

Yearbook of Paediatric Endocrinology 2018

Editors

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Preface

The Yearbook of Paediatric Endocrinology counts years from June to June, when we submit the manuscripts to our publisher, and so much happened since June 2017.

Our 13 Associate Editors and their coauthors do not take anything for granted and have once again done an enormous work to discern this year's advances. You will see that we cite papers on genomics and genetics, molecular biology and systems biology, evolutionary biology, clinical trials and medical reports to provide new insights in paediatric endocrinology, as the complexity of our field increases.

Among other highlights, the Yearbook 2018 describes: new treatments (MC4R agonist for monogenic obesity; long-term outcomes of rhGH in chronic inflammatory disease; FGF23 antibody in children with XLH; oral GnRH antagonist), new genes (the CLCN2 chloride channel in primary hyperaldosteronism; genetic heterogeneity in T1DM; and new genes in severe obesity and hypogonadotropic hypogonadism), new mechanisms (Stella insufficiency in oocytes induced by maternal obesity; noncanonical thyroid hormone receptor signalling; epigenetic control of puberty; hypothalamic stem cells control ageing speed; estrogen receptors and excess autoimmune disease in women) and other findings with important implications (consensus definition of fetal growth restriction in newborns; remission of childhood overweight on the risk of T2DM; the 'nocebo' effect; how your Pediatric Department can support Global Health).

A growing number of included papers describe *non-genetic inheritance* (NGI). Transgenerational epigenetic inheritance is the form of NGI that has gained eminence: germline transmission of DNA methylation patterns, histone modification and small RNAs trigger the inheritance of traits, including child growth, puberty and development. But according to a new book by Russell Bonduriansky and Troy Day *Extended Heredity: A New Understanding of Inheritance and Evolution* (Princeton University Press), "Epigenetic inheritance is only the tip of the NGI iceberg." NGI also includes adaptive parental effects, social learning, the inherited microbiome, and structural inheritance in single-celled eukaryotes in predicting adaptive responses.

In this Preface, we annually highlight a prize given in the field of endocrinology. Time

and again, metabolic regulation attracts the highest accolades, and we salute Jeffrey Hall, Michael Rosbash, and Michael Young, recipients of the 2017 Nobel Prize for Physiology or Medicine, for their discoveries of molecular mechanisms controlling the biological clock. We also mark each year important science anniversaries: in 1918, L. Greiving described the nervous connections between the hypothalamus and pituitary gland – a central dogma of endocrinology. Greiving then discovered the tract of unmyelinated nerve fibers running down the neural stalk into the posterior pituitary. But 1918 was also the year of the Spanish flu, killing 50 million people, and World War I ended. Ninety-nine years later it was shown that these hardships in childhood were associated with worse physical and mental health, education, cognitive ability and subjective wellbeing at older ages, and that hardships matter more if experienced in childhood (Havari E & Peracchi F. Growing up in wartime: Evidence from the era of two world wars. *Econ Hum Biol.* 2017;25:9-32).

We thank Chris Kelnar and his team for their contribution over the last six years; his initiatives in evidence based medicine are now firmly embedded throughout the Yearbook. This year we welcome Anne-Simone Parent, who leads a new chapter devoted to *Puberty*, and Olle Söder now devotes his chapter to *Gender Dysphoria and DSD*. We are tremendously grateful to ESPE for their continuing endorsement of the Yearbook series and to BioScientifica for their support. This 2018 edition is the first to be published online only and **we welcome your feedback** on whether you wish to receive this in future as: online only, online plus in print, or only in print.

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DOI:10.1530/ey.15.P1

1. Pituitary and Neuroendocrinology

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This year has been very rich in highly interesting papers in Neuroendocrinology. Some papers reported in this selection described new mechanisms, but also new mouse models to understand or to investigate pediatric endocrinopathies. In these 12 papers, one of them stands out as highly remarkable by the originality of the hypothesis, the quality of the work but also for the perspectives in medicine. This paper by Zhang et al. demonstrates the importance of hypothalamic stem/progenitor cells in the control of ageing and the involvement of exosomal microRNA secreted by these cells in this process. Although this study has been performed in adult mice, we may speculate similar mechanisms may be involved in humans. In this selection, we also report papers on new mouse models which pave the way for the development of novel treatments in rare neuroendocrine diseases.

DOI:10.1530/ey.15.1

New mechanisms

1.1 Female sexual behavior in mice is controlled by kisspeptin neurons

Hellier V, Brock O, Candlish M, Desroziers E, Aoki M, Mayer C, Piet R, Herbison A, Colledge WH, Prevot V, Boehm U, Bakker J
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To read the full abstract: [Nat Commun 2018;9:400](#)

Pheromones play a crucial role to identify potential mates and sexual motivation in mice. These molecules are detected by a specialized circuit which initiates in the nasal septum and then relies on GnRH neurons in the hypothalamus in a sex-dependent manner. Female pheromones induce LH/testosterone release in male mice whereas male pheromones induce LH release in female mice. Kisspeptin is a potent stimulator of GnRH release. Its expression is sexually dimorphic in the hypothalamus, and it is the relay of the negative feedback of sexual steroids on GnRH neurons. In addition, the same group recently showed that a specific population of Kisspeptin neurons located

in the anterior part of the hypothalamus of female mice are activated by male pheromones. These neurons were therefore natural candidates as a hub to control both sexual behavior and ovulation.

Here, the authors performed elegant and complementary experiments to support their hypothesis. Surprisingly, part of the kisspeptin effect on sexual behavior is not mediated through Kisspeptin receptor expressed on GnRH neurons. The results reported in this paper proposed that neurons expressing NO synthase could be one of these neurons. Additional experiments are needed to dissect the precise role of these neurons in the control of sexual behavior by kisspeptin. Altogether, these data showing the role of kisspeptin in sexual behavior in mice are in accordance with recent evidence that Kisspeptin enhances limbic activity in response to sexual stimuli in men¹. In the future, it will be interesting to dissect how this mechanism is developing at the time of puberty.

1. Comminos AN, Wall MB, Demetriou L, Shah AJ, Clarke SA, Narayanaswamy S, Nesbitt A, Izz-Engbeaya C, Prague JK, Abbara A, Ratnasabapathy R, Salem V, Nijher GM, Jayasena CN, Tanner M, Bassett P, Mehta A, Rabiner EA, Honigsperger C, Silva MR, Brandtzaeg OK, Lundanes E, Wilson SR, Brown RC, Thomas SA, Bloom SR, Dhillon WS Kisspeptin modulates sexual and emotional brain processing in humans. *J Clin Invest.* 2017;**127**(2):709-719

DOI:10.1530/ey.15.1.1

New mechanisms

1.2 Activation of temperature-sensitive TRPV1-like receptors in ARC POMC neurons reduces food intake

Jeong JH, Lee DK, Liu SM Chua SC, Jr., Schwartz GJ, Jo YH
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Medicine, New York, USA

To read the full abstract: [PLoS Biol 2018;16:e2004399](https://doi.org/10.1371/journal.pbio.2004399)

The hypothalamus plays a central role in the control of numerous physiological pathways and received afferent pathways from the brain and from the periphery. For instance, body temperature changes in peripheral tissues are conveyed to the

hypothalamus via the bloodstream. An increase of temperature within the hypothalamus results in an increase of hypothalamic neuron activity. TRPV receptors have been proposed to translate the rise of temperature in a neuronal signal and to a physiological response. The originality of this study is based on the hypothesis that hypothalamic neurons responding to an acute change of temperature should be located outside the blood-brain barrier (BBB). POMC neurons are anorexigenic. Some of POMC neurons in the arcuate nucleus (ARC) are located outside the BBB. It was therefore tempting to test the hypothesis that activation of ARC POMC neurons by changes in temperature could reduce food intake. These results link acute elevation in peripheral and brain temperature with acute reductions in food-intake via activation of TRPV-like receptors. This study provides additional evidence of the central role of the hypothalamus in the control of the homeostasis of numerous physiological pathways in addition to endocrine axes.

DOI:10.1530/ey.15.1.2

New mechanisms

1.3 Hypothalamic stem cells control ageing speed partly through exosomal miRNAs

Zhang Y, Kim MS, Jia B, Yan J, Zuniga-Hertz JP, Han C, Cai D
Department of Molecular Pharmacology, Diabetes Research Center, Institute of Aging, Albert Einstein College of Medicine, New York, USA

To read the full abstract: [Nature 2017;548:52-57](#)

The central nervous system contributes to ageing. The hypothalamus seems to be particularly important in this process. Recent studies have demonstrated a link between ageing and a decrease of neurogenesis in the hippocampus and the subventricular zone of the lateral ventricle in the brain. Neural stem/progenitor cells (NSC) reside in those regions in the brain and are involved in the neurogenesis. A link between the presence

of NSC, neurogenesis and ageing has thus been hypothesised. Recently, this group described the role of the hypothalamus in systemic ageing, and the unexpected function of GnRH to decelerate ageing¹.

Here, Zhang et al. extend the concept to adult NSC, which have been described in the hypothalamus (htNSC). With very elegant experiments, they show that loss of htNSC accelerates ageing, whereas implantation of htNSC resistant to neuroinflammation has an anti-ageing and longevity effect. In addition, they report an endocrine function of these cells, which secrete exosomal miRNAs. The inhibition of exosomal miRNAs secretion blocks the effect of htNSC on ageing. More surprisingly, treatment of mid-aged mice with exosomes reduces the effect of the ablation of NSC and could be related to GnRH. In addition, to describe a new mechanism, Zhang et al. propose a very innovative treatment based on the administration of purified exosomes.

1. Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, Yin Y, Li B, Liu G, Cai D Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. *Nature*. 2013;**497**(7448):211-216

DOI:10.1530/ey.15.1.3

New mechanisms

1.4 Disrupted-in-Schizophrenia-1 is essential for normal hypothalamic-pituitary-interrenal (HPI) axis function

Eachus H, Bright C, Cunliffe VT, Placzek M, Wood JD, Watt PJ
Department of Animal and Plant Sciences, University of Sheffield, Western Bank,
Sheffield, UK

To read the full abstract: [Hum Mol Genet 2017;26:1992-2005](#)

Mutations in human *DISC1* have been previously associated with mental illness, such as schizophrenia and depression. Moreover, *DISC1* has been shown to be important in regulating CNS neurogenesis through the Wnt/ β -catenin pathway. However the mechanism by which *DISC1* causes mental illness is not known. In this elegant work,

Eachus *et al.* used two homozygous mutant zebrafish lines to understand the role of *disc1*. The authors show that *disc1* affects hypothalamic development by controlling the proliferation of *Rx3*-positive hypothalamic progenitor neurons, that give rise to SF1 and Pomc1 neurons. Mutations of *disc1* lead to abnormal neuroendocrine differentiation, leading to decreased levels of cortisol after environmental stress. Hence this paper shows how developmental abnormalities of the hypothalamus, leading to endocrinopathies at early stages of development, lead to behavioral abnormalities in adulthood and places *disc1* as a new key player in hypothalamic development in fish model. POMC neurones form an integral part of the central melanocortin system regulating feeding behaviour and POMC deficiency leads to obesity in humans. Hence, it will be interesting to see whether these fish have abnormal regulation of feeding besides their behavioural abnormalities. Further studies in humans carrying mutations in *DISC1* show assess if these patients have HPA-axis abnormalities and if these biological mechanisms are evolutionarily maintained through different species.

DOI:10.1530/ey.15.1.4

New mechanisms

1.5 NOTCH activity differentially affects alternative cell fate acquisition and maintenance

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The Francis Crick Institute, London, United Kingdom

To read the full abstract: [Elife 2018;7. pii: e33318](https://doi.org/10.1038/433318a)

Here, Cheung et al. use sophisticated tissue specific genetic ablation in pituitary cell lineages to uncover an unexpected differential sensitivity of NOTCH activation signalling pathway in different cell lineages during the embryonic murine pituitary development. These findings are important as they further demonstrate the importance of NOTCH pathway in progenitor differentiation during pituitary development and consequently reveals new aspects of endocrine lineages and plasticity. Further work on the molecular differences on cell specific lineages and cell fate acquisition will be important to fine tune the mechanisms that generate pituitary plasticity. Importantly it will be useful to understand if these mechanisms are maintained in adult pituitary stem cells upon endocrine challenges to maintain adult organ homeostasis.

DOI:10.1530/ey.15.1.5

New mechanisms

1.6 Hypothalamic sonic hedgehog is required for cell specification and proliferation of LHX3/LHX4 pituitary embryonic precursors

Carreno G, Apps JR, Lodge EJ, Panousopoulos L, Haston S, Gonzalez-Meljem JM, Hahn H, Andoniadou CL, Martinez-Barbera JP
Developmental Biology and Cancer Programme, Birth Defects Research Centre, Great Ormond Street Institute of Child Health, University College London, London, UK

To read the full abstract: [Development 2017;144:3289-3302](https://doi.org/10.1093/dev/2017/144/3289-3302)

Aberrant development of the anterior pituitary can lead to congenital hypopituitarism (CH) in humans and hence understanding how this organ develops is critical to

understand CH. The anterior pituitary develops in intimate contact with the prospective hypothalamus, which secretes growth factors that are required for the pituitary gland to grow. In this elegant paper, from Martinez-Barbera's laboratory, they utilise a mouse transgenic line, *Hesx1^{Cre/+}* to either delete or activate *Shh* pathway, which is known to be important for midline development. By deleting *Shh* from the anterior hypothalamus, the authors show that *Shh* signalling in this tissue is critical for Rathke's pouch induction, hence dissecting out the role of this signalling during early development. Mutations in *hSHH* lead to holoprosencephaly, a severe midline defect that can be linked to congenital hypopituitarism. Indeed mutations in downstream effectors of *SHH*, such as *GLI2*, lead to CH with brain abnormalities in humans, demonstrating the clinical importance of components of this pathway in pituitary disease. How *Shh* activates or induces *Lhx3/Lhx4* in pituitary precursors remains unknown, but this work clearly shows that it acts upstream of these factors. Therefore, *Shh* secreting molecules could also potentially be used in stem cell differentiation protocols to differentiate progenitor cells into *Lhx3/Lhx4* RP progenitors.

DOI:10.1530/ey.15.1.6

Mechanism update

1.7 Fgf10(+) progenitors give rise to the chick hypothalamus by rostral and caudal growth and differentiation

Fu T, Towers M, Placzek MA

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To read the full abstract: [Development 2017;144:3278-3288](#)

This article from Plazek's laboratory describes a subpopulation of cells which express Fgf10 that are the precursors of the posterior pituitary gland. Importantly, these Fgf10 positive cells migrate rostrally to form the anterior hypothalamic region, but also migrate caudally to form the mammillary hypothalamic region. Cell lineage tracing

using injection of Dil in the early stage embryos allows beautiful tracing of the cells evidence for the embryonic origin of these early hypothalamic regions. Previous studies have used mouse transgenes under a promoter that labels other embryonic tissues, not only the hypothalamic primordium, making these experiments difficult to interpret. Together with the studies from Martinez-Barbera's laboratory, mentioned above (1.6), this work shows that *Fgf10* positive hypothalamic precursors cells respond to Shh signalling and that this is vital for their proliferation and maintenance. Hence, Shh is critical for infundibulum development and inhibition of Shh with cyclopamine inhibits infundibulum formation and leads to absence of RP.

Not many interventions lead to complete absence of the pituitary and therefore this study highlights a vital importance of Fgf10. Future work will reveal which cues trigger the migration of Fgf10+ve cells to form the anterior and mammillary hypothalamus and which genes are important in regulating this process. Such future studies may reveal new mechanisms important in the formation of the neuroendocrine hypothalamus and in turn endocrine homeostasis.

DOI:10.1530/ey.15.1.7

New mouse model

1.8 Hypothalamic loss of Snord116 recapitulates the hyperphagia of Prader-Willi syndrome

Polex-Wolf J, Lam BY, Larder R, Tadross J, Rimmington D, Bosch F, Cenzano VJ, Ayuso E, Ma MK, Rainbow K, Coll AP, O'Rahilly S, Yeo GS
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To read the full abstract: [J Clin Invest 2018;128:960-969](#)

Mouse models for PWS are urgently needed to facilitate drug development for treatment of hyperphagia and obesity in PWS patients. Here, the authors set out to create a mouse model that better recapitulates human PWS; they chose Snord116 as the target. Snord116 comprises a cluster of noncoding RNAs (ncRNAs) on paternal chromosome 15q11.2. Deletions that include *SNORD116* and 2 neighboring ncRNAs result in hyperphagia and other features of PWS in humans (1). SNORD116 is therefore a candidate for the hyperphagia in humans with PWS. Expression of *Snord116* snoRNAs increases within hypothalamic nuclei by weaning age in mice, in line with the characteristic appearance of hyperphagia in humans after initial feeding difficulties. All *Snord116* deletion mouse models reported so far (whether the deletion is monoallelic, biallelic, NPY specific or inducible) are smaller than controls, in line with the failure to thrive in PWS infants. However, they do not transition to obesity, as seen in humans with PWS, and therefore those models provided limited insights.

Therefore, these authors set out to generate a mouse with adult-onset Snord116 deficiency, by use of hypothalamic injections of (adenovirus associated) Cre with Lox-P flanked *Snord116* to reduce hypothalamic Snord116 expression in 10-week old mice. No difference in food intake was found 2 weeks after Cre delivery, but after 9 weeks the mice were heavier, and food intake corrected for body weight was ~25% higher without a change in energy expenditure. No significant changes were detected in the expression of *Pomc*, *Lepr*, *Npy*, *AgRP*, *Pcksk1*, or *Nhlh2* but there was an increase in the expression of *Socs3*, one of the genes of the family of suppressors of cytokine signaling, which is a target gene for Stat3 and a negative regulator of leptin signaling (2) amongst other cytokine signaling pathways. Indeed, overexpression of *Socs3* in POMC neurons results in increased body weight and adiposity (3) therefore supporting involvement of SOCS3 in the hyperphagia and obesity of PWS.

Thus, a mouse model mimicking the obesity and hyperphagia in PWS is now available. This will be useful for further research into PWS, although unfortunately currently the model requires individual stereotaxic hypothalamic injection with viral Cre to generate the necessary Snord116 deletion, and this may preclude the model to be used widely. The involvement of *Socs3* in the hyperphagia requires further study, since this may be a novel target for pharmacological intervention.

1. Duker AL, et al. Paternally inherited micro- deletion at 15q11.2 confirms a significant role for the SNORD116 C/D box snoRNA cluster in Prader-Willi syndrome. *Eur J Hum Genet.* 2010;18(11):1196–1201.
2. Buettner C et al. Leptin controls adipose tissue lipogenesis via central, STAT3-independent mechanism. *Nat Med* 2008;14(6):667-675.
3. Rooks, C.R. et al. Sympathetic denervation does not prevent a reduction in fat pad size of rats or mice treated with peripherally administered leptin. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 289, R92–R102 (2005).

DOI:10.1530/ey.15.1.8

New clinical investigation

1.9 Divergent responses to kisspeptin in children with delayed puberty

Chan YM, Lippincott MF, Kusa TO, Seminara SB
Harvard Reproductive Sciences Center and Reproductive Endocrine Unit,
Massachusetts General Hospital, Boston, MA, USA

To read the full abstract: [JCI Insight 2018;3. pii: 99109](#)

The effects of kisspeptin administration in adults are well known. Whatever the mode of administration, kisspeptin elicits an increase of LH and FSH blood levels in normal men and women. By analogy to rodents and non-human primates, it has been speculated that the response to kisspeptin is majorated at puberty in humans, which

could be explained by a higher sensitivity of GnRH neurons to Kisspeptin. The capacity of the gonadotropic axis to respond to Kisspeptin may thus represent an interesting functional trait, to test the ability of the gonadotropic axis to be fully reactivated in children with delayed or stalled puberty.

Here, Chan et al. report two groups of patients. One group were responders to kisspeptin and the other group were non-responders. Responder children showed spontaneous nighttime LH pulses and positive response to GnRH before pituitary priming, which indicates that their pubertal neurobiological reactivation of the gonadotropic axis had already started. Non-responders required 6-days of pituitary priming by exogenous GnRH in order to achieve a robust response to GnRH, which indicates a more severe functional defect in those children as compared to responders. The follow-up of these children will be important to establish their final diagnoses and to determine whether the 'kisspeptin stimulation test' might be a good predictor of the clinical outcomes for children with delayed or stalled puberty.

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Reviews

1.10 The versatile tanycyte: a hypothalamic integrator of reproduction and energy metabolism

Prevot V, Dehouck B, Sharif A, Ciofi P, Giacobini P, Clasadonte J
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Jean-Pierre Aubert Research Center, U1172, Lille, France

To read the full abstract: [Endocr Rev 2018;39:3,333](#)

This review is interesting for several reasons. It focuses on a specific type of cells lining the wall of the third ventricle in the median eminence of the hypothalamus. This region acts both as a secretor of neuropeptides and as a sensor of the metabolic status

of the periphery. These two functions imply a bidirectional physiological pathway: brain-to-periphery and vice-versa; different cellular mechanisms have been described. The interest developed for the last few years on the function of tanycytes in normal brain and their possible dysfunctions in neuroendocrine disorders has been justified by the importance to increase our knowledge on the control of the homeostasis by the brain. It is now obvious that tanycytes are involved in the control of key hypothalamic functions, such as reproduction and energy metabolism. These authors review recent evidence on the different types of tanycytes in the hypothalamus, their role in the blood-brain barrier, and also in the control of GnRH secretion. One paragraph is dedicated to the role of tanycytes in hypothalamic neurogenesis. This recent discovery was completely unexpected and opens a new area in neuroendocrine research. In the last part of this review, the authors discuss that tanycytes may be an interesting new therapeutic target not only in reproduction, but also in obesity and aging.

DOI:10.1530/ey.15.1.10

Reviews

1.11 Central hypothyroidism - a neglected thyroid disorder

Beck-Peccoz P, Rodari G, Giavoli C, Lania A
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To read the full abstract: [Nat Rev Endocrinol 2017;13:588-598](#)

Central hypothyroidism has received much interest in recent years, partly due to the discovery of new causal gene mutations. This is a comprehensive review on several aspects of central hypothyroidism. It discusses prevalence, and its variation between different countries; pitfalls in diagnosis, including assay interference; concurrent systemic illness and usefulness (or not) of TRH test and SHBG measurements; causes

of congenital central hypothyroidism, including new genetic causes such as *TLBX1* mutations and acquired hypothyroidism, including various forms of radiation, secondary causes, such as response to certain drugs, and various forms of hypophysitis.

Although acknowledging that this is not a consensus guideline, the paper gives recommendations for treatment, which may be used already in many clinics, such as starting with low dose treatment, keeping FT4 in upper normal range, giving thyroid hormone 30 minutes before breakfast and testing thyroid hormone levels before the thyroid hormone dose. Interestingly, they also suggest that levels of TSH >1.0 should be interpreted as a sign of under-treatment in central hypothyroidism as TSH decreases after initiation of treatment with Levothyroxine.

All in all, this review provides a comprehensive but concise update on central hypothyroidism.

DOI:10.1530/ey.15.1.11

Reviews

1.12 Growth hormone - past, present and future

Ranke MB, Wit JM

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Department of Pediatrics, Leiden University Medical Center, Leiden, Netherlands

To read the full abstract: [Nat Rev Endocrinol 2018;14:285-300](#)

This is an interesting review of the history of research in the field of GH-IGF1 and the clinical use of GH. It comprises a timeline starting in 1884 with the description of dwarfism (General Tom Thumb) and gigantism, and ending in 2015-16 describing the discovery of paternally inherited IGF2 mutations and PAPP-A mutations as causes for short stature. This is a pleasure to read, and you are sure to learn something new.

DOI:10.1530/ey.15.1.12

Neonatal Hypoglycemia

2. Antenatal and Neonatal Endocrinology

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Neonatal Hypoglycemia

A novel disorder of hyperinsulinaemic hypoglycaemia and polycystic kidneys

2.1 Polycystic Kidney Disease with Hyperinsulinemic Hypoglycemia Caused by a Promoter Mutation in Phosphomannomutase 2

Cabezas OR, Flanagan SE, Stanescu H, García-Martínez E, Caswell R, Lango-Allen H, Antón-Gamero M, Argente J, Bussell AM, Brandli A, Cheshire C, Crowne E, Dumitriu S, Drynda R, Hamilton-Shield JP, Hayes W, Hofherr A, Iancu D, Issler N, Jefferies C, Jones P, Johnson M, Kesselheim A, Klootwijk E, Koettgen M, Lewis W, Martos JM, Mozere M, Norman J, Patel V, Parrish A, Pérez-Cerdá C, Pozo J, Rahman SA, Sebire N, Tekman M, Turmpenny PD, Hoff WV, Viering DHHM, Weedon MN, Wilson P, Guay-Woodford L, Kleta R, Hussain K, Ellard S, Bockenhauer D

To read the full abstract: [J Am Soc Nephrol. 2017 Aug;28\(8\):2529-2539](#)

The association of hyperinsulinaemic hypoglycaemia (HH) and polycystic kidneys has not been reported before. Here, the authors studied 17 patients from 11 different families and found that all patients had a combination HH and polycystic kidneys. The

HH was mild and some patients required diazoxide therapy. In contrast the polycystic kidney disease was severe in some patients and a few patients had liver cysts as well. None of the patients described had any neurological phenotype. Recessive loss of function mutations in the phosphomannomutase 2 gene (PMM2) lead to a multisystem disorder called congenital disorder of glycosylation type 1A (CDG1A) with predominately neurological involvement. Prior to this study there have been case reports of HH associated with recessive loss of function mutations in PMM2 gene. However no previous studies have linked the association between HH and polycystic kidneys due to mutations in PMM2. All patients in the current study were found to have a promoter mutation in the PMM2 but none of the patients had any other clinical or biochemical features of CDG1A. The lack of neurological involvement and other clinical features of CDG1A suggested that the promoter mutation is likely to be tissue specific (pancreas and kidneys). The underlying mechanism/s leading to tissue specific deficiency of PMM2 are not completely known yet but could be related to the promoter mutation altering tissue specific chromatin loop formation. The promoter mutation lead to decreased transcriptional activity in patient kidney cells and impaired binding of the transcription factor zinc-finger 143 (ZNF143). This transcription factor preferentially occupies anchors of chromatin interactions connecting promoters with distal regulatory elements. It binds directly to promoters and associates with lineage-specific chromatin interactions and gene expression. Further studies will need to establish the molecular basis for the tissue specific loss of function of the promoter PMM2 mutations and the mechanism for the HH and polycystic kidneys.

DOI:10.1530/ey.15.2.1

Neonatal Hypoglycemia

International consensus on Beckwith-Wiedemann Syndrome

2.2 Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement

Brioude F, Kalish JM, Mussa A, Foster AC, Bliiek J, Ferrero GB, Boonen SE, Cole T, Baker R, Bertoletti M, Cocchi G, Coze C, De Pellegrin M, Hussain K, Ibrahim A, Kilby MD, Krajewska-Walasek M, Kratz CP, Ladusans EJ, Lapunzina P, Le Bouc Y, Maas SM, Macdonald F, Ōunap K, Peruzzi L, Rossignol S, Russo S, Shipster C, Skórka A, Tatton-Brown, Tenorio J, Tortora C, Grønsvkov K, Netchine I, Hennekam RC, Prawitt D, Tümer Z, Eggermann T, Mackay DJG, Riccio A, Maher ER

To read the full abstract: [Nat Rev Endocrinol. 2018 Apr;14\(4\):229-249](#)

Beckwith-Wiedemann syndrome (BWS) is a growth disorder characterized by neonatal hypoglycemia, macrosomia, macroglossia, hemihyperplasia, omphalocele, embryonal

tumors (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma), visceromegaly, adrenocortical cytomegaly, renal abnormalities (e.g., medullary dysplasia, nephrocalcinosis, medullary sponge kidney, and nephromegaly), and ear creases/pits.

Molecular genetic testing can identify epigenetic and genomic alterations of chromosome 11p15 in individuals with BWS. Detailed molecular diagnosis is a prerequisite for the precise prediction of tumor risk and the tumor spectrum. This is the first comprehensive international consensus guideline published on the clinical diagnosis and management of patients with BWS. The guideline provides 72 recommendations (covering typical BWS and atypical patients) for the clinical and molecular diagnosis of BWS patients. A modified clinical scoring system is now suggested, which represents the basis to initiate molecular diagnostics. Therapeutic and management recommendations comprise the major clinical questions in both typical and atypical BWS cases. The recommendations discuss the early monitoring of an increased tumor risk, treatment of the macroglossia and the abdominal wall defects, and therapeutic interventions for hypoglycemia. For most of the recommendations there was broad consensus, but on some issues (such as tumour risk monitoring) the consensus was limited. These guidelines and recommendations will need to be re-evaluated in the future once they have been implemented.

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Neonatal Hypoglycemia

Mutations in the FOXA2 gene link beta cell dysfunction with Hypopituitarism

2.3 Congenital Hyperinsulinism and Hypopituitarism Attributable to a Mutation in FOXA2

Vajravelu ME, Chai J, Krock B, Baker S, Langdon D, Alter C, De León DD

To read the full abstract: [J Clin Endocrinol Metab. 2018 Mar 1;103\(3\):1042-1047](#)

See Comment under 2.4.

DOI:10.1530/ey.15.2.3

Neonatal Hypoglycemia

2.4 Novel FOXA2 mutation causes Hyperinsulinism, Hypopituitarism with Craniofacial and Endoderm-derived organ abnormalities

Giri D, Vignola ML, Gualtieri A, Scagliotti V, McNamara P, Peak M, Didi M, Gaston-Massuet C, Senniappan S

To read the full abstract: [Hum Mol Genet. 2017 Nov 15;26\(22\):4315-4326](#)

These two papers describe the association of heterozygous FOXA2 mutations with hypopituitarism and hyperinsulinism. The forkhead/winged helix transcription factor Foxa2 is a major upstream regulator of Pdx1, a transcription factor necessary for pancreatic development and also plays a role in the developmental biology of the pituitary gland. Heterozygous deletions in FOXA2 have been previously reported to associate with a complex syndrome consisting of situs inversus, polysplenia, panhypopituitarism, and mildly dysmorphic facial features (1). Tissue specific deletion of FOXA2 leads to an imbalance in the beta to alpha cell ratio, profound

hypoglucagonemia, inappropriate hyperinsulinemia, and hypoglycemia in mice.

First, Vajravelu et al. show that the FOXA2 mutation leads to changes in key FOXA2 transactivation genes (*ABCC8*, *KNCJ11*, *HADH*) in the beta cell and in the pituitary gland (*GLI2*, *NKX2-2*, *SHH*).

Second, Giri et al. demonstrate strong expression of FOXA2 in the developing hypothalamus, pituitary, pancreas, lungs and oesophagus of mouse embryos using in situ hybridization and transfection assays showed impaired reporter activity. Thus these studies are beginning to provide a link between the pancreatic beta cell dysfunction (hyperinsulinism) and the role of FOXA2 in the developing hypothalamus and pituitary. Thus other cases of unexplained hyperinsulinism and hypopituitarism should be screened for possible mutations in FOXA2. Further experiments to understand the mechanism of the unregulated insulin secretion (and possible low glucagon levels) and the underlying mechanism of the hypopituitarism will shed more insights into the role of FOXA2 in the pancreas and pituitary gland.

1. Tsai EA, Grochowski CM, Falsey AM, Rajagopalan R, Wendel D, Devoto M, Krantz ID, Loomes KM, Spinner NB. Heterozygous deletion of FOXA2 segregates with disease in a family with heterotaxy, panhypopituitarism, and biliary atresia. *Hum Mutat.* 2015 Jun;36(6):631-7. doi: 10.1002/humu.22786. Epub 2015 Apr 21.

DOI:10.1530/ey.15.2.4

Atypical forms of congenital hyperinsulinism are associated with increased expression of the transcription factor NKX2.2 and increased numbers of somatostatin secreting cells

2.5 Atypical Forms of Congenital Hyperinsulinism in Infancy Are Associated With Mosaic Patterns of Immature Islet Cells

Han B, Mohamed Z, Estebanez MS, Craigie RJ, Newbould M, Cheesman E, Padidela R, Skae M, Johnson M, Flanagan S, Ellard S, Cosgrove KE, Banerjee I, Dunne MJ

To read the full abstract: [J Clin Endocrinol Metab. 2017 Sep 1;102\(9\):3261-3267](#)

At a histological level congenital hyperinsulinism (CHI) is classified into three forms, namely diffuse, focal and atypical. The atypical forms display histological mosaicism (heterogeneous populations of islets, which appear to be resting or quiescent and localized to particular domains/lobes of the pancreas) but the molecular and histological basis of the atypical forms of the disease are not well understood. Patients

with atypical CHI tend to present later in life and have decreased response to diazoxide and octreotide over time, suggesting some kind of resistance. This study shows that the expression of a key transcription factor called NKX2.2 and the number of delta cells in tissue from patients with atypical CHI is different compared to diffuse or focal CHI. Interestingly NKX2.2 expression was markedly increased in the pancreatic tissue (quiescent islets) of patients with atypical CHI and that this increased expression was observed in both beta and delta cells. In the human fetal pancreas, NKX2.2 expression is found in ~70% of somatostatin-producing delta cells. Although NKX2.2 expression persists in some postnatal delta cells (~25% of cells), the incidence of coexpression with somatostatin is only a fraction of that seen in the fetal pancreas, indicating that suppression of NKX2.2 expression is required for delta cell identity and normal function in the postnatal period. Thus the atypical CHI histology resembles that of a fetal pancreas and that the pathophysiology of CHI is much more complicated than a just a beta cell defect leading to unregulated insulin secretion. ~10% of patients have the atypical forms of CHI and currently the molecular basis of this type of CHI is not known in most patients. This study begins to shed light into the possible molecular basis of the atypical forms of CHI. Given that atypical CHI has mosaic histology novel imaging techniques which might help to distinguish the quiescent islets from normal pancreatic tissue could aid in surgical removal of the abnormal tissue with the possibility of curing the hypoglycemia.

DOI:10.1530/ey.15.2.5

Neonatal Hypoglycemia

Prophylactic dextrose gel for newborns at risk of hypoglycaemia does not reduce the admission rates to NICU

2.6 Prophylactic Dextrose Gel Does Not Prevent Neonatal Hypoglycemia: A Quasi-Experimental Pilot Study

Coors SM, Cousin JJ, Hagan JL, Kaiser JR

To read the full abstract: [J. Pediatr. 2018; 198:156-161](#)

See Comment under 2.7

DOI:10.1530/ey.15.2.6

Neonatal Hypoglycemia

Dextrose gel and breast feeding should be considered first-line oral treatment of infants with hypoglycemia

2.7 What Happens to Blood Glucose Concentrations After Oral Treatment for Neonatal Hypoglycemia

Harris DL, Gamble GD, Weston PJ, Harding JE

To read the full abstract: [J Pediatr. 2017 Nov;190:136-141](#)

Neonatal hypoglycaemia is common, affecting around 15% of at risk newborns such as preterm, IUGR and infants of diabetic mothers. Delay and inappropriate treatment of hypoglycemia can lead to irreversible brain damage. It is frequently managed by providing infants with an alternative source of glucose, given enterally with infant formula or intravenously with dextrose solution. This often means that mother and baby are separated and may inhibit breastfeeding. There are now several studies assessing the effectiveness of oral dextrose gel to treat neonatal hypoglycemia; the evidence suggests that it is effective and prevents NICU admissions. Oral dextrose gel is simple and inexpensive and can be administered directly to the buccal mucosa for

rapid correction of hypoglycaemia, in association with continued breastfeeding and maternal care. Treatment of infants with neonatal hypoglycaemia with 40% dextrose gel reduces the incidence of mother-infant separation and increases the likelihood of full breast feeding after discharge compared with placebo gel. There is no evidence of adverse effects during the neonatal period or at two years' corrected age. Oral dextrose gel should be considered first-line treatment for infants with neonatal hypoglycaemia.

The first study by Coors et al. shows that prophylactic dextrose administered to at risk newborns does not reduce the frequency of transient neonatal hypoglycemia or NICU admissions for hypoglycemia.

Second, Harris DL et al. report increased blood glucose levels after the administration of buccal dextrose gel to infants at risk of hypoglycemia.

Given the findings of Harris et al., is it not clear why the dextrose gel did not reduce the frequency of transient neonatal hypoglycemia or NICU admissions for hypoglycemia in the Coors study. The authors suggest that the high concentration of Insta-Glucose (77%) used may have caused a hyperinsulinemic response, or alternatively, exogenous enteral dextrose influences glucose homeostasis minimally during the first few hours when counter-regulatory mechanisms are especially active. Thus further studies are required understand the effectiveness of dextrose gel in the first few hours after birth to prevent and treating neonatal hypoglycemia.

DOI:10.1530/ey.15.2.7

Neonatal Hypoglycemia

MEHMO syndrome is an X-linked mental retardation syndrome associated with neonatal hypoglycaemia, hypopituitarism and early onset diabetes mellitus

2.8 Neonatal hypoglycemia, early-onset diabetes and hypopituitarism due to the mutation in EIF2S3 gene causing MEHMO syndrome

Stanik J, Skopkova M, Stanikova D, Brennerova K, Barak L, Ticha L, Hornova J, Klimes I, Gasperikova D

To read the full abstract: [Physiol Res. 2018 May 4;67\(2\):331-337](#)

See Comment under 2.10

DOI:10.1530/ey.15.2.8

2.9 EIF2S3 Mutations Associated with Severe X-Linked Intellectual Disability Syndrome MEHMO

Skopkova M, Hennig F, Shin BS, Turner CE, Stanikova D, Brennerova K, Stanik J, Fischer U, Henden L, Müller U, Steinberger D, Leshinsky-Silver E, Bottani A, Kurdiova T, Ukropec J, Nyitrayova O, Kolnikova M, Klimes I, Borck G, Bahlo M, Haas SA, Kim JR, Lotspeich-Cole LE, Gasperikova D, Dever TE, Kalscheuer VM

To read the full abstract: [Hum Mutat 2017 Apr;38\(4\):409-425](#)

See Comment under 2.10

DOI:10.1530/ey.15.2.9

Neonatal diabetes mellitus

2.10 Two novel EIF2S3 mutations associated with syndromic intellectual disability with severe microcephaly, growth retardation, and epilepsy

Moortgat S, Désir J, Benoit V, Boulanger S, Pendeville H, Nassogne MC, Lederer D, Maystadt I

To read the full abstract: [Am J Med Genet A. 2016 Nov;170\(11\):2927-2933](#)

The vast majority of proteins that a cell secretes or displays on its surface first enter the endoplasmic reticulum (ER), where they fold and assemble. Only properly assembled proteins advance from the ER to the cell surface. The ER coordinates protein biosynthetic and secretory activities in the cell. Alterations in ER homeostasis cause accumulation of misfolded/unfolded proteins in the ER. To maintain ER homeostasis, eukaryotic cells have evolved the unfolded protein response (UPR), an essential adaptive intracellular signaling pathway that responds to metabolic, oxidative stress, and inflammatory response pathways. The UPR has been implicated in a variety of diseases including metabolic disease, neurodegenerative disease, inflammatory disease, and cancer. Signaling components of the UPR are emerging as potential targets for intervention and treatment of human disease. MEHMO syndrome (OMIM# 300148) is a recently described disorder characterized by X-linked intellectual disability, epileptic seizures, hypogonadism, hypogonitalism, microcephaly, and obesity (2). It is caused by mutations in the EIF2S3. The EIF2S3 gene encodes the alpha subunit of eukaryotic translation initiation factor 2 (eIF2), crucial for initiation of protein synthesis and regulation of the ER stress response. MEMHO syndrome

patients may have multiple endocrine manifestations including short stature, hypogonadism and obesity. In addition the manuscript by Stanik J et al report neonatal hypoglycaemia, hypopituitarism and neonatal diabetes mellitus. Thus MEMHO syndrome comes in the category of defects in the ER stress response and includes disorders such as Wolcott-Rallison syndrome, Wolfram syndrome, Microcephaly, Epilepsy, and Diabetes Syndrome (MEDS) and the syndromic form of intellectual disability and diabetes caused by mutations in the *PPP1R15B* (3-6).

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DOI:10.1530/ey.15.2.10

FOXP3 mutations can lead to early onset diabetes mellitus with no other clinical manifestations

2.11 FOXP3 mutations causing early-onset insulin-requiring diabetes but without other features of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

Hwang JL, Park SY, Ye H, Sanyoura M, Pastore AN, Carmody D, Del Gaudio D, Wilson JF, Hanis CL, Liu X, Atzmon G, Glaser B, Philipson LH, Greeley SAW, T2D-Genes Consortium

To read the full abstract: [Pediatr Diabetes. 2018 May;19\(3\):388-392](#)

Mutations in *FOXP3* are associated with a severe, early-onset, autoimmunity syndrome known in males known as IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked; OMIM [Online Mendelian Inheritance in Man] 304930). The gene maps to chromosome Xp11.23 and encodes a 431-amino acid protein, also named 'scurfin', required for the generation and functioning of

CD4⁺CD25⁺ regulatory T lymphocytes. FOXP3-expressing CD4⁺ T cells are potent suppressors of self-reactive T-cell activation and proliferation, presumably via direct cell-cell interaction. The lack of these cells results in an uncontrolled autoimmune reactivity in male patients with hemizygous *FOXP3* mutations. Most patients with IPEX syndrome described to date developed symptoms shortly after birth or during the first 3–4 months of life. The most common findings are enteropathy (nearly 100% of patients), diabetes (~70%), skin disease (~65%), failure to thrive (~50%), thyroiditis (~30%), and recurrent infections (~20%). Less common features include autoimmune cytopenias, pneumonitis, nephritis, hepatitis, vasculitis, arthritis, myositis, and alopecia as well as lymphadenopathy and splenomegaly. The life expectancy of patients with IPEX syndrome rarely extends beyond infancy. However, a milder phenotype has been reported in a number of patients, who can live longer, sometimes into adulthood. Enteropathy was present in virtually all of them, although diabetes was frequently absent. Here, Hwang et al. describe cases of early onset diabetes mellitus (one at the age of 2.1 years) due to *FOXP3* mutations and no other clinical features of the IPEX syndrome. These observations suggest that diabetes mellitus may be the only presenting feature of *IPEX* syndrome in some patients and other clinical features might develop later in life.

DOI:10.1530/ey.15.2.11

Neonatal diabetes mellitus

Neonatal diabetes with autoimmunity can be associated with LRBA Mutations

2.12 Recessively Inherited LRBA Mutations Cause Autoimmunity Presenting as Neonatal Diabetes

Johnson MB, De Franco E, Lango Allen H, Al Senani A, Elbarbary N, Siklar Z, Berberoglu M, Imane Z, Haghghi A, Razavi Z, Ullah I, Alyaarubi , Gardner D, Ellard S, Hattersley AT, Flanagan SE

To read the full abstract: [Diabetes 2017 Aug;66\(8\):2316-2322](#)

Biallelic mutations in the human lipopolysaccharide responsive beige-like anchor (LRBA) gene lead to a primary immunodeficiency known as LRBA deficiency, characterized early-onset hypogammaglobulinemia, severe autoimmune manifestations, enteropathy, lymphoproliferation, and recurrent respiratory tract infections. Neonatal diabetes mellitus (NDM) has not been previously described in patients with LRBA mutations. In this study, the proband was diagnosed at 7 weeks of age with diabetes and additional autoimmunity and 3 other patients presented before 6 months of age. The other patients had diabetes onset between 6 and 12 months. Only 1 patient was

positive for GAD antibody of those that were tested. However these patients had other autoimmune conditions including hematological manifestations, autoimmune enteropathy, and hypothyroidism. Identifying the underlying genetic etiology is clinically important for these patients as understanding the disease mechanism may allow the use of personalized therapy.

Abatacept, a CTLA-4 mimetic that replaces the action of the lost suppressive receptor, has been used to treat patients with LRBA mutations and all showed improvement in their autoimmune features. However it has not been used to treat patients with LRBA mutations and diabetes yet. Interestingly LRBA-deficient mice do not manifest features of diabetes mellitus. This study suggests that mutations in LRBA are a relatively common etiology of neonatal or infancy-onset diabetes when patients have additional early-onset autoimmune disease and are born to consanguineous parents. Testing for LRBA mutations should be considered in all patients with newly diagnosed neonatal diabetes and in those with infancy-onset diabetes (<12 months), especially when a recessive inheritance is suspected or additional autoimmune features are present. A genetic diagnosis is critical not only for counseling on recurrence risk but also for allowing immunomodulatory agents such as abatacept to be considered as part of the treatment regimen. This study increases the total number of genetic causes of neonatal diabetes to 25, and the genetic causes of severe early-onset autoimmunity that includes neonatal diabetes to 4; the others being *FOXP3*, *IL2RA*, and *STAT3*.

DOI:10.1530/ey.15.2.12

Gestational Diabetes Mellitus: Neonatal and long-term consequences

Primary cells isolated from the umbilical cord of offspring born to mothers with GDM maintain metabolic and molecular imprints of maternal hyperglycemia

2.13 Gestational Diabetes Alters Functions in Offspring's Umbilical Cord Cells With Implications for Cardiovascular Health

Amrithraj AI, Kodali A, Nguyen L, Teo AKK, Chang CW, Karnani N, Ng KL, Gluckman PD, Chong YS, Stükel W

To read the full abstract: [Endocrinology. 2017 Jul 1;158\(7\):2102-2112](#)

Gestational diabetes mellitus (GDM) produces fetal hyperglycemia with increased lifelong risks for the exposed offspring to cardiovascular and other diseases. In-utero exposure to GDM alters metabolic programming in newborns and their placenta, cord

tissues, and cord blood. Human umbilical cord mesenchymal stromal cells (hUC-MSCs) of Wharton's jelly origin undergo adipogenic, osteogenic, and chondrogenic differentiation in vitro. Exposure of these hUC-MSCs to maternal gestational diabetes seems to have a dramatic impact on the metabolic, angiogenic and proliferative ability of these cells. Exposure of these umbilical cord mesenchymal stromal cells to gestational diabetes induces a low proliferative rate, increases population doubling time, reduces cell viability and increases cell death. In addition umbilical cord mesenchymal stromal cells exposed to gestational diabetes have reduced glucose utilization and anti-cancerous ability while enhanced angiogenic ability. The mechanisms by which the hyperglycemia from the gestational diabetes impacts these changes in the hUC-MSCs is not clear. This study found reduced expression of an antiapoptotic protein called BCL-xL in the hUC-MSCs exposed to gestational diabetes. In addition there was increased expression of genes related to blood vessel formation in the human umbilical vein endothelial cells exposed to gestational diabetes. A key gene involved in atherosclerosis (CD44) was under expressed in the GDM group. These studies suggest that GDM induces complex adverse effects on growth, angiogenic and anti-cancerous potential of human umbilical cord mesenchymal stromal cells and this may have long-term impact on the fetus.

DOI:10.1530/ey.15.2.13

Gestational Diabetes Mellitus: Neonatal and long-term consequences

Review focussing on the short- and long-term consequences of exposure to hyperglycaemia in utero

2.14 Short- and long-term consequences for offspring exposed to maternal diabetes: a review

Burlina S, Dalfrà MG, Lapolla A

To read the full abstract: [J Matern Fetal Neonatal Med. 2017 Oct 16:1-8](#)

Gestational diabetes mellitus (GDM) is one of the common metabolic diseases during pregnancy, affecting ~14% of all pregnancies. Better recognition of the risk factors of GDM, combined with more universal screening for the disease in many countries, has led to the increased detection of GDM along with other forms of pregestational diabetes. There is growing evidence that GDM increases the risk of several short- and long-term adverse consequences for the fetus and mother, the most significant of

which is a predisposition to the metabolic syndrome and Type 2 diabetes. Maternal and childhood obesity as well as cardiovascular disease are also potential long-term consequences of GDM. Studies have suggested defects in insulin sensitivity and insulin secretion even in the absence of impaired glucose tolerance in adult offspring. In animal models, exposure to a hyperglycemic intrauterine environment also leads to the impairment of glucose tolerance in the adult offspring. These metabolic abnormalities can be transmitted to the next generation, suggesting that in utero exposure to maternal diabetes has an epigenetic impact. At the cellular level, there is impairment in pancreatic beta-cell mass and function. Several mechanisms such as defects in pancreatic angiogenesis and innervation, or modification of parental imprinting, may be implicated, acting either independently or in combination. Although the exact mechanism by which GDM increases the risk of obesity and diabetes in offspring is poorly understood, recent studies indicate that placentas exposed to maternal GDM have modified patterns of DNA methylation in the leptin and adiponectin genes. Future randomized trials will help to determine if early intervention could decrease the risk for gestational diabetes and whether long term adverse outcome are preventable and importantly the association with degree of maternal hyperglycemia in pregnancy and future morbidity.

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Gestational Diabetes Mellitus: Neonatal and long-term consequences

Gestational weight gain above certain recommendations is associated with adverse outcome for both child and mother

2.15 Association of Gestational Weight Gain With Maternal and Infant Outcomes: A Systematic Review and Meta-analysis

Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, Li N, Hu G, Corrado F, Rode L, Kim YJ, Haugen M, Song WO, Kim MH, Bogaerts A, Devlieger R, Chung JH, Teede HJ

To read the full abstract: [JAMA 2017 Jun 6;317\(21\):2207-2225](#)

Excessive and insufficient gestational weight gain are associated with adverse pregnancy outcomes, including small for gestational age (SGA), large for gestational age (LGA), macrosomia, cesarean delivery, gestational diabetes mellitus (GDM), preeclampsia, postpartum weight retention, and offspring obesity. The Institute of Medicine (IOM; now known as the National Academy of Medicine) recommendations on gestational weight gain were developed in 1990 to guide clinical practice. These

aimed to reduce the incidence of low-birth-weight babies and were based on a 1980 National Natality Survey of a largely white population. The updated IOM guidelines in 2009 incorporated World Health Organization (WHO) categories of maternal body mass index (BMI; for underweight, <18.5; normal weight, 18.5-24.9; overweight, 25-29.9; and obese, ≥30) and recommended less gestational weight gain for obese women. The 2009 guidelines identified maternal and infant relationships with gestational weight gain but were based on lower general population BMI with limited ethnic diversity. The 2009 IOM guidelines are endorsed by the American College of Obstetricians and Gynecologists, although they are not universally implemented.

This large meta-analysis aimed to address the key question: what is the association between gestational weight gain above or below the Institute of Medicine guidelines and maternal and infant outcomes? The summary findings were that in 1.3 million pregnancies, gestational weight gain below the recommendations (in 23% of women) was associated with higher risk of small for gestational age and preterm birth and lower risk of large for gestational age and macrosomia. Gestational weight gain above recommendations (47%) was associated with lower risk of small for gestational age and preterm birth and higher risk of large for gestational age, macrosomia, and cesarean delivery. There are several limitations, which the authors acknowledge. For example the meta-analysis did not include studies from developing countries and excluded non-English-language articles and the meta-analysis could not be performed for GDM because of inconsistent primary data.

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Maternal obesity

Maternal obesity impacts placental lipid metabolism leading to increased lipid accumulation

2.16 Effect of Maternal Obesity on Placental Lipid Metabolism

Calabuig-Navarro V, Haghiac M, Minium J, Glazebrook P, Ranasinghe GC, Hoppel C, Hauguel de-Mouzon S, Catalano P, O'Tierney-Ginn P

To read the full abstract: [Endocrinology 2017 Aug 1;158\(8\):2543-2555](#)

Maternal obesity and gestational diabetes (GDM) are associated with a higher risk for maternal, and offspring complications and appear to be mediated at least partly by an aberrant placental morphology and function, with altered nutrient transport capacities. The human placenta adapts to mild maternal diabetes by limiting placental glucose transfer, and consequently protecting the fetus to a certain degree from excessive glucose exposure. In the maternal circulation, fatty acids are primarily transported in lipoproteins, which are not taken up by the placenta in an appreciable extent. Both placental lipoprotein lipase and endothelial lipase hydrolyze maternal plasma lipoprotein, triglycerides and phospholipids, and liberated FA can be taken up by the placenta. Non-esterified fatty acids can cross placental membranes through facilitated diffusion. This process is mediated by a family of transmembrane fatty acid transporters, fatty acid binding proteins, fatty acid translocase (FAT/CD36) and the MFSD2a transporter. Placental lipid content depends on maternal supply. Therefore, maternal dyslipidemia

status may be expected to alter lipid composition in placental tissue. GDM alters the placental fatty acid content and the expression of genes involved on fatty acid transfer to the fetus.

To test the hypothesis that placental fatty acid oxidation capacity is impaired and fatty acid esterification is enhanced in obese women, this study assessed the following: (1) acylcarnitine profiles, lipid content, and expression of key components of fatty acid esterification and oxidation pathways in placentas of lean and obese women, and (2) [3 H]-palmitate oxidation and esterification in trophoblasts isolated from placentas of lean and obese women. The key finding was that maternal obesity is associated with an increase in lipid esterification and storage, and a decrease in mitochondrial fatty acid oxidation, which is compensated for by an upregulation of peroxisomal fatty acid oxidation. Altogether, these changes may serve to limit the amount of maternal lipid transferred to the fetus. Consistent with previous reports studies, lipid content was higher in placentas from obese as compared with lean women. PPAR γ , a lipid-activated transcription factor, regulates the expression of lipid esterification and storage genes in several tissues and this was upregulated in placentas of obese women. Placental fatty acid concentrations may be elevated in obese women due to either increased maternal supply, secondary to maternal insulin resistance and increased lipolysis, or lower placental FA oxidation. It is speculated that elevated fatty acid concentrations within the placenta activate PPAR γ . In turn, PPAR γ stimulates the transcription of DGAT1, SCD1, and ACC, key genes involved in lipid esterification and storage. Further studies are necessary to confirm this hypothesis in placental tissue, although others have described such a mechanism in adipose and hepatic tissues in mice and non pregnant subjects.

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Maternal obesity

Maternal obesity induces embryonic defects by affecting the levels of DPPA3 gene in mice

2.17 Embryonic defects induced by maternal obesity in mice derive from Stella insufficiency in oocytes

Han L, Ren C, Li L, Li X, Ge J, Wang H, Miao YL, Guo X, Moley KH, Shu W, Wang Q

To read the full abstract: [Nat Genet. 2018 Mar;50\(3\):432-442](#)

Maternal obesity is associated with poor outcomes across the reproductive spectrum including infertility, increased time to pregnancy, early pregnancy loss, congenital abnormalities and neonatal complications. Adverse effects are detectable as early as the oocyte and preimplantation embryo stage, and that these early effects may contribute to lasting morbidity in offspring, underscoring the importance of optimal maternal weight and nutrition before conception. The impacts of abnormal maternal metabolic environment on oocyte quality and pregnancy outcomes have been studied in diabetic mouse models. Female mice with models of type 1 diabetes produce oocytes that are smaller, show impaired maturation and increased granulosa cell apoptosis and display poor reproductive outcomes including growth restriction and congenital anomalies. The growth restriction and congenital abnormalities result from a maternal oocyte effect rather than a diabetic uterine environmental effect, as transfer of one-cell zygotes derived from diabetic mothers to control non-diabetic mothers failed to rescue

the developmental defects. Likewise, high fat diet mouse models of obesity display similar negative impacts on the oocyte, the embryo, and pregnancy outcomes. Oocytes from obese mice are smaller, show delayed meiotic maturation, have increased follicular apoptosis and their offspring exhibit embryonic developmental defects and growth retardation.

In this study the authors report an important role of DPPA3 (developmental pluripotency associated 3, also known as Stella or PGC7) in mediating the phenotypic effects of maternal obesity in embryos and offspring. Dppa3 has been described in mice as an important maternal factor produced by the oocyte that participates in protecting the maternal genome from oxidation of methylated cytosines (5mC) to hydroxymethylated cytosines (5hmC). Dppa3 is also required for normal mouse preimplantation development. The study identified substantial reductions of Stella protein in mature oocytes from obese mice. Zygotes derived from obese mothers are disrupted in the normal maternal-paternal pronuclear asymmetry in CpG methylation, consistent with the demonstrated role of Stella in inhibiting demethylation of 5-methylcytosine (5mC). Notably, overexpression of Stella in oocytes suppressed the developmental defects of embryos produced from oocytes derived from obese mothers. The high fat diet in mice not only reduced DPPA3, but also led to global hypomethylation across the genome. Interestingly when DPPA3 was overexpressed in the oocytes of high fat diet fed mice this restored the epigenetic remodeling in zygotes. These findings indicate that Stella insufficiency in the oocyte may represent a key connection between maternal metabolic syndrome, embryo development and, potentially, alterations in offspring physiology. The molecular mechanism/s by which maternal high fat diet modulates Stella protein levels in mouse oocytes is still unclear and further studies on will shed light on Stella.

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Impact of diet on central inflammatory response

Dietary composition, age, and sex determine the central inflammatory response associated with the long-term outcomes of excess weight gain

2.18 The Hypothalamic Inflammatory/Gliosis Response to Neonatal Overnutrition Is Sex and Age Dependent

Argente-Arizón P, Díaz F, Ros P, Barrios V, Tena-Sempere M, García-Segura LM, Argente J, Chowen JA

To read the full abstract: [Endocrinology. 2018 Jan 1;159\(1\):368-387](#)

Hypothalamic inflammation has been linked to the development and progression of obesity and its sequelae. Obesity in rodents and humans is associated with gliosis of the arcuate nucleus, a key hypothalamic region for the regulation of energy homeostasis and adiposity. Gliosis, the activation of astrocyte and microglial cell populations, is a hallmark of central nervous system injury and is detectable using either immunohistochemistry or in vivo magnetic resonance imaging (MRI). The activation of the hypothalamic inflammatory processes and gliosis depends not only on weight gain but also on the diet inducing this weight gain and the early nutritional status. A high fat diet in mice leads to increased inflammation, increased oxidative damage, decreased antioxidant enzymes activity and levels, changes in the Krebs cycle enzyme activities, and inhibition of mitochondrial respiratory chain complexes in the

brain structures. In addition to this the impairment of intracellular and epigenetic mechanisms, such as hypothalamic autophagy and changes in the methylation pattern of certain genes, have been implicated in susceptibility to diet induced obesity. The above study assessed the impact of neonatal overnutrition on astrocyte response in Wistar rats. Although the Wistar rats started to accumulate excessive fat mass as early as postnatal day (PND) 10 there was no increase in hypothalamic cytokine levels, markers of astrocytes or microglia, or inflammatory signaling pathways were observed. Signs of hypothalamic gliosis and inflammation were found in overweight PND 150 male rats, including an increase in the number of astroglia, increased levels of TNF α and activation of JNK. Females were not overweight at this age and showed no signs of hypothalamic inflammation/gliosis. Thus, not only is postpubertal weight/adiposity gain different in males and females in response to early overnutrition, but the central inflammatory response also differs. Estrogens are known to be protective against excess weight gain, and ovariectomy of postpubertal females results in weight gain and increased inflammation and therefore this might explain the difference in males and females. The inflammation and astrogliosis in the hypothalamus were associated with an increase in the level of fatty acids in males and not in females. Free fatty acids are known to induce neuroinflammation, endoplasmic reticulum stress, and dysregulation of neuropeptide synthesis. These observations suggest that neonatal overnutrition may also lead to hypothalamic inflammation possibly due to the increased levels of fatty acids and that oestrogens might be protective in females. Some of these protective effects of estradiol could be mediated through astrocytes. Further understanding of the differential responses of males and females to nutritional challenges is necessary to develop specific treatments for obesity according to sex.

