton A: Proximo-distal skeletal length disproportion in lower limbs of girls with adolescent idiopathic scoliosis compared with normal girls: tibial length/foot length is greater bilaterally and associated with left-right tibial length asymmetry [Abstract]. Clin Anat 2010, 24(1):467.

38. Burwell RG, Aujla RK, Kirby AS, Freeman BJ, Cole AA, Dangerfield PH, Polak F, Pratt RK, Webb JK, Moulton A: Ultrasound femoral anteverision (FAV) is decreased and asymmetric after school screening for adolescent idiopathic scoliosis (AIS): femora show torsional anomalies that if in the trunk may initiate the deformity [Abstract]. Clin Anat 2007, 20(7):855.

39. Burwell RG, Aujla RK, Kirby AS, Dangerfield PH, Freeman BJ, Cole AA, Polak F, Pratt RK, Webb JK: Ultrasound femoral anteverision (FAV) and tibial torsion (TT) after school screening for adolescent idiopathic scoliosis (AIS). Stud Health Technol Inform 2008, 140:225-230.

40. Burwell RG, Aujla RK, Kirby AS, Freeman BJ, Cole AA, Dangerfield PH, Polak F, Pratt RK, Webb JK, Moulton A: Ultrasound femoral anteversion/tibial torsion correlations are significant, abnormal and asymmetric after school screening for adolescent idiopathic scoliosis (AIS): lower limb torsional markers for initiation of the torsional trunk deformity of AIS? [Abstract]. Clin Anat 2007, 20(7):855.

41. Burwell RG, Aujla RK, Kirby AS, Dangerfield PH, Freeman BJ, Cole AA, Polak F, Pratt RK, Webb JK: Ultrasonographic femoral anteversion (FAV) relative to tibial torsion (TT) is abnormal after school screening for adolescent idiopathic scoliosis (AIS): evaluation by two methods. Stud Health Technol Inform 2008, 140:37-43.

42. Burwell RG, Aujla RK, Kirby AS, Freeman BJ, Cole AA, Dangerfield PH, Polak F, Pratt RK, Webb JK, Moulton A: Ultrasonic tibial torsion (TT) and TT asymmetry are not abnormal after school screening for adolescent idiopathic scoliosis (AIS): in scoliosis boys TT is decreased relative to scoliosis girls without asymmetry - the result of altered maturation at knee tibial growth plates? [Abstract]. Clin Anat 2007, 20(7):855.

43. Wang S, Qiu Y, Zhu Z, Ma Z, Xia C, Zhu F: Histomorphometric study of the spinal growth plates from the convex side and the concave side in adolescent idiopathic scoliosis. J Orthop Surg 2007, 2(1):9.

44. Day G, Frawley K, Phillips B, McPhee TB, Labrom R, Askim G, Mueller P: The vertebral body growth plate in scoliosis: a primary disturbance in growth? Scoliosis 2008, 3:3.

45. Faciszewski T, Arlet V, Gowor T, Aubl M, Alini M: Elevated synthetic activity in the convex side of scoliotic intervertebral discs and endplates compared with normal tissues. Spine 2001, 26(10):E198-206.

46. Burwell RG, Aujla RK, Kirby AS, Dangerfield PH, Moulton A, Cole AA, Polak F, Pratt RK, Webb JK: Body mass index of girls in health influences menarche and skeletal maturation: a leptin-sympathetic nervous system focus on the trunk with hypothalamic asymmetric dysfunction in the pathogenesis of adolescent idiopathic scoliosis? Stud Health Technol Inform 2008, 140:225-230.

47. Burwell RG, Aujla RK, Kirby AS, Dangerfield PH, Moulton A, Cole AA, Polak F, Pratt RK, Webb JK: Relation of trunk width timing to body mass index in girls and boys - suggesting a normal developmental mechanism that arose in human evolution to conserve energy in bipedalism [Abstract]. Clin Anat 2008, 21(7):746.

48. Burwell RG, Aujla RK, Cole AA, Dangerfield PH, Moulton A: Normal adolescent boys like girls show energy priority of growth in trunk width and unlike girls also in limb segments: leptin effects, central and/or peripheral? [Abstract]. Clin Anat 2009, 22(3):411.

49. Burwell RG, Aujla RK, Randall TL, Dangerfield PH, Moulton A: At age 5-10 years in normal girls and boys, body mass index (BMI) subsets reveal energy priority of trunk width growth and in the limbs of boys: sexually dimorphic developmental mechanisms that arose in evolution with bipedalism? [Abstract]. Clin Anat 2009, 22(7):855-6.

50. Burwell RG, Aujla RK, Randall TL, Dangerfield PH, Moulton A: Normal girls age 5-10 years with relatively higher body mass index (BMI) show less skeletal growth attainment than boys: evidence suggesting central leptin resistance in the somatotropic axis of juvenile girls [Abstract]. Clin Anat 2009, 22(7):856.

51. Burwell RG, Dangerfield PH, Freeman BJ: Concepts on the pathogenesis of adolescent idiopathic scoliosis. Bone growth and mass, vertebral column, spinal cord, brain, skull, extraspinal left-right skeletal length asymmetries, disproportions and molecular pathogenesis. Stud Health Technol Inform 2008, 131:52.

52. Burwell RG, Aujla RK, Kirby AS, Dangerfield PH, Moulton A, Freeman BJ, Cole AA, Polak F, Pratt RK, Webb JK: Leg-arm length ratios correlate with severity of apical vertebral rotation in girls after school screening for adolescent idiopathic scoliosis (AIS): a dynamic pathomechanism in the initiation of the deformity? Stud Health Technol Inform 2008, 140:89-93.

53. Nesse RM, Stensr SC, Omenn GS: Medicine needs evolution. Science 2006, 311:1071. and Nesse RM: Digesting evolution. Nature 2009, 460:461.
55. Burt A, Trivers R: Genes in Conflict. The Biology of Selfish Genetic Elements Cambridge, Massachusetts London, England, The Belknap Press of Harvard University Press; 2006.

56. Ward K, Nelson LM, Chettier R, Braun JT, Ogilvie JW: Genetic profile predicts curve progression in adolescent idiopathic scoliosis [Abstract]. Scoliosis Research Society 43rd Annual Meeting and Course, Salt Lake City, Utah, USA, September 10-13 2008:59.

57. Netherlands: Future research in scoliosis. In Scoliosis 1979 Edited by: Zorab PA, Siegler D: London: Academic Press; 1980:263-270.

58. Bagnall K: How can we achieve success in understanding the aetiology of AIS? Stud Health Technol Inform 2008, 135:61-74.

59. Sevastik J: The "thoracospinal" concept of the early development of idiopathic scoliosis. Experimental and clinical considerations. In International Symposium on 3D Scoliotic Deformities joined with the Vith International Symposium on Spinal Deformity and Surface Topography Edited by: Danseaux J, dition de l’cole Polytchnique de Montreal Gustav Fischer Verlag; 1992:193-7.

60. Parent S, Newton PO, Wenger DR: A biomechanical analysis of the vertebral and rib deformities in structural scoliosis. Eur Spine J 2000, 9(3):252-60.

61. Veldhuizen AG, Veder DJ, Sirois S, Sirois S: The aetiology of idiopathic scoliosis: biomechanical and neuromuscular factors. Eur Spine J 2000, 9(3):178-84.

62. Burwell RG, Dangerfield PH: Adolescent idiopathic scoliosis: hypotheses of causation. In Etiology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art Reviews: Spine Volume 14. Issue 2 Edited by: Burwell RG, Dangerfield PH, Lowe TG, Margules JY, Philadelphia, Hanley & Belfus Inc; 2000:319-331.

63. Guo X, Chau W-W, Chau X-L, Cheng J-C-Y, Relative anterior spinal overgrowth in adolescent idiopathic scoliosis. Results of disproportionate endochondral-membranous bone growth. J Bone Joint Surg Br 2003, 85-B:1026-31.

