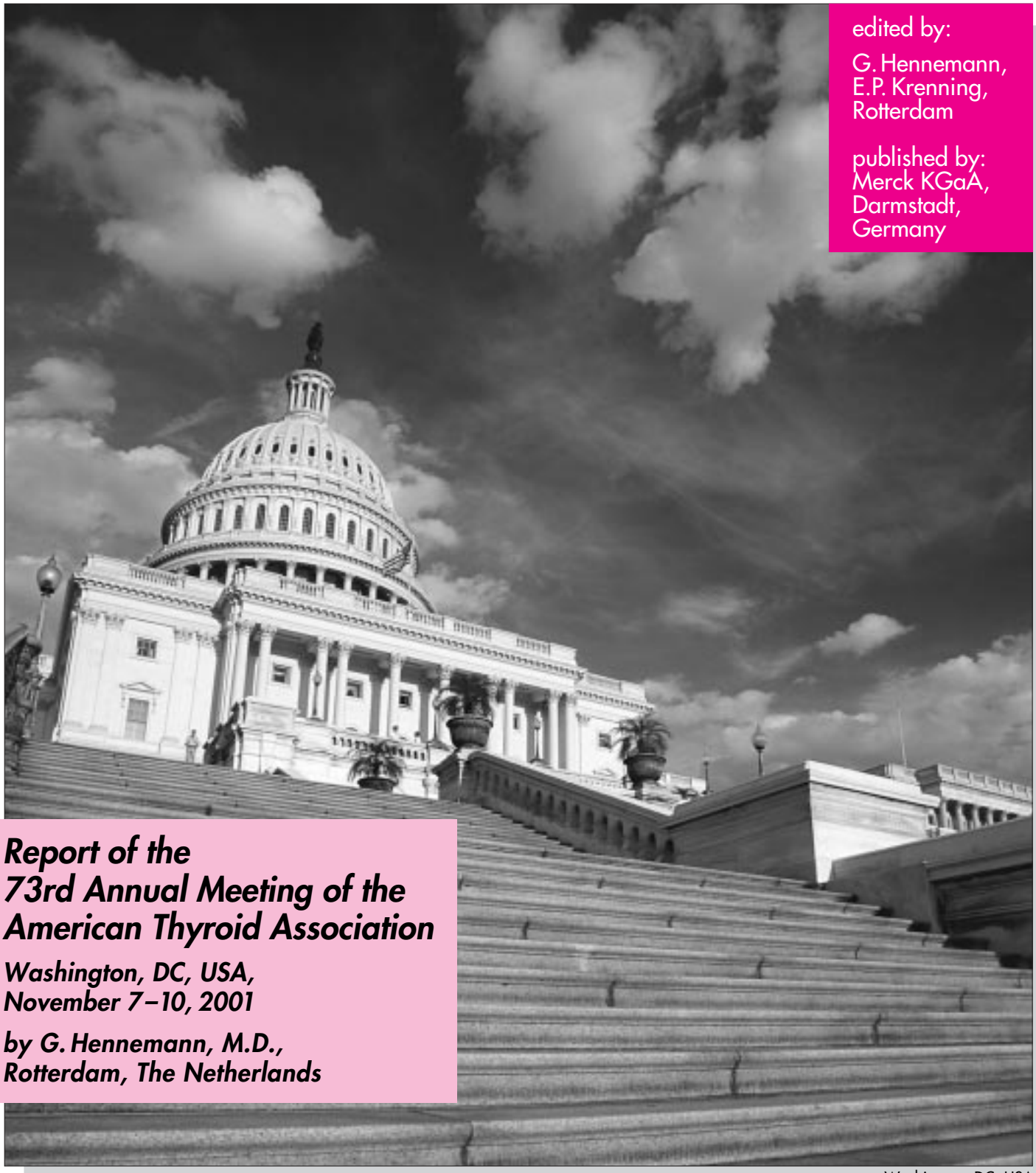
Thyroid International

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Report of the 73rd Annual Meeting of the American Thyroid Association

Washington, DC, USA, November 7–10, 2001

by G. Hennemann, M.D., Rotterdam, The Netherlands

Washington, DC, USA

Report of the 73rd Annual Meeting of the American Thyroid Association

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The meeting was originally planned to take place from September 12 to 16, 2001, but was postponed because of the disaster of September 11th.

This issue is dedicated to all innocent victims of that terrible day.

Thyroid International

Edited by: *G. Hennemann, M.D., Rotterdam*
E. P. Krenning, M.D., Rotterdam

This is the title of a publication series by Merck KGaA, Darmstadt, Germany. We are publishing papers from renowned international thyroid experts in order to pass on the extensive experience which the authors possess in their field to a wide range of physicians dealing with the diagnosis and therapy of thyroid diseases.

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Report of the 73rd Annual Meeting of the American Thyroid Association

This report summarizes those communications that have a clinical bearing.

