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Report of the 12th International Thyroid Congress October 22-27,2000, Kyoto, Japan

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



Heian-Shrine, Kyoto, Japan

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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 12th International Thyroid Congress

The meeting was attended by about 1000 scientists from all over the world. About 600 reports were communicated orally or by poster.
This report covers those communications that have a direct clinical bearing.

THYROID CARCINOMA

Wartofsky et al., Washington, DC, USA, evaluated the clinical utility of rhTSH-stimulated thyroglobulin testing without a thyroid scan in the follow-up of patients with differentiated thyroid carcinoma. In this multicenter study patients were included who completed primary therapy consisting of near-total or total thyroidectomy and remnant ablation between 1 and 10 years prior to enrolment and receiving thyroid hormone suppression therapy with a TSH level of < 0.5 mU/ml and a Tg level < 5 ng/ml. The still ongoing study is aimed to include a total of 500 patients. The interim data were as follows: of 118 patients (mean age 47.7 years) 64 % had papillary, 13 % follicular, 20 % papillary/follicular, and 3 % Hürtle cell carcinoma. After rhTSH 14 % had elevations in Tg of at least 2 ng/ml. Although no further data are present, the authors conclude that rhTSH-stimulated Tg testing may be useful in the follow-up of such patients, but further data are required to definitely define clinical utility. (Comment: Indeed this is a very preliminary study in that for instance no information is available how these results compare to Tg response after "classical" T_4 withdrawal.) Also ***Lippi et al.,*** Pisa, Italy, studied the usefulness of rhTSH stimulation in 40 patients after total thyroidectomy and ^{131}-I ablation for differentiated thyroid carcinoma. All patients had undetectable serum Tg on T_4 TSH suppressive therapy. Results of rhTSH administration were compared with serum Tg levels two months after T_4 withdrawal. In 20/40 patients Tg became detectable after rhTSH with a peak value 3 days after injection. Metastases were detected in all these patients. Serum Tg became also detectable after T_4 withdrawal in the same patients and levels were usually higher than after rhTSH. Similarly, serum Tg remained undetectable in the other 20 patients in whom serum Tg was also negative after rhTSH. (Comment: The number of patients studied is limited but if these results are confirmed in more patients, T_4 withdrawal in the follow-up of patients treated for differentiated thyroid carcinoma may be replaced by rhTSH stimulation.) ***Collins et al.,*** Chicago, IL, USA and Naples and Catanzaro, Italy, investigated RET-PTC rearrangements in 30 patients with papillary thyroid carcinoma who received neck radiation treatment during childhood and in 34 patients with papillary thyroid carcinoma without a radiation history. They found in 86.7 % of the irradiated group RET rearrangement versus 52.9 % in the non-irradiated group ($p = 0.006$). The authors conclude that although RET rearrangement is not restricted to tumors from irradiated patients, the increased prevalence supports the strong association with radiation exposure. ***Fatemi et al.,*** Cantara St. Panorama City and Santa Monica, CA, USA , tested the changes of TgAb in 27 patients with differentiated thyroid carcinoma over a median period of 5.6 years. They found that in 12 patients TgAb became negative who were judged to be disease free. Seven patients, in whom metastases persisted, maintained constant TgAb levels whereas in 7 other patients with progressive metastases TgAb levels increased. The authors conclude that persistent loss of TgAb is consistent with the disease free

state if serum Tg is also undetectable. In general they find that serum TgAb patterns appear to reflect changes in circulating Tg antigen and can serve as a tumor marker in patients with differentiated thyroid carcinoma. Furthermore, they found that an increase in TgAb following radioactive iodine treatment is a common phenomenon and may be a marker of therapeutic benefit. (Comment: These findings are interesting and readily explainable on the basis of the notion that TgAb disappears from the circulation when the antigen Tg becomes negative.) ***Park et al.,*** Seoul, Korea, did a similar study in a total of 147 consecutive patients with differentiated thyroid carcinoma. Among the different groups that they discerned there were two groups of patients with TgAb, one without detectable Tg and another with detectable Tg. They found that in both groups persistently elevated TgAb after total thyroid ablation indeed might point to recurrent carcinoma. These authors recommend routine TgAb measurement especially in patients with a low Tg level after total thyroid ablation. ***Hamilton et al.,*** Seattle, Washington, USA, compared sensitivity of carcinoma detection using physical examination combined with ultrasound in 3,430 subjects of the Hanford Thyroid Disease Study. Fine needle aspiration biopsy was offered to persons with palpable thyroid nodules or with non-palpable nodules with a diameter of at least 1.5 cm. A total of 243 patients had palpable nodules. Of the remaining 3,187 subjects without a palpable nodule, 1,165 had 1 or more nodule on ultrasound including 27 subjects with a total of 30 nodules with a diameter ≥ 1.5 cm. Adequate aspiration was obtained in 19/27 subjects revealing benign nodules in 18/19. From these and other data the authors conclude that, while ultrasound is clearly more sensitive in detecting anatomical abnormalities than physical examination, their results suggest that the use of ultrasound as a routine procedure is unlikely to yield a large number of cancers not detected by careful palpation. (Comment: These results are very welcome to me, as routine ultrasound examination of the thyroid is increasingly performed and leads to increased risks of morbidity (fine needle aspiration) and certainly increased medical costs without substantial benefit. Routine thyroid ultrasound scanning in patients without palpable abnormalities of the thyroid should be discouraged. On the other hand, in a recent report by ***Marqusee et al.,*** Annals of Internal Medicine 133, 696, 2000, it is shown that the yield of detection of carcinoma, in subjects referred to a thyroid clinic because of *suspected nodules,* is increased using ultrasound scanning.) ***Ceccarelli et al.,*** Pisa, Italy, performed whole body scanning in 315 patients after total thyroid ablation for thyroid carcinoma and showing undetectable Tg after discontinuation of TSH-suppressive T_4 treatment. In all those patients whole body scanning was negative for metastatic disease, but in 120 some uptake was present in the thyroid bed that was subsequently treated with another ^{131}I dose. Of those patients 99.4% showed complete disappearance of thyroid bed uptake. The authors conclude that control whole body scanning is unnecessary in patients who have undetectable Tg off T_4 therapy. (Comment: These results are very useful and not unexpected as it is accepted that in general serum Tg is sensitive and specific in the detection of residual/recurrent differentiated thyroid carcinoma.) ***Sasou et al.,*** Morioka, Japan, confirmed that in papillary thyroid carcinoma very often multifoci are present in the thyroid. They examined total thyroids removed in 239 patients with papillary thyroid carcinoma. Multifoci were found in 61.1%: in the same lobe 23.0%, opposite lobe 13.0%, and both lobes 25.1%. (Comment: These findings are not new and show again that multifocity is present in the majority of thyroids harboring papillary carcinoma. Another matter, however, is to what extent these multifoci will become biologically active if left in situ. However, the general opinion is that (near) total thyroidectomy, certainly in nodules with diameter >1cm, is the first treatment option in papillary thyroid carcinoma.) ***Lee et al.,*** Seoul, Korea, tested the utility of preoperatively FDG-PET scanning in 22 patients

with ^{131}I scan negative papillary thyroid carcinoma. In 85 cervical lymph node groups dissected, 56 lymph node groups revealed metastases on histological examination. The sensitivity and specificity of FDG-PET to detect these metastases was 80% and 83% respectively. The authors conclude that in patients with ^{131}I negative scans preoperative FDG-PET scanning is useful in detection of lymph node metastases. ***Nilsson et al.,*** Göteborg and Sahlgrenska, Sweden, studied the mechanism of stunning (inhibition of iodine uptake by thyroid tissue after diagnostic ^{131}I whole body scanning in patients treated for differentiated thyroid carcinoma) in pig thyrocytes in primary culture. They found that iodine uptake immediately after ^{131}I exposure was not inhibited but was decreased after 3 days. The inhibition was counteracted by perchlorate or lack of TSH-stimulation during ^{131}I exposure. Their results indicate that the stunning effect is caused selective inhibition of iodide transporting mechanisms. ***Moncayo et al.,*** Innsbruck, Austria, tested treatment of metastatic thyroid carcinoma with Yttrium labeled somatostatin analogs in 19 patients with known metastases (2 follicular, 7 papillary, 3 oncocytic, 4 medullary, and 3 anaplastic carcinoma) in whom ^{131}I whole body scanning was negative. Uptake in tumor tissue was found in 15 patients with tracer Yttrium labeled somatostatin and they were so far treated with 1–7 cycles Yttrium labeled somatostatin with doses of 925 MBq or 1,295 MBq per cycle. The preliminary results show improvement in 4 patients, stable disease in 5, and progression in 2, while 4 patients died. (Comment: Although preliminary, these results show that this therapeutic approach may be of value in patients who do not show ^{131}I uptake in metastatic tissue.)