64. Porter RW: The pathogenesis of idiopathic scoliosis: uncoupled neuro-osseous growth? Eur Spine J 2001, 10:473-481.

65. Deane G, Duthie RB: A new projectional look at articulated scoliotic spines. Acta Orthop Scand 1973, 44(4):351-65.

66. Guo X, Chau W-W, Chau X-L, Cheng J-C-Y: Relative anterior spinal overgrowth in adolescent idiopathic scoliosis - a test of the ‘vicious cycle’ pathogenetic hypothesis: Summary of an electronic focus group debate of the IBSE. Scoliosis 2006, 1:16.

67. Somervelle EW: Rotational lordosis: the development of a single curve. J Bone Joint Surg Br 1952, 34-B:421-7.

68. Roaf R: The anatomy of idiopathic scoliosis. J Bone Joint Surg Br 1966, 48-B:786-92.

69. Deane G, Duthie RB: A new projectional look at articulated scoliotic spines. Acta Orthop Scand 1973, 44(4):351-65.

70. Veldhuizen AG, Veder DJ, Sirois S, Sirois S: The aetiology of idiopathic scoliosis: biomechanical and neuromuscular factors. Eur Spine J 2000, 9(3):178-84.

71. Burwell RG, Dangerfield PH: Adolescent idiopathic scoliosis: hypotheses of causation. In Etiology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art Reviews: Spine Volume 14. Issue 2 Edited by: Burwell RG, Dangerfield PH, Lowe TG, Margules JY, Philadelphia, Hanley & Belfus Inc; 2000:319-331.

72. Burwell RG: Aetiology of idiopathic scoliosis: current concepts. Pediatr Rehabil 2003, 6(3-4):137-70.

73. Parent S, Newton PO, Wenger DR: Adolescent idiopathic scoliosis: etiology, anatomy, natural history and bracing. AAOS Instructional Course Lectures 2005, 54:529-536.

74. Goldberg Cj, Moore DP, Fogarty EE, Dowling FE: Scoliosis: a review. Pediatr Surg Int 2008, 24:129-144.

75. Weinstein SL, Dolan LA, Cheng JC, Danielsson A, Morcuende JA: Adolescent idiopathic scoliosis. Lancet 2007, 369(9523):527-37.

76. Wang WJ, Yeung HY, Chu WC-W, Tang NL-S, Lee KM, Burwell RG, Cheng JCY: Top theories for the etiopathogenesis of adolescent idiopathic scoliosis. J Pediatr Orthop 2009 in press.

77. Miller NH: Genetics of familial idiopathic scoliosis. Clin Orthop Rel Res 2007, 462:6-10.

78. Cheng JC, Tang NL, Yeung HY, Miller N: Genetic association of complex traits: using idiopathic scoliosis as an example. Clin Orthop Rel Res 2007, 464-32-44.

79. Gao X, Gordon D, Zhang D, Browne R, Helms C, Gillum J, Weber S, Devroy S, Swaney S, Dobbins M, Morcuende J, Sheffield V, Lovett M, Bowcock A, Herring J, Wise C: CHD7 gene polymorphisms are associated with susceptibility to idiopathic scoliosis. Am J Hum Genet 2007, 82(5):957-68.

80. Stokes IAF: Huetter-Volkmann effect. In Etiology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art Reviews: Spine Volume 14. Issue 2 Edited by: Burwell RG, Dangerfield PH, Lowe TG, Margules JY, Philadelphia, Hanley & Belfus Inc; 2000:349-358.

81. Stokes IAF: Analysis and simulation of progressive adolescent scoliosis by biomechanical growth modulation. Eur Spine J 2007, 16:1621-8.

82. Stokes IAF, Burwell RG, Dangerfield PH: Biomechanical spinal growth modulation and progressive adolescent scoliosis - a test of the ‘vicious cycle’ pathogenetic hypothesis: Summary of an electronic focus group debate of the IBSE. Scoliosis 2006, 1:16.

83. Somervelle EW: Rotational lordosis: the development of a single curve. J Bone Joint Surg Br 1952, 34-B:421-7.

84. Roaf R: The anatomy of idiopathic scoliosis. J Bone Joint Surg Br 1966, 48-B:786-92.

85. Deane G, Duthie RB: A new projectional look at articulated scoliotic spines. Acta Orthop Scand 1973, 44(4):351-65.

86. Neugebauer H: Scoliosis, metabolism and growth of the vertebral column. Arch Orthop Unfallchir 1976, 85(1):87-99.

87. Millner PA, Dickson RA: Idiopathic scoliosis: biomechanics and biology. Eur Spine J 1996, 5:362-73.

88. Cheng JCY: Osteopenia. In Etiology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art Reviews: Spine Volume 14. Issue 2 Edited by: Burwell RG, Dangerfield PH, Lowe TG, Margules JY, Philadelphia, Hanley & Belfus Inc; 2000:339-48.

89. Gao X, Chau W-W, Chau X-L, Cheng J-C-Y: Relative anterior spinal overgrowth in adolescent idiopathic scoliosis. Results of disproportionate endochondral-membranous bone growth. J Bone Joint Surg Br 2003, 85-B:1026-31.

90. Porter RW: The pathogenesis of idiopathic scoliosis: uncoupled neuro-osseous growth? Eur Spine J 2001, 10:473-481.

91. Lidström J, Fribern S, Lindström L, Sahlström T: Postural control in siblings to scoliosis patients and scoliosis patients. Spine 1988, 13(9):1070-4.

92. Edgar M: Neural mechanisms in the etiology of idiopathic scoliosis. In Etiology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art Reviews: Spine Volume 14. Issue 2 Edited by: Burwell RG, Dangerfield PH, Lowe TG, Margules JY, Philadelphia, Hanley & Belfus Inc; 2000:459-68.

93. Williamson JB: Postural control. In Etiology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art Reviews: Spine Volume 14. Issue 2 Edited by: Burwell RG, Dangerfield PH, Lowe TG, Margules JY, Philadelphia, Hanley & Belfus Inc; 2000:401-9.

94. Geisselle AE, Kransdorf MJ, Geyer CA, Jelinek JS, Van Dam BE: Magnetic resonance imaging of the brain stem in adolescent idiopathic scoliosis. Spine 1991, 16(7):761-63.