AUTOIMMUNITY

Brix and Hegedüs, Odense, Denmark, investigated the possible occurrence of genetic anticipation (i.e. a decrease in the age of onset as disease is passed through generations) in autoimmune thyroid disease (AITD). Seventy-four parent-child pairs with AITD from 57 multiple affected families were studied. Twenty-seven and 26 pairs were concordant for Graves' disease and Hashimoto's thyroiditis respectively. In the remaining 21 pairs, the clinical phenotype differed between parents and their offspring. Overall, mean age at diagnosis of AITD was 51.5 (range 16–78) years in the parents and 32.3 (range 16–60) years in the offspring ($p < 0.001$). Essentially similar results were obtained after subdividing the pairs into those concordant for Graves' disease and for Hashimoto's thyroiditis. Controlling for gender and smoking habits did not change the results. *(Comment:* Genetic anticipation has already been described for rheumatoid arthritis and chronic inflammatory bowel disease. This phenomenon has been linked to unstable expanded trinucleotide repeat sequences and the authors suggest to investigate this aspect as well in AITD.) ***Tait et al.,*** Birmingham, UK, looked for coexistent AITD in the type I diabetes Warren Repository, being a DNA resource of 507 families for the identification of type 1 diabetes genetic determinants. In this repository they now looked for coexistent autoimmune disease and found this to be present in 72% of families. In 50% of these, the autoimmune disease was present in a first degree relative. The commonest coexisting disease was thyroid disease present in 34% of families. The distribution of type I diabetes over the gender of siblings was equal while autoimmune thyroid disease was 3 times more frequent in female siblings. Furthermore type I diabetes in a parent was 3 times more common in males but autoimmune thyroid disease about 2.5 times more frequent in mothers. The authors conclude that the high degree of clustering of different autoimmune diseases supports a common etiological mechanism. *(Comment:* The fact that distribution of type I diabetes is different over the sexes as compared to autoimmune thyroid disease suggests, apart from a common genetic susceptibility to autoimmune disease in general (see above), also the presence of different (other) etiological factors for both conditions.)

HYPOTHYROIDISM

Bellini-Peterson et al., Sao Paulo, Brazil, investigated prospectively lipid profiles in 124 patients with subclinical hypothyroidism (mean TSH 15 ± 10.9 mU/l) and compared results with 80 matched healthy controls (mean TSH 1.7 ± 1.0 mU/l). They found elevated total cholesterol in 79% of patients vs 20% of controls ($p < 0.0001$). LDL were elevated in 64.5% vs 41.2% ($p < 0.001$), VLDL 73.4% vs 28.7% ($p < 0.001$) and serum triglycerides 57.2% vs. 13.7% ($p < 0.01$). No differences were present for HDL levels. Also mean levels of total cholesterol, VLDL and triglycerides were higher in patients. A positive correlation was present between TSH levels and these three parameters and this was also true for TPO-Ab values with total cholesterol and triglycerides. *(Comment:* Again this study shows an increase in risk factors for cardiovascular diseases in subclinical hypothyroidism nowadays termed mild hypothyroidism. See also Meier et al., JCEM, 86, 4860, 2001, showing that treating subjects with mild thyroid

failure with L-thyroxine not only normalizes risk factors but also improves clinical symptomatology. In the same issue of the JCEM a debate is being published between pro- and opponents of thyroxine therapy in mild thyroid failure. My personal opinion (despite the results in the next report) is in favor of treatment in persistent subclinical hypothyroidism.) ***Duntas et al.,*** Athens, Greece, investigated an other aspect of risk factor development in subclinical hypothyroidism by measuring plasma levels of oxi-LDL in 29 patients with subclinical hypothyroidism, 33 with overt hypothyroidism and 57 healthy controls. They found a significant mean increase of oxi-LDL of 34.5% in overt hypothyroidism but an insignificant elevation of 7.2% in subclinical hypothyroidism.

Two communications were related to perinatal thyroid hormone deficiency and brain development in humans. Thus, ***Rovet et al.,*** Ontario, Canada, assessed visual processing deficits in perinatal and neonatal thyroid hormone deficiency. They studied 48 three months-old infants: 17 offspring of hypothyroid women, 9 with early-treated congenital hypothyroidism (CH) and 22 normal controls. They found visual deficits in 45% of pre- and neonatal thyroid hormone deficiency and in 17% of controls ($p = 0.02$). The **same group** also reported a study with regard to development of memory, in 79 children in the age from 7–12 years, 44 of whom had congenital hypothyroidism and 35 controls. They tested episodic-, semantic- and recognition memory. Selective memory disturbances were found more in the thyroid hormone deficient group, suggesting hippocampal damage. The authors plan to further study neuro-imaging of the hippocampus in this type of children.

HYPERTHYROIDISM

Three studies were reported showing effects of hyperthyroidism on different aspects of body composition/functioning. ***Brennan et al.,*** Rochester, Minnesota, USA, found that in subjects with hyperthyroidism low levels exist of myosin heavy chain (MHC) I in combination with altered ratios of MCH IIa and IIx isoforms. MHC I are an important component of type I muscle fibers that subserve activities requiring sustained effort or endurance, while MCH II isoforms are in particular present in type II fibers, subserving fast short-term switch. The here described changes are an explanation for complaints of muscle weakness and fatigability in hyperthyroidism. ***Dittmar et al.,*** Mainz, Germany, studied body composition, total body potassium, and bone mineral density in 199 patients with hyperthyroidism (140 women) and found, as compared to controls, that in hyperthyroid women bone cell mass and extracellular water was lowered while the ratio extracellular mass/body cell mass was elevated and fat mass was not different. Hyperthyroid men did not differ in body composition from controls. In the female patients bone cellular mass correlated negatively with free T_3 and positively with total body potassium and bone mineral density. The authors conclude that the lowered body cellular mass in hyperthyroid women is primarily caused by loss in muscle mass. *(Comment:* Why no changes in men? Testosteron again?) ***Biondi et al.,*** Naples, Italy, assessed left ventricular characteristics at rest in 20 hyperthyroid patients (14 females). They found a higher heart rate (37%), wider pulse pressure (55%) but unchanged mean arterial pressure. Stroke and cardiac index were markedly increased by 21% and 64% respectively. Systemic vascular resistance was lower (43%) and ejection fraction higher than in controls (11%) and diastolic volume index was increased (11%). All the here mentioned differences were highly significant. The general finding is that there is an enhanced resting left ventricular performance in hyperthyroidism in humans, predominantly reflecting a significant increase in heart rate and preload rather than changes in afterload and myocardial contractility.