DOI:10.1530/ey.15.2.18

Islet dysfunction in IUGR rats: Novel insights

Novel mechanisms of islet dysfunction in intrauterine growth restricted rats

2.19 Transcriptomic Analysis Reveals Novel Mechanisms Mediating Islet Dysfunction in the Intrauterine Growth-Restricted Rat

Rashid CS, Lien YC, Bansal A, Jaeckle-Santos LJ, Li C, Won KJ, Simmons RA

To read the full abstract: [Endocrinology. 2018 Feb 1;159\(2\):1035-1049](https://doi.org/10.1038/4191035a)

Placental insufficiency leads to intrauterine growth restriction (IUGR) which in the fetus leads to hypoxemia and hypoglycemia. IUGR fetuses are characterized by having higher circulating catecholamine concentrations and lower circulating insulin concentrations, as well as impaired glucose stimulated insulin secretion. In cases of severe IUGR, fetuses have smaller and less vascularized pancreatic islets with fewer pancreatic beta cells. In less severe IUGR the pancreatic defects are less pronounced. This suggests that the degree of impaired islet development may correlate with the severity of placental insufficiency, a phenomenon observed in animal models of placental insufficiency. These findings also show that reduced insulin secretion in IUGR fetuses is not solely due to smaller islets and less beta cells. Thus, the fetal beta

cell links fetal nutrient supply with fetal nutrient metabolism and anabolic signals for growth. Children and adults that were formerly SGA fetuses develop insulin resistance and type 2 diabetes mellitus later in life. The risk for developing type 2 diabetes is due to a combination of both an increased risk of insulin resistance and an increased risk of impaired beta cell development and function. In this study, in order to get a better understanding of how IUGR leads to changes in islet function the authors assessed the impact of IUGR on the islet transcriptome over a time course of 2 and 10 weeks in a rat model. At 2 weeks of age the rats were mildly glucose intolerant whereas at 10 weeks they were frankly hyperglycemic. The transcriptome and gene analysis showed important temporal changes in the IUGR islets. There were significant changes (increased expression) at 2 weeks of in genes regulating amino acid metabolism, genes regulating the extracellular matrix and mesenchymal stromal cell-derived factors. In contrast some of these same genes were decreased in adult islets. A key finding of this study was the observation that multiple genes regulating fibrosis in IUGR islets at 2 weeks of age were differentially expressed, suggesting fibrogenesis participates fundamentally in the initiation of the abnormal islet phenotype in diabetes. Fibrogenesis induces immune-cell trafficking and remodeling of the extracellular matrix. Stellate-cell activation and fibrosis were the most enriched pathways in 2- and 10-week-old IUGR islets, and fibrogenesis was also identified as a dysregulated pathway in human diabetic islets. This study underscoring the importance of performing analyses at time points before the development of diabetes and during the progression of the disease.

DOI:10.1530/ey.15.2.19

miRNA's and Placental function

Placental miRNAs dysregulation in maternal obesity may be involved in mediating growth-promoting effects in offspring of obese mothers

2.20 Dysregulation of Placental miRNA in Maternal Obesity Is Associated With Pre- and Postnatal Growth

Carreras-Badosa G, Bonmatí A, Ortega FJ, Mercader JM, Guindo-Martínez M, Torrents D, Prats-Puig A, Martínez-Calcerrada JM, de Zegher F, Ibáñez L, Fernández-Real JM, López-Bermejo A, Bassols J

To read the full abstract: [J Clin Endocrinol Metab. 2017 Jul 1;102\(7\):2584-2594](#)

Maternal obesity and nutrient excess *in utero* increase the risk of future metabolic diseases. The mechanisms underlying this process are poorly understood, but probably include genetic, epigenetic alterations and changes in fetal nutrient supply. Placenta, and particularly amniotic fluid, is the *in utero* environment that could modify fetal growth and adiposity by exerting stimulatory or inhibitory effects on fetal genome expression. Examples of epigenetic mechanisms are DNA methylation, histone modifications and microRNAs (miRNAs). miRNAs are a class of noncoding endogenous RNA molecules approximately 22 nucleotides long that regulate gene expression at the transcriptional or posttranscriptional level by suppressing translation

of protein coding genes or cleaving target mRNAs to induce their degradation. The expression of placental miRNAs is altered during pregnancy in such pathological conditions as preeclampsia, small-for-gestational-age newborns and fetal congenital heart defects, but their role in obesity has not yet been investigated. It is known that miRNAs regulate gene expression in the amniotic fluid during obesity and the expression profile of miRNAs is altered in maternal obesity. This study highlights the fact that the placenta responds to the maternal obesogenic environment by expressing a specific placental miRNA profile. The authors identified eight placenta obesity-associated miRNAs, four of which (miR-100, miR-1285, miR-296, and miR-487) were related to prenatal and postnatal growth parameters. Among them, miR-296 was present in second-trimester plasma samples and was associated with placental expression as well as with prenatal and postnatal growth. These miRNAs were associated with metabolic parameters, predictors of lower birth weight and increased postnatal weight gain. From a functional point of view these miRNAs were related to cell proliferation and insulin signaling pathways. Interestingly not all the miRNAs in the placenta were detectable in the maternal serum.

This may reflect related processes in which placental dysfunction attenuates miRNA biogenesis and alters exosome dependent or exosome-independent release of miRNAs into the plasma. The effect of the miRNAs that are not released into the maternal plasma during pregnancy could be exerted via a paracrine regulation between trophoblasts and fetal cells, through the fetal circulation, or by an autocrine regulation of the trophoblasts themselves, through the regulation of several proteins released by the trophoblast and involved in the regulatory mechanism of fetal growth.

DOI:10.1530/ey.15.2.20

PCOS, Metformin and big heads

Overweight PCOS mothers treated with Metformin give birth to offspring with larger heads

2.21 Fetal Growth and Birth Anthropometrics in Metformin-Exposed Offspring Born to Mothers With PCOS

Hjorth-Hansen A, Salvesen Ø, Engen Hanem LG, Eggebø T, Salvesen KÅ, Vanky E, Ødegård R J

To read the full abstract: [Clin Endocrinol Metab. 2018 Feb 1;103\(2\):740-747](#)

Polycystic ovary syndrome (PCOS) is characterized by oligo-amenorrhoea, clinical and/or biochemical hyperandrogenism, polycystic ovaries, infertility and, commonly, insulin resistance, hyperinsulinaemia, morbid obesity and type 2 diabetes. The insulin-sensitizing drug metformin ameliorates the endocrinopathy of PCOS by reducing hyperinsulinaemia-mediated hyperandrogenism, facilitating resumption of predominantly ovulatory normal menses. The use of metformin during pregnancy seems to be safe and there is no evidence that metformin is teratogenic whether given to women with type 2 diabetes mellitus, gestational diabetes or PCOS. Metformin during pregnancy in women with PCOS does not adversely affect their neonates birth

weight or length, or growth in the first 18 months of life. In this study the authors examined the in-utero ultrasound measurements of the fetuses to explore the effect of metformin versus placebo on fetal and birth anthropometrics in PCOS offspring compared with those in a reference population. The results were related to maternal body mass index (BMI). The main finding was that metformin-exposed offspring had larger head circumference (HC) compared with offspring in the placebo group. This was evident already at gestational week 32. Birth weight and length did not differ between the metformin and placebo groups. The metformin effect of larger HC was seen only among offspring of mothers with hyperandrogenic phenotype; among those with normo-androgenic phenotype, there was no difference between the groups. The effect of prenatal metformin exposure seems to translate differently depending on maternal BMI and/or metabolic status. Offspring who are exposed to metformin and born to normal-weight mothers had significantly smaller HC and were shorter and lighter than metformin-exposed offspring of overweight/obese mothers. In contrast, in the placebo group there was no difference in head size, birth length, and birth weight between offspring of normal weight and those of overweight/obese mothers. This indicates a growth restrictive effect of metformin among normal-weight mothers with PCOS.

However, because of the small sample size, a metformin effect according to maternal androgen status must be interpreted with great caution and should be addressed in future studies.

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3. Thyroid

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A selection of papers with high impact challenging current knowledge and practice in pediatric thyroidology were published during the last year. On the molecular level, the

proof of intracellular compartmentalization of the TSH/TSHR signaling cascade changes our view on TSH/TSHR signaling adding a new level of regulation. On the hormonal level, the fact that thyroid hormones regulate cardiac function and metabolic activity mainly by a noncanonical thyroid hormone receptor independent way provides new insights how thyroid hormones are acting in different target tissues to fulfill physiological functions. Finally, new long-term data on school performance of offspring of mothers with thyroid disease during pregnancy extends our knowledge on the effect of the whole spectrum of severity of hypo- and hyperthyroidism in the first trimester. The outcome was identical in offspring in all groups, providing reassurance for pregnant women with thyroid diseases. Alongside these three papers, this chapter aims at giving an overview on relevant thyroid papers published from July 2017 to June 2018.

DOI:10.1530/ey.15.3

Thyroid development

3.1 GLIS3 is indispensable for TSH/TSHR-dependent thyroid hormone biosynthesis and follicular cell proliferation

Kang HS, Kumar D, Liao G, Lichti-Kaiser K, Gerrish K, Liao XH, Refetoff S, Jothi R, Jetten AM

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To read the full abstract: [J Clin Invest 2017;127:4326-4337](https://doi.org/10.1177/0950268817703337)

Mutations in the Krüppel-like zinc finger transcription factor GLI-similar 3 (*GLIS3*) have first been associated with a syndrome combining two rare genetic endocrine diseases, namely neonatal diabetes and congenital hypothyroidism (OMIM #610199)¹. Since then, 12 patients have been reported so far with a broad spectrum of a multi-organ disease including growth delay, renal cystic dysplasia, liver fibrosis, congenital glaucoma and osteopenia, besides neonatal diabetes and congenital hypothyroidism. In a large cohort of Chinese patients with congenital hypothyroidism without further multi-organ disease, the prevalence of *GLIS3* mutations was 0.3%². The role of *GLIS3* has been extensively described for beta cell differentiation. However, the role of *GLIS3* for thyroid follicular cell differentiation and function remained unknown.

Here, Kang et al. elucidated the critical role of *GLIS3* for thyroid growth and function by extensive description and functional studies in a murine model. First, they showed that *GLIS3* has a key role for murine postnatal thyroid follicular cell proliferation, acting mainly through AKT1 independent activation of the mTORC1 signaling pathway. However, and in contrast to the human phenotypes ranging from thyroid agenesis to thyroid gland in situ, they found no effect of *GLIS3* deficiency on embryonic thyroid development in their model, an aspect that will need further attention. Second, they showed that *GLIS3* directly binds to promoters of several genes encoding proteins of the thyroid hormone biosynthesis machinery and upregulates their transcription. The most important upregulation was observed for the sodium/iodide symporter (*Nis*) gene, which has been shown to be the limiting step for onset of thyroid hormone synthesis in the human embryonic thyroid.

In summary, these results extend our knowledge on the complex intracellular TSH-receptor signaling and identified the transcription factor *GLIS3* a key regulator of TSH mediated thyroid hormone synthesis and proliferation.

1. Senée V, Chelala C, Duchatelet F, Feng D, Blanc H, Cossec JC, Charon C, Nicolino M, Boileau P, Cavener DR, Bougnères P, Taha D, Julier C. Mutations in *GLIS3* are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. *Nat Genet* 2006;38:682-687.

2. Fu C, Luo S, Long X, Li Y, She S, Hu X, Mo M, Wang Z, Chen Y, He C, Su J, Zhang Y, Lin F, Xie B, Li Q, Chen S. Mutation screening of the *GLIS3* gene in a cohort of 592 Chinese patients with congenital hypothyroidism. *Clin Chim Acta* 2018;476:38-43.

DOI:10.1530/ey.15.3.1

Thyroid development

3.2 A branching morphogenesis program governs embryonic growth of the thyroid gland

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To read the full abstract: [Development 2018;145. pii:dev146829](#)

Branching morphogenesis is a key process during organogenesis of ductal and exocrine organs, e.g. lung, kidney, pancreas, and liver¹. Regulatory components and local interactions for lung branching morphogenesis have been described in detail, mostly relying on receptor-ligand interactions between embryonic domains, respectively the lung endodermal epithelium and the surrounding mesenchyme. Folliculogenesis is the major step of structural differentiation of the embryonic thyroid

gland and a prerequisite for onset of thyroid hormone synthesis. During folliculogenesis, thyroid follicular cell precursors start to adhere laterally and polarize to develop functionally different cell compartments with distinct expression of the thyroid hormone biosynthesis machinery at the apical and the basolateral membrane. Here, Liang et al. describe in extensive developmental experiments in the murine model a growth pattern of the embryonic murine thyroid reminiscent of the classic branching morphogenesis. This process was active during late thyroid development (E12-E14) before progenitor differentiation. In analogy with other organs, Sox9 expression identified a subset of proliferating progenitors at the tip of the branching thyroid follicular cell population. Branching growth of the thyroid was stimulated by mesenchymal Fgf10. Fgf10 inactivation caused normal migration of the thyroid but defective proliferation, folliculogenesis and formation of angiofollicular units. In summary, these results provide evidence for a branching morphogenetic process as major driver for proliferation and structural differentiation of the embryonic thyroid follicular cell population and provide possible molecular mechanisms for thyroid dysgenesis due to thyroid hypoplasia.

1. Affolter M, Zeller R, Caussinus E. Tissue remodeling through branching morphogenesis. *Nat Rev Mol Cell Biol* 2009;10:831-842.

DOI:10.1530/ey.15.3.2

Mechanisms of the year

3.3 Internalized TSH receptors en route to the TGN induce local Gs-protein signaling and gene transcription

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To read the full abstract: [Nat Commun 2017;8:443](#)

G-protein-coupled receptors (GPCRs) are a large family of receptors localized at the cell membrane, detecting specific ligands such as hormones, neurotransmitters, odors, pheromones. Further, GPCRs are the main element for the photoisomerization process, necessary to convert a photon impulse to an electrical signal in photosensitive ganglion cells of the retina. GPCRs are involved in a large spectrum of physiological processes and disordered GPCR function causes a variety of human diseases¹. Extracellular binding of specific ligands to GPCRs leads to conformational changes of the GPCRs, activation of the G-proteins at the internal side of the cell membrane and activation of intracellular signaling pathways, which are the cAMP/PKA signaling pathway and the phosphatidylinositol signaling pathway. While the first steps of GPCR activation at the cell membrane are well characterized,

recent data suggested that GPCRs could be internalized in different intracellular compartments. More specifically, the observation of co-localized TSH/TSHR complexes with G-protein in the Golgi apparatus raised the question whether GPCR signaling might be active not only in the early endosomal compartment close to the inner side of the cell membrane but also in other intracellular compartments.

To address this aspect of GPCR physiology, here Godbole et al. performed an elegant study directly visualizing the whole process of ligand binding at the cell surface, internalization and activation of the TSH/TSHR G-protein complex, and its intracellular trafficking by quantification of cAMP/PKA signaling during this whole process. The authors propose a compartmentalized model of TSHR signaling: Internalization of TSH/TSHR complex on binding into an early endosomal compartment, retrograde trafficking of TSH/TSHR complex within the endosome to the Golgi apparatus, G-protein activation only in close contact of the TSH/TSHR G-protein containing endosome close to the Golgi apparatus, and cAMP/PKA signaling at the Golgi apparatus only near the nucleus. Further, the authors showed that the retrograde trafficking of the TSHR was required for efficient PKA-dependent nuclear phosphorylation of the cAMP response element binding protein (CREB), and TSH-induced gene expression. In summary, the authors show functional evidence for multiple intracellular sites of GPCR signaling, providing new insights into GPCR physiology and opening new avenues for pharmaceutical research.

1. Weis WI, Kobilka BK. The molecular basis of G protein coupled receptor activation. *Annu Rev Biochem* 2018;87:897-919.

DOI:10.1530/ey.15.3.3

3.4 Noncanonical thyroid hormone signaling mediates cardiometabolic effects *in vivo*

Hones GS, Rakov H, Logan J, Liao XH, Werbenko E, Pollard AS, Praestholm SM, Siersbaek MS, Rijntjes E, Gassen J, Latteyer S, Engels K, Strucksberg KH, Kleinbongard P, Zwanziger D, Rozman J, Gailus-Durner V, Fuchs H, Hrabe de Angelis M, Klein-Hitpass L, Kohrle J, Armstrong DL, Grontved L, Bassett JHD, Williams GR, Refetoff S, Fuhrer D, Moeller LC
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To read the full abstract: [Proc Natl Acad Sci U S A 2017;114:E11323-E11332](https://doi.org/10.1073/pnas.1711132114)

The mechanism of thyroid hormone (TH) action is classically attributed to thyroid hormone receptor (THR) binding to thyroid hormone responsive elements (TRE) in promoters of target genes, directly controlling gene expression in target tissues. Thus, THRs alpha (TRa) and beta (TRb) function as TH dependent transcription factors. A recent new nomenclature proposed by Flamant et al. in 2017 classified this canonical TH signaling through binding of TH to either TRa or TRb as THR-dependent signaling of TH with direct binding to DNA (type 1)¹.

However, recent data described in detail a direct activation of the PI3K pathway by

THR-dependent signaling without DNA binding (type 3) being essential for normal development of hippocampal synapses in the mouse². However, besides synapse development, knowledge on the role of this noncanonical TH/THR signaling is scarce. Here, Hones et al. used different mouse models to dissect the different roles and actions of canonical *versus* noncanonical TH/THR signaling. They compared in detail the phenotypes of THR knockout mice (with abolished canonical and noncanonical TH/THR signaling), with a newly generated mouse model abolishing selectively THR binding to TREs (abolished canonical signaling), but with preserved binding of TH to mutated THR (noncanonical signaling). The key findings were that the metabolic and cardiac actions of TH were not disrupted if canonical TH action (type 1, THR binding to DNA) was abolished. In summary, this paper extends our knowledge on thyroid hormone physiology by providing evidence for noncanonical type 3 TH/THR signaling (without DNA binding) by both TRa and TRb to regulate energy metabolism (body temperature, blood glucose, and lipid levels) and cardiac function (heart rate).

1. Flamant F, Cheng SY, Hollenberg AN, Moeller LC, Samarut J, Wondisford FE, Yen PM, Refetoff S. Thyroid hormone signaling pathways: time for a more precise nomenclature. *Endocrinology* 2017;158:2052-57.

2. Martin NP, Marron Fernandez de Velasco E, Mizuno F, Scappini EL, Gloss B, Erxleben C, Williams JG, Stapleton HM, Gentile S, Armstrong DL. A rapid cytoplasmic mechanism for PI3 kinase regulation by the nuclear thyroid hormone receptor, TRbeta, and genetic evidence for its role in the maturation of mouse hippocampal synapses *in vivo*. *Endocrinology* 2014;155:3713-3724.

DOI:10.1530/ey.15.3.4

3.5 Controlled Antenatal Thyroid Screening II: effect of treating maternal suboptimal thyroid function on child cognition

Hales C, Taylor PN, Channon S, Paradise R, McEwan K, Zhang L, Gyedu M, Bakhsh A, Okosieme O, Muller I, Draman MS, Gregory JW, Dayan C, Lazarus JH, Rees DA, Ludgate M
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To read the full abstract: [J Clin Endocrinol Metab 2018;103:1583-1591](#)

The Controlled Antenatal Thyroid Screening (CATS) study started in 2002 and was the first randomized controlled trial to evaluate the effect of screening and treatment of mild hypothyroidism during pregnancy on child cognition¹. A large number of women (n=21,846) were recruited at a median of 12 gestational weeks in UK and Italy, and offspring of mothers with gestational mild hypothyroidism (median TSH 3.6 mU/L) or hypothyroxinemia (median FT4 11.1 pmol/L) were evaluated at age of 3 years. No difference in IQ was found then between children of treated and untreated mothers. The same results were confirmed by a more recent study (Casey et al.)² presented in the 2017 Yearbook. They reported no difference on offspring cognition up to age 5 years born to mothers treated or not treated for subclinical hypothyroidism (median TSH 4.4 mU/L) or hypothyroxinemia (median FT4 0.83 ng/dl) at 16.7 or 17.8 gestational weeks, respectively.

Here, Hales et al report CATSII, which is the age 9.5 years cognitive assessment of CATS children initially evaluated at 3 years, and represents the longest follow-up of a randomized controlled trial on this topic. Again, the authors found no difference in any IQ measure between offspring of treated or untreated mothers with suboptimal gestational thyroid function. However, a high number of children initially evaluated were lost to follow-up for CATSII: only 119/303 children of the original treatment group and 98/306 children of the control group were available for IQ testing at 9.5 years. On the other hand, here the authors also studied children of mothers with optimal gestational thyroid function from the original CATS cohort as a further control group. The authors did not find a significant difference in the odds of IQ <85 between offspring of mothers with optimal *versus* suboptimal gestational thyroid function, irrespective of treatment. In summary, there was a lack of treatment effect if started in the second trimester. However, the question remains, whether earlier intervention with LT4 substitution in the first trimester would have a positive effect on child cognitive development and at what TSH or FT4 levels such a treatment effect could be expected and treatment recommended. Further studies are awaited.

1. Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012; 366:493-501

2. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, Reddy UM, Wapner RJ, Thorp JM, Jr., Saade G, Tita AT, Rouse DJ, Sibai B, Iams JD, Mercer BM, Tolosa J, Caritis SN, VanDorsten JP, Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units N. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. *N Engl J Med* 2017; 376:815-825

DOI:10.1530/ey.15.3.5

Maternal thyroid disease during pregnancy

3.6 Maternal thyroid function and child educational attainment: prospective cohort study

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To read the full abstract: [BMJ 2018;360:k452](#)

The role of thyroid hormones during early gestation is well established by animal studies. In humans, previous studies have shown that maternal hypothyroxinemia was associated with either an early reduction in psychomotor scales (e.g. Bayley scale of infant development) or later in late infancy or adolescence. However, randomized controlled trials on the effect of antenatal screening and treatment of mild thyroid disorders did not show any difference in cognitive function between children of mothers treated and not treated (see also paper 3.6)^{1,2}.

The present observational study offers the advantage of a long-term assessment of school performance and education achievement in a large number of UK mother-children pairs. The authors found no significant difference in long-term school performance at any assessment for any thyroid disorder. They concluded that first trimester suboptimal thyroid function is unlikely to have effects on school performance.

The strengths of this important observational study are: 1) comparison of the effect over the whole spectrum of maternal thyroid diseases (subclinical and overt hypothyroidism, isolated hypothyroxinemia and subclinical and overt hyperthyroidism, isolated hyperthyroxinemia) on offspring intellectual development, 2) detection of maternal thyroid disease as early as in the first trimester, when embryonic cerebral development is completely dependent on transplacental transfer of maternal thyroid hormone, 3) evaluation of all children by "real-life" standardized school tests, and 4) re-evaluation of all children 3 times until 15 years of age. Interestingly, there were no expected trends of decreasing school performance with increasing severity of hypo- or hyperthyroidism. Two possible limitations need to be kept in mind: the small sample size with overt hypothyroidism (n=17 with TSH <10 mU/L; n=17 with TSH >10mU/L), and incomplete information on maternal iodine status. Nevertheless, these results are reassuring and important.

1. Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012; 366:493-501

2. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, Reddy UM, Wapner RJ, Thorp JM, Jr., Saade G, Tita AT, Rouse DJ, Sibai B, Iams JD, Mercer BM, Tolosa J, Caritis SN, VanDorsten JP, Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units N. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. *N Engl J Med* 2017; 376:815-825

DOI:10.1530/ey.15.3.6

Congenital hypothyroidism

3.7 Mean high-dose L-thyroxine treatment is efficient and safe to achieve a normal IQ in young adult patients with congenital hypothyroidism

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To read the full abstract: [J Clin Endocrinol Metab 2018;103:1459-1469](#)

The ESPE guidelines on CH recommend an initial LT4 dose of 10-15 microgram/kg per day¹. Infants with severe CH, defined by a very low pretreatment TT4 or FT4 concentration, should be treated with the highest initial dose. However, little is known about long-term effects on developmental and anthropometric outcomes in CH children treated with initial high doses (>10 microgram/kg/day).

The strength of this study by Aleksander et al. is the detailed characterization of the participants to provide comprehensive data on intellectual and somatic outcomes. No IQ difference could be found between patients and healthy siblings, considering all possible biases. Further, no difference was detected for any anthropometric or metabolic parameter. Most importantly, thyroid hormone levels during the critical period of the first 24 months had no influence on intellectual outcomes. Additionally, the authors performed a detailed meta-analysis of all available studies evaluating mean

IQ in the context of CH severity and LT4 starting dose (<8 microgram/kg/d; 8-10 microgram/kg/d; >10 microgram/kg/d). Complete raw datasets of 4 studies were provided by the principal investigators of those previous studies: Patients with severe CH showed significantly lower IQ than patients with mild/moderate CH if treated with LT4 doses of <8 micrograms/kg/d or 8-10 micrograms/kg/d. Only high dose LT4 treatment was able to protect patients with severe CH from IQ loss.

These important results advocate for high dose LT4 treatment without adverse effects in adult life in accordance with a recent study from New Zealand² and the current ESPE guidelines. Concerns raised recently concerning worse intellectual outcome in CH patients at the age of 11 years after episodes of overtreatment during the first two years of life³ were not confirmed in this study.

1. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, Polak M, Buler G; ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAAE; Congenital Hypothyroidism Consensus Conference Group. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. *J Clin Endocrinol Metab* 2014;99:363-384.

2. Albert BB, Heather N, Derraik JG, Cutfield WS, Wouldes T, Tregurtha S, Mathai S, Webster D, Jefferies C, Gunn AJ, Hofman PL. Neurodevelopmental and body composition outcomes in children with congenital hypothyroidism treated with high-dose initial replacement and close monitoring. *J Clin Endocrinol Metab* 2013;98:3663-3670.

3. Bongers-Schokking JJ, Resing WC, de Rijke YB, de Ridder MA, de Muinck Keizer-Schrama SM. Cognitive development in congenital hypothyroidism: is overtreatment a greater threat than undertreatment? *J Clin Endocrinol Metab* 2013;98:4499-4506.

DOI:10.1530/ey.15.3.7

Congenital hypothyroidism

3.8 Are lower TSH cutoffs in neonatal screening for congenital hypothyroidism warranted?

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To read the full abstract: [Eur J Endocrinol 2017;177:D1-D12](#)

Newborn screening (NBS) is an invaluable tool for identification of CH; however almost 70% of newborns worldwide do not benefit from NBS at all. In countries with NBS, lowering of TSH cut-offs over the years led to major controversy on the optimal TSH screening cut-off. In this very interesting debate paper, arguments are presented for and against the lowering of TSH cutoffs at NBS. The arguments in support of lowering TSH cutoffs are based on: 1) the higher detection rate and consequent higher

treatment rate of children with CH, and 2) the likelihood to improve health and developmental outcomes in early screened and treated infants. Arguments against lower TSH cut-offs are: 1) not all children detected by lower TSH cut-offs with mild CH would profit from treatment, and 2) an important proportion of mild CH detected by low TSH cut-offs were transient on re-evaluation at age 3 years.

The authors present all available data pro and contra TSH cut-off lowering. However, the debate remains unsolved in the absence of high-quality evidence and in light of studies with contradictory results, e.g. on developmental outcome in infants with mildly elevated TSH at NBS^{1,2,3}. All the authors agree on two further points: special attention should be given 1) to the iodine status of infants and mothers, and 2) to realize access to NBS programs and care for all newborns worldwide.

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2. Trumpff C, De Schepper J, Vanderfaeillie J, Vercruyse N, Van Oyen H, Moreno-Reyes R, Tafforeau J, Vandevijvere S. Neonatal thyroid-stimulating hormone concentration and psychomotor development at preschool age. *Arch Dis Child* 2016; 101:1100-1106

3. Lain SJ, Bentley JP, Wiley V, Roberts CL, Jack M, Wilcken B, Nassar N. Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. *Lancet Diabetes Endocrinol* 2016;4:756-765

DOI:10.1530/ey.15.3.8

3.9 Antithyroid drugs and congenital malformations: a nationwide Korean cohort study

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To read the full abstract: [Ann Intern Med 2018;168:405-413](#)

Newly-diagnosed or pre-existing Graves' hyperthyroidism affects up to 1% of all pregnant women and is associated with adverse effects on pregnancy outcome and offspring. Clinical care of women with hyperthyroidism during pregnancy remains challenging as antithyroid drugs (ATD) can be harmful to the fetus.

Here, Seo et al. analysed data from the Korean National Health Insurance Database on about 2.9 million mother-child pairs, to evaluate the association between first trimester ATD use and congenital malformations. The key findings of this important paper are: 1) increased risk for congenital malformations was identified for both methimazole (MMI) and propylthiouracil (PTU), but MMI was associated with higher risk for congenital malformations than PTU, confirming previous studies¹. 2) Most importantly, and for the first time, the authors provide evidence for a dose dependent

association of MMI with congenital malformations, further supporting caution with MMI use if a pregnancy is planned. Further studies are needed for more precise teratogenic threshold definition of MMI. 3) Women who switched from MMI to PTU during early pregnancy or even in the 3 months before conception had a similar risk for MMI associated congenital malformations as mothers who remained on MMI. This finding is of great interest and needs to be replicated by future studies.

In the context of their new findings, the authors discuss the current American Thyroid Association (ATA) guideline that recommends to switch from MMI to PTU during early pregnancy to avoid MMI associated malformations². They argue against an ATD switch because it exposes the embryo for a certain period to two different teratogens, further increasing malformation risk. The safest option seems to be to switch as early as possible from MMI to PTU in women who plan pregnancy. This paper provides important new information concerning risk of malformations and ATD use in pregnancy.

1. Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. *J Clin Endocrinol Metab* 2013;98:4373-4381.

2. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2017;27:315-389.

DOI:10.1530/ey.15.3.9

Graves' disease

3.10 Long-term outcome of thyrotoxicosis in childhood and adolescence in the west of Scotland: the case for long-term antithyroid treatment and the importance of initial counselling

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To read the full abstract: [Arch Dis Child 2018;103:637-642](https://doi.org/10.1136/archdischild.2018.103.637-642)

Management of thyrotoxicosis in children and adolescents remains challenging and treatment varies considerably among institutions. The patient's age, clinical status and likelihood of remission should be considered when counseling patients and parents. Nevertheless, individual prognosis of antithyroid drug treated Graves' disease in children is highly variable and studies with data on long-term outcome are scarce. Recommendation 58 of the 2016 American Thyroid Association guidelines state that children with Graves' disease can be treated with either methimazole or thyroidectomy at any age. Alternatively, radioiodine ablation is a further option, but not before 5 years of age, and between 5-10 years only if radioiodine activity is <10mCi.

In this retrospective study, Kourime et al. analyzed long-term outcomes in a cohort of pediatric patients with hyperthyroidism. First, they showed that the hyperthyroid phase

of Hashimoto's thyroiditis had a high remission rate, as expected from its pathophysiology. Second, they confirmed the low remission rate for Graves' disease, with a variable time for remission, and they advocate for individualized duration of antithyroid drug treatment instead of a standard (e.g. 2 years) treatment period. These findings corroborate previous recommendations by Léger et al.^{1,2} for continuous treatment, rather than treatment cycles of 2 years. Finally, the authors point out that adherence to ATD use and thyroxine replacement when needed was low, underlying the importance for initial education and counseling of families at diagnosis of thyrotoxicosis.

In the context of these remaining clinical and therapeutic problems in the treatment of pediatric Graves' disease, results from ongoing studies using new immune modulating therapies such as TSHR-specific antibodies are awaited.

1. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* 2016;1343-1421.

2. Leger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C, French Childhood Graves' Disease Study G. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. *J Clin Endocrinol Metab* 2012;97:110-119.

3. Leger J, Carel JC. Management of endocrine disease: arguments for the prolonged use of antithyroid drugs in children with Graves' disease. *Eur J Endocrinol* 2017;177:R59-R67.

DOI:10.1530/ey.15.3.10

Pediatric thyroid cancer

3.11 DICER1 mutations are frequent in adolescent-onset papillary thyroid carcinoma

Wasserman JD, Sabbaghian N, Fahiminiya S, Chami R, Mete O, Acker M, Wu MK, Shlien A, de Kock L, Foulkes WD

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To read the full abstract: [J Clin Endocrinol Metab 2018;103:2009-2015](#)

Thyroid cancer in children and adolescents has a higher rate of regional and distant metastases, and recurrence rate than in adults. However, little is known about the molecular origin of thyroid carcinoma in children. *DICER1* encodes for an endoribonuclease responsible for processing RNA into small interfering RNA and miRNA. *DICER1* syndrome (OMIM #601200) has been recently described resulting

from truncating mutations in the *DICER1* gene causing a wide spectrum of benign and malignant tumors in children, such as pleuropulmonary blastoma, cystic nephroma, and pituitary blastoma. The risk for multinodular goiter and thyroid cancer in *DICER1* germline mutation carriers has recently been shown to be highly increased¹.

Here, Wasserman et al. investigated the prevalence of *DICER1* mutations in thyroid specimens after thyroidectomy in pediatric patients with personal or family history of syndromic cancers. In contrast to data from adult thyroid cancer series with very low prevalence of *DICER1* mutations, *DICER1* mutations were found in a high proportion of pediatric tissues. Histology in the tissues with *DICER1* mutations was classified as either papillary thyroid carcinoma, or benign follicular nodular disease. Somatic genetic alterations in *DICER1* need to be considered as a new cause of papillary thyroid carcinoma in the pediatric age group.

1. Khan NE, Bauer AJ, Schultz KAP, Doros L, Decastro RM, Ling A, Lodish MB, Harney LA, Kase RG, Carr AG, Rossi CT, Field A, Harris AK, Williams GM, Dehner LP, Messinger YH, Hill DA, Stewart DR. Quantification of thyroid cancer and multinodular goiter risk in the *DICER1* syndrome: a family-based cohort study. *J Clin Endocrinol Metab* 2017;102:1614-1622.

DOI:10.1530/ey.15.3.11

Pediatric thyroid cancer

3.12 Thyroid nodules in pediatric patients: sonographic characteristics and likelihood of cancer

Richman DM, Benson CB, Doubilet PM, Peters HE, Huang SA, Asch E, Wassner AJ, Smith JR, Cherella CE, Frates MC

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To read the full abstract: [Radiology 2018;171170](#)

Current American Thyroid Association (ATA) guidelines recommend the application of adult ultrasound criteria to classify thyroid nodules in children and adolescents¹. However, few studies have evaluated the sonographic and demographic features that

could predict malignancy in a large cohort of young patients with thyroid nodules. Here, Richman et al. report the largest series so far of sonographic features of pediatric thyroid nodules/cancers. First, the study confirmed earlier results of higher rates of malignancy in thyroid nodules in pediatric patients than in adults. Second, the authors confirmed that criteria for malignancy in adults were useful in children. Further, in contrast to adults, they revealed that risk for malignancy increased with size of the nodule in the pediatric age group. In summary, these results provide a specific pediatric view on thyroid nodules, sharpening our eyes, but not changing the current criteria for indication of fine needle aspiration.

1. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinayer CA, Hamilton J, Hay ID, Luster M, Parisi MT, Rachmiel M, Thompson GB, Yamashita S, American Thyroid Association Guidelines Task Force. Management Guidelines for children with thyroid nodules and differentiated cancer. *Thyroid* 2015;25:716-759.

DOI:10.1530/ey.15.3.12

Thyroid stem cells

3.13 Pluripotent stem cell differentiation reveals distinct developmental pathways regulating lung- versus thyroid-lineage specification

Serra M, Alysandratos KD, Hawkins F, McCauley KB, Jacob A, Choi J, Caballero IS, Vedaie M, Kurmann AA, Ikonoumou L, Hollenberg AN, Shannon JM, Kotton DN

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To read the full abstract: [Development 2017;144:3879-3893](#)

Regenerative medicine techniques are being widely investigated for organs without regenerative capacity, such as lung. Whether pluripotent stem cell derived thyroid

organoids will be used in the future as a regenerative medicine approach to treat hypothyroidism is unclear. In the context of an easily available, very cheap and non-invasive substitutive therapy with levothyroxine, the cost-risk balance clearly speaks against such a novel approach. However, as pneumocyte and thyroid follicular cell precursors share a key transcription factor, NKX2-1, research in the field of lung development always gives new insights into thyroid development. In 2015, these authors published a paper detailing the generation of differentiated and functionally active thyroid follicular cells from induced pluripotent stem cells¹. Chemical activation of specific pathways resulted in successful lineage induction. In this current paper, they further optimized their protocols to independently generate thyroid and lung progenitors from mouse and human pluripotent stem cells, that are highly useful for regenerative medicine or *in vitro* pharmaceutical or developmental studies.

1. Kurmann AA, Serra M, Hawkins F, Rankin SA, Mori M, Astapova I, Ullas S, Lin S, Bilodeau M, Rossant J, Jean JC, Ikonoumou L, Deterding RR, Shannon JM, Zorn AM, Hollenberg AN, Kotton DN. Regeneration of thyroid function by transplantation of differentiated pluripotent stem cells. *Cell Stem Cell* 2015;17:527-542.

DOI:10.1530/ey.15.3.13

ATA Scientific statement

3.14 American Thyroid Association Scientific Statement on the use of potassium iodide ingestion in a nuclear emergency

Leung AM, Bauer AJ, Benavente S, Brenner AV, Hennessey JV, Hurley JR, Milan SA, Schneider AB, Sundaram K, Toft DJ
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UCLA David Geffen School of Medicine, Los Angeles, California

To read the full abstract: [Thyroid 2017;27:865-877](#)

This very complete paper reviews all available knowledge and information on three main aspects of a nuclear emergency and prevention of thyroid cancer by ingestion of

potassium iodide: geographical, legal, logistic and communication aspects are discussed for an optimal protection of the population at risk in case of nuclear emergency. Further, health effects of radioactive iodine (^{131}I) for thyroid disease are discussed in detail. Of special interest are the potential routes of ^{131}I isotope exposure, such as inhalation of radioactive gases, and ingestion of ^{131}I by directly contaminated food (vegetables), or uptake of accumulated ^{131}I in meat or milk from cows, that ingested contaminated pasture grasses. All information rely on experiences and studies after three major nuclear accidents: Three Mile Island (1979), Chernobyl (1986), and Fukushima (2011) comparing radiation doses and other relevant parameters of nuclear contamination. Finally, the evidence for potential benefit, the necessary doses, and potential side effects are presented in detail. This is an important and comprehensive statement of the American Thyroid Association (ATA), especially for populations living in the proximity of nuclear plants.

DOI:10.1530/ey.15.3.14

Post-Fukushima thyroid cancer risk

3.15 Japanese food data challenge the claimed link between Fukushima's releases and recently observed thyroid cancer increase in Japan

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Hannover, Germany

To read the full abstract: [Sci Rep 2017;7:10722](#)

This paper elegantly describes how precise quantification of ingested radioactive iodine in the Japanese population was measured after the Fukushima catastrophe. The mainstay of such a detailed analysis by the Ministry of Health, Labor and Welfare was

the sequential quantification and documentation of all sources of radioactive iodine ingestion in the air, and in the complete food chain in all relevant geographic regions starting within one week after the Fukushima nuclear fallout. As the food chain is the most important source of radioactive iodine over months after a nuclear emergency, the authors gathered all available data from pre- and post-market specimens of vegetables (above ground and below ground), fruits and berries, mushrooms, algae, fishery products, cattle milk and dairy products from the databases of the Ministry of Health, Labor and Welfare to get a comprehensive picture of average radioactive concentrations over time for the Japanese population. The authors then modelled, in conservative worst-case scenarios, exposure dose estimates for all age groups including infants, 1-6 year old children, 7-14 years old children, 15-19 year old adolescents and for each decade of adult life. Their conclusions are highly reassuring; however, the future will tell if these models were precise enough to realistically predict thyroid cancer risks.

DOI:10.1530/ey.15.3.15

Reviews

3.16 Global epidemiology of hyperthyroidism and hypothyroidism

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The authors provide complete information as far as available on the prevalence of hypothyroidism, hyperthyroidism and iodine deficiency all over the world. Nutritional iodine is a key determinant of thyroid disease risk. Further factors influencing thyroid disease prevalence are smoking, ageing, genetic susceptibility, and endocrine disruptors. Finally, a new risk group for thyroid disease are patients treated with novel therapeutics, including immune checkpoint inhibitors. This highly interesting paper reveals geographical differences and regions where action is needed for better thyroid health of their populations.

DOI:10.1530/ey.15.3.16

To read the full abstract: [Nat Rev Endocrinol 2018;14:301-316](#)

3.17 Diagnostic utility of molecular and imaging biomarkers in cytological indeterminate thyroid nodules

de Koster EJ, de Geus-Oei LF, Dekkers OM, van Engen-van Grunsven I, Hamming J, Corssmit EPM, Morreau H, Schepers A, Smit J, Oyen WJG, Vriens D
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To read the full abstract: [Endocr Rev 2018;39:154-191](#)

This extensive paper reviews current state of knowledge concerning possible diagnostic accuracy of all available biomarkers used for molecular diagnostics and in nuclear medicine for investigation of thyroid nodules of indeterminate cytology.

DOI:10.1530/ey.15.3.17

Growth and Growth Factors

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Several interesting articles have been published in the field of growth and growth factors during the last twelve months. Here, we report a series of papers mainly selected on the basis of their potential clinical impact. A group of papers focused on the efficacy and/or safety of GH treatment in different conditions associated with short stature, such as Prader-Willi syndrome, GH deficiency alone or associated with

type 1 diabetes, small-for-gestational age and achondroplasia. The use of a combination of genomic analyses has allowed the detection of new genetic variants associated with different forms of intrauterine growth retardation, including small-for-gestational age and Silver-Russell syndrome. In this context, a new definition of fetal growth restriction to be adopted in clinical practice and in clinical trials has been provided by an international panel of experts. Activating mutations in the STAT3 gene have been associated with immune dysfunction and severe growth failure. The prevalence of ACAN gene mutations in a large cohort of subjects with idiopathic short stature has been reported for the first time. Interestingly, a large-scale population-based study has related childhood stature with ischemic stroke and intracerebral hemorrhage. Finally, the key role of IGF2 in cartilage development and glucose metabolism during postnatal long bone growth has been elucidated in an elegant *Igf2* knockout murine model. We hope you find the selected papers helpful for your daily work as a clinician or researcher in the fascinating field of growth and growth disorders.

DOI:10.1530/ey.15.4

Important for clinical practice

4.1 Growth hormone treatment in children with Prader-Willi syndrome: three years of longitudinal data in prepubertal children and adult height data from the KIGS database

Bakker NE, Lindberg A, Heissler J, Wollmann HA, Camacho-Hübner C, Hokken-Koelega AC, on behalf of the KIGS Steering Committee
Dutch Growth Research Foundation, Rotterdam, The Netherlands

To read the full abstract: [J Clin Endocrinol Metab 2017; 102:1702-1711](#)

Short stature is a common feature of children with Prader-Willi syndrome (PWS) as well as hypotonia, hyperphagia, obesity, hypogonadism, behavioral disturbances and hypothalamic dysfunction. Alterations in the GH/IGF1 axis are common in patients with PWS, GH deficiency occurring in approximately 74% and IGF-1 deficiency in nearly 100% [1]. These patients show reduced spontaneous 24-hour GH secretion, insufficient response to GH stimulation testing, sub-normal levels of IGF-1 and reduced pubertal spurt. GH treatment increases height in PWS children and, besides its positive effects on growth, improves body composition, motor development, energy expenditure, bone mineralization and cardiovascular health. Although GH is widely used in PWS patients, the available evidence on long-term efficacy and safety on a large cohort of GH-treated PWS children are limited.

This study sheds light on the long-term efficacy of GH treatment in PWS children by analysing data collected in the largest available international database. Although GH therapy was far less effective in stimulating growth than in non-PWS GH subjects, these results confirm the effectiveness of this treatment in children with PWS leading to an average final height of -1.2 SDS, corresponding to 170 cm in males and 156 cm in girls, consistent with previous studies performed in smaller numbers [2-4]. GH was effective not only in increasing height but also in controlling the progression of obesity. BMI increased during GH treatment, but remained within the normal range, in contrast to the natural tendency of progressive worsening of obesity in children with PWS. Consistent with this finding are previous reports showing an improvement of body composition [5-8].

The overall safety of GH therapy was satisfactory with a mortality rate less than the reported 3% annual mortality rate in patients with PWS younger than 30 years [9].

Nevertheless, the high number of patients with scoliosis and sleep apnea as well as the occurrence of diabetes mellitus (10 cases) and leukemia (2 cases) suggest the need of close monitoring of patients with PWS in general and particularly in those undergoing GH therapy [10].

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DOI:10.1530/ey.15.4.1

Important for clinical practice

4.2 Efficacy of growth hormone treatment in children with type 1 diabetes mellitus and growth hormone deficiency-an analysis of KIGS data

Bonfig W, Lindberg A, Carlsson M, Cutfield W, Dunger D, Camacho-Hübner C, Holl RW

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To read the full abstract: [J Pediatr 2018; 198: 260-264](#)

The incidence of T1DM in children <15 years is increasing at an overall annual relative rate of 3.9% (95% CI 3.6-4.2) [11]. The prevalence of GHD is estimated at approximately 1:4000 to 1:10000 [12-14]. Management of the very rare patients who have both T1DM and GHD raises questions of efficacy and safety of GH therapy. Treatment adds to their multiple daily injections and, while insulin is a life-saving therapy, GH is not, leading to consider short stature a less relevant problem and consequently reducing the adherence to GH therapy in the long run. Moreover, GH and insulin exert opposite effects on glucose metabolism, GH antagonizing insulin action, so discouraging its use in T1DM.

To date, only sporadic case reports and very few studies have assessed the results of GH therapy in children with GHD and T1DM. A recent study in a small cohort of Italian children showed that GH treatment in T1DM children is effective and safe [15]. Consistently, Bonfig et al. here describe a larger retrospective study, reporting that GH treatment induces similar growth responses in GHD children, with or without T1DM, and raising no safety issues. These findings are in contrast with previous results showing that GH treatment is less effective in promoting growth when both diseases coexist, showing a median height gain of only 0.3 SDS over a 2-year course of treatment [16]. This discrepancy may depend on the late diagnosis and start of GH

treatment and/or inadequate GH dosage out of concern for metabolic side effects in that older study. Unfortunately, in the current study no information regarding metabolic profile and insulin demands during GH treatment was provided. Another major weakness is the short-term analysis, which focused only on the first year growth response.

Overall, these recent findings suggest that the diagnosis of T1DM should not discourage GH replacement therapy in truly GH deficient patients, although the decision to start this kind of multi-injection therapy should be limited to "classical" GHD and should be carefully weighed taking into account the burden for the patients and their families. Further studies are needed to evaluate the efficacy and safety of long-term GH therapy and its impact on metabolic profile and insulin requirement in children with T1DM.

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DOI:10.1530/ey.15.4.2

Important for clinical practice

4.3 Cardiovascular risk factors and carotid intima media thickness in young adults born small for gestational age after cessation of growth hormone treatment: a 5-year longitudinal study

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To read the full abstract: [Lancet Diabetes Endocrinol 2017;5:975-985](#)

Whereas most SGA children experience spontaneous catch-up growth leading to the achievement of normal adult height, approximately 10% remain short and are candidates for GH therapy. SGA subjects have increased cardio-metabolic disease risk [17] and the effects of GH treatment on blood pressure, body composition, glucose metabolism and lipid profile have been investigated [18]. Recently, interest has been focused on the cardiovascular disease risk in adults treated with GH during childhood. Data from the French SAGhE (Safety and Appropriateness of GH therapy in Europe) study cohort have shown increased cerebrovascular mortality rate [19], although not confirmed in other SAGhE cohorts [20]. In theory, children born SGA, having intrinsic higher cardio-metabolic risk, might be at even higher risk if exposed to long-term GH therapy.

This longitudinal study evaluated cardiovascular disease risk factors in SGA young adults, treated with GH during childhood and followed-up for 5 years after therapy discontinuation. Five years after cessation of GH therapy, blood pressure and cIMT were similar between treated and untreated SGA. Furthermore, after an initial increase

probably due to gains in fat mass, lipid levels tended to be lower in treated than in untreated SGA. Finally, GH treatment was not associated with increased risk of metabolic syndrome. These findings are consistent with previous data showing no adverse effect of GH therapy on the metabolic profile of young adults treated with GH during childhood and observed for 5 years after cessation of treatment [21].

Overall, these results are reassuring, showing no potential adverse effect of GH therapy on cardio-metabolic health of SGA subjects and suggest that GH treatment may be even beneficial for lipid profile. However, longer follow-up studies are needed to monitor the possible occurrence of cardio-metabolic diseases many years after GH therapy cessation.

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DOI:10.1530/ey.15.4.3

Important for clinical practice

4.4 Consensus Based Definition of Growth Restriction in the Newborn

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To read the full abstract: [J Pediatr 2018; 196:71-76](#)

Fetal growth restriction describes a fetus who fails to achieve their biological growth potential, remaining smaller than its genetic potential, and occurs in ~10% of pregnancies [22]. FGR and SGA are terms that are often and wrongly used in an interchangeable way. SGA does not inevitably entail a pathological condition, but rather is based on a statistical deviation of size from population-based references. By contrast, FGR indicates that the fetus has not reached its optimal growth, due to some underlying problem. Recently, using a Delphi procedure, a consensus definition of FGR was achieved [23]. That definition was based on antenatal ultrasound parameters, and provided clear criteria to distinguish between SGA and FGR, allowing tailored monitoring and management.

Here, Beune et al. describe a consensus-based definition of growth restriction in newborns, including, for the first time, not only auxological measures but also prenatal

factors. Birth weight <3rd percentile is only parameter that allows the diagnosis of growth restriction on its own. Otherwise at least 3 of 5 defined criteria have to be fulfilled. This study underlines that the commonly used single cut-off of birth weight (or birth length) <10th percentile can be misleading, as this includes many non-growth restricted subjects, whereas other growth restricted newborns can exceed this threshold. The Delphi procedure, used to reach these consensus-definitions, involved a panel of experts, who received feedback on the results of the previous round, while in subsequent rounds, questions became more precise to reach consensus [24]. One of the strengths of this procedure is the anonymity of individual responses, ruling out the influence of dominant individuals and peer pressure.

This consensus fills the void of a universally accepted definition of growth restriction in newborns, which has led to communication problems between healthcare professionals and has prevented comparison of cohorts and studies. However, a consensus-based agreement does not last perpetually. Over time, changes may be required as new evidence arises. Future studies should prospectively test the utility of this consensus definition.

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DOI:10.1530/ey.15.4.4

Important for clinical practice

4.5 Growth hormone improves cardiopulmonary capacity and body composition in children with growth hormone deficiency

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To read the full abstract: [J Clin Endocrinol Metab 2017; 102\(11\):4080-4088](#)

GH influences the structure and function of the heart. Untreated GHD adults have a worse cardiometabolic disease risk profile characterized by altered body composition, unfavorable changes in metabolism, reduced left ventricular mass and cardiac output and decreased exercise capacity [25-26]. GH replacement therapy normalizes the parameters associated with higher cardiovascular disease risk [27]. In children, GH replacement therapy, although mainly used to improve linear growth, has also effects on lipids, body composition and cardiovascular disease risk factors. The impact of

GHD and GH replacement therapy on cardiopulmonary functional capacity of paediatric patients is unknown.

Consistent with findings in GHD adults, this prospective paediatric case-control study clearly shows that GHD affects cardiac structure, body composition and cardiopulmonary functional capacity and short-term GH therapy normalizes these features. On the basis of these results, the authors go as far as suggesting to perform cardiopulmonary exercise stress testing in the baseline evaluation of untreated GHD patients to unmask mild alterations of aerobic capacity. However, this advice is based on data on a small group of 21 patients. Further studies on larger cohorts of GHD children are needed before drawing definitive conclusions.

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DOI:10.1530/ey.15.4.5

New therapeutic options

4.6 Final adult height in long-term growth hormone-treated achondroplasia patients

Harada D, Namba N, Hanioka Y, Ueyama K, Sakamoto N, Nakano Y, Izui M, Nagamatsu Y, Kashiwagi H, Yamamuro M, Ishiura Y, Ogitani A, Seino Y
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To read the full abstract: [Eur J Pediatr 2017; 176:873-879](#)

Achondroplasia (ACH) is the most common genetic form of disproportionate short stature, occurring in 1:15,000–1:40,000 live births [28]. Most patients have a gain of function mutation in the transmembrane domain of the fibroblast growth factor receptor 3 (FGFR3), leading to prolonged intracellular MAPK signaling. FGFR3 works as a negative regulator of bone development. FGFR3 over-activation alters the terminal chondrocyte differentiation into hypertrophic chondrocytes, shortening the proliferation phase. ACH involves long bones, vertebrae and base of skull, resulting in short-limbed severe short stature, relative macrocephaly with prominent forehead, midface hypoplasia, lumbar lordosis, trident configuration of hands and hydrocephalus, secondary to foramen magnum narrowing. ACH patients have severe growth retardation and experience decreased pubertal growth spurt, ultimately leading to extremely short adult height which on average is 130 (118–145) cm in males and 120 (112–136) cm in females.

Currently, few therapeutic options are available and effective treatment is still lacking. Limb lengthening remains the most effective measure to increase final height in ACH patients. However, this surgical procedure is associated with many co-morbidities,

including stiffness of the Achilles tendon, recurrent fractures, asymmetry of the legs, focal bacterial infection, and pain. A recent paper reported that the overall height increase obtained with limb lengthening ranges from 6 to 12 cm [29]. Several trials have evaluated the effect of GH treatment in ACH children, and a recent meta-analysis reported a change in mean height SDS from -5.0 to -4.0 during 5-years GH treatment [28]. However, the data are limited by small sample sizes, poor study design, and lack of intention-to-treat analyses.

Here, Harada et al. report a retrospective study showing that the increase in adult height attributable to GH therapy was on average 3.5 cm in males and 2.8 cm in females, slightly improving the effect obtained by limb lengthening alone. The wide individual variability in the response to therapy suggests that other factors such as genetic background, dose, age at start, adherence and duration of treatment may influence the long-term response. Unfortunately, study limitations such as the retrospective design, the small number of patients and the heterogeneous treatment regimens make this study inconclusive. Although ACH is an approved indication for GH therapy in Japan, there is no robust evidence that this treatment is worthwhile. As the pathogenesis of ACH is related to defects in enchondral ossification due to FGFR3 gain of function mutations, future targeted treatments might rely on the use of inhibitors of receptor signaling, antibody blockade of receptor activation, and negative interference with FGFR3 downstream pathways [30].

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DOI:10.1530/ey.15.4.6

4.7 Hypomethylation of HOXA4 promoter is common in Silver-Russell syndrome and growth restriction and associates with stature in healthy children

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To read the full abstract: [Sci Rep 2017; 16:7:15693](https://doi.org/10.1038/s41598-017-15693-2)

SRS is a rare congenital disorder, characterized by intrauterine growth restriction, postnatal growth impairment and a wide range of signs and symptoms such as dysmorphic features, severe feeding difficulties, body asymmetry, and neurodevelopmental delay. The molecular etiology is heterogeneous. Loss of methylation on chromosome 11p15 (11p15LOM) is detected in 20-60% and maternal uniparental disomy of chromosome 7 (mUPD7) in approximately 5-10%. Other chromosome abnormalities may occur in single cases. Nevertheless, in 40% of SRS cases the molecular etiology is unknown. SRS is currently a clinical diagnosis based

upon the Netchine-Harbison scoring system (NH-CSS) [31].

The current study, using a genome-wide DNA methylation analysis, shows the presence of an epigenetic feature shared by most SRS subjects, independently of the molecular etiology. The HOXA4 gene region was hypomethylated in 55% of SRS subjects. HOXA4 hypomethylation was present also in the majority of subjects with severe intrauterine growth restriction and was also correlated with short stature in healthy subjects (controls). Hypomethylation of the HOXA4 promoter region has been associated with increased expression of HOXA4 in blood [32], indicating that this region influences gene expression. HOXA4 belongs to the Homeobox (HOX) gene family, encoding transcription factors that regulate various functions, including cell differentiation and embryonic development. Several HOX genes have been related to human disorders including skeletal abnormalities suggesting that abnormal HOXA4 methylation may be involved in the skeletal malformations observed in many SRS patients. In addition, the methylation of HOXA3, a gene mapping near HOXA4, has been related to birth weight, suggesting a role of this region on human growth. Limitations of the study include the poor characterization of the SRS subjects, involving a mixture of adult and pediatric patients and a vague diagnosis of "severe growth restriction". Furthermore, methylation varies with time and the age at analysis may affect results. Nevertheless, this study opens new avenues for epigenetic investigations in the field of human growth.

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4.8 Targeted next generation sequencing approach in patients referred for Silver-Russell syndrome testing increases the mutation detection rate and provides decisive information for clinical management

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To read the full abstract: [J Pediatr 2017; 187:206-12](#)

SRS is a clinically heterogeneous imprinting disorder. Although the understanding of its genetic basis has gradually advanced, about 40% of patients still have an unknown molecular defect. In subjects with unknown etiology, diagnosis is primarily clinical, based upon the Netchine-Harbison scoring system (NH-CSS) [31]. However, several diseases have signs and symptoms that overlap with the clinical features of SRS, and differential diagnosis includes a wide range of genetic disorders.

This study examined a cohort of children with a clinical diagnosis of SRS based on NH-CSS. The use of a targeted next generation sequencing (NGS) approach, comprising genes associated with differential diagnoses of SRS or proposed as SRS candidate genes, increased the detection rate of disorders overlapping with SRS. In 4 of the 15 patients with NH-CSS based clinical diagnosis, a genetic cause was identified (namely Bloom syndrome, Mulibrey nanism, KBG syndrome, IGF1R), thus leading to a detection rate for disease-causing mutations of 26.7%. These results also indicate

that the application of targeted NGS analysis significantly increases the current (epi)mutation detection rate up to approximately 70% of patients with NH-CSS defined SRS. The identification of a specific molecular defect is needed not only to confirm the clinical diagnosis, but also to subdivide patients into specific molecular subgroups and offer a tailored management and therapeutic approach. The mutations detected in this cohort of SRS patients included a pathogenic mutation causing Bloom syndrome, a rare genetic disorder characterized by high likelihood of developing cancers thus representing a contraindication for GH therapy, commonly used in SRS to treat short stature. Another genetic condition detected by targeted NGS was Mulibrey nanism, a rare autosomal recessive condition presenting with severe pre- and post-natal growth failure, characteristic dysmorphic features but normal neurological development. The phenotype of Mulibrey nanism is variable and may overlap with SRS [33]. Its diagnosis should prompt cardiac assessment and follow-up as cardiac complications are a characteristic feature. Moreover, in Mulibrey nanism, the risk for Wilms tumors and ovarian fibrothecomas is increased. Notably, no mutations were detected in subjects without a clinical score indicative of SRS, thus underlining the importance of a careful physical examination and precise phenotyping to drive genetic analysis.

