This year’s screening for thyroid publications with relevance or interest for pediatric endocrinologists resulted in the description of several clusters of publications gathered around four topics: thyroid hormone transport, Hashimoto’s encephalitis, thyroid cancer in childhood, and congenital hypothyroidism related to thyroid dysgenesis. In addition, several very stimulating papers were published with the most notorious in terms of impact factor published in *Nature Medicine* and the most numerous involving 96,278 participants. A new function for a new hormone resembling TSH and a new disease for each textbook of pediatric endocrinology are on the top of the list of new findings among over 3,000 publications screened.

**A new disease related to an almost new paradigm: MCT8 deficiency**

So far it has been assumed that thyroid hormones – due to their lipophilicity – enter target cells just by slipping through the membrane. After the initial description of a specific transport molecule for thyroid hormone in 2003 [1], a new paradigm of thyroid hormone physiology has emerged. It turns out that as everything in nature, also the entering of thyroid hormone in its target cell is well regulated and the gatekeeper is the MCT8 transporter, at least in the brain. The identification of patients with mutations in this transporter and their severe neurological phenotype accelerated research on this new field of thyroidology. Based on the neurological phenotype of severe muscular hypotonia and abnormal development, it is evident that this molecule seems to have a central non-redundant function in brain physiology and further research into this mechanism will accompany our yearbook project for a long time.

Papers are summarized which give an overview of the MCT transporter family, the phenotypes identified and new information on the expression of the MCT8 gene in the brain.

**Thyroid hormone transporters**

Friesema EC, Jansen J, Milici C, Visser TJ

Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

*Vitam Horm* 2005;70:137–167

**Summary:** Thyroid hormone is essential for the development of the brain and the nervous system. Cellular entry is required for conversion of thyroid hormones by the intracellular deiodinases and for binding of T3 to its nuclear receptors. Several transporters capable of thyroid hormone transport have been identified. Functional expression studies using *Xenopus laevis* oocytes have so far identified two categories of transporters involved in thyroid hormone uptake (i.e., organic anion transporters and amino acid transporters). Among the organic anion transporters, both Na+/taurocholate cotransporting polypeptide and various members of the organic anion transporting polypeptide family mediate transport of iodothyronines. Because iodothyronines are a particular class of amino acids derived from tyrosine residues, it is no surprise that some amino acid transporters have been shown to be involved in thyroid hormone transport. Monocarboxylate transporter 8 was characterized. MCT8 is a very active and specific thyroid hormone transporter, encoded by a gene located on the X chromosome. MCT8 is highly expressed in liver and brain but is also widely distributed in other tissues. MCT8 shows 50% amino acid identity with a system T amino acid transporter 1 (TAT1). TAT1, also called MCT10, has been characterized to transport aromatic amino acids but no iodothyronines.
Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation

Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands
Lancet 2004;364:1435–1437

Background: It was tested whether mutations in MCT8 cause severe psychomotor retardation and high serum triiodothyronine (T3) concentrations in 5 unrelated young boys with elevated T3 but no symptoms of hyperthyroidism in whom thyroid hormone receptor mutations were excluded.

Result: In 2 patients, gene deletions of 2.4 and 24 kb were recorded and in 3 patients missense mutations Ala150Val, Arg171 stop, and Leu397Pro were identified.

Conclusion: It was suggested that this novel syndrome of X-linked psychomotor retardation is due to a defect in T3 entry into neurons through MCT8, resulting in impaired T3 action and metabolism.

X-linked paroxysmal dyskinesia and severe global retardation caused by defective MCT8 gene

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J Neurol 2005;252:663–666

Summary: A further unusual neurological phenotype associated with MCT8 mutations, namely paroxysmal kinesigenic dyskinesias (PKD), provoked by certain stimuli including changing of clothes or diapers, has been described. It is not clear how the MCT8 defect causes PKD. PKD have been previously noted in patients with thyroid abnormalities. This novel X-linked condition widens the spectrum of secondary PKD.

Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene

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Am J Hum Genet 2005;77:41–53

Background: Allan-Herndon-Dudley syndrome was among the first of the X-linked mental retardation syndromes to be described (in 1944) and among the first to be regionally mapped on the X chromosome (in 1990). Six large families with the syndrome have been identified, and linkage studies have placed the gene locus in Xq13.2. Infancy and childhood in the Allan-Herndon-Dudley syndrome are marked by hypotonia, weakness, reduced muscle mass, and delay of developmental milestones. Facial manifestations are not distinctive, but the face tends to be elongated with bifrontal narrowing, and the ears are often simply formed or cupped. Some patients have myopathic facies. Generalized weakness is manifested by excessive drooling, forward positioning of the head and neck, failure to ambulate independently, or ataxia in those who do ambulate. Speech is dysarthric or absent altogether. In adult life, hypotonia gives way to spasticity. Hands exhibit dystonic and athetoid posturing and fisting. Cognitive development is severely impaired. No major malformations occur, intruterine growth is not impaired, head circumference and genital development are usually normal. Behavior tends to be passive, with little evidence of aggressive or disruptive behavior.