GRAVES' OPHTHALMOPATHY (GO)

Isozaki et al., Tokyo, Japan, studied the effects of somatostatin and its analogue octreotide on the proliferation of fibroblasts taken from retro-orbital tissue of patients operated for Graves' ophthalmopathy. They performed this study because Graves' ophthalmopathy patients have been successfully treated with octreotide showing a decrease in proptosis. Proptosis in Graves' ophthalmopathy is, at least in part, caused by proliferation of fibroblasts

leading to increased synthesis of glycosaminoglycans. Their studies showed that both somatostatin and octreotide have a potent inhibitory activity on proliferation of these fibroblasts and the effect was not signaled via the TSH receptor. ***Szucs-Farkas et al.,*** Debrecen, Hungary, measured muscle volume and connective tissue volume in 50 orbits of 25 patients with Graves' ophthalmopathy and in 20 orbits of 10 healthy controls using magnetic resonance imaging. They found that the major contributor to eye protrusion in Graves' ophthalmopathy is muscle enlargement while contribution of connective tissue expansion is less marked. *(Comment:* an important common factor for volume expansion of retro-orbital connective tissue and extra-ocular muscles is the proliferation of fibroblasts with secondary water retention by produced glycosaminoglycans.) ***Lisi et al.,*** Pisa, Italy, studied the distribution of thyroglobulin in orbital tissues from patients with GO. They did this because several decades ago Kriss et al. hypothesized that retrograde transported Tg via the lymphatics could move to retro-orbital tissues and in this way act as an autoantigen in the pathogenesis of the ophthalmopathy. The authors found Tg, using immunoprecipitation, in 3/7 patients and, using ELISA, in 4/7 cases in retrobulbar fibroadipose tissue and in inflamed palpebral skin. In addition, ELISA Tg was also detected in extra-ocular muscles. The results support the previously forwarded hypothesis by Kriss, in that Tg may act as a co-antigen in the pathogenesis of GO.

IODINE DEFICIENCY

Bülow Pederson et al., Denmark, registered new cases of hyper- and hypothyroidism in two areas of Denmark i.e. Aalborg with moderate iodine deficiency (mean urinary iodine 45 μg/l), and Copenhagen with mild iodine deficiency (61 μg/l). The registration started one year before and two years after a low grade of iodine prophylaxis became available by the voluntary use of iodized table salt (1998). In moderate iodine deficiency the incidence rates of hyperthyroidism in these 3 years were 119.7, 129.9 and 127.7 per 100.000/year as compared to 83.3, 81.3 and 84.3 per 100.000/year ($p < 0.01$) in mild iodine deficiency. The figures for hypothyroidism were 29.0, 27.6 and 35.4 per 100.000/year, and 50.7. 50.5 and 52.0 per 100.000/year ($p < 0.01$) respectively. No significant changes in hyper- and hypothyroidism in both areas occurred during this 3 year observation period. The results show that even small differences in iodine intake are associated with considerable differences in incidence of hyper- and hypothyroidism i.e. an increased incidence of hyperthyroidism in moderate iodine deficiency versus an increased incidence of hypothyroidism in mild iodine deficiency. Overall these data show that a considerable decrease in rate of hyperthyroidism but an almost double increase in rate of hypothyroidism occurs when shifting from moderate to mild iodine deficiency. ***Boyage et al.,*** Fremantle, Westmead and Gosford, Australia, reported two studies. One was conducted in India in 128 children, age 4–5 years, with sufficient iodine intake (median urinary iodine 279 μg/l). Despite this more than adequate iodine intake they (still!) found a significant negative correlation between iodine excretion and thyroid volume. The authors question if this correlation is due to the presence of dietary goitrogens or due to a residual effect of previous iodine deficiency. The nutritional status of these children was good. The other report was conducted in Australia, in 324 primary school children aged 5–13.1 years having a median urinary iodine excretion of 82 μg/l. Only 14% of subjects had values below 50 μg/l. No goiter formation in these children despite less than optimal iodine excretion. The thyroid volume of these children appeared to be much smaller than the normative values proposed by WHO/ICCIDD and the authors underline the importance of local reference values for the interpretation of thyroid volumes in the sense of goitrous or non-goitrous. They also state that conclusions with regard to absence or presence of endemic goiter purely from median urinary iodine excretion values is insufficient when studies are performed in areas with marginal iodine deficiency. *(Comment:* I would say also in iodine sufficient areas, see the above results from India.)