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DOI:10.1530/ey.15.4.8

4.9 Childhood stature and growth in relation to first ischemic stroke or intracerebral hemorrhage

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To read the full abstract: [Stroke 2018;49:579-585](#)

Height is regulated by interplay of several factors, including genetic background, intra- and extra-uterine environment, nutrition, and others. Adult height has been inversely related with stroke risk [34] and coronary artery disease [35]. Only a few small studies [36-37] have addressed the relationship between childhood height and stroke risk. This large-population based study shows a significant association between childhood height at age 7 to 13 and risk of both IS and ICH in men and IS in women. Growth between 7 and 13 years of age was not associated with risk of IS and ICH. The results of this study are consistent with previous findings showing an association between short stature and risk of both stroke and coronary artery disease. However, overweight and obesity may be potential confounding factors as they are associated with higher risk of stroke in adulthood [38]. Unfortunately, the authors did not take into account the potential effect of weight or BMI, as well as lipid profile and blood

pressure, in the association analysis. The proposed explanation for this association was that childhood height is an indicator of other factors experienced during early life, maybe *in utero*, expressing their effects on growth as well as on stroke risk in adulthood. An alternative and simpler explanation is that height and other measurements of body size have a positive correlation with the diameter of arteries. In shorter individuals, the proportionally smaller caliber of arteries facilitates the development of atherosclerotic plaque thus predisposing to higher risk of stroke.

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DOI:10.1530/ey.15.4.9

4.10 Genetic screening confirms heterozygous mutations in *ACAN* as a major cause of idiopathic short stature

Hauer NN, Sticht H, Boppudi S, Büttner C, Kraus C, Trautmann U, Zenker M, Zweier C, Wiesener A, Jamra RA, Wiczorek D, Kelkel J, Jung AM, Uebe S, Ekici AB, Rohrer T, Reis A, Dörr HG, Thiel CT
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To read the full abstract: [Sci Rep 2017; 22\(7\):12225](#)

The GH/IGF1 axis has historically been considered the most relevant regulator of growth. However, defects in the GH/IGF1 axis can be identified only in a minority of children with short stature. Human growth is dependent on chondrocyte proliferation and hypertrophy as well as structure and function of extracellular matrix in the growth plate [39]. The rate of growth plate chondrogenesis is regulated by many intracellular, paracrine and extracellular matrix factors, as well as endocrine mechanisms. Aggrecan, encoded by *ACAN* gene, is the most abundant proteoglycan of the growth plate cartilage and plays a key role in cartilage and bone morphogenesis. The *ACAN* gene mutation leads to aggrecan deficiency, abnormal structure of the cartilage extracellular matrix, decreased chondrocyte proliferation, and accelerated hypertrophic chondrocyte differentiation.

The clinical spectrum associated with *ACAN* mutations ranges from spondyloepimetaphyseal dysplasia, characterized by severe short stature, brachydactyly, and midface hypoplasia, to milder skeletal dysplasia, associated with variably compromised adult height. ISS has recently been associated with *ACAN*

haploinsufficiency. Carriers of heterozygous mutations in *ACAN* have short stature with normal, delayed or advanced BA, early growth cessation, early-onset osteoarthritis and degenerative disc disease, suggesting dysfunction of the articular cartilage and intervertebral disc cartilage [40].

The present study identified heterozygous defects in *ACAN* in 6 of 428 patients with the "diagnosis" of ISS (1.4%), suggesting that *ACAN* mutations may be the most common cause of ISS after deletions and mutations of the *SHOX* gene, which account for ~2.4% of ISS patients [41]. The reported patients' height varied between -0.9 and -5.9 SDS but a genotype-phenotype relationship was not found. Most of these patients presented an advanced bone age and proportionate or mildly disproportionate short stature. Three patients in this study showed delayed bone age, suggesting that bone age advancement has no predictive value for *ACAN* mutations. The identification of *ACAN* mutations may have therapeutic implications as anecdotal evidence suggests a modest response to GH, of a similar magnitude to that seen in ISS [40-42]. In conclusion, these findings suggest that *ACAN* mutations are a relatively common cause of short stature and have to be considered in the differential diagnosis of ISS.

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DOI:10.1530/ey.15.4.10

New perspectives

4.11 Genetic analyses in small-for-gestational-age newborns

Stalman SE, Solanky N, Ishida M, Alemán-Charlet C, Abu-Amro S, Alders M, Alvizi L, Baird W, Demetriou C, Henneman P, James C, Knecht LC, Leon LJ, Mannens MMAM, Mul AN, Nibbering NA, Peskett E, Rezwan FI, Ris-Stalpers C, van der Post JAM, Kamp GA, Plötz FB, Wit JM, Stanier P, Moore GE, Hennekam RC

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To read the full abstract: [J Clin Endocrinol Metab 2018; 103:917-925](#)

SGA is often defined as a birth weight and/or length < -2 SDS for gestational age and gender [43]. A frequent cause of SGA is fetal growth restriction (FGR), often associated with perinatal mortality and morbidity and also implicated in a higher risk of cardio-metabolic disease in adulthood. Currently, no tools are available to predict or prevent FGR. Both genetic and environmental factors may affect fetal growth, but the underlying molecular mechanisms are still unclear. Genetic and epigenetic factors account for 30-50% of the variation in birth weight [44]. Chromosomal anomalies account for up to 19% of FGR fetuses, while the rate of submicroscopic duplications/deletions and single-gene disorders in FGR with normal karyotype is not defined [44]. A recent study showed that genomic microarray analysis (CMA) identifies sub-microscopic anomalies in 6.8% of fetuses with early growth restriction after common aneuploidies were excluded [45]. To date, the use of CMA is recommended for a fetus with one or more major malformations identified by ultrasound. Epigenetic mechanisms also explain abnormal fetal growth in conditions such as Silver-Russell and Beckwith-Wiedemann syndrome.

Here, Stalman et al. investigated the efficacy of a combined genomic analysis to achieve a molecular diagnosis in SGA newborns. In 19% of SGA subjects, the

combination of array-CGH, genome-wide methylation disturbances and whole exome sequencing identified a genetic abnormality, likely responsible for the low birth weight. Array-CGH yielded abnormalities in three patients: i) mosaic trisomy of chromosome 16; ii) mosaic monosomy X; and iii) deletion of 11p13-p14.1 causing WAGR syndrome (Wilms tumor, aniridia, genital anomalies, and mental retardation). Differential methylation was seen in 12 patients, of whom 9 had differential methylation in more than one gene. A methylation abnormality potentially involved in SGA was detected in imprinted genes at the 11p15.5 region associated with FGR: CDKN1C, KCNQ1, IGF2AS, INS, and IGF2. CNVs were identified in 14% of patients, a rate higher than that previously reported in SGA [46]. Most variants detected by exome sequencing were of unclear clinical relevance. These findings point out that the cause of FGR is polygenic and in most patients involving genetic changes which alone do not affect growth, being present also in controls. However, the cohort of SGA newborns in this study is too small to draw definitive conclusions, especially taking into account the broad heterogeneity of conditions associated with FGR. The proposed molecular genetics approach needs further evaluation to assess its cost/effectiveness and impact on the clinical management of children born SGA.

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DOI:10.1530/ey.15.4.11

New mechanisms

4.12 Partial growth hormone insensitivity and dysregulatory immune disease associated with *de novo* germline activating STAT3 mutations

Gutiérrez M, Scaglia P, Keselman A, Martucci L, Karabatas L, Domené S, Martín A, Pennisi P, Blanco M, Sanguineti N, Bezrodnik L, Di Giovanni D, Caldirola MS, Azcoiti ME, Gaillard MI, Denson LA, Zhang K, Husami A, Yayah Jones NH, Hwa V, Revale S, Vázquez M, Jasper H, Kumar A, Domené H

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To read the full abstract: [Mol Cell Endocrinol 2018; 15:473:166-177](#)

Signal transducers and activators of transcription (STAT) proteins are transcription factors transiently activated by different ligands such as cytokines, growth factors, or peptides, which trigger intracellular tyrosine phosphorylation along the JAK-STAT signaling pathway. Phosphorylated STAT induces target gene expression, influencing cell proliferation, differentiation, and apoptosis. The activation of STATs is strictly regulated, whereas their deregulation leads to several disorders, ranging from susceptibility to infection, autoimmunity, and growth impairment.

STAT3 is a cytosolic protein involved in intracellular signaling transduction from cytokines, including several interleukins (IL), interferons (IFN α/β and γ) and growth factors and is involved in cell growth, apoptosis, organogenesis, inflammation, infection and oncogenesis. Activating mutations in the STAT3 gene are associated with multiple early-onset autoimmune conditions and growth failure. For example, a recent case report described a heterozygous *de novo* variant within the transactivation domain

of STAT3 in an SGA boy with progressive postnatal growth failure, late infancy onset type 1 diabetes and autoimmune thyroid disease, bicytopenia, and lymphoproliferative disease in subsequent years [47].

Here, Gutiérrez et al. describe two unrelated children, sharing clinical features such as short stature and immunological abnormalities. Patient 1 showed congenital autoimmune hypothyroidism, eczema, chronic diarrhea, recurrent oral candidiasis, severe respiratory infections. Patient 2 had history of IPEX-like syndrome with dermatitis, chronic diarrhea, colitis, autoimmune hypothyroidism. After ruling out anomalies in two candidate genes (STAT5B and FOXP3), whole exome sequencing was performed and identified two *de novo* STAT3 mutations. Both mutations were GOF and increased STAT3 transcriptional responses to GH. Both patients partially shared features with previously reported cases with STAT3 GOF mutations, and had undetectable IGF-1 levels with relatively high GH concentrations.

Activating mutations of STAT3 and inactivating mutations of STAT5b result in overlapping clinical features, including endocrine and immunological abnormalities [48]. Here, the authors discovered that both *de novo* STAT3 GOF mutations had a negative effect on STAT5b transcriptional activity. The mechanisms underlying this interaction have not been elucidated. SOCS3 may play a role as it is activated by STAT3 and negatively regulates STAT5. In conclusion, this study reveals a new form of IGF-1 deficiency and indicates an inhibitory role of STAT3 in the GH signalling pathway.

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New paradigms

4.13 An essential role for IGF2 in cartilage development and glucose metabolism during postnatal long bone growth

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To read the full abstract: [Development 2017; 144:3533-3546](#)

Endochondral ossification is the process by which the embryonic cartilaginous scaffold of most bones is gradually replaced by bone. During this process chondrocytes proliferate, undergo hypertrophy and maturation and form the growth plate, essential for bone growth. Postnatal bone growth is tightly regulated by both systemic and local factors, many of which not yet identified.

IGF2 has an established role in fetal development and growth; its expression has been found in several tissues during the early postnatal period [49] but that relevance is not fully elucidated. IGF2 is involved in the regulation of the musculoskeletal system and is an osteoblast survival factor influencing cell replication, collagen production and

matrix apposition [50]. IGF2 is expressed in the growth plate and its mutations have been recently recognized as responsible for severe postnatal growth restriction in humans [51].

In this elegant study in a murine model, the authors demonstrate that IGF2 regulates chondrocyte development by modulating a) progression of chondrocytes from the proliferating to the hypertrophic phase; b) perichondrial cell proliferation and differentiation; c) chondrocyte glucose metabolism, keeping both anaerobic glycolysis and oxidative phosphorylation under control. In humans, a nonsense mutation (p.Ser64Ter) in *IGF2* was identified in a family with some members who had severe prenatal and postnatal growth restriction [51]. The results of this experimental study provide evidence for a key role of IGF2 in cartilage growth thus explaining at least part of the phenotype observed in patients with *IGF2* mutation.

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5. Bone, Growth Plate and Mineral Metabolism

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The chapter on bone, growth plate and mineral metabolism has some themes that tend to recur year after year. Vitamin D is one such topic. Yet, every year brings new

essential information on this vitamin, which has often been suggested to be a miracle cure for several disorders. Links to many outcomes exist, but solid data on actual benefits beyond prevention and treatment of rickets are scarce. This year the selected vitamin D papers suggest that once vitamin D sufficiency is attained, maybe not so much extra benefit will be gained for bone strength or fracture resistance. Hypophosphatemic rickets is another theme that has repeatedly been brought up in the chapter, as we have over the years followed the development of an FGF23 antibody for treatment of XLH. It has been a long path from identification of FGF23 as the "phosphatonin" to the first preclinical studies and small-scale clinical trials in adults with XLH. Finally, we have come to the stage when we can report on the first randomized trial of FGF23 antibody treatment in children with XLH. The results are very promising and we may have reached a phase when this new drug is coming to our clinics to complement the therapeutic arsenal for XLH. In addition to these recurring themes, the chapter reports, among others, on new biomarkers, new genes and on novel means to analyse growth plate regulators and function.

DOI:10.1530/ey.15.5

New and repurposed therapies

5.1 Burosumab Therapy in Children with X-Linked Hypophosphatemia

Carpenter TO, Whyte MP, Imel EA, Boot AM, Hogler W, Linglart A, Padidela R, Van't Hoff W, Mao M, Chen CY, Skrinar A, Kakkis E, San Martin J, Portale AA
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To read the full abstract: [N Engl J Med 2018;378:1987-1998](#)

FGF-23 is the primary regulator of phosphate homeostasis and acts by inhibiting phosphate reabsorption in the kidney (1). Loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homolog X-linked (*PHEX*) results in excess circulating FGF-23, which impairs renal phosphate reabsorption causing hypophosphatemia, and decreases the synthesis of the active metabolite of vitamin D, 1,25-dihydroxyvitamin D.

Conventional therapy for XLH consists of multiple daily doses of oral phosphate salts and vitamin D metabolites or analogues as replacement therapy. Frequent and high doses of oral phosphate supplementation causes gastrointestinal symptoms (abdominal pain and diarrhoea) in children and despite frequent administrations it only transiently

increases serum phosphorus levels. Consequently, there is incomplete healing of rickets, residual skeletal deformity, and persistent short stature. Transient increases in phosphate cause hyperparathyroidism which is counteracted by simultaneous administration of alfacalcidol or calcitriol, which induces risks of metabolic and endocrine abnormalities such as hypercalciuria and nephrocalcinosis.

Burosumab is a recombinant human IgG1 monoclonal antibody that reduces function of FGF-23. Preliminary data in adults with XLH indicate that it improves phosphate balance (2). In this phase 2 study in children between 5-12 years of age, burosumab increased renal tubular phosphate reabsorption and reduced severity of rickets. The healing of rickets contributed to concurrent improvements in growth and physical activity and a reduction in pain. Burosumab was also safe with very few adverse effects. Effectiveness of burosumab in XLH provides new hope for patients with XLH and suggests that it may be beneficial in other elevated FGF-23 conditions such as tumour induced osteomalacia and renal failure.

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DOI:10.1530/ey.15.5.1

5.2 Increased intracellular proteolysis reduces disease severity in an ER stress-associated dwarfism

Mullan LA, Mularczyk EJ, Kung LH, Forouhan M, Wragg JM, Goodacre R, Bateman JF, Swanton E, Briggs MD, Boot-Handford RP

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To read the full abstract: [J Clin Invest 2017;127:3861-3865](https://doi.org/10.1093/clininvest/cvz017)

Metaphyseal chondrodysplasia, Schmid type (MCDS) is an orphan disease with highly abnormal endochondral ossification causing shortening and deformities of the limbs, impairment of mobility and chronic pain. As for most skeletal dysplasias, current treatment options remain symptomatic due to the lack in causal therapeutic measures. In the actual study the authors took advantage of the well-described pathogenesis in MCDS: In contrast to other collagenopathies, collagen X mutations do not directly lead to structural deficits but induce ER-stress by accumulation of misfolded protein. The authors hypothesize that by pharmacologically upregulating autophagy, enhanced protein clearance would ameliorate ER-stress and improve associated pro-apoptotic and differentiation-inhibiting effects.

Using a testing battery of known effectors of ER-stress and protein degradation,

Mullan et al. identified carbamazepine (CBZ, Tegretol®) as sole active compound regarding MCDS-specific cellular characteristics. Carbamazepine has been shown to induce both autophagy by cellular depletion of myo-inositol and proteasome activity by unknown mechanisms (1, 2). The authors could show both in vitro and in vivo an ameliorated chondrocyte phenotype and improved linear growth in mice. Interestingly, the drug was able to stimulate misfolded protein degradation by both autophagy and by proteasomal pathways, thus being effective for mutations being dependent on either pathway.

Given the positive safety profile of CBZ in pediatric patients, this study impressively resulted in an EMEA orphan drug license for the use CBZ in MCDS. Thus, the work of Mullan et al. did not only result in a new therapeutic option in MCDS but may also give hope for further rare diseases benefitting from repurposing well-established drugs.

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DOI:10.1530/ey.15.5.2

New genes and gene mutations

5.3 CYP3A4 mutation causes vitamin D-dependent rickets type 3

Roizen JD, Li D, O’Lear L, Javaid MK, Shaw NJ, Ebeling PR, Nguyen HH, Rodda CP, Thummel KE, Thacher TD, Hakonarson H, Levine MA

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To read the full abstract: [J Clin Invest 2018;128:1913-1918](#)

Two rare genetic forms of vitamin D-dependent rickets exist: VDDR-1 caused by mutations in the genes encoding either the renal 1- α hydroxylase (*CYP27B1*: VDDR-1A) or the hepatic 25-hydroxylase (*CYP2R1*: VDDR-1B) and VDDR-2 caused by mutations in the vitamin D receptor signalling due to mutations in the gene encoding the vitamin D receptor (*VDR*: VDDR-2A) or the heterogeneous nuclear ribonucleoprotein C (*HNRNPC*: VDDR-2B).

Here, the authors describe two cases of rickets in children who had detectable serum vitamin D₃ but low serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D which increased only after administration of very large doses of vitamin D or calcitriol and declined rapidly thereafter. Serum 24,25-dihydroxyvitamin D was low, suggesting that increased vitamin D metabolite inactivation by CYP24A1 did not account for apparent vitamin D deficiency. Whole exome sequencing analysis identified a recurrent de novo missense mutation, c.902T>C (p.I301T), in *CYP3A4* in both subjects. The protein encoded by *CYP3A4*, cytochrome P450 3A4, localizes to the endoplasmic reticulum and is mainly expressed in the liver and in the intestine. This gain-of-function mutation in *CYP3A4* leads to vitamin D deficiency through accelerated vitamin D metabolite inactivation. The authors named this dominant form of VDDR as VDDR-3. In addition, this study suggests that genetic and induced variation in *CYP3A4* activity and associated accelerated vitamin D inactivation may act as a modifier on the amount of vitamin D that is necessary to maintain vitamin D homeostasis. This finding expands the genetic forms of VDDR’s, summarised in the Table below.

Table 1. Genetic and biochemical features of the various forms of VDDRs.

VDDR	Defective gene and protein	Biochemical hallmark	References
VDDR:1A	<i>CYP27B1</i> : renal 1- α hydroxylase	Ca: N or ↓ 25-OHD: N; 1,25(OH) ₂ D: ↓	1
VDDR:1B	<i>CYP2R1</i> : hepatic 25-hydroxylase	Ca: N or ↓ 25-OHD: ↓; 1,25(OH) ₂ D: ↓	2
VDDR:2A	<i>VDR</i> : vitamin D receptor	Ca: N or ↓; 25-OHD: N; 1,25(OH) ₂ D: ↑	3
VDDR:2B	<i>HNRNPC</i> : heterogeneous nuclear ribonucleoprotein C	Ca: N or ↓; 25-OHD: N; 1,25(OH) ₂ D: ↑	4
VDDR:3	<i>CYP3A4</i> : Cytochrome P450 3A4	Ca: ↓; 25-OHD: ↓ 1,25(OH) ₂ D: ↓ which increased only after administration of very large doses of vitamin D or calcitriol and declined rapidly thereafter	5

Abbreviations: VDDR, vitamin D-dependent rickets; Ca, serum calcium; 25-OHD, 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25, dihydroxyvitamin D; N, normal; ↑, increased; ↓, decreased

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New genes and gene mutations

5.4 Mutations That Alter the Carboxy-Terminal-Propeptide Cleavage Site of the Chains of Type I Procollagen Are Associated With a Unique Osteogenesis Imperfecta Phenotype

Cundy T, Dray M, Delahunt J, Hald JD, Langdahl B, Li C, Szybowska M, Mohammed S, Duncan EL, McInerney-Leo AM, Wheeler PG, Roschger P, Klaushofer K, Rai J, Weis M, Eyre D, Schwarze U, Byers PH
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To read the full abstract: [J Bone Miner Res 2018;33\(7\):1260-1271](#)

Osteogenesis imperfecta (OI) is characterized by early-onset skeletal fragility, often short stature, blue sclerae and some other features. OI is caused by mutations in the two genes encoding type I collagen, namely COL1A1 and COL1A2. Some previous

reports have indicated that when the mutation involves the C-propeptide cleavage site in either one of the proteins encoded by these genes, the resulting phenotype could be very different, namely that of high bone mineral density and mild skeletal fragility (1). Apart from isolated patients, no larger series with this type of mutation have been reported. Here, the authors managed to recruit a large cohort including 29 subjects from 8 different families with 7 different pathogenic missense variants that alter the C-propeptide cleavage site. Based on the findings, it is clear that this rare class of pathogenic variants results in a distinctive OI phenotype with variable expression, mild to moderate disease severity, moderate fracture rate, high bone mass and increased bone mineral density. The findings suggest that high bone mass does not necessarily translate into a low fracture risk.

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DOI:10.1530/ey.15.5.4

New genes and gene mutations

5.5 Aggrecan Mutations in Nonfamilial Short Stature and Short Stature Without Accelerated Skeletal Maturation

Tatsi C, Gkourogianni A, Mohnike K, DeArment D, WitcheI S, Andrade AC, Markello TC, Baron J, Nilsson O, Jee YH

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To read the full abstract: [J Endocr Soc 2017;1:1006-1011](#)

Besides its structural role in the extracellular matrix, aggrecan orchestrates a plethora of key mechanisms in endochondral ossification, such as embryonic morphogen distribution, regular indian hedgehog (IHH) / Sox9 expression and columnar chondrocyte orientation. Thus, homozygous loss-of-function mutations in the *ACAN* gene, encoding aggrecan, cause severe skeletal phenotypes with strong affection of linear growth and chondrocyte maturation. Heterozygous *ACAN* mutations feature a milder, variable phenotypic spectrum of skeletal disorders and short stature. Recently,

the prevalence of *ACAN* mutations was described as high as 1.4% in European and Chinese idiopathic short stature (ISS) cohorts (1,2).

Here, Tatsi et al. report a detailed case that extends the known clinical characteristics of patients with *ACAN* mutations. The authors report novel heterozygous *ACAN* mutations in two unrelated ISS patients not fulfilling the classical strong criteria for *ACAN*-related disease, such as familial occurrence and advanced bone age. The absence of these features may easily lead to clinical exclusion of *ACAN* mutations as the underlying cause. The findings of this study suggest that a high rate of underdiagnosis may exist and that the recent prevalence studies may underestimate the prevalence. It is therefore important that the threshold to investigate *ACAN* should be lowered in genetic diagnostics for ISS.

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DOI:10.1530/ey.15.5.5

Towards evidence-based vitamin D supplementation

5.6 Effect of Higher vs Standard Dosage of Vitamin D₃ Supplementation on Bone Strength and Infection in Healthy Infants: A Randomized Clinical Trial

Rosendahl J, Valkama S, Holmlund-Suila E, Enlund-Cerullo M, Hauta-Alus H, Helve O, Hytinantti T, Levälähti E, Kajantie E, Viljakainen H, Mäkitie O, Andersson S

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To read the full abstract: [JAMA Pediatr 2018;172\(7\):646-654](https://doi.org/10.1093/ped/kty014)

Vitamin D deficiency in infants can lead to impaired bone mineralization and rickets. Since the 1920s, vitamin D has been used to prevent and treat rickets, but the optimal supplementation dose for bone health was unclear. Similarly, potential extra-skeletal benefits of vitamin D in childhood have been inadequately explored. Acute infections in infants are a major cause of global morbidity and mortality. Observational studies have reported independent associations between low serum concentrations of 25-hydroxyvitamin D (25OHD) and susceptibility to infection. Vitamin D supplementation is widely used but the dosing is not based on evidence from randomized trials.

The aim of this study was to investigate if a higher dose (1200 IU) of supplemental vitamin D₃ administered to healthy infants from age 2 weeks to 2 years increases bone strength or decreases incidence of infections compared with the standard dose (400 IU). This randomized clinical trial of 975 infants found no difference in bone strength or incidence of infections between intervention groups at 24 months of age. Thus, study suggests that in healthy infants of northern European descent, daily supplementation with 1200 IU of vitamin D₃ provides no additional benefits compared with supplementation with 400 IU for bone strength or incidence of infections in early childhood. This study used peripheral quantitative computed tomography (pQCT), which is superior to dual-energy x-ray absorptiometry, to assess bone density and strength parameters. However, it should be noted that most infants were vitamin D sufficient at baseline and compliance was high. The outcome of a similar intervention might have been different in a vitamin D deficient cohort of infants, as demonstrated in recent meta-analysis by Martineau et al. (1). In any case, this study, the first of its kind, brings important, solid evidence to guide in establishing population-based vitamin D dose guidelines.

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DOI:10.1530/ey.15.5.6

Fractures, vitamin D and steroids – unclear associations

5.7 Vitamin D and Fracture Risk in Early Childhood: A Case-Control Study

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To read the full abstract: [Am J Epidemiol 2017;185:1255-1262](#)

Vitamin D and adequate dietary calcium intake are important for skeletal health and therefore it was expected that vitamin D concentration would be associated with

increased fracture risk. However, here, the authors did not find any statistically significant association between concurrent 25(OH)D concentration and fracture risk. In addition, the main dietary source of vitamin D in Canada, milk intake, was also not statistically significantly associated with reduced risk of fractures.

Previous studies have reported a high prevalence of 25(OH)D deficiency (<50 nmol/L), among children with fractures (1); however, none of those studies included a comparison group of children without fractures. In this study, controls were obtained from the TARGet Kids! primary-care research network and were matched to cases on age, sex, height, and season. Another strength of this study was that fractures were confirmed by radiography. One of the limitations of this study is that 25(OH)D levels in the study population were sufficiently high to have minimized fracture risk from vitamin D insufficiency, and results from this study therefore may not be generalizable to other populations with lower 25(OH)D levels.

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DOI:10.1530/ey.15.5.7

Fractures, vitamin D and steroids – unclear associations

5.8 Association Between Inhaled Corticosteroid Use and Bone Fracture in Children with Asthma

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To read the full abstract: [JAMA Pediatr 2018;172:57-64](#)

Corticosteroids are a well-known risk factor for compromised bone health. There have been concerns regarding the use of inhaled corticosteroids in children with asthma. It is often stated that poor disease control is a greater risk for bones than the medication itself. The evidence however has not been overwhelming. Corticosteroids directly interfere with osteoclast and osteoblast functioning, resulting in decreased bone

formation, increased resorption, and calcium loss from the skeleton. This can predispose corticosteroid users to osteoporosis and increased risk of bone fracture. The primary objective of this study was to determine the association between inhaled corticosteroid use and first fracture after asthma diagnosis in children. The study population comprised of 19,420 children with asthma who were eligible for public drug coverage through the Ontario Drug Benefit Program in Ontario, Canada. This population-based study demonstrated no clinically important association between inhaled corticosteroids and fracture in children with asthma. However, there was an increased risk of fracture associated with systemic corticosteroid use. Clinicians using inhaled corticosteroids to optimize the control of childhood asthma should be reassured by the lack of association with fractures. Fear of fracture is not a reason to limit the use of inhaled corticosteroids. In fact, good asthma control might decrease the likelihood of asthma exacerbations and need for systemic corticosteroids. This in turn may potentially lead to a reduced fracture risk.

DOI:10.1530/ey.15.5.8

Life-long skeletal consequences of delayed puberty

5.9 Genetically Determined Later Puberty Impacts Lowered Bone Mineral Density in Childhood and Adulthood

Cousminer DL, Mitchell JA, Chesi A, Roy SM, Kalkwarf HJ, Lappe JM, Gilsanz V, Oberfield SE, Shepherd JA, Kelly A, McCormack SE, Voight BF, Zemel BS, Grant SF

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To read the full abstract: [J Bone Miner Res 2018;33:430-436](#)

Bone mass increases dramatically during puberty. The process of sexual maturation is therefore likely to impact lifelong bone health. Bone mineral density (BMD) tracks throughout life and later age at menarche is associated with increased osteoporosis risk in women, possibly because of combined effects of later menarche and lower peak bone mass in young adulthood. Genome-wide association studies have identified 380 variants associating with pubertal timing (1). Recent studies have found that pubertal timing and adult aBMD share a common genetic etiology (2). Here, the authors aimed to determine if there is an association between genetic loci

implicated in timing of puberty, both individually and as polygenic risk scores (GRS) representing the "genetic load" of puberty-delaying variants, and aBMD at multiple skeletal sites in healthy children. The researchers used data from the Bone Mineral Density in Childhood Study (BMDCS), including bone and growth measurements during annual visits for up to seven years in over 2,000 healthy children, adolescents and young adults during 2002 to 2010. The study findings show that a genetic risk for later puberty is associated with lower lumbar spine aBMD. This association was stronger in girls in childhood but was evident in adulthood in both sexes. Similarly, the study findings gave some evidence that genetically determined later puberty associated also with lower femoral neck aBMD. During adolescence pubertal maturation and bone acquisition develop in parallel and the relationship between genetic variation, timing of puberty and BMD is likely to be complex. The molecular and functional mechanisms linking these processes should be elucidated in future studies to gain insight into potential means to optimize bone health across these critical periods.

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2. Day FR, Bulik-Sullivan B, Hinds DA, Finucane HK, Murabito JM, Tung JY, Ong KK, Perry JR. Shared genetic aetiology of puberty timing between sexes and with health-related outcomes. *Nat Commun.* 2015;6:8842.

DOI:10.1530/ey.15.5.9

Growth velocity as a laboratory parameter

5.10 A degradation fragment of type X collagen is a real-time marker for bone growth velocity

Coghlan RF, Oberdorf JA, Sienko S, Aiona MD, Boston BA, Connelly KJ, Bahney C, LaRouche J, Almubarak SM, Coleman DT, Girkontaite I, von der Mark K, Lunstrum GP, Horton WA

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To read the full abstract: [Sci Transl Med 2017;9\(419\)](#)

Can growth velocity be monitored by a lab test? Previous approaches to this methodological challenge focused on the correlation of linear growth to more established parameters such as C-type natriuretic peptide (CNP). Potentially more specific markers of endochondral ossification - with the exception of amino-terminal

propeptide of CNP (NTproCNP) - have drawn little attention so far. Here, Coghlan et al. identified Collagen X fragments (CXM) as an entirely novel parameter and were able to employ a specific ELISA for clinical testing. As high amounts of type X collagen are synthesized by hypertrophic chondrocytes, chondroclastic activity and extra-cellular matrix degradation liberate fragments of this highly specific growth plate matrix compound.

Validation was performed in a population of 83 healthy children revealed an impressively high correlation with growth velocity ($r^2=0.88$), although the relatively small sample set especially for higher velocity values has to be taken in account. In addition, CXM has to match with other parameters such as NTproCNP, for which age and Tanner-specific data already have been established (1). While further studies will clarify the advantages of individual competing parameters, Coghlan et al. have taken the perspective of clinical "live growth monitoring" another step forward.

1. Olney RC, Permuy JW, Prickett TC, Han JC, Espiner EA. Amino-terminal propeptide of C-type natriuretic peptide (NTproCNP) predicts height velocity in healthy children. *Clin Endocrinol (Oxf)*. 2012;77(3):416-422.

DOI:10.1530/ey.15.5.10

GNAS and subcutaneous ossifications

5.11 Ossifications in Albright Hereditary Osteodystrophy: Role of Genotype, Inheritance, Sex, Age, Hormonal Status, and BMI

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To read the full abstract: [J Clin Endocrinol Metab 2018;103:158-168](#)

Defects at the GNAS locus give rise to various phenotypes, several of which are associated with subcutaneous ossifications (SCOs), which cause significant morbidity among the affected individuals. A subgroup of patients with paternally inherited GNAS mutations have progressive osseous heteroplasia (POH), characterized by severe heterotopic ossifications involving the deep connective tissue and skeletal muscle without the AHO phenotype or hormonal abnormalities. This study excluded patients with concomitant POH and rather aimed to explore the prevalence and risk factors of SCOs in other GNAS defects. The study is the largest to date and utilized prospectively collected data by a single examiner over a period of 16 years.

The study showed a high prevalence of SCOs in patients with mutations in GNAS; the prevalence was similar in PHP1A and PPHP, indicating that paternal imprinting, hormonal resistance, biochemical parameters and BMI are not involved in the pathogenesis of SCOs. The degree of SCO formation correlated with the severity of the GNAS mutation, and the SCOs were more frequent and extensive in males than in females. The severity increased with age. There are no successful drug therapies to date for the SCOs in AHO. Understanding the etiology for SCO formation – or preventing their invasion to deeper tissues - could lead to new treatment modalities.

The disorders related to GNAS locus are complicated and their diagnosis and treatment are challenging. The recently published international Consensus Statement (1) should prove useful in patient management.

1. Mantovani G, Bastepe M, Monk D, de Sanctis L, Thiele S, Usardi A, Ahmed SF, Bufo R, Choplin T, De Filippo G, Devernois G, Eggermann T, Elli FM, Freson K, García Ramírez A, Germain-Lee EL, Groussin L, Hamdy N, Hanna P, Hiort O, Jüppner H, Kamenický P, Knight N, Kottler ML, Le Norcy E, Lecumberri B, Levine MA, Mäkitie O, Martin R, Martos-Moreno GÁ, Minagawa M, Murray P, Pereda A, Pignolo R, Rejnmark L, Rodado R, Rothenbuhler A, Saraff V, Shoemaker AH, Shore EM, Silve C, Turan S, Woods P, Zillikens MC, Perez de Nanclares G, Linglart A. Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement. *Nat Rev Endocrinol.* 2018 Jun 29. doi: 10.1038/s41574-018-0042-0. [Epub ahead of print] Review.

DOI:10.1530/ey.15.5.11

Klotho in the control of osteocyte activity

5.12 Klotho expression in osteocytes regulates bone metabolism and controls bone formation

Komaba H, Kaludjerovic J, Hu DZ, Nagano K, Amano K, Ide N, Sato T, Densmore MJ, Hanai JI, Olauson H, Bellido T, Larsson TE, Baron R, Lanske B
Division of Bone and Mineral Research, Harvard School of Dental Medicine, Boston, Massachusetts, USA; Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan

To read the full abstract: [Kidney Int 2017;92:599-611](#)

Klotho was originally identified as a senescence-related protein because mice carrying hypomorphic Klotho alleles (kl/kl) develop premature aging with low bone turnover and osteoporosis. Primary function of Klotho is to form a specific receptor complex with fibroblast growth factor (FGF) receptor 1 (FGFR1) through which it mediates the biological function of FGF23, which in the kidney inhibits renal phosphate reabsorption and suppresses 1,25-dihydroxyvitamin D [1,25(OH)₂D] synthesis. In chronic kidney disease, circulating FGF23 levels increase as a compensatory response

to maintain a normal phosphate balance. High FGF23 in end-stage kidney disease exerts toxic effects on the cardiovascular and immune systems in a Klotho-independent manner.

Recent investigations have discovered the presence of Klotho in osteocytes (1). The functional role of Klotho in osteocytes is however poorly characterized. Here, the authors generated a mouse model using an osteocyte-specific deletion of the Klotho gene to explore the functional role of Klotho in osteocytes. Interestingly the deletion of Klotho from osteocytes resulted in a marked increase in bone formation and bone volume, along with the enhanced expression of osteoblastic marker genes at 5 weeks of age; this increase in bone volume was also observed in 12-week-old Dmp1-Klotho^{-/-} mice. Furthermore, in vitro experiments conducted using Klotho overexpression in MC3T3.E1 cells caused the inhibition of mineralization and osteogenic activity during osteocyte differentiation, consistent with in vivo observations. These results collectively indicate that Klotho is a negative regulator of bone formation. This is in sharp contrast to kl/kl mice that exhibit low-turnover osteoporosis. Klotho in osteocytes could be a novel therapeutic target for managing primary and secondary osteoporosis in children.

1. Rhee Y, Bivi N, Farrow E, Lezcano V, Plotkin LI, White KE, Bellido T. Parathyroid hormone receptor signaling in osteocytes increases the expression of fibroblast growth factor-23 in vitro and in vivo. *Bone*. 2011;49(4):636-43.

DOI:10.1530/ey.15.5.12

Live insights to growth plate biology

5.13 Imaging IGF-I uptake in growth plate cartilage using in vivo multiphoton microscopy

Serrat MA, Ion G

Department of Biomedical Sciences, Joan C. Edwards School of Medicine,
Marshall University, Huntington, West Virginia

To read the full abstract: [J Appl Physiol \(1985\) 2017;123:1101-1109](#)

IGF-1 is a major regulator of growth plate chondrocyte proliferation. While knockout studies reveal substantial impact from both systemic as well from locally-derived

IGF-1, transport and distribution patterns within the growth plate remain unknown. Theoretical approaches have been developed to understand the distribution of IGF-1 within the growth plate but have not been proven in vivo thus far. Here, the authors used multiphoton microscopy to track fluorescently labeled IGF-1 take up into growth plate cartilage in vivo for the first time. In contrast to inert molecules, the distribution of IGF-1 followed a very distinct pattern with indication of intracellular localization as early as 30-90 minutes after systemic application. Stunningly, perichondrial tissue exhibited the opposite pattern of efficiently trapping IGF-1 in the matrix, assuming a storage function. Using state-of-the-art technology, this study provides novel insights into local growth factor trafficking, as well as the role of different tissue compartments. Similar studies on further key regulators of linear growth may shed new light on growth plate regulation and identify new strategies for specific drug delivery.

DOI:10.1530/ey.15.5.13

5.14 Growth plate expression profiling: Large and small breed dogs provide new insights in endochondral bone formation

Teunissen M, Riemers FM, van Leenen D, Groot Koerkamp MJA, Meij BP, Alblas J, Penning LC, Miranda-Bedate A, Tryfonidou MA
Faculty of Veterinary Medicine, Department of Clinical Sciences of Companion Animals, Utrecht University, Utrecht, The Netherlands

To read the full abstract: [J Orthop Res 2018;36:138-148](#)

Dogs are growth biologists' best friends – due to the broad intra-species variance in body size, canine breeds offer a unique opportunity to study genetic differences mainly affecting linear growth. In their previous publication, the authors found drastic differences between miniature and large dog breeds in known key regulators of the

growth plate such as IHH, PTHrP, and IGF-BPs (1). In the present study, the group took the concept to a next level and extended the study approach by using Microarray technology. Further, the authors addressed the essential issue of spatial expression in growth plate tissue by validating array-derived data in individual growth plate zone samples. This two-level approach allowed identification of new body-size related differences including BMP2 and BMP6 expression in proliferative chondrocytes and osseous expression of BMPRIb.

While some new regulators might still have remained under the radar due to the use of total growth plate sample for Microarray analysis, the identification of known chondrocyte differentiation regulators validated this compelling study design. Follow-up studies with focus on further regulatory pathways are hoped for.

1. Tryfonidou MA, Hazewinkel HA, Riemers FM, Brinkhof B, Penning LC, Karperien M. Intraspecies disparity in growth rate is associated with differences in expression of local growth plate regulators. *Am J Physiol Endocrinol Metab.* 2010 Dec;299(6):E1044-52.

DOI:10.1530/ey.15.5.14

Gender Dysphoria and Disorders of Sex Development

6. Preface

Olle Söder, MD, PhD & Anna Nordenström, MD, PhD
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The current chapter on gender dysphoria (GD) in children and adolescents and disorders/differences of sex development (DSD) is a novel addition to the Yearbook and presented here for the first time. The reason for adding the chapter is obvious for all pediatric endocrinologists as the knowledge and numbers of patients in these areas have increased heavily during the past few decades. This situation has created clinical and ethical challenges for pediatric endocrinologists looking after patients with GD and DSD. From a scientific point of view much less is known about the biology and

pathophysiology behind GD/transsexualism when compared to DSD, although transsexualism is often referred to as the DSD of the brain. In contrast several novel genes and molecular mechanisms behind DSD have been delineated during the past year that will be discussed in this chapter. For GD phenotypically most but certainly not all cases show an early onset (preschool) pointing to a possible congenital developmental background. However, a late onset (most commonly peripubertal) may indicate environmental or epigenetic influences. A total of 20 articles were chosen covering epidemiological, molecular, clinical, reviews, editorials and other aspects of the two themes. The selected articles are sorted under different headings such as new genes, important for clinical practice, new hope, new paradigms and others. We realize that there are many other excellent papers within the fields published during the past year that we may have missed and yet others which we could not include due to space limitation. The selection obviously represents our own biases but we hope you find it interesting and useful for your daily work in the pediatric endocrinology clinic or experimental setting.

DOI:10.1530/ey.15.6

New mechanisms

6.1 International Gender Diversity Genomics Consortium. The Biological Contributions to Gender Identity and Gender Diversity: Bringing Data to the Table

Polderman TJC, Kreukels BPC, Irwig MS, Beach L, Chan YM, Derks EM, Esteva I, Ehrenfeld J, Heijer MD, Posthuma D, Raynor L, Tishelman A, Davis LK, and the International Gender Diversity Genomics Consortium.

Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA.

To read the full abstract: [Behav. Genet. 2018 Mar;48\(2\):95-108.](#)
[See comment on 6.2](#)

DOI:10.1530/ey.15.6.1

New mechanisms

6.2 Structural connections in the brain in relation to gender identity and sexual orientation

Burke SM, Manzouri AH, Savic I.

Brain & Development Research Centre, Department of Developmental and Educational Psychology, Leiden University, Leiden, The Netherlands; Department of Women's and Children's Health, Karolinska Institute and University Hospital, Stockholm, Sweden

To read the full abstract: [Sci Rep. 2017 Dec 20;7\(1\):17954](https://doi.org/10.1038/s41598-017-17954-4)

[Comments on 6.1 and 6.2] Gender dysphoria (GD) is still an enigma when it comes to the biological background and pathophysiology. Many different theories have been put forward but none is yet prevailing due to a poor evidence base. Earlier anatomical studies searching for gender specific brain structures that could be associated with gender identity (GI) have indicated the presence of such loci but more modern brain imaging methods as used in the paper by Burke et al. (6.2) described here have failed to support these observations. Findings of monozygous twins who are discordant to GI disorder excludes simplistic genetic causes. Currently there is no "objective" diagnostic method available for GD and it is presently not possible to diagnose

experimental animals or human infants with GD as it requires a critical component of verbal expression. Analysis of reproductive behavior in animals does not distinguish sexual orientation from GI. The importance of psychosocial factors for the expression of GD is generally agreed.

The first paper (6.1) by Polderman et al. from the International Gender Diversity Genomics Consortium defines the important concepts and reviews the evidence that GI is influenced at least in part by innate factors including genes. They hypothesize that GI is a multifactorial complex trait with a heritable polygenic component. The authors argue that increasing the awareness of the biological diversity underlying GI development is relevant to all domains of social, medical, and brain research.

Secondly, Burke et al. (6.2) used advanced neuroimaging technology (fractional anisotropy) which is a measure of brain white matter connections that have shown consistent sex differences. Transgender males and females were investigated and compared with homosexual and heterosexual male and female cis-gender controls. Although the interpretation was complex the results suggested that brain areas involved in the processing of the perception of self and body ownership were affected in GD but not in homosexual subjects. Taken together, these two papers support a complex biological and genetic background to GI which seems to involve white matter trajectories rather than distinct brain loci. Much more is expected from the research areas discussed here.

DOI:10.1530/ey.15.6.2

Important for clinical practice

6.3 Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline

Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GG.

New York Presbyterian Hospital, Columbia University Medical Center, New York, New York 10032; VU University Medical Center, 1007 MB Amsterdam, Netherlands; and others.

To read the full abstract: [J Clin Endocrinol Metab 2017 Nov 1;102\(11\):3869-3903](#)

This Endocrine Society endorsed paper is an update of the 2009 version, also published in JCEM, with clinical guidelines for endocrine management of patients with GD. The major focus is on adult patients but a large part is also focusing on children and adolescents with GD, contributed by co-authors with pediatric endocrinology and psychology expertise. Detailed advice on endocrine work-up, treatment, follow-up and other issues is presented. Since the authors represent origins from a number of professional organizations including ESPE and several continents, the guidelines given by this paper are supported by a broad experience and expertise. This article is a must for pediatric endocrinologists dealing with GD. Another paper (Tangpricha V et al.), based on the present guidelines, discusses several GD cases and their management, and these serve as excellent training scenarios.

Tangpricha V, Hannema SE, Irwig MS, Meyer WJ 3rd, Safer JD, Hembree WC. American Association of Clinical Endocrinologists/Endocrine Society Update on Transgender Medicine: Case discussions. *Endocr Pract.* 2017 Dec;23(12):1430-1436.

DOI:10.1530/ey.15.6.3

Important for clinical practice

6.4 The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets

Wiepjes CM, Nota NM, de Blok CJM, Klaver M, de Vries ALC, Wensing-Kruger SA, de Jongh RT, Bouman MB, Steensma TD, Cohen-Kettenis P, Gooren LJG, Kreukels BPC, den Heijer M.

Department of Endocrinology, VU University Medical Center, Amsterdam, the Netherlands; Center of Expertise on Gender Dysphoria, VU University Medical Center, Amsterdam, the Netherlands, and others.

To read the full abstract: [J Sex Med. 2018 15\(4\)](#)

This is an important paper with a follow-up covering more than 11,000 GD patients from a single clinic in the Netherlands, looking after most (>95%) of the GD patients of the country. Long-term follow-up to adulthood of children and adolescents with GD is still lacking as the recent rapid increase of these groups has not yet resulted in substantial numbers of adults to study. In particular, very little data is available on later regrets in children and adolescents with GD after hormone therapy and surgery resulting in irreversible effects on the body. Further, and not uncommon in pediatrics, organizational problems of the health care may have created difficulties to follow-up post transition pediatric GD patients into adult care. Although most GD patients in this study were adults an important part was adolescents. The data presented is re-assuring as the regrets were few. This is supported by other studies (in adults) also showing that regrets are sparse and trends to fewer regrets in more recent years. These observations have been interpreted as effects of a higher quality of the current work-up and diagnostic efforts for GD patients compared to previously.

DOI:10.1530/ey.15.6.4

Position paper

6.5 Statement on gender-affirmative approach to care from the pediatric endocrine society special interest group on transgender health

Lopez X, Marinkovic M, Eimicke T, Rosenthal SM, Olshan JS, and Pediatric Endocrine Society Special Interest Group on Transgender Health. Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

To read the full abstract: [Curr Opin Pediatr. 2017 Aug;29\(4\):475-480](#)

This is one of several editorials and position papers that has been published during the

past year. It originates from the North American Pediatric Endocrine Society and its special interest group for transgender health. This article is of value for pediatricians dealing with any aspect of transgender health in children and adolescents as it provides a good source of relevant definitions, information and references to the latest literature as a basis to deliver the best medical care. There is still a weak evidence base for our decisions in this field, but it seems clear that an affirmative approach in the management of transgender youth is of great importance. Several additional position papers and editorials worth reading have also been published during the past year, see, e.g., Barret J; Chipkin S. et al.).

Barrett J. Gender dysphoria: assessment and management for non-specialists. *BMJ*. 2017 Jun 30;357:j2866.

Chipkin SR, Kim F. Ten Most Important Things to Know About Caring for Transgender Patients. *Am J Med*. 2017 Nov;130(11):1238-1245.

DOI:10.1530/ey.15.6.5

New treatments

6.6 Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review

Chew D, Anderson J, Williams K, May T, Pang K.

Department of Pediatrics and Discipline of Paediatrics, Adelaide Medical School and Robinson Research Institute, The University of Adelaide, Adelaide, Australia.

To read the full abstract: [Pediatrics. 2018 Apr;141\(4\)](#)

[See comment on 6.8.](#)

DOI:10.1530/ey.15.6.6

New treatments

6.7 Puberty suppression in transgender children and adolescents

Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A.
Centre and Discipline of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Division of Psychiatry and Clinical Neurosciences and Division of Paediatrics and Child Health, School of Medicine, Faculty of Health and Medical

Sciences, University of Western Australia, Perth, WA, Australia

To read the full abstract: [Lancet Diabetes Endocrinol. 2017 Oct;5\(10\):816-826](#)

[See comment on 6.8](#)

DOI:10.1530/ey.15.6.7

New treatments

6.8 Efficacy and Safety of Pubertal Induction Using 17 β -Estradiol in Transgirls

Hannema SE, Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA. Department of Pediatrics, Leiden University Medical Centre, Leiden, The Netherlands.

To read the full abstract: [J Clin Endocrinol Metab. 2017 Jul ;102 \(7\):2356-2363](#)

[Comments on 6.6, 6.7 and 6.8] These 3 papers deal with endocrine pharmacological treatment of patients with GD.

The first article by Chew et al. (6.6), from Australia, systematically reviews different pharmacological treatments in adolescents with GD, including GnRH analogs, hormonal receptor blockers and estrogen and androgen administration. The aim was to identify evidence on physical, psychosocial, and cognitive effects of the endocrine treatments. Only a small number of published papers fulfilled the high quality inclusion criteria and they were all observational. Pediatric endocrinologists active in this field form a solid experience base to support the current therapies. However, there is yet only low-quality evidence suggesting that the endocrine treatments for GD adolescents can achieve their wanted physical effects. Further, there is yet no evidence concerning the psychosocial and cognitive effects of these treatments in GD patients.

The second paper by Mahfouda et al. (6.7) reviews puberty suppression treatment in children with GD with respect to published evidence for physical, psychological and cognitive effects. Again, the authors found only a few published papers meeting evidence forming quality criteria. It seems clear that treatment is reasonably, safe but its efficacy is unproven. No quality data on psychological effects and other aspects of the treatment was available.

The third paper by Hannema et al. (6.8) from the Netherlands focuses specifically on estrogen treatment in adolescent transgirls (biologically male with female gender identity). A relatively small number (n=28) were treated for 1 year or more with 17-beta estradiol 2 mg daily to induce puberty. A median serum concentration was 100 pM estradiol, although some patients had much lower levels. Efficacy was proven by recording breast development; >80% reached Tanner 4-5 after 3 years of treatment. An important message from this study is that the treatment was safe. Accordingly, the authors argue that there is no need to measure metabolic and organ specific blood chemistry parameters.

Taken together, and as stated repeatedly in this chapter, it is clear from these and other publications (e.g., Tack L et al.) that the evidence base for endocrine treatments used in GD is weak. The approaches taken in the 3 papers above are important to improve this situation.

Tack L, Heyse R, Craen M, Dhondt K, Bossche HV, Laridaen J, Cools M. Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents. *J Sex Med.* 2017;14(5):747-757.

DOI:10.1530/ey.15.6.8

New hope

6.9 Fertility Preservation for Transgender Adolescents

Chen D, Simons L, Johnson EK, Lockart BA, Finlayson C.

Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.

To read the full abstract: [J Adolesc Health. 2017 Jul;61\(1\):120-123](#)

Recent developments in assisted reproduction technologies (ART) have changed the scene for fertility wishes in a number of disorders, including GD. Fertility preservation

is now routinely offered to postpubertal adolescent and adult GD patients at increasing numbers of medical centers. For biological boys, this is a non-invasive procedure and follows routine measures in sperm collection and cryopreservation. For biological girls, however, this is more complicated as it involves hormonal stimulation and invasive procedures to collect eggs before cryopreservation. There are also an increasing number of reports of children being born to transmen after temporary suspension of androgen treatment after years of therapy in persons who have avoided genital surgery with castrating effects. This paper by Chen et al. shows that fertility preservation services including ART show low rates of utilization despite such possibilities being actively promoted. Further, even though gametes have been collected and cryopreserved, it remains to be seen how frequently these materials will be used by the donor in the future. More developments are expected in this area.

DOI:10.1530/ey.15.6.9

Food for thought

6.10 I am your trans patient

Lewis EB, Vincent B, Brett A, Gibson S, Walsh RJ.

This group of authors act as private persons in the present context and do not refer to any university affiliation for this task.

To read the full abstract: [BMJ. 2017 Jun 30;357:j2963](#)

This group of 5 transgender and non-medical professional authors has written a unique

“What Your Patient is Thinking” article published in the BMJ. Their aim was to tell health care providers, and others who manage transgender people, how they want to be received and treated and what went wrong in many previous meetings with the health care system and members of society. This is an important paper, which should be read by all medical doctors. Transgender people constitute a particularly sensitive and vulnerable group, but also other groups of patients deserve to be mentioned in this context in future articles on “What Your Patient is Thinking”. Again, this subject is particularly relevant for pediatricians as long-term follow-up of our patients into adulthood is difficult to pursue. Therefore, it is rare to obtain distinct views from adult patients on what was good and what was bad in the previous pediatric management. For those who care for transgender youth and adults, this paper is a must.

DOI:10.1530/ey.15.6.10

6.11 Elimination of the male reproductive tract in the female embryo is promoted by COUP-TFII in mice

Zhao F, Franco HL, Rodriguez KF, Brown PR, Tsai MJ, Tsai SY, Yao HH.
Reproductive Developmental Biology Group, National Institute of Environmental Health Sciences, Durham, NC, USA.

To read the full abstract: [Science. 2017 Aug 18;357\(6352\):717-720](#)

[See comment on 6.13](#)

DOI:10.1530/ey.15.6.11

6.12 Loss of Function of the Nuclear Receptor NR2F2, Encoding COUP-TF2, Causes Testis Development and Cardiac Defects in 46,XX Children

Bashamboo A, Eozenou C, Jorgensen A, Bignon-Topalovic J, Siffroi JP, Hyon C, Tar A, Nagy P, Sólyom J, Halász Z, Paye-Jaouen A, Lambert S, Rodriguez-Buritica D, Bertalan R, Martinerie L, Rajpert-De Meyts E, Achermann JC, McElreavey K.

To read the full abstract: [Am J Hum Genet. 2018 Mar 1;102\(3\):487-493](#)

[See comment on 6.13](#)

DOI:10.1530/ey.15.6.12

Disorders of Sex Development: New Paradigm

6.13 A Novel Homozygous Missense Mutation in the FU-CRD2 Domain of the R-spondin1 Gene Associated with Familial 46,XX DSD

Naasse Y, Bakhchane A, Charoute H, Jennane F, Bignon-Topalovic J, Malki A, Bashamboo A, Barakat A, Rouba H, McElreavey K.

Laboratoire de Génétique Moléculaire Humaine, Département de la Recherche Scientifique, Institut Pasteur du Maroc, Casablanca, Morocco

To read the full abstract: [Sex Dev. 2017;11\(5-6\):269-274](#)

[Comments on 6.11, 6.12 and 6.13] Evidence for factors necessary for female sexual development are presented in the above 3 publications. Studies of 46,XX DSD individuals show compelling evidence for factors necessary for female development and to counteract male development. The paradigm that female development is the default pathway has proven to be untrue. Studies of individuals with 46,XX DSD have revealed more factors and proof for active processes necessary for the female development.

First, Zhao et al. (6.11) report on studies on mice that challenge the notion that the Wolffian ducts regress if simply unexposed to androgens. They show that the nuclear receptor COUP-TF2 in the mouse is necessary for elimination of Wolffian ducts. An enhanced kinase signaling seems to be involved, possibly regulated via androgens.

Second, Bashamboo et al. (6.12) report the first evidence COUP-TF2 is necessary for uncompromised ovarian development in humans. A mutation in the gene resulted in formation of testis tissue and androgen production in 3 individuals with 46,XX karyotype. The findings indicate that nuclear receptors may have divergent functions affecting the heart and genitalia. They show that COUP-TF2 is a “pro-ovary” and “anti-testis” sex-determining factor in human female gonads. Importantly, COUP-TF2

seems to be the underlying theme of pro-female and anti-male function in both mice and humans. There is emerging evidence that nuclear receptors are important in human ovarian development and that nuclear receptors have divergent functions in both mouse and human biology.

Thirdly, Naasse et al. (6.13) report a missense mutation in the RSPO-1 gene in 2 siblings with 46,XX testicular DSD and ovotesticular DSD. This study establishes the importance of RSPO-1 for female ovarian development. In ovarian differentiation, upregulation of WNT4 is initially promoted by RPSO-1 expression. Lack of RSPO-1 enables the gonad to develop along the testis pathway resulting in testicular DSD with male gender, and ovotesticular DSD with female gender in the two siblings, respectively. Similar to previous cases with RSPO-1 mutations, the siblings had palmoplantar keratoderma, and in addition, hearing deficits related to the role of R-spondins as activators of both WNT/CTNBN1 and WNT/planar cell polarity (PCP) in signaling in cell differentiation and cancer. Interestingly, in mice, both *Rspo1* and *Wnt4* are regulators of cell proliferation in the early gonad regardless of its sex. Simultaneous ablation of *Rspo1* and *Wnt4* impairs proliferation of cells of the coelomic epithelium, and leads to the differentiation of a reduced number of Sertoli cells and the formation of hypoplastic testes with few seminiferous tubules (see Chassot et al.). Moreover, mutations in WNT4 have been found to cause Mayer-Rokitansky-Küster-Hauser syndrome in a small subgroup of patients with signs of hyperandrogenaemia (see Ledig et al.). Hence, both RSPO-1 and WNT4 are important players in multiple steps in differentiation and development. Our knowledge and understanding of the complexity of the different factors involved in sex development is increasing. Studies of individuals with syndromic forms of DSD have contributed important pieces of information in the past and will probably continue to do so in the future.

Chassot AA, Bradford ST, Auguste A, Gregoire EP, Pailhoux E, de Rooij DG, Schedl A, Chaboissier MC. WNT4 and RSPO1 together are required for cell proliferation in the early mouse gonad. *Development*. 2012;139(23):4461-72.

Ledig S, Wieacker P. Clinical and genetic aspects of Mayer-Rokitansky-Küster-Hauser syndrome. *Med Genet*. 2018;30(1):3-11. doi: 10.1007/s11825-018-0173-7. Review.

DOI:10.1530/ey.15.6.13

6.14 GATA4 Variants in Individuals With a 46,XY Disorder of Sex Development (DSD) May or May Not Be Associated With Cardiac Defects Depending on Second Hits in Other DSD Genes

Martinez de LaPiscina I, de Mingo C, Riedl S, Rodriguez A, Pandey AV, Fernández-Cancio M, Camats N, Sinclair A, Castaño L, Audi L, Flück CE. Endocrinology and Diabetes Research Group, BioCruces Health Research Institute, Cruces University Hospital, CIBERDEM, CIBERER, UPV-EHU, Barakaldo, Spain.

Here, Martinez de LaPiscina et.al. investigated gene-gene interactions in 46,XY DSD. GATA4 is known to be associated with 46,XY DSD and has also been described to cause congenital heart defects. The authors characterize 3 individuals with 46,XY DSD, and GATA4 variants; 1 patient with and 2 without congenital heart defects. They show that additional mutations/variants in other genes, LRP4 and LHCGR, resulted in a different phenotypic manifestation of GATA4 mutations, with or without concomitant heart defect. This paper highlights the complexity of the genetics in genital development and its interactions with other genes. The use of whole genome sequencing has opened a whole new era of genetics. It is likely that in the future complex interactions between two or more genes in the pathways involved in sex determination and differentiation will be revealed.