Result: Mutations in the monocarboxylate transporter 8 gene (MCT8) have been found in each of the six families studied.

Conclusion: Although clinical signs of thyroid dysfunction are usually absent in affected males, the disturbances in blood levels of thyroid hormones suggest the possibility of systematic detection through screening of high-risk mental retardation male populations.
The monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone-sensitive neuron populations

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Endocrinology 2005; 146: 1701-1706

Background: To provide a clue to the cellular function of MCT8 in brain, the expression of MCT8 mRNA in the murine central nervous system was studied by in situ hybridization histochemistry.

Result: In addition to the choroid plexus structures, the highest transcript levels were found in neo- and allocortical regions (e.g. olfactory bulb, cerebral cortex, hippocampus, and amygdala), moderate signal intensities in striatum and cerebellum, and low levels in a few neuroendocrine nuclei. Colocalization studies revealed that MCT8 is predominantly expressed in neurons.

Conclusion: Together with the spatiotemporal expression pattern of MCT8 during the perinatal period, these results strongly indicate that MCT8 plays an important role for proper central nervous system development by transporting thyroid hormone into neurons as its main target cells.

Together, these articles represent a fascinating progress within a 12-month period on a topic that has not been discussed in clinical thyroid medicine at all. The widening of the phenotypical spectrum of MCT8 deficiency as shown by the most recent report of Schwartz et al. in patients with Allan-Herndon-Dudley syndrome represents the most intriguing effort because it shows the phenotype in older patients and the role of MCT8 as part of the multiple causes of X-linked mental retardation. A characteristic feature of patients with Allan-Herndon-Dudley syndrome is muscular hypotonia in the first year of life with later spastic paraplegia, a symptom not recognized in the younger patients so far. However, as for all new essential discoveries, more questions have arisen than have been answered so far. What is the real physiological role of MCT8? Why is its impact on brain function much higher than on other organs, e.g. heart? The course of T4 in the brain is complex including the transport of T4 in cells where it will be converted to T3 by deiodinase type 2 followed by further transport into neurons where the T3 receptor is activated. MCT8 seems to intervene at the step of transfer of locally produced T3 into the target neuron but far more studies are needed to resolve this pathway in detail. In addition, who can explain why T3 is elevated and T4 is normal with almost normal TSH in these patients? The function of MCT8 in the liver most likely contributes to this prismatic thyroid hormone constellation and further studies are necessary to clarify this picture too. In any case, elevated plasma T3 in these patients will give rise to a rebirth of T3 measurements in clinical practice.

Triiodothyronine stimulates food intake via the hypothalamic ventromedial nucleus independent of changes in energy expenditure

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Endocrinology 2004; 145: 5252-5258

Background: Increased food intake is characteristic of hyperthyroidism, although this is presumed to compensate for a state of negative energy balance. In this study the authors tested whether thyroid hormone T3 directly stimulates feeding at the level of the hypothalamus.

Result: Peripheral administration of T3 doubled food intake in ad libitum-fed rats over 2 h and induced expression of the immediate early gene, early growth response-1, in the hypothalamic ventromedial nucleus (VMN), whereas maintaining plasma-free T3 levels within the normal range. Injection of T3 directly into the VMN produced a 4-fold increase in food intake in the first hour. The majority of T3 in the brain is reported to be produced by tissue-specific conversion of T4 to T3 by the enzyme type 2
iodothyronine deiodinase (D2). Hypothalamic D2 mRNA expression showed a diurnal variation, with a peak in the nocturnal feeding phase. Hypothalamic D2 mRNA levels also increased after a 12- and 24-hour fast, suggesting that local production of T3 may play a role in this T3 feeding circuit.

**Conclusion:** Thus, a novel hypothalamic feeding circuit in which T3, from the peripheral circulation or produced by local conversion, stimulates food intake via the VMN is proposed.

In this paper the authors open a new avenue, exploring the influence of thyroid hormones on eating behavior. After the fundamental findings of leptin’s effect on the hypothalamic regulation of the pituitary-thyroid axis, and thereby an anorexigenic effect via activation of metabolism, the reciprocal link has now been established. It is T3 itself which can act directly on the central regulation of body weight and satiety. (Will it turn out that this central function of T3 also requires the MCT8 transport?) Further research focusing on the potential of thyroid hormone-derived ligands as tools to treat obesity will need to separate these opposing effects: to develop agonists which increase metabolism but not food intake.

**Thyroid hormone administration enhances remyelination in chronic demyelinating inflammatory disease**

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*Proc Natl Acad Sci USA* 2004;101:16363–16368

**Background:** Chronic disabilities in multiple sclerosis are believed to be due to neuron damage and degeneration, which follow remyelination failure. Due to the presence of numerous oligodendrocyte precursors inside demyelination plaques, one reason for demyelination failure could be the inability of oligodendrocyte precursor cells to turn into myelinating oligodendrocytes.