THYROID CARCINOMA

Hay et al., Rochester, Minnesota, USA, report their 8 year experience with percutaneous ethanol ablation

(PEA) treatment in 22 selected patients with papillary thyroid carcinoma with 45 recurrent non-life-threatening neck nodal metastasis (NNM). All patients were initially treated by total thyroidectomy, 20/22 had received radioiodine remnant ablation. Treatment discomfort was minimal. At the time of this presentation 90% had post treatment exams with a mean follow-up of 25 months. As compared to initial mean volume of nodal metastases, average volumes reduced by 84% and 96% at 12 and 24 months respectively. *(Comment:* This is an interesting report. Further follow-up however should give more definite answers, for instance if metastases will vanish completely and if not, will that negatively influence prognosis of subjects.) ***Sarkar et al.,*** New York, New York, USA, performed thyroid imaging with I^{-131} and FDG in 9 patients treated for Hurthle cell thyroid carcinoma over a period of 2–3 years. The patients underwent a total of 12 sets of imaging studies. Both FDG and I^{-131} showed no metastasis in 4 patients. The remaining 5 patients had a total of 8 FDG studies that were positive for metastases in lungs, lymph nodes, bone, and kidney. Serum TG was elevated in all these patients during high TSH. I^{-131}-imaging was positive only in 1 patient. These preliminary results suggest the necessity of routine FDG-PET in this type of patients. ***Movshovich et al.,*** New York, New York, USA, analyzed I^{-131} whole body scans in 24 patients with metastatic Hurthle cell carcinoma and found in 50% of these patients radioactive iodine avid metastasis on either diagnostic or post-therapy whole body scanning. *(Comment:* I suggest that for the moment in thyroid Hurthle cell carcinomas both I^{-131}- and FDG-imaging may be necessary.) ***Sharaf et al.,*** New York, New York, USA, hypothesized that an isolated neck recurrence, especially in older patients, is not a trivial event and is often followed by disease progression. They determined retrospectively long-term clinical outcome in 59 patients with papillary thyroid carcinoma treated for an isolated neck recurrence who were declared free of disease after initial treatment. After detection of recurrence the median follow-up was 4 years (mean 7 years range 1–22 years). At the time of final follow-up 54% of patients were again declared free of disease, 20% had persistent stable disease, 12% had locally progressive disease, and 14% had subsequently developed distant metastases. From their analysis the authors found that in patients older than 45 years ultimate distant metastases developed in 19% vs 9% when younger than 45 years ($p = 0.004$). *(Comment:* Thus it seems that the presence of isolated lymph node metastasis in the neck in papillary carcinoma is not that innocent after all!) ***Taguba et al.,*** Cleveland, Ohio, USA, investigated the sensitivity and specificity of TSH-receptor (TSHR) mRNA serum measurement in 38 patients with well differentiated thyroid carcinoma, previously treated with near total thyroidectomy, and compared results with Tg mRNA serum signals. No TSHR or Tg mRNA signals were detected in 10 controls and in 7/8 patients with benign thyroid disease. In the patients with treated carcinoma they found the diagnostic sensitivity of TSHR- and Tg transcripts to be equal i.e. 67%. Diagnostic specificity, positive and negative predictive values for TSHR mRNA signals were 97, 86, and 93% respectively, and for Tg mRNA signals 90, 67, ad 90% respectively. Overall concordance with RAI scans for TSHR- and Tg mRNA were 89% and 84% respectively. *(Comment:* I would not be surprised if a combination of these two tests would give even better results. However the number of subjects in particular in the control groups is very small.) ***Chen et al.,*** Washington DC, New York-New York, and Los Angeles, California, USA, determined if rhTSH testing in patients with recurrent thyroid carcinoma would enhance clinical accuracy of measurement of Tg mRNA. For this purpose 75 patients undergoing screening for recurrent thyroid carcinoma were evaluated. Presence of thyroid tissue was defined as uptake on rhTSH I^{-131} scan, detectable Tg immunoassay, positive post-therapy scan, and/or pathologic evidence of thyroid tissue. Using a value of 1.6 Tg-18S as a cut-off, sensitivity and specificity were 75% and 74% respectively and without rhTSH stimulation 50% and 72%.

Furlan et al., Toronto, Canada, analyzed fine needle aspiration biopsy (FNAB) and frozen section (FS) test performance for well-differentiated thyroid carcinoma. Between 1998 and 2000, 268 patients underwent FNAB and FS for thyroid carcinoma and/or benign thyroid nodule. Test accuracy was 70.1% for

FNAB and 65.7% for FS in thyroid carcinoma. FS sensitivity and specificity were 35% and 99.2%, and for FNAB these values were 82.1% and 57% respectively. ***Sievert et al.,*** Meneola, New York, Chapel Hill, North Carolina, Jamaica, New York, Elmhurst, New York, USA, compared tumor recurrence and survival in patients undergoing extensive surgery, n = 27, and lobectomy, n = 18, for differentiated thyroid carcinoma in a retrospective study. Seventy-four percent and 72% respectively of patients received RAI. Patients were diagnosed between 1980 and 2000. Local recurrences were found in 6/27 (22%), and 3/18 (17%) respectively, being not significantly different. Neither was there any difference between the two groups with regard to Kaplan-Maier survival analysis using time to recurrence as an endpoint. *(Comment:* This study has several limitations: It is a retrospective study. It is not indicated on what basis patients were selected for lobectomy or extensive surgery. The number of patients is small and the follow-up time is limited. My personal opinion is that (near) total thyroidectomy should always be performed in patients with differentiated thyroid carcinoma irrespective of the expansion of the tumor as long as there is controversy about the necessary extensiveness of the operation.) ***Sheikh et al.,*** New York, New York, USA, tested the efficacy of I^{-124} in estimating the radiation dose to individual lesions in patients selected for treatment with I^{-131}. They did a pilot study in 5 patients and administered 148 MBq I^{-124} and obtained PET scans at 4, 20, and 44 hours. Patients were subsequently treated with I^{-131}. There was a high concordance of individual lesions between I^{-124} diagnostic- and I^{-131} post therapeutic scans. The variation of predicted radiation dosis observed ranged widely between 0.003–0.85 cGy/MBq. From the results the authors conclude that I^{-124} is an important new agent in the evaluation of thyroid patients who are likely to receive a therapeutic dose of I^{-131} in that it can provide accurate estimates of the radiation dose to the individual lesions. ***McGriff et al.,*** Bethesda, Maryland, USA, did a MEDLINE and EMBASE systematic literature search (1934–2001) concerning the question if T_4 suppression therapy is beneficial in patients treated for thyroid carcinoma. They identified 24 clinical trials out of which only 9 studies met the inclusion criteria. Out of a combined cohort of 3060 patients, 2101 patients (69%) were reported as being on T_4 suppressive therapy. The weighted average of the mean periods of follow-up for the combined cohort was 9.4 years. The analysis showed that the group of patients on T_4 suppressive therapy had significantly less major adverse clinical events when compared to patients not being on T_4 suppressive therapy ($p = 0.001$). *(Comment:* The authors consider their results still preliminary as they conclude that more large-scale studies, either prospective or derived from on-going registries are needed to better define the effect of T_4 suppression on the clinical course.)