DOI:10.1530/ey.15.6.14

To read the full abstract: [Front Endocrinol \(Lausanne\). 2018 Apr 4;9:142](#)

When should an extensive genetic investigation be performed?

JC, Siffroi JP, McElreavey K, Bashamboo A.
Human Developmental Genetics, Institut Pasteur, Paris 75724, France.

6.15 Mutations involving the SRY-related gene SOX8 are associated with a spectrum of human reproductive anomalies

Portnoi MF, Dumargne MC, Rojo S, Witchel SF, Duncan AJ, Eozenou C, Bignon-Topalovic J, Yatsenko SA, Rajkovic A, Reyes-Mugica M, Almstrup K, Fusee L, Srivastava Y, Chantot-Bastaraud S, Hyon C, Louis-Sylvestre C, Validire P, de Malleray Pichard C, Ravel C, Christin-Maitre S, Brauner R, Rossetti R, Persani L, Charreau EH, Dain L, Chiauzzi VA, Mazen I, Rouba H, Schluth-Bolard C, MacGowan S, McLean WHI, Patin E, Rajpert-De Meyts E, Jauch R, Achermann

To read the full abstract: [Hum Mol Genet. 2018 Apr 1;27\(7\):1228-1240](#)

[See comment on 6.16](#)

DOI:10.1530/ey.15.6.15

When should an extensive genetic investigation be performed?

6.16 Family history is under-estimated in children with isolated hypospadias: a French multicenter report of 88 families.

Ollivier M, Paris F, Philibert P, Garnier S, Coffy A, Fauconnet-Servant N, Haddad M, Guys JM, Reynaud R, Faure A, Merrot T, Wagner K, Bréaud J, Valla JS, Dobremez E, Gaspari L, Daures JP, Sultan C, Kalfa N.
Département de Chirurgie et Urologie Pédiatrique, Hôpital Lapeyronie, CHU de Montpellier et Université Montpellier, Montpellier, France.

To read the full abstract: [J Urol. 2018 Apr 30. pii: S0022-5347\(18\)43073-X](#)

[Comments on 6.15 and 6.16] There is ongoing discussion regarding when extended genetic tests are indicated in DSD. There is also a discussion regarding what should be included in the definition of DSD. Are mild forms of hypospadias a type of DSD and where should we draw the line for more extensive investigations? Both of these papers present data in favour of more frequent investigations, even in some mild cases.

First, Portnoi et al. (6.15) report that SOX8 is expressed in the developing gonad in humans, is of importance for sex determination and mutations can cause a large spectrum of severity. Two patients with 46,XY DSD had chromosomal arrangements

involving the HMG-box of SOX8. The authors also analyzed SOX8 in infertile men (n= 274) and women (n= 257). Mutations in SOX8 were more common in infertile men (3.5%) and in women with premature ovarian failure (5.1%) than in controls. The results strengthening the notion that factors causing DSD in some patients can, in a less severe form, cause infertility in others. This finding extends the discussion about which patients should undergo extensive genetic investigations of the sex development pathways.

Family history on fertility issues has an important clinical bearing, and can serve to guide the genetic investigations. In addition, mutations identified to cause infertility may contribute important information for understanding sex differentiation and development. Previously, familial clustering of hypospadias was reported as ~10% and the risk of recurrence in male siblings to be ~15%.

Ollivier et al. (6.16) report a French multicenter study showing that hereditary cases are considerably more common than previously thought. Family histories should be taken more carefully. When the authors asked about heredity in a structured way, and on two occasions, a substantial number of cases were revealed to have one or more relatives with genital anomalies. Such information should prompt a more extensive genetic investigation. Hence, repeated questioning of family history, both concerning genetic anomalies and infertility, are important and should inform further genetic investigations. Familial cases of hypospadias are not more severe; hence, severity should not be the only parameter when deciding about genetic investigations.

DOI:10.1530/ey.15.6.16

Psychological aspects

6.17 Methodological Issues for Psychological Evaluation across the Lifespan of Individuals with a Difference/Disorder of Sex Development

D'Alberton F, Vissani S, Ferracuti C, Pasterski V.
Department of Pediatrics, S. Orsola-Malpighi Bologna University Hospital, Bologna, Italy.

To read the full abstract: [Sex Dev. 2018;12\(1-3\):123-134](#)

There is a paucity of psychological follow-up studies in DSD patients. This is especially problematic since differences in sex development often affect the individual in fundamental ways that are related to their self-perception and social experiences. In this paper, the authors explain, in an illustrative way, the different strategies that can be used in the clinic to identify and assess psychological issues in individuals with DSD. This article gives useful information for clinicians and researchers to identify, assess and address the specific questions and psychological issues that may arise. The methodological issues discussed in the article provide the tools for such work. As exemplified by the next article (6.18), individuals with a DSD seem to be more vulnerable and may need professional psychological support, which should be included in all multidisciplinary teams.

DOI:10.1530/ey.15.6.17

Psychological aspects

6.18 Increased psychiatric morbidity in women with complete androgen insensitivity syndrome or complete gonadal dysgenesis.

Engberg H, Strandqvist A, Nordenström A, Butwicka A, Nordenskjöld A, Hirschberg AL, Frisén L.
Karolinska Institutet, Stockholm Sweden

To read the full abstract: [J Psychosom Res. 2017 Oct;101:122-127](#)

The results of this study clearly show individuals with a DSD condition have

psychological difficulties, and not only in countries with a less well developed health care systems, as reported by Khorashad et al. 2018. The findings indicate that having a DSD may impose a type of stress and vulnerability that is more common than seen in other types of endocrine conditions, possibly since sex and gender issues are fundamental and intrinsically related to the sense of self and personal identity. Individuals with DSD may be more vulnerable than other groups and the health care system and the teams taking care of individuals with a DSD should be aware of this and provide the psychological or psychiatric support when needed.

Khorashad BS, Aghili Z, Kreukels BPC, Reid AG, Roshan GM, Hirdfar M, Talaei A, Cohen Kettens PT. Mental Health and Disorders of Sex Development/Intersex Conditions in Iranian Culture: Congenital Adrenal Hyperplasia, 5- α Reductase Deficiency-Type 2, and Complete Androgen Insensitivity Syndrome. Arch Sex Behav. 2018 May;47(4):931-942.

DOI:10.1530/ey.15.6.18

Reviews of clinical importance

6.19 Disorders of sex development.

Witchel SF

Division of Pediatric Endocrinology, Children's Hospital of Pittsburgh of UPMC,
University of Pittsburgh, Pittsburgh, PA, USA

To read the full abstract: [Best Pract Res Clin Obstet Gynaecol 2018 Apr;48:90-102](#)

[See comment on 6.20](#)

DOI:10.1530/ey.15.6.19

Reviews of clinical importance

6.20 Caring for individuals with a difference of sex development (DSD): a Consensus Statement

Cools M, Nordenström A, Robeva R, Hall J, Westerveld P, Flick C, Köhler B, Berra M, Springer A, Schweizer K, Pasterski V; COST Action BM1303 working group.

Department of Paediatric Endocrinology, Ghent University Hospital, University of Ghent, Ghent, Belgium.

To read the full abstract: [Nat Rev Endocrinol. 2018 May 16](#)

[Comments on 6.19 and 6.20] These two publications, a review and a consensus statement, are especially useful in the clinical care for individuals with disorders affecting the sex development, albeit in different ways. Since the Chicago consensus in 2005, the knowledge of the pathophysiology and molecular genetics behind disorders of sex development has developed rapidly. The diagnostics in DSD has new possibilities with the use of molecular genetic investigations and the implementation whole genome sequencing.

First, Witchel (6.19) provides a comprehensive update on embryology, genetics, classification of DSD. It gives useful advice for how to perform a well-structured clinical and genetic initial investigation to reach a molecular diagnosis. Valuable aspects and advice for the clinical management of individuals with a DSD in multidisciplinary teams are discussed.

Secondly, (6.20) the consensus statement was developed by a European multidisciplinary group of experts, including patient representatives, in the COST Action DSDNet. The diagnostics in DSD has improved with the implementation of molecular and whole genome sequencing. Knowledge of a specific diagnosis allows personalized care. However, a prerequisite is knowledge about the natural course of the disorder and its short term as well as long term effects. Despite improvements in management and the formation of multidisciplinary teams, individuals with a DSD often have difficulties finding health care specialists knowledgeable in the field of their specific DSD. To further the understanding of long term outcomes and effects of these conditions and improve the current and future management, a structured follow up is needed. This consensus covers a large number of issues of importance for both somatic and psychological follow up of individuals with a DSD and may be important for teams and clinicians both in pediatric and adult care. The authors address both clinical management of DSD and the need for future studies that can be facilitated by a structured clinical follow up and the use of registries.

DOI:10.1530/ey.15.6.20

New concept: Epigenetic control of puberty

7. Puberty

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In the puberty field, this year brought new evidence regarding the epigenetic control of puberty. Recent studies confirm that the epigenetic switch from transcriptional repression to activation plays a crucial role in the hypothalamic mechanism controlling

the timing of mammalian puberty.

We can also see that, although sometime difficult to differentiate in term of clinical presentation, constitutional delay of growth and puberty and hypogonadotropic hypogonadism have a different genetic architecture. Along this line, this chapter summarizes the discovery of new genes involved in hypogonadotropic hypogonadism. My aim was to present a mix of experimental and clinical studies. This summary also presents new understanding of the role of kisspeptin in puberty, the incidence of long term psychopathology in patients with early onset of puberty and the secular trends in growth and puberty in Turner patients.

DOI:10.1530/ey.15.7

New concept: Epigenetic control of puberty

7.1 Trithorax dependent changes in chromatin landscape at enhancer and promoter regions drive female puberty

Toro CA, Wright H, Aylwin CF, Ojeda SR, Lomniczi A
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To read the full abstract: [Nat Commun. 2018 Jan 4;9\(1\):57](#)

The hypothalamic-pituitary-gonadal axis controls the onset of puberty and the acquisition of the reproductive function. A subset of neurons in the anterior hypothalamus secretes gonadotropin-releasing hormone (GnRH) which, through its pattern of release controls all aspects of reproduction throughout life. The secretory activity of GnRH neurons depends on trans-synaptic and glial inputs mediated by neurotransmitters and cell-cell signaling molecules¹. Primary trans-synaptic mechanisms underlying pulsatile GnRH release involve a specialized subset of neurons located in the arcuate nucleus of the medial basal hypothalamus. They have been termed KNDy neurons, because they produce kisspeptin, neurokinin B and dynorphin. The authors had previously shown that the secretory activity of KNDy neurons is kept in check during female prepubertal development by an epigenetic mechanism of transcriptional repression, exerted by the Polycomb group (PcG) of transcriptional silencers¹⁻³. PcG proteins repress the Kiss1 gene to prevent the premature initiation of

the pubertal process, and this effect takes place against a backdrop of repressive chromatin, that is, rich in histone modifications associated with gene repression and depleted of histone modifications associated with gene activation.

Here, the authors now show that, on the one hand, MLL1 recruited to the promoter region of Kiss1 and Tac3 establishes a permissive chromatin configuration required for transcriptional activation. On the other hand, MLL3 acts at an ARC-specific Kiss1 enhancer site to implement a chromatin structure that facilitates enhancer activation. As these changes take place, eviction of key member of the PcG complex from the Kiss1 enhancer and from the Kiss1 (encoding Kisspeptin) and Tac3 (encoding Neurokinin B) promoters results in loss of PcG-mediated repression at each of these genomic sites. Thus, the authors identified the presence of both repressive and stimulatory epigenetic pathways regulating Kiss1 and Tac3 expression in KNDy neurons. This suggests that a switch from epigenetic repression to activation within these neurons underlies the developmental process by which GnRH release increases by late juvenile development to bring about the pubertal process.

1. Lomniczi A, Wright H, Ojeda SR. Epigenetic regulation of female puberty. *Front Neuroendocrinol.* 2015 Jan;36:90-107.

2. Lomniczi A, Wright H, Castellano JM, Matagne V, Toro CA, Ramaswamy S, Plant TM, Ojeda SR. Epigenetic regulation of puberty via Zinc finger protein-mediated transcriptional repression. *Nat Commun.* 2015 Dec 16;6:10195

3. Lomniczi A, Loche A, Castellano JM, Ronnekleiv OK, Bosch M, Kaidar G, Knoll JG, Wright H, Pfeifer GP, Ojeda SR. Epigenetic control of female puberty. *Nat Neurosci.* 2013 Mar;16(3):281-9.

DOI:10.1530/ey.15.7.1

Review: Epigenetic control of female puberty

7.2 Hypothalamic Epigenetics Driving Female Puberty

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To read the full abstract: [J Neuroendocrinol. 2018; 30\(7\): e12589](#)

Classically, the re-awakening of the GnRH system around puberty is considered to be under the control of a variety of genes that work in coordinated networks operating in

the hypothalamus¹. Very recent evidence suggests that a dual mechanism of epigenetic regulation affecting the transcriptional activity of neurons involved in stimulating gonadotropin-releasing hormone release plays a fundamental role in the timing of puberty. The interaction between epigenetic activation and repression of gene transcription seems to be the core of a process by which epigenetic mechanisms are able to modulate the development of the pubertal process. Further studies will be needed to identify how epigenetic pathways convey information from a wide range of environmental signals to hypothalamic neurons regulating the onset of puberty.

1. Ojeda SR, Lomniczi A. Puberty in 2013: Unravelling the mystery of puberty. *Nat Rev Endocrinol.* 2014 Feb;10(2):67-9.

DOI:10.1530/ey.15.7.2

Adolescence and behavior

7.3 Age at Menarche, Depression, and Antisocial Behavior in Adulthood

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To read the full abstract: [Pediatrics. 2018 Jan;141\(1\)](#)

Changes in biology, appearance, self-perception, behavior, and emotion make puberty one of the most pivotal phases in life. Although puberty presents challenges for all adolescents, girls who mature early are particularly vulnerable. Early pubertal timing in

girls has been reported to be associated with increased prevalence and severity of psychopathology through late adolescence¹. However, very few studies have focused on the long term impact of earlier development. This study suggests that girls who experienced earlier menarche continued to show higher rates of depressive symptoms and antisocial behaviors in early-to-middle adulthood even after accounting for demographic and contextual variables commonly associated with vulnerability for mental health. A challenge for future researchers is to specify the cognitive, social, neural, and biological mechanisms that mediate this continued risk and hopefully reverse them.

1. Mendle J, Turkheimer E, Emery RE. Detrimental Psychological Outcomes Associated with Early Pubertal Timing in Adolescent Girls. *Dev Rev.* 2007 Jun;27(2):151-171.

DOI:10.1530/ey.15.7.3

Adolescence and behavior

7.4 Media use and brain development during adolescence

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To read the full abstract: [Nat Commun. 2018 Feb 21;9\(1\):588](#)

Media-related activities take up roughly 6–9 hours of the average American youth's day. Likely, this plays an important role in adolescent development. Recently, cognitive neuroscience studies have used structural and functional magnetic resonance imaging (fMRI) to examine brain changes over the course of adolescence. Cognitive and socio-affective development in adolescence is accompanied by extensive changes in the structure and function of the adolescent brain¹. Structurally, white matter connections increase, allowing for more successful communication between the prefrontal cortex

and the subcortical striatum. Pruning rates increase in adolescence, resulting in a decrease in synaptic density. In parallel, dynamic nonlinear changes in grey matter volume continue over the whole period of adolescence. Interestingly, changes in grey matter volume are observed most extensively in brain regions that are important for social understanding and communication such as the medial prefrontal cortex, superior temporal cortex and temporal parietal junction. Studies indicate a specific window of sensitivity to social rejection in adolescence, which may be associated with the enhanced activity of striatum and subgenual anterior cingulate cortex. Likewise, being socially accepted through "likes" resulted in increased activity in the ventral striatum in children, adolescents and adults. This response is blunted in adolescents who experience depression, or who have experienced a history of maternal negative affect. Data suggest that peer sensitivities are possibly larger in adolescents than in older age groups. Critical question for future research is how neural correlates observed in this review predict future behavior or emotional responses in adolescents.

1. Blakemore SJ, Mills KL. Is adolescence a sensitive period for sociocultural processing? *Annu Rev Psychol.* 2014;65:187-207.

DOI:10.1530/ey.15.7.4

7.5 Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk

Day FR, Thompson DJ, Helgason H, Chasman DI, Finucane H, Sulem P, et al
MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine,

To read the full abstract: [Nat Genet. 2017 Jun;49\(6\):834-841](#)
See comment on 7.6

DOI:10.1530/ey.15.7.5

Genetic variants and timing of puberty

7.6 Differential Impact of Genetic Loci on Age at Thelarche and Menarche in Healthy Girls

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To read the full abstract: [J Clin Endocrinol Metab. 2018 Jan 1;103\(1\):228-234](#)

[Comments on 7.5 and 7.6] Remarkably, the timing of puberty shows important differences between individuals¹. Based on twin studies, differences in pubertal timing are considered to depend on genetic factors which account for up to 60-70% of the variance, while environmental factors also influence pubertal timing. Based on recall of age at menarche, almost 400 genetic loci have been shown to be associated with this late pubertal event, explaining 7.4% of the population variance². The first study reports an enlarged genomic analysis for age at menarche in a very large sample of women using densely imputed genomic data. These findings increase by more than three-fold the number of independently associated signals and bring growing evidence for a significant role of imprinted genes in the regulation of puberty timing. In addition, the

reported data support new causal links with susceptibility to sex-steroid-sensitive cancers in women and men. Increasing age at menarche was associated with lower risk for breast, ovarian and endometrial cancer in women, and lower risk of prostate cancer in men.

The vast majority of genome wide studies focus on age at menarche to identify genetic determinants of puberty timing. However, the initial clinical hallmark of female pubertal onset is thelarche. In the second study, a population-based study comprising 1478 healthy Danish girls, the researchers observed a differential impact of genetic variations in FSHR and FSHB on timing of thelarche and menarche. Whereas LIN28B (rs7759938) was associated with both thelarche and menarche, FSHB c.2211G.T and FSHR c.229G.A were associated with age at thelarche, but not with age at menarche. This study is the first to report a differential impact of distinct genetic loci on different female pubertal milestones. It stresses the value of precise endpoint definition in genetic association studies.

1. Parent AS, Franssen D, Fudvoye J, Gérard A, Bourguignon JP. Developmental variations in environmental influences including endocrine disruptors on pubertal timing and neuroendocrine control: Revision of human observations and mechanistic insight from rodents. *Front Neuroendocrinol.* 2015 Jul;38:12-36.

2. Perry JR, Day F, Elks CE, Sulem P, Thompson DJ, et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature.* 2014 Oct 2;514(7520):92-97.

DOI:10.1530/ey.15.7.6

Genetic architecture of hypogonadotropic hypogonadism and delayed puberty

7.7 Genes underlying delayed puberty

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To read the full abstract: [Mol Cell Endocrinol. 2018 May 4; S0303-7207\(18\)30149-7](#)
See comment on 7.8

DOI:10.1530/ey.15.7.7

Genetic architecture of hypogonadotropic hypogonadism and delayed puberty

7.8 Congenital hypogonadotropic hypogonadism and constitutional delay of growth and puberty have distinct genetic architectures

Cassatella D, Howard SR, Acierno JS, Xu C, Papadakis GE, Santoni FA, Dwyer AA, Santini S, Sykiotis GP, Chambion C, Meylan J, Marino L, Favre L, Li J, Liu X, Zhang J, Bouloux PM, Geyter C, Paepe A, Dhillo WS, Ferrara JM, Hauschild M, Lang-Muritano M, Lemke JR, Flück C, Nemeth A, Phan-Hug F, Pignatelli D, Popovic V, Pekic S, Quinton R, Szinnai G, l'Allemand D, Konrad D, Sharif S, Iyidir ÖT, Stevenson BJ, Yang H, Dunkel L, Pitteloud N
Service of Endocrinology Diabetology and Metabolism, Lausanne University Hospital, Lausanne, Switzerland

To read the full abstract: [Eur J Endocrinol. 2018 Apr;178\(4\):377-388](#)

[Comments on 7.7 and 7.8] Familial self-limited delayed puberty is highly heritable and has a clear genetic basis as described in the review written by Sasha Howard. Recent studies suggest that the genetic basis of self-limited delayed puberty is likely to be highly heterogeneous and involve abnormalities of GnRH neuronal development, function, and its downstream pathways, metabolic and energy homeostatic derangements, and transcriptional regulation of the hypothalamic-pituitary-gonadal axis. Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder affecting approximately 1:4000 births¹. It is caused by GnRH deficiency, and subsequently results in altered activation of the hypothalamic-pituitary-gonadal axis that controls

sexual maturation and fertility. Congenital delay of growth and puberty (CDGP) and CHH are part of a continuum of GnRH deficiency, ranging from transiently delayed to a complete absence of puberty. Therefore, CDGP, also termed self-limited delayed puberty, and CHH appear to be part of the same clinical spectrum². In contrast to CHH, CDGP is a common disease, observed in 2–2.5% of the population. Currently, the differential diagnosis between CHH and CDGP at early adolescence remains challenging, as both conditions present with isolated delay in puberty.

Cassatella et al. studied a cohort of 116 CHH probands of European descent ($n=61$ Kallmann Syndrome, $n=55$ normosmic CHH) and 72 unrelated probands with CDGP of primarily Finnish European origin. Ethnically matched controls were used to compare individual variant and gene mutation frequencies. They found that the genetic profiles of CHH and CDGP were different. CHH and CDGP differed in the number of patients harboring mutations in individual CHH genes (51% vs 7%). Nearly two-thirds of familial CHH probands carried mutations in CHH genes (61%), while the frequency in sporadic CHH probands was lower (44%). *FGFR1* and *CHD7* were the most frequently mutated genes in CHH probands. CHH and CDGP patients also differed in their overall mutational load of CHH genes (oligogenicity). The majority of CHH genes were inherited in an oligogenic fashion in CHH probands, a trend not observed in CDGP probands. Larger studies examining gene pathways, rather than individual genes identified by genome-wide association studies, are required to further elucidate the genetic overlap between CHH and CDGP.

1. Mitchell AL, Dwyer A, Pitteloud N & Quinton R. Genetic basis and variable phenotypic expression of Kallmann syndrome: towards a unifying theory. *Trends in Endocrinology and Metabolism* 2011; 22: 249–258.
2. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, Dwyer AA, Giacobini P, Hardelin JP, Juul A et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism – pathogenesis, diagnosis and treatment. *Nature Reviews Endocrinology* 2015 ; 11: 547–564.

DOI:10.1530/ey.15.7.8

Genetic architecture of hypogonadotropic hypogonadism and delayed puberty

7.9 Contributions of Function-Altering Variants in Genes Implicated in Pubertal Timing and Body Mass for Self-Limited Delayed Puberty

Howard SR, Guasti L, Poliandri A, David A, Cabrera CP, Barnes MR, Wehkalampi K, O'Rahilly S, Aiken CE, Coll AP, Ma M, Rimmington D, Yeo GSH, Dunkel L. Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, U

To read the full abstract: [J Clin Endocrinol Metab. 2018 Feb 1;103\(2\):649-659](#)

A minimum level of energy availability is required for the onset of puberty, whereas increased fat mass has been shown to be associated with precocious onset of puberty^{1,2}. Recent genome-wide association studies have identified several loci for age at menarche also associated with obesity³⁻⁵. Whether such genes may regulate pubertal timing exclusively via impact on fat mass or via other body mass index (BMI)-independent mechanisms is unknown. Here, Howard et al. performed whole-exome sequencing in 67 families with delayed puberty and 35 controls. They identified potentially pathogenic, rare variants in genes in linkage disequilibrium with genome-wide association studies of age at menarche loci in 283 genes. Of these, five genes were implicated in the control of body mass. After filtering for segregation with trait, only one candidate gene, fat mass and obesity-associated gene (FTO), was retained. FTO has been previously described in the literature as involved in pathways of energy homeostasis and growth. It was the first obesity-susceptibility gene identified through genome wide association studies and continues to be the locus with the largest effect on BMI and obesity risk. FTO has been identified as an amino acid sensor acting, via mTOR, to influence appropriate levels of development and translation⁶. It is expressed within the hypothalamus in several sites critical for energy balance, including in the arcuate nucleus within pro-opiomelanocortin neurons⁷. *In*

silico analysis indicated that the patients' mutations may have a subtle effect in protein-protein interaction and lead to a change in FTO activity *in vivo*. Those patients with delayed puberty identified with FTO variants showed reductions in body mass. The FTO variants carried by the DP patients may result in reduced fat mass, which would in turn contribute to a delay in the timing of pubertal onset. FTO deficiency *in vivo* results in delayed puberty marked by vaginal opening in mice. Notably, body weight was not significantly different between the two pup genotype groups. In summary, those results have identified variants in FTO as a potential contributory factor in the development of self-limited delayed puberty.

1. Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. *Pediatrics*. 2001;108(2):347-353.
2. He Q, Karlberg J. BMI in childhood and its association with height gain, timing of puberty, and final height. *Pediatr Res*. 2001;49(2):244-251.
3. C.E. Elks, J.R. Perry, P. Sulem, D.I. Chasman, N. Franceschini, C. He, K.L., et al. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat Genet* 2010; 42: 1077-85.
4. M. den Hoed, U. Ekelund, S. Brage, A. Grontved, J.H. Zhao, S.J. Sharp, K.K. Ong, N.J. Wareham, and R.J. Loos, Genetic susceptibility to obesity and related traits in childhood and adolescence: influence of loci identified by genome-wide association studies. *Diabetes* 2010; 59: 2980-8.
5. L. Fernandez-Rhodes, E.W. Demerath, D.L. Cousminer, R. Tao, J.G. Dreyfus, T. Esko, et al. Association of adiposity genetic variants with menarche timing in 92,105 women of European descent. *Am J Epidemiol* 2013; 178: 451-60.
6. Speakman JR. The "fat mass and obesity related" (FTO) gene: mechanisms of impact on obesity and energy balance. *Curr Obes Rep*. 2015;4(1):73-91.
7. Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, Galvanovskis J, Rorsman P, Robins P, Prieur X, Coll AP, Ma M, Jovanovic Z, Farooqi IS, Sedgwick B, Barroso I, Lindahl T, Ponting CP, Ashcroft FM, O'Rahilly S, Schofield CJ. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science*. 2007;318(5855):1469-1472.

DOI:10.1530/ey.15.7.9

7.10 DCC/NTN1 complex mutations in patients with congenital hypogonadotropic hypogonadism impair GnRH neuron development

Bouilly J, Messina A, Papadakis G, Cassatella D, Xu C, Acierno JS, Tata B, Sykiotis G, Santini S, Sidis Y, Elowe-Gruau E, Phan-Hug F, Hauschild M, Bouloux PM, Quinton R, Lang-Muritano M, Favre L, Marino L, Giacobini P, Dwyer AA, Niederländer NJ, Pitteloud N
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To read the full abstract: [Hum Mol Genet. 2018 Jan 15;27\(2\):359-372](#)

See comment on 7.11

DOI:10.1530/ey.15.7.10

New genes in hypogonadotropic hypogonadism

7.11 KLB, encoding β -Klotho, is mutated in patients with congenital hypogonadotropic hypogonadism

Xu C, Messina A, Somm E, Miraoui H, Kinnunen T, Acierno J Jr, Niederländer NJ, Bouilly J, Dwyer AA, Sidis Y, Cassatella D, Sykiotis GP, Quinton R, De Geyter C, Dirlewanger M, Schwitzgebel V, Cole TR, Toogood AA, Kirk JM, Plummer L, Albrecht U, Crowley WF Jr, Mohammadi M, Tena-Sempere M, Prevot V, Pitteloud N

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To read the full abstract: [EMBO Mol Med. 2017 Oct;9\(10\):1379-1397](#)

[Comments on 7.10 and 7.11] During embryonic development, GnRH neurons originate in the olfactory placode and migrate through the nasal mesenchyme using the olfactory/vomeroneasal axons as a scaffold to reach their final destination in the basal forebrain^{1,2}. This migratory process has been well-described in rodents, and is tightly controlled by a complex network of genes encoding molecular cues that drive GnRH neuron motility, cell adhesion and directionality². Defects disrupting the genesis, migration of GnRH neurons and/or synthesis and secretion of GnRH in humans can lead to congenital hypogonadotropic hypogonadism (CHH). Alteration of the prenatal development and/or migration of GnRH neurons is generally associated with Kallmann syndrome (KS), and disruption of the synthesis, release or signaling of GnRH is commonly associated with normosmic CHH (nCHH). The two studies summarized here illustrate the role of new factors involved in GnRH neurons development and migration.

First, Bouilly et al. tested a hypothesis based on the observation that causal mutations in CHH have illustrated the crucial role of fibronectin type 3 (FN3)-domain containing proteins in GnRH neuron development. For this reason, using whole exome sequencing in CHH patients, the authors filtered their results to include only those genes encoding proteins containing FN3-domains. This strategy identified rare sequence variants in genes encoding for the FN3-domain encoding protein deleted in colorectal cancer (DCC) and its ligand Netrin-1 (NTN1). Proband had severe GnRH deficiency with absent puberty, and all males had a history of micropenis with/without cryptorchidism. *In vitro* analysis revealed that all identified NTN1 and DCC variants

do not impair transcript or protein expression but modify biological activity and causes signaling defects. NTN1 mutations affected GnRH neuron migration using immortalized GnRH neurons cell motility assays. Netrin-1 and DCC are expressed in the developing human vomeronasal organ (VNO), the surrounding tissue extending from the VNO towards the forebrain, and in GnRH neurons. Moreover, Netrin-1 was also expressed in other cell types belonging to the migratory cell population. In summary, this study further illustrates the role of loss-of-function mutations in FN3-domain encoding proteins in CHH. This underlines the role of these proteins in cell migration and axonal guidance in GnRH neurons during embryonic development.

Secondly, Xu et al. hypothesized that defects in the FGF21/KLB/FGFR1 signaling pathway may underlie GnRH deficiency in both humans and rodents. Fibroblast growth factor receptor 1 (FGFR1) plays a crucial role in GnRH neuron fate specification during embryonic life, but also in GnRH network homeostasis and FGFR1 mutations are present in approximately 10% of CHH cases and are often associated with incomplete penetrance and variable expressivity. The authors noted that a CHH FGFR1 mutation decreased signaling of the metabolic regulator FGF21 by impairing the association of FGFR1 with β -Klotho (KLB), the obligate co-receptor for FGF21. Genetic screening of 334 CHH patients identified seven heterozygous loss-of-function Klb mutations. The clinical spectrum ranged from severe GnRH deficiency with micropenis and cryptorchidism to milder forms such as CHH with reversal or fertile eunuch syndrome. All Klb mutants were confirmed to be loss of function *in vitro* as well as *in vivo* using a rescue assay in *C. elegans*. Klb deficient mice showed a normal distribution of hypothalamic GnRH neurons and axonal projections to the median eminence, indicating normal embryonic GnRH neurons development. However, they exhibited delayed puberty and subfertility due to a hypothalamic defect. Intraperitoneal injection of Kisspeptin injections also induced LH secretion in both wild-type and Klb knock-out females, suggesting that GnRH neurons were present and could respond to stimulation. These results implicate Klb in hypothalamic GnRH secretion. Klb mutations impair FGF21 signaling in patients with congenital GnRH deficiency with a high frequency of associated metabolic defects. This supports the key role of the hepatokine FGF21, as a key link between metabolism and reproduction.

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DOI:10.1530/ey.15.7.11

Kisspeptin and puberty

7.12 Role of Kisspeptin and Neurokinin B in Puberty in Female Non-Human Primates. Review

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To read the full abstract: [Front Endocrinol \(Lausanne\). 2018 Apr 6;9:148](#)

Pubertal onset and subsequently reproduction result from the awakening of a complex neuroendocrine machinery leading to the acceleration of the gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus. Several neuronal, glial or peripheral factors have been identified as playing a major role in the onset of puberty¹. This paper reviews data obtained in non-human primates illustrating the crucial role played by kisspeptin and neurokinin B (NKB) in this pubertal activation of GnRH secretion. Both kisspeptin and NKB signaling appear to contribute to the pubertal increase in GnRH release independently or in concert in females while there seems to have no interaction between kisspeptin and NKB in sexually immature females. The contribution of direct NKB signaling to GnRH release, however, may be secondary, as NKB signaling to GnRH release does not change across puberty, whereas NKB signaling to kisspeptin

release greatly increases. Thus, in females, kisspeptin signaling appears to be the main force driving the pubertal GnRH release increases. The role of NKB in the pubertal increase in GnRH release, however, requires further experiments. In females, reciprocal signaling pathways between kisspeptin and NKB neurons could provide the necessary efficiency and flexibility for the stimulation of GnRH release, which ensures complex reproductive functions, such as cyclic ovulations and pregnancy.

Separately, Chan et al.² recently described the first report of kisspeptin administration to pediatric subjects. Adult cohorts show either uniform responsiveness to kisspeptin (healthy adults) or uniform lack of responsiveness (adults with idiopathic hypogonadotropic hypogonadism). The ability to use kisspeptin to probe GnRH neuronal function presents a potential solution to a frequently encountered clinical challenge: the child presenting with delayed puberty. Children with delayed/stalled puberty showed a wide range of responses, with some showing a robust response and others showing little to no response. Further follow-up will determine whether responses to kisspeptin predict future pubertal entry for children with delayed puberty. The kisspeptin stimulation test has the potential to be a physiologically based method for diagnosing idiopathic hypogonadotropic hypogonadism in childhood.

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DOI:10.1530/ey.15.7.12

Secular trends and Turner syndrome

7.13 Secular Trends on Birth Parameters, Growth, and Pubertal Timing in Girls with Turner Syndrome

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To read the full abstract: [Front Endocrinol \(Lausanne\). 2018 Feb 28;9:54](#)

Secular trends in birth parameters¹⁻³, growth^{4,5}, and timing of puberty⁶⁻⁸ are observed in normal populations. Changes in nutrition, better access to health care, and other environmental factors have been implicated as causative factors for those changes. Here, the authors assessed secular trends in birth parameters, spontaneous growth and pubertal development in patients with Turner syndrome. They found a highly significant secular trend for GH-untreated height at 8 years of age. In addition, secular trends for height were present at the start of GH treatment and at the start of puberty. Reported secular trends in height in normal populations differ between countries. Eastern and developing countries still show marked positive secular trends, while Western countries show only small or even negative secular trends in growth. In contrast, Turner syndrome girls included a wide variety of ethnicities, yet the positive secular trend in height SDS at the age of 8 years was observed for all, irrespective from their country of residence. The authors also found a small positive secular trend for birth weight, but only a minor trend in birth length. These findings are consistent

with other data on healthy term infants. Finally, they also found a substantial decline in the age at spontaneous thelarche, of about 2 years between those born before 1980 to those born in 2000–2004. Furthermore, the prevalence in spontaneous puberty onset doubled between before 1980 to 1995–1999. In addition to these environment-related trends, awareness for Turner syndrome seems to have improved, leading to earlier ages at the start of GH and pharmacological induction of puberty.

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8 Adrenals

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P8.

For this year's chapter on 'Adrenals', we have searched the PubMed for articles on 'adrenal' or 'steroidogenesis' published in English between June 1, 2017 and May 31, 2018. Our search yielded more than 5,000 citations. We have examined all citations individually and selected the following collection of basic research and clinical articles. Whenever possible, we have avoided topics that have been discussed in the Yearbook 2017, unless progress in the field has been incremental. Emerging themes for this year's chapter include: i) Mutations in the CLCN2 chloride channel cause Familial Hyperaldosteronism type II; ii) the ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man; iii) advances in the diagnosis and treatment of 21-hydroxylase deficiency; iv) guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients; and v) the role of microRNAs in glucocorticoid action.

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8.1 CLCN2 chloride channel mutations in familial hyperaldosteronism type II

Scholl UI, Stölting G, Schewe J, Thiel A, Tan H, Nelson-Williams C, Vichot AA, Jin SC, Loring E, Untiet V, Yoo T, Choi J, Xu S, Wu A, Kirchner M, Mertins P, Rump LC, Onder AM, Gamble C, McKenney D, Lash RW, Jones DP, Chune G, Gagliardi P, Choi M, Gordon R, Stowasser M, Fahlke C, Lifton RP
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To read the full abstract: [Nat Genet. 2018; 50\(3\): 349-354](#)

See comment on 8.2

DOI:10.1530/ey.15.8.1

8.2 A gain-of-function mutation in the CLCN2 chloride channel gene causes primary aldosteronism

Fernandes-Rosa FL, Daniil G, Orozco IJ, Göppner C, El Zein R, Jain V, Boulkroun S, Jeunemaitre X, Amar L, Lefebvre H, Schwarzmayr T, Strom TM, Jentsch TJ, Zennaro MC
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To read the full abstract: [Nat Genet. 2018; 50\(3\): 355-361](#)

[Comments on 8.1 and 8.2] Primary aldosteronism (PA) is the most common form of secondary hypertension, affecting 3–5% of the general hypertensive population and 8–10% of patients referred to specialist hypertension services, although it is very rare in children (1). In comparison to essential hypertension, increased aldosterone concentrations in PA are associated with increased cardiovascular risk (probably due to MR expressed in endothelial, vascular smooth muscle and immune cells) in particular coronary artery disease, heart failure, renal damage and stroke (2). The main causes of PA are bilateral adrenal hyperplasia (BAH) and unilateral aldosterone-producing adrenal adenoma (APA), whereas inherited forms of PA, such as familial hyperaldosteronism (FH) type 1 and 3, account for fewer than 1% of cases. Gain-of-function mutations in different genes, encoding cation channels (*KCNJ5*, *CACNA1D*, *CACNA1H*) and ATPases (*ATP1A1*, *ATP2B3*), regulating intracellular ion homeostasis and plasma membrane potential, have been described in APAs and familial forms of PA, but the pathophysiology of many cases is still unknown.

In 1992, Stowasser et al. described a multiplex kindred with autosomal dominant PA that was clinically distinct from FH-I, and hence called it FH-II (3). The responsible gene in this kindred had not been identified. In the first study by Scholl et al., the authors recruited an additional affected individual of this kindred and performed exome sequencing of 3 affected subjects. They also analyzed 80 additional probands with unsolved early-onset PA. 8 probands had novel heterozygous variants in *CLCN2*, including 2 de novo mutations and 4 independent occurrences of a mutation encoding an identical p.Arg172Gln substitution; all relatives with early-onset PA carried the *CLCN2* variant found in the proband. In the second study by Fernandes-Rosa et al., the

authors performed whole-exome sequencing in patients with early-onset PA and identified a de novo heterozygous c.71G>A/p.Gly24Asp mutation in the *CLCN2* gene, encoding the voltage-gated CIC-2 chloride channel, in a patient diagnosed with PA at 9 years of age.

CIC-2, the chloride channel encoded by *CLCN2*, is expressed in many tissues, including brain, kidney, lung and intestine. In addition, *CLCN2* RNA is found in the adrenal gland. Immunohistochemistry with an antibody specific for CIC-2 showed intense staining of human adrenal zona glomerulosa, consistent with a role in regulating aldosterone production. Patch-clamp analysis of glomerulosa cells of mouse adrenal gland slices showed hyperpolarization-activated Cl⁻ currents that were abolished in *Clcn2*^{-/-} mice. The p.Gly24Asp variant, located in a well-conserved 'inactivation domain', abolished the voltage- and time-dependent gating of CIC-2 and strongly increased Cl⁻ conductance at resting potentials. Expression of CIC-2^{Asp24} in adrenocortical cells increased expression of aldosterone synthase and aldosterone production. The above studies show that a gain-of-function mutation affecting the CIC-2 chloride channel underlies a genetic form of secondary arterial hypertension and identify CIC-2 as the foremost chloride conductor of resting glomerulosa cells. It is likely that the increased Cl⁻ currents induced by the CIC-2 variants could depolarize the zona glomerulosa cell membrane, thereby opening voltage-gated calcium channels that trigger autonomous aldosterone production by increasing intracellular Ca²⁺ concentrations. It is also hypothesized that the increased Cl⁻ currents may overcome the hyperpolarizing currents of K⁺ channels that normally determine the glomerulosa cell resting potential. These findings implicate the activity of an anion channel in the regulation of aldosterone biosynthesis, PA and hypertension.

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2. **Savard S, Amar L, Plouin PF, Steichen O.** Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. *Hypertension.* 2013; 62(2): 331-6.

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DOI:10.1530/ey.15.8.2

New Mechanisms

8.3 Ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man

Kalafatakis K, Russell GM, Harmer CJ, Munafo MR, Marchant N, Wilson A, Brooks JC, Durant C, Thakrar J, Murphy P, Thai NJ, Lightman SL
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To read the full abstract: [Proc Natl Acad Sci U S A. 2018; 115\(17\): E4091-E4100](#)

The hypothalamic-pituitary-adrenal axis is a critical neurohormonal network that regulates homeostasis and coordinates the stress response. Glucocorticoids (GCs) are critical for life and are key regulators of cognitive, metabolic and immunologic homeostasis (4). Clinical studies in healthy human subjects, using functional neuroimaging techniques, have clearly demonstrated the importance of GCs in the neural response to stress. During the basal physiological state, plasma cortisol concentrations display circadian rhythmicity, which is important for synaptic function and is made up from an underlying ultradian rhythm that can be modified by internal or external stressors (5). Current cortisol replacement therapy for patients with adrenal

insufficiency cannot mimic physiologic cortisol secretion and results in significant morbidity, such as impaired health-related quality of life, adverse metabolic and cardiovascular risk profiles, increased concentrations of proinflammatory cytokines, as well as reduced activity, low motivation, and mental fatigue, with associated high levels of unemployment and disability benefits.

Here, Kalafatakis et al. demonstrate that an oscillating pattern of plasma cortisol is important for maintenance of healthy brain responses as measured by functional neuroimaging and behavioral testing. These data highlight the crucial role of GC rhythmicity in (i) modulating sleep behavior and working memory performance, and in (ii) regulating the human brain's responses under emotional stimulation. Current optimal cortisol replacement therapies for patients with primary or secondary adrenal insufficiency are associated with poor psychological status, and these results suggest that closer attention to aspects of chronotherapy will benefit these patients and may also have major implications for improved glucocorticoid dynamics in stress and psychiatric disease.

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DOI:10.1530/ey.15.8.3

8.4 Dynamic responses of the adrenal steroidogenic regulatory network

Spiga F, Zavala E, Walker JJ, Zhao Z, Terry JR, Lightman SL
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To read the full abstract: [Proc Natl Acad Sci U S A. 2017; 114\(31\): E6466-E6474](#)

Cortisol production is tightly regulated in a dynamic way within the hypothalamic-pituitary adrenal system, which seems further embedded in a wider steroidogenic regulatory network (SRN). Normally, the connection from ACTH to cortisol production is in line with the HPA axis, but there are stressful events, in which the connection is lost, and the sensitivity of the adrenal cortex to ACTH seems “decoded in a context-dependent manner”, as described by the authors. While the components of this network have been described in numerous studies, the exact dynamic interplay between the players has not been investigated in great details so far.

To this end, here, Spiga et al. devised a mathematical model to simulate the effect of physiologic as well as an inflammatory stress-like, robust ACTH stimulation on the dynamic cascade of few essential components of the SRN, ultimately leading to cortisol production. Predictions obtained by the model were then verified by in vitro

experiments in rats. Interestingly, the prediction for both physiologic and large scale ACTH stimulation was pretty good. However, this prediction failed to simulate cortisol production directly induced by stimulation of the immune system; e.g. through endotoxin LPS, which is known to act via the HPA axis and on adrenocortical cells directly. But when including immune pathways in the SRN, the resulting model was also able to simulate the cytokines’ effects on cortisol production as assessed in the rat experiments. Overall, this study reveals further evidence for an intra-adrenal feedback loop for the regulation of cortisol production involving SF-1, DAX-1, STAR, the GR as well as cytokines, as previously suggested (6-8). It enhances our understanding of dissociated conditions as seen during inflammation, in which cortisol concentrations remain high after ACTH is normalized.

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DOI:10.1530/ey.15.8.4

New Mechanisms

8.5 Multipotent peripheral glial cells generate neuroendocrine cells of the adrenal medulla

Furlan A, Dyachuk V, Kastrić ME, Calvo-Enrique L, Abdo H, Hadjab S, Chontorotzea T, Akkuratova N, Usoskin D, Kamenev D, Petersen J, Sunadome K, Memic F, Marklund U, Fried K, Topilko P, Lallemand F, Kharchenko PV, Ernfors P, Adameyko I

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To read the full abstract: [Science. 2017; 357\(6346\)](#)

Current textbooks teach that adrenergic chromaffin cells of the adrenal medulla

originate from a sympathoadrenal cell lineage of the neural crest nearby the dorsal aorta. Here, Furlan et al. demonstrate a novel origin of these neuroendocrine cells of the medulla arising predominantly from Schwann cell precursors (SCP) of peripheral nerves. Previously it had been shown that SCPs serve as multipotent stem cells that can differentiate into various cell types, most importantly parasympathetic nerve cells. Using genetic cell fate tracing, SCP and nerve ablation, as well as chromaffin differentiation interference studies in mice, the authors show that most chromaffin cells of the adrenal medulla originated from SCP. They describe lineage segregation of chromaffin cells from sympathoblasts, and the specific gene program driving SCP into chromaffin cells via a defined bridge transition phase. Overall, the adrenal medulla seems to be formed in two steps. Organogenesis step one consists of expansion of the SCPs; step two, proliferation of the chromaffin cells. Peripheral nerves provide niches for progenitor cells and avenues for cell migration also important for neuroendocrine organ development. This new finding may have implications on the understanding of neuroblastoma and pheochromocytoma, which both mostly arise from the adrenal gland region.

DOI:10.1530/ey.15.8.5

Important for Clinical Practice

8.6 Susceptibility to corticosteroid-induced adrenal suppression: a genome-wide association study

Hawcutt DB, Francis B, Carr DF, Jorgensen AL, Yin P, Wallin N, O'Hara N, Zhang EJ, Bloch KM, Ganguli A, Thompson B, McEvoy L, Peak M, Crawford AA, Walker BR, Blair JC, Couriel J, Smyth RL, Pirmohamed M

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To read the full abstract: [Lancet Respir Med. 2018 Mar 15. pii: S2213-2600\(18\)30058-4](#)

Inhaled corticosteroids (ICS) are recommended for adults and children with asthma, as well as for chronic obstructive pulmonary disease (COPD). Although ICS are generally well-tolerated and have fewer systemic adverse effects than oral corticosteroids, some patients still develop systemic adverse effects. Adrenal suppression is a clinically important adverse effect, particularly in children with asthma, in whom its diagnosis can be challenging because presentation may range from asymptomatic biochemical changes to non-specific lethargy to florid adrenal crisis and death. Inter-individual variation in susceptibility to adrenal suppression is

striking, however, its etiology remains unclear, given that clinical factors account for only a small proportion of the variance (9). This is the first pharmacogenomic study to investigate the association between a patient's genotype and corticosteroid-induced adrenal suppression. A polymorphism in the *PDGFD* gene locus was identified in a cohort of children with asthma in a genome-wide association study and found to be associated with adrenal suppression. This finding was validated in another paediatric asthma cohort and in a cohort of adults with chronic obstructive pulmonary disorder (COPD). A meta-analysis of the cohorts showed genome-wide significance.

Platelet-derived growth factors (PDGFs) direct the migration, differentiation, and function of various specialised mesenchymal cell types. PDGF receptors are required for development of steroid-producing cells in many organs, including the testes, ovaries, and adrenal cortex. Moreover, *PDGFD* is highly expressed in human adrenal gland, unlike *PDGFA*, *PDGFB*, and *PDGFC*, and the expression of *PDGFD* correlates negatively with cortisol secretion in adrenocortical adenomas. These data support the idea of a link between inter-individual variation in susceptibility to corticosteroid-induced adrenal suppression and a patient's genotype, potentially through variation in the *PDGFD* gene locus. In addition, they offer the potential to develop translational pathways to prevent corticosteroid-induced adrenal suppression, thereby improving the benefit-risk ratio of this important therapy.

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DOI:10.1530/ey.15.8.6

Important for Clinical Practice

8.7 Longitudinal assessment of illnesses, stress dosing and illness sequelae in patients with congenital adrenal hyperplasia

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To read the full abstract: [J Clin Endocrinol Metab. 2018; 103\(6\):2336-2345](#)

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by impaired cortisol production in the adrenal cortex. Classic CAH represents the most common cause of primary adrenal insufficiency in childhood (10). Infant mortality in patients with CAH has decreased since the advent of neonatal screening (11), however, fatal adrenal crises still occur. Here, the authors characterized the rates and causes of glucocorticoid stress dosing and related consequences [emergency room (ER) visits, hospitalizations, adrenal crises] in a large cohort of CAH patients followed prospectively at the NIH Clinical Center for 23 years, who received patient education regarding glucocorticoid stress dosing at each visit. They investigated the association of these outcomes with phenotype, age, daily medication doses, and hormonal evaluations. They report a comprehensive evaluation of illness episodes, glucocorticoid stress dosing habits, and associated outcomes of this large cohort of patients with CAH. Intensive, frequent, and repeated glucocorticoid stress dose teaching allowed patients to often be successfully managed at home during illness episodes; however, adrenal crises requiring hospitalizations and

hypoglycemia still occurred. Children had higher rates of illnesses and stress dosing than adults [OR=3.27 (95% CI: 1.74-6.15), $P=0.002$ OR=4.99 (95% CI: 3.35, 7.42), $P<0.0001$ respectively], while adults had more ER visits, hospitalizations, and adrenal crises, and were also more likely to stress dose for reasons contrary to the authors' guidelines. Among children with classic CAH, the most robust predictors of glucocorticoid stress dosing and illnesses were young age and replacement doses (low glucocorticoid and high mineralocorticoid). Although the majority of patients stress-dosed appropriately with illnesses, hypoglycemia occurred in 11 children, with one patient having encephalopathy and probable long-term sequelae.

These findings indicate that patients with CAH are at risk for developing adrenal crises, despite receiving comprehensive preventative education and guidelines aimed at optimizing home management. Revised guidelines for the management of infectious illnesses in patients with CAH are needed and should include frequent glucocorticoid dosing, in addition to guidance regarding carbohydrate and fluid intake aimed at prevention of hypoglycemia, especially during early childhood. Furthermore, these aspects of care should be better communicated to our patients with CAH.

10. **Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ.** Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016; 101(2): 364-89.

11. **Gidlöf S, Falhammar H, Thilén A, von Döbeln U, Ritzén M, Wedell A, Nordenström A.** One hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort study. *Lancet Diabetes Endocrinol.* 2013; 1(1): 35-42.

DOI:10.1530/ey.15.8.7

Important for Clinical Practice

8.8 Noninvasive prenatal diagnosis of 21-hydroxylase deficiency using target capture sequencing of maternal plasma DNA

Ma D, Yuan Y, Luo C, Wang Y, Jiang T, Guo F, Zhang J, Chen C, Sun Y, Cheng J, Hu P, Wang J, Yang H, Yi X, Wang W, Asan, Xu Z

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To read the full abstract: [Sci Rep. 2017; 7\(1\): 7427](https://doi.org/10.1038/s41598-017-07427-7)

Prenatal dexamethasone treatment has been suggested over three decades ago to prevent virilization of a female fetus affected with 21-hydroxylase deficiency due to genetic mutations in the CYP21A2 gene. However, current treatment guidelines for

CAH regard this treatment still as experimental, mainly because follow-up studies of treated fetuses revealed significant side effects in the neurocognitive development. However, if prenatal diagnosis and treatment of 21-hydroxylase deficiency is considered, a proper method for genetic diagnosis is required to avoid unnecessary treatment of unaffected pregnancies. Until recently, this was done by invasive, and thus not risk-free methods on fetal material obtained by chorionic villus sampling or amniocentesis around 10-12 weeks gestation. More recently the possibility of fetal sexing from a maternal blood sample around 6-8 weeks gestation has brought a first advantage for 46,XY pregnancies.

Here, Ma et al. developed a reliable, cost-effective, non-invasive method to diagnose CYP21A2 mutations from family trios using targeted capture sequencing based on haplotype linkage analysis. They were able to diagnose the genotype of 14 fetuses at risk for CAH correctly from maternal plasma DNA obtained at 8-19 weeks gestation. It appears that this method has the potential to analyze different types and locations of mutations in the same process, which is certainly needed for CYP21A2 analysis, and may be of use for non-invasive prenatal diagnosis of other monogenetic disorders.

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Important for Clinical Practice

8.9 The short cosyntropin test revisited - new normal reference range using LCMSMS

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To read the full abstract: [J Clin Endocrinol Metab. 2018; 103\(4\):1696-1703](#)

How we measure steroids has been a constant debate in recent years because current routinely used immunoassays lack both specificity and sensitivity. Therefore, chromatographic, mass spectrometric methods have been pushed forward for their higher sensitivity and specificity, and for their advantage to provide multiple measurements in the same sample. Both equipment and methods are now developed and standardized for routine clinical use, with liquid chromatography, tandem mass spectrometry (LCMSMS) providing a prominent method.

Here, Ueland et al. nicely demonstrate that when using novel measurement methods, we also need to re-standardize the normative values. This also applies to cortisol and 17-hydroxyprogesterone values measured after standard ACTH stimulation testing

(250µg) for diagnosing adrenal insufficiency (AI) or non-classic CAH (NCCAH). Applying old cut-off levels for immunoassays (which are higher) would result in false-positive diagnosis of AI as well as false-negative diagnosis of NCCAH. Over the past year, there were several publications providing information on novel standardized steroid LCMSMS methods and data on new normative values (12, 13). Although journals are not always keen to publish them, we need to share this information to be able to standardize these novel diagnostic methods between laboratories. This will also be of importance for cut-off values of other clinical tests such as the low-dose ACTH test (1µg) or the dexamethasone suppression tests.

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DOI:10.1530/ey.15.8.9

Important for Clinical Practice

8.10 Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

Annane D, Pastores SM, Rochweg B, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Umberto Meduri G, Olsen KM, Rodgers SC, Russell JA, Van den Berghe G
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To read the full abstract: [Crit Care Med. 2017; 45\(12\): 2078-2088](#)

This guideline replaces/updates the 2008 recommendations regarding the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in adult and pediatric patients. In CIRCI, inadequate glucocorticoid-mediated anti-inflammatory activity is observed in relation to the severity of the critical illness due to somehow disrupted HPA axis, cortisol and receptor to signalling transduction; but the exact mechanism is only poorly understood. The recommendation was achieved by a multispecialty team of 16 international specialists (including endocrinologists and a paediatrician) reviewing the literature and grading its relevance according to established standards (GRADE method). It recommends two possible lab tests for diagnosing

CIRCI, e.g. either a random plasma cortisol of $< 10 \mu\text{g/dL}$ (276 nmol/L) or a 60 min-cortisol response to high-dose (250 μg) of ACTH of $< 9 \mu\text{g/dL}$ (248 nmol/L). Experts recommend against the use of corticosteroids in sepsis without shock and suggest its use only in patients with septic shock that does not respond to fluid and vasopressor therapy. In addition, the use of corticosteroids is recommended for hospitalized adult patients with moderate to severe acute respiratory distress syndrome, but not in patients with major trauma/non-septic inflammatory response syndrome. Of note, this guideline was published before the results of the two most-comprehensive studies so far reported on mortality outcomes of hydrocortisone (HC) treatment in septic shock patients (14, 15). However, as discussed below (8.12), even these studies were not able to give a clear answer about the possible benefit or harm of HC. Therefore, the current guidelines may still remain valid.

14. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med* 2018; 378:797-808.

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DOI:10.1530/ey.15.8.10

8.11 Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial

Isidori AM, Venneri MA, Graziadio C, Simeoli C, Fiore D, Hasenmajer V, Sbardella E, Gianfrilli D, Pozza C, Pasqualetti P, Morrone S, Santoni A, Naro F, Colao A, Pivonello R, Lenzi A

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To read the full abstract: [Lancet Diabetes Endocrinol. 2018; 6\(3\): 173-185](#)

Adrenal insufficiency (AI), caused by adrenal failure (primary) or hypothalamo-pituitary failure (secondary), has a prevalence of 250–450 per 1 million (16). AI is potentially life-threatening and requires lifelong glucocorticoid replacement therapy. Modified-release hydrocortisone preparations have been developed to mimic the physiological cortisol rhythm and improve compliance (17, 18). The once-daily, modified-release hydrocortisone tablet was developed to prevent the afternoon peaks seen with conventional therapies given in multiple daily doses. Use of once-daily, modified-release hydrocortisone improves cardiovascular disease risk factors, glucose metabolism, and quality of life in controlled trials (19–21). However, the mechanisms involved remain unexplained.

This study is the first non-sponsored, randomised controlled trial to investigate the effect of once-daily, modified-release hydrocortisone versus standard therapy on metabolism in patients with primary or secondary AI. Patients with AI on standard therapy had impaired cell immunity and increased frequency of infections, probably due to disruption of normal circadian rhythm of cortisol by use of multiple daily hydrocortisone doses. They also showed that two of the most deleterious effects of glucocorticoid overtreatment—weight gain and increased HbA1c—can be prevented by changing the timing of administration without altering the dose. In addition,

switching from multiple-daily to once-daily glucocorticoid administration restored immune-cell homeostasis and reduced the frequency of infections. They also provided a molecular mechanism: low-grade inflammation leads to selective depletion of the immunoglobulin receptor, CD16, from the surface of natural killer cells. Such low-grade inflammation could also account for some of the symptoms reported by patients with adrenal insufficiency on standard glucocorticoid therapy (e.g. fatigue, impaired quality of life) and the increased risk of atherosclerosis even in the absence of the usual predisposing factors.

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DOI:10.1530/ey.15.8.11

8.12 Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J
ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group

To read the full abstract: [N Engl J Med. 2018; 378\(9\): 797-808](#)

Sepsis has been identified by the WHO as a global health priority, however, there has been no proven pharmacologic treatment other than the appropriate antibiotic agents, fluids and vasopressors as required. Reported death rates among hospitalized patients with sepsis range between 30-45% (22). Glucocorticoids have been used as an adjuvant therapy for septic shock for more than 40 years, however, uncertainty remains about their safety and efficacy (23).

Here, the authors performed a prospective randomized placebo controlled study in patients with septic shock on mechanical ventilation. Patients received hydrocortisone

(at a huge dose of 200 mg per day) or placebo for 7 days or until death or discharge from the intensive care unit (ICU), whichever came first. The primary outcome was death from any cause at 90 days. They found that administration of hydrocortisone did not result in lower 90-day mortality than placebo among patients with septic shock. They observed a more rapid resolution of shock and a lower incidence of blood transfusion among patients who received hydrocortisone than among those who received placebo. Patients assigned to receive hydrocortisone had a shorter time to ICU discharge and earlier cessation of the initial episode of mechanical ventilation than those assigned to placebo. There were no other significant between-group differences. Patients assigned to receive hydrocortisone had more adverse events than did those assigned to placebo, but these events did not affect patient-centered outcomes. In conclusion, in patients with septic shock undergoing mechanical ventilation, continuous infusion of hydrocortisone did reduce mortality at 90 days. Thus a patient-related discussion of benefits versus harm between the pediatric intensivist and endocrinologist before administering hydrocortisone for septic shock would be recommended.