OPHTHALMIC GRAVES' DISEASE (OGD)

Heufelder et al., Marburg, Germany, treated 16 patients with OGD, who were resistant to treatment with prednisone + orbital irradiation, with methotrexate 15 mg/week. Response to therapy was assessed by clinical activity scores (CAS) and NOSPECS. A successful outcome was observed in 12 patients at 6 weeks of therapy, largely due to changes in soft tissue involvement, eye muscle motility and proptosis. TRAK measurements that were elevated in 15/16 patients prior to therapy declined markedly in 13/15 patients. Serious side effects were not observed and the authors conclude that methotrexate therapy may be effective and well tolerated in active OGD patients who are resistant to prednisone + orbital irradiation. (Comment: This is a new development in treatment of OGD that is most welcome.) ***Stamato et al.,*** Sao Paulo, Brazil, compared the effectiveness of 1.5 mg/day colchicine for 3 months versus 0.75 mg/kg/day prednisone for 1 month and subsequently decreasing to zero in 2 months, in two groups each of 10 patients with active OGD who were euthyroid for at least 3 months. Success rate was assessed by clinical activity score (CAS) and MRI. All patients showed symptomatic relief and improvement in appearance. Inflammatory symptoms decreased in 100% of orbits in colchicine treated patients and in 85% in prednisone treated patients. CAS decreased in 10 orbits (50%) and 11 orbits (55%) of these groups respectively. MRI abnormalities decreased similarly in both groups. No side effects of colchicine were seen. (Comment: The following step is to evaluate if colchicine has an effect on CAS in prednisone resistant patients with OGD and vice versa.) ***Rendl et al.,*** Würzburg, Germany, performed iodine-123-interleukin-2 orbital scintigraphy in 2 patients with active OGD, 2 patients with inactive OGD, and 4 controls. Uptake in active OGD orbits was two times higher than in controls, while uptake in inactive OGD was not different from controls. (Comment: This study shows results that are interesting but very preliminary. If confirmed, interleukin-2 may be of use both in diagnosis. What about basiliximab [IL-2 receptor antagonist] for treatment in scintigraphy – pos. patients?) ***Inaba et al.,*** Osaka, Japan, measured retinal blood flow by pulsed Doppler mode at the branch of the central retinal artery from which a resistant index (RI) was calculated in 47

patients with treated OGD versus 70 age- and sex-matched normal controls. RI and proptosis were positively correlated in OGD subjects but not in controls. Antithyroid drug treatment in 20 Graves' disease patients with OGD significantly reduced RI during the course of medication. The reduction in RI during drug treatment significantly correlated with pulse pressure and ultrasound distensibility of the carotid artery. Patients with OGD only to fat accumulation had normal RI in contrast to patients with extraocular muscle enlargement. The authors suggest that RI changes may result from cardiovascular effects and/or activity of retro-obital inflammation in extraocular muscles. ***Terwee et al.,*** Amsterdam and Utrecht, The Netherlands, discussed interpretability of changes in quality of life assessment in OGD patients in different categories depending on aim of treatment i.e. improvement of visual functioning or of appearance. The patients were divided in different treatment groups such as radiotherapy, decompression, eyelid lengthening, and blepharoplasty. On the basis of their analysis and depending on the setting of the study they suggest that a change in 6 points of this score indicates a significant change in daily functioning of patients for less than major therapies. For major therapies, however, at least a change of 10 points indicates significant improvement. ***Prummel et al.,*** Amsterdam and Utrecht, The Netherlands, performed a randomized placebo-controlled study on the beneficial effects of radiotherapy in patients with mild OGD. Eighty-eight consecutive patients with mild OGD, defined as mild eye muscle motility impairment and absence of severe soft tissue swelling, proptosis, or impaired visual acuity, were either irradiated (10 daily fractions of 2 Gy each) or sham irradiated. All patients were euthyroid for >2 months and untreated for OGD. Radiotherapy resulted in a success rate of 52% versus 27% in sham irradiated subjects. The quality of life score improved similarly in both groups. The authors conclude that, although radiotherapy is effective, in this group of patients the improvements are too modest to justify its routine use in such patients. ***Wakelkamp et al.,*** Amsterdam, The Netherlands, measured soluble factors of adhesion molecules in 62 patients with untreated OGD and 62 controls matched for sex, age and smoking habits. The following factors were measured: sICAM-1, sVCAM-1, and sELAM-1. They found that these three factors were elevated in OGD as compared to controls, and that smoking is associated with increased sICAM-1 and lower sVCAM-1 levels independently of the presence or absence of OGD. Furthermore, sICAM-1 levels correlated with severity of OGD. (Comment: These results are interesting as adhesion molecules play a key role in autoimmune inflammatory processes and part of these adhesion molecules can circulate in blood as soluble factors.) ***Marino et al.,*** Pisa, Italy, investigated if thyroglobulin was present in retroorbital tissues of 3 patients with OGD who were operated for decompression and compared the results with extraocular tissue obtained from 2 autopsies of subjects without OGD or thyroid disease. They found intact Tg both in soluble and membrane-associated fractions of orbital tissue extracts in patients but not in controls. An anti-T_4 antibody captured Tg in orbital tissues of patients indicating that this Tg was of thyroidal origin. The investigation was done by the authors as it has been suggested in the past that Tg may migrate from the thyroid to the retroorbital tissues and may act as an antigen in the development of OGD in patients with Graves' disease. (Comment: The theory that thyroglobulin could migrate to the orbita and act as an antigen in the development of OGD was advanced by J.P. Kriss in the early 70's and is still not excluded as a realistic possibility. The number of subjects in the here reported study are very limited but the results are of interest.)

SODIUM IODIDE SYMPORTER (NIS)

Godbole et al., Lucknow, India, studied the expression of NIS in normal and cancerous breast tissue as it is known that iodine accumulation is elevated in breast tumor tissue. They found 4–6 fold increased expression of NIS in breast carcinoma tissue as

compared to normal breast tissue. Plasma inorganic iodine was also increased in breast carcinoma patients as compared to controls. After chemotherapy both NIS expression and plasma iodine levels decreased significantly. The authors suggest that their finding may open the way to radioactive iodine treatment in patients with breast carcinoma. ***Smit et al.,*** Leiden en Wageningen, The Netherlands, transfected human NIS cDNA in human thyroid carcinoma cell lines that lost the capability to concentrate iodine. They could re-establish iodine uptake in these cells that could virtually completely be inhibited by perchlorate. (Comment: These studies open the possibility for transfection of NIS in humans with thyroid carcinoma when tumor tissue has lost its capability to concentrate iodide.) ***Dohan et al.,*** New York, NY, USA, and Budapest, Hungary, investigated NIS expression by immunoblot analysis, immunohistochemistry and flow cytometry in patients with different types of carcinoma. They found expression negative in 1 thyroid medullary carcinoma, and positive in 7/14 thyroid papillary carcinomas, and 4/5 thyroid follicular carcinomas. Furthermore, 9/16 cardia tumors, 3/12 oesophageal carcinomas and 9/16 breast carcinomas showed expression as well. ***Spitzweg et al.,*** Rochester, MN, USA, and Marburg, Germany, tested if it is possible to express NIS functionally in prostate carcinoma in vivo in mice. Xenografts derived from a human prostatic adenocarcinoma cell line were established in athymic nude mice and transfected with NIS cDNA. NIS protein expression in the mice was confirmed immunohistochemically and after intratumoral administration of radioactive iodine. Administration of ^{131}-iodine reduced tumor volume by 75% as compared to control tumors. (Comment: This report is one of the most important ones of this meeting and opens a possibility to treat patients with prostate carcinoma with radioactive iodine after transfection of NIS.)