95. Taylor TKF: The brain stem and adolescent idiopathic scoliosis - a hypothesis. In Etiology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art
null
133. Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM, Tataranni PA: Brain abnormalities in human obesity: a voxel-based morphometry study. Neuroimage 2006, 31(4):1419-25.
134. Edelman GM: Learning in and from brain-based devices. Science 2007, 318:1103-5.
135. Nissinen M, Heliovaara M, Seitsamo J, Poussa M: Trunk asymmetry, posture, growth, and risk of scoliosis. A three-year follow-up of Finnish prepubertal school children. Spine 1993, 18(1):8-13.
136. Hagglund G, Karlberg J, Willner S: Growth in girls with adolescent idiopathic scoliosis. Spine 1992, 17:108-111.
137. Nordwall A, Willner S: A study of skeletal age and height in girls with idiopathic scoliosis. Clin Orthop 1975, 110:6-10.
138. Goldberg Cj, Dowling FE, Fogarty EE: Adolescent idiopathic scoliosis - early menarche, normal growth. Spine 1993, 18(5):529-35.
139. Goldberg Cj: Skeletal growth. In: Etiology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art Reviews: Spine Volume 14, Issue 2 Edited by: Burwell RG, Dangerfield PH, Lowe TG, Margules JY. Philadelphia, Hanley & Belfus Inc 2000:401-409.
140. Cole AA: Anthropometry in preoperative adolescent idiopathic scoliosis. In: Quantitative study of scoliosis before and after surgery: DM thesis Volume Chapter 1. University of Nottingham, UK: 12:43.
141. Burwell RG, Aujla RK, Kirby AS, Dangerfield PH, Freeman BJ, Moulton A, Cole AA, Polak Fj, Pratt RK, Webb JK: Tibio-femoral index (TFI) of torsion: an increase with age in normal subjects but girls screened for scoliosis suggests earlier skeletal maturation: an ultrasound study [Abstract]. Clin Anat 2007, 21(2):195.
142. Jiang H, Greidanus N, Moreau M, Mahood C, Raso V, Russell G, Bag- nall K: A comparison of the innervation characteristics of the lateral spinal ligaments between normal subjects and patients with adolescent idiopathic scoliosis. Acta Anat (Basel) 1997, 160(3):200-7.
143. Cheng JCY, Guo X, Sher AHL: Posterior tibial nerve somatosensory cortical evoked potentials in adolescent idiopathic scoliosis. Eur Spine J 2003, 12(6):501-506.
144. Usman ON, Boni T, Pfirrmann CW, Curt A, Min K: Preoperative radiological and electrophysiological evaluation in 100 adolescent idiopathic scoliosis patients. Eur Spine J 2003, 12(1):35-38.
145. Choi WCW, Shi L, Wang D, Paus T, Burwell RG, Man GCW, Cheng A, Yeung HY, Lee KM, Heng PA, Cheng JCY: Variations of semicircular canals orientation and left-right asymmetry in adolescent idiopathic scoliosis (AIS) comparing with normal controls: MRA morphometry study using advanced image techniques. Stud Health Tech Inform 2008, 140:333. Also, 6th Annual World Congress for Brain Mapping and Image Guided Therapy, Annual Congress of the IBMIPS, 26-29 August 2009, Harvard Medical School, Boston, USA.
146. Mihala D, Calancie B: Cervical and thoracic spine organization different in idiopathic scoliosis? [Abstract]. Stud Health Tech Inform 2008, 140:350.
147. Lafosse C, Kerckhofs E, Vereeck L, Troch M, Van Hoydonck G, Moer- mans M, Sneyers C, Broeckx J, Dereymaeker L: Postural abnormalities and contraversive pushing following right hemisphere brain damage. Neuropsychol Rehabil 2007, 17(3):374-96.
148. MacNeilage PF, Rogers LJ, Vallortigara G: Origins of the left & right brain. Sci Am 2009, 301(1):60-7.
149. Burwell RG, Cole AA, Cook TA, Grivas TB, Kiel AW, Moulton A, Thirlwall AS, Upadhyay SS, Webb JK, Wemmes-Holden SA, Whitwell DJ, Wojcik AS, Wytters DJ: Pathogenesis of idiopathic scoliosis. The Nottingham concept. Acta Orthop Belg 1992, 58:33-38.
150. Machida M, DaSilva J, Yamada T, Kimura J, Saito M, Sasaki T, Yamagishi M: Experimental scoliosis in melanin-deficient C57BL/6j mice without paineconomy. J Pineal Res 2006, 41(1):1-7.
151. Nicolopoulo KS, Burwell RG, Webb Jk: Stature and its components in adolescent idiopathic scoliosis. Cephalo-caudal disproportion in the trunk of girls. J Bone Joint Surg Br 1985, 67(4):594-601.
152. Siu King Cheung C, Tak Keung Lee W, Kit Tse Y, Ping Tang S, Man Lee K, Guo X, Qin L, Chiu Yin Cheng J: Abnormal peri-pubertal anthropometric measurements and growth pattern in adolescent idiopathic scoliosis: a study of 598 patients. Spine 2003, 28(18):2152-7.
153. Abitbol MM: Evolution of the sacrum in hominoids. Am J Phys Anthropol 1987, 74(1):65-81.
154. Boulay C, Tardieu B, Bénié C, Hequet J, Marty C, Prat-Pradal D, Legeye J, Duval-Buépère G, Pélissier J: Three-dimensional study of pelvic asymmetry on anatomical specimens and its clinical perspectives. J Anat 2008, 210(1):35-45.
155. Wu LP, Li YK, Li YM, Zhang YQ, Zhong SZ: Variable morphology of the sacrum in a Chinese population. Clinic Anat 2009, 22(5):619-26.
156. Jubb S, Steer T, Holmes C: The 'Healthy Living' Social Market Initiative: A Review. In Proceedings of British Scoliosis Society 33rd Annual Meeting 23rd-24th April 2009, in The Curve, Rutland Street, Leicester, LE1 1SB UK: J Bone Joint Surg Br, Suppl in press 2009.
157. Smith FM, Latchford G, Hall RM, Millner PA, Dickson RA: Indications of disordered eating behaviour in adolescents with idiopathic scoliosis. J Bone Joint Surg Br 2002, 84(3):392-394.
158. Davey RC, Cochrane T, Dangerfield PH, Chockalingam N, Dorgan JC: Anthropometry and body composition in females with adolescent idiopathic scoliosis. In International Research Society of Spinal Deformities Symposium 2004 Edited by: Savatzky B. University of British Columbia; 2004:332-326.
159. Dangerfield PH, Davey RC, Cochrane T, Dorgan JC: Body composition in females with adolescent idiopathic scoliosis (AIS)[Abstract]. J Bone Joint Surg Br 2005, 88-B(Suppl II):230.
160. Cheng CSK, Lee WTK, Tse YK, Lee KM, Guo X, Qin L, Cheng JCY: Generalized osteopenia in adolescent idiopathic scoliosis: association with abnormal pubertal growth, bone turnover, and calcium intake? Spine 2006, 31(2):330-338.
161. Qiu Y, Sun X, Qiu X, Li W, Zhu Z, Zhu F, Wang B, Yu Y, Qian B: Decreased circulating leptin level and its association with abnormal pubertal growth, bone turnover, and calcium intake? Spine 2006, 31(2):330-338.
162. Grivas TB, Arvaniti A, Platiotou C, Manesioti M, Fergadi A: Comparison of body weight and height between normal and scoliotic children. Stud Health Tech Inform 2002, 91:47-53.
163. Goldberg Cj, Moore DP, Fogarty EE, Dowling FE: Interrelationship between Cobb angle progression, BMI and growth rate in girls with adolescent idiopathic scoliosis [Abstract]. Proceedings of British Scoliosis Society 33rd Annual Meeting 23rd-24th April 2009, in The Curve, Rutland Street, Leicester, LE1 1SB UK: J Bone Joint Surg Br, Suppl in press 2009.
164. Smith FM, Latchford Gj, Hall RM, Dickson RA: A cross-sectional investigation of eating pathology in adolescent females with scoliosis and diabetes. Adol Health 2008, 42(1):58-63.
165. Alborghetti A, Scimeca G, Manesioti M, Fergadi A: Comparison of body weight and height between normal and scoliotic children. Stud Health Tech Inform 2002, 91:47-53.
166. Goldberg Cj, Moore DP, Fogarty EE, Dowling FE: Interrelationship between Cobb angle progression, BMI and growth rate in girls with adolescent idiopathic scoliosis [Abstract]. Proceedings of British Scoliosis Society 33rd Annual Meeting 23rd-24th April 2009, in The Curve, Rutland Street, Leicester, LE1 1SB UK: J Bone Joint Surg Br, Suppl in press 2009.
tate, Lung, Colorectal, Ovarian (PLCO) Cancer Screening Trial, Jacobs KB, Chanock SJ, Hayes RB, Bergmann S, Bennett AJ, Bingham SA, Duhamel M, Donwain M, Cauchi S, Connell JM, Cooper C, Smith GD, Day I, Dina C, Deloukas P, Dehghan A, Dunning A, Easton D, Evans DG, Ford I, Frayling TM, Gao F, Gevers D, Gooderham N, Grant S, Groenen PI, Gunter MJ, Haffner SM, Haseman JK, Henderson BE, Hirschhorn JN, Hoppu K, Hoppu S, Hunter DJ, Ioannou A, Iso H, K火焰 J, Klarskov L, Kraft P, Landi MT, Langefeld CD, Liu G, Liu S, Lindgren CM, Luan J, MacLennan AJ, Magnani JL, Manjer J, Mariani G, Matsuzaki A, Mennel R, Melbye M, Mettermann A, Milosavitch A, Mulligan AM, North KE, Ong K, Palotie A, Psaty BM, Risch N, Rodriguez-Cartagena A, Ruczinski I, Sandgren K, Schiffrin E, Schoenfeld J, Shi H, Sletten D, Spudich J, Stendahl U, Su W, Sun Y, Tong W, Tseng YH, Tucker A, Vatten LJ, Vermeulen M, Viikari-Juntura E, Wang Z, Wilkens LR, Yu M, Yu K, Zeggini E, Zhao Y, Zucchetto L, Perussi E, Petrelli N, Pettersson F, Pelletier MG, Perdriolle R, Bjure J, Nachemson A: Scoliosis. 181.