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DOI:10.1530/ey.15.8.12

New Genes

8.13 Activating PRKACB somatic mutation in cortisol-producing adenomas

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To read the full abstract: [JCI Insight. 2018; 3\(8\). pii: 98296](#)

Adrenocortical cells depend on cAMP/PKA signaling for growth and steroidogenesis. Several adrenal disorders manifesting with Cushing syndrome (CS) are due to activation of the PKA pathway, including Carney complex and primary pigmented nodular adrenal disease (due to germline mutations of PRKA1RA), McCune-Albright

syndrome (due to mosaic mutations of GNAS (Gsa subunit)), as well as other nodular adrenal disorders caused by germline or somatic mutations of phosphodiesterases 11A or 8B. Cortisol-producing adenomas (CPA) are the most common cause of adrenal CS. They are also due to activating mutations in the PKA signaling pathway. Recently, somatic mutations of protein kinase cAMP-activated catalytic subunit α (PRKACA) have been found in CPA leading to loss of interaction with R subunits and thus an increase in total PKA activity. In this article, a somatic mutation (S54L) in the catalytic subunit β (PRKACB) has been found in a CPA leading to severe CS likely due to disruption of stability of type I PKA holoenzyme. Although found only in one case of CPA so far, disease-causality is likely as previous studies have already established a possible role for PRKACB in tumorigenesis, and a triplication of the gene has been recently reported in a patient with Carney complex (24). Therefore, PRKACB should be regarded as a novel candidate gene associated with endocrine active tumors.

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DOI:10.1530/ey.15.8.13

8.14 Modeling Congenital Adrenal Hyperplasia and Testing Interventions for Adrenal Insufficiency Using Donor-Specific Reprogrammed Cells

Ruiz-Babot G, Balyura M, Hadjidemetriou I, Ajodha SJ, Taylor DR, Ghataore L, Taylor NF, Schubert U, Ziegler CG, Storr HL, Druce MR, Gevers EF, Drake WM, Srirangalingam U, Conway GS, King PJ, Metherell LA, Bornstein SR, Guasti L
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To read the full abstract: [Cell Rep. 2018; 22\(5\): 1236-1249](#)

Primary or secondary adrenal insufficiency (AI) results from adrenal failure or impairment of the hypothalamic-pituitary axis, respectively. The most frequent cause of primary AI is autosomal recessive congenital adrenal hyperplasia (CAH). Patients with AI need life-long treatment with exogenous steroids, which can be challenging, given that currently available formulations do not mimic physiologic cortisol secretion. The ability to generate donor-specific and functional adrenocortical-like cells would facilitate: (1) the next generation of cell-based treatments for AI; (2) the modeling of adrenal-specific diseases; and (3) the testing of personalized interventions on cells derived from patients. Donor- and disease-specific steroidogenic cells as surrogates for disease modeling have been lacking up to now. More significantly, their use could

be exploited for the development of cell-based treatment modalities for AI.

Here, the authors show that the use of a single cell fate regulator (SF1/NR5A1), in conjunction with PKA and LHRH signaling, can stably reprogram human adult skin-, blood-, and urine-derived cells into hiSCs. Forced expression of other key TFs involved in adrenogonadal differentiation, alone or in combination, was insufficient to induce hiSCs, nor did their expression with SF1 enhance reprogramming. However, given that there is endogenous expression of DAX1, PBX1, CITED2, and WT1 in non-reprogrammed cells, it is entirely possible that those factors participate in hiSC induction along with SF1, although the higher dosages delivered by their constructs did not improve reprogramming. Activation of the WNT pathway through WNT4 is associated with zona glomerulosa differentiation, which is prevented by PKA activation. Treatment of hiSCs with recombinant WNT4 did not result in changes of zonal-specific markers nor cortisol secretion; it is possible that, in this experimental setting, forced-expression of SF1 bypasses key differentiation events occurring physiologically at the capsule/subcapsular region during the normal self-renewal/zonal specification of the gland. The functionality of hiSCs makes them an unmatched tool to obtain surrogate adrenocortical cells for in vitro disease modeling. With this in mind, the authors derived hiSCs from patients with CAH, showing an altered steroid profile. Importantly, the decrease in cortisol production in hiSCs derived from CAH patients was rescued on expression of the exogenous native forms, irrespective of the defective steroidogenic enzyme. These findings provide an effective tool with many potential applications for studying adrenal pathobiology in a personalized manner and open venues for the development of precision therapies.

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New Concerns

8.15 Cognitive impairment in adolescents and adults with congenital adrenal hyperplasia

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To read the full abstract: [Clin Endocrinol \(Oxf\). 2017; 87\(6\): 651-659](#)

Patients with CAH are treated with lifelong glucocorticoid (GC) replacement therapy and, for the classic form of the disease, treatment with fludrocortisone is also necessary. During different periods throughout life, it may be difficult to achieve optimal dosing of GC replacement therapy, leading to over- or under-treatment and, therefore, a plausible negative effect on cognition overtime. The additive negative

effect of salt-wasting crises and hypoglycaemia may also contribute to the cognitive outcome seen among patients with CAH. In the present study, the authors investigated the cognitive function in adolescents and adults with CAH by comparing intellectual ability and executive functions, as well as learning and memory between patients and general population controls. Individuals with CAH had normal general intelligence, learning and memory, but performed poorer than controls on tests assessing verbal and visuospatial working memory and inhibition. Prenatal dexamethasone treatment may have a more pronounced negative effect in female patients. There were no significant differences between phenotypes, and the glucocorticoid dose at the time of neurocognitive testing did not correlate with the cognitive outcome in patients with CAH. However, patients with a null genotype performed worse than patients with a non-null genotype in measures of general cognitive ability (estimates of IQ). These findings highlight the importance of optimal therapy in patients with CAH, with glucocorticoid formulations that would mimic more closely physiologic cortisol secretion.

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New Concerns

8.16 Quantitative brain MRI in congenital adrenal hyperplasia: in vivo assessment of the cognitive and structural impact of steroid hormones

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To read the full abstract: [J Clin Endocrinol Metab. 2018;103\(4\):1330-1341](#)

Glucocorticoids exert an inverted U-shaped influence on human cognition, particularly on acquiring and consolidating memory (25), whereas androgens have an overall beneficial effect on cognitive control, verbal memory, and spatial cognition in humans (26). Although previous studies in patients with CAH have consistently identified impairments in short-term and working memory performance, thought to relate to excess glucocorticoid exposure, the relationship between these cognitive abnormalities and changes in brain structure has not previously been investigated.

Here, the authors hypothesized that neural abnormalities would correlate with cognitive performance and that increased glucocorticoid exposure would be associated with poorer performance on neuropsychometric tests and reductions in neural volumes, FA, and total choline. Using multiple quantitative imaging modalities in conjunction with neuropsychological assessment enabled them to identify functionally significant biomarkers of the disease process (CAH) and treatment effects (steroid exposure) in patients with CAH. Patients had global abnormalities of cerebral white matter, with

localized reductions in neural volumes in regions of the brain that have previously been documented to contain high concentrations of androgen, mineralocorticoid, and glucocorticoid receptors (25). The mesial temporal lobe was affected bilaterally, with significant reductions in white matter microstructure, right hippocampal volume, and left mesial temporal lobe choline. Interestingly, although markers of androgen exposure did not relate to the identified CNS abnormalities, exposure to higher glucocorticoid doses was associated with significantly worse cognitive performance and abnormal mesial temporal lobe total choline and white matter mean diffusivity. These findings demonstrated that CAH has a profound impact on normal brain and cognitive development, with the effects we describe most marked in the mesial temporal lobe. There is also a significant association between current glucocorticoid replacement regimens and cognitive and CNS abnormalities.

The recent development of more physiological glucocorticoid replacement regimens and other modalities that offer improved control of altered steroidogenesis in CAH may provide opportunities to use the biomarkers identified in the current study (mean diffusivity, mesial temporal lobe total choline) to assess the impact treatments on the CNS in patients with CAH. These findings are also relevant to the wider population, of whom 1% are on long-term glucocorticoid therapy (27).

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DOI:10.1530/ey.15.8.16

New Paradigms

8.17 A zebrafish model of X-linked adrenoleukodystrophy recapitulates key disease features and demonstrates a developmental requirement for *abcd1* in oligodendrocyte patterning and myelination

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X-linked adrenoleukodystrophy (ALD) is caused by genetic mutations in the ABCD1 gene coding for a peroxisomal transmembrane protein responsible for the metabolism of very long chain fatty acids (VLCFA). It manifests with a broad phenotype mainly involving the peripheral and central nervous system and the adrenals. However, the exact pathological mechanisms are largely unknown and treatment options are scarce. The newly developed zebrafish model developed here, by Bowles et al., provides new hope for better understanding this often devastating neurodegenerative disease. Unlike previous mouse models, the zebrafish model seems to better recapitulate human ALD. In addition to showing elevated VLCFA and alterations in myelination, it also reveals novel insight into *Abcd1* as an important protein for oligodendrocyte generation and patterning. The model is also foreseen to be useful for testing of therapeutic drugs.

To read the full abstract: [Hum Mol Genet. 2017; 26\(18\): 3600-3614](#)

DOI:10.1530/ey.15.8.17

New Paradigms

8.18 PKA signaling drives reticularis differentiation and sexually dimorphic adrenal cortex renewal

Dumontet T, Sahut-Barnola I, Septier A, Montanier N, Ploton I, Roucher-Boulez F, Ducros V, Lefrançois-Martinez AM, Pointud JC, Zubair M, Morohashi KI, Breault DT, Val P, Martinez A
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To read the full abstract: [JCI Insight. 2018;3\(2\). pii: 98394](#)

The (human) adrenal cortex undergoes massive changes in structure and function from fetal to postnatal life, with the first consisting of a small outer definitive zone and a larger inner fetal zone, and the latter finally consisting of three distinct layers, namely the zona glomerulosa (ZG), fasciculata (ZF) and reticularis (ZR). However, details about how these layers are formed are largely missing. Recent cell lineage-fate tracing studies in mice revealed that the adult definitive and the fetal adrenal cortex derive from common precursor cells expressing Sf1, and that the definitive cortex is constantly renewed from a stem/progenitor cell pool residing (sub-) capsular. Differentiation of these cells in a centripetal direction form the ZG and ZF. In this process, RSPO/WNT/ β -catenin drive ZG formation, inhibit ZF, and promote

tumorigenesis when constitutively active. By contrast, cAMP/PKA drive ZF formation, inhibit ZG and counteract β -catenin induced tumorigenesis. Loss of PKA signaling results in cortex atrophy due to altered ZF differentiation, while excess PKA activity leads to nodular hyperplasia with glucocorticoid excess in both mice and men as shown in human PRKAR1A mutations and in the Prkar1a (AdKO mouse), in which PKA is constitutively active.

Here, the authors study the AdKO mouse model to show that PKA accelerates and expands ZF renewal and provokes the formation of the X-zone, which corresponds to the human ZR. Interestingly, they found that this effect of PKA to promote the differentiation to ZR-like cells was only specifically seen with definitive progenitor cells, but not with fetal progenitor cells, and that this effect was negatively regulated by androgens. Thus, this study gives first insight into how the formation of ZR might be stimulated and regulated postnatally in the first 6-8 years of age before becoming steroidogenically active in the production of DHEA at adrenarche. It also suggests that this process is sex-specific, regulated by androgens produced in the male gonad. The authors suggest that this may explain why females are more susceptible to disorders of the adrenal cortex, such as Cushing's syndrome (CS) or adrenocortical cancers (ACC). The question remains whether this may also imply that women with androgen excess syndromes, such as polycystic ovary syndrome (PCOS), are protected from CS or ACC. Or, on the contrary, do they have disrupted androgen regulation on PKA, given the fact that women with hyperandrogenic PCOS often have a medical history of preceding premature adrenarche?

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Reviews

8.19 The role of microRNAs in glucocorticoid action

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To read the full abstract: [J Biol Chem. 2018; 293\(6\): 1865-1874](#)

MicroRNAs (miRNAs) are short RNA species, generally 19–22 nucleotides in length, which mediate post-transcriptional down-regulation of protein expression (28). Given that miRNAs exert such pervasive effects on biological processes, it is not surprising that they have an effect on GC action at several points. Their touch is often light, in the sense that individual miRNAs alter expression of their targets only modestly. Nevertheless, each miRNA can hit several targets, and each target may be hit by several different miRNAs. Therefore, coherent and coordinated changes of miRNA abundance can affect complex biological processes profoundly. Furthermore,

functional interactions between miRNAs and target transcripts are based on limited sequence complementarity. Such regulatory complexity creates two sets of major challenges. The first are essentially challenges of methodology and bio-informatics. These challenges are increasingly being met through improvements in miRNA target prediction algorithms, systems biological approaches, better methodologies, and more widespread adoption of best-practice experimental controls. The second set of challenges relate to the therapeutic exploitation of knowledge gained. In this context, advances are likely to be most rapid in situations where insensitivity to GCs is a pressing clinical problem, for example in hematological malignancies and GC-resistant asthma. Even where good therapeutic targets can be clearly identified, it remains to be seen whether a mimic or antagonist of a single miRNA species will be sufficient to exert therapeutic effects. If targeting more than one miRNA proves necessary, this will create additional barriers to development, in part because of the problem of predicting and mitigating off-target effects. This field of endeavour is an exciting one, but success is far from certain.

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DOI:10.1530/ey.15.8.19

Reviews

8.20 Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia

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To read the full abstract: [Cochrane Database Syst Rev. 2017; 11:CD008727](#)

Glucocorticoids (GCs), such as prednisone (prednisolone) or dexamethasone, are essential agents in the treatment of acute lymphoblastic leukemia (ALL), the most common malignancy in childhood. They are administered in highly supraphysiologic

doses in cyclic courses. Thus, every pediatric endocrinologist fears HPA axis suppression with consequent cortisol deficiency and higher susceptibility for infections in these patients. However, it is unclear, how often adrenal insufficiency occurs, for how long, and whether it is associated with increased infection. To answer these questions, a Cochrane data analysis was performed, but found only 10 valid studies, which could not be pooled. It is clear that GC therapy for ALL leads to transient adrenal insufficiency (AI), but most children recover within a few to 34 weeks. Interestingly, 2 RCTs found no difference with regard to AI frequency and duration between prednisone and dexamethasone treatments, but in one observational study recovery from AI was faster in prednisone treated individuals compared to dexamethasone, which is maybe the most potent and long-acting corticosteroid in clinical use. Fluconazole treatment (an antifungal drug and CYP inhibitor) prolonged AI. Data on risk association of high-dose GCs with infections in ALL are ambiguous. Therefore, further studies are needed to formulate guidelines for GC replacement therapy and characterize the relationship between GC therapy and infections in ALL.

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Food for thought

8.21 Steroidogenesis: Unanswered Questions

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To read the full abstract: [Trends Endocrinol Metab. 2017; 28\(11\):771-793](#)

Walter Miller summarizes in this review currently unsolved questions in steroidogenesis and provides some ideas as to how they might be solved. Eleven areas are identified, some are more specifically related to the adrenal cortex. In brief, a) novel adrenal androgens from alternat(ive) pathways have been described recently. What is their specific role in hyperandrogenic disorders? Or, b) what exact physiologic role has the human fetal adrenal; and what triggers its involution after birth? Or, c) why is CAH due to 21-hydroxylase deficiency rare in African-Americans? Miller shows that “research in steroidogenesis is more exciting than ever” and necessitates attention from the full range of scientific approaches including clinical, translational and basic studies.

DOI:10.1530/ey.15.8.21

9. Oncology and chronic disease

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As usual, the year in research in Oncology and chronic disease has been very rich. Most of the highlighted papers investigate the effects of cancer treatment on the endocrine system. Issues related to long-term surveillance strategies represent an emerging topic of discussion.

Furthermore, a few key points about growth retardation as a common complication of different chronic systemic diseases in children have been defined:

- the therapeutic switch from glucocorticoids to biologic agents has dramatically

changed the clinical scenario of chronic inflammatory diseases. The use of these agents early in the course of the disease has been correlated with a dramatic improvement of growth outcome. The restoration of a normal linear growth rate seems to be directly related with an early response to therapy and with the achievement of a sustained remission.

- treatment with recombinant human growth hormone (rhGH) has been proposed to help children with chronic systemic conditions (such as chronic kidney disease and severe juvenile idiopathic arthritis) to attain a height more in keeping with their peers, but until now the scientific evidence regarding the effect of rhGH on adult height was scarce. A few data published this year seem to confirm that long-term rhGH therapy reduces the deceleration of linear growth and ultimately improves final height.

DOI:10.1530/ey.15.9

Late consequences of tumour therapy: prevention and monitoring

9.1 Late outcomes of adult survivors of childhood non-Hodgkin lymphoma: A report from the St. Jude Lifetime Cohort Study

Ehrhardt MJ, Sandlund JT, Zhang N, Liu W, Ness KK, Bhakta N, Chemaitilly W, Krull KR, Brinkman TM, Crom DB, Kun L, Kaste SC, Armstrong GT, Green DM, Srivastava K, Robison LL, Hudson MM, Mulrooney DA
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To read the full abstract: [Pediatr Blood Cancer. 2017;64\(6\):e26338](https://doi.org/10.1093/pedipr/2017/64/6/e26338)

Through a comprehensive, risk-based clinical assessment and validation of medical events, this study provides a detailed health status characterization of adult survivors of

paediatric non-Hodgkin lymphoma (NHL). Survivors showed an increased risk of suffering from one or more components of the metabolic syndrome (obesity 35%, hypertension 9%, elevated fasting glucose 2.5%, and high cholesterol 1%), well known cardiovascular risk factors. Many survivors experienced physical performance limitations and a mild or severe neurocognitive impairment was detected in more than two-thirds of them. As the authors point out, the evaluation of physical performances appears of interest because the early identification of functional limitations may enhance the ability to reduce modifiable cardiovascular risk factors in these patients. Possible limitations of this study were the selection bias (participants were more likely to be female, younger, and fewer years from NHL). Treatment protocols are now different from those used decades ago in both intensity and omission of irradiation, thus it appears difficult to generalize the conclusions to recent NHL survivors. While the high prevalence of cardiovascular risk factors represents a well-known complication in hematologic cancer survivors, the most relevant merit of this study was to point the attention on limitations of neurocognitive performance and physical function. Early recognition of these conditions offers an opportunity to improve the quality of life of these patients.

DOI:10.1530/ey.15.9.1

Late consequences of tumour therapy: prevention and monitoring

9.2 Anthropometry in Long-Term Survivors of Acute Lymphoblastic Leukemia in Childhood and Adolescence

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To read the full abstract: [J Adolesc Young Adult Oncol. 2017;6:294-298](#)

The difficulties in defining obesity in childhood cancer survivors have been emphasised. In these patients, body mass index (BMI) has been confirmed to be a poor predictor of body fatness, because of their impaired linear growth, body composition changes (decreased lean mass and fat redistribution) and abdominal adiposity. The present study focused on arm anthropometry as a simple tool to assess

fat mass and lean body mass. The authors suggest that arm anthropometry could represent a valuable tool in low- and middle-income countries, where the vast majority of young people with cancer live and the access to sophisticated expensive measures of body composition is limited. However, a significant limitation of this study is its failure to consider and differentiate abdominal obesity. Abdominal obesity can be easily measured by the waist to hip ratio in adults with normal stature, and by the waist-to-height ratio in growing children and short adults. Both these parameters have been strongly associated with cardiovascular disease, an emerging problem in childhood cancer survivors.

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DOI:10.1530/ey.15.9.2

Late consequences of tumour therapy: prevention and monitoring

9.3 Growth and pubertal patterns in young survivors of childhood acute lymphoblastic leukemia

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To read the full abstract: [J *Pediatr Endocrinol Metab.* 2017;30:869-877](https://doi.org/10.1530/ey.2017.30.869-877)

Several previous studies had focused on the early risk of metabolic syndrome or its components in survivors of childhood acute lymphoblastic leukaemia (ALL), while fewer data are available on pubertal development in these subjects. The merit of this study was to carefully investigate growth and pubertal development in a large cohort of childhood ALL survivors, who were treated and followed at a single institution. The cohort included a relatively high proportion of patients who reached final adult height and completed pubertal development (63%); furthermore, relevant parameters such as target height were considered. Although the cohort is heterogeneous regarding to treatments (five successive protocols used between 1985 and 2011), the study group is adequately homogeneous regarding to the primary disease and not having undergone bone marrow transplantation. The results show that growth pattern and pubertal development are normal in most survivors of childhood ALL treated with chemotherapy alone. Increased risk of endocrine disturbances, particularly early puberty and reduced final height, was observed in patients exposed to CRT.

DOI:10.1530/ey.15.9.3

Late effects of tumour therapy: molecular evidences of premature cellular aging

9.4 Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging

Ariffin H, Azanan MS, Abd Ghafar SS, Oh L, Lau KH, Thirunavakarasu T, Sedan A, Ibrahim K, Chan A, Chin TF, Liew FF, Jeyamogan S, Rosli ES, Baharudin R, Yap TY, Skinner R, Lum SH, Hainaut P
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To read the full abstract: [Cancer. 2017;123:4207-4214](#)

Metabolic syndrome and early cardiovascular disease are well-known long-term complications of cancer treatment during childhood, but the underlying causes are still unclear. It had been already demonstrated that the abnormalities of the immune system, that are characteristic of the elderly population, may become evident earlier in childhood cancer survivors (1), and these abnormalities have been interpreted as signs of premature cellular aging. The current study reports that the leukocytes from a cohort of asymptomatic young adult survivors of childhood acute lymphoblastic leukaemia (ALL) show positive markers of chronic inflammation and aging (higher inflammatory cytokines and shorter leukocyte telomere length). The authors speculate

that the cellular damage may be more pronounced in younger children because the insults related to cancer treatment occur within a developmental window of high sensitivity, considering that telomere attrition rate is highest during infancy and early childhood (2). In addition, traumatic experiences associated with cancer may become embedded epigenetically and lead to modifications in gene expression (3). Adverse life events at a young age increase the odds of short telomeres, whereas similar experiences in adulthood have not shown comparable biologic effects (4). It is noteworthy that survivors who were diagnosed before 5 years of age had shorter leukocyte telomere length compared with those who were diagnosed later. As the authors state, understanding the cellular processes that drive accelerated aging may facilitate the development of targeted interventions to stop, or at least slow down, these processes.

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DOI:10.1530/ey.15.9.4

Late effects of tumour therapy: good and bad news on prevention strategies

9.5 Diagnosing and monitoring endocrine dysfunction, diabetes and obesity in a cohort of adult survivors of childhood cancer

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To read the full abstract: [Endocr Pract. 2017;23:1394-1401](#)

The study describes an American population of childhood cancer survivors from an unusual but interesting perspective. The authors evaluated the frequency of routine endocrine testing, in addition to the frequency of endocrine dysfunction, diabetes and

obesity. The study found that the prevalence of endocrine disorders was significantly lower than in previous reports. However, the results seem to be explained by the low prevalence of endocrine tests in this patient cohort. A possible limitation is the heterogeneity of the cohort regarding cancer type. Moreover, the prevalence of endocrine disorders was calculated based on the whole cohort, rather than of patients with relevant symptoms or signs. It may be supposed that the accessibility and participation in screening programs for cancer survivors significantly differ from one country to another, also in relation to the presence and efficiency of a national health system. The study reminds clinicians of the importance of a periodic endocrine screening in these patients. Perhaps it should be the task of the referring oncologist, who primarily follows these patients, to start the screening of hormonal function in order to help these patients understand the need for long-life endocrine monitoring. Endocrinologists need to better collaborate with oncologists, allowing an adequate transition to avoid losing these patients to follow up.

DOI:10.1530/ey.15.9.5

Late effects of tumour therapy: good and bad news on prevention strategies

9.6 Development of the functional social network index for adolescent and young adult cancer survivors

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To read the full abstract: [Cancer. 2018;124:2220-2227](#)

The Brief Coping Orientation to Problem Experience (brief COPE) questionnaire was designed to explore the coping strategies used by individuals in response to stress. It has been used to research various populations with chronic health conditions (1). 'Betweenness centrality' is a measure of centrality in a graph based on shortest paths.

In a communications network, a node with higher betweenness centrality would have more control over the network, because more information will pass through that node (2). This study compared those instruments with a new index, FSNI to analyse social network in AYA CSs. It is well known that these patients need careful physical and psychological support to maintain a satisfactory quality of life. Accurate identification of "at risk subjects" is necessary to improve social relationships, in particular for those patients (e.g. lymphoma and chemotherapy treated) who showed a higher FSNI. As underlined by the authors, it would be interesting to evaluate relationship characteristics, in particular in terms of age of friends/relatives, to better identify the degree of dependence on them. It would also be interesting to extend the analysis to CSs with onset of cancer in early childhood, for whom the risk of persistent dependence on parents and relatives is high and could interfere with the process of achieving independence during adolescence.

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DOI:10.1530/ey.15.9.6

Growth, growth hormone and puberty in chronic diseases: novel insights from clinical practice

9.7 Growth outcomes after GH therapy of patients given long-term corticosteroids for Juvenile Idiopathic Arthritis

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To read the full abstract: [J Clin Endocrinol Metab. 2017;102:4578-4587](#)

In chronic inflammatory diseases, inflammatory cytokines and exogenous glucocorticoid exposure affect growth through systemic effects on the GH-IGF-1 axis and local effects on the growth plates. Low plasma IGF-1 levels are related to systemic GH insufficiency or to hepatic GH resistance. Changes in IGF binding proteins have also been reported. At the growth plates, cytokines and glucocorticoids suppress chondrocyte proliferation, increase apoptosis, decrease expression of cartilage matrix proteins, and may alter GH and/or IGF-1 signalling (1). Sustained

exposure to inflammatory cytokines may have irreversible adverse effects on growth plate chondrogenesis that may explain the partial and inconsistent catch-up growth seen after remission achievement and the weaker growth response to rhGH therapy in patients with long-lasting disease. This study analyzed data collected by 3 prospective clinical trials of rhGH in 58 patients receiving glucocorticoid therapy for systemic or polyarticular Juvenile Idiopathic Arthritis (JIA). rhGH was effective in arresting the decrease in height SDS during the years preceding treatment. Height SDS increased from baseline by a median of 1.0 SD, but rhGH therapy failed to fully restore the genetic growth potential. Overall, the target height was missed by 9 cm and only half had an adult height within their target height. The main determinants of growth outcome were severity of inflammation and age and height at GH initiation. In the authors' opinion, the disease-related loss of height observed in some forms of JIA, the unpredictable severity of the disease, and the limiting effects of chronic inflammation on the growth response to rhGH support the initiation of therapy as soon as growth deceleration appears, before the growth deficiency becomes severe.

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DOI:10.1530/ey.15.9.7

Growth, growth hormone and puberty in chronic diseases: novel insights from clinical practice

9.8 Growth and weight gain in children with juvenile idiopathic arthritis: results from the ReACCh-Out cohort

Guzman J, Kerr T, Ward LM, Ma J, Oen K, Rosenberg AM, Feldman BM, Boire G, Houghton K, Dancy P, Scuccimari R, Bruns A, Huber AM, Watanabe Duffy K, Shiff NJ, Berard RA, Levy DM, Stringer E, Morishita K, Johnson N, Cabral DA, Larché M, Petty RE, Laxer RM, Silverman E, Miettunen P, Chetaille AL, Haddad E, Spiegel L, Turvey SE, Schmeling H, Lang B, Ellsworth J, Ramsey SE, Roth J, Campillo S, Benseler S, Chédeville G, Schneider R, Tse SML, Bolaria R, Gross K, Feldman D, Cameron B, Jurencak R, Dorval J, LeBlanc C, St Cyr C, Gibbon M, Yeung RSM, Duffy CM, Tucker LB

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To read the full abstract: [Pediatr Rheumatol Online J. 2017Aug 22;15\(1\):68](#)

This large prospective study analysed growth in children with JIA during a 3-year period from diagnosis. Interesting findings emerge: the heights and weights of these patients, clearly compromised in historical cohorts, appeared nearly normal. Increased

risk of growth impairment was noted in patients with systemic arthritis, due to the more frequent use of systemic steroids. This study used limited analyses of growth. For example, the authors used a change of 1.0 Z-scores relative to baseline to indicate growth impairment, however this cut-off could include normal periods of relative stasis or rapid growth. Moreover, a child who was obese at baseline and reduced by 1.0 BMI Z-scores during follow-up, becoming closer to his/her ideal BMI, was defined as having "poor weight gain", instead of "desirable weight loss". Furthermore, the reported growth impairment, estimated in a 3-year period, may be transitory and final height and weight may be unaffected due to delayed puberty and late growth spurt. Most children had not completed their growth at the last assessment, and data on target heights were unavailable. Furthermore, these data may be no longer so relevant. The 2013 update of the American College of Rheumatology juvenile arthritis treatment recommendations (1) include initial monotherapy with biologics as an option in children with systemic arthritis.

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DOI:10.1530/ey.15.9.8

Growth, growth hormone and puberty in chronic diseases: novel insights from clinical practice

9.9 Growth hormone treatment improves final height and nutritional status of children with chronic kidney disease and growth deceleration

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To read the full abstract: [J Endocrinol Invest. 2018;41:325-331](#)

Growth failure is common in children with chronic kidney disease (CKD) and has a multifactorial etiology. The hypothalamus-pituitary axis is intact, but there is a resistance to growth hormone (GH) action in target tissues, secondary to decreased density of GH receptors, impaired signal transduction and reduced levels of free insulin-like growth factor 1 (IGF-1) due to increased levels of inhibitory IGF-binding proteins (IGFBPs). Additional factors contributing to growth deceleration include: severity and duration of CKD, ethnicity, primary renal disease, malnutrition, metabolic acidosis, renal osteodystrophy, and long-term steroid therapy (1-2). Several studies in children with CKD reported that growth hormone (rhGH) therapy increases height velocity, but data on final height are lacking. A recent systematic review summarized randomized controlled trials (RCTs) published 1966-2011 (3); rhGH therapy increased height velocity and height at 1 year, but all studies showed a consistent waning of effectiveness with longer treatment duration. No RCT reported final height data, but a few non-RCT studies suggested that rhGH improves final height (2-4). Haffner et al. (4) compared 38 initially prepubertal CKD children treated with rhGH (0.33 mg/kg weekly) for a mean of 5.3 years to 50 untreated CKD children. Mean final height of rhGH-treated children was 165 cm for boys and 156 cm for girls, which was 1.4 SD above their baseline height SDS. In contrast, the final height of untreated CKD children was 0.6 SD below their baseline height SDS. The North American Pediatric Renal

Transplant Cooperative Study reported that final height SDS was higher in 513 rhGH-treated children (SDS = -1.83) than in 2263 concurrent untreated controls, (-2.60) (5). The French Society of Pediatric Nephrology reported that of 49 patients with a baseline height SDS between -2 to -3 (the French criteria for rhGH), 65% had an adult height >-2 SDS (6). Italian Medicine Agency criteria considers rhGH therapy for CKD children with height <-2 SDS and/or height velocity <25th percentile, in the absence of contraindications and is discontinued at renal transplantation. Therefore a new RCT with untreated controls is unethical. Despite the limitations of its retrospective and non-randomized design, the data suggest that rhGH-untreated patients manifest growth deceleration despite a better height SDS at baseline. On the contrary, height SDS of rhGH-treated patients progressively improved, and final height SDS was not different between the two groups. Moreover, rhGH treatment improved the deficit in BMI SDS from baseline to age at final height.

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Growth, growth hormone and puberty in chronic diseases: novel insights from clinical practice

9.10 Pubertal development in children with chronic kidney disease

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To read the full abstract: [Pediatr Nephrol. 2017;32:949-964](#)

This is a comprehensive review on growth and sexual maturation during puberty in children with chronic kidney disease (CKD). Despite attention to preserve growth potential during pre-puberty and the availability of recombinant human growth hormone (rhGH), the achievement of normal pubertal height gain remains a challenge in CKD. In pre-dialysis patients, therapies to improve pubertal growth rely on preservation of renal function and use of rhGH. In patients with end-stage CKD, early transplantation with steroid withdrawal within 6 months allows for normal pubertal

development in most patients. No randomized controlled trial (RCT) has tested the impact of rhGH during puberty in CKD, but this could address questions regarding both short-term growth responses and also final height. As for other chronic diseases characterized by growth deceleration and pubertal delay, innovative treatments have been proposed, including recombinant IGF-1, as a monotherapy or in combination with rhGH, and targeting suppression of cytokine signalling. The latter is a theoretical possibility because the chronic inflammatory state associated with CKD contributes to GH resistance (1). Gonadotropin-releasing hormone analogs arrest pubertal progression, but the potential growth benefit would occur at the psychological cost of delayed sexual maturation. Since epiphyseal growth plate fusion is induced by local estrogen action, the inhibition of estrogen synthesis represents a potential therapeutic option. In boys, aromatase inhibitors may extend the growth phase, without affecting pubertal development and thereby increase the window for rhGH therapy. Although some case reports are promising, evidence on its efficacy and safety is needed. In particular, the osteopenic effect of aromatase inhibitors on the reduced bone mass and density in CKD children should be assessed in controlled prospective trials before such treatment can be recommended

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DOI:10.1530/ey.15.9.10

Biologic agents in chronic inflammatory diseases: lights and shadows

9.11 Perianal pediatric Crohn disease is associated with a distinct phenotype and greater inflammatory burden

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To read the full abstract: [J Pediatr Gastroenterol Nutr. 2017;65:293-298](#)

Growth deceleration and impaired pubertal growth spurt are common concerns in patients with early onset inflammatory bowel disease (IBD) (1-2). Previous studies confirmed the efficacy and safety of infliximab, an anti-tumor necrosis factor alpha (TNF- α) antibody, in achieving clinical remission in luminal Crohn's disease (CD) and in facilitating linear growth (3). The present study describes in depth the specific characteristics of children with perianal CD (pCD), a sub-category of CD patients that

appears to exhibit a higher level of inflammation. Previous studies reported a higher rate of intestinal resection in patients with pCD. As the authors state, the lack of this association in the present cohort could be linked to the currently recommended prompt start of anti-TNF α agents in the presence of perianal disease, that alters the natural history of the disease. This study reports reduced height Z-scores in children with pCD. It should be noted that height data were not correlated to the target height. Similarly, no data about growth velocity, pubertal stage and/or bone age of patients were available. For these reasons, it appears interesting to investigate in more detail the growth aspects in this sub-category of patients with IBD.

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DOI:10.1530/ey.15.9.11

Biologic agents in chronic inflammatory diseases: lights and shadows

9.12 Growth Improvement with Adalimumab Treatment in Children with Moderately to Severely Active Crohn's Disease

Walters TD, Faubion WA, Griffiths AM, Baldassano RN, Escher J, Ruemmele FM, Hyams JS, Lazar A, Eichner S, Huang B, Li Y, Thakkar RB

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To read the full abstract: [Inflamm Bowel Dis. 2017;23:967-975](#)

Approximately one-third of children and adolescents with Crohn disease (CD) suffer from growth failure and delayed puberty, leading in some to psychological and social dysfunction, especially in boys. Pubertal delay in CD may also impact the normal growth spurt and lead to short adult height. The aim of therapy in children with CD is to achieve remission, improve quality of life, and enable patients to attain full adult height potential. The IMAGINE 1 study (ClinicalTrials.gov identifier, NCT00409682) was a 52-week, phase 3, multicenter, randomized, double-blind trial that assessed the efficacy and safety of 2 induction doses and 2 maintenance dose regimens of adalimumab (ADA) in 6 to 17-year-old patients with moderately to severely active CD. This paper reports the effect of ADA treatment on linear growth in a group of 100 children participating in this study. Restoration of normal growth was associated with clinical remission and was particularly relevant in patients showing early and good response to ADA therapy.

DOI:10.1530/ey.15.9.12

Biologic agents in chronic inflammatory diseases: lights and shadows

9.13 Biologic agents are associated with excessive weight gain in children with inflammatory bowel disease

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To read the full abstract: [Dig Dis Sci. 2017;62:3110-3116](#)

This retrospective single-centre study is the first to report the impact of anti-tumor necrosis factor (anti-TNF) therapy on weight gain in children with inflammatory bowel disease (IBD). The results are consistent with data in adults, in whom weight gain during anti-TNF treatment was negatively correlated to pre-treatment BMI (1). A similar study of children with juvenile idiopathic arthritis also reported a significant

increase in BMI SDS (2). In these children, weight often directly reflects disease activity. Anti-TNF therapy increased weight gain and prevalence of obesity, particularly in children <10 years. Even if the conclusions are similar to those in adults, here data at 24 months from baseline and at last follow-up visit were available only for a small number of patients. Moreover, the effect of puberty was not considered. Fat mass and adiposity distribution change during puberty and patients with IBD patients often have pubertal delay. Further studies, performed in larger and more homogenous populations also in term of duration of the disease, could be useful in order to exclude possible confounding factors related to a long-lasting disease and its impact on linear growth.

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DOI:10.1530/ey.15.9.13

Bone health monitoring in chronic disease: broaden existing knowledge

9.14 Structural basis of bone fragility in young subjects with inflammatory bowel disease: a high-resolution pQCT study of the SWISS IBD Cohort (SIBDC)

Pepe J, Zawadzinski S, Herrmann FR, Juillerat P, Michetti P, Ferrari-Lacraz S, Belli D, Ratib O, Rizzoli R, Chevalley T, Ferrari SL
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To read the full abstract: [Inflamm Bowel Dis. 2017;23:1410-1417](#)

This cross-sectional study analyzed bone health status by high-resolution peripheral

quantitative computed tomography (HRpQTC) of a Swiss Cohort of young patients with inflammatory bowel disease (IBD) in comparison to healthy controls, matched for sex, age, height and fracture history. The results showed subtle abnormalities in bone microarchitecture that were not evident on dual-energy x-ray absorptiometry (DXA). These abnormalities seemed to be directly correlated with the disease and the fracture risk, considering the significant differences in comparison to controls. These data suggest that HR-pQTC might become the gold standard technique to identify modifications of bone architecture, despite its higher costs. The lower exposure to radiation of HR-pQTC, compared to DXA, is an additional benefit. It is noteworthy that this study analysed data of patients with mean age at diagnosis 17.3 years; this suggests the need to validate the results also in patients with childhood-onset IBD. More attention should be given to growth measures and pubertal staging, while in this study puberty was evaluated only by a self-assessment questionnaire (as several other clinical variables) and anthropometric parameters were not converted into Z-scores.

DOI:10.1530/ey.15.9.14

Late-effects of non-therapeutic radiation on thyroid: the history of atomic bomb survivors

9.15 Thyroid dysfunction and autoimmune thyroid disease among atomic bomb survivors exposed in childhood

Imaizumi M, Ohishi W, Nakashima E, Sera N, Neriishi K, Yamada M, Tatsukawa Y, Takahashi I, Fujiwara S, Sugino K, Ando T, Usa T, Kawakami A, Akahoshi M, Hida A

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To read the full abstract: [J Clin Endocrinol Metab. 2017;102:2516-2524](https://doi.org/10.1093/ajph/102.2516-2524)

The Adult Health Study (AHS) is a clinical program established in 1958 by the Radiation Effects Research Foundation (RERF) as a subset of the Life Span Study to examine the late effects of atomic bomb exposure (1-2). This cross-sectional analysis

evaluated the dose-response effect of radiation exposure on the prevalence of thyroid dysfunction and autoimmune thyroid disease in a large cohort of Hiroshima and Nagasaki atomic bomb survivors exposed to low-dose radiation in childhood. Almost 60 years after this exposure, the increased risk of thyroid disease was not evident anymore, neither was a relationship between thyroid disease prevalence and radiation dose. As stressed by the authors, the study design was necessarily cross-sectional, so they could not examine changes in radiation effects over time. Survival rates represent another possible confounding factor, even if reduced life expectancy has been associated with high-dose radiation exposure due to increased cancer risk and here the authors analysed only those with low-dose exposure. The conclusions are reassuring, but it remains to confirm these findings also in subjects with additional risk factors, such as pre-existing thyroid disease.

1. Atomic Bomb Casualty Commission. Research plan for joint ABCC-NIH Adult Health Study in Hiroshima and Nagasaki. In: ABCC Technical Report 11-62. Hiroshima and Nagasaki, Japan; 1962.

2. Radiation Effects Research Foundation. A Brief Description of the Radiation Effects Research Foundation. Hiroshima, Japan: Letterpress Co.; 2013.

DOI:10.1530/ey.15.9.15

10 Type 1 diabetes Mellitus

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DOI:10.1530/ey.15.10

Aetiology and heterogeneity of Type 1 diabetes (T1DM)

10.1 TCF7L2 genetic variants contribute to phenotypic heterogeneity of T1DM

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To read the full abstract: [Diabetes Care. 2018;41:311-317](#)

Some researchers assume that the etiology of T1DM is distinct from that of Type 2 diabetes mellitus. T1DM is characterized by autoimmune phenomena leading to the destruction of pancreatic islets and most importantly of beta-cells. Genetic factors are thought to influence the likelihood of autoimmune phenomena developing into overt autoimmune disease. Type 2 diabetes on the other hand is characterized by genetic susceptibility and mainly obesity traits leading to an exhaustion of the pancreatic insulin-synthesizing cell populations and insulin resistance in adipose tissue and other

organs. Both, the exhaustion of the insulin synthesizing capacity on the one hand side and insulin resistance and glucose intolerance on the other hand can occur in different stages of both T1DM and Type 2 diabetes.

Here, the group from the Baylor College, Houston, Texas, investigated TCF7L2 gene variants in more than 800 patients with T1DM. TCF7L2 is thought to play a role in Type 2 diabetes and namely the development of insulin resistance even at a young age. Surprisingly, and unexpectedly Type 2 diabetes-linked TCF7L2 variants were associated with single autoantibody (among those ≥ 12 years old), higher C-peptide AUC, and lower glucose AUC levels during an OGTT at new-onset T1DM. The authors conclude that carriers of the TCF7L2 variant had a milder immunologic and metabolic phenotype at T1DM diagnosis. Thus, a genetic background that increases the risk to develop type 2 diabetes actually led to a milder manifestation of the autoimmune type of the disease. It is completely unclear which Type 2 diabetes-like pathogenic mechanisms may be linked to this phenomenon. In any case, this study shows that different and variable pathogenetic mechanisms cause T1DM and/or Type 2 diabetes and in the end the two disease may yet be different disease entities with common end-points namely glucose intolerance and destruction or loss of the insulin reserve.

DOI:10.1530/ey.15.10.1

Aetiology and heterogeneity of Type 1 diabetes (T1DM)

10.2 Higher parental occupational social contact is associated with a reduced risk of incident pediatric T1DM: mediation through molecular enteroviral indices

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To read the full abstract: [PLoS One. 2018;13:e0193992](https://doi.org/10.1371/journal.pone.0193992)

Enterovirus infections in children are associated with an almost 10-fold higher risk of

T1DM. In these families in parents and siblings enterovirus can frequently be detected by PCR. However, the role of enteroviral infections in the pathogenesis of T1DM is complex. Although enterovirus infections are less prevalent T1DM incidence increases. Herd immunity could be an explanation in this constellation. High social contact occupations are associated with a greater infection rate. This may reboost established immune responses against pathogens. Beneath the effect of occupational contacts, hand hygiene of the children was analyzed in this study. Higher parental occupational social contact is strongly associated with a reduced T1D risk in children with a strong dose response. In part this can be explained by antibodies in mothers of newborn children that had contact with enterovirus before pregnancy. On the other hand, children's better hand hygiene protects against T1D risk. Combination of both protective factors is associated with an almost 10-fold T1D risk reduction. So hand hygiene to prevent children's enteroviral infection plays an important role in protecting against beta cell autoimmunity.

DOI:10.1530/ey.15.10.2

Aetiology and heterogeneity of type 1 diabetes

10.3 Frequency and phenotype of T1DM in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank

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Exeter, UK

To read the full abstract: [Lancet Diabetes Endocrinol. 2018;6:122-129](#)

T1DM formerly called juvenile or insulin dependent diabetes has so far been considered to be a disease of children adolescents and young adults according to traditional teaching. LADA or late autoimmune diabetes of the adult is known since several decades, however the older the patient with new onset diabetes the more likely he will be diagnosed as Type 2 diabetes because of the high background Type 2 prevalence. There is not much data available on the frequency of T1DM in adults older than 30 years. As one would assume those adults (31-60 years) with T1DM onset are more likely to have a normal or slightly elevated BMI, need often insulin within the first year of diagnosis and present more frequently with DKA. For appropriate treatment with insulin, diabetologists should keep in mind that slim patients in middle age could have T1DM. Especially parents of children in our treatment with new onset diabetes should be indicated that they could develop T1DM.

DOI:10.1530/ey.15.10.3

Continuous glucose monitoring, insulin pumps and artificial pancreas

10.4 Revisiting the relationships between measures of glycemic control and hypoglycemia in Continuous Glucose Monitoring Data Sets

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To read the full abstract: [Diabetes Care. 2018;41:326-332](#)

The question whether or not T1DM patients with low HbA1c levels, which are thought to characterize good metabolic control, in fact experience hypoglycemia and most importantly severe hypoglycemia more frequently than T1DM patients with high HbA1c levels and hence worse metabolic control has been discussed controversially. However, it is commonly agreed upon that many patients with well controlled diabetes as reflected by low HbA1c levels suffer from a lower number of hypoglycemia. Importantly, the number of severe hypoglycemic episodes is reduced in people with well controlled diabetes. Diabetes education, the knowledge of hypoglycemia risk factors and adherence to treatment protocols as well as frequent blood glucose monitoring and adjustment of insulin doses are all thought to reduce the risk of

hypoglycemia in patients with good metabolic control.

Here, continuous glucose monitoring data was used to assess the time spent in hypoglycemia as defined glucose levels below 3.9, 3.3, 3.0, or 2.8 mmol/L. Lower HbA1c values were associated with increased hypoglycemia risk, although the magnitude of risk depended upon the biochemical definition of hypoglycemia applied. The authors conclude, that real-time CGM may reduce the percentage time spent in hypoglycemia, and that this might change the relationship between HbA1c and hypoglycemia.

However, many other studies have shown that people with diabetes who know the risk of, and are able to prevent, hypoglycemia adequately have in fact lower HbA1c levels and are in good metabolic control. This provides evidence for the fact that diabetes education and treatment adherence leads to good metabolic control which is reflected by in fact both low HbA1c and at the same time a low rate of hypoglycemia episodes. The strength of this study may be seen in the fact that different definitions/biochemical thresholds of low blood sugar were analyzed and attention is drawn to the very fact that previous studies which were comparing HbA1c levels and hypoglycemia risk might have used different definitions and therefore had to arrive at different conclusions: if only very low blood sugar levels are considered as reflecting hypoglycemia people who know their diabetes and measure their blood sugar levels often will have less hypoglycemia episodes and at the same time exhibit low HbA1cs. This is reassuring for those who emphasize the importance to achieve good metabolic control as reflected by low HbA1c levels even in young children.

DOI:10.1530/ey.15.10.4

Continuous glucose monitoring, insulin pumps and artificial pancreas

10.5 Cost-effectiveness of continuous glucose monitoring for adults with T1DM compared with self-monitoring of blood glucose: the DIAMOND randomized trial

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To read the full abstract: [Diabetes Care. 2018;41:1227-1234](#)

Health care is being delivered by organizations that can be regarded as representing 'health industries'. Health care providers work within complex financial constraints and frequently within for profit settings and tight financial frameworks. Hence, health provision is more and more driven by cost-effectiveness and the willingness of either patients or health insurances or societies to pay costs of a given service. Mortality and

morbidity as well as social participation and quality of life as assessed as measuring QALYs (quality-adjusted life years) are considered endpoints for both the efficacy and effectiveness within clinical studies as well as for the financial adequacy and cost-effectiveness. As there are many patients with diabetes cost-effectiveness of diabetes care is considered an important financial issue in a society.

Re-imburement of continuous glucose monitoring devices as well as of insulin pumps for the treatment of T1DM by insurance companies and public health agencies largely depends upon its cost-effectiveness and efficacy.

The DIAMOND clinical trial evaluated the societal cost-effectiveness of continuous glucose monitoring (CGM) in adult patients with T1DM (T1D) using multiple insulin injections and showed an overall cost-effectiveness. The authors concluded that CGM is worthwhile when used in adults. It is important to note that costs of CGM has to be weighed against the costs of test strip use, morbidity, mortality and quality of life as well as participation in the work force. All of these aspects will be even more pronounced when analyzed in the pediatric population since the factor of time and longitudinal calculations will extend the findings in adults and might actually show that the calculations done for the adult population will be exceeded and advantages of CGM over conventional treatments will even be more pronounce at a young age.

DOI:10.1530/ey.15.10.5

Continuous glucose monitoring, insulin pumps and artificial pancreas

10.6 Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with T1DM

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To read the full abstract: [Diabetes Care. 2018;41:303-310](#)

One of the major short term complications of T1DM is the imminent risk of hypoglycemia during insulin treatment. In addition and importantly, long term

complications of diabetes include those induced by frequent hypoglycemia, namely neurologic and developmental impairment upon frequent hypoglycemic episodes at a young age. In addition, it is debated of whether or not reduction of hypoglycemia may lead to deterioration of metabolic control as measured by HbA1c levels.

In this study from Australia, the Medtronic MiniMed 640G pump with Suspend before low (predictive low-glucose management [PLGM]) was compared with sensor-augmented pump therapy (SAPT) alone. The primary outcome, percentage time in hypoglycemia with sensor glucose (SG) <3.5 mmol/L (63 mg/dL), was significantly reduced in the trial arm when the prediction device was in place. Most importantly, during the six months study protocol the reduction of hypoglycemia did not lead to impaired metabolic control. This study clearly shows that (1) good metabolic control can be achieved with a low rate of hypoglycemia, (2) predictive-low-glucose management using insulin pump therapy can substantially and significantly reduce the time in hypoglycemia and (3) reduction of hypoglycemia using SAPT occurred both during the day and the night and also severe hypoglycemia could successfully be prevented.

DOI:10.1530/ey.15.10.6

Continuous glucose monitoring, insulin pumps and artificial pancreas

10.7 Closed-loop control during intense prolonged outdoor exercise in adolescents with T1DM: the artificial pancreas ski study

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To read the full abstract: [Diabetes Care. 2017;40:1644-1650](#)

Exercise is thought to lead to more stable metabolic control but may also be associated

with an increased risk of hypoglycemia. The selection of sport disciplines does not differ between youngsters with diabetes and their healthy siblings. Also, patients with diabetes are not restricted in respect to their sporting activities but seem to engage more vigorously in sports than their peers or siblings. Intensive winter sport activities such as alpine skiing pose an exceptional threat for hypoglycemia both because of the outdoor nature of the sport in cold temperature and the high intensity and long lasting character of the exercise. In this publication by Breton et al. the use of a closed-loop artificial pancreas system (CLC) in adolescents with T1DM actually improved glycemic control and reduced exposure to hypoglycemia during prolonged intensive winter sport activities, despite the added challenges of cold and altitude. This study clearly shows the feasibility, safety and superiority of closed-loop insulin delivery system over conventional insulin therapy under real-time, practical, day-to-day challenges of adolescents. The time of the artificial pancreas is here!

DOI:10.1530/ey.15.10.7

Continuous glucose monitoring, insulin pumps and artificial pancreas

10.8 Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with T1DM

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To read the full abstract: [JAMA. 2017;318:1358-1366](https://doi.org/10.1093/ajph/2017.318.1358-1366)

Here, the authors compared the metabolic control in young patients with T1DM with

insulin pump therapies versus multiple injection treatment modalities using the data from 30 579 patients younger than 20 years of age of 446 centers in a prospective population-based cohort study. While it is very clear that pump therapy, compared with injection therapy, was associated with lower rates of severe hypoglycemia and diabetic ketoacidosis and HbA1c levels were lower with pump therapy than with injection therapy it remains unclear why this is so: there could be a treatment allocation bias, in such it could be that patients with better adherence to therapy are put on insulin pumps more readily than patients whose HbA1c at the very beginning is higher and who show low treatment adherence and high rates of psychosocial risks. In addition, more educated and more involved families may push more for pumps. Also, patients on pump therapy may benefit more from better diabetes education regimens than patients on more conventional therapies. Needless to say, pump therapy is safe, has proven to be practical and feasible in the day-to-day setting and offers benefits that should be offered to any child with diabetes worldwide. In view of the fact that until to this very day, insulin is still not offered to many children with diabetes in poor countries, one has to acknowledge that there is yet a long way before this will be achieved.

DOI:10.1530/ey.15.10.8

Continuous glucose monitoring, insulin pumps and artificial pancreas

10.9 Improving the clinical value and utility of CGM systems: issues and recommendations: a joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group

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To read the full abstract: [Diabetes Care. 2017;40:1614-1621](#)

See comment on 10.10

DOI:10.1530/ey.15.10.9

Continuous glucose monitoring, insulin pumps and artificial pancreas

10.10 International consensus on use of continuous glucose monitoring

Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, Garg S, Heinemann L, Hirsch I, Amiel SA, Beck R, Bosi E, Buckingham B, Cobelli C, Dassau E, Doyle FJ 3rd, Heller S, Hovorka R, Jia W, Jones T, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Maahs D, Murphy HR, Nørgaard K, Parkin CG, Renard E, Saboo B, Scharf M, Tamborlane WV, Weinzimer SA, Phillip M
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To read the full abstract: [Diabetes Care. 2017;40:1631-1640](#)

[Comments on 10.9 and 10.10] These two publications describe guidelines made by the international learned societies on the use of continuous glucose monitoring devices. It is important to learn from these publications that education and guidance are pivotal before continuous glucose monitoring should be made available and that its use should indeed be closely monitored by the professional diabetes team. Anxieties and psychological distress can then be prevented. It has been shown that in the long term those patients who actually use CGM continuously will benefit from it.

DOI:10.1530/ey.15.10.10

Comorbidities – short and long-term complications

10.11 Association between inflammatory markers and progression to kidney dysfunction: examining different assessment windows in patients with T1DM

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To read the full abstract: [Diabetes Care. 2018;41:128-135](#)

Renal damage and kidney failure are amongst the most detrimental co-morbidities of T1DM. In order to be able to prevent renal disease in the first place and treat progression of diabetic renal disease to kidney failure, the mechanisms that lead from high blood glucose levels to damage of the vascular bed of the glomerulus and to end stage renal dysfunction need to be fully understood.

In this study, the very large data sets from the Diabetes Control and Complications

Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort were used to explore the long term interrelationship of inflammation and progression of diabetic kidney disease during a 28 year long time period. To determine whether biomarkers of inflammation and endothelial dysfunction are associated with the development of kidney dysfunction and the time frame of their association, traditional biomarkers of inflammation (C-reactive protein and fibrinogen), and interleukin-6 (IL-6) and soluble tumor necrosis factor receptors 1 and 2 (sTNFR-1/2), as well as markers of endothelial dysfunction (soluble intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin [sE-selectin]), and fibrinolysis (total and active plasminogen activator inhibitor-1 [PAI-1]) were measured. Plasma markers of inflammation, endothelial dysfunction, and fibrinolysis were indeed related to the progression of kidney dysfunction during both short-term and long-term follow-up of patients with in T1DM.

These data show that the mechanisms, by which chronic high blood glucose levels lead to damage to the glomerular vascular bed, involve inflammatory processes and that these are characterized by early vascular dysfunction in the kidneys. These findings may well lead to new treatment concepts, whereby early anti-inflammatory intervention may be considered in order to prevent endothelial damage particularly in the kidney.

DOI:10.1530/ey.15.10.11

Comorbidities – short and long-term complications

10.12 Risk of severe hypoglycemia in T1DM over 30 years of follow-up in the DCCT/EDIC study

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To read the full abstract: [Diabetes Care. 2017;40:1010-1016](#)

Professor Tamberlane and co-workers investigated the rates of severe hypoglycemia in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort after approximately 30 years of follow-up. In earlier studies, high rates of

hypoglycemic episodes had been found to be associated with lower HbA1c levels and intensified insulin treatment strategies. Now, in this reanalysis and extensive follow-up of a sub-cohort of the initial DCCT cohort, it has become clear that rates of severe hypoglycemia equilibrated over time between the two DCCT/EDIC treatment groups, hence conventional and intensified treatment arms in association with advancing duration of diabetes and similar HbA1c levels.

The authors rightfully acknowledge that severe hypoglycemia persists and remains a challenge for patients with T1DM across their life span. However, it has become very clear that good glycemic control does not lead to more severe and more frequent hypoglycemia. In fact, good metabolic control as shown by low HbA1c levels is associated with lower risk for both hypoglycemia and ketoacidosis. It is assumed that this might be most likely to education and high adherence to treatment protocols as well as due to frequent blood glucose measurements.

DOI:10.1530/ey.15.10.12

Comorbidities – short and long-term complications

10.13 Prevalence of celiac disease in 52,721 youth with T1DM: international comparison across three continents

Craig ME, Prinz N, Boyle CT, Campbell FM, Jones TW, Hofer SE, Simmons JH, Holman N, Tham E, Fröhlich-Reiterer E, DuBose S, Thornton H, King B, Maahs DM, Holl RW, Warner JT

Australasian Diabetes Data Network (ADDN); T1D Exchange Clinic Network (T1DX); National Paediatric Diabetes Audit (NPDA) and the Royal College of Paediatrics and Child Health; Prospective Diabetes Follow-up Registry (DPV) initiative.

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To read the full abstract: [Diabetes Care. 2017;40:1034-1040](#)

Researchers from The Children's Hospital at Westmead, Sydney, Australia as well as scientists from institutions from three different continents, America, Europe and

Australia have combined their data from large diabetes registries in order to: examine the prevalence of celiac disease (CD) in populations of patients with T1DM; investigate international differences in the prevalence of CD; and characterize the clinical characteristics of youth with coexisting T1DM and CD versus T1DM only.

CD is common in patients with T1DM and the differences of prevalence might reflect differences in screening strategies and differences in medical services in different countries and cultural differences between continents, rather than true differences in prevalence of CD. The clinical course of T1DM did not differ between patients with CD or those without. However, patients with T1DM and CD were shorter than patients with T1DM only. It is well known that untreated CD may cause growth failure and short stature. It might be hypothesized that some patients with T1DM and CD in these cohorts had CD diagnosed too late to prevent growth impairment or even growth failure. Screening for CD should therefore be advocated and carried out meticulously. In addition, close monitoring of growth, weight and pubertal development in pediatric and adolescent populations is mandatory. This is even more so in populations with chronic diseases such as T1DM.

DOI:10.1530/ey.15.10.13

Comorbidities – short and long-term complications

10.14 Diabetic ketoacidosis at diagnosis of T1DM predicts poor long-term glycemic control

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To read the full abstract: [Diabetes Care. 2017;40:1249-1255](#)

Children and adolescents who present in ketoacidosis at manifestation of the disease might represent a subgroup of patients that may have less resilience factors in their

families, less adherence to medical advice, might be less attentive to medical symptoms and might be less knowledgeable of medical issues. In addition, they may carry biologic risk factors - be it either genetic or exogenous - that lead to a more severe onset and more dramatic course of the disease. Lastly, less endogenous insulin reserve may be present in patients who enter ketoacidosis than in those who remain in a somewhat more stable metabolic condition during manifestation.