THE CHERNOBYL ACCIDENT

Ostapenko et al., Minsk, Belarus, and New York, NY, USA, evaluated 5,965 subjects who were less than 18 years of age at the time of the Chernobyl accident and who were living in contaminated areas. Anti-TPO and/or anti-Tg were present in 6.3% of subjects (F/M = 2/1). Anti-TPO only was seen in 3%, anti-Tg only in 1.7% , and anti-TPO + anti-Tg in 1.6% of subjects. In females the prevalence of circulating antibodies was highest being 13.1%. The prevalence of autoantibodies increased with thyroid volume and was present in 10.4% of subjects with multinodular goiter and 18.5% in subjects with thyroid carcinoma. (Comment: This study shows again that not only thyroid carcinoma is increased in children exposed to radioactive fall-out but also autoimmune thyroiditis.) Similar findings were reported by ***Petrenko et al.,*** Minsk, Belarus. They found a prevalence of both TPO antibodies and Tg antibodies of 6.23% in a cohort of 5,179 subjects living in the Gomel district at the time of the accident. The group of 323 subjects with circulating autoantibodies was subdivided in 3 groups depending on the dose radioactivity received: A) >30 cGy; B) 30–100 cGy, and C) >100 cGy. All these subjects were living in an area of mild iodine deficiency. Both in group A and C a positive correlation was found between the level of TPO antibodies and serum TSH. This relationship was not present in group B. Despite this latter aspect these preliminary data suggest a causal relationship between the dose of radioactivity absorbed by the thyroid and the magnitude of autoimmune thyroiditis. ***Reiners et al.,*** Würzburg, Germany, and Minsk, Belarus, reported that since the Chernobyl accident the incidence of thyroid carcinoma in children increased from 0.2 to 4.0 cases per 100,000 in 1995. Since 1996 this incidence is decreasing in children but still increasing in adults: from 2.1 in 1996 to 10.7 in 1999 per 100,000 adults. Between April 1993 and March 2000, 199 children from Belarus with advanced thyroid carcinoma were operated and subsequently treated with ^{131}-I. In 99% papillary carcinoma was found and in 1% follicular carcinoma. Up to now, 169 children received one or more treatments with ^{131}-I. In 142/169 (84%) children a complete remission was

reached, 68% of these children having distant metastases. In the remaining 16% a partial remission was observed. The authors conclude that in these children the prognosis of treated carcinoma is relatively good. (Comment: From this report it is inferred that these tumors readily take up radioactive iodine.) ***Shakhtarin et al.,*** Obninsk, Russia, evaluated the combined effect of iodine deficiency and irradiation to the thyroid in 3 groups of children between 7 and 14 years of age: group 1 consisted of 1,305 girls and 1,255 boys who were living in an area of mild iodine deficiency (median urinary iodine excretion 7.5–10 mg/dl) and were not exposed to radioactive fall-out; group 2 consisting of 449 girls and 439 boys lived in an area of similar iodine deficiency but received irradiation to the thyroid; group 3 consisting of 494 girls and 467 boys received an equal dose of radioactivity as group 2 but iodine deficiency of the area was more severe (median urinary iodine excretion 5.0–7.5 mg/dl). In group 1, diffuse goiter occurred in girls and boys in 7.7% and 7.3% and nodular goiter in 0.6% and 0.2 % respectively. In group 2 these figures are 22% and 23.2%, and 1.8% and 2.5%, while in group 3 they were 35.8% and 31.3%, and 3.8% and 3.2%. (Comment: From these figures one can calculate that the effects of iodine deficiency and irradiation on the development of these thyroid disorders are rather additive than synergistic, while gender is equally affected.) ***Williams et al.,*** Cambridge, UK, Minsk, Belarus, and Kiev, Ukraine, reported that after the Chernobyl accident the observed/expected (O/E) ratio of carcinoma reached a plateau of about 70 in 1997. Ninety-six percent of tumors were papillary carcinomas, the majority showing a largely solid and follicular pattern (SF) and the minority the classic papillary architecture (C). In post-Chernobyl children the proportion of C-type increased with age at operation but remained at less than a quarter of all papillary carcinomas, i.e. much less than found in non-exposed tumors. The SF morphology correlates with ret/PTC3 rearrangement. This type is more likely to cause rapid progression of the tumor. Follicular carcinomas show a small recent increase, maybe because this tumor has a longer latent period than papillary carcinoma. Thus, the incidence of follicular carcinoma may remain increased. ***Saenko et al.,*** Nagasaki, Japan, Pisa, Italy, and Obninsk, Russia, similarly show a prevalence of ret/PTC rearrangements in thyroid papillary carcinomas after the Chernobyl accident. They find however a slightly lower prevalence in Russian children as compared to children from Belarus and Ukraine. ***Bazyltchik et al.,*** Minsk, Belarus, and Würzburg, Germany, tested intellectual development in a group of 235 children from the Gomel region who were exposed to radioactive fall-out after the Chernobyl accident. These children were exposed either in utero or between the age of 0–1.5 years. Results were compared with a group of 105 children from a non-irradiated area. The exposed children were grouped according to the irradiation dose received and results of intellectual performance were tested in these 3 groups. The mean thyroid dose in children with an IQ $\geq$ 110 was 34.6 cGy; in the group with an IQ 90-109, 68.2 cGy, and in the group IQ < 90, 78 cGy. Results between group 1 and group 2, and group 2 and group 3 were all significant $p < 0.01$ and $p < 0.001$ respectively. The mean IQ was significantly higher in children who received a dose < 50 cGy (n = 61) as compared to children who received a dose > 50 cGy (n = 52), 100.0 Points vs 71.7 points respectively ($p < 0.01$). The authors could not find any thyroid function abnormality as assessed on the basis of TSH, FT_4 and FT_3 in any of these groups. They state that further studies including TRH testing and analysis of any differences in social economic environment could explain these differences in intellectual development.

IODINE PROPHYLAXIS

Shan et al., Shenyang and Liaoning, China, investigated the prevalence of overt and subclinical hypothyroidism in 2 rural communities. The inhabitants of one community were still living in

a borderline iodine-deficient area, whereas the other community was subjected to iodine prophylaxis since 1996. Results in the iodine-deficient area: mean urinary iodine excretion 103.1 ug/L, overt hypothyroidism 0.27%, subclinical hypothyroidism 1.91%. Area with iodine prophylaxis: mean urinary iodine excretion 374.8 ug/L, overt hypothyroidism 0.92%, subclinical hypothyroidism 5.08%. The prevalence of TPO antibodies was significantly higher in subclinical hypothyroidism than in euthyroidism in both areas: 19.05% vs 5.26%, and 22.5% vs 3.28% respectively. Tg antibodies showed the same tendency. The authors conclude that during iodine prophylaxis the risk of developing autoimmune hypothyroidism was increased. (Comment: Of course it is of interest to know if this increased risk of hypothyroidism continues on a long-term basis.) ***The same authors*** reported as well the prevalence of overt and subclinical hyerthyroidism in the same areas. The results for the iodine-deficient area were: overt hyerthyroidism 0.44% and of subclinical hyperthyroidism 5.9%. These values were for the area with iodine prophylaxis 0.44% and 6.7% respectively. These values were not significantly different between the two areas. For the two areas the prevalence of TPO antibodies and Tg antibodies in overt hyperthyroidism were 61% and 47%, and 33.3% and 32.4% respectively (no significant differences). Neither were there significant differences in antibody prevalence between the two areas in subclinical hyperthyroidism. (Comment: Contrary to what may have been expected, is no increase seen in the prevalence of hyperthyroidism in the area where iodine prophylaxis was introduced in 1996.) ***Riccabona et al.,*** Innsbruck, Austria, reported changes in thyroid pathology during iodized salt prophylaxis that was introduced in Austria since 1990. Goiter prevalence in school children dropped from 45.9% in 1964 to 3% todate. Mean iodine urinary excretion increased in the same period from 35.9 ug/g creatinine to 145 ug/g creatinine. In patients referred for thyroid pathology, the prevalence of hyperthyroidism due to autonomous adenomas decreased from 12.5% to 3.9% while Graves' disease increased from 1% to 3.5%. Thyroiditis type Hashimoto increased from 0.25% to 9.8%. Hypothyroidism increased from 5% to 25.8% (partially due to more sensitive methods to diagnose subclinical hypothyroidism (23.1% of cases). In thyroid patients referred to the clinic, anatomically normal thyroids increased from 27% to 48%, diffuse goiter decreased from 22.5% to 11% and nodular goiter decreased from 50% to 40%. The incidence of thyroid carcinoma rose from 3.07/100,000/year in 1960 to 7.8/100,000/year in 1995.