182. Denoel C, Ismael Aguirre MF, Bianco G, Mahaudens PH, Vanwijck R, Ilieopoulos P, Korovessis P, Koureas G, Zacharatos S, Stergiou P: Genetic Investigation of ANTHropometric Traits (G.I.ANT): a study on scoliosis. 183. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lin N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccasecca RM, Sanza S, Scheet P, Weeden MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, et al.: Genetic Investigation of ANThropometric Traits (G.I.ANT): scoliosis. 184. Kishida Y, Hirao M, Tamai N, Nampei A, Fujimoto T, Nakase T, Rüther U: Regional scoliosis. 185. Malendowicz LK, Rucinski M, Belloni AS, Ziolkowska A, Nussdorfer G: Leptin and the regulation of bone remodeling by the sympathetic nervous system. 186. Allison SJ, Baldock PA, Herzog H: The control of bone remodeling by neuropeptide Y receptors. 187. Crown A, Clifton DK, Steiner RA: Leptin and the regulation of bone remodeling by the sympathetic nervous system. 188. Perdriolle R, Bjure J, Nachemson A: Scoliosis. 189. Elefteriou F, Takeda S, Ebihara K, Magre J, Patano N, Kim CA, Ogawa Y, Liu X, Ware SM, Craig WN, Roberts J, Vinson C, Nakao K, Capeau J, Karsenty G: Leptin gene regulation in bone formation. 190. Thomas T: The complex effects of leptin on bone metabolism through multiple pathways. 191. Elefteriou F, Ahn JD, Takeda S, Starbuck M, Yang X, Liu X, Kondo H, Richards WG, Bannan TW, Noda M, Clement K, Vaissé C, Karsenty G: Leptin regulation of bone resorption by the sympathetic nervous system and CART. 192. Allison SJ, Baldo PA, Herzog H: The control of bone remodeling by neuropeptide Y receptors. 193. Crown A, Clifton DK, Steiner RA: Leptin signaling in the integration of bone remodeling and reproduction. 194. Iliopoulos P, Korovessis P, Koureas G, Zacharatos S, Stergiou P: The role of the autonomic nervous system in the etiology of idiopathic scoliosis. 195. Patel MS, Elefteriou F, Karsenty G: Cocaine and amphetamine-regulated transcript may regulate bone remodeling as a circulating molecule. 196. Timpson N, Sayers A, Davey Smith G, Tobias J: Common variants near MC4R are associated with fat mass and weight and risk of obesity. 197. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lin N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccasecca RM, Sanza S, Scheet P, Weeden MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, et al.: Genetic Investigation of ANThropometric Traits (G.I.ANT): scoliosis. 198. Kishida Y, Hirao M, Tamai N, Nampei A, Fujimoto T, Nakase T, Rüther U: Regional scoliosis. 199. Malendowicz LK, Rucinski M, Belloni AS, Ziolkowska A, Nussdorfer G: Leptin and the regulation of bone remodeling by the sympathetic nervous system. 200. Badman MK, Flier JS: The adipocyte as an active participant in energy balance and metabolism. 201. Morton GJ: Hypothalamic leptin regulation of energy homeostasis and glucose metabolism. 202. Taubes G: Insulin resistance. Prosperity’s plague. 203. Eliaclott KL, Halatchev IG, Cone RD: Interactions between gut peptides and the central melanocortin system in the regulation of energy homeostasis. 204. Elmqquist JK: Hypothalamic pathways underlying the endocrine, autonomic, and behavioral effects of leptin. 205. Burton RG, Patterson JF, Webb JK, Wojcik AS: School screening for scoliosis - the multiple AT1 system of back shape appraisal using the Scoliometer with observations on the sagittal decline angle. 206. Timpson N, Sayers A, Davey Smith G, Tobias J: How does body fat influence bone mass in childhood? A Mendelian randomisation approach. 207. Garson S, Sinna R, Debrun A: Asymmetric evolution of anterior chest wall blood supply in female adolescents with progressive right-convex thoracic idiopathic scoliosis. 208. Moore VM, Cockington RA, Robinson JS: The role of the autonomic nervous system in the etiology of idiopathic scoliosis: prospective electron microscopic and histological study. 209. Rüther U: Regional scoliosis.
mass but are not protected from deleterious skeletal effects of ovariectomy. Endocrinology 2009, 150(1):144-52.

216. Nakajima R, Inada H, Koike T, Yamano T: Minocycline induces apoptosis of hypothalamic neurons. Neuroreport 2005, 16(14):1447-51.

217. Morris JC, Coope A, Morari J, Cintia DE, Roman EA, Pauli JR, Romantos T, Carvalheira JB, Oliveira AL, Saad MJ, Velloso LA: High-fat diet induces apoptosis of hypothalamic neurons. PLoS ONE 2009, 4(4):e5045.

218. Mori H, Hanada R, Hanada T, Aki D, Moshima R, Nishimakura H, Torisu T, Chien KA, Yasukawa H, Yoshimura A: Socs3 deficiency reduces resistance to obesity in mice with hypertension. J Hypertens 2007, 25(11):2079-85.

219. Eikelis N, Schlaich M, Aggarwal A, Kaye D, Esler M: Interactions between leptin and the human sympathetic nervous system. Horm Res 2003, 60(3):163-70.

220. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin MC, Ducy P, Karsenty G: Endocrine regulation of energy metabolism by the skeleton. Cell 2007, 130(4):653-67.

221. Takahashi M, Higuchi J, Shiosaka S, Sano Y, Asashima M, Takeda Y: Activation of the leptin receptor by a ligand-induced conformational change of constitutive receptor. Proc Natl Acad Sci USA 2007, 104(19):7926-31.

222. Mark AL, Correia ML, Rahmouni K, Haynes WG: Selective leptin resistance: a new concept in leptin physiology with cardiovascular implications. J Hypertens 2002, 20(7):1245-50.

223. Correia ML, Haynes WG, Rahmouni K, Morgan DA, Sivitz WI, Mark AL: The concept of selective leptin resistance: evidence from studies in diet-induced obesity. J Diabetes 2002, 51(2):439-42.

224. Rahmouni K, Morgan DA, Morgan GM, Mark AL, Haynes WG: Role of selective leptin resistance in diet-induced obesity hypertension. Diabetes 2005, 54(7):2127-32.

225. Hazzard WR, Fifer MA, O’Rahilly S: The blood-brain barrier as a cause of obesity. Proc Natl Acad Sci U S A 2000, 97(6):2476-81.

226. Lee CE, Elmquist JK, Yoshimura A, Flier JS: Endoplasmic reticulum stress induces leptin resistance through direct interaction of C-reactive protein with leptin. Nat Med 2006, 12(4):425-32.

227. Nakajima R, Inada H, Koike T, Yamano T: Minocycline induces apoptosis of hypothalamic neurons. Neuroreport 2005, 16(14):1447-51.

228. Morris JC, Coope A, Morari J, Cintia DE, Roman EA, Pauli JR, Romantos T, Carvalheira JB, Oliveira AL, Saad MJ, Velloso LA: High-fat diet induces apoptosis of hypothalamic neurons. PLoS ONE 2009, 4(4):e5045.

229. Howard JK, Cave BJ, Oksanen LJ, Tzameli I, Bjorbaek C, Flier JS: Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3. Nat Med 2004, 10(7):734-8.