In this paper, once again the occurrence of ketoacidosis at manifestation of T1DM is linked to poor long-term glycemic control. The authors carefully excluded that this association might be confounded by sociodemographic factors. Thus, ketoacidosis at manifestation of T1DM poses a risk factor for worse metabolic control during the later course of the disease. Patients with a history of ketoacidosis at onset therefore should be closely monitored and special care should be provided to ensure better metabolic control in the long term.

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Comorbidities ” short and long-term complications

10.15 ACE inhibitors and statins in adolescents with T1DM

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To read the full abstract: [New Engl J Med 2017; 377:1733-1745](#)

We are still unable to reach treatment goals in all children and adolescents with T1DM. The usually earliest microvascular complication developed in adolescents and young

adults is microalbuminuria. Therefore this trial focused on the prevention of microalbuminuria in high risk adolescents with an albumin-to-creatinine ratio in the upper third with an ACE inhibitor. Using a 2x2 factorial design, they tested the influence of statins and an ACE-inhibitor on microalbuminuria, intima media thickness, lipids and other cardiovascular risk factors.

Neither ACE inhibitor nor statin reduced the albumin-to-creatinine ratio. ACE inhibitors reduced the incidence of microalbuminuria by 43%, but that was not considered statistical significant due to the null results on the primary outcome. This result has to be discussed in the knowledge of recent data from the DCCT, which show that even intermittent microalbuminuria predicts cardiovascular disease risk in T1DM. A delayed legacy effect of early treatment with ACE inhibitors or statins could still occur, as reported in other trials. Therefore follow-up of the study cohort will be essential to evaluate the potential benefits of early intervention with ACE inhibitors and statins.

DOI:10.1530/ey.15.10.15

Psychology and quality of life

10.16 Factors associated with diabetes-specific health-related quality of life in youth with T1DM: the global TEENS study

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To read the full abstract: [Diabetes Care. 2017;40:1002-1009](#)

Quality of life (QOL) measures have increasingly been considered as end-points of medical interventions. Both general QOL and health- and disease-specific quality of life

can be assessed using well defined and validated questionnaires. The TEENS study is an international, cross-sectional study of youth with T1DM. 5,887 participants were followed in 20 countries across 5 continents. To assess disease and health related quality of life (D-HRQOL), participants completed the PedsQL Diabetes Module 3.0. Interestingly, the lower the HbA1c, the better the quality of life in youth and young adults with T1DM. Three diabetes-management behaviors were also related to optimal glycemic control, which represent potentially modifiable factors for clinical interventions to improve D-HRQOL as well as glycemic control. These data show that good metabolic control not only improves measures of morbidity, comorbidity and mortality, but also day-today living, and namely quality of life. Overall, efforts to achieve good metabolic control pays off, both in the short and long term, and for psychosocial wellbeing as well as in physical and somatic health.

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Psychology and quality of life

10.17 Strengths, risk factors, and resilient outcomes in adolescents with T1DM: results from diabetes MILES Youth-Australia

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To read the full abstract: [Diabetes Care. 2017;40:849-855](#)

Coping strategies for people with chronic diseases include working on risk factors as

well as using and employing resilience factors in daily coping strategies. Both strengths and difficulties may be experienced by people with T1DM. In this study, strengths were strongly related to key resilient outcomes, even in the presence of well-documented psychological and family risk factors adolescents, diabetes strengths were strongly related to key resilient outcomes, even in the presence of well-documented psychological and family risk factors in a large sample of adolescents with T1DM.

It remains unclear whether or not strengths reduce or buffer risks and difficulties. Given the associations with self-management, HbA1c, and general quality of life, monitoring and enhancing psychological strengths to cope with diabetes may support resilience promotion during a vulnerable developmental period, i.e. adolescence. Lack of resilience factors and use of may lead to impaired quality of life and bad metabolic control in vulnerable periods of life.

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10.18 Increasing risk of psychiatric morbidity after childhood onset T1DM: a population-based cohort study

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To read the full abstract: [Diabetologia. 2018;61:831-838](#)

T1DM in childhood and adolescence is a high burden for patients and family members.

This is reflected by research that shows an increased incidence of psychiatric disorders in this patient group. Especially depression, eating disorders and anxiety disorders seem to be more prevalent. However data are mainly from small cohorts or regional limited. The aim of the authors of this study was to focus on sex differences, duration of diabetes and age at diabetes onset in a national cohort from Denmark. T1DM in this analysis was associated with a two to threefold increased risk of eating disorders and a 55-95% increase in the risk of mood disorders in both sexes. The risk of personality disorders increased only in girls whereas the risk for substance-misuse was increased only in boys. In this cohort the risk increases over time with the highest risk after 5 or more years after diagnosis of diabetes. This study result implicates once more the need for diagnostic and preventive strategies regarding the elevated risk of psychiatric comorbidity.

DOI:10.1530/ey.15.10.18

Prevention

10.19 Infant Feeding and Risk of T1DM in Two Large Scandinavian Birth Cohorts

Lund-Blix NA, Dydensborg Sander S, Størdal K, Nybo Andersen AM, Rønningen KS, Jøner G, Skrivarhaug T, Njølstad PR, Husby S, Stene LC
Department of Pediatric Research, Oslo University Hospital, Rikshospitalet, Oslo, Norway

To read the full abstract: [Diabetes Care. 2017;40:920-927](#)

Breast feeding has been identified as one albeit weak protective factor protecting from the development of for example obesity, autoimmune disease and in particular T1DM.

The mechanisms of this preventive effect are not known. One explanation might still be a confounding effect of social status, overall healthy lifestyles in the families in whom breast feeding is more prevalent or alike.

In this large cohort study from two Scandinavian cohorts, evidence is provided that supports the notion that breastfeeding reduces the risk of T1DM. However, no dose-effect was seen: among those subjects who had been breastfed, no evidence indicated that prolonging full or any breastfeeding was associated with a reduced risk of T1DM. It therefore could very well be that it is not mother's milk or any constituent in it that is protective but any other factor associated with or related to breast feeding. Nevertheless, the data may support the concept of breastfeeding as one protective factor against T1DM. It is important to note that more research is needed as to the potential mechanism by which breast feeding may act as a protective factor against T1DM since this would eventually lead to prevention and large scale protection against the disease.

DOI:10.1530/ey.15.10.19

Prevention

10.20 Effect of hydrolyzed infant formula vs conventional formula on risk of T1DM. The TRIGR randomized clinical trial

Writing Group for the TRIGR Study Group, Knip M, Åkerblom HK, Al Taji E, Becker D, Bruining J, Castano L, Danne T, de Beaufort C, Dosch HM, Dupre J, Fraser WD, Howard N, Ilonen J, Konrad D, Kordonouri O, Krischer JP, Lawson ML, Ludvigsson J, Madacsy L, Mahon JL, Ormiston A, Palmer JP, Pozzilli P, Savilahti E, Serrano-Rios M, Songini M, Taback S, Vaarala , White NH, Virtanen SM, Wasikowa R

To read the full abstract: [JAMA. 2018;319:38-48](#)

Earlier observational studies showed that dietary exposure to complex proteins in newborns and early infants is associated with beta cell autoimmunity and increase the risk for T1DM. Several studies avoiding certain proteins, such as gluten and casein, have been conducted without reducing the risk for T1D in genetically susceptible children. Therefore, these authors conducted an elaborate clinical trial, which randomized 2159 children to either an extremely hydrolyzed formula or conventional formula milk. Unfortunately, the use of the extremely hydrolyzed formula did not change the occurrence of T1DM in the first 10 years of life. The results suggest that the use of an extremely hydrolyzed formula cannot be recommended to prevent T1DM in high risk children. However one point was not discussed in the paper. Infants were included with a mean age of 2 months. Before inclusion all had a different feeding including breast feeding or several formulas. The authors cannot exclude that an earlier intervention from the first day would have shown other results.

DOI:10.1530/ey.15.10.20

Prevention

10.21 Loss of intra-islet heparan sulfate is a highly sensitive marker of T1DM progression in humans

Simeonovic CJ, Popp SK, Starrs LM, Brown DJ, Ziolkowski AF, Ludwig B, Bornstein SR, Wilson JD, Pugliese A, Kay TWH, Thomas HE, Loudovaris T, Choong FJ, Freeman C, Parish CR

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To read the full abstract: [PLoS One. 2018;13:e0191360](https://doi.org/10.1371/journal.pone.0191360)

Up to now most studies to prevent autoimmune T1DM have focused on directly suppressing the autoimmune response rather than to better understanding the intrinsic requirements for beta cell survival. In this trial intracellular heparan sulfate was investigated as an essential requirement for the survival of beta cells and a marker for beta cell damage. Heparan sulfate depletion by heparanase plays an important role in the pathogenesis of T1DM. This opens the door for a possible intervention mechanism in T1DM development or progression. Replacement of heparin sulfate or inhibition of heparanase activity could improve the survival of beta cells. Such a scenario could be tested in a study in patients with new onset T1DM.

DOI:10.1530/ey.15.10.21

Prevention

10.22 Effect of oral insulin on prevention of diabetes in relatives of patients with T1DM: a randomized clinical trial

Writing Committee for the T1DM TrialNet Oral Insulin Study Group, Krischer JP, Schatz DA, Bundy B, Skyler JS, Greenbaum CJ
University of South Florida, Tampa, FL, USA

To read the full abstract: [JAMA. 2017;318:1891-1902](#)

Insulin is one of the autoantigens involved in the pathogenesis of T1DM. Therefore

several trials with insulin given orally, nasal or subcutaneous have been conducted to prevent the development of T1DM in genetically high risk populations. This trial design built on the results of DPT-1 and included further investigations related to first phase insulin release. A dose of 7.5 mg/d did not prevent T1DM in the high risk population of autoantibody positive T1DM relatives. Possibly ongoing trials with higher insulin doses might show better effects on beta cell autoimmunity and T1DM incidence. Knowledge of pre-diabetes staging has informed several prevention trials and epidemiological studies in high risk populations. Individuals with two or more beta cell antibodies are now classified as Stage 1. Without intervention, most of these will develop abnormal glucose tolerance (Stage 2) and then clinically manifest T1DM (Stage 3). The overall rate of progression from Stage 1 to 3 is ~9.5% per year.

DOI:10.1530/ey.15.10.22

Therapy and interventions

10.23 Effect of financial incentives on glucose monitoring adherence and glycemic control among adolescents and young adults with T1DM: a randomized clinical trial

Wong CA, Miller VA, Murphy K, Small D, Ford CA, Willi SM, Feingold J, Morris A, Ha YP, Zhu J, Wang W, Patel MS

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To read the full abstract: [JAMA Pediatr. 2017;171:1176-1183](#)

Adolescence is certainly the most difficult age for reaching T1DM treatment and

HbA1c goals. In this age group, most patients have deteriorated metabolic control, and higher risk for acute complications, such as severe hypoglycemia and DKA. Getting into therapeutic contact is very hard in this period of life for diabetes teams and parents. Several concepts to improve this situation have been tested with different, mostly frustrating results. Financial incentives is a plausible idea to improve therapeutic adherence and metabolic control. Here, this trial showed that an incentive of US \$60 for a 3-month period of blood glucose testing 4 times a day improved the glucose monitoring goals during the reward period, but did not persist beyond that, and failed to improve HbA1c. Although adolescents are very accessible for incentives in a psychological context, monetary incentives are controversial as not all human behavior is related to monetary incentives after all. Social incentives like family activities could be more effective, but are not easy to put into a trial context. Intrinsic motivation however would be most desirable in diabetes management because it has a long lasting effect.

DOI:10.1530/ey.15.10.23

Therapy and interventions

10.24 Management of T1DM with a very low-carbohydrate diet

Lennerz BS, Barton A, Bernstein RK, Dikeman RD, Diulus C, Hallberg S, Rhodes ET, Ebbeling CB, Westman EC, Yancy WS Jr, Ludwig DS
Division of Endocrinology, and New Balance Foundation Obesity Prevention Center, Boston Children's Hospital and Harvard Medical School, Harvard University, Boston, MA, USA

To read the full abstract: [Pediatrics. 2018;14. pii: e20173349](#)

On social media, parents of children with T1DM can find several sources that

recommend 'low carb diets'. Especially on lay community websites, such diets are recommended to eliminate blood glucose spikes and improve metabolic control. On the other hand, parents should be aware that the risk for hypoglycemia and especially diabetic ketoacidosis are increased. Higher risk of dyslipidaemia was also found in an adult observational study. A very low carb diet (VLCD) is typically defined as 20-50g carbohydrate consumption per day (i.e. 5-10% of carbohydrates as proportion of calories). Here, the authors describe an online survey of adults and parents of children who followed a VLCD. The mean reported HbA1c was 5.7%, and almost all participants achieved ADA glycemic targets. Many of the participants reported dissatisfaction with their professional diabetes care team due to discussions about their diet. This survey supports the need for a randomized controlled trial in both adults and children with T1DM under control of nutritional components like lipids, vitamins and micronutrients.

DOI:10.1530/ey.15.10.24

Therapy and interventions

10.25 A phase 3 multicenter, open-label, prospective study designed to evaluate the effectiveness and ease of use of nasal glucagon in the treatment of moderate and severe hypoglycemia in children and adolescents with T1DM in the home or school setting

Deeb LC, Dulude H, Guzman CB, Zhang S, Reiner BJ, Piché CA, Pradhan S, Zhang XM

Department of Pediatrics, Florida State University College of Medicine, Tallahassee, FL, USA

Severe hypoglycemia is one of the most threatening events in management of diabetes for parents and relatives. Although parents and patients are taught about the management in the acute situation, many are unable to use injectable glucagon. For moderate hypoglycemia, injectable glucagon seems to be no alternative for most caregivers. Nasal glucagon is now available for clinical trials, but is not yet licensed for the market. The authors present a homecare setting trial that proves the concept of effectiveness and safety of nasal glucagon in children and adolescents. However, for market authorization there are still some steps to go, including with studies of pharmacodynamics in the situation of hypoglycemic blood glucose levels and randomized trials comparing injectable and nasal profiles. Nasal delivery would make management of moderate or severe hypoglycemia much easier. Also sick days management with low blood glucose levels could be more simple with low doses of nasal glucagon without hospitalization.

To read the full abstract: [Pediatr Diabetes. 2018 19\(5\):1007-1013](#)

DOI:10.1530/ey.15.10.25

11. Preface

Martin Wabitsch, Stephanie Brandt, Christian Denzer, Adriana Nunziata, Julian Roos, Daniel Tews, Julia von Schnurbein
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We have been very happy to get around 2,000 papers out of our established search

strategy in PubMed, which have been saved in our 2018 Yearbook EndNote database. We have then selected 20 papers (1%), which in our mind have been the most exciting ones. The highlights in this year's chapter are publications about new adipokines - microRNAs released from adipose tissue and asprosin which has orexigenic and glucogenic activities - , about newly discovered genes causing monogenic childhood obesity, about fascinating treatment options for monogenic obesity, as well as about new aspects of obesity surgery in adolescents. The 2018 Yearbook chapter on obesity and weight regulation comprises further exciting articles covering a broad research area.

DOI:10.1530/ey.15.11

Estimation of target weight

11.1 Simulation of Growth Trajectories of Childhood Obesity into Adulthood

Ward ZJ, Long MW, Resch SC, Giles CM, Cradock AL, Gortmaker SL
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Boston, USA

To read the full abstract: [N Engl J Med. 2017 Nov 30;377\(22\):2145-2153](#)

A broad range of public health and clinical efforts appear to have stabilized early childhood obesity rates in the United States (1). However, this simulation study shows that more than half of all children between the ages of 2 and 19 years in 2016 will be obese by the age of 35 years. The important effect of early-onset obesity on obesity in adulthood is demonstrated by this simulation study, since obese children at 2 years of age have only a 1-in-5 chance of not being obese by the age of 35 years. Obesity at older age halved this chance. The findings of this study highlights once more the importance of promoting a healthy weight throughout childhood.

1. Hales CM, Fryar CD, Carroll MD, et al. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. *JAMA*. 2018 Apr 24;319(16):1723-1725

DOI:10.1530/ey.15.11.1

New insight into obesity comorbidities

11.2 Impact of severe obesity on cardiovascular risk factors in youth

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Department of Pediatrics, Yale University, New Haven, CT, USA

To read the full abstract: [Journal of Pediatrics 2018;192:105-114](#)

Rising degree of obesity has been shown to predict increased metabolic risk in obese children and adolescents (1). Nonetheless, it is unclear if BMI categories can be successfully applied to populations of obese children and adolescents for a

risk-adapted stratification of therapeutic approaches, and here especially for the indication of pharmacologic and bariatric interventions. Here, Zabarsky et al. demonstrate the limitations of a simple, BMI-based categorization of the degree of obesity in the pediatric age range. As has been shown before, clustering of cardiovascular risk factors rises significantly with increasing degree of obesity and also with increasing weight gain during follow-up. But importantly, the “dose-response” relationship between obesity and metabolic risk seems to plateau above the threshold for class III obesity (BMI 140-160% of the 95th percentile), which – according to the authors – roughly corresponds to an adult BMI >40 kg/m² in their population. Therefore, the challenge of developing an accurate and easy-to-use clinical classification system for metabolic risk specifically in severely obese children and adolescents remains unsolved for now.

1. Skinner AC, EM Perrin, LA Moss, JA Skelton. Cardiometabolic Risks and Severity of Obesity in Children and Young Adults. N Engl J Med 2015; 373:1307-1317.

DOI:10.1530/ey.15.11.2

11.3 Body mass index and kidney disease-related mortality in midlife: A nationwide cohort of 2.3 million adolescents

Twig G, Vivante A, Bader T, Derazne E, Tsur AM, Levi M, Goldberger N, Leiba A, Kark JD

The Israel Defense Forces Medical Corps, Tel Hashomer, Israel

To read the full abstract: [Obesity 2018;26\(4\):776-781](#)

Here, Twig et al. shed light on an important, but not well investigated facet of the complex, multi-organ system chronic disease simply termed 'obesity'. Using the large statistical power of this impressive, nation-wide database, the authors demonstrate high hazard ratios for obesity-related kidney mortality in a relatively young cohort, which even exceed the previously reported estimates for cardiovascular mortality in the same study population (1, 2). The presented data strongly confirms that adolescent BMI confers increased risk for acute or chronic kidney disease and mortality in mid-adulthood and therefore contradicts previous notions of a potential protective role of obesity in CKD (3). Nonetheless, the underlying pathophysiology of the observed association between BMI at young ages and kidney disease mortality in later life remains unclear. Observations of lower glomerular filtration rates in obese children or increased urinary excretion of biomarkers for kidney injury in severely obese

adolescents point to a potential causal relationship beyond classic cardio-metabolic disease traits, such as type 2 diabetes and hypertension (4, 5). Taken together, this raises the question whether a to-be-developed screening strategy for subclinical kidney disease in overweight and obese adolescents might be feasible approach to identify high-risk subjects, and more importantly, might provide the basis for effective secondary or tertiary prevention of end-stage renal disease in adulthood.

1. Twig G, G Yaniv, H Levine, A Leiba, N Goldberger, E Derazne, D Ben-Ami Shor, D Tzur, A Afek, A Shamiss, Z Haklai, JD Kark. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. *N Engl J Med* 2016; 374:2430-2440
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5. Xiao N, P Devarajan, TH Inge, TM Jenkins, M Bennett, MM Mitsnefes. Subclinical kidney injury before and 1 year after bariatric surgery among adolescents with severe obesity. *Obesity (Silver Spring)* 2015; 23:1234-1238

DOI:10.1530/ey.15.11.3

11.4 Early Childhood BMI Trajectories in Monogenic Obesity due to Leptin-, Leptin Receptor- and Melanocortin 4 Receptor Deficiency

Kohlsdorf K, Nunziata A, Funcke JB, Brandt S, von Schnurbein J, Vollbach H, Lennerz B, Fritsch M, Greber-Platzer S, Fröhlich-Reiterer E, Lüdeke M, Borck G, Debatin KM, Fischer-Posovszky P, Wabitsch M
Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and

To read the full abstract: [Int J Obes \(Lond\). 2018 Feb 27.](#)

See comment on 11.7

DOI:10.1530/ey.15.11.4

11.5 Loss-of-function mutations in ADCY3 cause monogenic severe obesity

Saeed S, Bonnefond A, Tamanini F, Mirza MU, Manzoor J, Janjua QM, Din SM, Gaitan J, Milochau A, Durand E, Vaillant E, Haseeb A, De Graeve F, Rabearivelo I, Sand O, Queniat G, Boutry R, Schott DA, Ayesha H, Ali M, Khan WI, Butt TA, Rinne T, Stumpel C, Abderrahmani A, Lang J, Arslan M, Froguel P
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To read the full abstract: [Nat Genet. 2018 Feb;50\(2\):175-179.](#)

See comment on 11.7

DOI:10.1530/ey.15.11.5

New Developments in Monogenic Obesity

11.6 Evaluation of a melanocortin-4 receptor (MC4R) agonist (setmelanotide) in MC4R deficiency

Collet TH, Dubern B, Mokrosinski J, Connors H, Keogh JM, Mendes de Oliveira E, Henning E, Poitou-Bernert C, Oppert JM, Tounian P, Marchelli F, Alili R, Le Beyec J, Pépin D, Lacorte JM, Gottesdiener A, Bounds R, Sharma S, Folster C, Henderson B O'Rahilly S, Stoner E, Gottesdiener K, Panaro BL, Cone RD, Clément K, Farooqi IS, Van der Ploeg LHT

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To read the full abstract: [Mol Metab. 2017 Oct; 6\(10\): 1321-1329](#)

See comment on 11.7

DOI:10.1530/ey.15.11.6

11.7 MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency

Clément K, Biebermann H, Farooqi IS, Van der Ploeg L, Wolters B, Poitou C, Puder L, Fiedorek F, Gottesdiener K, Kleinau G, Heyder N, Scheerer P, Blume-Peytavi U, Jahnke I, Sharma S, Mokrosinski J, Wiegand S, Müller A, Weiß K, Mai K, Spranger J, Grüters A, Blankenstein O, Krude H, Kühnen P

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To read the full abstract: [Nat Med 2018, May;24\(5\):551-555](#)

[Comments on 1.1, 1.5, 1.6 and 1.7] All four here presented articles have monogenic obesity as their theme. While patients with monogenic obesity are rare, these individuals bear a heavy disease burden. Furthermore, these rare natural mutations provide us with an intricate insight into the mechanisms of weight regulation. Hence, this is an important topic to study.

First, Kohlsdorf et al. studied the hypothesis that the clinical course could indicate which obese patients to investigate for monogenic obesity. Due to their special cohort, they are able provide us with a reliable and easy to follow suggested cut-offs to suspect a leptin- or leptin receptor deficiency. For simplicity, this is BMI >25kg/m² at age 2 years, and BMI >30kg/m² at age 5 years, which roughly equates to BMI-SDS > 4 at these ages. However, these cut-offs are not applicable for patients with other forms of monogenic obesity, such as heterozygous *MC4R* mutations. In fact, while some patients with other forms of autosomal-recessive obesity might have comparable early-onset obesity (1), many published cases of monoallelic forms of monogenic obesity show a later and less pronounced increase in BMI (2, 3, 4). For those patients, other cut-offs or indicators for diagnostic work-up have yet to be defined.

Secondly, Saeed et al. tackled another problem in diagnosing patients with monogenic obesity. Even in cohorts with severe early-onset obesity, only 5-10% of patients have a genetic diagnosis identified. In earlier publications, Saeed and other colleagues from Pakistan showed that in a society like in Pakistan, where on the one hand, consanguineous marriages are common, but on the other hand, rates for severe obesity are still low, up to 30% of patients with severe early-onset obesity carry one of the known monogenic obesity variants (5, 6). However, this still leaves 70% undiagnosed. Therefore, here, they performed whole exome sequencing in these patients and in very thorough filtration steps identified homozygous variants in *ADCY3*. This gene encodes adenylate cyclase 3, a member of a family of 10 related cyclases, catalyzing the synthesis of cAMP from ATP. In genome-wide association studies, an *ADCY3* is a known locus for BMI and fat mass (7, 8, 9) and *Adcy3* knock-out mice have increased food consumption, reduced physical activity, leptin insensitivity and an age-related increase in adiposity (10). The authors also showed, in at least 3 patients, that their variants led to a reduced cAMP production under stimulation. This is very convincing evidence for a new form of autosomal recessive monogenic obesity. Just as in *Adcy3* knock-out mice (11), these 3 patients were also anosmic – a feature that should now be important to assess in patients with severe early-onset obesity. *ADCY3* has also been suggested as a new target for anti-obesity drugs (12), making this finding even more relevant.

When initiating molecular diagnostics, the question always arises whether or not the results will be of any benefit to the patient, or more for scientific purposes. It is therefore of special reward to physicians to read about successful intervention-studies. Most forms of monogenic obesity originate from a defect in the leptin-melanocortin pathway leading ultimately to reduced melanocortin-4-receptor (*MC4R*) activation. However, until very recently, studies of synthetic *MC4R* agonists failed to significantly reduce food intake and body weight, but increased blood pressure and heart rate (13, 14). Then, in 2016, Peter Kühnen and colleagues reported in a seminal publication that patients with pro-opiomelanocortin (POMC)-deficiency were treated very effectively and safely with the *MC4R* agonist, setmelanotide (15). Two further setmelanotide treatment studies are presented here.

Collet et al. focused on patients with *MC4R* variants. The *MC4R* receptor is a seven-transmembrane G-protein coupled receptor. Its activation in turn activates *Gas* and increases cAMP production (for review see (16)). Collet et al. first thoroughly characterized *MC4R* variants according to their effects on cAMP production. However, apart from the known observation that biallelic *MC4R* mutations cause a more severe phenotype (17), they did not find a genotype-phenotype correlation. Next, they examined the ability of setmelanotide *in vitro* and *in vivo* to overcome reduced *MC4R* function. While setmelanotide *in vitro* stimulated cAMP production, even in loss-of-function mutations, the responses in heterozygous carriers (mice and men) were less than in non-mutation carriers, which is hardly surprising.

Finally, Clément et al. studied a more promising patient group. Patients with leptin receptor mutations lack α -MSH just as much as POMC patients do, hence their response to setmelanotide was similar to that in patients with POMC deficiency. The authors also tried to elucidate the mechanism of action of setmelanotide. As commented above, most earlier research focused on the stimulatory effects of *MC4R* on cAMP production. However, recent evidence shows that *MC4R* at least partly promotes satiety via activation of phospholipase C- β (PLC) (18). The authors showed that setmelanotide *in vitro* increased both cAMP production and PLC activation. In addition, as many of the authors contributed to both intervention studies, Clément et al. extended the studies of Collet et al. to show that some *MC4R* variants, which

according to their ability to stimulate cAMP production had been classified as ‘like-wildtype variants’, actually have a reduced ability to activate PLC and this can be rescued by setmelanotide *in vitro*.

Looking at all four papers together, we can conclude that molecular diagnostics in patients with early-onset obesity is worthwhile as some patients with monogenic obesity can receive a specific treatment. In addition, new diagnostic tools, such as whole exome sequencing, might discover new obesity genes, which in return might inform the development of new anti-obesity drugs. An excellent example is setmelanotide, which represents an extremely promising treatment option for a variety of monogenic disorders with defects upstream of *MC4R*. Setmelanotide might also be effective for patients with certain *MC4R* variants, but further research is needed to identify for which variants it is beneficial. Coming back to the first here presented paper, while we now know when to suspect leptin- or leptin receptor deficiency, we need more data to guide diagnostic testing for other forms of monogenic obesity.

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New Developments in Monogenic Obesity

11.8 Early-onset obesity: unrecognized first evidence for GNAS mutations and methylation changes

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To read the full abstract: [J Clin Endocrinol Metab 2017; 102 \(8\): 2670-2677](#)

These case reports lead to an important conclusion which changes our diagnostic work-up of early-onset childhood obesity. The authors shows that thorough work-up

of clinical cohorts, combined with genetic and epigenetic analyses, can define new characteristic features of known disorders. PHP1A, and surprisingly also PHP1B, show the common feature of early-onset obesity combined with severe hyperphagia. This phenotype might relate to silencing of paternal *Gsa* expression, combined with absent or diminished maternal *Gsa* expression due to genetic or epigenetic GNAS changes, in parts of the central nervous system that contribute to the regulation of food intake and energy expenditure. Especially, resistance at the *Gsa* coupled MC4-receptor and/or MC3-receptor in the hypothalamus might contribute to the excessive weight gain. The diagnosis of PHP1A and PHP1B in patients with early-onset obesity would have major importance for genetic counselling and parental support. Although in some of the described patients, early-onset obesity was the only first sign of PHP1, this diagnosis should be considered especially in patients with additional features of PHP1, such as short stature, brachydactyly, subcutaneous calcifications, suspicious lab values such as low serum calcium, and high levels of PTH or TSH.

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The brain decides weight gain

11.9 Neural correlates of familial obesity risk and overweight in adolescence

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The results of this study suggest that, compared to adolescents with a low risk, lean adolescents with a high familial obesity risk show a weaker activation of neural systems subserving attentional self-regulation in response to food-denoting words. These same changes were found in overweight or obese adolescents. It is interesting that exposure even to food words (which are relatively minimal food cues compared to food images which are more commonly used in functional MRI studies of food cue responsiveness) revealed significant differences between obesity risk groups. The findings are unique and were obtained in a relatively small sample size, hence they should be considered preliminary and deserving of replication.

To read the full abstract: [NeuroImage 2017; 159: 236-247](#)

DOI:10.1530/ey.15.11.9

Smelling, tasting and weight gain

11.10 The Sense of Smell Impacts Metabolic Health and Obesity

Riera CE, Tsaousidou E, Halloran J, Follett P, Hahn O, Pereira MMA, Ruud LE, Alber J, Tharp K, Anderson CM, Brönneke H, Hampel B, Filho CDM, Stahl A, Brüning JC, Dillin A

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To read the full abstract: [Cell Metab. 2017, Volume 26, Issue 1](#)

Riera *et al.* developed ways to temporarily eliminate the sense of smell in adult mice. They discovered that mice lacking smell could eat a high-fat diet and stay significantly thinner than littermates with a normal sense of smell. Conversely, mice with hyperosmia gained more weight than wild-type mice on a high-fat diet. The fact that smell-deficient mice show an increase in energy expenditure suggests that the odor of what we eat may play an important role in how the body deals with calories. These new findings give us interesting insights in so far uninvestigated coherences but further research is needed to show the transferability of the findings in rodents to humans. Similarly, olfaction has well-established functions in rodent reproductive behaviour (acting via the vomeronasal organ), which are disputed in humans who lack the vomeronasal organ (1).

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DOI:10.1530/ey.15.11.10

Smelling, tasting and weight gain

11.11 How non-nutritive sweeteners influence hormones and health

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To read the full abstract: [Trends in Endocrinology & Metabolism 2018; 29 \(7\): 455-467](#)

Interestingly, although NNS were developed to decrease energy intakes, there are no epidemiological studies showing that NNS consumption is associated with lower risk

of obesity. However, it has to be kept in mind that a major problem in such studies is reverse causality. Overweight people choose NNS to help lose weight.

The present review of the available literature shows that NNS consumption is significantly associated with higher not lower body weight, and in particular with larger waist circumference. NNS stimulate the secretion of insulin and incretins, and are able to alter the gut microbiome. Some studies show that NNS stimulate the differentiation of preadipocytes into adipocytes. Furthermore, NNS influence nutrient sensing by the brain. Since exposure to NNS in children and adolescents often occurs inadvertently, for example via NNS in tooth paste, medication, and even breast milk, it is difficult to precisely assess the amount and type of NNS exposure. However, since NNS is so widely used in processed foods, it is of exceptional importance to further study its effects on human health. Such studies should also consider the possible influence of NNS on bone mass and reproductive function.

DOI:10.1530/ey.15.11.11

Hungry fat cells

11.12 Asprosin is a centrally acting orexigenic hormone

Duerrschmid C, He Y, Wang C, Li C, Bournat JC, Romere C, Saha PK, Lee ME, Phillips KJ, Jain M, Jia P, Zhao Z, Farias M, Wu Q, Milewicz DM, Sutton VR, Moore DD, Butte NF, Krashes MJ, Xu Y, Chopra AR

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To read the full abstract: [Nat Med. 2017 Dec; 23\(12\): 1444–1453](#)

This study highlights the importance of asprosin in the regulation of appetite. This peptide hormone was first described by Romere et al. in 2016 (1), who reported 2 patients with neonatal progeroid syndrome (NPS) due to truncating heterozygous mutations in the fibrillin-gene (*FBNI*). The *FBNI* gene encodes profibrillin which is cleaved by the protease furin, yielding mature fibrillin and a C-terminal cleavage product, asprosin. The mutation led to a 50% reduced asprosin concentration in serum, associated with extreme leanness. Usually, partial or general lipodystrophy

leads to insulin resistance, which is not the case in these patients (1, 2). Asprosin is highly expressed in adipose tissue and its secretion stimulates hepatic glucose release and acts as an orexigenic agent in the hypothalamus (1). Like leptin, asprosin concentration rises with fasting and decreases with refeeding.

The authors showed that a single subcutaneous injection of recombinant asprosin in mice was able to rescue the hypophagia in *Fbni*^{NPS/+} mice, suggesting an interaction with AgRP+ neurons. Additionally, asprosin inhibited by 85% signaling of anorexigenic POMC+ neurons. However, it might also be possible that asprosin promotes appetite by interacting with other anorexigenic or orexigenic neurons. A pharmaceutical treatment option in obese and insulin resistant patients might be to decrease asprosin concentrations by neutralizing antibodies. In this mouse model, antibodies neutralized asprosin, thereby lowering the activity of AgRP+ neurons and resulting in a reduced daily food intake. In summary, this work is highly relevant to further understand the regulation of hunger and satiety. Effects of asprosin should also be considered when investigating the leptin-melanocortin pathway in other studies.

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DOI:10.1530/ey.15.11.12

Adipose tissue – a main source of miRNAs

11.13 Adipose-derived circulating miRNAs regulate gene expression in other tissues

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To read the full abstract: [Nature 2017, 542, 450–455](#)

Adipose tissue is no longer considered a passive energy store. Instead, it is well established as an important endocrine contributor. Here, the authors comprehensively show that the function of the adipose tissue as an endocrine organ is not limited to classical adipokines, but also includes miRNAs and maybe other non-coding RNAs. This study indicates that the adipose tissue is the main source of circulating miRNAs, not only in mice but also in humans. They dissected the role of the different adipose tissue depots and showed that adipose tissue derived miRNAs operate in an endocrine manner in distant tissues, such as the liver. In summary, the authors show for the first time the importance of adipose tissue on the whole circulating miRNome, and the impact of adipose tissue derived miRNAs on metabolic processes in other tissues.

DOI:10.1530/ey.15.11.13

Adipose tissue – a main source of miRNAs

11.14 Adipose Tissue Macrophage-Derived Exosomal miRNAs Can Modulate In Vivo and In Vitro Insulin Sensitivity

Ying W, Riopel M, Bandyopadhyay G, Dong Y, Birmingham A, Bae Seo J, Ofrecio J, Wollam J, Hernandez-Carretero A, Fu W, Li P, Olefsky J
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Here, the group of Jerrold Olefsky identified adipose tissue macrophages as important sources of microRNAs regulating metabolic processes not only within the adipose tissue depot, but also in an endocrine way in other distant tissues. The application of exosomes derived from ATMs isolated from obese mice caused insulin resistance both *in vitro* and *in vivo*. In obese mice, the exosomes of lean mice attenuated obesity-induced insulin resistance. Finally, these results confirmed the causal effect of miR-155 from macrophages in mediating systemic insulin resistance. By this comprehensive work, the authors revealed exosomes as the possible missing link between obesity-induced chronic tissue inflammation and insulin resistance. Therefore, exosomal miRNAs are potential treatment strategies or biomarkers for metabolic and other diseases.

To read the full abstract: [Cell 2017, Volume 171, Issue 2](#)

DOI:10.1530/ey.15.11.14

BAT: The story goes on

11.15 Three-Dimensional Adipose Tissue Imaging Reveals Regional Variation in Beige Fat Biogenesis and PRDM16-Dependent Sympathetic Neurite Density

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To read the full abstract: [Cell Metab. 2018, 27, 226-236](#)

Upon sustained cold exposure, white adipose tissue (WAT) can undergo substantial remodeling, characterized by the appearance of thermogenic brown-like or beige adipocytes. This “browning” of white fat depot also happens in humans and is associated with anti-obesity and anti-diabetic effects. This is why WAT “browning” is

considered as a highly promising therapeutic target in obesity prevention and treatment. Interestingly, browning capacity differs upon WAT depot location and the heterogeneity of browning within one adipose depot was not well understood.

Tissue clearing has been used since the beginning of the last century to microscopically assess thicker tissue samples (1). Here, Chi et al. used this method to clear both visceral and subcutaneous adipose tissue of cold-exposed mice in order to image adipose browning in the complete fat depot by light sheet fluorescence microscopy. UCP1 positivity was detected only in subcutaneous fat and was stronger in the inguinal depot. Epididymal visceral fat was resistant to browning, as reported earlier, and showed less sympathetic nerve projections compared to subcutaneous fat. These observations are critical when investigating brown adipogenesis in WAT with conventional methods – one should be aware of the heterogeneity of browning potential. It would be interesting to see whether this method could be transferred to human WAT browning.

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DOI:10.1530/ey.15.11.15

BAT: The story goes on

11.16 Non-invasive Measurement of Brown Fat Metabolism Based on Optoacoustic Imaging of Hemoglobin Gradients

Reber J, Willershäuser M, Karlas A, Paul-Yuan K, Diot G, Franz D, Fromme T, Ovsepian SV, Bézière N, Dubikovskaya E, Karampinos DC, Holzapfel C, Hauner H, Klingenspor M, Ntziachristos V
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To read the full abstract: [Cell Metab. 2018, 27, 689-701](#)

The gold standard for the determination of BAT activity is the measurement of glucose uptake upon cold exposure using [¹⁸F]-FDG PET/CT. However, due to the use of ionizing radiation, this technique cannot be used repeatedly in longitudinal studies in

humans. Alternatively, magnetic resonance imaging (MRI) and near-infrared fluorescence imaging (NIR) have been used to assess blood flow in BAT, but those methods do not accurately distinguish between WAT and BAT.

MSOT is an imaging technique that illuminates tissue with transient light. The light pulses are absorbed by the tissue, which then undergo thermo-plastic expansion that gives rise to detectable ultrasound waves. MSOT can scan tissues using light of different wavelengths, which excites different photo-absorbing molecules in the specimen (1). Here, the authors used light of spectral range 700-970 nm, which excites oxygenated hemoglobin. The system is limited by the low penetration depth of 5 cm, but provides high-resolution real-time images *in situ* and is able to detect BAT activation in mice and humans. Because MSOT does not require ionizing radiation or tracers, it is suitable for repeated assessments of brown fat activation, which is not possible by PET/CT.

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DOI:10.1530/ey.15.11.16

BAT: The story goes on

11.17 Cold-induced brown adipose tissue activity alters plasma fatty acids and improves glucose metabolism in men

Iwen KA, Backhaus J, Cassens M, Wabl M, Hedesan OC, Merkel M, Heeren J, Sina C, Rademacher L, Windjäger A, Haug AR, Kiefer FW, Lehnert H, Schmid SM
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To read the full abstract: [JCEM 2017,102\(11\):4226-4234](#)

It has been recently demonstrated that activation of brown adipose tissue (BAT) in humans improves glucose homeostasis and insulin sensitivity and is associated with accelerated lipid metabolism (3, 4), suggesting BAT activation as an option not only for obesity prevention, but also in diabetes management. There is recent evidence that cold exposure regulates insulin secretion in rats (5), but this has not been investigated in

humans so far. The present study indicates that insulin secretion is unaffected by cold exposure in humans, at least in the short term. However, mouse studies usually use longer periods of cooling, which is infeasible in humans. Thus, it could be that long-term cold adaptations would have an influence on insulin secretion in humans as well. It is not clear whether insulin secretion is altered by sympathetic activation alone or whether BAT is involved in this process. It would be interesting to see whether BAT activation would have similar or different outcome in diabetic, insulin-resistant patients.

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2. Chondronikola, M. *et al.* Brown Adipose Tissue Activation Is Linked to Distinct Systemic Effects on Lipid Metabolism in Humans. *Cell Metab.* 2016. doi:10.1016/j.cmet.2016.04.029

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DOI:10.1530/ey.15.11.17

Prebiotics reduce fat mass

11.18 Prebiotics Reduce Body Fat and Alter Intestinal Microbiota in Children Who Are Overweight or With Obesity

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To read the full abstract: [Gastroenterology. 2017 Sep;153\(3\):711-722](#)

In adults, prebiotic intake is associated with improvements in satiety, postprandial glucose and insulin concentrations (1). The effect of prebiotic intervention in overweight/obese children has been rarely studied. This clinical trial showed that supplementation with oligofructose-enriched inulin for 16 weeks decreased BMI z-score, percent body fat and percent trunk fat. Previous data in children with overweight and obesity showed that prebiotic supplementation, independent of other lifestyle changes, improved subjective appetite ratings (2), but another trial found no effect of oligofructose supplementation for 12 weeks on BMI z-score, percentage

body weight reduction and total body fat (3); that was also a randomized, double-blinded, placebo-controlled trial of n=97 overweight and obese (BMI >85th percentile) children (7-18 years) who were randomly assigned to receive placebo (maltodextrin) or oligofructose for 12 weeks. In comparison to the study presented here by Nicolucci et al., that previous study by Parnell et al. did not assess the totality of changes in gut microbial composition and FBAs. Hence, the findings of Nicolucci et al. provide a foundation for larger clinical trials in overweight/obese children and adolescents. Prebiotics are non-invasive and a plausible dietary intervention in overweight/obese children. Further studies with larger sample sizes and a longer duration of supplementation are awaited with interest.

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2. Liber A, Szajewska H. Effect of oligofructose supplementation on body weight in overweight and obese children: a randomised, double-blind, placebo-controlled trial. *Br J Nutr.* 2014 Dec 28;112(12):2068-74.

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DOI:10.1530/ey.15.11.18

Bariatric surgery – new findings

11.19 Factors associated with long-term weight-loss maintenance following bariatric surgery in adolescents with severe obesity

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To read the full abstract: [Int J Obes \(Lond\). 2018 Jan;42\(1\):102-107](#)

This cohort of n=50 adolescents who underwent bariatric surgery is highly important, since such long-term follow-up data are rare. Until today, only this study cohort described here by Ryder et al. and the Swedish nationwide study (AMOS) of adolescents with severe obesity who underwent laparoscopic Roux-en-Y gastric bypass (3) have such long-term data for weight/BMI development and provide the opportunity to study why adolescents maintain or regain weight after bariatric surgery. Here, Ryder et al. found no significant differences in weight-related and eating

behavior, health responsibility, physical activity/inactivity, or dietary habits at FAB-5+ visit between long-term maintainers and re-gainers. Of importance is the result of significant differences in overall QOL and QOL sub-domain scores between maintainers and re-gainers. Long-term maintainers had better QOL than re-gainers at FAB-5+ visit. A limitation is that they have no information on weight-related and eating behavior, health responsibility, physical activity/inactivity, dietary habits or QOL before bariatric surgery (baseline). Further studies should collect such information at baseline to identify which baseline factors determine the subsequent long-term outcomes after bariatric surgery in adolescents.

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3. Olbers T, Beamish AJ, Gronowitz E, Flodmark CE, Dahlgren J, Bruze G, Ekblom K, Friberg P, Göthberg G, Järholm K, Karlsson J, Mårild S, Neovius M, Peltonen M, Marcus C. Laparoscopic Roux-en-Y gastric bypass in adolescents with severe obesity (AMOS): a prospective, 5-year, Swedish nationwide study. *Lancet Diabetes Endocrinol*. 2017 Mar;5(3):174-183.

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11.20 Intra-gastric balloon as an adjunct to lifestyle programme in severely obese adolescents: impact on biomedical outcomes and skeletal health

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To read the full abstract: [Int J Obes 2018; 42: 115-118](#)

Intra-gastric balloons have now been used for more than 30 years in the treatment of extreme obesity. There are more than 30 studies published with almost 5,000 patients on the efficacy and safety of gastric balloons. However, due to several, sometimes severe side effects and the lack of convincing long-term outcomes, this treatment approach has been used less frequently in the last two decades. Since recent studies have shown that conservative treatment approaches are not successful in adolescents

with extreme obesity, the use of intra-gastric balloons might be a therapeutic option in such cases in which the benefit-risk-evaluation for bariatric surgery is not convincingly positive. Especially for younger adolescents, the insertion of an intra-gastric balloon may help to improve weight and metabolic health during a maximal balloon application duration of 12 months. During this important time period, patients might either adapt their lifestyle in terms of food intake and physical activity behavior to a more healthy one being able to maintain the achieved weight loss (as has been shown for 2 of 10 patients of this study). In addition, while carrying the intra-gastric balloon, young patients might be prepared for a subsequent definitive bariatric procedure. There are some convincing arguments that in young adolescents with extreme obesity the intra-gastric balloon should be used prior to a definitive bariatric procedure.

This study reports sustained improvements in HBA1c and insulin AUC despite weight gain after removal of the intra-gastric balloon. However, since there was no control group, these maintained improvements might also be due to the fact that parameters of insulin sensitivity improve during late puberty and early adulthood, independent of weight changes in adolescents with obesity. Therefore, this result may not be directly related to the intra-gastric balloon.

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11.21 Improving adherence to healthy dietary patterns, genetic risk, and long term weight gain: gene-diet interaction analysis in two prospective cohort studies

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To read the full abstract: [BMJ. 2018 Jan 10;360:j5644](#)

On the basis of scientific evidence and dietary recommendations, several diet quality scores have been developed to evaluate the healthfulness of dietary patterns. Previous studies show that improvement in adherence to healthy dietary patterns is associated with less weight gain (2, 3, 4). But, until now, no study had assessed the interaction between changes in adherence to healthy dietary patterns over time and genetic

susceptibility to obesity on long term weight gain. Here, Wang et al. show that people with higher genetic predisposition to obesity seem more susceptible to the favorable effects of improving diet quality on weight management. This supports treatment programmes aiming at improving dietary patterns and contradicts the perception that obesity due to a high genetic predisposition has a poor prognosis. Therefore, it seems important to improve adherence to healthy diets to prevent weight gain, particularly in people genetically predisposed to obesity. However, the question remains: how can we effectively motivate and support overweight and obese patients to improve their adherence to a healthy diet?

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3. Tobias DK, Zhang C, Chavarro J, et al. Healthful dietary patterns and long-term weight change among women with a history of gestational diabetes mellitus. *Int J Obes (Lond)* 2016;40:1748-53. 10.1038/ijo.2016.156
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12. Type 2 Diabetes, Metabolic Syndrome and Lipid Metabolism

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This year was significant for several articles that shed light on the genetics of type 2 diabetes (T2DM) in children. Rapidly emerging genomics tools enable study of large cohorts, identifying the genetic predisposition to obesity and T2DM, and

understanding mechanisms of how these genes impact insulin secretion and resistance. Even in the genomic era, it is not genes alone, but the interplay of genetic and environmental factors that determines phenotype. The importance of remission of childhood overweight on the risk of T2DM in adulthood indicates the need of early weight-loss interventions. The discovery of new hormones connects obesity and the metabolic syndrome (MetS), and a fish model helps us further understand insulin resistance. The effect of 'superfoods' on parameters of the MetS was reviewed this year. Finally, regarding lipids, many pediatricians still do not recognize the importance of lipid screening and treatment in children. Data of the beneficial effects of statins, as well as the lack of negative impact on cognitive impairment of low LDL, will hopefully promote embracing the guidelines of early screening.

DOI:10.1530/ey.15.12

Type 2 diabetes: Important for clinical practice

12.1 Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes

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To read the full abstract: [N Engl J Med 2018;378:1302-1312.](#)

While it is well known that being overweight in childhood and early adulthood is linked to a higher risk of T2DM later in life, the question arises as to whether diabetes risk would change if overweight children lose weight. This large-scale longitudinal study demonstrated that men who had remission of overweight between ages 7 and 13 years, and subsequently maintained a normal weight in early adulthood, had no increase in T2DM risk compared to men who were never overweight. This message is of utmost importance, as chubbiness in young children is often viewed as a sign of good health. Indeed, in the National Health and Nutrition Examination Survey, parents

were asked whether they considered their children, ages 2-5 years, to be overweight, underweight, or just about the right weight. The proportion of parents who inappropriately perceived their overweight children as just about the right weight was 95%, and as high as 78% of parents perceived their obese child as being just about the right weight.¹ Furthermore, a recent study found that while providers recognize the importance of addressing weight during a well-child visit, they prefer not to conduct obesity management on their own.² The findings, that remission of overweight before puberty and maintenance of a normal weight until early adulthood can attenuate the increased risk of T2DM posed by childhood overweight at 7 years of age, suggest that weight-loss interventions should target overweight children before puberty. Hopefully, these researchers will provide data on females as well.

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DOI:10.1530/ey.15.12.1

New Paradigm

12.2 Childhood BMI and Adult Type 2 Diabetes, Coronary Artery Diseases, Chronic Kidney Disease, and Cardiometabolic Traits: A Mendelian Randomization Analysis

Geng T, Smith CE, Li C, Huang T
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To read the full abstract: [Diabetes Care 2018;41:1089-1096](#)

These findings show that a 1-SD increase in childhood BMI was associated with a 47–83% increased relative risk of T2DM and a 28% increased relative risk of CAD in adult life, yet childhood BMI was not associated with adult chronic kidney disease. This is the first study to examine the causal relationship between childhood BMI and cardio-metabolic diseases in adult life using Mendelian randomization. Mendelian randomization uses genetic variants to determine whether an observational association

between a risk factor and an outcome is consistent with a causal effect.³ The method is analogous to a randomized controlled trial in which randomization to genotype takes place and is less likely to be affected by confounding and reverse causation. Individuals who carry more genetic BMI-increasing variants are compared to those who carry fewer and are assessed for the development of the outcome of interest. Since these genetic variants are typically unassociated with confounders, differences in the outcome between genetic groups can be directly attributed to causal differences in the risk factor, here BMI. In the current study, 15 single nucleotide polymorphisms (SNPs) were used to create a genetic risk score that summed the number of BMI-increasing alleles. Results demonstrated that childhood BMI is itself a causal factor for T2DM and CAD, further stressing the public health impact of childhood BMI modification. Based on two meta-analyses of RCTs of lifestyle interventions for children with obesity that resulted in -0.29 to -0.63 SD reductions in BMI, with better results in children younger than 12 years, the authors calculated that such a decrease in childhood BMI could translate into a reduction in adult T2DM and CAD risks of up to 27% and 9%, respectively.

3. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA* 2017; **318**(19): 1925-1926.

DOI:10.1530/ey.15.12.2

New mechanisms

12.3 The rs7903146 Variant in the TCF7L2 Gene Increases the Risk of Prediabetes/Type 2 Diabetes in Obese Adolescents by Impairing beta-Cell Function and Hepatic Insulin Sensitivity

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To read the full abstract: [Diabetes Care 2017;40:1082-1089](#)

Transcription factor 7-like 2 (TCF7L2) is a [protein](#) encoded by the TCF7L2 [gene](#) located on chromosome 10q25.2-q25.3 and is involved in the development of a wide variety of cell lineages and organs. The rs7903146 [single nucleotide polymorphism \(SNP\)](#) within the TCF7L2 gene was first reported in 2006 by Grant et al. to be associated with T2DM in an Icelandic case-control study⁴, and is the common variant

with the largest effect on T2DM susceptibility discovered to date. However, studies in adolescents were lacking.

Here, Cropano et al. describe, in a youth cohort, that each copy of the T (risk) allele of rs7903146 was associated with a 1.5-2 fold increased odds for IGT, depending on ethnicity. Furthermore, longitudinal follow-up suggested that this TCF7L2 risk genotype is associated with a high risk of maintaining IGT or progressing to T2DM. The T allele of TCF7L2 rs7903146 has profound effects on beta-cell function, as reflected by a reduced disposition index and an altered proinsulin secretory efficiency. Moreover, its effects seem to extend to the liver by reducing insulin's ability to suppress hepatic endogenous glucose production. These effects seem to occur in parallel, thus playing a critical role in two of the major defects that are key to the development of hyperglycemia. The rs7903146 risk variant in TCF7L2 affects functional beta-cell capacity early in the course of T2DM development in obese adolescents.

4. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J *et al.* Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nature genetics* 2006; **38**(3): 320-3.

DOI:10.1530/ey.15.12.3

New mechanisms

12.4 Type 2 Diabetes Variants Disrupt Function of SLC16A11 through Two Distinct Mechanisms

Rusu V, Hoch E, Mercader JM, Tenen DE, Gymrek M, Hartigan CR, DeRan M, von Grotthuss M, Fontanillas P, Spooner A, Guzman G, Deik AA, Pierce KA, Dennis C, Clish CB, Carr SA, Wagner BK, Schenone M, Ng MCY, Chen BH, Consortium M, Consortium STD, Centeno-Cruz F, Zerrweck C, Orozco L, Altshuler DM, Schreiber SL, Florez JC, Jacobs SBR, Lander ES
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To read the full abstract: [Cell 2017;170:199-212 e20](#)

T2DM has a disproportionate impact on persons of Latin American descent. GWAS in Mexican and other Latin American samples identified a haplotype containing four missense SNPs, all in SLC16A11, that were much more common in individuals with Native American ancestry than in east Asian, European and African samples. The association was stronger in younger, leaner people with T2DM.⁵ Individuals who carry the risk haplotype develop T2DM two years earlier, on average, and generally at a lower BMI than non-carriers. People who inherited copies from both parents are

about 50% more likely to have diabetes than non-carriers.

The human SLC16 gene family comprises 14 members. The family is also known as the monocarboxylate transporter (MCT) family since the first members to be identified were the proteins responsible for the proton-linked transport of important monocarboxylate metabolites such as pyruvate, L-lactate and ketone bodies across the plasma membrane, as well as a high affinity thyroid hormone transporter (MCT8) and an aromatic amino acid transporter. The SLC16 family members are involved in a wide range of metabolic pathways including energy metabolism of the brain, skeletal muscle, heart and tumor cells; gluconeogenesis, T-lymphocyte activation, bowel metabolism, spermatogenesis, pancreatic β -cell malfunction, thyroid hormone metabolism, and drug transport.

Here, Rusu et al. uncovered two distinct mechanisms by which SLC16A11 variants disrupt the gene's function in liver cells. Some genetic variations in SLC16A11 simply decrease its expression in the liver. Other variants disrupt its interaction with Basigin - a chaperone glycoprotein that plays an important role in targeting the monocarboxylate transporters of SLC16A11 to the plasma membrane. The disruption changes the location of SLC16A11 within the cell and affects cellular fatty acid and lipid metabolism in the liver. The findings suggest that reviving SLC16A11 function may be beneficial for treating T2DM, thus opening new avenues in the search for therapeutics. 5. The STDC. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. *Nature* 2014; **506**(7486): 97-101.

DOI:10.1530/ey.15.12.4

New Mechanism

12.5 Role of DNA Methylation in Type 2 Diabetes Etiology: Using Genotype as a Causal Anchor

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To read the full abstract: [Diabetes 2017;66:1713-1722](#)

This study examined whether genetic variants predisposing to T2DM exert their influence on disease via changes in DNA methylation in a young, non-diabetic, cross-sectional cohort. The examination of young subjects who are disease-free enables exploration of SNP-methylation relationships without assessing methylation differences that result from reverse causation. About half of known T2DM SNPs were found to be associated with variation in DNA methylation. To understand whether methylation is a causal pathway to future disease or a non-causal biomarker, the association

between the mQTL and diabetes was extracted from 26,488 T2DM cases and 83,964 controls (from DIAGRAM consortium data). For almost all T2DM SNP associations, no evidence was found that methylation is a key pathway for SNP effects on T2DM. Only one methylation site, that associated with a T2DM risk variant in *KCNQ1* (encoding potassium voltage-gated channel KQT-like subfamily, member 1), was found likely to be on the causal pathway to disease in later life. *KCNQ1* is a gene encoding the pore-forming subunit of a voltage-gated K⁺ channel that plays a key role in the repolarization of the cardiac action potential, as well as in water and salt transport in epithelial tissues. Mutations in the *KCNQ1* gene cause the long QT syndrome and deafness. *KCNQ1* is also expressed in pancreatic islets, and blockade of the channel with *KCNQ1* inhibitors stimulates insulin secretion. This gene exhibits tissue-specific imprinting, with preferential expression from the maternal allele in some tissues, and biallelic expression in others. The *KCNQ1* gene is located on chromosome 11 in a region containing several imprinted genes that are linked to Beckwith-Wiedemann syndrome. Intronic SNPs in the *KCNQ1* genomic region have been associated with lower pancreatic β -cell insulin secretion in individuals with T2DM in a manner dependent on parental origin and hypermethylation of the maternal allele of *KCNQ1* is suggested to affect early pancreas development.

DOI:10.1530/ey.15.12.5

Concepts revised

12.6 Monogenic Diabetes in Overweight and Obese Youth Diagnosed with Type 2 Diabetes: The TODAY Clinical Trial

Kleinberger JW, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, Linder B, Shuldiner AR, Tollefsen S, White NH, Pollin TI, for the for the TODAY Study Group

To read the full abstract: [Genetics in Medicine 2018;20:583-590](#)

Maturity Onset Diabetes of the Young (MODY) is a heterogeneous group of monogenic forms of diabetes characterized by pancreatic beta-cell dysfunction, with autosomal dominant inheritance. Fourteen distinct MODY genetic subtypes have been identified. A definitive diagnosis of MODY is very challenging because of similar or

overlapping clinical phenotypes between diabetes subtypes.

Here, Kleinberger et al. assessed the prevalence of MODY in adolescents aged 10-17 years diagnosed with T2DM according to American Diabetes Association criteria. The findings show that a considerable proportion of youth diagnosed with T2DM actually have undiagnosed MODY. Furthermore, clinical and laboratory data such as degree of obesity and C-peptide level could not differentiate between MODY and T2DM. Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle. The current study demonstrates the importance of distinguishing the different types of diabetes. Seven patients with Glucokinase MODY were unnecessarily treated, whereas those with HNF4A-MODY and HNF1A-MODY failed treatment and could benefit if treated with sulfonylurea drugs, rather than metformin or rosiglitazone. The findings of this study indicate the importance of genetic testing and proper genetic interpretation for providing optimal treatment to youth with diabetes.