IODINE DEFICIENCY

Pretell et al., Lima, Peru, and Darmstadt, Germany, assessed progress of iodine prophylaxis in 11 Latin American countries using the Merck ThyroMobil, able to quickly perform thyroid ultrasonography, to measure thyroid volume and to analyze urinary iodide concentration, as well as iodide concentration in salt. In total 145 sites were selected for analysis, a total of 13,283 school children were assessed for ultrasound and a total of 6,672 school children were assessed for urinary iodide concentrations, whereas a total of 1,352 salt samples were analyzed. The major findings were that, except for Guatemala, all other countries had urinary iodine excretion above 100 ug/l (mean 250 ug/l). In all countries thyroid volumes were less than considered normal by WHO standards for goiter. Only 4 countries had salt iodine content of at least 15 ppm in more than 90% of samples. The general conclusion was that these countries in general show great progress in attacking iodine deficiency using iodized salt, but that there were still areas with persisting iodine deficiency. ***Knudsen et al.,*** Copenhagen, Glostrup and Aalborg, Denmark, investigated the role of iodine intake in the association between smoking and goiter formation in an epidemiological study including 4,649 randomly selected subjects from two areas with different iodine status. They found serum Tg and thyroid volume positively associ-

ated with smoking ($p < 0.001$). The association was stronger in the area with the lowest iodine intake. No association was found between solitary nodules and smoking. All associations between smoking and thyroid abnormalities were dose dependent and ex-smokers had an intermediate value between present en never smokers. On the basis of their analysis the authors concluded that 50% of goiters in the population could be attributed to smoking and that the effect is aggravated by deficient iodine intake. ***Bulow-Pedersen et al.,*** Aalborg, Denmark, developed a computer based system linked to all the thyroid diagnostic laboratories in Denmark for analysis of the relationship of hyper- and hypothyroidism in two population cohorts with moderate and mild iodine deficiency. They found that the incidence of hyperthyroidism was significantly ($p < 0.01$) higher in the area with lowest iodine intake (91.5/100,000/year vs 64.9/100,000/year). The opposite relationship was present for hypothyroidism (26.3/100,000/year vs 36.7/100,000/year [$p = 0.028$]). Hyper- and hypothyroidism in both areas were more common in females vs males. Incidences of both affections were increasing with age, with highest age-specific incidences for both hyper- and hypothyroidism > 80 years. The increase in hyperthyroidism in iodine deficiency is mainly due to development of multinodular toxic goiter. The results suggest that even minor increases in iodine intake will prevent a considerable proportion of cases of hyperthyroidism, although the incidence of hypothyroidism also starts at low levels of iodine supplementation. (Comment: the authors sought to define the exact level of iodine intake that would both avoid increase in hyperthyroidism and in hypothyroidism. Their studies however suggest that it is either one or the other.)

AUTOIMMUNITY

Philips et al., Southampton, Cardiff, and London, UK, analyzed if beside heredity, a low birth weight could as well determine the development of circulating thyroid autoantibodies. Of twins born between 1950 and 1955, representing 45 monozygous and 91 dizygous pairs, blood was taken for measurement of TPO-Ab and Tg-Ab. Overall TPO-Ab were present in 49/156 (31%) of women and in 7/116 (6%) of men. Of 26 monozygous female pairs 8 were concordant for Tg-Ab and 5 pairs discordant, resulting in a proband-wise concordance rate of 76% while these values for the dizygous female pairs were 3 and 8 pairs, and 30% respectively. Similar concordance rates were found for TPO-Ab. These figures underline the importance of genetic factors in autoantibody development. Tg antibodies were more prevalent in monozygous twins than dizygous twins (30% vs 17%, $p = 0.01$). These latter results were explained on the notion that birth weights of monozygous twins tend to be lower than in dizygous twins. Another finding was that within the monozygous pairs, those twins who had a lower birth size, had a higher prevalence of TPO antibodies ($p = 0.01$). As in monozygous twins differences in birth weight are determined by the environmental conditions in utero, the authors suggest that apparently environmental factors are also of significance in development of thyroid autoantibodies in later life. ***Parkes et al.,*** Cardiff, UK, did a randomized placebo controlled double blind study in that 0.1 mg T_4 or placebo was administered to 335 postpartum women (known to be TPO-Ab positive at 14 weeks of gestation) between 6–24 weeks postpartum. Serum FT_3, FT_4 and TSH were measured at 6, 12, 16, 20, and 24 weeks postpartum. They found that before randomization about 20% of these women had a raised FT_3. In the T_4 treated group biochemical thyrotoxicosis developed in 68,6% which is highly significantly elevated versus the placebo group, showing hyperthyroidism in 19.2%. (Comment: What would the mechanism be of this high percentage of thyrotoxicosis in T_4 treated women? Already present thyroid autonomy or induction of Graves' disease by T_4? This latter phenomenon has been described.) ***Koutras et al.,*** Athens, Greece, followed development of thyroid

autoantibodies in two groups of pregnant women. Group A (n = 78) had an abnormal TSH (<0.3–>3.7 μU/ml), group B (n = 343) had a normal TSH (≥ 0.3–≤3.7 μU/ml). In group A, a significantly higher prevalence of thyroid hormone autoantibodies was found in the third trimester as compared to the first and the second trimesters ($p < 0.001$). This phenomenon was also present in subjects of group B ($p < 0.01$). When subjects were divided according to a TSH < or > 2 μU/ml, thyroid autoantibody positive women occurred more frequently in the subgroup with a TSH >2 μU/ml of group B ($p = 0.005$). Urinary iodine excretion was adequate in these women. The authors conclude that thyroid autoimmunity in pregnancy already develops antepartum and those with antibodies frequently show TSH levels in the upper normal range. (Comment: the authors also report that in antibody positive women with a TSH in the upper normal range, free- and total T_4 are lowered ($p = 0.05$). In that case T_4 treatment of these women should seriously being considered to ensure optimal intellectual development of the offspring.) ***Ozawa et al.,*** Tokyo, Japan, conducted a prospective study in 110 patients with painless thyroiditis , in 10 of whom being related to pregnancy (postpartum thyroiditis). Patients were followed for several years at a two months intervals. Fifty-four patients were followed for less than 3 years (group A) and 56 patients for more than 3 years (group B). In group A, 13% of patients developed a relapse while this was the case in 66.1% of patients in group B. In group A female to male ratio was 44/10 and in group B 49/7. Gender had no influence on the relapse rate. Several patients showed more than 1 or 2 relapses. In patients with relapse, the titer of antimicrosomal antibodies was significantly higher ($p < 0.05$) than in those who had only one attack. When patients became pregnant almost invariably postpartum thyroiditis developed. The authors report that no deterioration of thyroid function occurred, even in those with frequent relapses and persisting antimicrosomal antibodies. (Comment: The absence of development of thyroid dysfunction i.e. hypothyroidism is remarkable in that other studies reported frequencies of at least 20%.)