230. Eikelis N, Schlaich M, Aggarwal A, Kaye D, Esler M: Interactions between leptin and the human sympathetic nervous system. Horm Res 2003, 60(3):163-70.

231. Gat-Yablonski G, Shtaif B, Abraham E, Phillip M: Protection from selective leptin resistance in diet-induced obesity. Proc Natl Acad Sci USA 2007, 104(19):19476-81.

232. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin MC, Ducy P, Karsenty G: Endocrine regulation of energy metabolism by the skeleton. Cell 2007, 130(4):653-67.

233. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin MC, Ducy P, Karsenty G: Endocrine regulation of energy metabolism by the skeleton. Cell 2007, 130(4):653-67.

234. Mark AL, Correia ML, Rahmouni K, Haynes WG: Selective leptin resistance: a new concept in leptin physiology with cardiovascular implications. J Hypertens 2002, 20(7):1245-50.

235. Correia ML, Haynes WG, Rahmouni K, Morgan DA, Sivitz WI, Mark AL: The concept of selective leptin resistance: evidence from studies in diet-induced obesity. J Diabetes 2002, 51(2):439-42.

236. Rahmouni K, Morgan DA, Morgan GM, Mark AL, Haynes WG: Role of selective leptin resistance in diet-induced obesity hypertension. Diabetes 2005, 54(7):2127-32.

237. Ladyman SR, Tups A, Augustine RA, Stock-Arnadez AM, Kokay IC, Grattan DR: Loss of hypothalamic response to leptin during pregnancy associated with development of melanocortin resistance. J Neuroendocrinol 2009 in press.

238. Tam J, Fukumura D, Jain RK: A mathematical model of murine metabolic regulation by leptin: energy balance and defense of a stable body weight. Cell Metab 2009, 9(1):52-63.

239. Banks WA: The blood-brain barrier as a cause of obesity. Curr Pharm Des 2008, 14(16):1606-14.

240. White CL, Whitington A, Barnes MJ, Wang Z, Bray GA, Morrison CD: HF diets induce hypothalamic PTP1B and induce leptin resistance through both leptin-dependent and -independent mechanisms. Am J Physiol Endocrinol Metab 2009, 296(4):E291-9.
individualized standard for evaluation of outcome in early onset spinal deformity. Spine 2005, 30(24):2824-9.

257. Mac-Thiong JM, Berthonnaud E, Dimar JR, Betz RR, Labelle H: Sagittal alignment of the spine and pelvis during growth. Spine 2004, 29(15):1642-7.

258. Boulay C, Tardieu C, Hecquet J, Benaim C, Mouillelasse B, Marty C, Prat-Pradell D, Legaye J, Duval-Beaupère G, Pelissier J: Sagittal alignment of the spine and pelvis regulated by pelvic incidence: standard values and prediction oflordosis. Eur Spine J 2006, 15(4):145-22.

259. Aiello L, Dean C: The hominid pelvis. In An Introduction to Human Evolutionary Anatomy Volume 20. London: Academic Press; 1990:429-456.

260. Zhang G, Granger R: The origin of big brains. In Big Brain. The origins and future of human intelligence Volume Chapter 11. New York; Palgrave Macmillan; 2008:139-159.

261. Burwell RG, Auja R, Cole AA, Dangerfield PH, Moulton A: Body frame size and pelvic width as a reference standard for weight? Possible biological significance and evolutionary origin [abstract]. Clin Anat 2009, 22(3):410-1.

262. Hung WY, Qin L, Cheung CSK, Lam TP, Ng BKW, Tse YK, Go X, Lee KM, Cheng JCY: Osteopenia: a new prognostic factor of curve progression in adolescent idiopathic scoliosis. J Bone Joint Surg Am 2005, 87-A:2709-2716.

263. Szalay EA, Bosch P, Schwebel RM, Bubbeg T, Tandberg D, Sherman F: Adolescents with idiopathic scoliosis are not osteoporotic. Spine 2008, 33(7):802-6.

264. Kasenan AS, Clifton DK, Steiner R: Emerging ideas about kisspeptin-GPR54 signaling in the neuroendocrine regulation of reproduction. Trends Neurosci 2007, 30(10):504-11.

265. Roseweir AK, Kaufman AS, Smith JT, Guerrero KA, Morgan K, Pielecka-Fortuna J, Pineda R, Gotthals TL, Tena-Sempere M, Moenter SM, Steiner RA, Millar RP: Discovery of potential kisspeptin antagonists delineate physiological mechanisms of gonadotropin regulation. J Neurosci 2009, 29(12):3920-9.

266. Wiwon M, Calabrese E: Best in small doses. New Sci 2008, 199(2687):36-9.

267. Mattson MP: Awareness of hormesis will enhance future research in basic and applied neuroscience. Crit Rev Toxicol 2008, 38(7):633-9.

268. Martin A, David V, Malaval L, Lafage-Proust MH, Vico L, Thomas T: Opposite effects of leptin on bone metabolism: a dose-dependent balance related to energy intake and insulin-like growth factor-I pathway. Endocrinology 2007, 148(7):3149-25.

269. Nomura Y, Kitamura K, Arai H, Segawa M: Melatonin receptor 1B (MTNR1B) gene polymorphism is associated with the occurrence of adolescent idiopathic scoliosis. Spine 2007, 32(16):1748-53.

270. Qiu XS, Tang NL, Yeung HY, Cheng JCY, Qiu Y: Lack of association between the promoter polymorphism of the MTNR1B gene and adolescent idiopathic scoliosis. Spine 2008, 33(20):2583-7.

271. Qiu XS, Tang NL, Yeung HY, Cheng JCY, Qiu Y: Lack of association between the promoter polymorphism of the MTNR1B gene and adolescent idiopathic scoliosis. Spine 2008, 33(20):2583-7.

272. Qiu XS, Tang NL, Yeung HY, Cheng JCY, Qiu Y: Lack of association between the promoter polymorphism of the MTNR1B gene and adolescent idiopathic scoliosis. Spine 2008, 33(20):2583-7.

273. Kasenan AS, Clifton DK, Steiner R: Emerging ideas about kisspeptin-GPR54 signaling in the neuroendocrine regulation of reproduction. Trends Neurosci 2007, 30(10):504-11.

274. Roseweir AK, Kaufman AS, Smith JT, Guerrero KA, Morgan K, Pielecka-Fortuna J, Pineda R, Gotthals TL, Tena-Sempere M, Moenter SM, Steiner RA, Millar RP: Discovery of potential kisspeptin antagonists delineate physiological mechanisms of gonadotropin regulation. J Neurosci 2009, 29(12):3920-9.

275. Wiwon M, Calabrese E: Best in small doses. New Sci 2008, 199(2687):36-9.

276. Mattson MP: Awareness of hormesis will enhance future research in basic and applied neuroscience. Crit Rev Toxicol 2008, 38(7):633-9.

277. Martin A, David V, Malaval L, Lafage-Proust MH, Vico L, Thomas T: Opposite effects of leptin on bone metabolism: a dose-dependent balance related to energy intake and insulin-like growth factor-I pathway. Endocrinology 2007, 148(7):3149-25.

278. Nomura Y, Kitamura K, Arai H, Segawa M: Melatonin receptor 1B (MTNR1B) gene polymorphism is associated with the occurrence of adolescent idiopathic scoliosis. Spine 2007, 32(16):1748-53.

279. Qiu XS, Tang NL, Yeung HY, Cheng JCY, Qiu Y: Lack of association between the promoter polymorphism of the MTNR1B gene and adolescent idiopathic scoliosis. Spine 2008, 33(20):2583-7.

280. Qiu XS, Tang NL, Yeung HY, Cheng JCY, Qiu Y: Lack of association between the promoter polymorphism of the MTNR1B gene and adolescent idiopathic scoliosis. Spine 2008, 33(20):2583-7.
293. Diene G, de Gaury JS, Tauber M: Is scoliosis an issue for giving growth hormone to children with Prader-Willi syndrome? Am J Dis Child 1995, 149(12):1004-6.