DOI:10.1530/ey.15.12.6

Metabolic syndrome: New Paradigm

12.7 Insulin resistance in cavefish as an adaptation to a nutrient-limited environment

Riddle MR, Aspiras AC, Gaudenz K, Peuss R, Sung JY, Martineau B, Peavey M, Box AC, Tabin JA, McGaugh S, Borowsky R, Tabin CJ, Rohner N
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To read the full abstract: [Nature 2018;555:647-651](#)

An important model system in evolutionary developmental biology ('evo-devo') are the surface dwelling (surface fish) and cave adapted (cavefish) morphs which differ in numerous traits. Cavefish is a generic term for fresh water fish adapted to life in caves and other underground habitats. Living in darkness, pigmentation and eyes are useless, or even a disadvantage because of their energy requirements, and therefore cavefish are typically pale and blind. Importantly, as they are almost entirely cut off from the outside world, their subterranean homes provide no food for most of the year, and they live in prolonged starvation with the exception of food from springtime floods that sweep in nutrients in the form of worms and algae. To survive under these conditions, cavefish have evolved starvation resistance and binge eating when food becomes available. During restricted rations, they lose weight more slowly than their surface counterparts. Here, Riddle et al. compared laboratory-raised cavefish and surface fish and found

higher blood glucose levels after feeding in the cavefish. Investigation of short and long-term fasting showed higher blood glucose levels in cavefish compared to a minor decrease in surface fish; however, after 21 days, cavefish showed a marked decrease in blood glucose levels compared to a minor decrease in surface fish, suggesting that dysregulated glucose homeostasis is a feature of cave populations. To investigate the underlying genetic mechanism, the researchers sequenced all known genes in the insulin pathway. A difference was detected in the coding of the insulin receptor gene (*insra* gene) between surface fish and cavefish. Remarkably, this mutation is identical to a change in the Rabson-Mendenhall Syndrome, which is characterized by severe insulin resistance.

To examine the effect of this mutation in fish, the authors used CRISPR-Cas gene-editing to generate zebrafish carrying the same *insra* mutation.⁶ These zebrafish developed insulin resistance and overweight. The weight gain is puzzling, as humans and rodents lacking functional insulin receptors have growth retardation and low body fat. Another unexpected finding is that cavefish have a respectable lifespan of >14 years, similar to that of the surface fish. Elevated blood-glucose levels can damage tissue if the glucose bonds with proteins in a process termed glycation, which is linked to a range of health problems in patient with diabetes. However, cavefish do not have high levels of glycated proteins, so they have apparently evolved a yet-identified compensatory mechanism. Identifying this glycation-inhibiting mechanism has major potential biomedical importance.

6. Retaux S. The healthy diabetic cavefish conundrum. *Nature* 2018; **555**(7698): 595-597.

DOI:10.1530/ey.15.12.7

New Mechanism

12.8 Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection

Thaiss CA, Levy M, Grosheva I, Zheng D, Soffer E, Blacher E, Braverman S, Tengeler AC, Barak O, Elazar M, Ben-Zeev R, Lehavi-Regev D, Katz MN, Pevsner-Fischer M, Gertler A, Halpern Z, Harmelin A, Aamar S, Serradas P, Grosfeld A, Shapiro H, Geiger B, Elinav E

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To read the full abstract: [Science 2018;359:1376-1383](https://doi.org/10.1126/science.1257833)

The metabolic syndrome (MetS) is associated with dysfunctions of the intestinal barrier, leading to increased permeability and translocation of microbial molecules into the intestinal lamina propria and to circulation. The entry of pathogens through an impaired barrier leads to an increased risk of infection, as well as to chronic inflammation in obese and diabetic individuals.

In a series of elegant experiments, Thaiss et al. here defined the molecular and cellular disruptors of intestinal barrier function. Studying leptin deficient and leptin resistant mice, they first demonstrated elevated amounts of microbial pattern recognition receptor ligands, indicative of influx of microbial products. Then they demonstrated that tight and adherence junction structures were among the genes whose expression was most strongly abrogated. Neither leptin signaling nor obesity per se explained the severity of barrier dysfunction. Studying other components of the MetS that may contribute to barrier dysfunction, the authors revealed that hyperglycemia per se resulted in dysfunction of intestinal epithelial adherence junctions in a mouse model of type 1 diabetes. Treatment with insulin prevented the loss of adherence junction integrity. Isolated intestinal epithelial cells from hyperglycemic mice featured elevated amounts of metabolites along the glycolytic cascade and GLUT2 was discovered as the molecule involved in the intestinal epithelial cell barrier dysfunction. Hyperglycemia causes retrograde transport of glucose into intestinal epithelial cells via GLUT2, followed by alterations in intracellular glucose metabolism and transcriptional reprogramming. The authors suggest that the impact of hyperglycemia on epithelial barrier function might be relevant beyond the gastrointestinal tract and affect other mucosal surfaces, such as the respiratory tract.

DOI:10.1530/ey.15.12.8

Important for clinical practice

12.9 Maternal Thyroid Antibodies Associates with Cardiometabolic Risk Factors in Children at the Age of 16

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To read the full abstract: [J Clin Endocrinol Metab 2017;102:4184-4190](#)

The Northern Finland Birth Cohort 1986 has yielded remarkable data over the last decade. Firstly, they reported that first-trimester antibody positivity is a risk factor for perinatal death, which was not affected by thyroid hormone status. They reported that maternal thyroid dysfunction and TPO-Ab positivity during pregnancy modified thyroid function parameters of offspring in adolescence. In the current paper, they report that adolescent offspring of mothers who were TPO-Ab-positive during pregnancy had a two-fold higher odds to develop MetS at age 16 years. [Children of mothers with hyperthyroidism](#) had better insulin sensitivity than children of euthyroid mothers. Maternal thyroid antibodies were associated more strongly than maternal

thyroid hormones with cardio-metabolic risk factors in the children. More than half (55%) of the mothers with TPO-Ab positivity during pregnancy were euthyroid, suggesting that the effect was not driven by maternal TSH or thyroid hormone concentrations.

Developmental plasticity is defined as the ability of an organism to develop in various ways, depending on the particular environment.⁷ This concept explains the ability of the fetus to adapt to the intrauterine environment at the cost of modifying long-term health prospects. In an unfavorable environment, characterized by fetal hormonal or chemical imbalance or by maternal stress or disease, adaptation is possible but may come at the price of compromised health potentials decades later. The authors suggest two possible mechanisms. One is that TPO-Ab could be linked to the MetS via inflammation, as thyroid antibodies are related to higher levels of interleukins, which are markers of systemic inflammation that are detected in conjunction with the MetS. A second possibility is a common genetic predisposition both to autoimmune and cardio-metabolic risk factors. Long-term follow-up will show whether children of mothers with thyroid peroxidase antibody positivity are more prone to cardiovascular disease and diabetes later in life.

7. Michels KB. Developmental plasticity: Friend or foe? *Evolution, Medicine, and Public Health* 2017; **2017**(1): 183-184.

DOI:10.1530/ey.15.12.9

12.10 The Association Between Serum Vaspin and Omentin-1 Levels in Obese Children with Metabolic Syndrome

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To read the full abstract: [J. *Obes* 2018;16:76-81](#)

In this study, a lower level of serum omentin-1 and a higher level of vaspin were detected in pubertal obese children with MetS compared with obese children without MetS. MetS is characterized by central obesity, and increased visceral adipose tissue mass is associated with higher prevalence of insulin resistance; these pose risks for T2DM and cardiovascular diseases. Adipose tissue is not only a site of storage for excess energy but also an *endocrine organ* that secretes several hormones called adipocytokines, such as adiponectin, resistin, leptin, visfatin, apelin, and retinol-binding protein 4 (RBP 4), which are involved in energy homeostasis and metabolism.

Vaspin (Visceral Adipose tissue-derived Serpin) is a recently identified adipocytokine that serves as an insulin sensitizer with anti-inflammatory effects.⁸ Vaspin-transgenic mice are protected against diet-induced obesity, glucose tolerance impairment, and fatty liver, whereas vaspin-deficient mice develop glucose intolerance. The administration of recombinant vaspin improves glucose tolerance and insulin sensitivity in obese mice and reverses the altered expression of genes related to insulin resistance.

However, contrary to expectations, in this study, vaspin levels were higher in obese children with MetS than in obese non-MetS children. Furthermore, vaspin levels were not correlated with fasting glucose, HOMA-IR. As vaspin levels were correlated to CRP levels, the authors suggest that vaspin initially alters inflammation rather than insulin resistance.

Omentin-1 is expressed mainly in visceral (omental and epicardial) fat. Its expression is decreased in (pre)adipocytes by glucose and insulin and is stimulated by fibroblast growth factor-21 and dexamethasone. Omentin-1 has crucial roles in the maintenance of body metabolism and insulin sensitivity, and has anti-inflammatory, anti-atherosclerotic and cardiovascular protective effects. Serum levels of omentin-1 were recently shown to increase after weight loss in obese children with MetS.⁹ An olive oil-rich diet, aerobic training, and treatment with atorvastatin and antidiabetic drugs (metformin, pioglitazone and exenatide) are effective means of increasing circulating omentin-1 levels.¹⁰

8. Feng R, Li Y, Wang C, Luo C, Liu L, Chuo F *et al.* Higher vaspin levels in subjects with obesity and type 2 diabetes mellitus: A meta-analysis. *Diabetes Research and Clinical Practice* 2014; **106**(1): 88-94.

9. Meizhen Z, Xinrui T, Chunyan Y, Li W, Yingchun T, Yanfeng X. Serum levels of omentin-1 are increased after weight loss and are particularly associated with increases in obese children with metabolic syndrome. *Acta Paediatrica* 2017; **106**(11): 1851-1856.

10. Adipose Tissue-Derived Omentin-1 Function and Regulation. In: *Comprehensive Physiology*.

DOI:10.1530/ey.15.12.10

12.11 Ultrasonographic Quantitative Analysis of Fatty Pancreas in Obese Children: Its Correlation with Metabolic Syndrome and Homeostasis Model Assessment of Insulin Resistance

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To read the full abstract: [J Pediatr 2018;193:134-138.e1](#)

Obesity promotes visceral fat deposition, which may result in profound metabolic consequences that contribute directly to insulin resistance, and risk of cardiovascular disease and malignancy. Obese individuals are at increased risk of fatty liver disease, which can lead to steatohepatitis and subsequently advanced liver fibrosis. Less is known about fat deposition in the pancreas and its health consequences.

Pancreatic steatosis can be classified into the subtypes: fatty replacement, fatty infiltration, lipomatous pseudo-hypertrophy, non-alcoholic fatty pancreas disease (NAFPD) and non-alcoholic fatty steato-pancreatitis (NASP). The fat composition of

the pancreas of obese mice shows a higher content of triglycerides and free fatty acids than in lean mice. Increased intracellular triglyceride accumulation in β -cells ultimately results in reduced insulin secretion, insulin resistance, cell apoptosis and a vicious cycle of fatty replacement. The cause and effect relationship between the MetS and NAFPD has not yet been established.¹¹

Here, Kim et al. assessed fatty pancreas by the pancreato-perihepatic fat index (PPHFI) on transabdominal ultrasonography and related the values to MetS and insulin resistance. PPHFI is calculated as the ratio of mean brightness of the pancreatic body to that of perihepatic fat. PPHFI was positively correlated with MetS and insulin resistance, and had a slightly higher accuracy than the HOMA-IR value for diagnosing MetS in obese children and adolescents. The odds of MetS increased by four-fold with an increase in PPHFI, and by two-fold with a higher HOMA-IR value. It is suggested that fatty pancreas causes β -cell dysfunction, and then, might induce T2DM. PPHFI also showed positive correlations with levels of TG, LDL cholesterol, ALT, insulin and fasting plasma glucose; systolic blood pressure; diastolic blood pressure; HOMA-IR value and BMI. Transabdominal ultrasonography is relatively easy, cost-effective, and free of radiation, making it a potentially useful screening tool.

11. Romana B, Chela H, Dailey F, Nassir F, Tahan V. Non-alcoholic fatty pancreas disease (NAFPD): A silent spectator or the fifth component of metabolic syndrome? A literature review. *Endocrine, metabolic & immune disorders drug targets* 2018.

DOI:10.1530/ey.15.12.11

Review of the year

12.12 Effects of superfoods on risk factors of metabolic syndrome: a systematic review of human intervention trials

van den Driessche JJ, Plat J, Mensink RP

To read the full abstract: [Food & Function 2018;9:1944-1966](#)

"Functional foods" are foods that have a potentially positive effect on health beyond basic nutrition. Oatmeal is a familiar example of a functional food as it contains soluble fiber that can lower cholesterol levels. Foods are often modified to have health benefits, for example fortified orange juice with calcium to improve bone health. The term "superfood" has become a buzzword in the language of food and health; this is mostly perpetuated by marketing efforts. Search queries in Google of the top

volume U.S. food trend health benefits show a year-on-year growth. Superfood is a non-medical term popularized in the media to refer to a nutrient dense food that may have health-promoting properties such as reducing risk of disease or improving any aspect of physical or emotional health. So-called superfoods may have an unusually high content of antioxidants, vitamins, or other nutrients. This review aimed to provide data based on controlled human intervention studies that examined the impact of superfood items on parameters related to the MetS. Of note, as of 2007, the marketing of products as "superfoods" is prohibited in the [European Union](#) unless accompanied by a specific authorized health claim supported by credible scientific research. Nevertheless, this review is interesting, and includes details of the ingredients in each item (such as anthocyanidins, flavonoids, alpha-linoleic acid), the participants in the studies (healthy, females only, obese, etc.) and the effects on the measured outcomes. In general, the tested superfoods showed only limited evidence for effects on MetS parameters.

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Hyperlipidemia: New treatments

12.13 Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children with Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label)

Braamskamp M, Langslet G, McCrindle BW, Cassiman D, Francis GA, Gagne C, Gaudet D, Morrison KM, Wiegman A, Turner T, Miller E, Kusters DM, Raichlen JS, Martin PD, Stein EA, Kastelein JJP, Hutten BA

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To read the full abstract: [Circulation 2017;136:359-366](#)

The National Heart, Lung and Blood Institute Panel on integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommended a universal screening approach that would include one-time testing of all children aged 9-11 years for dyslipidemia. This recommendation has raised controversy regarding the identification and treatment of lipid abnormalities in children. Despite these

recommendations, universal screening has not become routine: 68% of pediatricians never/rarely/sometimes screened healthy 9- to 11-year-olds.¹² One of the reasons against universal screening in children has been the lack of long-term studies evaluating the effectiveness of screening for dyslipidemia in childhood in delaying or reducing the incidence of cardiovascular-related events.

Several important findings arise from this study. First, a significant difference in carotid intima-media thickness was detected between children with HeFH and unaffected age-matched siblings. This baseline difference was already observed from a younger age; this supports the initiation of treatment even earlier than currently recommended, before the process of atherosclerosis is detectable. Second, treatment with rosuvastatin lowered LDL cholesterol by up to 45%; the therapy was safe and did not influence either growth or puberty. Most importantly, two years of rosuvastatin treatment eliminated the difference in carotid intima media thickness between children with HeFH and their healthy siblings. These findings support the value of early initiation of aggressive LDL-C reduction in children with heterozygous HeFH to reduce cardiovascular risk.¹³

12. de Ferranti SD, Rodday AM, Parsons SK, Cull WL, O'Connor KG, Daniels SR *et al.* Cholesterol Screening and Treatment Practices and Preferences: A Survey of United States Pediatricians. *The Journal of Pediatrics* 2017; **185**: 99-105.e2.

13. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A *et al.* Statins for children with familial hypercholesterolemia. *Cochrane Database of Systematic Reviews* 2017; (7).

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Important for clinical practice

12.14 Cognitive Function in a Randomized Trial of Evolocumab

Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Robinson JG, Honarpour N, Wasserman SM, Ott BR, EBBINGHAUS Investigators
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To read the full abstract: [N Engl J Med 2017;377:633-643](#)

Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates levels of plasma LDL-C by interacting with the LDL receptor. After binding and internalization, PCSK9 directs the LDL receptor to lysosomal degradation and inhibits its recycling to the cell surface, and thus accelerates the degradation of hepatic LDL receptors. This reduces the capacity of the liver to remove LDL-C from the circulation. Evolocumab, a monoclonal antibody against PCSK9, substantially reduces LDL-C levels. However, given the importance of cholesterol in synapse formation and function, the potential adverse cognitive effects of cholesterol-reducing drugs are a reasonable concern, particularly in the case of lipophilic statins that are able to cross the blood-brain barrier.¹⁴ Data from several sources have suggested that low levels of either LDL-C or

the monoclonal antibodies may be associated with impaired cognitive function.

Here, Giugliano et al. prospectively evaluated cognition in patients with clinically evident atherosclerosis. The mean age of the patients was 63 years, 72% were men. At the time of randomization, median LDL-C was 92 mg/dl (2.40 mmol/l). Evolocumab, as compared with placebo, neither improved nor worsened executive function, working memory, episodic memory or psychomotor speed. Similar findings were also demonstrated in 661 patients in the evolocumab group who had an LDL-C <25 mg/dl. Of note, the follow up period was short. Thus, we will have to wait for the ongoing 5-year extension of the trial in approximately 500 patients. The findings of the long term study are particularly important as a dedicated study, HAUSER-RCT, is being conducted to examine the efficacy and safety of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia.¹⁵

14. P. GR, Francois M, Kenton Z, Christopher K, Jingjing S, Huei W *et al.* Design and rationale of the EBBINGHAUS trial: A phase 3, double-blind, placebo-controlled, multicenter study to assess the effect of evolocumab on cognitive function in patients with clinically evident cardiovascular disease and receiving statin background lipid-lowering therapy—A cognitive study of patients enrolled in the FOURIER trial. *Clinical Cardiology* 2017; **40**(2): 59-65.

15. Gaudet D, Langslet G, Gidding SS, Luirink IK, Ruzza A, Kurtz C *et al.* Efficacy, safety, and tolerability of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia: Rationale and design of the HAUSER-RCT study. *Journal of Clinical Lipidology* 2018.

DOI:10.1530/ey.15.12.14

12.15 A *LIMA1* variant promotes low plasma LDL cholesterol and decreases intestinal cholesterol absorption

Zhang Y-Y, Fu Z-Y, Wei J, Qi W, Baituola G, Luo J, Meng Y-J, Guo S-Y, Yin H, Jiang S-Y, Li Y-F, Miao H-H, Liu Y, Wang Y, Li B-L, Ma Y-T, Song B-L

To read the full abstract: [Science 2018;360:1087-1092](https://doi.org/10.1126/science.1253015)

During the Cardiovascular Risk Survey in western China, a Kazakh family with inherited low levels of LDL-C was identified. The Kazakhs are mainly descendent from the Turkic and medieval Mongol peoples, they live in isolated regions and usually marry within their own ethnic group. They exhibit often unique differences in single nucleotide variants (SNVs) across their genomes. To identify the causal SNV(s), samples from three subjects exhibiting low LDL-C (38-70 md/dl) and one exhibiting normal LDL-C were analyzed by whole-exome sequencing. A frameshift mutation in the *LIMA1* gene was identified. Given that LDL-C is influenced by both endogenous cholesterol biosynthesis and intestinal cholesterol absorption, the campesterol to lathosterol ratio was measured. The *LIMA1* mutation was associated with a significantly lower Ca:L ratio than in non-carriers, suggesting that *LIMA1*-mutation

carriers have reduced intestinal cholesterol absorption.

In a mice model, *LIMA1* was highly expressed in the small intestine, mainly localized on the brush border membrane, and modestly expressed in the liver. Oral administration of radiolabeled cholesterol to intestine-specific *Lima1*-deficient (*I-Lima1*^{-/-}) mice showed lower cholesterol uptake than in wild-type (WT) littermates. In diet induced hypercholesterolemia mice, the cholesterol contents in VLDL, LDL and HDL were all markedly lower in *I-Lima1*^{-/-} than in WT mice.

The absorption of cholesterol in the intestine is mediated by the key transmembrane protein Niemann-Pick C1-like 1 (NPC1L1). In intestine-specific *Lima1* deficient (*I-Lima1*^{-/-}) mice, *LIMA1* was specifically depleted from the mouse intestine without affecting the level of NPC1L1. To reveal the mechanism by which *LIMA1* mediates dietary cholesterol absorption, the *LIMA1*-containing complex from WT mouse intestinal epithelial cells was immunoprecipitated and its binding proteins were identified by tandem mass spectrometry. *LIMA1* was found to bind NPC1L1 and myosin, suggesting that *LIMA1* may bridge myosin to NPC1L1, forming a triplex that facilitates cholesterol absorption. Ezetimibe, a drug that lowers plasma cholesterol levels by decreasing cholesterol absorption in the small intestine, reduces enterocyte uptake and absorption of cholesterol by binding to NPC1L1. Pharmacological targeting through the *LIMA1* pathway might provide a new strategy to improve cardiovascular health.

DOI:10.1530/ey.15.12.15

New Concerns

12.16 Lipid Profiles, Inflammatory Markers, and Insulin Therapy in Youth with Type 2 Diabetes

Levitt Katz LE, Bacha F, Gidding SS, Weinstock RS, El Ghormli L, Libman I, Nadeau KJ, Porter K, Marcovina S; TODAY Study Group
Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, USA

To read the full abstract: [J Pediatr 2018;196:208-216.e2](#)

Insulin deficiency or resistance activates intracellular hormone-sensitive lipase; this increases the release of non-esterified fatty acids from triglycerides stored in centrally distributed adipose tissue. High circulating levels of non-esterified fatty acids increase hepatic triglyceride synthesis, which in turn increases secretion of apolipoprotein B (apoB). Indeed, dyslipidemia is a common feature in T2DM. The risk of cardiovascular disease is greater at any given level of serum cholesterol in patients with diabetes, and its association with hypertriglyceridemia is stronger than in the general population. Cardio-metabolic disease risk is further increased both by poor glycemic control and by systemic inflammation, specifically hs-CRP.

Among T2DM adults, diabetic dyslipidemia can be partly corrected by insulin

treatment and improved blood glucose control. The aim of the current study was to determine the impact of insulin therapy on lipid profiles and inflammatory markers in adolescents with T2DM and poor glycemic control. The mean HbA1c prior to initiation of insulin treatment was $9.7 \pm 1.7\%$. After 6 months of insulin therapy, the decrease in HbA1c was approximately $-0.11 \pm 2.1\%$. Prior to initiation of insulin treatment, lipid and inflammatory markers were rising steadily. After insulin therapy, lipid markers for total cholesterol, LDL-C, apoB, and triglycerides continued to rise, but at a slower rate. Those with the greatest reduction in HbA1c had the greatest reduction in total cholesterol, LDL-C, and apoB. Triglyceride level was independent of HbA1c level. Nevertheless, the small dense, more atherogenic LDL particles did not decline. Furthermore, the inflammatory markers: IL-6 and hs-CRP continued to rise steadily after insulin therapy. BMI remained stable over time.

The authors raised concern that starting insulin therapy in youth with T2DM may not protect against premature atherosclerosis. In a recent study that assessed barriers to taking glucose-lowering oral medications, about 70% and 80% of TODAY participants reported missing one or more doses in the two- or three-month interval since their last visit at 6 and 24 months, respectively.¹⁶ It is possible that these patients did not comply with insulin treatment as well, and that this might explain the lack of improvement in their metabolic profile.

16. Venditti EM, Tan K, Chang N, Laffel L, McGinley G, Miranda N *et al.* Barriers and strategies for oral medication adherence among children and adolescents with Type 2 diabetes. *Diabetes Research and Clinical Practice* 2018; **139**: 24-31.

DOI:10.1530/ey.15.12.16

13. Global Health for the Paediatric Endocrinologist

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and Diabetes. It is very comforting to witness the rapid increase in high quality research papers that challenge guidelines commonly made for and used in resource-rich settings and that propose new approaches based on the specific characteristics of resource-limited settings. We found many papers on the topic of Developmental Origins of Health and Disease/Type 2 diabetes, on congenital hypothyroidism and on growth/ development and highlight them in three sections of this yearbook chapter.

DOI:10.1530/ey.15.13

Welcome to the 3rd edition of this chapter on Global Health in Pediatric Endocrinology

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.1 Supporting Global Health at the Pediatric Department Level: Why and How

Pitt MB, Moore MA, John CC, Batra M, Butteris SM, Airewele GE, Suchdev PS, Steinhoff MC on behalf of the American Board of Pediatrics Global Health Task Force

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To read the full abstract: [Pediatrics 2017; 139\(6\)](#)

This article provides guidelines for leaders in academic institutions in high-income countries who wish to develop a global health stream in their department. We should not forget that over the last 25 years, major changes in our world have decreased the distances between nations. Pediatric residents who train in high income countries are increasingly expressing interests in global health. In our mind, this reflects as much the personal interest of the younger generation in supporting children who live in resource-limited countries as the bidirectional need for such a change. For instance, in pediatric

endocrinology, and as illustrated in several other papers in this section, the future generation of pediatric endocrinologists (whether in high-income or in low-income countries) will benefit from the increased knowledge that results from global interaction. The identification of the appropriate laboratory tests to access in resource-limited countries could also generate a healthy reflection on the most appropriate use of often expensive and invasive tests in high-income countries; understanding attitudes towards newborn screening for congenital hypothyroidism or towards the quality of life of children with disorders of sex development in resource-limited settings may help the pediatric resident to optimize the care of immigrant populations in high-income countries; researching the relationship between immune function and growth in children in South America will bring new knowledge that can be applied to our understanding of growth in high-income countries. Finally, we should also not forget that global health does not only apply to children living in resource-limited settings but also to immigrant or indigenous populations living in high-income countries. Their access to medical care is often poor. For instance, in 2017, in Canada, the life expectancy of the Inuit (a group of culturally similar indigenous peoples inhabiting the Arctic regions of Greenland, Canada and Alaska and who were present for several thousands of years prior to the arrival of the first Europeans) was 64 years for men and 73 years for women, respectively; 15 and 10 years lower than for the general population of Canada.

DOI:10.1530/ey.15.13.1

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.2 Worldwide burden of cancer attributable to disease and high body-mass index: a comparative risk assessment

Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, Ezzati M
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To read the full abstract: [Lancet Diabetes Endocrinol 2018; 6\(2\):95-104](#)

As non-communicable diseases (NCDs) are reaching epidemic levels, emerging data elucidate the devastating non-metabolic long-term risks of overweight, obesity and diabetes. Using published relative risk analysis and cancer incidence estimates from the GLOBOCAN project, the authors provide a thorough risk analysis of site-specific cancers including colorectal, gallbladder, pancreatic, liver, breast, and endometrial cancer attributable to high BMI, diabetes, and the combination of the two. Their

estimate that 6% of new cancers are due to the combined effect of high BMI and diabetes is substantial and, more concerning, is projected to increase by 20-30% over the next 10 years. Interestingly, the attributable cases in women are almost double that of men and account for the majority of the projected increase. There was significant regional variability with regards to cancer specific proportions of total cancer burden as well as PAF of cancer attributable to high BMI, diabetes or both, possibly explained by variations in risk factor prevalence. PAFs in low-and middle-income regions were lower than in most high-income regions, although in the absence of disease registries and reliable ascertainment, both diabetes and cancer epidemiologic data from many low- and middle-income countries should be interpreted with caution. However, even when data inaccuracy is taken into account, it is alarming that the proportion of cancer cases attributable to the increase in prevalence of high BMI and obesity was largest in low- and middle-income countries across sub-Saharan Africa and Asia. Most likely, this reflects the rapidly increasing rates of obesity, diabetes and non-communicable diseases in these regions. Immediate preventive public health measures and care delivery efforts need to be identified and put in place to curb this epidemic and its foreseeable short- and long-term detrimental health consequences.

DOI:10.1530/ey.15.13.2

How does paediatric endocrinology and diabetes fit in the global initiatives?

Sewankambo NK
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13.3 Effects of the Informed Health Choices primary school intervention on the ability of children in Uganda to assess the reliability of claims about treatment effects: a cluster-randomised controlled trial

Nsagni A, Semakula D, Oxman AD, Austvoll-Dahlgren A, Oxman M, Rosenbaum S, Morelli A, Genton C, Lewin S, Kaseje M, Chalmers I, Fretheim A, Ding Y,

To read the full abstract: [Lancet 2017; 390: 374-88](#)

See comment on 13.4

DOI:10.1530/ey.15.13.3

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.4 Effects of the Informed Health Choices podcast on the ability of parents of primary school children in Uganda to assess claims about treatment effects: a randomised controlled trial

Semakula D, Nsangi A, Oxman AD, Oxman M, Austvoll-Dahlgren A, Rosenbaum S, Morelli A, Glenton C, Lewin S, Kaseje M, Chalmers I, Fretheim A, Kristoffersen DT, Sewenkambo NK
College of Health Sciences, Makerere University, Kampala, Uganda

To read the full abstract: [Lancet 2017; 390\(10092\): 389-398](https://doi.org/10.1136/bmj-2017-023983)

[Comment on 13.3 & 13.4] Access to quality medical care is often difficult in resource-limited settings and depends upon the collaboration of key stakeholder groups, including global/regional health policymakers, national governments and health system managers, the pharmaceutical industry and trained clinicians and health workers. In addition, patient advocacy groups (parents and children) are expected to play a major role in promoting access to health care. For instance, Caring and Living as Neighbours (CLAN, www.clanchildhealth.org) has identified patient groups as the

main driver in advocating for essential medicines availability in resource-limited settings. These groups are the main pillars of their intervention.

In a recently released “Call to Action”, “non-communicable diseases” (NCD) Child (<http://www.ncdchild.org/>) emphasizes the importance of promoting “*health literacy of children, youth and their families to ensure the most effective use of essential medicines and equipment*”. In 2 studies, the researchers target young children (pediatric study 13.3) and their parents (adult study 13.4). The pediatric study (13.3) randomized whole schools while the adult study randomized individuals.

The pediatric study (13.3) shows that a simple curriculum taught at school increased knowledge and critical thinking about informed health choices. The curriculum comes as a small book (“The Health Choices Book: learning to think carefully about treatments, a health science book for primary school children”) that is used by the classroom teacher to discuss 12 basic concepts around treatment adequacy. Children in classrooms where the curriculum was delivered scored much higher on a knowledge test taken at the end of the intervention, compared to the children who did not receive the intervention.

The adult study (13.4) shows that a podcast on Informed Health Choices increased the ability of parents to assess claims about the effects of treatments. The duration of such effects and whether they translate into changed attitudes towards medicines is unclear. One can also wonder whether health literacy could lead to conflicts with traditional healers who commonly serve as the primary healthcare providers, in particular in rural areas.

DOI:10.1530/ey.15.13.4

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.5 Access to pathology and laboratory medicine services: a crucial gap

Wilson ML, Fleming KA, Kuti MA, Looi LM, Lago N, Ru K
Department of Pathology and Laboratory Services, Denver Health, Denver, CO, USA

To read the full abstract: [Lancet 2018; 391\(10133\):1927-1938](#)

See comment on 13.7

DOI:10.1530/ey.15.13.5

How does paediatric endocrinology and diabetes fit in the global initiatives?

Department of Pathology, Aga Khan University Hospital Nairobi, Nairobi, Kenya

13.6 Improving pathology and laboratory medicine in low-income and middle-income countries: roadmap to solutions

Sayed S, Cherniak W, Lawler M, Tan SY, El Sadr W, Wolf N, Silkensen S, Brand N, Looi LM, Pai SA, Wilson ML, Milner D, Flanigan J, Fleming KA

To read the full abstract: [Lancet 2018; 391\(10133\):1939-1952](#)

See comment on 13.7

DOI:10.1530/ey.15.13.6

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.7 Delivering modern, high-quality, affordable pathology and laboratory medicine to low-income and middle-income countries: a call to action

Horton S, Sullivan R, Flanigan J, Fleming KA, Kuti MA, Looi LM, Pai SA, Lawler M

School of Public Health and Health Systems, University of Waterloo, Waterloo, ON, Canada

To read the full abstract: [Lancet 2018; 391\(10133\):1953-1964](#)

[Comment on 13.5, 13.6 & 13.7] Published just a week before the World Health Organization put out their first Essential Diagnostics List (http://www.who.int/medical_devices/diagnostics/WHO_EDL_2018.pdf), this series of 3 papers highlights the previously often unrecognized but important role of pathology and laboratory medicine (PALM) services in low- and middle-income countries (LMIC). Increasingly, modern medicine relies on diagnostic testing to confirm clinical diagnoses, including through in vitro diagnostics, devices, pathology and radiology procedures – often avoiding morbidity, mortality and a negative economic impact from a wrong diagnosis. Endocrine conditions such as diabetes and lipid metabolism disorders are prime examples that can be difficult to diagnose, classify, treat and monitor based on clinical grounds, especially in their asymptomatic stages. While in high-income countries PALM are used for 2 out of 3 health conditions, LMICs continue to have limited access to PALM services despite bearing a disproportionate share of the global burden of disease with much scarcer access to resources.

The first paper (13.5) outlines key barriers to setting up PALM in LMICs, including a shortage of human resources and workforce capacity, a lack of continuing medical education, an inadequate infrastructure for laboratory services, and absence of standards for rational use of resources, quality, and accreditation. *In the second paper*

(13.6), the case is made for a universal health coverage supported laboratory and health system that is aligned with the Sustainable Development Goals. Avoiding the mistakes of vertical, siloed programs, successes from programs such as PEPFAR should be incorporated, including investment into an improved infrastructure, a solid health care workforce, the wise use of task shifting and task sharing with community health workers, and the value and cost-effectiveness of high quality care along the care delivery cascade. The delivery package proposed aligns with needs for non-communicable disease programs in LMICs (including those suitable for pediatric endocrine services), suggesting evidence based, innovative, locally adapted health care delivery services that incorporate PALM and are integrated into a national health system strategy, conceptualized by local leaders with support from international organizations and stakeholders. *The third paper (13.7)* takes on a political, systems, advocacy and financing perspective to establishing sustainable high-quality PALM services in LMICs. Actionable recommendations are outlined and should be understood as an attempt at not only holding local and international stakeholders responsible for implementing the required services, but also at assuming responsibility among the PALM professionals to take leadership and advocate.

The challenges, potential solutions and proposed political and advocacy strategies for PALM services are fully relevant for global pediatric endocrinology and diabetes. Many parallels exist and several of the outlined suggestions for PALM are immediately applicable to establishing pediatric endocrine services in LMICs. Further, as capacity for pediatric endocrinology in LMICs is increasing through subspecialty training programs such as the Pediatric Endocrinology Training Center for Africa (PETCA) and the Pediatric Endocrinology Education Program for Haiti (PEEP-H), graduates seeking to establish their endocrine practices in their countries will need available, affordable and accessible PALM services to effectively deliver their care. Global efforts to achieve the Sustainable Development Goals need to be leveraged to align national and international stakeholders, move towards universal health coverage, and develop national strategic health care plans that are appropriately resourced to facilitate locally adapted, quality, cost-effective and equitable care – including in subspecialties like endocrinology.

DOI:10.1530/ey.15.13.7

Type 1 and Type 2 Diabetes in Resource-Limited Settings

13.8 Developmental Origins of Health and Disease: the relevance to developing nations

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To read the full abstract: [Int Health 2018; 10: 66-70](#)

This article summarizes the concept of Developmental Origins of Health and Disease (DOHaD) and emphasizes its potential relevance to the marked increase in non-communicable diseases, including Type 2 diabetes, observed in low-resource

settings. This is an important topic as the DOHaD concept may be a strong contributing factor to the developing Type 2 diabetes epidemic. Geographical differences between the contribution of maternal nutrition, birthweight and postnatal nutrition are not considered in this article but are likely to influence the relevance of the DOHaD concept across regions. For instance, a large part of the clinical knowledge on DOHaD comes from work performed in India, where small for gestational age (SGA) is highly prevalent. Readers interested in this topic should look at the work by Caroline Fall (Southampton, UK) which focuses on the Indian subcontinent and at the publications by the research team of the New Delhi cohort (started in 1969). Whether the determinants specific to India also apply to other parts of the world where SGA (see Lee et al., *Lancet Global Health*, 1, No. 1, e26–e36, July 2013) and severe underweight in childhood (see article by NCD Risk Factor Collaboration in the “Growth and Development” subsection of this chapter) seem much less prevalent need to be investigated. There may be country-specific solutions to decrease the adverse consequences of poor fetal development.

DOI:10.1530/ey.15.13.8

Type 1 and Type 2 Diabetes in Resource-Limited Settings

13.9 Type 2 diabetes in adolescents and young adults

Lascar N, Brown J, Pattison H, Barnett AH, Bailey CL, Bellary S
School of Life and Health Sciences and Aston Research Centre for Healthy Aging,
Aston University, Birmingham, UK

To read the full abstract: [Lancet Diabetes Endocrinol 2018; 6:69-80](#)

The prevalence of T2DM in youth is increasing dramatically worldwide, but the bulk of the increase is expected to take place in Africa, South East Asia and South America. Although genetic factors may seem to be the obvious reason for such geographical differences, a careful analysis of the existing literature suggests that many factors need to be considered: ethnic differences in the genes associated with obesity or with insulin

action/secretion have not been clearly identified; the role of intrauterine retardation and postnatal growth that has been well-studied in India may not be as relevant in other settings, the importance of environmental factors; of chronic infections/inflammation and of the nutritional transition may differ from country to country; little data is available on physical activity in youth living in different cultures and the effect of the known differences in the quality of the national healthcare systems on the recognition and management of T2DM remains poorly understood. Understanding the determinants underpinning the expected worldwide increase in the prevalence of T2DM in youth is important as it may lead to country-specific guidelines for the prevention of this public health epidemic that are different from guidelines published in high-income countries where most studies are performed.

This review also raises the important question of access to medicines. Access to insulin is presently insufficient in many low-income countries and could further aggravate the economic consequences of this epidemic.

DOI:10.1530/ey.15.13.9

Type 1 and Type 2 Diabetes in Resource-Limited Settings

13.10 Diabetes in sub-Saharan Africa: from clinical care to health policy

Atun R, Davies JI, Gale EAM, Barnighausen T, Beran D, Kengne AP, *et al.*
Harvard TH Chan School of Public Health, Harvard University, Boston, MA, USA

To read the full abstract: [Lancet Diabetes Endocrinol 2017; 5\(8\):622-667](#)

The Lancet Diabetes and Endocrinology Commission provides a comprehensive, evidence-based review of diabetes in sub-Saharan Africa, one of the most important emerging diseases and markers of the global epidemic of non-communicable diseases. The authors provide a detailed analysis of the significant knowledge gaps in the global epidemiology and burden of diabetes and its complications in sub-Saharan Africa and emphasize the need to develop local systems to ascertain population representative data. The commission delineates the current health system's barriers adequate diabetes care delivery in the region, concluding that sub-Saharan Africa remains ill equipped in terms of diagnostic and monitoring tools, adequately trained health care professionals, access to essential therapeutics, and availability of guidelines and disease registries. They add an estimate of the economic burden of diabetes, including direct cost to the

individual and indirect cost to countries, including the expected tripling in cost until 2030 and the anticipated inability of health systems in the region to assimilate this financial burden.

Strategies to formulate an appropriate health system response are discussed, including the development of service delivery models that are adapted to the reality of low- and middle-income countries and that enable an effective cascade of care from primary prevention to screening, diagnosis, treatment, and long-term care. A decentralized approach that integrates chronic disease care and borrows from successful HIV care delivery models is suggested and should include task shifting from physicians and nurses to community health workers as well as the use of smart information technology. An appropriate medical, social, and political context is required and may be fostered by aligning the health systems response with global targets (such as the Sustainable Development Goals), and by developing a concerted response from national governments, civil society, third party donors and international agencies such as the World Health Organization, the World Bank, the Global Fund, as well as national (USAID) and international (UN based) organizations.

Concerted action and adequate funding by local, national and international stakeholders to develop effective, affordable, and locally adapted responses to the oncoming epidemic of diabetes and non-communicable diseases in low- and middle-income countries is urgently needed.

DOI:10.1530/ey.15.13.10

Type 1 and Type 2 Diabetes in Resource-Limited Settings

13.11 Insights from the WHO and National Lists of Essential Medicines: Focus on Pediatric Diabetes Care in Africa

Rowlands A, Ameyaw E, Rutagarama F, Dipsesalema J, Majaliwa ES, Mbogo J, Ogle GD, Chanoine JP

Endocrinology and Diabetes Unit, British Columbia Children's Hospital and University of British Columbia, Vancouver, BC, Canada; Global Pediatric Endocrinology and Diabetes (GPED)

To read the full abstract: [Horm Res Paediatr. 2018; Jul 26:1-1](#)

As the global burden of non-communicable diseases (NCD) is rising to epidemic levels worldwide, efforts are underway to build capacity for childhood NCDs in low- and middle-income countries (LMICs), including among health care providers in pediatric endocrinology. With increased ability to recognize and diagnose pediatric endocrine conditions in resource-constrained settings, limited access to essential medicines is becoming more palpable. Following their initial assessment of effective translation of

the World Health Organization (WHO) Essential Medicines List (EML) to national EMLs in Central America, this second paper by Rowlands et al. focuses on the African continent. While most of the medicines deemed essential in pediatric endocrinology were present on both WHO and national EMLs, not all were – including life-saving medications like fludrocortisone and diazoxide – and only 50% of the medicines included on the author's master list were included. More concerning but maybe not surprisingly, neither the WHO nor the national EMLs were reliably predictive of access to insulin and glucagon. The authors verified actual availability and affordability of these two most important medicines for diabetes care with pediatric endocrinologists in 5 African countries of variable Gross National Income and found highly variable actual access. A review of aspects of the health systems in these 5 countries that can affect access to medicines, including health care coverage schemes, outreach capacity to remote regions, government supported special programs, and involvement of the private sector and international support programs are among potential factors that may modulate access.

Stakeholders in the public and private sector need to take action to increase transparency of listed and actual availability of essential medicines, and develop evidence-based recommendations for the procurement and reliable disposition of cost-effective essential medicines.

DOI:10.1530/ey.15.13.11

Type 1 and Type 2 Diabetes in Resource-Limited Settings

13.12 Clinical profile of diabetes at diagnosis among children and adolescents at an endocrine clinic in Ghana

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International Diabetes Federation Life for a Child Program, Glebe, NSW, Australia

To read the full abstract: [World J Diabetes 2017; 8\(9\):429-435](#)

This is the first paper to describe the clinical presentation and social determinants in youth with diabetes residing and cared for at a single tertiary care center in Ghana that is supported by the International Diabetes Federation's Life for a Child (LFAC) program. As demonstrated by the ability to conduct and publish this study, LFAC not only provides insulin and diabetes supplies for patients, but is also a vehicle for clinical

and research capacity building. While the robustness of study data was limited by the absence of important laboratory tests such as electrolytes and blood gas to determine diabetic ketoacidosis (DKA), or C-peptide, pancreatic auto-antibodies, and genetic studies to evaluate diabetes type, the study nonetheless adds valuable information to a very small body of literature on phenotypes and social determinants in youth with diabetes in low-income countries. The authors confirm clinical observations from similar settings including a female predominance, high rates of DKA and infections at diagnosis, a high crude death rate, and increasing apparent diabetes prevalence as clinical care becomes accessible. Unfortunately, data on glycemic control over time did not seem to be available. However, social challenges were identified including low literacy in 1/4 caregivers, absence of schooling in 1/5 youth, inappropriate grade for age in a similar number along with limited school attendance due to diabetes, and poor coping in 1/6 youth. Further investigations are needed to relate the clinical phenotypes and identified social factors to glycemic control and complications, and to develop and evaluate models of diabetes care delivery that are well-adapted to the described population and setting.

DOI:10.1530/ey.15.13.12

Type 1 and Type 2 Diabetes in Resource-Limited Settings

13.13 High Rates of Ocular Complications in a Cohort of Haitian Children and Adolescents with Diabetes

Robinson ME, Altener K, Carpenter C, Bonnell R, Jean-Baptiste E, von Oettingen J

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To read the full abstract: [Pediatr Diabetes 2018; 19: \(6\) 1124](#)

In this cross-sectional study performed in Haiti, the authors found that 18% of the children and adolescents with diabetes had signs of retinopathy and that 16% had a cataract. This prevalence is clearly much higher than reported in young patients with diabetes living in high-income countries. Importantly, ocular complications occurred early in Haitian patients, 4.9 years after diagnosis of diabetes for retinopathy and 3.0

years for cataract. The prevalence of ocular complications increases with duration of diabetes and poor quality of diabetes management. Not unexpectedly, the management of diabetes is suboptimal in Haiti, one of the poorest countries in the world where healthcare resources are very limited. Indeed, mean HbA1c was 9.8%. Prevalence of retinopathy, but not of cataract, increased with longer duration of diabetes. Whether African ancestry, which is characteristic of Haiti, also predisposes to eye complications, is unknown.

The 2014 ISPAD guidelines recommend retinopathy screening “annually from age 10 or at onset of puberty if this is earlier, after 2 to 5 years’ diabetes duration”. In settings such as Haiti where eye complications seem to develop early, these guidelines may need to be revised and a more intensive and earlier assessment of eye complications may be warranted. Although data are currently not available, it is likely that other micro- and macrovascular complications are also more common in Haitian children with Type 1 diabetes. This study supports the need for capacity building in pediatric endocrinology in Haiti, a task that the authors of this article are presently carrying out through the Pediatric Endocrinology Education Program for Haiti (PEEP-H).

DOI:10.1530/ey.15.13.13

13.14 Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis

Wheeler E, Leong A, Liu CT, Hievert MF, Strawbridge R, Podmore C *et al.*

Department of Human Genetics, Wellcome Trust Sanger Institute, Genome Campus, Hinxton, Cambridge, UK

To read the full abstract: [PLoS Med 2017;14\(9\):e1002383](https://doi.org/10.1371/journal.pmed.1002383)

This GWAS meta-analysis combined data from five well known ethnically diverse cohorts (Framingham Heart Study, Atherosclerosis Risk in Communities Study, Multiethnic Study of Atherosclerosis, Taiwan-MetaboChip Study for Cardiovascular Disease, and Singapore Prospective Study) to evaluate glycemic and erythrocytic genetic variants impacting HbA1c in individuals of European, African American, and East Asians ancestry. The study found new and known glycemic and erythrocytic

genetic variants to influence HbA1c and determined that these variants' contribution to T2DM risk is strongly determined by ancestry. The paper thus sheds light on important questions on the differential interpretation of HbA1c based on ethnic background. Genetic glycemic variants, while increasing T2DM risk in Europeans and East Asians, are not associated with increased risk in African Americans. Conversely, genetic erythrocytic variants, in particular the G202A variant in *G6PD*, confer up to 0.8% lower HbA1c values in African Americans, suggesting higher numbers of false negatives on T2DM screening when using the current HbA1c threshold of >6.5%; the optimal threshold to diagnose T2DM in this population is likely lower. This important finding not only underscores the importance to consider genetic determinants in the development, choice and interpretation of screening and diagnostic tests, but also highlights the need to advocate for equitable inclusion of populations of diverse ancestry in biomedical research. A relatively small number of persons of African and Asian ancestry was one of the main limitations of this study, limiting the discovery of new ancestry-specific variants in the very populations in whom questions remain about the interpretation the HbA1c, including about its diagnostic threshold, extrapolation of estimated average glucose, estimation of glycemic control, and complication risk.

DOI:10.1530/ey.15.13.14

Advances in the Diagnosis and Management of Congenital Hypothyroidism

The five papers included in this section reflect the increasing interest by resource-limited countries in developing such a program but also highlight specific points that need to be considered in countries that embark in this wonderful initiative to make it successful.

13.15 Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial

Gowachirapant S, Jaiswal N, Melse-Boonstra A, Galetti V, Stinca S, Mackenzie I, Thomas S, Thomas T, Winichagoon P, Srinivasan K, Zimmerman MB
Institute of Nutrition, Mahidol University, Nahjorn Pathom, Thailand; Division of Human Nutrition, Wageningen University and Research, Wageningen, Netherlands; St John's Research Institute, Bangalore, India; Department of Health Sciences and Technology, Swiss Federal Institute of Technology, Zurich, Switzerland; Hearing Impairment Research Group, Liverpool School of Tropical Medicine, Liverpool, UK

This prospective, randomized trial investigates the benefits of iodine supplementation (200 mcg per day) in pregnant women from Thailand and India on the neurological development of their children. Iodine readily crosses the placenta and is required for the synthesis of thyroid hormones by the fetal thyroid gland. In addition, iodine is actively concentrated by the mammary gland and serves as the sole source of iodine for the breastfed infant. The authors chose a dose of 200 mcg of iodine per day, between the dose proposed by the American Thyroid Association and the European Thyroid Association (150 mcg) and the dose proposed by the WHO (250 mcg) for pregnant and lactating women.

The study found no benefit of iodine supplementation during pregnancy on several developmental tests administered to the child at the age of 4-5 years. However, these results need to be interpreted in the context of a population of euthyroid pregnant women with an initial, pre-supplementation urinary iodine excretion (commonly used as a proxy for iodine intake) of ~130 mcg/L, only moderately below the threshold for iodine deficiency. This is much higher than the urinary concentrations associated with severe iodine deficiency (defined as a median urinary iodine concentration of less than 20 mcg/L) and with severe developmental delay in the offspring. In addition, the children in this study were iodine-sufficient at the age of developmental evaluation (4-5 years).

These data should not lead us to conclude that iodine supplementation during pregnancy is not important but rather show that very mild iodine deficiency during pregnancy does not affect neurodevelopment in the child and that supplementation of the pregnant mother with 200 mcg of iodine per day is safe.

To read the full abstract: [Lancet Diabetes Endocrinol 2017; 5:853-63](#)

DOI:10.1530/ey.15.13.15

Advances in the Diagnosis and Management of Congenital Hypothyroidism

13.16 Incidence of congenital hypothyroidism in China: data from the national newborn screening program, 2013-2015

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To read the full abstract: [J Pediatr Endocrinol Metab 2018; 31\(6\):601-608](#)

This article summarizes the findings of likely the largest program of neonatal congenital hypothyroidism (CH) screening in the world. This is a truly impressive effort. The overall incidence of CH was 1/2421, in line with other reports that also observed a relatively high incidence of CH in neonates born in Asia. However, a visual

interpretation of Figure 2 suggests that about 1:10,000 neonates had a TSH between 10 and 20 mU/L. Several factors, duly acknowledged by the authors, make it difficult to determine which proportion of these abnormal TSH values were associated with permanent CH and whether all recalled neonates received L-thyroxine therapy, either for a few weeks or long-term.

A modest elevation of the TSH between 3 and 7 days of life (when screening was performed) could be due to several causes. First, although the National Iodine Deficiency Disorders Elimination Program, which was launched in China in 1993, successfully decreased the prevalence of goiter in schoolchildren from 20.4 percent in 1995 to 8.8 percent in 1999, it appears that areas of relative iodine deficiency are still present in coastal regions of China. This could account for a high number of mildly elevated TSH observed in this program. Second, immaturity of the hypothalamo-pituitary-thyroid axis is commonly observed in preterm neonates. In 2010, prematurity was estimated to affect 7.8% of all Chinese neonates. Finally, in a Chinese population, heterozygosity for a common TPO gene founder mutation (2268insT) was found to be 16 times more common in infants with transient neonatal hypothyroidism. It will be important to address these questions in order to optimize the cost-effectiveness of this impressive investment by the Chinese Health authorities.

DOI:10.1530/ey.15.13.16

Advances in the Diagnosis and Management of Congenital Hypothyroidism

13.17 Assessment of knowledge, attitudes and practices towards newborn screening for congenital hypothyroidism before and after a health education intervention in pregnant women in a hospital setting in Pakistan

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To read the full abstract: [Int Health 2018; 10\(2\):100-107](#)

This article addresses the important issue of acceptance of the congenital screening for congenital hypothyroidism (CH) by the population in general and the families in particular. While it is usually obvious for the health professional that screening for CH is beneficial to the potentially affected neonate, culture, level of education, superstition, poor communication by the authorities and sometimes cost associated with additional care of the neonate are only a few of the factors that play a key role in ensuring acceptance of a screening program.

These authors acknowledge an important limitation of the study, which is that (because of limited funding), information about the relevance and importance of the screening for congenital hypothyroidism was only provided to pregnant mothers. They appropriately suggest that a communication campaign at all levels (government, health professionals, media) should accompany the large-scale implementation of a regional of national program.

DOI:10.1530/ey.15.13.17

Advances in the Diagnosis and Management of Congenital Hypothyroidism

13.18 Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism

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To read the full abstract: [Int J Endocrinol Metab 2017; 15\(3\):e55451](#)

Systematic neonatal screening for congenital hypothyroidism (CH) was first proposed by Dr Jean Dussault, a Canadian (adult) endocrinologist, in 1974. It was rapidly implemented in most high-income countries in the late 1970's and 1980's. Ideally, a screening program should be highly sensitive (able to correctly identify affected neonates) and highly specific (able to correctly identify non-affected neonates): the

lower the specificity, the higher the recall rate.

Thanks to an increase in capacity building in pediatric endocrinology in many low-income countries and to an increasing global interest in non-communicable diseases (NCDs) such as CH, more regional or national screening programs are being planned. Based on screening programs performed mainly in high income countries, the incidence of permanent CH is estimated to be 1/3000-1/4000. However, the incidence and cause (dysgenesis vs. dysmorphogenesis) of permanent CH varies with ethnic origin. In addition, little is known on the incidence of CH in low income countries where CH screening is not yet available.

Here, Mehran et al. describe that programs recall many unaffected neonates and they summarize the many factors that affect the recall rate, including differences in laboratory techniques, sample collection (cord blood vs. postnatal), choice of the primary marker (TSH vs. FT4), iodine deficiency or excess, human error and recall cut-off. Defining the cut-off for recall of a program is a key aspect. A high cut-off may not guarantee the recall of ALL neonates affected with permanent CH but may be sufficient to recall the most severely affected neonates who will benefit from L-thyroxine treatment for the successful prevention of mental retardation. A low cut-off value will lead to the recall of many more neonates, including those who present with mildly, permanently elevated TSH concentrations but who are not at risk for cerebral damage. This question needs to be debated when assessing the cost-benefit ratio of a neonatal CH screening.

DOI:10.1530/ey.15.13.18

Advances in the Diagnosis and Management of Congenital Hypothyroidism

13.19 Newborn Screening Guidelines for Congenital Hypothyroidism in India: Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) - Part I: Screening and Confirmation of Diagnosis

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To read the full abstract: [Indian J Pediatr 2018; 85\(6\):440-447](#)

In 2017, the population of India was estimated at 1.28 billion. With a birth rate of 19/1000, it means that 24.4 million babies are born each year in India. More than half of the births take place at home, in particular in rural India. Assuming an incidence of

1:2500 for congenital hypothyroidism (CH), close to 10,000 babies are born with CH each year in India. These numbers highlight the enormous challenge of designing and implementing a systematic screening for CH in this vast country.

Our colleagues from the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) should be commended for producing this consensus document that is the first step towards a national screening program for CH. The proposed guidelines take into account specific characteristics of India. First, they suggest that health professionals choose between cord blood screening and postnatal screening (Guthrie card). This is important in a country where many mothers and neonates may not stay close to the hospital long enough to get postnatal screening. Second, they propose that the health professional sends the sample to either a central laboratory, where available, or to a local laboratory. While central laboratories are likely to offer a better overall organization (reflecting the handling of a greater number of samples) and a better quality control, it may be easier and faster to deliver the samples to a local laboratory.

An important characteristic of India is the high number of home deliveries. India would be a perfect candidate for point of care testing of TSH, which consists of measuring TSH at the bedside (home, hospital) using a portable device. However, while in development, the technology of point of care testing of TSH is not yet available. Once it is, it may become the preferred method of testing for countries, such as India, where many babies are delivered at home or where families are difficult to reach.

DOI:10.1530/ey.15.13.19

Growth and Development

An increasing number of publications focuses on characteristics of growth and development that are specific to children and youth living in resource-limited countries. Some articles offer thought-provoking hypotheses that may change the way we think about the interaction between growth and the environment.

13.20 Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents and adults

NCD Risk Factor Collaboration (NCD-RisC). 1040 collaborators

To read the full abstract: [Lancet 2017; 390\(10113\):2627-2642](#)

Over the past 10 years, the prevalence of Type 2 diabetes (T2DM) has increased

disproportionately in Africa, South East Asia, the Middle East and the Asia Pacific region. Interestingly, although we need more studies investigating the prevalence of T2DM in Latin America, the prevalence of T2DM in youth living in these countries does not seem to have increased markedly.

This report on the worldwide prevalence of obesity and underweight in youth is an invitation to reflect on the determinants of T2DM in youth in various low-income settings. The association of intrauterine growth retardation and of postnatal obesity is known to be a major risk factor for the development of T2DM in youth. The world map of the prevalence of underweight in children age 5-19 years shows that the Indian sub continent, and, to a smaller extent, South East Asia, the Middle East and Sub Saharan Africa all have a high prevalence of underweight in young children (likely reflecting a mix of pre- and post- natal growth retardation). The prevalence of underweight in Latin America is low. In contrast, the world map of the prevalence of obesity shows a high prevalence in Latin America and in the Middle East, contrasting with a lower prevalence in Africa and in India (although the risk for metabolic syndrome is higher in Indians compared to non-Indians for a similar body mass index, reflecting differences in body composition). These data suggest that the respective roles of obesity and of pre/postnatal growth retardation may differ in various low-income settings, which in turn may call for country-specific public health policies.

DOI:10.1530/ey.15.13.20

Growth and Development

13.21 Early childhood linear growth faltering in low-income and middle-income countries as a whole-population condition: analysis of 179 Demographic and Health Surveys from 64 countries (1993-2015)

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To read the full abstract: [Lancet Glob Health 2017; 5\(12\):e1249-e1257](#)

This paper adds to the understanding of the factors underlying stunting in low-and middle-income countries (LMIC), a phenomenon that is adaptive to undernutrition, and associates with overall poorer health status and unfavorable social determinants of health. Previously thought to be secondary to predominantly individual and household-level factors, this study elegantly demonstrates that stunting in LMICs can primarily be attributed to population-wide community-level factors.

The authors first used statistical modeling to demonstrate how the trends of the HAZ population mean, standard deviation (SD), and 5th and 95th centiles change based on the proportion of the population that is exposed to factors impairing growth. If a trend is driven by only subgroup, the population SD increases, whereas the SD remains steady if the trend occurs across the whole population. The study team then analyzed cross-sectional data from 0-3 year-old children from Demographic and Health Surveys (DHS) in 64 LMIC, including over half in sub-Saharan Africa and none in North America, to assess the trajectory of early childhood HAZ, and evaluate for individual vs. population-driven growth faltering. They demonstrate that the overall mean HAZ declined over time, confirming early childhood growth faltering, and that across regions the HAZ dispersion remained symmetric during the first 3 years of life when growth faltering is most likely to occur, suggesting that the overall mean HAZ decline over time is experienced by children across the entire HAZ z-score spectrum rather than only by a high-risk group such as the extremely stunted.

While the study's limitations include factors inherent to survey-based data, including anthropometric measurement errors and sample heterogeneity, its results supported by consistent multiple well-designed sensitivity analyses. Early childhood stunting in LMIC may be less attributable to different individual genetic, epigenetic and environmental exposures, but rather may be rooted in community-level social and macroeconomic factors. This represents an important public health concern that needs further in-depth study.

DOI:10.1530/ey.15.13.21

Growth and Development

13.22 Evidence for energetic trade-offs between physical activity and childhood growth across the nutritional transition

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To read the full abstract: [Sci Rep 2018; 8\(1\):369](#)

The effect of improving socio-economic conditions on growth has been well described in Europe in the 19th and 20th centuries. For instance, in Norway, height increased by 0.3 cm every 10 years between 1830-1875 and then by 0.6 cm every 10 years between 1875-1930. However, the respective roles of nutrition and physical activities has not been clarified.

The authors present their work as an almost pure natural experiment of the role of physical activity on growth in children. Indeed, over 20 years, in a small remote community in South East Mexico, major changes took place, including introduction of mechanised farming, road access to the community and availability of running water.