**Result:** Thyroid hormone enhances and accelerates remyelination in an experimental model of chronic demyelination, i.e., experimental allergic encephalomyelitis in congenic female Dark Agouti rats immunized with complete guinea pig spinal cord. Thyroid hormone, when administered during the acute phase of the disease, increases expression of platelet-derived growth factor receptor, restores normal levels of myelin basic protein mRNA and protein, and allows an early and morphologically competent reassembly of myelin sheaths.

**Conclusion:** Thyroid hormone exerts a neuroprotective effect with respect to axonal pathology.

This paper shows for the first time that thyroid hormone is sufficient to restore myelin expression in a rodent model of multiple sclerosis. Although these results are intriguing in terms of hope for treatment in multiple sclerosis, the findings are interesting from an endocrine point of view, because T3 seems to play a role in myelination. If thyroid hormones play a role also in myelination during the initial development of neuronal connections and not only during repair, this will be even more interesting for pediatricians. Even more, one might envision that other conditions which are characterized by remyelination, e.g. after neuronal trauma, might benefit from increased thyroid hormone action.

**News about Hashimoto’s encephalopathy**

**Progressive dementia caused by Hashimoto’s encephalopathy – report of two cases**

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*Eur J Neurol* 2004;11:711–713

**Summary:** Dementia induced by Hashimoto’s encephalopathy seems to be a rare condition. The authors report 2 patients who revealed a syndrome consisting of a rapid progressive dementia with myoclonus. In both patients, the detection of thyroid antibodies enabled the diagnosis of Hashimoto’s encephalopathy.
The symptoms receded completely during a high-dose glucocorticoid therapy. In patients with rapidly progressive dementia or with dementia of unknown origin, Hashimoto’s encephalopathy should be considered.

**Hashimoto’s encephalopathy: an unusual cause of seizures in the intensive care unit**

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**Summary:** Two adolescent females presented with encephalopathy and raised venous lactate. Both had subtle signs of neurocognitive deterioration before initial presentation. Extensive investigation revealed elevated thyroid antibody titer, suggesting Hashimoto’s encephalopathy. Symptoms rapidly resolved in both cases after steroid treatment.

**Conclusion:** Hashimoto’s encephalopathy should be considered in cases of unexplained encephalopathy presenting to the intensive care unit. Teenage girls with an antecedent history suggestive of thyroid disease or progressive cognitive decline warrant special attention. Antithyroid antibodies should be measured even if standard thyroid function tests are normal. Although the etiology is unknown, prompt steroid responsiveness suggests an inflammatory or autoimmune disorder, and patients should be treated accordingly.

**Brain perfusion abnormalities in patients with euthyroid autoimmune thyroiditis**

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**Background:** Brain perfusion abnormalities have recently been demonstrated by single-photon emission computed tomography (SPECT) in rare cases of severe Hashimoto’s thyroiditis encephalopathy; moreover, some degree of subtle central nervous system involvement has been hypothesized in Hashimoto’s thyroiditis, but no direct evidence has been provided so far. The aim of the study was to assess cortical brain perfusion in patients with euthyroid Hashimoto’s thyroiditis without any clinical evidence of central nervous system involvement by means of $^{99m}$Tc-ECD brain SPECT.

**Results:** Sixteen adult patients with Hashimoto’s thyroiditis entered this study with the diagnosis of coexistence of high titers of antithyroid autoantibodies and diffuse hypoechogenicity of the thyroid on ultrasound in association with normal circulating thyroid hormone and TSH concentrations. Nine consecutive adult patients with non-toxic nodular goiter and 10 healthy subjects matched for age and sex were included as control groups. All patients underwent $^{99m}$Tc-ECD brain SPECT. As assessed by visual examination, $^{99m}$Tc-ECD cerebral distribution was irregular and patchy in Hashimoto’s thyroiditis patients, hypoperfusion being more frequently found in frontal lobes. The asymmetry index revealed abnormalities in 12 of 16 Hashimoto’s thyroiditis patients, in 3 of 9 non-toxic nodular goiter patients and in none of the normal controls. A significant difference in the mean asymmetry index was found between patients with Hashimoto’s thyroiditis and both patients with non-toxic nodular goiter ($p < 0.003$) and normal controls ($p < 0.001$), when only frontal lobes were considered.

**Conclusion:** These results show the high prevalence of brain perfusion abnormalities in euthyroid Hashimoto’s thyroiditis. These abnormalities are similar to those observed in cases of severe Hashimoto’s encephalopathy and may suggest a higher than expected involvement of central nervous system in thyroid autoimmune disease.
Hashimoto’s encephalopathy: myth or reality? An endocrinologist’s perspective
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Summary: Since the first description of a case of episodic encephalopathy associated with Hashimoto’s thyroiditis in 1966, many cases of corticosteroid-responsive encephalopathy associated with positive antithyroid antibodies, clinical Hashimoto’s thyroiditis, or spontaneous autoimmune thyroid failure have been reported. These patients have neurologic manifestations of encephalopathy unrelated to other known causes. The condition has thus been termed ‘Hashimoto’s encephalopathy’. The literature shows no proven association between thyroid disease and the neurologic process. Although the association of a common endocrine condition and a rare neurologic disease may occur by chance, this type of encephalopathy probably has an autoimmune nature and thus is more likely to occur in the background of another autoimmune condition such as autoimmune thyroid disease. Until the pathogenesis of these coincident conditions is better defined, the term ‘corticosteroid-responsive encephalopathy associated with autoimmune thyroiditis’ is more accurate and descriptive than Hashimoto’s encephalopathy. Advances in the field may clarify this seemingly inconsistent terminology.