D'Avanzo et al., San Francisco, California, USA, compared prognostic scoring systems including TNM, EORTC, AGES, AMES, and MACIS in a selected group of 86 patients with treated follicular thyroid carcinoma. A number of 19 out of 86 patients died from carcinoma with a mean follow-up period of 9 years. Kaplan-Meier analysis indicated that all scoring systems predicted survival time, but that the MACIS classification was the best predictor. ***Robbins et al.,*** New York, New York, USA, retrospectively analyzed, in patients who underwent total thyroidectomy for thyroid carcinoma, the efficacy of thyroid remnant ablation after off T_4 for 4–6 weeks following thyroidectomy or on T_4 and receiving rhTSH in 45 and 37 patients respectively. Successful ablation was found in 38/45 (84.2%) and 32/37 (86.5%) of patients. The authors conclude that the choice of preparation for a remnant ablation should be made on considerations other than efficacy, such as quality of life, cost and convenience. ***Golger et al.,*** Toronto, Ontario, Canada, assessed the efficacy of a 3 weeks withdrawal of T_4 suppression therapy in 146 patients treated for differentiated thyroid carcinoma. They found that in 128/146 (88%) of patients TSH was >20 mIU/L and in 87/146 (60%) >40 mIU/L. Assessment of quality of life showed that the degree of this disability was tolerated well by most patients. The authors suggest that 3 weeks of T_4 withdrawal is a useful first line test and in those patients with insufficient TSH response, hrTSH stimulation may be considered. ***Baloch et al.,*** Philadelphia, Pennsylvania, USA, compared inter-

institutional results (i.e. outhouse diagnosis of referred patients with in-house diagnosis) of thyroid fine needle aspiration biopsies (FNAB) in 183 patients. In 28/183 (26%) patients significant disagreements were noted. In 16/183 (15%) the diagnosis was changed from benign to malignant and in 12/183 (11%) the reverse was the case. Histologic follow-up was available in 109/183 cases and overall accuracy of outside diagnosis was 73% and of inside diagnosis 85%. *(Comment:* This is not de first publication on discrepancies between cytological diagnoses. Obviously many factors may explain differences, probably one of the most important being the grade of experience of the cyto-pathologist. Maybe the solution to this problem is to create national centers for cytologic diagnosis instead of having this done in one's own hospital.) ***Fatemi et al.,*** Los Angeles, California, USA, analyzed long-term recurrence risk in 44 patients treated (near total thyroidectomy, I^{-131} remnant ablation and absence of Tg antibodies) for papillary thyroid carcinoma. At the end of a median follow-up of 7.6 years patients were classified as disease free or recurrent/persistent disease. In this study the question was asked whether the long-term risk for recurrence or persistence was different in patients with stimulated serum Tg values < 1.0 ng/ml vs values between 1–10 ng/ml. The results showed that risk for recurrence or persistence did not differ in both groups. *(Comment:* I consider these results as preliminary mainly because the follow up period is relatively short for a tumor that generally grows so slowly.)

Bhala et al., Rochester, Minnesota, USA, studied 23 patients with Cowden disease (19 females), mean age at diagnosis 44 years. Cowden disease is a benign/malignant tumor predisposition syndrome of multiple organs, due to mutations of the PTEN gene. Twenty-one out of 23 (91%) patients had evidence of thyroid disease and in 17/21 the thyroid diagnosis predated the diagnosis of Cowden disease. Twenty/twenty-one patients underwent thyroidectomy. Pathologic diagnosis revealed 6/20 multinodular goiter, 10/20 follicular adenoma, and 4/20 thyroid carcinoma. ***Tuttle et al.,*** New York, New York, and Washington, DC, USA, tested the hypothesis that vascular endothelial growth factor (VEGF) would be higher in patients with recurrent or persistent thyroid carcinoma than those cured after treatment and also that TSH would stimulate VEGF levels further in patients with recurrent/persistent disease. Their study comprised 69 patients with differentiated carcinoma including 21 patients with no evidence of disease and 48 patients with local or distant metastases. They found that serum VEGF is significantly elevated in patients with metastatic differentiated carcinoma, but not in those with poorly differentiated thyroid cancer metastases. TSH did not appear to stimulate VEGF in any group of patients. *(Comment:* The mean level of VEGF in patients with metastatic disease was substantially higher (416 ± 62 pg/ml) than in patients without disease (185 ± 25 pg/ml) suggesting little overlap.) ***Robbins et al.,*** New York, New York, USA, measured the clinical accuracy of rhTSH stimulated Tg in a group of 368 patients with low risk recurrence for differentiated thyroid carcinoma. Patients who had not had a remnant ablation, those with TSH-suppressed Tg levels > 2 ng/ml, those with distant metastases, all with TNM stage III or IV and all with aggressive histology, were eliminated from the study. Of the remaining 114 "low-risk" patients 91/114 had stimulated Tg levels < 2 ng/ml, 85/91 a negative diagnostic WBS that was positive in 6/91. It was noted that these 6 patients also prior had an abnormal diagnostic WBS. From their results the authors conclude that when prior diagnostic WBS is negative in low-risk patients, Tg response to rhTSH is sufficient to monitor for residual disease.