SUBCLINICAL HYPOTHYROIDISM

Lankarani et al., Mayo Clinic, Rochester, MN, USA, analyzed from a group of 2,655 subjects, 3 groups of patients all having a serum TSH between 5–10 mU/l. Group 1 consisted of 235 patients with positive microsomal antibodies. Group 2 were 203 subjects without microsomal antibodies and group 3 were 100 subjects in whom microsomal antibodies were not measured. The study was related to analysis of predictors of progression of hypothyroidism. When TSH was >6.0 mU/l, hypothyroidism progressed in 36% of patients. These values were for a TSH >7.0 mU/l, 48% and a TSH >9.0 mU/l, 67%. Furthermore progression was higher when microsomal antibodies were present. (Comment: It was already known that the risk of developing overt hypothyroidism is much increased when autoantibodies to the thyroid are present in the serum. However, the new aspect of this study is the fact that the higher the initial TSH, the more patients progress to unequivocal hypothyroidism. Age and gender were not related to the risk of progression.) ***Brenta et al.,*** La Rioja, Argentina, assessed cardiac function in 10 patients with subclinical hypothyroidism (TSH 11 ± 4.2 μU/ml) before and 6 months after T_4 substitution to a TSH 1.9 ± 1.1 μU/ml. Results were compared with a control group. Multigated equilibrium radionucleide ventriculography was performed to assess systolic and diastolic ventricular function. The Time to Peak Filling Rate, a parameter of diastolic function, was significantly prolonged as compared to restoration to euthyroidism which latter value was not diffferent from controls. The authors conclude that diastolic heart function is impaired in subclinical hypothyroidism. ***Caraccio et al.,*** Pisa, Italy, measured if nitric oxide (NO) mediated endothelium (END)-dependent vasodilatation (VD) was impaired in 8 fertile women

with subclinical hypothyroidism. Results were compared with a matched control group. NO-mediated END-dependent VD was measured in the forearm. In subjects with subclinical hypothyroidism VD appeared to be reduced, caused by a reduction of NO availability. (Comment: It has been shown (Hak et al., Annals of Internal Medicine, 132: 270-278, 2000) that subclinical hypothyroidism leads to increased risk of aortic atherosclerosis by a mean factor of 1.7 and of myocardial infarction of 2.3 and this may be related, at least in part, to the in this report described phenomenon.) ***Monzani et al.,*** Pisa and Rome, Italy, used conventional echo-Doppler and ultrasonic videodensitometry, to assess left ventricular function and structure in 20 patients with subclinical hypothyroidism (mean TSH 5.32 ± 1.80 mU/l). Results were compared to a carefully age- and sex-matched control group. The patients were re-evaluated 12 months after LT_4 replacement therapy or placebo. The patients showed a significantly lower Cyclic Variation Index (CVI) than controls both for the septum and the posterior wall ($p < 0.0001$). Also Peak A and Isovolumic Relaxation Time were significantly increased. CVI was positively correlated with FT_3 but inversely related to TSH. After 12 months of LT_4 replacement the different parameters normalized as compared to controls. In the placebo group similar abnormalities were described that did not change during placebo treatment. (Comment: This is another example of disturbed cardiac function in subclinical hypothyroidism. It is not known however if these abnormalities lead to a change in quality of life and/or frequency of heart disease.) ***Dagre et al.,*** Athens, Greece, examined arterial stiffness, using Augmentation Index (AI), Augmentation Pressure (AP), and time travel of reflected wave (CTI) (all markers of arterial compliance), that were all measured by the PWV Medical Blood Pressure Analysis System, in 3 groups of subjects i.e. 12 subjects with a TSH < 2 mU/l, 11 with TSH 2.01–4.0 mU/l, and 12 with TSH > 4 mU/l. The authors found that TSH levels correlated inversely with CTI. Furthermore AI and AP were significantly negatively correlated with CTI. The authors concluded that not only in subjects with an elevated TSH but also in those who had TSH values in the upper 50 percentile a decreased arterial compliance was present. They caution against considering the latter group as always completely euthyroid.

GRAVES' HYPERTHYROIDISM

Martino et al., Pisa, Italy, assessed the effect of two different regimens of lithium administration to patients who were going to be treated with ^{131}-I for hyperthyroid Graves' disease. One group consisted of 7 patients who received lithium therapy for 6 days, starting from the day of ^{131}-I administration. The other group consisting of 6 patients received lithium on the day methimazole was discontinued (5 days prior to ^{131}-I therapy) which was continued for 14 days. A third group consisting of 8 patients receiving only ^{131}-I. The preliminary results showed that especially in the 14 days lithium treatment group any increase of thyroid hormone levels after discontinuation of methimazole is prevented and furthermore, that maximal intrathyroidal radioactivity after treatment is highest. (Comment: Although the results are preliminary indeed, they are promising and show that additional treatment with lithium after discontinuation of methimazole increases the effectiveness of a therapeutic dose of radioactive iodine and prevents a relapse thyreotoxicosis immediately after discontinuation of antithyroid drug treatment.) ***Kumar et al.,*** New Delhi, India, and Vienna, Austria, did a similar study in that they evaluated the effective half-life of ^{131}-I in the thyroid gland after 131-I therapy in patients with Graves' hyperthyroidism with and without additional lithium therapy. Eighty consecutive patients (age 21–70 years) were randomly assigned either to radioiodine alone or radioiodine + lithium. The effective half-life of ^{131}-I was significantly prolonged as compared to no lithium (5.85 vs 4.93; $p = 0.001$). There was no significant difference in cure rate of hyperthyroidism

at 12 months of follow-up, however patients who received lithium needed lower doses of ^{131}I. ***Brix et al.,*** Odense, Denmark, assessed the genetic influence on the development of Graves' disease in a historical cohort of 4,883 female same sex twin pairs consisting of 1,327 twin pairs born between 1870 and 1920 who participated in questionnaire survey's during the 1950's, 1960's and 1970's, and a cohort of 3,556 same sex female twin pairs born between 1953 and 1976 who participated in a questionnaire survey in 1994. Overall, the crude probandwise concordance rates were 0.34 and 0.04 in female monozygotic and dizygotic twin pairs respectively ($p < 0.01$). Model-fitting analysis suggested that approximately 76% of the liability to develop Graves' disease is attributable to genetic factors. The authors conclude that genetic factors play a major role in the development of Graves' disease whereas environmental factors are of less importance. (Comment: It is not possible, to deduce from this important study, to what extent environmental and genetic factors act synergistically or only additionally in the development of Graves' disease. For that analysis studies of monozygotic and dizygotic twins are necessary of pairs that are separated and live in different environmental circumstances, for instance differences in iodine intake, stress factors, social factors and others.)

HYPERTHYROIDISM

Obuobie et al., Cardiff, UK, measured peripheral arterial and central aortic pressure wave forms, allowing the determination of indices of arterial stiffness: augmentation of central pressure (AG) and the augmentation index (AI) in 20 hyperthyroid patients and 20 age- and sex-matched controls. Hyperthyroid patients were assessed at baseline and 4 months of treatment. AG and AI were significantly less in untreated patients as compared to controls but patients values normalized at 4 months of treatment. The authors conclude that in untreated hyperthyroidism arterial stiffness is decreased, resulting in an increased vascular compliance that is normalized upon treatment. ***Helal et al.,*** Clamart Cedex, France, evaluated the ability of TC-99M-sestamibi (MIBI) to visualize suppressed thyroid tissue in hyperthyroid patients with iodine excess or autonomous nodular disease. They studied 6 patients with toxic multinodular goiter, 4 patients with toxic adenoma, and 8 patients with iodine excess. In addition to MIBI, all patients were scanned with iodine-123. In 3/4 toxic adenoma patients, the contralateral functionally suppressed lobe not seen on the ^{123}I scan, was visualized on MIBI scanning. In patients with toxic multinodular goiter with or without iodine excess, MIBI scanning gave clearer images and was able to detect non-autonomous (functionally suppressed) areas. The authors conclude that MIBI imaging of the thyroid gland is useful in toxic (multi)nodular goiter to visualize functionally suppressed tissue surrounding the autonomous nodule(s), not detectable by radio-active iodine. They furthermore found that in iodine excess, MIBI still gives a clear imaging of the thyroid. (Comment: MIBI scanning can thus differentiate between hyperthyroidism in patients with an absent or suppressed contra-lateral lobe) ***Sgarbi et al.,*** Sao Paulo and Campinas, Brazil, assessed cardiac performance in 10 patients with subclinical hyperthyroidism before treatment when TSH was suppressed and after antithyroid drug treatment resulting in normal mean TSH. Results before and after treatment were: 24-h average heart rate, 81 vs 73/min, $p = 0.004$; atrial premature beats: 120 vs 12/24h, $p = 0.007$; ventricular extrasystoles 22.5 vs 1.4/24h, $p = 0.03$. Doppler-echocardiography detected a reduction of the left ventricular mass index (88.0 vs. 27.4, $p = 0.008$), intraventricular septum diastolic thickness (0.88 vs 0.75 cm, $p = 0.001$) and left ventricular posterior wall diastolic thickness (0.89 vs 0.76 cm, $p = 0.002$). The authors suggest that subclinical hyperthyroidism is associated with a compromised cardiac function and morphology. They additionally report that the untreated patients had an increased mean velocity of circumferential fiber shortening ($p = 0.04$) as com-

pared to controls. (Comment: The issue whether cardiac performance is compromised in subclinical hyperthyroidism is still controversial in that some studies also show no significant cardiac effects. The controversy may be partly generated by the fact that to my opinion subclinical hyperthyroidism due to increased thyroid function (mostly multinodular goiter) cannot be compared with subclinical thyrotoxicosis due to T_4 treatment. The thyroid hormone profile is completely different in these two entities, in that in the hyperthyroid type mean FT_3 is elevated, however still within the normal range, but mean FT_4 mostly normal, whereas the reverse is true in subclinical thyrotoxicosis due to T_4 treatment. Furthermore, the present report does not indicate whether the value before treatment and after reaching euthyroidism in the patients group are different from those in matched healthy controls. The issue is still open!) ***Kumeda et al.,*** Osaka, Japan, evaluated bone metabolism in 19 premenopausal patients with Graves' disease who still had suppressed TSH but normal FT_3 and FT_4 levels during antithyroid drug treatment and compared the results with 30 premenopausal Graves' disease patients with normal TSH during treatment. They found no difference between the groups with regard to serum calcium, phosphate, intact-PTH or urinary calcium excretion. Serum bone alkaline phosphatase, bone formation markers and urinary excretion of pyridinoline and deoxypyridinoline were significantly higher in the TSH suppressed group. TSH correlated negatively with bone turnover parameters whereas TSH receptor antibodies were positively related to these parameters. The authors conclude that it is important to achieve a normal TSH during antithyroid drug treatment in order to normalize bone turnover. TSH receptor antibodies were sensitive markers for increased bone turnover in patients with Graves' disease during antithyroid drug treatment.

NODULAR GOITER

Three reports were communicated studying the effect of L-thyroxine treatment in nodular goiter. Thus ***Corapcioglu et al.,*** Ankara, Turkey, evaluated the effects of TSH suppressive T_4 treatment on nodular size in 101 patients with non-toxic nodular goiter living in an area of moderate iodine deficiency and compared the results with 44 matched control patients not treated with LT_4. In the T_4 treated group mean nodular size decreased from 14.52 ml to 13.3 ml ($p < 0.02$) and these values for the control group were 12.03 and 11.82 respectively ($p = 0.9$). These results were obtained after a mean period of 20 months. ***Vulpoi et al.,*** Lasi, Romania, treated 53 patients with a single thyroid nodule with T_4 for one year and compared the results with 26 patients with a single nodule without treatment. A decrease in nodule volume of 50% as detected by ultrasound was considered as successful. In the TSH suppressed group a successful response was found in 37% of subjects whereas a decrease of 50% occurred only in 27% of the control group ($p = 0.56$). The subjects studied in this report were living in an area of borderline iodine deficiency. Lastly, ***Wemeau et al.,*** Lille, Lyon, Reims, Strasbourg and Paris, France, did a similar study in which 64 patients with a single benign nodule were treated with T_4 and 59 patients with a placebo. In the T_4 treated group the mean largest nodule dimension decreased from 19.4 to 16 mm ($p = 0.006$) whereas these values for the placebo group were 20.3 and 20.4 mm respectively. These findings were obtained after 18 months of follow-up. At the same time points the mean nodule volume in the T_4 treated groups decreased from 2.76 to 2.39 ml ($p = 0.01$) whereas these figures were for the placebo group 3.5 and 4.1 ml. (Comment: Although these three reports show a statistically significant reducing effect of T_4 treatment on nodule size, the effects are very limited and my personal opinion is that, considering the side effects of T_4 treatment, especially in older patients, this approach is of little practical value in the treat-

ment of this type of patients.) ***Bianchini et al.,*** Sao Paulo, Brazil, performed percutaneous ethanol injection (PEI) in 27 patients with solid nodules, 24 with cystic or mixed nodules, and 19 with autonomous nodules. Mean reduction after 1 year was 62.4%, 85.4%, and 70.1% respectively. (Comment: According to the authors the effects were obtained in 2 to 5 sessions and the treatment was at low cost and well-tolerated.) ***Knudsen et al.,*** Copenhagen, Glostrup and Aalborg, Denmark, examined the association between alcohol consumption and the prevalence of thyroid abnormalities in a population study including 4,649 subjects, randomly selected within certain age groups from the general population in two areas with mild and moderate iodine deficiency. Results were corrected for confounding factors. Subjects with moderate alcohol intake (8–28 drinks/week for women or 8–42 for men) or high intake (>28 for women and >42 for men/week) had lower prevalence of thyroid abnormalities than abstainers. Odds ratios compared to abstainers for thyroid enlargement were 0.74 for moderate, and 0.44 for high alcohol consumption. These values were for solitary nodules 0.64 and 0.41 respectively. No association was found between alcohol intake and multinodularity of the thyroid. The mean thyroid volume for abstainers was 13.5 ml, and in subjects with high alcohol consumption 10.9 ml ($p < 0.001$). Both wine and beer consumption had the same effect. (Comment: To my knowledge this is a new possible factor influencing thyroid disease. However, it is not known if this is a beneficial effect or a toxic effect. Neither is there any idea about the mechanism. It would be interesting to assess if thyroid autoimmunity is suppressed in alcohol consumption. For the moment I will continue using alcohol!)

THYROID HORMONE RESISTANCE (THR)

Mansen et al., Stockholm, Sweden, and New York, NY, USA, assessed the role of thyroid receptor α 1 (TRα1) in the expression of the cardiac genes for sarcoplasmic reticulum ca^{2+} ATPase, phospholamban, myosin heavy chain and Na-K-ATPase, in transgenic mice lacking the TRa1. This study was performed because TRα1 is presumed to play an important role in mediating thyroid hormone effects in the heart. For instance, TRα1 is said to play an important role in heart rate regulation. The authors however, found no effect regarding expression of the genes of these proteins in these mice, indicating that as yet uncharacterized genes play a role in the expression of these proteins. From these results they conclude that TRα1 is probably not involved in regulation of heart rate in contrast to previous reports. ***Hashimoto et al.,*** Boston, MA, USA, studied neurological function in mice lacking thyroid hormone receptor β (TRβ) and found that these animals displayed abnormalities in the hypothalamic-pituitary-thyroid axis, liver function and cardiac function. In addition, these mice showed severe vestibulomotor dysfunction. Also learning defects were present and reduced expression of brain derived neurotropic factor but not of Myelin Basic Protein and Tyrosine kinase receptor B. (Comment: Their studies show the importance of TRβ in mediating thyroid hormone effect in various tissues.) ***Vlaeminck et al.,*** Lille, Strasbourg and Paris, France, studied the effect of administration of dextrothyroxine ($D\text{-}T_4$) in patients with pituitary resistance to thyroid hormone. Due to this defect subjects are hyperthyroid caused by overproduction of thyroid hormone. Nine patients from 5 kindreds were treated with a mean dose of 4.4 mg $D\text{-}T_4$/day for a mean period of 5 years. Goiter was initially present in 8 patients and disappeared in 6. Hyperthyroidism, initially present in all patients, improved in 7. In 6/9 patients in whom TSH level was increased prior to treatment, serum TSH normalized. The authors conclude that successful control of biochemical and clinical hyperthyroidism in pituitary resistance to thyroid hormone can be obtained by treatment with DT_4. (Comment: Successful treatment with TRIAC in these patients has also been reported.)

OTHER TOPICS

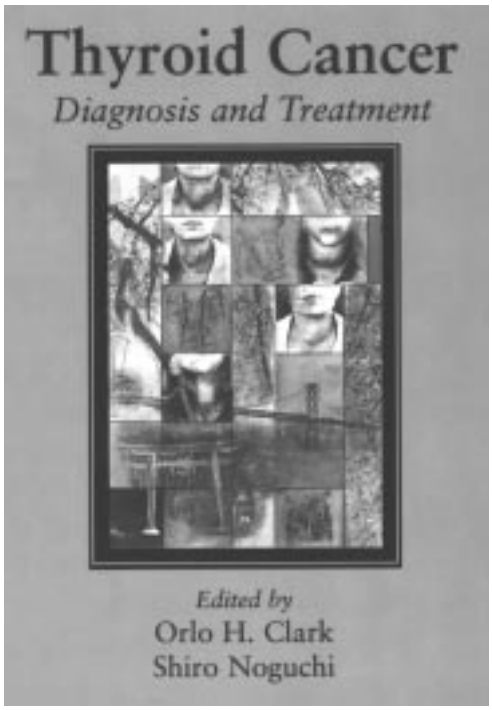
Silvestri et al., Prato, Italy, examined the role that **thyroid diseases** could play in 60 patients complaining of **chronic cough.** Thyroid disease was diagnosed in 39 (34 females)/60 patients. Their mean age was 58.7 years. Fourteen had thyroiditis, 22 goiter, and 3 a combination of those. 18/39 patients were submitted to specific medical thyroid treatment or underwent thyroid surgery. In all patients cough disappeared after treatment. The remaining 21/39 patients had causes for chronic cough that were not related to any thyroid condition. From their analysis the authors conclude that chronic cough is significantly related to thyroid disease ($p < 0.001$) and to gender being more prevalent in females ($p < 0.01$). (Comment: Although I am not convinced about a causal relationship between chronic cough and thyroid disease as a control group is lacking in this study, thyroid diseases probably do not protect from chronic cough! The report of this group is certainly interesting and we should keep their hypothesis in mind when being confronted with such patients.) ***Van Wassenaer et al.,*** Amsterdam, The Netherlands, who previously reported that L-T_4 supplementation to infants <30 weeks of gestation only improves 2 years developmental outcome in infants treated at <27 weeks, **tested T_4 supplementation effects in children at early school age** who were supplemented with L-T_4 at <30 weeks of gestation. They performed a randomized, placebo controlled, double-blind trial of T_4 supplementation (8 μg/kg birth weight/day) during the first 6 years of life in 200 infants <30 weeks of gestation. Cognitive outcome was 10 IQ points better in T_4 children of 25 and 26 weeks but worse in children born at 29 weeks. Behavioural outcome was better in T_4 treated children of 25 and 26 weeeks but worse in children of 27 weeks. Motor outcome was better in children <29 weeks and neurological outcome was better in children <29 weeks but worse in children of 29 weeks. The authors conclude that at early age the effects of neonatal T_4 supplementation change from positive to negative at 29 weeks. ***Smyth et al.,*** Doublin, Ireland, analyzed **co-existing thyroid disease** in 778 patients **with breast cancer** over a 10 year period. In 5.5% of patients, primary hypothyroidism was present and in 3.6% hyperthyroidism. Non-toxic goiter was present in 32.0% as assessed by ultrasound (>18.0 ml). Both hypothyroidism and non-toxic goiter prevalences were significantly greater than in matched controls ($p < 0.05$ and < 0.001 respectively). The distribution of serum TSH showed a significant preponderance of both suppressed TSH and elevated TSH as compared to matched controls. TPO antibodies were present in 33.2% of the whole patients group as compared to 18.3% in controls ($p < 0.01$). Similar findings were true for Tg antibodies. Five year disease free survival was 73.0% in thyroid antibody positive patients and 55.0% in antibody negative patients ($p < 0.05$). (Comment: This group has more often shown that there is a significant co-existence between breast carcinoma and thyroid disorders, the mechanism of which is as yet unknown. Their latest results suggest that the presence of thyroid autoantibodies is a prognostic positive sign.) ***Kasagi et al.,*** Kyoto, Japan, who stated that iodine intake in Japan varies between 0.1 mg per day to 20 mg per day, undertook a study to assess the frequency of **iodine induced reversible primary hypothyroidism.** Thirty-three consecutive hypothyroid patients (26 women) with a mean age of 54 years and without the history of destructive thyroiditis within the previous year, were asked to refrain from taking any iodine-containing drugs and foods such as seaweed products for 1–2 months. The initial TSH serum level of 52.0 ± 55.3 mU/l decreased to 11.4 ± 11.0 mU/l after iodine restriction. Twenty-two patients showed a reduction of TSH to less than 50% of initial levels and the mean ratio of TSH after/before iodine restriction in these subjects was 0.21 and in the remaining 11 subjects 1.06. From their results the authors conclude that thyroid function improved in two-third of these subjects, especially in those in whom technetium uptake was >2.0%.

Book Review

By Martin Schlumberger,
Institut Gustave Roussy, Villejuif, France.

Despite the huge number of meetings, discussions, studies and publications on thyroid cancers, many controversies persist. They are mainly due to the relative rarity of the disease, to the excellent prognosis of most tumors, to the absence of controlled trials and to the frequent absence of significant changes in their outcome resulting from modifications of any treatment and/or follow-up protocol.

In this context, two surgeons who are among the leading experts in the field, present the state of the art in the management of thyroid cancer patients. Many aspects remain controversial, and one of the main interests of the book is that the authors provide a well-documented rationale for the various approaches used in their respective Institutions.



OH Clark, S. Noguchi.
Thyroid Cancer; Diagnosis and Treatment.
published by Quality Medical Publishing, Inc., St. Louis, Missouri, USA

The book (447 pages) is divided into 19 chapters and 5 parts. It is a combination of clinical and basic data, most of which were acquired in San Francisco and at the Noguchi Clinic, with management strategies and more general ideas that can be applied to other tumor types.

The first part of the book is a general overview of thyroid cancer based on the large series of patients treated at the Noguchi Clinic. This is followed by a comprehensive review of the evaluation of thyroid nodules, cytology and histopathology. The description of thyroid cancer according to the extent of disease is more original and particularly relevant; this is the case with the prognostic significance of extra-capsular invasion of lymph nodes and its impact on regional recurrences whatever the initial tumor size. In addition, the controversial prognostic significance of Graves' disease is extensively discussed and data from the Noguchi Clinic strongly argue in favor of a protective effect of this disease on the outcome of thyroid carcinoma.

The second part of the book deals with imaging tools and technology. In these chapters, the use of ^{131}I for total body scintigraphy and for treatment is described as well as the value of ultrasonography, CT scan and MRI. Unfortunately, no follow-up protocol is provided and the respective role of each of these techniques is difficult to appraise. Furthermore, the value of thyroglobulin measurement, the PET scan, and of recombinant human TSH is only partly reported, despite the large number of recent data. In contrast, the authors insist on the role of thallium and sestamibi, despite decreasing interest in most centers.

The third part is a detailed description of surgical approaches, including total and partial thyroidectomy, and an extensive rationale is provided for each approach. S. Noguchi then explains surgical options, for both the thyroid gland and lymph nodes, based on data obtained in his clinic.

In the fourth part, the management of medullary thyroid carcinoma is presented by JF Moley, an authority in the field. He demonstrates the central role of surgery in the treatment of this disease, including in patients with local and regional recurrences and in those with persistently elevated calcitonin levels; in these patients liver metastases should be excluded before surgery by venous catheterisation for calcitonin measurement and laparoscopy. Then, locally recurrent thyroid carcinoma is discussed, including risk factors and treatment. The rare but difficult case of unresectable thyroid carcinomas is dealt with indicating original strategies combining percutaneous ethanol injection, intraoperative radiotherapy and arterial infusion therapy; remarkable results have been obtained on limited series of patients.

Unfortunately, there are very few data on follow-up and on the role of thyroglobulin in patients with papillary and follicular thyroid carcinoma, and even the respective significance of total body scanning with ^{131}-I and of serum thyroglobulin measurement is not discussed.

The fifth part presents advances in molecular biology. In the first chapter OH Clark explains with numerous examples how important it is for a surgeon to be educated and trained in the basic sciences and how much this may improve the treatment of thyroid cancer patients. Indeed, these ideas should not be restricted to the thyroid field. Then data on oncogenes and tumor suppressive genes in thyroid carcinoma are extensively described, as well as the role of RET in medullary thyroid carcinoma. Two of his special fields of interest, angiogenesis and TSH suppressive therapy, are then discussed. Studies on angiogenesis may open new fields of research and treatment. TSH suppressive therapy is clearly useful in patients with disease, and OH Clark presents very significant data. However, in patients with no evidence of disease, as demonstrated by reliable modern techniques, it is difficult to think let alone show that suppressive treatment may be beneficial. Such patients represent at least 80% of all patients treated for papillary or follicular carcinoma and unfortunately this point is not addressed. Finally, progress in the field of thyroid cancer is rapid and this may explain why there is no mention of the iodide symporter, despite the fact that it is currently at the center of most scientific discussions concerning papillary and follicular thyroid carcinoma.

In conclusion, I strongly recommend the reading of this excellent book to all persons that are involved in the field of thyroid cancer, including surgeons but also thyroidologists, endocrinologists, nuclear medicine specialists, pathologists and even basic researchers.

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Statutes for the Merck European Thyroid von Basedow Research Prize donated by Merck KGaA, Darmstadt, Germany

1. The prize is to exclusively and directly honour special scientific work in the field of the thyroid gland and serves also to recognized and encourage young scientists. DM 20,000 per year are available. In exceptional cases, the jury may decide to divide the prize.

2. Young scientists who are domiciled in Europe and have not completed their 40th year of life may apply for the prize. Employees of industrial firms are exclused. The candidates are to hand in manuscripts of (original plus nine copies) their as yet unpublished works to the President of the German Society of Endocrinology by October 31 of the year prior to the prize-giving.

3. In addition to basic research, work involved in both diagnostic as well as therapeutic problems in this specific field also may be considered for the prize. The submitted reports must not exceed 25 type-written pages à 30 lines. The number of figures and tables is to amount to no more than 1/3 of the complete report. The manuscript, in either English or German, must be drawn up according to the regulations of a scientific journal. All rights are exclusively in the control of the author. After confirmation of receipt, the author may offer his work to a journal for publication.

4. The prize project should not include more than two authors. If more authors have cooperated in a project, the team should decide on the two main authors to be named for the prize project; if necessary, the remaining authors must give their consent in writing. The curriculum vitae stating the scientific career of the author(s) must be enclosed with the prize project. The author(s) must affirm in writing that at the time of submission the manuscript had not been published or handed in for publication in a journal (exception: published abstracts).

5. A jury decides on who is to receive the prize. The jury may decide not to donate the prize if the manuscripts received are not worthy. The decision of the jury is mandatory for all participants and is not subject to judicial inquiry. If not awarded, the prize may in exceptional cases be made available in the following year for additional manuscripts which are worthy.

6. The jury comprises: The President and two members of the Board of the German Society of Endocrinology, the speaker and two members of the Thyroid Section nominated by the Board of the German Society of Endocrinology and one representative from the Pharmaceutical Section of E. Merck, Darmstadt. Other experts (without the right to vote) may be included in the assessment. The chairman of the jury is the President of the German Society of Endocrinology.

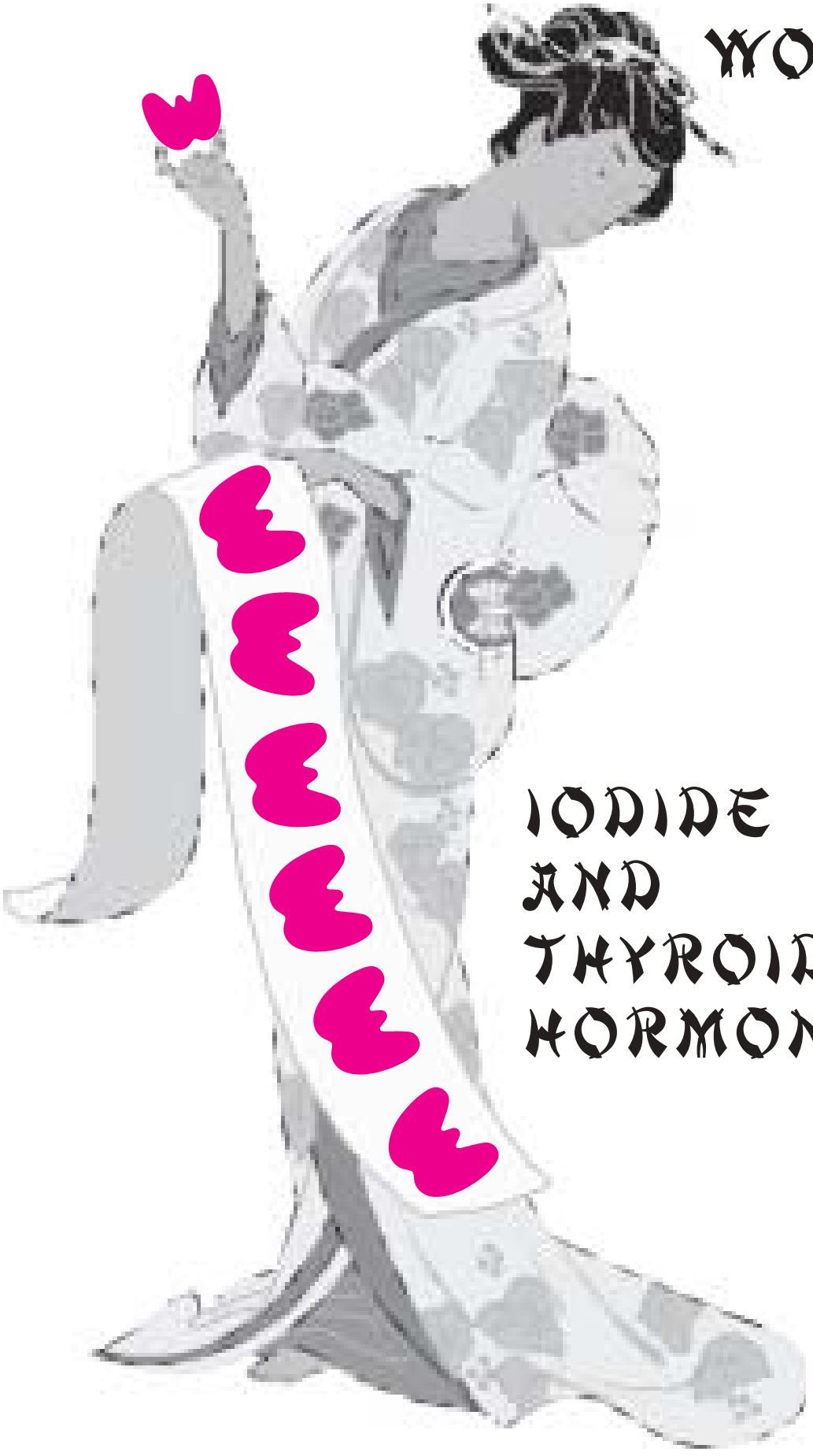
7. The jury decides with a 2/3 majority. In exceptional cases, decisions given in writing form absent jury members may be considered. A member of the jury may not take part in assessing a manuscript if it originates from his working circle. In this case, the President calls another member of the Society from the same field to the jury.

8. The prize is usually awarded once a year at the annual meeting of the German Society of Endocrinology.

9. The President of the Society will invite applications for the prize for the subsequent year at the annual meeting. The secretary and press agent of the Society will arrange announcements in several languages for the competition to be advertised in medical journals.

The President of the
German Society of Endocrinology

COMPETENCE AND EXPERIENCE
FOR THYROID SPECIALISTS
WORLDWIDE



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AND
THYROID
HORMONES

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