294. Civardi G, Vicentini R, Grugni G, Cantello R: Corticospinal physiology in patients with Prader-Willi syndrome: a transcranial magnetic stimulation study. Arch Neurol 2004, 61(10):1585-9.

295. Myers SE, Davis A, Whitman BY, Santiago JV, Landt M: Genetic concentrations in Prader-Willi syndrome infants and children: changes during development. Clin Endocrinol (Oxf) 2000, 52(1):101-5.

296. Haqq AM, Garambo SC, Muehlbauer M, Newgard CB, Svetkey LP, Vidil A, Journeau P, Soulie A, Padovani JP, Pouliquen JC: Evolution of scoliosis in six children treated with growth hormone. J Pediatr Orthop B 2001, 10(3):197-200.

297. Proto C, Romualdi D, Cento RM, Romano C, Campagna G, Lanzone A: Free and total leptin serum levels and soluble leptin receptor levels in teenage obese: the Prader-Willi and the Down syndromes. Metabolism 2007, 56(8):1076-80.

298. Morgan E: Explaining the fat layer. In The scars of evolution. What our bodies tell us about human origins Volume Ch 10. London: Souvenir Press; 1990:141-23. And not even a theory to cover our nakedness. Neuro Sci 2001, 39(4):Sr1-4.

299. Kuzawa CW: Adipose tissue in human infancy and childhood: an evolutionary perspective. Am J Phys Anthropol 1998, 117:209.

300. Bramble DM, Lieberman DE: Endurance running and the evolution of Homo. Nature 2004, 432(7015):345-52.

301. Burton FD: Fire. The spark that ignited human evolution. Albuquerque:University of New Mexico Press; 2009:231.

302. Gerendai I, Halasz B: Asymmetry of the neuroendocrine system. News Physiol Sci 2001, 16:92-5.

303. Kasibhatla B, Wos J, Peters KG: Targeting protein tyrosine phosphatase to enhance insulin action for the potential treatment of diabetes. Curr Opin Investig Drugs 2007, 8(10):805-13.

304. Skogland LB, Miller JA: Genetic association study of insulin-like growth factor-I (IGF-I) gene with curve severity and osteopenia in Prader-Willi syndrome (PWS) infants and children. Acta Paediatr Scand 2009, 98(4):309-13.

305. Skogland LB, Miller JA: Growth hormone receptor gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 2006, 31(10):1131-6.

306. Poitel T, Obata K, Ng BK, Katada Y, Yoshino A, Sakazume S, Tomita Y, Sakuta R, Nikikawa N: Growth hormone therapy and scoliosis in patients with Prader-Willi syndrome. Am J Med Genet 2006, 140(15):1623-7.

307. de Lind van Wijngaarden R, de Klerk LW, Festen DA, Otten BJ, Houwen-Koelega AC: The potential of growth hormone treatment in children with Prader-Willi syndrome. Scoliosis Research Society 43rd Annual Meeting and Course, Salt Lake City, Utah, USA, September 10-13 2008 :109.

308. Neugebauer H: Brace and hormone therapy of idiopathic scoliosis. Report of a 6-year investigation. Wien Klin Wochenschr Suppl 2007, 22:3-10.

309. Drop SL, De Waal WJ, De Munick Keizer-Schrama SM: Sex steroid treatment of constitutionally tall stature. Endocr Rev 1998, 19(5):540-58.

310. Inoue M, Minami S, Nakata Y, Kirahara H, Otsuka Y, Isobe K, Takaso M, Tokunaga M, Nishikawa S, Maruta T, Moriya H: Association between estrogen receptor gene polymorphisms and curve severity of idiopathic scoliosis. Spine (Phila Pa 1976) 2002, 27(21):2357-62.

311. Wang HY, Qiu Y, Zhang L, Sun Q, Qiu X: He Y: Association of estrogen receptor gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 2006, 31(10):1311-6.

312. Imoto H, Qiu Y, Zhang L, Sun Q, Qiu X: He Y: Association of estrogen receptor gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 2007, 32(27):305-9.

313. Kulis A, Zarzycki D, jakiewicz J: Concentration of estradiol in girls with idiopathic scoliosis. Ortop Traumatol Rehabil 2006, 8(4):455-9.

314. Raczkowski JW: The concentrations of testosterone and estradiol in girls with adolescent idiopathic scoliosis. Neuroendocrinol Letters 2007, 28(3):302-304.

315. Burwell RG: Biology is the future of scoliosis treatment. Stud Health Technol Inform 2002, 88:309-15.

316. Burwell RG, Dangerfield PH: The NOTOM hypothesis for idiopathic scoliosis: is it nullified by the delayed puberty of female rhythmic gymnasts and ballet dancers with scoliosis? Stud Health Technol Inform 2002, 91:11-14.

317. Burwell RG, Dangerfield PH: A possible neuroendocrine method for delaying the adolescent growth spurt and slowing scoliosis curve progression based on the NOTOM hypothesis. Potential of a medical treatment for progressive juvenile and adolescent idiopathic scoliosis. J Bone Joint Surg Br 2003, 85-B(Suppl III):190-1.

318. King AG: Modification of the spinal peak growth velocity as a possible treatment for adult scoliosis. Stud Health Technol Inform 2002, 91:489-491.

319. Warren MP, Brooks-Gunn J, Hamilton LH, Warren LF, Hamilton WG: Scoliosis and fractures in young ballet dancers. Relation to delayed menarche and secondary amenorrhea. N Engl J Med 1986, 314(21):1391-2.

320. Warren MP, Steibel AL: Exercise and female adolescents: effects on the reproductive and skeletal systems. J Am Med Womens Assoc 1999, 54(3):115-20.

321. Roth JA, Kim BG, Lin WL, Cho MJ: Melatonin promotes osteoblast differentiation and bone formation. J Biol Chem 1999, 274(31):22041-7.

322. Man GC, Yeung HY, Wang WJ, Lee KM, Ng BK, Hung WY, Qiu Y, Cheng JC: The effect of melatonin on proliferation and differentiation of osteoblasts in adolescent idiopathic scoliosis vs. normal control (Abstract). Stud Health Technol Inform 2008, 140:373.

323. Man CGW, Wang W, Yeung HYB, Ng KWB, Hung WY, Lee KMS, Ng TB, Qiu Y, Cheng JC: Abnormal responses to melatonin in osteoblasts cultured from adolescent idiopathic scoliosis

324. Doquier PL, Mounsy M, Joreut M, Bastin C, Rombouts JJF: Orthopaedic concerns in children with growth hormone therapy. Acta Orthop Scand 2004, 75(4):299-305.

325. Hindmarsh PC, Pringle PJ, Stanhope R, Brook CG: The effect of a continuous infusion of a somatostatin analogue (octreotide) for two years on growth hormone secretion and height prediction in tall children. Clin Endocrinol 1995, 42(5):509-15.

326. Nagai T, Obata K, Ogata T, Murakami N, Katada Y, Yoshino A, Sakazume S, Tomita Y, Sakuta R, Nikikawa N: Growth hormone therapy and scoliosis in patients with Prader-Willi syndrome. Am J Med Genet 2006, 140(15):1623-7.

327. Kuzawa CW: Adipose tissue in human infancy and childhood: an evolutionary perspective. Am J Phys Anthropol 1998, 117:209.

328. Skogland LB, Miller JA: Genetic association study of insulin-like growth factor-I (IGF-I) gene with curve severity and osteopenia in Prader-Willi syndrome (PWS) infants and children. Acta Paediatr Scand 2009, 98(4):251-2.

329. Yeung HY, Tang NL, Lee KM, Ng BK, Hung VW, Kwok R, Guo X, Qin L, Chen G: Genetic association study of insulin-like growth factor-I (IGF-I) gene with curve severity and osteopenia in adolescent idiopathic scoliosis. Stud Health Technol Inform 2006, 123:18-24.