Fatourechi et al., Rochester, Minnesota, USA, determined the effect of RAI therapy in 20 patients who were Tg-positive, but diagnostic scan-negative after initial treatment (thyroidectomy and RAI remnant ablation) for follicular cell derived thyroid carcinoma. Two groups could be discerned, one group showing macro-metastases (n = 13) and another group showing only micro-metastases (diameter < 1 cm) (n = 7). Follow-up of the total group was 33 months. In patients with macro-metastases, tumor mass progressed substantially during follow-up as did serum Tg. However, in the group with micro-metastases patients remained stable both on tumor

mass and serum Tg. *(Comment:* Although follow-up is really short in these patients and the number of patients small, these preliminary results suggest that in patients with micro-metastases tumor cells remain dormant or at least grow at a non detectable rate for the time of observation.)

THE CHERNOBYL ACCIDENT

Ostapenko et al., Minsk, Belarus, New York, New York, Rockville, Maryland, USA, report the correlation between urinary iodine concentration and the following: serum Tg levels, thyroid volume and the presence of thyroid carcinoma and thyroid nodules, in 11,200 Belarusian subjects who were under the age of 18 at the time of the I^{-131} fallout. Moderate iodine deficiency (20–50 μ/L urine) was present in 27.3% and severe iodine deficiency (< 20 μg/L) in 11.8%, and normal iodine excretion (>100 μg/L) in 32.1%. The mean serum Tg concentrations were 15.5, 20.4, and 10.3 ng/ml respectively. Antithyroid antibodies were similar in the three groups. When the two groups with iodine deficiency were taken together, thyroid volume was increased about 3 times in the iodine deficiency group as compared to the control group, the prevalence of thyroid nodules and thyroid carcinoma was not different in iodine deficiency and sufficiency, 7.3% vs 7.2%, and 0.46% vs 0.39% respectively. *(Comment:* Contrary to the general notion, this study does not confirm that development of benign and malignant nodules after exposure to I^{-131} is increased when iodine deficiency is present.) ***Yamashita et al.,*** Nagasaki, Japan, completed a 10-year screening program examining more than 200,000 children around Chernobyl and found the highest prevalence of thyroid nodules and carcinoma in the Gomel region in Belarus. Therefore further studies were conducted in the Gomel area comparing children with regard to development of thyroid carcinoma either born before or after the Chernobyl accident. A total group of 21,000 children were examined. No increase in carcinoma development was seen in children born after the accident. The authors therefore conclude that short-lived radioactive fallout is highly suspected to have induced thyroid carcinoma in children at the time of the accident.

MISCELLANEOUS

Singh et al., Los Angeles, California, USA, previously published that chronic administration of calcium carbonate reduces T_4 absorption and increases serum TSH levels (JAMA 283:2822-2825,2000). They now report the acute effect of administration of 2.0 g of calcium carbonate on the absorption of 1 mg LT_4 in seven normal volunteers. They found a mean reduction in T_4 absorption from 83.7% (without calcium carbonate) to 57.9% (with calcium carbonate), 120 minutes after administration.

Wilcox et al., San Juan Capistrano, California, USA, tested the hypothesis that automated, hormone analog free T_4 methods measure concentrations of protein bound T_4 rather than free T_4. The assays studied were Access® (Beckman), ACS 180 (Bayer), AxSym (Abbott) and Immno 1 (Bayer). They found reproducible results in three experiments for each kit and the results showed that in no assay free T_4 was measured but rather protein bound T_4 concentrations irrespective if they used albumin, transthyretin or TBG as the T_4 binding-protein. The results also showed that these kits were not able to measure free T_4 accurately, when all T_4 was in the free moiety. (For further reading of work of this group on this subject, see JCEM:79,76-79,1994, and JCEM 79,1373-1375,1994.)

Fatourechi et al., Rochester, Minnesota, USA, retrospectively studied if corticosteroid therapy modified the long-term outcome of subacute thyroiditis. They analyzed 97 patients fulfilling their criteria as having subacute thyroiditis who were diagnosed between 1970 and 1997. Thirty-four/ninety-seven patients were treated with a median dose of 40 mg prednisone/day, range 15–120 mg, duration range 6 days to 6 months. In 40/97 of patients NSAIDs were administered and in 23/97 no NSAIDs or corticosteroids were used. Of the patients treated with corticosteroids 23% developed permanent hypothyroidism, whereas this was only in 8% of the non-corticosteroid group. The authors conclude that administration of the corticosteroids does not prevent development of hypothyroidism. *(Comment:* As this is a retrospective analysis, these data should be

interpreted with care in the sense that patients treated with corticosteroids might have been suffering from more severe thyroiditis than the non-corticosteroid group. In other words, although the conclusion of the authors per se is correct, it is certainly not ruled out that administration of corticosteroids can prevent development of permanent hypothyroidism in a subset of patients.)