The increasingly recognized association of a wide spectrum of central nervous system symptoms with Hashimoto’s thyroiditis and the uncertainty of whether the two conditions are causally related are nicely summarized in the very informative review by Dr. Fatourechi. However, her suggested term ‘corticosteroid-responsive encephalopathy associated with autoimmune thyroiditis’ correctly describes the uncertainty of a causal relation but seems unpractical for daily clinical communication. The paper by Dr. Piga and colleagues provided further evidence that altered thyroid function does not contribute to the central disturbance because it shows that brain perfusion is altered in euthyroid patients with autoimmune markers. The most important and consistent finding in all these case reports is the effect of glucocorticoid treatment. While the question of whether central nervous system involvement and Hashimoto’s thyroiditis are associated or causally related is still open, thyroid antibodies are an important marker to identify patients who will benefit from an efficient glucocorticoid treatment.

News about thyroid autoimmune mechanisms

Degenerate self-reactive human T-cell receptor causes spontaneous autoimmune disease in mice
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Nat Med 2004;10:920–926

Background: Thyroid autoimmune disorders comprise more than 30% of all organ-specific autoimmune diseases and are characterized by autoantibodies and infiltrating T cells. The pathologic role of infiltrating T cells is not well defined. To address this issue, transgenic mice were generated expressing a human T-cell receptor derived from the thyroid-infiltrating T cell of a patient with thyroiditis and specific for a cryptic thyroid-peroxidase epitope.

Results: The transgenic T cells had an activated phenotype in vivo, and mice spontaneously developed destructive thyroiditis with histological, clinical and hormonal signs comparable with human autoimmune hypothyroidism.

Conclusion: The results highlight the pathogenic role of human T cells specific for cryptic self epitopes. This new ‘humanized’ model will provide a unique tool to investigate how human pathogenic self-reactive T cells initiate autoimmune diseases and determine how autoimmunity can be modulated in vivo.
Autoimmune thyroid diseases are clinically evaluated by the determination of autoantibodies. However, the thyroid gland is heavily infiltrated by T cells and the respective role of B and T cells is not clearly established. Here, the authors show that a human T-cell receptor from a patient with Hashimoto’s thyroiditis can infiltrate and destroy a mouse thyroid and recapitulate the disease. These results call for several comments. First, that destructive thyroiditis can occur in mice whose immune system is simplified to this T-cell receptor, in the absence of B or other T cells. This means that a single T cell directed against a thyroid peroxidase epitope is enough to recapitulate the disease. Second, mice with an otherwise intact immune system have a milder phenotype, indicating the possibility of regulatory processes, of obvious clinical importance. Last, the mouse strain used is the one susceptible to thyroglobulin-induced thyroiditis, showing that even with a specified T-cell receptor, the genetic background is important. This model will be useful to evaluate the natural history of the disease and the role of several key players in the immune system. It might also lead to a better understanding of the central manifestations of the disease, as discussed above.

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A new function for a new hormone: OGH/GPB5

Resistance to diet-induced obesity in mice globally overexpressing OGH/GPB5

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Proc Natl Acad Sci USA 2005;102:2496–2501

Background: Recently, a glycoprotein hormone β-subunit was identified (OGH, also called GPB5) that, as a heterodimer with the α-subunit GPA2, serves as a second ligand for the thyroid-stimulating hormone receptor. Mice in which the OGH gene is deleted (OGH−/−) are indistinguishable from WT littermates in body weight, response to high-fat diet, metabolic parameters, body composition, and insulin tolerance.

Results: Mice engineered to transgenically globally overexpress OGH (OGH-TG) develop approximately 2-fold elevations in their basal thyroid levels and weigh slightly less than WT littermates despite increased food intake because of an increase in their metabolic rates. Moreover, when OGH-TG mice are challenged with a high-fat diet, they gain significantly less weight and body fat than their wt littermates. The OGH-TG mice also have reduced blood glucose, insulin, cholesterol, and triglycerides. In contrast to other approaches in which the thyroid axis is activated, OGH-TG mice exhibit only minor changes in heart rate and blood pressure.

Conclusion: These findings suggest that constitutive low-level activation of the thyroid axis (via OGH or other means) may provide a beneficial therapeutic approach for combating diet-induced obesity.