This led to a decrease in physical activity (e.g. less work on the farm) and to an increase in sedentarity (e.g. more time at school) in the children of this community. The authors however acknowledge that calorie intake, which was not measured, likely increased, although nutrition remained largely traditional with little influence of market food. Their main conclusion is that reduced physical activity was associated with greater increases in weight and height. The most likely interpretation was that those calories that are not burned by physical activity become available for growth and for fat deposition. There are however several important points to remember. First, in contrast to populations in high-income countries, overweight and obesity were virtually non-existent in this small Mexican community. Hence, these results may not apply to high-income countries where caloric intake is usually much greater than the minimum required for growth. Second, energetic trade-offs may not be the only explanation for the effect of physical activity on growth. For instance, physical activity also affects body composition, sleep, mental health and, relevant to the pediatric endocrinologist, hormone secretion. Third, the changes observed over 20 years (water, electricity, roads) may have other consequences that indirectly affect growth, such decreased infectious load (see 13.24). Finally, only prepubertal children were studied, so that the effect of physical activity on growth can not be extrapolated to adult height and weight. Nevertheless, this study emphasizes the need for additional studies on the likely multifactorial effects of physical activity on growth.

DOI:10.1530/ey.15.13.22

Growth and Development

13.23 Trade-offs between immune function and childhood growth among Amazonian forager-horticulturalists

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To read the full abstract: [Proc Natl Acad Sci USA 2018; 115\(17\) E3914-E3921](#)

Pediatric endocrinologists have long known that chronic disease, such as severe asthma or inflammatory bowel disease, leads to slower growth and short stature. But it is not always clear whether this is due to the disease (decreased oxygen to the tissues, decreased absorption of calories, infections), to the treatment (corticosteroid exposure) or to a combination of the two. Pediatric endocrinologists also know that optimization of caloric intake and weight is associated with a better prognosis in children with chronic inflammatory diseases.

The provocative hypothesis tested by Urlacher et al. is that low level inflammation, which does not have severe, visible consequences on the child (such as anorexia or

decreased physical activity), contributes to stunting. Their study was performed in a population of children living with chronic parasitic infection in a very low resource setting. In this cross-sectional and longitudinal study, they investigated the relationship between levels of C-reactive protein (CRP, a measure of acute immune activity indicating mild, but costly, systemic inflammation over a period of days), IgG (an intermediate-duration measure of adaptive humoral immune function against viruses and bacteria over a period of months) and IgE (a measure of chronic, relatively low-cost, anti-parasitic adaptive immune function over a period of several years), on short-term (1 week) and long-term (20 months) growth. They observed that increased inflammation was associated with slower growth. They also introduced the concept of "trade-off", meaning that the calories used to develop and maintain the inflammatory response can't be used for growth. Finally, they observe that this mechanism is mostly relevant to children with insufficient fat reserves, suggesting that better nutrition could alleviate the detrimental effects of chronic inflammation.

The effect of such a mechanism on growth in resource-limited settings is unknown, but chronic, low grade inflammatory response could represent an additional mechanism contributing to stunting and, therefore, to the development of non-communicable diseases (such as Type 2 diabetes). Whether chronic low-grade inflammation in the pregnant mother would also affect fetal growth and contribute to intra uterine growth retardation is another intriguing question.

DOI:10.1530/ey.15.13.23

Growth and Development

13.24 Comparison of Tanner staging of HIV-infected and uninfected girls at the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria

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To read the full abstract: [J Pediatr Endocrinol Metab 2017; 30\(7\): 725-729](#)

This cross-sectional case-control study reports that 8 to 18-year-old girls with perinatal HIV infection are less likely to have attained thelarche, menarche and pubarche than healthy peers matched for age and socio-economic status. Girls with perinatal HIV infection were on average over 1.5 years older than healthy girls at the time they reached Tanner II breast development, and there were trends towards reaching menarche 0.5 years later, and Tanner II pubic hair 1.1-year later. Pubarche

was earlier than thelarche in both cases and controls, as previously reported in the Nigerian population. Overall, less than half of the girls with perinatal HIV infection had reached thelarche and pubarche, which likely limited the study's power to detect statistically significant differences in the attainment of more advanced pubertal stages. Interestingly, the average ages at thelarche (12.4 ± 1.99 years) and menarche (12.8 ± 1.3 years) in girls with perinatal HIV infection were quite similar, compared to the expected 2 to 2.5 years duration for individual girls to progress from Tanner II to menarche. Rather than implying a later onset but faster paced puberty, this finding may either result from reporting bias, or could suggest that those who reached menarche could represent a sub-group of girls with perinatal HIV infection who undergo normal puberty.

More studies in boys and girls of various ethnic backgrounds are needed to further explore socio-demographic and environmental differences in pubertal development. Longitudinal cohort studies that prospectively document pubertal onset, progression, timing of menarche and their correlation with bone age, as well as HIV control and anti-retroviral use, inflammatory markers and cytokines, and co-infections and co-morbidities are needed to better characterize the relationship between perinatal HIV infection and pubertal development.

DOI:10.1530/ey.15.13.24

14 Science and Medicine

Ze'ev Hochberg and Ken Ong

Why do women have more autoimmune disease than men?

14.1 Estrogen receptor α contributes to T cell-mediated autoimmune inflammation by promoting T cell activation and proliferation

Mohammad I, Starskaia I, Nagy T, Guo J, Yatkin E, Väänänen K, Watford WT, Chen Z

To read the full abstract: [Sci. Signal. 2018;11:eaap9415](#)

Women are more frequently affected by autoimmune disorders than men. A role for estrogen was suggested by the observation that the development of inflammatory bowel disease was associated with oral contraceptive use. Women also respond to infection and vaccination with higher antibody production and a T helper 2 (TH2) cell-dominant immune responses, whereas men usually show TH1 cell-biased immune

responses.

Here, Mohammad et al. identify a direct role for estrogen in the development of autoimmune T cell responses through its estrogen receptor α (ER α) in a mouse model of colitis. ER α -expressing T cells were more activated after stimulation, proliferated more, and expressed more proinflammatory cytokines than T cells lacking this receptor. Other scientists have shown that the X-chromosome also matters; individuals with Klinefelter syndrome (47,XXY) have increased incidence of systemic lupus (SLE). This suggests that X chromosome dosage could be an important risk factor in SLE. Souyris et al. (1) recently demonstrated that Toll-like receptor 7 (TLR7), which is encoded on the X chromosome, escapes X inactivation in B cells and myeloid cells in females and Klinefelter individuals. TLR7 binds single-stranded RNA and activates type I interferon signaling, a pathway that is also activated in SLE patients. Thus, biallelic expression of TLR7 appears to contribute to greater SLE risk.

1. Souyris M, Cenac C, Azar P, Daviaud D, Canivet A, Grunenwald S, Pienkowski C, Chaumeil J, Mejia JE, Guery JC. TLR7 escapes X chromosome inactivation in immune cells. *Sci Immunol* 2018; Jan 26;3(19). pii: eaap8855.

DOI:10.1530/ey.15.14.1

And why do women live longer?

14.2 Women live longer than men even during severe famines and epidemics

Zarulli V, Barthold Jones JA, Oksuzyan A, Lindahl-Jacobsen R, Christensen K, Vaupel JW

To read the full abstract: [Proc Natl Acad Sci U S A 2018;115:E832-E840](#)

Women live longer than men in nearly all modern populations. They can expect to live longer than men almost anywhere in the world. This pervasive inequality has intrigued researchers for decades, and many conclude that the gap has biological foundations, which are modulated by social and environmental conditions.

Here, Zarulli et al. studied data on survival of male and female Freed Liberian slaves between 1820-1843; plantations slaves in Trinidad in the early 19th century; the Ukrainian, Irish and Swedish famines in 1933, 1845-1849, and 1772-1773,

respectively; and the Icelandic epidemics in 1846 and 1882. In all of these settings, with the partial exception of the Trinidad slaves (in the case of the lower-bound scenario), females lived longer than males. They cite the fact that under very harsh conditions females survive better than males even as infants, when behavioral and social differences may be minimal or favor males, lending support to a biological explanation for the female survival advantage, which may subsequently be influenced by socially and environmentally determined risks, opportunities, and resources. Consistent with a biological basis, females live longer than males in most monkeys and apes for which data are available, in both captive and wild populations. The sexual dimorphism in resilience becomes smaller later in life, when estrogens disappear, which may suggest a hormonal basis, which could act on health (e.g. protection from cardiovascular disease) or behaviors (e.g. women take fewer risks than men). There are different ways of describing the same coin; a previous study found that an increased men's mortality in a list of specific entities is the reason, rather than a female survival advantage. But whatever the epidemiology, the mechanism must lie with the main sex-specific factors, the X- and Y-chromosomes and sex hormones.

DOI:10.1530/ey.15.14.2

Sow during infancy and reap later

14.3 Early life experience drives structural variation of neural genomes in mice

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To read the full abstract: [Science 2018;359:1395-1399](#)

Brain development and behavior are influenced by early life experiences, such as nutrients, stress, adversity and maternal care. While we believe the epigenome is the mediator, these authors investigated whether the genome itself of individual brain cells could be changed by environmental factors. A possible mechanism relies on mobile DNA sequences that change their position within the genome by a DNA-based (transposition) or RNA-based (retrotransposition) mechanism. They show that pups

subjected to low maternal care or maternal separation for the first 2 weeks accumulated LINE-1 retrotransposons specifically in the hippocampus, known for its plasticity, but not in the frontal cortex - a somatic mosaic event.

The generation of genomic diversity by LINE-1 elements is a dynamic, lifelong process that begins during embryonic development. Retrotransposition activity is increased as neural progenitors differentiate into neurons. When the brain undergoes extensive growth and differentiation in early life, it uncovers the sensitivity of LINE-1 to experiences. LINE-1 retrotransposition rates are higher in the mouse brain compared with other tissues, and more so in the hippocampus, a region sensitive to environmental stimuli. During the first week of life, the hippocampus still undergoes extensive cell division and differentiation, and fosters retrotransposition. These results indicate that plasticity occurs at the level of the DNA sequence in response to environmental perturbations. Similar changes in the human hippocampus, where emotions are formed and processed may account for the imprinting of environmental cues around age 1-year (the equivalent of the mouse's 2nd week) on reproductive (sexual) function later in life.

DOI:10.1530/ey.15.14.3

Sow during infancy and reap later

14.4 Epigenetic correlates of neonatal contact in humans

Moore SR, McEwen LM, Quirt J, Morin A, Mah SM, Barr RG, Boyce WT, Kobor MS

To read the full abstract: [Development and Psychopathology 2017;29:1517-1538](#)

Work in rodents, already some years ago, showed that epigenetic changes can be transmitted trans generations. This study shows that in humans, the simple act of touching during infancy has lifelong consequences on gene expression through epigenetic changes that sustain for at least 4 years. Children who were distressed as infants and received less physical contact had a molecular profile in their cells that was underdeveloped for their age. The parents of 94 infants kept a diary of their infants' behavior (sleeping, fussing, crying or feeding) as well as the duration of caregiving

that involved bodily contact at age 5-week-old. At age 4 1/2 years old, their cheek DNA was sampled. They found consistent methylation differences between high-contact and low-contact children at 5 specific DNA sites: the glucocorticoid receptor gene, nuclear receptor subfamily 3, group C, member 1 (NR3C1), μ -opioid receptor M1 (OPRM1) and oxytocin receptor (OXTR; related to the neurobiology of social bonds), and brain-derived neurotrophic factor (BDNF; involved in postnatal plasticity). Furthermore, the children who experienced higher distress and received relatively little contact had an "epigenetic age" that was lower than would be expected, given their actual age.

It is interesting to speculate what might be the consequence of these early life epigenetic changes. Another recent study (1) suggested that belief in conspiracy theories stems in part from negative early childhood experiences with caregivers!

1. Green, Douglas. Anxious attachment and belief in conspiracy theories. *Personality and Individual Differences*, 2018; 125: 30 DOI: 10.1016

DOI:10.1530/ey.15.14.4

Gut flora is shaped by the environment

14.5 Environment dominates over host genetics in shaping human gut microbiota

Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, Costea PI, Godneva A, Kalka IN, Bar N

To read the full abstract: [Nature 2018;555:210](#)

Up to now, it was thought that genetics would play a major role in shaping the gut flora. However, this study, in a cohort of 1,046 healthy Israeli individuals with a

well-defined clinical phenotype, suggests that only 2-8% of human microbiome variability is explained by genetics, as compared to 92-98% explained by environmental influences. This study shows that the microbiome is not significantly associated with genetic ancestry or with individual SNPs. There was significant similarity among the microbiomes of genetically unrelated individuals who share a household, but no such similarity among relatives without a history of household sharing. The gut's microbiome is mostly influenced by lifestyles; our diets, physical activity and medication history. It was recently reported that the microbiome has an important impact on immune responses, and it seems that this may be a new route whereby lifestyles may influence immune and other health outcomes. An obvious yet unknown question arising from such observations is whether manipulating the microbiome could influence later health and disease.

DOI:10.1530/ey.15.14.5

We are roundheads

14.6 The evolution of modern human brain shape

Neubauer S, Hublin J-J, Gunz P

To read the full abstract: [Science Advances 2018;4:eaao5961](https://doi.org/10.1126/sciadv.aba0596)

Present-day humans have globular brains and globular endocasts with steep frontal, bulging parietal, and enlarged, rounded cerebellar areas with small and retracted faces. In contrast, Neandertals and other archaic Homo individuals have anterior-posteriorly elongated flat endocasts. These differences are well-visualized in their paper: [http://advances.sciencemag.org/content/4/1/eaao5961/tab-figures-data](https://advances.sciencemag.org/content/4/1/eaao5961/tab-figures-data). Following the

discovery of the most ancient H. sapiens at Jabel Irud in Morocco of 300,000 years ago, this study suggests that our round skull evolved to include our pre-frontal cortex as recently as 50,000 y.a. As the researchers study the skulls and not the brains, they cannot be sure which modern structures were missing from the ancient brains. Yet, these results suggest that our cognitive capacity, generated from the prefrontal cortex, are also as recent, and that the flat skull of our predecessors could not contain a functioning frontal cortex. They also suggest that the cerebellum and the postcentral gyrus, which is involved in sensory, attention, memory and planning functions, are among the brain regions that developed most recently. It is interesting that 50,000 y.a. is about the time when *Homo Sapiens* started to produce bone tools and to paint its caves.

DOI:10.1530/ey.15.14.6

Eat healthily to save the planet

14.7 Evaluating the environmental impacts of dietary recommendations

Behrens P, Kiefte-de Jong JC, Bosker T, Rodrigues JF, de Koning A, Tukker A

To read the full abstract: [Proceedings of the National Academy of Sciences 2017:201711889](#)

Changing your diet can improve both your health and the environment. This study shows that the national dietary recommendations to reduce intakes of animal products can reduce environmental impacts in most high-income nations. We all recommended diets to our patients, and nations recommend diets to their populations. But what is the environmental impact of a diet? Food production accounts for 19-29% of greenhouse gas emissions and increase as the world's population grow. Yet, it is subject to individual dietary choices. This study compares the environmental impacts of average

dietary intakes and a nation-specific recommended diet across 37 middle- and high-income nations. The study shows that choosing to follow national recommendations over the average national diet would have the biggest environmental savings in the United States, Australia, Brazil, and Canada. Most of these savings are due to reductions of meat intakes. There are reductions also in most EU nations, with Greece, Ireland, and the Netherlands saving the most. In upper-middle-income nations, a smaller positive impact was observed, and in lower-middle-income nations they found increase in greenhouse gases and land use and derangement of soil quality because guidelines in these nations emphasize a higher consumption of animal products to combat low levels of protein in the diet. Further benefits on the environment can be achieved with recommendations to decrease dietary meat and dairy products. Thus, in well-off countries, adopting national recommendation is good for the environment, but recommendations need to be tailored to a country's unique environment and economy. These principles have been successfully applied with the Nordic and Mediterranean recommendations. Other than changing your diet to be more healthy and ethical, we have one more reason to change, for our environment.

DOI:10.1530/ey.15.14.7

Imprinting without DNA methylation

14.8 Maternal H3K27me3 controls DNA methylation-independent imprinting

Inoue A, Jiang L, Lu F, Suzuki T, Zhang Y

To read the full abstract: [Nature 2017;547:419](#)

Since the identification of DNA methylation as a master regulator of genomic imprinting more than 20 years ago, it has been the only known mammalian germline imprinting mark. However, recent studies have identified several imprinted genes capable of maintaining paternal allele-specific expression in the absence of oocyte

DNA methylation. Here, the researchers find 76 genes that are paternally expressed (maternal alleles repressed) due to a DNA-methylation-independent mechanism. These genes are involved in and essential for embryonic development. A disease based on this new mechanism is Beckwith-Wiedemann syndrome of excess growth caused by mutation or deletion of imprinted genes within the chromosome 11p15.5 region, with disruption of the H19/IGF2-imprinting control region. The dynamics of non-DNA imprinting are strikingly different from DNA methylation-dependent imprinting that is largely maintained in both embryonic and extra-embryonic lineages. Non-DNA histone imprinting is probably established during oogenesis and maintained in preimplantation embryos, while it begins to dilute in the inner-cell mass of the blastocyst, and is almost completely lost in the epiblast of E6.5-9.5 embryos. A clinical consequence is that yet unexplained growth disorders might be revealed by future tests of histone methylation.

DOI:10.1530/ey.15.14.8

The ancient wisdom of refraining from consanguinity

14.9 Ancient genomes show social and reproductive behavior of early Upper Paleolithic foragers

Sikora M, Seguin-Orlando A, Sousa VC, Albrechtsen A, Korneliusen T, Ko A, Rasmussen S, Dupanloup I, Nigst PR, Bosch MD

To read the full abstract: [Science 2017;eaao1807](https://doi.org/10.1126/science.1257521)

Consanguinity is common in some modern cultures. This study examined the question whether ancient humans, who often had limited choices of mates, bred among close relatives. Here, Sikora et al. report genome sequences from 4 early humans buried

close together in western Russia about 34,000 years ago. The individuals clustered together genetically and came from a population with a small effective size, but they were not very closely related. Thus, these people may represent a single social group that was part of a larger mating network, similar to contemporary hunter-gatherers. Humans of that time were already organized in small groups with limited within-band kinship and inbreeding, and with wide social, mating networks, resembling the way in which many present-day hunter-gatherers live today. The lack of close inbreeding might help to explain the survival advantage of anatomically modern humans. Until recently, our understanding of the socio-cultural milieu of Paleolithic humans was limited to what can be inferred from the archeological record. Genomics and the art of retrieval of ancient genomes make it possible to address socio-cultural milieu from a new angle.

DOI:10.1530/ey.15.14.9

CRISPR-Cas9 gene therapy

14.10 Correction of a pathogenic gene mutation in human embryos

Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, Koski A, Ji D, Hayama T, Ahmed R, Darby H, Van Dyken C, Li Y, Kang E, Park AR, Kim D, Kim ST, Gong J, Gu Y, Xu X, Battaglia D, Krieg SA, Lee DM, Wu DH, Wolf DP, Heitner SB, Belmonte JCI, Amato P, Kim JS, Kaul S, Mitalipov S

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To read the full abstract: [Nature 2017;548:413-419](#)

Over recent years, the Yearbook has followed the rapid advances in CRISPR-Cas9 gene editing technology, initially as a widely adopted research tool, but also as an emerging form of gene therapy. Here, Ma et al. report the first use of CRISPR-Cas9 to efficiently and safely correct a pathogenic heterozygous mutation in human embryos. These embryos carried a dominantly inherited 4 base-pair deletion in the

gene MYBPC3. Mutations in this gene account for 40% of all known genetic causes of hypertrophic cardiomyopathy, which is the most common cause of sudden death in otherwise healthy young athletes. CRISPR-Cas9 induces DNA double-strand breaks at specific genomic sequences, which are then repaired by endogenous mechanisms, including homology-directed repair, during which the normal, non-mutated sequence can be restored if a normal template is provided. Here, unaffected oocytes provided the healthy non-mutated alleles. Furthermore, by targeting oocytes arrested in meiosis, before the first zygotic division, they achieved high efficiency (72.4% of injected embryos were fully corrected) with very low level of mosaicism. CRISPR-Cas9 has a potential drawback of creating off-target mutations at other sites in the genome. While the current study showed very high specificity, as have most other experimental studies, more concerning evidence of off-target effects, occurring beyond the immediate vicinity of the target site, has been very recently identified using newer long-range DNA sequencing techniques (1). Hence, CRISPR-Cas9 is moving cautiously towards clinical use.

1. Kosicki M, Tomberg K, Bradley A. Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. *Nat Biotechnol* 2018. Jul 16. doi: 10.1038/nbt.4192.

DOI:10.1530/ey.15.14.10

DNA-independent gene editing

14.11 RNA editing with CRISPR-Cas13

Cox DB, Gootenberg JS, Abudayyeh OO, Franklin B, Kellner MJ, Joung J, Zhang F

To read the full abstract: [Science 2017;358:1019-1027](#)

The gene-editing system CRISPR-Cas9 continues to surge through molecular biology labs and article titles. This article provides a new lab shelf, manipulating RNA, not

DNA. This RNA editor could be used to treat conditions that are short term in nature, such as local inflammation. The RNA tool focuses on single-letter mutations in the DNA, A to I mutations that account for more than 40% of all the mutations. The authors named the new system REPAIR: RNA Editing for Programmable A to I Replacement. REPAIR successfully converted A to I at target sites at an average rate of 20-40%. With DNA editing, once you make a permanent change it is hard to undo it. Whereas with RNA, once you stop the RNA editing REPAIR system, then those changes will revert as new RNA is produced.

DOI:10.1530/ey.15.14.11

The 'nocebo' effect: psychogenic but truly harmful

14.12 Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase

Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, Collins R, Sever P, ASCOT Investigators
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To read the full abstract: [Lancet 2017;389:2473-2481](https://doi.org/10.1016/S0140-6736(17)32481-1)

We are all familiar with the 'placebo' effect, when the psychological anticipation of a 'benefit' of treatment is so strong that it adds to or even outweighs the actual physical benefits. Many doctors have even admitted to prescribing placebo tablets, or "sugar

pills" to their patients, for example for pain relief in irritable bowel syndrome. Such practice is not illegal, but it does raise ethical concerns issues regarding lack of openness between doctor and patient.

Here, Gupta et al. provide convincing evidence for the 'nocebo' effect. This occurs when the psychological anticipation of 'harm' related to a treatment is so strong that it augments the actual physical harm. Statins cause myopathy in ~1:10,000 patients per year, including one reported case of non-fatal rhabdomyolysis. However, the authors describe "the widespread media coverage that has arisen from claims that statin therapy causes side-effects in up to one fifth of patients" has caused patients to overestimate the harms of statin treatment. This was robustly shown by this large study, which found an excess of muscle-related statin adverse effects only during the open (non-blinded) phase of the trial (hazard ratio = 1.41; p=0.006), but not while the treatments were blinded (hazard ratio 1.03; p=0.72). The authors discuss that such nocebo effects can cause real harm, by dissuading many patients from continuing on effective treatments, resulting in thousands of otherwise avoidable cardiovascular disease events. We need to be aware of, and make efforts to dispel, untrue lay beliefs about our treatments.

DOI:10.1530/ey.15.14.12

The nature of scientific progress

14.13 Tragedy, Perseverance, and Chance - The Story of CAR-T Therapy

Rosenbaum L

Dr. Rosenbaum is a national correspondent for the Journal

To read the full abstract: [N Engl J Med 2017;377:1313-1315](#)

“In 2010, 5-year-old Emily Whitehead was diagnosed with acute lymphoblastic

leukemia.” So begins this remarkable story of how Emily became the first child to receive CART-19 (chimeric antigen receptor T-cell) therapy. She remains alive and well, and her successful treatment re-energised a whole line of research – the first CART therapy was licensed in US in August 2017. This perspective article describes the long and eventful research route towards successful cancer immunotherapy, which started in 1893 when surgeon William Coley found that streptococcus injection shrunk an inoperable osteosarcoma. As well as the wonderful insights into our powerful immune system, this article describes the methodical but also opportunistic nature of scientific progress, and the inventive but also determined characteristics of the pioneering scientists and families.

DOI:10.1530/ey.15.14.13

14.14 Disease model discovery from 3,328 gene knockouts by The International Mouse Phenotyping Consortium

Meehan TF, Conte N, West DB, Jacobsen JO, Mason J, Warren J, Chen CK, Tudose I, Relac M, Matthews P, Karp N, Santos L, Fiegel T, Ring N, Westerberg H, Greenaway S, Sneddon D, Morgan H, Codner GF, Stewart ME, Brown J, Horner N, International Mouse Phenotyping C, Haendel M, Washington N, Mungall CJ, Reynolds CL, Gallegos J, Gailus-Durner V, Sorg T, Pavlovic G, Bower LR, Moore M, Morse I, Gao X, Tocchini-Valentini GP, Obata Y, Cho SY, Seong JK, Seavitt J, Beaudet AL, Dickinson ME, Herculat Y, Wurst W, de Angelis MH, Lloyd KCK, Flenniken AM, Nutter LMJ, Newbigging S, McKerlie C, Justice MJ, Murray SA, Svenson KL, Braun RE, White JK, Bradley A, Flicek P, Wells S, Skarnes WC, Adams DJ, Parkinson H, Mallon AM, Brown SDM, Smedley D
European Molecular Biology Laboratory, European Bioinformatics Institute, Hinxton, UK

To read the full abstract: [Nat Genet 2017;49:1231-1238](https://doi.org/10.1038/ng.1231)

This large international initiative is a major collaboration across 25 research institutes that was set up as part of the scientific community's response to concerns regarding the notoriously poor reproducibility of scientific research. Up to now, many mouse gene knock-outs have been made and reported, but inconsistency between findings is widespread; this may arise due to bias in animal selection, focus on one sex or on one isogenic mouse background, or use of poor statistical methods. To address this, the International Mouse Phenotyping Consortium is performing systematic phenotyping of, eventually all, single gene knock-out mice. They study both males and females, at least 7 mice of each sex, and use a carefully standardised pipeline assessment of 509 phenotypes, covering diverse neurological, behavioral, metabolic, cardiovascular, pulmonary, reproductive, respiratory, sensory, musculoskeletal and immunological parameters. The findings are producing new models of mendelian diseases, novel mendelian disease candidate genes, and new functional knowledge of genes about which we knew very little – which is highly relevant and timely information in our current era of emerging whole exome/genome sequencing in our patients. Limitations include the focus on only adult phenotypes, and currently the database of genes is yet incomplete. But if you are interested in a particular gene, this online database is a great starting point <http://www.mousephenotype.org/>.

DOI:10.1530/ey.15.14.14

Nurtured by our parent's genes

14.15 The nature of nurture: Effects of parental genotypes

Kong A, Thorleifsson G, Frigge ML, Vilhjalmsón BJ, Young AI, Thorgeirsson TE, Benonisdóttir S, Oddsson A, Halkorsson BV, Masson G, Gudbjartsson DF, Helgason A, Björnsdóttir G, Thorsteinsdóttir U, Stefansson K
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To read the full abstract: [Science 2018;359:424-428](#)

This ground-breaking study shows that your genetic make-up may influence your appearance, behaviour and health risks, not only by acting directly on your biology, but also indirectly, through the effects on your parents and how they cared and “nurtured” you. Such parental effects are obvious for very early life traits, such as birth weight,

where there are well-known examples of maternal alleles that alter pregnancy glycaemia and hence influence fetal growth and adiposity. However, here, similar effects are shown for many long-lasting traits, including educational attainment, adult height and BMI, age at first child, and cigarette smoking. Unsurprisingly, for many nutritional and health-related traits, they found that mothers have stronger nurturing effects than fathers. Although not studied here, similar indirect effects could manifest between siblings. These indirect effects inflate estimates of the direct effects of genetic variants. Furthermore, the analyses allow quantification of the effects of another source of such overestimation, that due to assortative mating – which is the phenomenon whereby we choose partners who are more likely to resemble ourselves both physically and mentally. The findings highlight the importance of family data and underline the important message that our genes do not totally determine our behaviours and health outcomes. We have the power to modify our genetic susceptibilities through our lifestyle and health choices, both for ourselves and for our children.

DOI:10.1530/ey.15.14.15

Evolutionary public health

14.16 Human reproduction and health: an evolutionary perspective

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University Medical College, Krakow, Poland

To read the full abstract: [Lancet 2017;390:510-520](#)

It is well recognized that reproductive traits have major relevance to reproductive 'fitness' and are therefore among the most highly targeted by natural selection.

Evolutionary theory argues that investment in reproduction requires trade-offs in other traits, which are likely to be disadvantageous for other vital functions, and other aspects of health and survival. This review article brings together many of these arguments, starting from a broad inclusion of evolutionary, hormonal, genetic and demographic perspectives, but also develops an interesting focus on non-communicable diseases from a public health perspective. This review forms part of a series of papers in *The Lancet* on evolutionary public health, co-ordinated by Jonathan Wells, Institute of Child Health, London. They argue that life history theory together with mathematical modelling should inform the timing of interventions during the life-course to promote both reproductive fitness and health, and predict long-term consequences, mindful of differences between settings, particularly in nutritional availability.

DOI:10.1530/ey.15.14.16

Who could have predicted it

14.17 Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, Hibbert S, Budnik N, Zampedi L, Dickson J, Li Y, Aviles-Olmos I, Warner TT, Limousin P, Lees AJ, Greig NH, Tebbs S, Foltynie T

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To read the full abstract: [Lancet 2017;390:1664-1675](https://doi.org/10.1016/S0140-6736(17)31664-1)

Whoever could have imagined that a compound discovered as being secreted by enteroendocrine cells in the gut could have a role in treating Parkinson's disease? GLP-1 does indeed have diverse actions on several peripheral organs (including tongue, stomach, adipose tissues, muscle, pancreas and liver) and on the brainstem to regulate food consumption and glycaemia. Pre-clinical studies in rodents had shown

apparent effects of GLP-1 on promoting neurite outgrowth and protecting hippocampal neurons from apoptotic insult, and even stimulating adult neurogenesis, particularly of neurons positive for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. The positive findings of this randomised, placebo-controlled trial of exenatide, administered peripherally at licensed diabetes doses, open new treatment avenues for neurological diseases and highlight the remarkable gut-brain axis: the close synergy in biochemical signaling between these organs.

From a broader perspective, the identification of unanticipated alternative treatment targets for existing medicines can be lucrative for companies. Alternatively, the emergence of unanticipated off-target side effects can destroy a promising new agent, often late in the pharmacological pipeline after costly investment, and can prove much more costly for companies and patients if discovered by post-marketing surveillance. 'Genomic target validation' is an alternative hypothesis-free approach that aims to flush out unanticipated drug effects, whether good or bad, at a much earlier stage of drug development, and has attracted recent major investments <https://www.gsk.com/en-gb/media/press-releases/gsk-and-23andme-sign-agreement-to-leverage-genetic-insights-for-the-development-of-novel-medicines/>.

DOI:10.1530/ey.15.14.17

Be careful what your friends think

14.18 Assessing Social Contagion in Body Mass Index, Overweight, and Obesity Using a Natural Experiment

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RAND Corporation, Boston, MA, USA

To read the full abstract: [JAMA Pediatr 2018;172:239-246](#)

Social contagion refers to the spreading of a behaviour, idea, attitude, or even an emotion, across a social group due to imitation and conformity by its members. The idea that obesity may spread due to social contagion is based on its observed clustering across networks of individuals, who are joined by other types of social similarities

(e.g. friendships and residences). However, previous analyses were based on observational data and are prone to confounding and self-selection into social networks. This study took a unique approach, leveraging the natural experiment of military assignment, which except in rare cases is beyond the control of the individual. The findings show that families who are assigned to US counties with higher rates of obesity are more likely to be overweight or obese. The effects strengthened with longer duration of residence. The findings were not explained by differences in the built environment that might influence outdoor physical activity. In our efforts to control overweight and obesity, we need to understand and tackle the 'social norms' held by populations and population subgroups, which can often foster unhealthy attitudes, beliefs and behaviours towards food, exercise, and weight status, even from very early ages (1).

1. Guell C, Whittle F, Ong KK, Lakshman R. Toward Understanding How Social Factors Shaped a Behavioral Intervention on Healthier Infant Formula-Feeding. *Qual Health Res* 2018;28:1320-1329.

DOI:10.1530/ey.15.14.18

15 Editor's Choice
Ken Ong and Ze'ev Hochberg

Seeing is believing: childhood overweight and obesity

15.1 Development of the MapMe intervention body image scales of known weight status for 4-5 and 10-11 year old children

Jones AR, Tovee MJ, Cutler LR, Parkinson KN, Ells LJ, Araujo-Soares V, Pearce MS, Mann KD, Scott D, Harris JM, Adamson AJ
Institute of Health & Society, Human Nutrition Research Centre, Newcastle University, Newcastle upon Tyne, UK

To read the full abstract: [J Public Health \(Oxf\) 2017;1-9](#)

Our efforts to control overweight and obesity in children are severely hampered because most of their parents (and indeed most of their health professionals!) cannot visually recognise an obese child, let alone one who is overweight. This is particularly

difficult at around the ages 4-6 years old because this coincides with the BMI nadir on growth charts – all children are naturally thinner at around this age. Some authors have previously produced line drawings, but those are crude and do not relate to BMI measures or centiles.

Here, the authors used 3-dimensional photonic images of hundreds of children at ages 4-5 and 10-11 years old, which are the ages of the UK national child measurement programme. They then mapped these onto a range of realistic 'skins' or 'morphs', to generate computer-predicted images that correspond accurately to any specific child BMI centile. Finally, they used qualitative focus groups and interviews to choose the most 'human like' and acceptable morphs and to discuss their usefulness and acceptability. They say that these images could be used in various ways: to help parental acceptance of their child's overweight/obese status; to explore self-image and self-evaluation of body image; and to inform and engage other caregivers and health professionals. You can see the charts here: <https://academic.oup.com/view-large/figure/112151669/fig129f02.tif>

DOI:10.1530/ey.15.15.1

Global burden of obesity

15.2 Health Effects of Overweight and Obesity in 195 Countries over 25 Years

The Global Burden of Disease 2015 Obesity Collaborators

To read the full abstract: [N Engl J Med 2017;377:13-27](https://doi.org/10.1016/S0140-6736(17)31021-2)

Other estimates of the global trends and projections in obesity have been published. In this regard, the current analysis provides similar, albeit equally worrying, data on the trends towards more obesity across all regions of the world. Moreover, a particular advance of this current study, which was funded by the Bill and Melinda Gates Foundation, is to model the global burden of obesity with regard to its co-morbidities

and mortality. In 2015, excess body weight accounted for ~4 million deaths and 120 million disability-adjusted life-years worldwide. A substantial proportion of these deaths and co-morbidities occurred in those who were within the overweight (non-obese) weight categories, suggesting that overweight is not safe or even advantageous for health as other had claimed. In many countries, the rate of increase in childhood obesity has been greater than the rate of increase in adult obesity and in 2015, China and India had the highest numbers of obese children. In 2013, the World Health Organization called for a halt in the increase in the prevalence of overweight among children and in recent years, several countries have announced national policies and targets with this aim. No major successes have yet been shown at a national level, but one of the most promising approaches world-wide to effectively reduce childhood obesity is the Amsterdam 'whole city' Healthy Weight Programme, which reported a "12% drop over three years in the proportion of overweight and obese children" (<https://www.bmj.com/content/361/bmj.k2534>).

DOI:10.1530/ey.15.15.2

Interventions for overweight and obesity do work

15.3 Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years

Mead E, Brown T, Rees K, Azevedo LB, Whittaker V, Jones D, Olajide J, Mainardi GM, Corpeleijn E, O'Malley C, Beardsmore E, Al-Khudairy L, Baur L, Metzendorf MI, Demaio A, Ells LJ

Health and Social Care Institute, Teesside University, Middlesbrough, UK

To read the full abstract: [Cochrane Database Syst Rev 2017;6:CD012651](#)

Here, the authors report an update of a Cochrane review, which was first published in 2003, and last updated in 2009. However, given the complexity of the evidence, the current update is now split into 6 reviews addressing different childhood obesity treatments at different ages. The bottom line is that multi-component behaviour-changing interventions are effective in reducing weight and BMI, and are safe, with very low occurrence of adverse events. An accompanying report shows similar

positive findings in overweight or obese adolescents aged 12-17 years (1). Several limitations were highlighted, including the low or very low quality of the evidence and high risk of bias, and heterogeneity between RCTs that could not be explained, and there remains the question over sustainability of the BMI reductions over the longer term. It is important to acknowledge those limitations, the need for more evidence regarding the most effective and cost-effective approaches, and how these individual-level behaviour change approaches might integrate with wider policy and systems level changes, e.g. to change food composition, advertising and infrastructure to promote physical activity. But meanwhile, it is untrue to say that we do not know what to do to reduce weight and BMI in overweight and obese children – such arguments sometimes hamper efforts to screen for childhood obesity, or are used by some health practitioners to defend not raising the issue as an incidental finding in the clinic.

1. Al-Khudairy L, Loveman E, Colquitt JL, Mead E, Johnson RE, Fraser H, Olajide J, Murphy M, Velho RM, O'Malley C, Azevedo LB, Ells LJ, Metzendorf MI, Rees K. Diet, physical activity and behavioural interventions for the treatment of overweight or obese adolescents aged 12 to 17 years. *Cochrane Database Syst Rev* 2017;6:CD012691.

DOI:10.1530/ey.15.15.3

15.4 Antibiotic Exposure in Early Life Increases Risk of Childhood Obesity: A Systematic Review and Meta-Analysis

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To read the full abstract: [Front Endocrinol \(Lausanne\) 2017;8:170](#)

Increasing sedentary behaviours and availability of high energy dense processed foods are the obvious culprits to explain the trends towards more overweight and obese populations around the world. However, we should remember that many other

hypotheses are proposed, including higher ambient room temperatures due to central heating, shorter sleep duration, more stress, estrogenic environmental chemicals etc. Among these hypotheses, the possible role of early life antibiotic exposure is growing in credence due to increasing evidence on the gut microbiome as a plausible biological mechanism in obesity, as well as much individual-level data on this association, as is well summarised by Shao et al. in this systematic review and meta-analysis. The overall associations are statistically robust, without much heterogeneity between studies, and they even find a clear dose-response relationship with increasing courses of antibiotics. The main drawback is the reliance on observational data, which means that confounding is the main alternative explanation. It is easy to imagine that in many developed settings, families who demand antibiotics for their infants may be from more deprived backgrounds and/or make other unhealthy diet and lifestyle choices that promote obesity. Hence, evaluation of this association in other settings, where obesity shows different social patterns, would be extremely helpful.

DOI:10.1530/ey.15.15.4

New treatments

15.5 Modified-Release and Conventional Glucocorticoids and Diurnal Androgen Excretion in Congenital Adrenal Hyperplasia

Jones CM, Mallappa A, Reisch N, Nikolaou N, Krone N, Hughes BA, O'Neil DM, Whitaker MJ, Tomlinson JW, Storbeck KH, Merke DP, Ross RJ, Arlt W
Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

To read the full abstract: [J Clin Endocrinol Metab 2017;102:1797-1806](#)

We know that conventional glucocorticoid therapies fail to mimic the normal diurnal profile of cortisol secretion, which should show an early morning surge in circulating

levels, followed by a gradual daytime reduction, and night-time suppression. The early morning surge in ACTH also drives adrenal androgen production, which is excessive in congenital adrenal hyperplasia (CAH). Chronocort is a modified-release hydrocortisone preparation, which produces peak circulating cortisol concentrations 6-8 hours after ingestion. This study shows that treatment of CAH with Chronocort reduced combined excretion of markers of impaired 21-hydroxylase activity (sum of 17OHP metabolites 17HP, pregnanetriol, and the 21-deoxycortisol metabolite PTONE) more than any other glucocorticoid preparation (hydrocortisone, prednisolone, or dexamethasone), and in particular it reduced the early morning surge in these metabolites. The authors also showed that alternative pathway androgen synthesis, from its substrate 17OHP, contributes significantly to DHT production in CAH patients on standard glucocorticoid therapy, rather than the classic pathway via DHEA, androstenedione, and testosterone. The large phase 3 trial of Chronocort in CAH patients recently completed patient enrolment and we look forward to its findings, which are expected in Q3 2018.

DOI:10.1530/ey.15.15.5

New treatments

15.6 Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist

Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, Diamond MP, Surrey E, Johnson NP, Watts NB, Gallagher JC, Simon JA, Carr BR, Dmowski WP, Leyland N, Rowan JP, Duan WR, Ng J, Schwefel B, Thomas JW, Jain RI, Chwalisz K

To read the full abstract: [N Engl J Med 2017;377:28-40](#)

We highlight this paper for 3 reasons. First, remarkably there are few robust data on effective treatment options for endometriosis. Subcutaneous GnRH antagonists are sometimes used off-label, but with very limited evidence. Secondly, the clear findings here confirm the pathogenesis of endometriosis as being driven by an over-active hypothalamo-pituitary-ovarian axis, and support the rationale for other therapeutic options to reduce ovulation and suppress circulating estradiol levels. Thirdly, could there be other childhood indications for an oral GnRH antagonist treatment? Unlike our traditional therapy, GnRH analogues, which cause profound depletion of pituitary gonadotrophins and estradiol levels after an initial surge, this GnRH antagonist rapidly reduces gonadotrophin and estradiol levels, particularly at the higher dose. Treatments for precocious puberty or to extend the duration of puberty and associated adolescent growing window might be possible uses to test in future trials.

DOI:10.1530/ey.15.15.6

New treatments

15.7 NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

Harrison SA, Rinella ME, Abdelmalek MF, Trotter JF, Paredes AH, Arnold HL, Kugelmas M, Bashir MR, Jaros MJ, Ling L, Rossi SJ, DePaoli AM, Loomba R
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To read the full abstract: [Lancet 2018;391:1174-1185](#)

Non-alcoholic fatty liver disease is highly prevalent in overweight and obese children and adults. It progresses to steatohepatitis (with raised liver transaminase levels) and

fibrosis, and eventually to cirrhosis. Detecting this, excluding other causes of liver disease, and monitoring its progress takes up much resource in the obesity clinic. But, frustratingly, there are currently no effective treatments, other than weight loss. The hormone fibroblast growth factor 19 (FGF19) is produced by the gut in response to absorption of bile acids and it acts on hepatocytes via the receptor functional growth factor receptor 4 (FGFR4). Here, it is shown to markedly reduce liver fat content, steatohepatitis, and non-invasive serum biomarkers of fibrosis, probably by acting on multiple pathogenic pathways. FGF19 is a potent inhibitor of bile acid synthesis and inhibits fatty acid synthesis and de novo lipogenesis. Recent data show that FGF19 also decreases markers of hepatic inflammation, and improves markers of fibrosis in patients with primary sclerosing cholangitis. There were concerns that endogenous FGF19 also confers hepatocellular carcinoma, but so far the engineered FGF19 analogue, NGM282, appears to be non-tumorigenic.

DOI:10.1530/ey.15.15.7

New mechanisms: food aversion

15.8 Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15

Hsu JY, Crawley S, Chen M, Ayupova DA, Lindhout DA, Higbee J, Kutach A, Joo W, Gao Z, Fu D, To C, Mondal K, Li B, Kekatpure A, Wang M, Laird T, Horner G, Chan J, McEntee M, Lopez M, Lakshminarasimhan D, White A, Wang SP, Yao J, Yie J, Matern H, Solloway M, Haldankar R, Parsons T, Tang J, Shen WD, Alice Chen Y, Tian H, Allan BB
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To read the full abstract: [Nature 2017;550:255-259](https://doi.org/10.1016/j.nature.2017.05.025)

Loss of appetite, and even aversion to food, is a common experience during periods of illness (e.g. infection and pyrexia) and/or treatment (e.g. chemotherapy). This response is distinct from the body's homeostatic mechanisms (the hypothalamic leptin receptor-AGRP-POMC-MC4R axis), which normally regulate appetite and weight gain in children, or weight maintenance in adults. Previous work identified the brainstem parabrachial nucleus as a mediator of the appetite suppression induced by the anorectic hormones, amylin and cholecystokinin. Here, the authors identify the receptor for GDF15 (also known as macrophage-induced cytokine 1, MIC-1), a member of the TGF-beta superfamily, which shows marked increases in circulatory concentrations during various conditions of stress, illness and inflammation, and

which has long been known to suppress food intake in mice. They show that its receptor, GFRAL, is expressed exclusively in the brainstem, and is undetectable in all other regions, including the hypothalamus.

Several other papers high profile have been published in the last 12 months on GDF15 and its receptor. While its role in human body weight regulation remains to be shown, its general relevance in humans has been demonstrated during pregnancy. Hyperemesis gravidarum (HG) is the medical term for the nausea, vomiting and aversion to various foods during the early period of pregnancy when the fetus is most sensitive to chemical teratogens. Petry et al. (1) reported that higher maternal circulating GDF15 levels are associated with pregnancy-related vomiting in humans. Fejzo et al. (2) identified genetic variants at this locus that alter GDF15 expression as being robustly associated with HG. Steve O'Rahilly (3) provides a thoughtful overview of these recent developments, and proposes an evolutionary model for this system of protective food aversion, as an example of 'allostasis' (as opposed to 'homeostasis').

1. Petry CJ, Ong KK, Burling K, Barker P, Perry JRB, Acerini CL, Hughes IA, Dunger DB, O'Rahilly S. GDF15 Concentrations in Maternal Serum Associated with Vomiting in Pregnancy: the Cambridge Baby Growth Study. (2017). bioRxiv. <https://doi.org/10.1101/221267>.

2. Fejzo MS, Sazonova OV, Sathirapongsasuti JF, Hallgrimsdottir IB, Vacic V, MacGibbon KW, Schoenberg FP, Mancuso N, Slamon DJ, Mullin PM, 23andMe Research Team. Placenta and appetite genes GDF15 and IGFBP7. *Nat Commun* 2018;9:1178.

3. O'Rahilly S. GDF15-From Biomarker to Allostatic Hormone. *Cell Metab*. 2017; 26(6):807-808.

DOI:10.1530/ey.15.15.8

New data: hormonal contraception and breast cancer

15.9 Contemporary Hormonal Contraception and the Risk of Breast Cancer

Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O
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To read the full abstract: [N Engl J Med 2017;377:2228-2239](#)

Paediatric endocrinologists often prescribe oral hormonal contraception preparations as

these are convenient options for the management of various conditions in adolescent girls (e.g. polycystic ovary syndrome features, hypogonadism). Therefore, we should understand the possible adverse effects. This huge national database study data provides robust estimates of the relatively small excess risk of breast cancer. Notably, there was little difference between the main types of combined oral contraceptive preparation on breast cancer risk, whether monophasic or triphasic, containing norethisterone or levonorgestrel, or even by estrogen dose. Furthermore, breast cancer risk was also increased with use of progestin-only products. Risk of breast cancer increased with duration of treatment, and appeared to rapidly disappear after discontinuation of relatively short treatment periods (<5 years). Hence, these findings are highly reassuring. It would be helpful to have similar robust information on risks of thromboembolism.

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Slow down and think!

15.10 The Rush to Publication: An Editorial and Scientific Mistake

Bauchner H

Editor in Chief, and The JAMA Network, Chicago, Illinois, USA

To read the full abstract: [JAMA 2017;318:1109-1110](#)

Here, Howard Bauchner provides a thoughtful article on the increasing rush to publishing science. As authors and readers, there are many apparent benefits. Over the past 5 years, the time from manuscript submission to article publication has halved for all JAMA journals. However, there are also major pitfalls, including the reduced time for manuscript review and identification of mistakes, which can appear obvious with slightly longer consideration. He gives the example of a study that created stem cells using chemical stimulation, which was retracted within months post-publication.

Other recent high-profile retractions followed the remarkable analyses of published trials by a UK anaesthetist, working on his own in a small seaside hospital and without any background in academia (1). By assessing the (im)probability of the distributions of baseline variables in reported trials, John Carlisle identified several with fabricated or

manipulated data, not only within his own field's journal *Anaesthesia*, but also in high profile journals *NEJM* and *JAMA*. This led to a recent retraction, and corrected re-analysis of the famous PREDIMED trial (2), to date the only RCT of the Mediterranean diet on cardiovascular disease, in which, we now learn, a large proportion were allocated rather than randomized to the treatment arms.

Bauchner, who is the Editor in Chief at *JAMA*, argues that the fault lies collectively with us all, rather than only with the journals. Whether we are journal editors, investigators, funders, or professional societies, we all want our papers to be reviewed and published as quickly as possible, and we even highlight late-breaking science sessions at our scientific conferences. Much of the onus to detect irregularities lies in the peer review process, which is often pressured by tight deadlines and very regular automated email reminders.

1. Carlisle JB. Data fabrication and other reasons for non-random sampling in 5087 randomised, controlled trials in anaesthetic and general medical journals. *Anaesthesia* 2017;72:944-952.

2. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Martinez-Gonzalez MA. Retraction and Republication: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med* 2013;368:1279-90. *N Engl J Med*. 2018 Jun 21;378(25):2441-2442.

DOI:10.1530/ey.15.15.10

Be careful what you feed them

15.11 A meat- or dairy-based complementary diet leads to distinct growth patterns in formula-fed infants: a randomized controlled trial

Tang M, Hendricks AE, Krebs NF

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To read the full abstract: [Am J Clin Nutr 2018;107:734-742](https://doi.org/10.1093/ajcn/107.734-742)

The higher protein contents of cow's milk based milk formulas (2.2 g/100 kcal) compared to breast milk (1.5 g/100 kcal) have been thought to underlie their faster growth, weight gain and childhood obesity promoting effects. Consequently, there is increasing interest in the benefits of low protein cow's milk based formulas (1.6-1.8 g/100 kcal) to reduce rapid infant weight gain and obesity. However, it is unclear whether the same issues relate to protein sources from infant complementary (solid or

semi-solid) foods.

Here, the authors report a well-performed RCT. The infants were provided the same standard, intact milk protein-based formula which they consumed ad libitum. The meat-based diet consisted of commercially available puréed meats, and the dairy-based diet consisted of infant yogurt, cheese, and a powdered concentrate of 80% whey protein. During the intervention period, between ages 5-12 months, both groups showed the same slight increase in weight-for-age z score (WAZ) compared to the WHO growth standards, consistent with formula-fed infants in many western populations. The main difference was that infants on dairy-protein foods faltered in their WHO length-for-age z score (LAZ), reducing by on average -0.30 over 7 months, and reaching a mean LAZ of ~-0.60 at age 12 months. Although unexpected, this decline in LAZ was similar to that in an earlier study of a low-protein, cereal-based diet by the same group. With attention shifting towards the very early prevention of overweight, we should be careful to understand and avoid compromising the essential nutritional requirements for linear growth. Other comprehensive guidance on infant complementary feeding was published recently (see: <https://www.gov.uk/government/collections/sacn-reports-and-position-statements>).

DOI:10.1530/ey.15.15.11

Obesity must be studied separately in men and women

15.12 TAp63 contributes to sexual dimorphism in POMC neuron functions and energy homeostasis

Wang C, He Y, Xu P, Yang Y, Saito K, Xia Y, Yan X, Hinton Jr A, Yan C, Ding H

To read the full abstract: [Nature Communications 2018;9:1544](#)

Obesity prevalence is generally higher in women than in men, and there is also a sex difference in body fat distribution. Sex differences in obesity can be explained in part by the influence of gonadal steroids on body composition and appetite; however, behavioural, and socio-cultural factors may also play a role. Here is the advantage of experimental animals: when male and female mice eat the same high-fat diet, males gain more weight than females. Is it the sex chromosomes or the sex hormones that leads to this sexual dimorphism?

Here, the authors compared the firing rate of many types of neurons of males and females and found a few that fired differently, including POMC neurons; female POMC neurons (anti orexigenic) fire faster than male neurons. They show that TAp63 gene, knockout of which causes obesity, is expressed more in females than in males. Selective knockout of the gene only in POMC neurons did not affect male mice, but, female mice developed male-like obesity and decreased the firing activity to the level of males. The story then goes as follows: female POMC neurons express more TAp63, which makes their POMC neurons to fire faster than males. This results in the females having less appetite, spending more energy and therefore being protected from gaining weight, which is nice in our current energy-rich life-style, but gave males an advantage in a thrifty environment. Obviously, females must also have other mechanisms to maintain their adipose tissue, and the bottom-line is that females tend to have more adiposity than males in our modern life-style. It means also that both animal and clinical research on obesity must be designed and analyzed to separately examine both men and women.

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The importance of being earnest about diurnal variation

15.13 A Transcriptional Circuit Filters Oscillating Circadian Hormonal Inputs to Regulate Fat Cell Differentiation

Bahrami-Nejad Z, Zhao ML, Tholen S, Hunerdosse D, Tkach KE, van Schie S, Chung M, Teruel MN

To read the full abstract: [Cell Metabolism 2018;27:854-868. e8](#)

People gain weight due to treatment with glucocorticoid (GC) drugs, but also in chronic stress and disrupted circadian rhythms. We now learn that fat-cell maturation increases if the trough in exposure to GC lasts less than 12 hours. A long pulse of

glucocorticoids lasting 48 hours led most of the cells to differentiate under the effect of PPAR-gamma, while shorter pulses with at least 12 hours between them resulted in minimal differentiation. They identified FABP4 protein as a key slow positive-feedback regulator of PPAR-gamma. Its feedback loop takes 34 hours activating FABP4, which in return activates PPAR-gamma. Loss of the normal GC circadian rhythm led to a doubling of the animals' fat mass. No increase in fat mass occurred if they boosted GC only during the normal circadian peak times, even when they increased peak GC levels 40-fold. Therefore, stress or GC medication do not cause weight gain, if they only act during the daytime. Conversely, continuous stress, or GC acting at night, such as in the case of Dexamethasone or Prednisone given at bedtime, results in weight gain. Here is another good reason to do our best to simulate the diurnal changes of GC in the treatment of hypocortisolism.

DOI:10.1530/ey.15.15.13

Memories that persist into adulthood

15.14 Epigenetic modulation of Fgf21 in the perinatal mouse liver ameliorates diet-induced obesity in adulthood

Yuan X, Tsujimoto K, Hashimoto K, Kawahori K, Hanzawa N, Hamaguchi M, Seki T, Nawa M, Ehara T, Kitamura Y

To read the full abstract: [Nature Communications 2018;9:636](#)

We know that good nutrition early in life has profound and long-lasting effects on body weight in later life. Malnutrition during pregnancy or infant formula feeding may be stored on the offspring genome as epigenetic memory and persist into adulthood, thereby influencing the susceptibility to metabolic diseases, such as obesity in later life. These authors had previously found that, during lactation, milk lipids serve as a ligand to activate PPAR α and its effect on liver fat metabolism. They also demonstrated that

administration of a synthetic PPAR α ligand to mouse dams during the perinatal period reduced DNA methylation of fatty-acid β -oxidation genes in the liver of the offspring. Here, using a genome-wide DNA methylation analysis, they identified the liver hormone Fgf21 as a PPAR α target gene for DNA demethylation during the perinatal period, which persists into adulthood to exert long-term effects on gene expression in response to environmental cues. This may account in part for the attenuation of diet-induced obesity. Other than the Fgf21 story, this study represents the first analysis of DNA methylation of a gene throughout life. It provides the proof of concept of epigenetic modulation in early life, through which the epigenetic status of a gene can be modified during the suckling period, and provides a critical time window to establish epigenetic memory, as according to the DOHaD hypothesis. Fgf21 regulates monosaccharide intake and preferences for sweet foods via signaling through FGF21 receptors in the suprachiasmatic nucleus and paraventricular nucleus of the hypothalamus. We now know that this pathway is epigenetically regulated during breastfeeding.

DOI:10.1530/ey.15.15.14

How dangerous is Bisphenol A really?

15.15 FDA Statement from Foods and Veterinary Medicine, on National Toxicology Program draft report on Bisphenol A

To read the full report: <https://www.fda.gov/NewsEvents>

The report, issued by the U.S. National Toxicological Program (NTP), presents the initial results of a multimillion dollar study conducted for more than 5 years by scientists at FDA's National Center for Toxicological Research. It looked at the effects of different doses of BPA evaluating chronic and early life exposure in two different groups of rodents. In the chronic part, laboratory animals were exposed to BPA from

pregnancy, through early-life development, and continuing through their entire lifetime. The doses ranged from low doses, that would be comparable to typical human exposures, to doses that vastly exceed human exposures. A variety of endpoints were evaluated. The study confirms the absence of health effects at typical human exposure levels. The actual article is yet to be published, so this report precedes usual peer review, so that other than the conclusions, we haven't seen yet the methods or the results. The Endocrine Society expressed concern with this statement, saying that "It is premature to draw conclusions based on the release of one component of a two-part report. Policymakers and regulators should reserve judgment until the full report is released", which will include data on additional endpoints. <https://www.endocrine.org/news-room/2018/endocrine-society-experts-express-concern-with-fda-statement-on-bpa-safety>

DOI:10.1530/ey.15.15.15

Emerging adulthood

15.16 Maturation is prolonged and variable in female chimpanzees

Walker KK, Walker CS, Goodall J, Pusey AE

To read the full abstract: [Journal of Human Evolution 2018;114:131-140](#)

Whereas the age at onset of puberty in the chimpanzee is not of much concern to most of us, the results show an interesting aspect. On average, the first birth is

delayed by 3.4 years after menarche. This period of 'emerging adulthood', should be included in models of apes, as well as human maturation where it lasts for 4-6 years after puberty. It is a period of relative infertility in the female's brain, a period of maturation, learning intimacy and mutual support, intensification of pre-existing friendships, family-oriented socialization, and the attainment of those social skills that are needed for mating and reproduction. It was proposed that emerging adulthood is a life-history stage that is the foundation of the high reproductive success of human beings. The period of emerging adulthood has an evolutionary context and developmental markers, and emerging adults require protection because they are still learning and maturing.

DOI:10.1530/ey.15.15.16

Neanderthal's' child growth

15.17 The growth pattern of Neandertals, reconstructed from a juvenile skeleton from El Sidrón (Spain)

Rosas A, Ríos L, Estalrich A, Liversidge H, García-Taberner A, Huguet R, Cardoso H, Bastir M, Lalueza-Fox C, de la Rasilla M

To read the full abstract: [Science 2017;357:1282-1287](https://doi.org/10.1016/j.science.2017.05.017)

This Neanderthal boy died 49,000 years ago from an unknown cause at a dental age of 7.7 years. Most of his bones agreed with this estimation. The authors claim that his general pattern of growth was like that of modern humans, except that the atlas and

mid-thoracic vertebrae matured later and remained at the 5-6-year stage of development. However, by modern standards, he was a short and sturdy individual with a height of 111 cm (-2.7 SDS by CDC2000 reference), and weight 26 kg (70th centile). Based on his cranial bones, his brain volume was only ~88% of the average adult Neanderthal's, which would be underdeveloped if he were one of us: a 7-year-old modern human's brain is 95% of an adult's. Also, the spine had not yet fully fused, something that happens to human children at around age 5 or 6 years old; thereafter the vertebrae grow concentrically like carpal bones. There's evidence from earlier studies that Neanderthals ate nuts and fungus as part of a mostly vegetarian diet and that they used plants that acted like natural painkillers. The authors discuss that "Clarifying differences and similarities in growth patterns between extinct humans, especially Neandertals, and modern humans helps us better define our own phylogenetic history".

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