Sellin et al., Houston, Texas, USA, report the effect of T_3 supplementation in 4 patients previously treated (surgery and/or irradiation) for suprasellar lesions and subsequently developing hypothalamic/pituitary dysfunction. It is known that this type of patients develops "hypothalamic" obesity resistant to almost all forms of therapy. After T_3 supplementation resulting in supraphysiological serum T_3 concentrations without symptoms or signs of thyrotoxicosis, all 4 patients lost weight (range 4.5–10 kg between 6 weeks and 15 months). *(Comment:* Of course it should be documented if in the long run weight reduction persists and if side effects of T_3 administration (e.g. on heart and bone) may still become evident.) ***Woeber,*** San Francisco, California, USA, determined serum T_4, T_3, and the T_4-T_3 ratio in 20 normal individuals (group A), 18 subjects with chronic autoimmune thyroiditis but normal TSH (group B), and 35 patients who became hypothyroid due to autoimmune thyroiditis and were on T_4 substitution with normal serum TSH (group C). They found that in groups A and B serum free T_4 and free T_3 were similar but free T_4 was significantly higher in group C, while the mean free T_3 was lower in group C as compared to groups A and B. Consequently, the molar ratio between free T_4 and free T_3 was higher in group C than in group A and B. The author concludes that in patients with primary hypothyroidism T_4 administration to normalize TSH may not be sufficient to normalize T_3 as well. *(Comment:* This finding has been reported earlier several times. It is about time that thyroid hormone preparations are being tested that are a combination of T_4 and T_3 in slow released form and in a ratio such that beside a normal serum TSH also normal free T_4 and free T_3 levels are reached.)

Knudsen et al., Copenhagen, Denmark, analyzed thyroid volume in 3,712 randomly selected women and found that in users of oral contraceptives (OC) the mean thyroid volume was 11.1 ml vs 12.1 ml ($p < 0.001$) in non-users as determined by ultrasound. Use of OC was thus associated with a decrease in thyroid volume (odds ratio 0.53, 95% confidence interval 0.37–0.74) and of palpable and visible goiter odds ratio 0.24 (0.07–0.81). Serum TSH in users was 1.35 vs 1.24 mU/l, in non-users ($p = 0.02$), and correspondingly serum Tg was higher among users than in non-users. The authors speculate that the lower thyroid volumes and goiter rate in OC could be due to suppression of a specific endogenous estrogen metabolite(s) or due to suppression of LH and FSH that have been demonstrated to possess stimulatory effects on the TSH receptor. *(Comment:* No explanation is provided for the statistically increased mean serum TSH in OC users and its apparent lack of effect on thyroid volume.)

Kokandi et al., Cardiff, Wales, UK, attempted to define the immunological events that lead to postpartum thyroid dysfunction in 50% of women who were found to be thyroid peroxidase antibody positive. Their analysis concentrated on the Th2 to Th1 immune switch thought to occur peripartum. When measured at 36 weeks antenatally, they found IL-4 expression by CD3+ and CD4+ lymphocytes to be significantly higher in the group that developed postpartum thyroid dysfunction as compared to those who remained euthyroid. Similarly IFN-gamma expression at this time point was higher in the thyroid dysfunction group. The results suggest a difference in Th2/Th2 balance prepartum in women destined to develop postpartum thyroid disease.

Two groups, ***Kon et al.,*** Chicago, Illinois, USA, and ***Gourgiotis et al.,*** Bethesda, Maryland, USA, report in total 9 patients who suffered from painful Hashimoto's thyroiditis that did not respond to anti-inflammatory agents. The patients underwent near-total or total thyroidectomy and prompt relieve of symptoms occurred in most patients. *(Comment:* This therapy is effective for this small subgroup of patients. It is however necessary to have the operation done by a very experienced thyroid surgeon, as thyroid fibrosis may be extensive in these cases.)

Pearce et al., Boston, Massachusetts, Washington, DC, and Atlanta, Georgia, USA, analyzed the effects on the thyroid of chronic iodine excess in peace corps volunteers between 1995 and 1998 when exposed to ingestion of severe iodine excess of 50–90 mg/day. Results were compared on an average of 30 weeks following correction of iodine intake. During iodine excess the mean serum iodine concentration was 30.6 μg I/dl and decreased to 8.4 μg I/dl after correction of iodine intake. In 47/101 subjects (46.5%) goiter was present during iodine excess but decreased to 30% when iodine intake was corrected. Serum TSH was suppressed in 5/100 and elevated in 22/100 subjects. These figures were during normal iodine intake 14/91 and 2/91 respectively. The mean TPO antibody titers were higher during iodine excess than afterwards. *(Comment:* Although abnormalities diminish on the average, 30 weeks following correction of iodine intake, substantial thyroid dysfunction was still present. I hope that we will hear the further follow-up of these abnormalities.)

Silva et al., Sao Paulo, Brazil, compared the efficacy of RAI treatment in multinodular goiter in 10 patients pretreated with rhTSH and compared the results in 8 patients treated with radioiodine only. The rhTSH patients had a significant higher mean Tg peak after RAI and a significant longer biological half-life of RAI. In both groups thyroid volume decreased by 68% to 86% after 6 and 12 months. The authors conclude that rhTSH stimulated RAI treatment may be useful as it results in more radiation delivered to the thyroid tissue as reflected by the longer biological half-life of RAI and the higher Tg peak after RAI administration. *(Comment:* The authors suggest that hypothyroidism however may be more frequent in the rhTSH group and my query is if due to stimulation of I^{-131} uptake in the thyroid, circulating protein-bound RAI may be higher in these patients, leading to a higher dose of whole body irradiation.)