330. Dinan TF, Willner S: Progression of a structural scoliosis during treatment with growth hormone. A case report. Acta Orthop Scand 1978, 49(3):264-8.

331. Wang ED, Drummond DS, Dormans JP, Moshang T, Davidson RS, Grucchio D: Scoliosis in patients treated with growth hormone. J Pediatr Orthop 1997, 17(6):708-11.

332. Vidal A, Journel Pou, Soule A, Padovani JP, Pouliquen JC: Evolution of scoliosis in six children treated with growth hormone. J Pediatr Orthop B 2001, 10(3):197-200.
Scoliosis 2008, 4:24
http://www.scoliosissci.com/content/4/1/24

Abstract. In the proceedings of Pediatric Orthopaedic Society of North America 25th Anniversary 2009 Annual Meeting Boston, Massachusetts, April 20-May 2 2009 Boston Marriott Copley Place, 212.

Wang WJ, Yeung YH, Man CWG, Lee KM, Ng BKW, QiY, Cheng JCY: Abnormal proliferative response of chondrocytes to melatonin in girls with adolescent idiopathic scoliosis. Stud Health Technol Inform 2008, 140:370.

Ahn G, Wang WJ, Hwang A, Cheng J, Qi Y: Expression of melatonin receptor in chondrocyte of adolescent idiopathic scoliosis. Stud Health Technol Inform 2008, 140:347.

Buommino E, Tufano MA, Balato N, Canozo N, Donnarumma M, Gallo L, Balato A, Ayala F: Osteopontin: a new emerging role in psoriasis. Arch Dermatol Res 2009, 301(6):397-404.

Taylor TFK, Melrose J: The role of the intervertebral disc in adolescent idiopathic scoliosis. In Etology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, of the Art Reviews. Spine Volume 14. Issue 2 Edited by: Burwell RG, Lowe TG, Margulies JY, Philadelphia, Hanley & Belfus Inc; 2000:359-369.

Roberts S, Caterson B, Urban JPG: Structure and composition of the cartilage end plate and intervertebral disc in scoliosis. In Etology of Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, of the Art Reviews. Spine Volume 14. Issue 2 Edited by: Burwell RG,Dangerfield PH, Lowe TG, Margulies JY, Philadelphia, Hanley & Belfus Inc; 2000:371-381.

Akhtar S, Davies JR, Caterson B: Ultrastructural localization and distribution of proteoglycan in normal and scoliotic lumbar discs. Spine 2001;30(1):103-9.

Yu J, Fairbank JC, Roberts S, Urban JP: The elastic fiber network of the anulus fibrosus of the normal and scoliotic human intervertebral disc. Spine 2005, 30(16):1815-20.

Berrham H, Steck E, Zimmerman G, Chen B, Carstens C, Nerlich A, Richter W: Accelerated intervertebral disc degeneration in scoliosis versus physiological ageing develops against a backround of enhanced anabolic gene expression. Biochem Biophys Res Commun 2006, 342(3):963-72.

Grivas TB, Vasiliadis E, Malakasis M, Mouzakis V, Segos D: Intervertebral disc biomechanics in the pathogenesis of idiopathic scoliosis. Stud Health Technol Inform 2006, 123:80-83.

Cren JK, Roberts S, Jaffray DC, Eisenstein SM, Duance VC: Matrix metalloproteinases in the human intervertebral disc: role in disc degeneration. Leon and Scoliosis. (Spine (Phila Pa 1976) 1977, 22(24):2877-84.

Burke JG, G Watson RW, Conhaye D, McCormack D, Dowling FE, Wahl MG, Fitzpatrick JM: Human nucleus pulposis can respond to a pro-inflammatory stimulus. (Spine (Phila Pa 1976) 2003, 28(14):2685-91.

Roberts S, Evans H, Trivedi J, Menage J: History and pathology of the human intervertebral disc. J Bone Joint Surg Am 2006, 88(Suppl 2):10-4.

Aulilia L, Papalo P, Pola E, Angelini F, Aulilia AG, Tamburrelli FC, Pola P: Logrosos CA: Association between IL-6 and MMP-3 gene polymorphisms and adolescent idiopathic scoliosis: a case-control study. Spine (Phila Pa 1976) 2007, 32(24):2700-2.

Sverrisdottir YB, Elam M, Caidah JK, Söderling AS, Herlitz H, Johannsson G: Intense sympathetic nerve activity in adults with hypotuitarism and untreated growth hormone deficiency. J Clin Endocrinol Metab 1998, 83(6):1881-5.

Sverrisdottir YB, Elam M, Caidahl K, Soderling AS, Herlitz H, Johannsson G: The effect of growth hormone (GH) replacement therapy on sympathetic nerve hyperactivity in hypopituitary adults: a double-blind, placebo-controlled, crossover, short-term trial followed by long-term open GH replacement in hypopituitary adults. J Hypertens 2003, 21(10):1905-14.

Mcmurray RD, Hackney AC: Interactions of metabolic hormones and adipose tissue and exercise. Sports Med 2005, 35(5):393-412.

Rezmini E, Casu M, Patrone V, Murielada G, Bianchi F, Giusti M, Merone D, Minuto F: Sympathovagal imbalance in acromegalic patients. J Clin Endocrinol Metab 2006, 91(1):15-20.

Andersson IJ, Bartland A, Nyström HC, Olsson B, Skatt O, Mobin-R, Johannson M, Bergström G: Reduced sympathetic responsiveness as well as plasma and tissue noradrenaline concentrations in growth hormone transgenic mice. Acta Physiol Scand 2004, 182(4):369-78.

Scott EM, Greenwood JP, Stoker JB, Mary DA, Gilbery SG: Sympathetic nerve hyperactivity is associated with increased peripheral vascular resistance in hypopituitary patients with growth hormone deficiency. Clin Endocrinol (Oxf) 2002, 56(6):759-63.

Capaldo B, Lenbo G, Rendina V, Vigorito C, Guida R, Cuocolo A, Fazio S, Sacca L: Sympathetic deactivation by growth hormone treatment in patients with dilated cardiomyopathy. Eur Heart J 1998, 19(4):623-7.

Ljung T, Holm G, Friborg P, Andersson B, Bengtsson BA, Svensson J, Dallman M, McEwen B, Bjørntorp P: The activity of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system in relation to waist/hip circumference ratio in men. Obes Res 2000, 8(7):497-55.

Sverrisdottir YB, Johannsson G, Jurgensten L, Wallin BG, Elam M: Is the somatotropic axis related to sympathetic nerve activity in healthy ageing men? J Hypertens 2001, 19(1):209-24.

Makinen J, Järveläinen J, Mäkelä H, Talja J, Roivainen P, Logroscino CA: Expression of melatonin receptor in chondrocyte of adolescent idiopathic scoliosis. J Clin Endocrinol Metab 1999, 84:3756-61.

Weltpert A, Pritzlaff CJ, Wideman L, Weltpert JY, Blummer JL, Abbott RD, Hartman ML, Veldhuis JD: Exercise-dependent growth hormone release is linked to markers of heightened central adrenergic outflow. J Appl Physiol 2000, 89(2):629-35.

Bartness TJ, Song CK: Thematic review series: adipocyte biology. Sympathetic and sensory innervation of white adipose tissue. J Lipid Res 2007, 48(8):1653-72.

Ascher MA: Foreword to Adolescent Idiopathic Scoliosis: Current Trends and Relevance to New Treatment Approaches, State of the Art Reviews. Spine Volume 14. Issue 2 Edited by: Burwell RG, Dangerfield PH, Lowe TG, Margulies JY, Philadelphia, Hanley & Belfus Inc; 2000:xiv-xv.

Weyer D, Tanesh KA, Veldhuizen AG, Cool JC, van Horn JR: Curve progression and spinal growth in brace treated idiopathic scoliosis. Clin Orthop Relat Res 2000, 377:169-79.

Sarwar J, Aujin CE: Growth considerations of the immature spine. J Bone Joint Surg Am 2009, 89(Suppl 1):81.1.