This paper confirms that the recently identified ‘new TSH’ is indeed active on the thyroid and participates in its control. It is fascinating that nowadays one can sit at the computer and find a new hormone. The colleagues from Regeneron were looking in silico in the genome to search for another glycoprotein hormone, which might sit around waiting to be explored. They end up fishing a TSH β-homologue protein as well as a so far unrecognized α-subunit partner, which heterodimerize to create a new player in the hormone system. The function of this hormone is subtle compared to TSH but has an effect on diet-induced obesity. Several questions occur, e.g. why does this compound influence thyroid action on metabolism and not on the heart? Also it is unclear whether OGH has arisen recently during evolution or represents a remnant of a former endocrine system.
Thyroid development and its disorders: genetics and molecular mechanisms

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Summary: Thyroid gland organogenesis results in an organ the shape, size, and position of which are largely conserved among adult individuals of the same species, thus suggesting that genetic factors must be involved in controlling these parameters. In humans, the organogenesis of the thyroid gland is often disturbed, leading to a variety of conditions, such as agenesis, ectopy, and hypoplasia, which are collectively called thyroid dysgenesis. The molecular mechanisms leading to thyroid dysgenesis are largely unknown. Studies in murine models and in a few patients with dysgenesis revealed that mutations in regulatory genes expressed in the developing thyroid are responsible for this condition, thus showing that thyroid dysgenesis can be a genetic and inheritable disease. These studies open the way to a novel working hypothesis on the molecular and genetic basis of this frequent human condition and render the thyroid an important model in the understanding of molecular mechanisms regulating the size, shape, and position of organs.

This review tells us whatever we ever wanted to know about thyroid development and thyroid dysgenesis. A comprehensive starting point for what comes next.

Linkage and mutational analysis of familial thyroid dysgenesis demonstrate genetic heterogeneity implicating novel genes

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Background: The pathophysiology of thyroid dysgenesis is not elucidated yet in the majority of cases. The unexpected familial clustering of congenital hypothyroidism due to thyroid dysgenesis suggests a genetically determined disorder. Four genes have been hitherto involved in thyroid development, including migration and growth. Three of these encode transcription factors (the thyroid transcription factors 1 and 2 (TTF1 or NKX2.1 and TTF2 or FOXE1) and PAX8) while the other encodes the thyrotropin hormone receptor (TSHR). Some mutations have been reported in patients affected by thyroid defects, which supports the relevance of these four genes in thyroid dysgenesis. However, their involvement in the general thyroid dysgenesis population remains questionable. Therefore, to document their involvement, a linkage analysis followed by mutational analysis in 19 multiplex thyroid dysgenesis families was performed.

Results: The LOD score results failed to prove linkage between any of the four genes and the thyroid dysgenesis phenotype, whatever the postulated mode of inheritance. Mutational analysis did not identify mutations in these cases.

Conclusion: The four genes were excluded in 5 out of the 19 investigated families, demonstrating the relevance of other genes. In conclusion, the present study demonstrates genetic heterogeneity in the thyroid dysgenesis disorder and suggests the involvement of novel genes.

Anatomical and molecular reinvestigation of lamprey endostyle development provides new insight into thyroid gland evolution

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Background: The thyroid gland of vertebrates is considered to be homologous to the endostyle of non-vertebrate chordates (cephalochordates, urochordates), a key character for understanding the origin
and evolution of the chordate body plan. In lampreys, the larval endostyle transforms into an adult thyroid gland during metamorphosis, reflecting evolutionary changes that occurred in the vertebrate lineage.

Methods: Semithin histological sections, immunohistochemical detection of thyroid hormone, and the molecular marker thyroid transcription factor 1 (Ttf1).

Results: It was found that a duct always persists to connect the endostyle lumen to the pharynx, a structure that resembles the thyroglossal duct in thyroid development and could further support the homology between endostyle and thyroid. The role of Ttf1 in specifying ventral fates in the endostyle is suggested.

Although Castanet et al. succeeded in collecting 19 families, which by far is the largest cohort published, no new mutation could be identified. The authors also tested linkage to the known four candidate genes for thyroid dysgenesis and ended up with the finding that none of the families showed linkage. While we hope that further studies in these families will identify at least one additional new gene, we have to face the fact that this disease is not a classical genetic disease. Despite this impressive collection of familial cases, more than 90% of cases occur sporadically and the majority of monozygotic twins are discordant. Most likely we have to learn from our colleagues in basic genetic and epigenetic departments before unraveling the mystery of thyroid dysgenesis. In the meantime it is nice to recognize that the thyroid comes from the depth of evolution, as shown in the paper about the lampreys’ prethyroid endostyle. It is fascinating to follow the expression of the genes known to be relevant in rodents and humans in this distant prevertebrate species. Based on these expression data, the authors demonstrate that the so-called endostyle, an organ in the pharyngeal region, expresses the gene known to be necessary for vertebrate thyroid development and function. They show that early in evolution the tools were already there but that it took some more time to develop our vertebrate thyroid gland, likely with the help of additional genes. Hopefully, newborn screening for congenital hypothyroidism can provide a normal developmental outcome to virtually all affected children in developed countries. If the affected children had to wait for genetic progress for their health, they would be in major trouble since we are still far away from understanding the molecular clues of this frequent congenital disease.

Novel mode of deoxyribonucleic acid recognition by thyroid hormone receptors: thyroid hormone receptor β-isoforms can bind as trimers to natural response elements comprised of reiterated half-sites

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Mol Endocrinol 2005;19:35–51

Background: Thyroid hormone receptors (TRs) regulate gene expression by binding to specific DNA sequences, denoted thyroid hormone response elements (TREs). The accepted paradigm for TRs proposes that they bind as homo- or heterodimers to TREs comprised of two AGGTCA half-site sequences. In the prototypic TRE, these half-sites are arranged as direct repeats separated by a four-base spacer. This dimeric model of TR binding, derived from analysis of artificial DNA sequences, fails to explain why many natural TREs contain more than two half-sites.

Results: The ability of different TR isoforms to bind to TREs possessing three or more half-sites was tested. The TRβ isoforms (TRβ0, TRβ1, TRβ2), but not TRα1, can bind to reiterated DNA elements, such as the rat GH-TRE, as complexes trimeric or greater in size. The TRβ0 isoform, in particular, formed homo- and heterotrimers (with the retinoid X receptor) with high efficiency and cooperativity, and TRβ0 preferentially used reporters containing these reiterated elements to drive gene expression in vivo.

Conclusion: The data demonstrate that TRβ isoforms can form multimeric receptor complexes on appropriately reiterated DNA response elements, providing a functional distinction between the TR isoforms and an explanation for TREs possessing three or more half-sites.
The authors wondered whether more than two binding sites existed in the response elements for thyroid hormone receptor, although textbooks state that thyroid hormone receptors bind as dimers to the DNA target sequences with two sites being enough. Here, the authors pursued this discrepancy and could demonstrate that thyroid hormone receptors bind as tri- and even tetramers. Why this new finding after more than 10 years of thyroid hormone receptor research? So far, most research had focused on the thyroid hormone receptor-α1 form but not on β, whereas only the β form binds as trimers. However, it makes sense that a team of three is more powerful than just a pair.

**New aspects of thyroid cell carcinoma in childhood**

The vast majority of scientific articles published in the last 12-month period under the heading ‘thyroid’ are related to thyroid tumors. Since thyroid cell tumors are rare in children (0.5–1 case per million children), only very few of these publications refer to thyroid tumors in children. This year seems to be an exception since several interesting publications describe aspects of thyroid cell carcinoma in children. In addition, since thyroid carcinoma biology might represent the other side of a coin of thyroid developmental defects, one might hope that we will learn more about the biology of thyroid cancer cells to understand more about thyroid development. Interestingly, the incidence of thyroid cell carcinomas is significantly higher in females, as is the case for thyroid dysgenesis – Why?

**Follicular cell-derived thyroid cancer in children**

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Horm Res 2005;63:145–151

The recent review by Dr. Leboulleux summarizes most of what we know about this topic.

**Dose-dependent generation of RET/PTC in human thyroid cells after in vitro exposure to γ-radiation: a model of carcinogenic chromosomal rearrangement induced by ionizing radiation**

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J Clin Endocrinol Metab 2005;90:2364–2369

*Background:* Ionizing radiation is a well-known risk factor for thyroid cancer in human populations. Chromosomal rearrangements involving the RET gene, known as RET/PTC, are prevalent in thyroid papillary carcinomas from patients with radiation history.

*Results:* The generation of RET/PTC in HTori-3 immortalized human thyroid cells exposed to a range of doses of γ-radiation and harvested 2, 5–6, and 9 days later was studied. The average rate of RET/PTC induction was $0.1 \times 10^{-6}$ after exposure to 0.1 Gy, $1.6 \times 10^{-6}$ after 1 Gy, $3.0 \times 10^{-6}$ after 5 Gy, and $0.9 \times 10^{-6}$ after 10 Gy. When adjusted for cell survival, the rate after 10 Gy was comparable with those after 5 Gy. RET/PTC1 was more common than RET/PTC3 after each dose, comprising 80% of all rearrangements.

*Conclusion:* This work provides additional evidence for a direct link between this genetic event and radiation exposure and offers a powerful experimental system for studying radiation-induced carcinogenesis in the thyroid gland.
**Diagnosis of thyroid cancer in children: value of gray scale and power Doppler ultrasonography**

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Radiology 2005;235:604–613

**Background:** Because thyroid cell cancer is rare in children, little consensus exists on the diagnostic procedure to investigate thyroid tumors in childhood. The authors therefore prospectively analyzed the accuracy of various diagnostic criteria for cancer in solid thyroid nodules in children on the basis of gray scale and power Doppler ultrasonographic (US) findings.

**Results:** In thyroid nodules with a diameter of $\leq 15$ mm, the most reliable diagnostic criteria for malignancy were an irregular outline (sensitivity 69.6%, specificity 86.4%; $p < 0.001$), subcapsular location (sensitivity 65.2%, specificity 86.4%; $p < 0.001$), and increased intranodular vascularization (sensitivity 69.6%, specificity 87.9%; $p < 0.01$). For thyroid nodules $> 15$ mm in diameter, the accuracy of US diagnosis was much lower than for smaller nodules. The only reliable criterion for cancer in this group was hypoechogenicity (sensitivity 60.0%, specificity 84.0%; $p < 0.01$).

**Conclusion:** These findings indicate that US is most helpful in the diagnosis of thyroid malignancy in thyroid nodules with a diameter of $\leq 15$ mm, with detection of irregular tumor outline, subcapsular location, and increased intranodular vascularization.

The Chernobyl disaster has told us that the younger the exposed children the more susceptible the thyroid to develop cancer. We also learned that in radiation-induced thyroid cancer (papillary cancer) a particular translocation almost always occurs affecting the RET gene and connecting it with the PTC gene. Now, the paper by Caudill et al. has demonstrated in vitro what had been observed after the radioactive fallout. They show that a close dose-response relationship exists between radiation dose and the rate of translocation.

At the same time, the high incidence of childhood radiation-induced thyroid cancer in the Belarus area allowed to refine the clinical diagnosis of this otherwise rare tumor. Lyshchik et al. showed that ultrasound is efficient in diagnosing carcinoma in tumors $< 1$ cm in diameter but not in larger nodules. Also, the data point out the most informative structural indices: irregular tumor outline, subcapsular location, and increased intranodular vascularization. However, in clinical practice, it should be remembered that ultrasound does not provide a pathological diagnosis and that fine-needle aspiration or surgery are the recommended approaches in the management of thyroid nodules.

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**Genetic classification of benign and malignant thyroid follicular neoplasia based on a three-gene combination**

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**Background:** Preoperative fine-needle aspiration-based cytology cannot always differentiate follicular carcinomas from benign follicular neoplasias. Because current methods fail to improve preoperative diagnosis of thyroid nodules, new molecular-based diagnoses should be explored. Therefore, a microarray-based study was conducted with a total of 114 samples to reveal the genetic profiles unique to follicular thyroid carcinomas and follicular adenomas, to identify the most parsimonious number of genes that could accurately differentiate between benign and malignant follicular thyroid neoplasia.

**Results:** Three genes – cyclin D2 (CCND2), protein convertase 2 (PCSK2), and prostate differentiation factor (PLAB) – were identified that allow the accurate molecular classification of follicular thyroid carcinomas and follicular adenomas, to identify the most parsimonious number of genes that could accurately differentiate between benign and malignant follicular thyroid neoplasia. Two independent validation sets revealed that the combination of these three genes could differentiate follicular thyroid carcinomas from follicular adenomas with a sensitivity of 100%, specificity of 94.7%, and accuracy of 96.7%. In addition, our model allowed the identification of follicular variants of papillary thyroid carcinoma with an accuracy of 85.7%.
Conclusion: Three-gene profiling of thyroid nodules can accurately predict the diagnosis of follicular thyroid carcinomas and follicular adenomas with high sensitivity and specificity, thus identifying promising targets for further investigation to ultimately improve preoperative diagnosis.

This methodological paper demonstrates the power of thyroid cancer expression profiling which will be helpful in the future to discriminate different forms of thyroid cancers that we even have not recognized yet (see next paper).

Low frequency of BRAF(T1796A) mutations in childhood thyroid carcinomas

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Background: A high prevalence of the activating BRAF mutation, BRAF(T1796A), is observed in adult papillary thyroid carcinomas. The prognosis of childhood papillary thyroid carcinomas is generally fairly good despite the fact that distant metastases are often documented in these cases. To investigate the differences between the characteristics of childhood and adult papillary thyroid carcinomas, both BRAF(T1796A) and RAS mutations were analyzed in 31 Japanese and 48 post-Chernobyl Ukrainian thyroid carcinomas.

Results: In the 31 Japanese childhood cases, BRAF(T1796A) was found in only one instance (3.2%), and no RAS mutations were detected. In the Ukrainian subjects, of the 15 childhood and the 33 adolescent and young adult papillary thyroid carcinomas examined, the BRAF(T1796A) mutation was found in zero and 8 cases, respectively, and RAS mutations were found in 2 of the young adult cases.

Conclusion: The differences in the prevalence of BRAF(T1796A) mutations between childhood and adult cases of papillary thyroid carcinomas may well reflect inherent differences in the clinical features of these cancers between the two age groups.

Based on these data, childhood and adult papillary thyroid carcinomas seem to be different biological entities. Although histological studies cannot discriminate these two tumor forms, genetic expression studies can. Expression profiling as described in the former paper will help further discriminate the adult from the childhood papillary thyroid carcinoma. It will be of great interest to understand key genes differentially expressed in thyroid tumors from patients of various ages.

A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves’ patients

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Summary: This report details the 26- and 36-year outcomes of 116 patients under the age of 20 years with Graves’ disease who were treated with radioiodine between 1953 and 1973. At the time of treatment, the patients’ ages ranged between 3 years 7 months and 19 years 9 months. The average length of follow-up in 1991–1992 was 26.1 years; that in 2001–2002 was 36.2 years. None of the patients developed cancer of the thyroid or leukemia. Early on, when the objective of treatment was euthyroidism, the dose of radioiodine was low, and retreatment was frequently needed. Later, the doses used were increased. Over time, all but 2 patients became hypothyroid. Pregnancies did not result in an unusual number of congenital anomalies or spontaneous abortions.

Conclusion: Treating young people with Graves’ disease with radioiodine is safe and effective over the long term.
Iodine-131 can induce thyroid cancer and children are more susceptible to radiation-induced neoplasms than adults, raising concerns regarding radioiodine treatment of children with Graves’ disease. This important paper now gives over 30 years of follow-up of children who received radioactive iodine during childhood or, more often, adolescence. The absence of thyroid cancer cases in this longitudinal follow-up study, the longest ever published, now provides safer grounds to treat pediatric patients with Graves’ disease around the world.

The promise of a new clinical study

Thyroid hormone supplementation for the prevention of morbidity and mortality in infants undergoing cardiac surgery

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Background: Paediatric studies have demonstrated that cardiopulmonary bypass is associated with a decline in thyroid hormone levels. Adult patients who undergo open heart surgery and receive T3 supplementation have demonstrated a dose-dependent increase in cardiac output which has been associated with an improved clinical outcome. Thyroid hormone supplementation in infants may also reduce postoperative morbidity and mortality.

Results: Two very small studies were identified that tested perioperative thyroid hormone supplementation or replacement in infants aged <1 year undergoing cardiac surgery [2, 3]. These studies lack evidence concerning the effects of T3 supplementation in infants undergoing cardiac surgery. Further randomized controlled trials which include sufficiently large subject numbers in a variety of different age strata (neonates, infants and older children) need to be undertaken.

The Triiodothyronine for Infants and Children Undergoing Cardiopulmonary Bypass (TRICC) study: design and rationale

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Summary: The TRICC study is a multicenter, randomized, clinical trial designed to determine safety and efficacy of T3 supplementation in children <2 years of age undergoing surgical procedures for congenital heart disease. Duration of mechanical ventilation after completion of cardiopulmonary bypass is the primary clinical outcome parameter with multiple secondary clinical and hemodynamic parameters. Nearly 200 patients will be randomly assigned to receive either T3 or placebo.

Exactly what the colleagues from the Cochrane group demanded after a careful review of the literature: a prospective randomized study in a large number of infants to assess the value of perioperative thyroid hormone administration. This publication represents a hope for better evidence-based data.
The use of LT4 as liquid solution improves the practicability and individualized dosage in newborns and infants with congenital hypothyroidism

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Study: Liquid LT4 solution was administered to 28 consecutive newborns with primary congenital hypothyroidism with a median dosage at start of 12.3 μg LT4/kg/day which was decreased to about 5 μg LT4/kg/day after 9 months. The median time of normalization of TSH (≤6 mU/l) was 2 weeks. In 21 patients, who received a median starting dosage of 12.7 μg LT4/kg (range 9.8–17.1 μg/kg), TSH levels normalized within a median of 1 week. Seven patients receiving only 10.1 μg LT4/kg normalized their TSH only after a median of 2 months.

Conclusion: As recommended, newborns with congenital hypothyroidism should normalize their TSH within 1–2 weeks. The initial dose necessary to normalize TSH is not lower when a liquid solution is used. The higher dose used in tablets is not due to inefficient absorption, but rather reflects the increased demand for thyroid hormone in the first weeks of life.

Life for infants with congenital hypothyroidism becomes easier when taking drops instead of tablets. The liquid solution of LT4 now available on the German market is efficient with a dose effect similar to tablets to suppress TSH. Liquid LT4 in the same dose as tablets is now a treatment option in newborns with congenital hypothyroidism.

A new dimension in population ultrasound screening

Prevalence of thyroid disorders in the working population of Germany: ultrasonography screening in 96,278 unselected employees

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Background: Germany continues to be iodine-deficient despite considerable improvement in the past years. To assess the current prevalence of diffuse and/or nodular thyroid disorders, a cross-sectional observational study in a non-random sample of the working population was carried out throughout Germany in 2001 and 2002. A total of 96,278 employees 18–65 years of age underwent ultrasonographic examinations by 230 experienced investigators. Data from volunteers with previous thyroid treatment (13.0% of total sample) were not included in the analysis.

Results: Abnormal findings (goiter and/or nodules >0.5 cm) were observed in 33.1% (men 32.0%, women 34.2%) of the examined patient population, an enlarged thyroid without nodules in 9.7% (men 11.9%, women 7.6%), nodules only without enlargement of the thyroid in 14.3% (men 11.5%, women 17.0%), and nodular goiter in 9.1% (men 8.6%, women 9.6%).

Conclusion: These results emphasize the importance of effective sonographic screening to detect early thyroid abnormalities in order to initiate preventive and therapeutic measures to prevent the onset or progression of disease and its sequel.

Thyroid abnormalities are obviously the most prevalent endocrine alteration of all, at least in Germany, with a prevalence of 31% and thyroid nodules being the most frequent finding. We hope that these data reflect former times of iodine deficiency and that the prevalence will fall with iodine
supplementation efficiently implemented during the last decade. However, thyroid nodules might also be due to aging, independently of iodine stocks, since there was a linear increase of nodule prevalence with age.

References