Bennedbaek et al., Odense and Roskilde, Denmark, tested feasibility and efficacy of US-guided interstitial laser photocoagulation (ILP) in 16 euthyroid patients with benign thyroid nodules. The mean thyroid nodule volume decreased from 10 ml to 5.4 ml after 6 months. Thyroid function remained unchanged. The treatment was well tolerated except for a transient mild local pain. The authors conclude that these preliminary results are promising as an alternative non-surgical therapy for benign solitary solid cold nodules.

Schwartz et al., Rochester, Minnesota, USA, analyzed the efficacy of local corticosteroid therapy for thyroid dermopathy in 178 patients. In this retrospective study from the period of January 1969 to November 1995 the average age at diagnosis was 53.1 years and the average follow-up 7.9 years. Topical corticosteroids were used in 53.9% of cases, especially the more severe ones. Dermopathy was pretibially localized in 99.4% of patients. Thirty-four percent of patients not treated with corticosteroids experienced a complete remission versus 18.7% who did receive local corticosteroid application. However, when complete and partial remission rates were taken together, no significant differences were present between the two groups. The conclusion of the authors is that local application of corticosteroids is questionable. *(Comment:* I am not sure that this conclusion is correct as the treatment group had significantly more severe dermopathy. As long as this matter has not been settled in a double blind controlled randomized study, I am inclined to still apply corticosteroids locally in patients with severe dermopathy.)

Yokozawa et al., Kobe, Japan, report the results in 22 (18 females) patients treated with percutaneous ethanol injection (PEI) for Graves' disease in 1979 and followed until 2001. In 8/22 patients euthyroidism was achieved during a mean follow-up period of 35 months, 12/22 patients were on antithyroid drugs during follow-up, and 2/22 were treated with I^{-131}. *(Comment:* In this preliminary study 14/22 patients were not rendered euthyroid by PEI. I consider this therapy as experimental for the moment. Further results are awaited to ascertain whether PEI is a suitable therapy for Graves' disease.)

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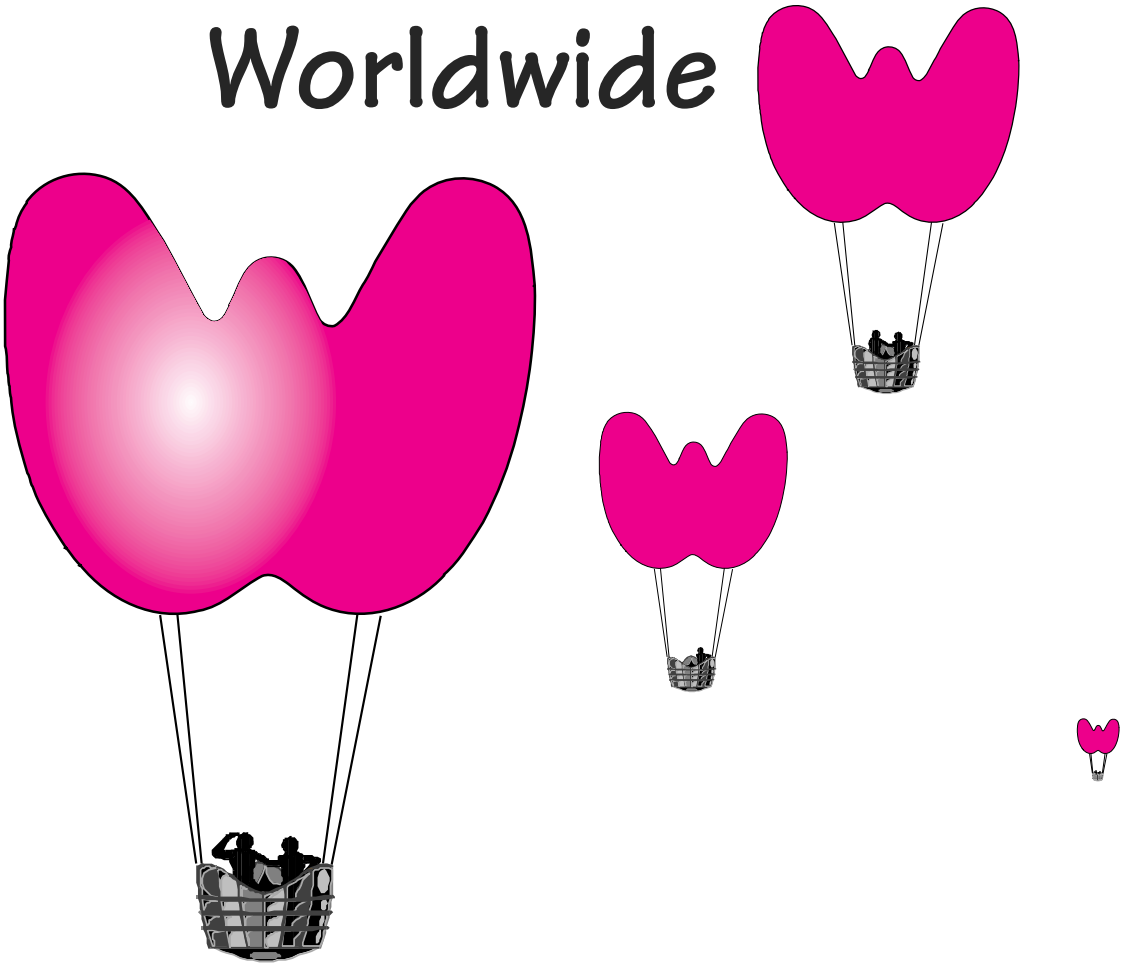
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