Milenkovic SM, Kozijancic RL, Belojevic GA: Left handedness and spine deformities in early adolescence. Eur J Epidemiol 2004, 19(10):969-72.

Goldberg CJ, Moore DP, Fogarty EE, Dowling FE: Handedness and scoliosis. J Bone Joint Surg Am 2006, 88(1):190-7.

Grivas TB, Vasiliadis ES, Polyzos VO, Mouzakis V: Trunk asymmetry and handedness in 8245 school children. Pediatr Rehabil 2006, 9(3):259-66.

Koovsreetailed JWM, Vincken JL, Bartels LW, Castelein RM: Analysis of pre-existent vertebral rotation in the normal spine. Spine 2006, 31(13):1467-72.

Burwell RG, Dangerfield PH, Freeman BJ, Aujin KA, Cole AA, Kirby AS, Pratt RK, Webb JK, Moulton A: Etiologic theories of idiopathic scoliosis: the breaking of bilateral symmetry in relation to left-right asymmetry of internal organs, right thoracic adolescent idiopathic scoliosis (AIS) and vertebrate evolution. Stud Health Technol Inform 2006, 123:1385-90.

Davids JR, Chamberlin E, Blackhurst DW: Indications for magnetic resonance imaging in presumed adolescent idiopathic scoliosis. J Bone Joint Surg Am 2006, 88(2):280-8.

Brockmeeyer D, Gologoly S, Smith MJ: Scoliosis associated with Chiari I malformations: the effect of suboccipital decompression on scoliosis curve progression. A preliminary study. Spine 2003, 28(12):2305-9.

Ungerslov VL, Bastrom T, Varley ES, Yzasb B, Newton PO: Left thoracic curves are not a mirror image of right thoracic idiopathic curves. Scoliosis Research Society. 44th Annual Meeting and Course, San Antonio, Texas, USA, September 23-26 2009:61.

Paus T: Mapping brain maturation and cognitive development during adolescence. Trends Cogn Sci 2005, 9(2):66-8.

Dangerfield PH, Taylor CJ: Anthropometric standards for term neonates. Early Hum Dev 1983, 8(3-4):225-33.

Dangerfield PH, Taylor CJ: Liverpool growth study: Neonatal anthropometric standards. In Human growth and development Edited by: Bomons J, Hauspie R, Sand A, Suzanne C, Hebbelinck M. London: Plenum Press; 1984:131-137.

Kratzsch J, Lammert A, Botzner A, Seidel B, Mueller G, Thiery J, Hebebrand J, Kiess W: Circulating soluble leptin receptor and...
free leptin index during childhood, puberty, and adolescence. J Clin Endocrinol Metab 2002, 87(10):4587-94.

379. Li HJ, Ji CY, Wang W, Hu Y: A two-study for sex-specific leptin, soluble leptin receptor, and free insulin-like growth factor I in pubertal females. J Clin Endocrinol Metab 2005, 90(6):3659-64.

380. Shapiro IM, Srinivas V: Metabolic consideration of epiphyseal growth: survival responses in a taxing environment. Bone 2007, 40(3):551-7.

381. Ahmed ML, Ong KK, Morrell DJ, Cox L, Drayer N, Perry L, Preece MA, Dunger DB: Longitudinal study of leptin concentrations during puberty: sex differences and relationship to changes in body composition. J Clin Endocrinol Metab 1999, 84(3):999-905.

382. Lin J, Barb CR, Mattarei RL, Kraelling RR, Chen X, Meinersmann RJ, Rampacek GB: Long form leptin receptor mRNA expression in the brain, pituitary, and other tissues in the pig. Domest Anim Endocrinol 2000, 19(1):53-5.

383. Serrat MA, Lovejoy CO, King D: Age- and site-specific decline in in vitro growth factor-I receptor expression is correlated with differential growth plate activity in the mouse hindlimb. Anat Rec (Hoboken) 2007, 290(4):375-81.

384. Zhao CQ, Liu D, Li H, Jiang LS, Dai LY: Expression of leptin and its functional receptor on disc cells: contribution to cell proliferation. Spine 2008, 33(23):E858-64.

385. Brown MF, Hukainen MV, McCarthy ID, Redfern DR, Batten JJ, Crock HV, Hughes SP, Polak JM: Sensory and sympathetic innervation of the vertebral endplate in patients with degenerative disc disease. J Bone Joint Surg Br 1997, 79(1):147-53.

386. Syme C, Abrahamowicz M, Leonard GT, Perron M, Piatot A, Qiuxi, Richer L, Totman J, Veillette S, Xiao Y, Gaudet D, Pausis T, Pausova Z: Intra-abdominal adiposity and individual components of the metabolic syndrome in adolescence: sex differences and underlying mechanisms. Arch Pediatr Adolesc Med 2008, 162(5):453-61.

387. Kott IM, Wright HM, Chace JA: Cutaneous patterns of sympathetic activity in clinical abnormalities of the musculoskeletal system. Acta Neuroveg. Wien 1964, 25:589-606.

388. Friedman JM: Causes and control of excess body fat. Nature 2009, 459:340-2.

389. Cannon B, Nedergaard J: Brown adipose tissue: function and physiological significance. Physiol Rev 2004, 84(1):227-359.

390. Nedergaard J, Bengtsson T, Cannon B: Unexpected evidence for active brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab 2007, 293(2):E444-52.

391. Farmer SR: Be cool, lose weight. Nature 2009, 458:839-40.

392. van Marken Lichtenbelt WD, Vanshommert JW, Smulders NM, Drosaerts JM, Kemeringink GJ, Bouvy ND, Schrauwen P, Teule GJ: Cold-activated brown adipose tissue in healthy men. N Engl J Med 2009, 360(15):1500-8.

393. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR: Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009, 360(15):1509-17.

394. Virtanen KA, Lidell ME, Orava J, Heglin M, Westergren R, Niemi T, Taattonen M, Laine J, Savisto NJ, Enerback S, Nuuttila P: Functional brown adipose tissue in healthy adults. N Engl J Med 2009, 360(15):1518-25.

395. Whelan J: The fat that makes you thin. New Sci 2009, 203(2721):39-41.

396. Heaney RP, Davies KM, Barger-Lux MJ: Calcium and weight: clinical studies. J Am Coll Nutr 2002, 21(2):1525-1535.

397. Zivinjak M, Smolej Naranci N, Sizovicza L, Franke D, Hrenovik J, Bisov T, Tomas Z, Sdrcevcek J, Tavcar M, Lazic M: Gender-specific growth patterns of transversal body dimensions in Croatian children and youth (2 to 18 years of age). Coll Antropol 2008, 32(2):419-31.

398. Mehta MH: The rib-vertebra angle in the early diagnosis between resolving and progressive infantile scoliosis. J Bone Joint Surg Br 1972, 54(2):230-43.

399. Kristmunsdottrir F, Burwell RG, James JJ: The rib-vertebra angles on the convexity and concavity of the spinal curve in infantile idiopathic scoliosis. Clin Orthop Relat Res 1985, 201:205-9.

400. Grieser TB, Burwell RG, Vasiliadis ES, Webb JK: A segmental radiological study of the spine and rib—cage in children with progressive infantile idiopathic scoliosis. Scoliosis 2006, 1:17.

401. Burwell RG, Dangerfield PH, Vernon CL: Anthropometry and scoliosis. In Scoliosis, Proceedings of a Fifth Symposium Edited by: Zorab PA. London: Academic Press; 1977:123-163.

402. Dangerfield PH, Burwell RG, Vernon CL: Anthropometry and scoliosis. In Spinal Deformities Volume Chapter 14. Second edition. Edited by: Roaf R. Tunbridge Wells, Kent, UK; 1980:259-28.

403. Whelan J: The fat that makes you thin. New Sci 2009, 203(2721):39-41.

Publish with BioMed Central and every scientist can read your work free of charge

“BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime.”
Sir Paul Nurse, Cancer Research UK

Your research papers will be:
- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp