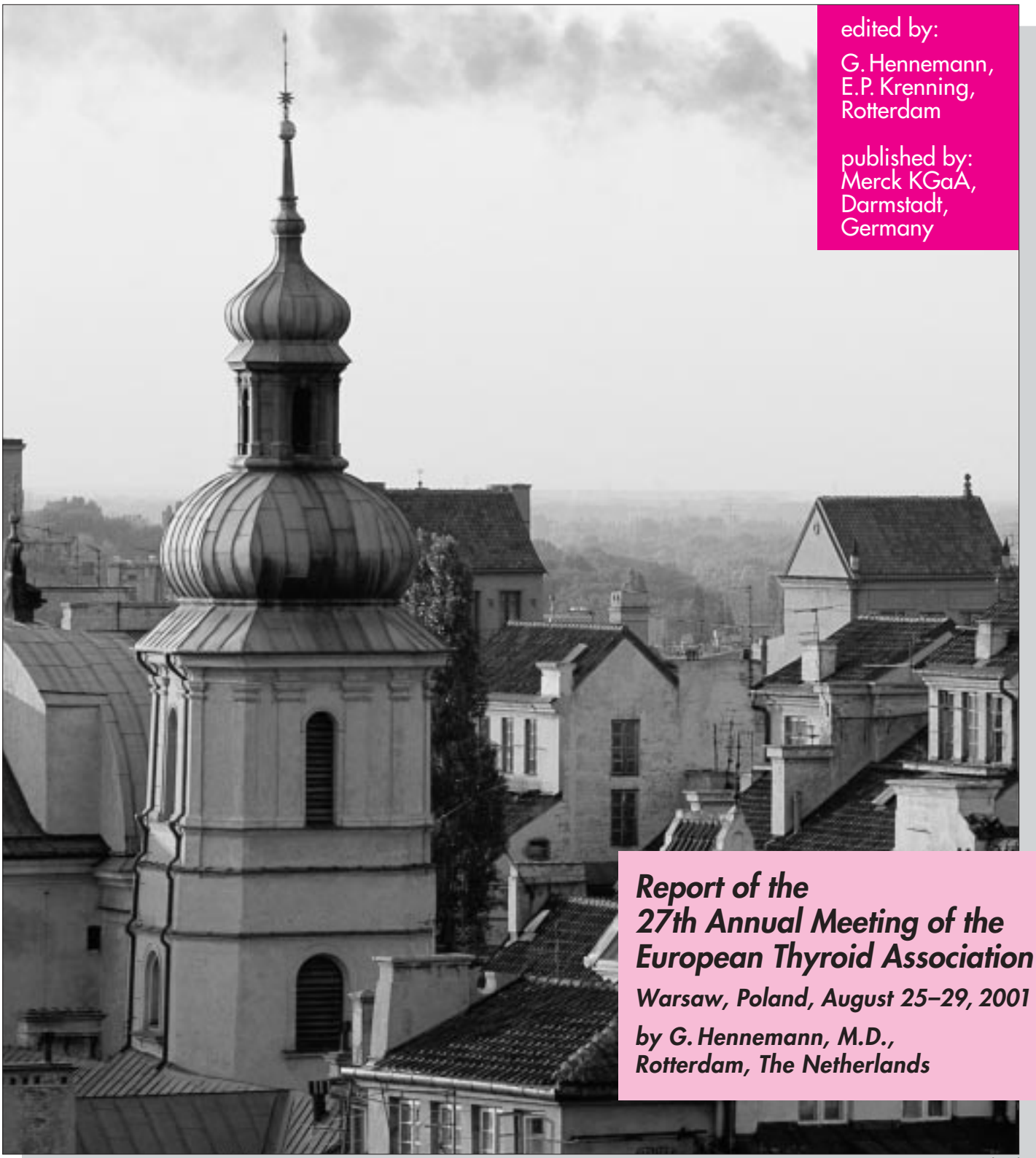
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Report of the 27th Annual Meeting of the European Thyroid Association

Warsaw, Poland, August 25–29, 2001

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

Warsaw, Poland

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3. Ludgate M. "Animal models Graves' and eye disease".
4. Laurberg P. and Faber J. "Sublinical thyroid disease: to treat or not to treat?".

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

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This report summarizes those communications that have clinical relevance.

HYPOTHYROIDISM

Schütz et al., Berlin, Germany, report further on a new syndrome of congenital hypothyroidism, pulmonary defects, choreoathetotic movement disorder and mental retardation due to haploinsufficiency of the NKX2-1 gene. This gene, originally named thyroid transcription factor 1 (TTF-1), plays an essential role in the development of different organs including the thyroid. They now describe two patients, one with a heterozygous GG insertion at nucleotide position 2595 in exon 3 of this gene and another patient with a heterozygous C->T transition at position 2517. *(Comment:* Still more causes of congenital hypothyroidism are being characterized since cloning of essential genes, playing a role in either thyroid development or function, are being performed. Newly identified causes are inactivating mutations in the genes of TSH, the TSH receptor, TPO, thyroglobulin, NIS, Pendrin, Pax-8 and the here reported one). ***Olivieri et al.,*** Rome, Italy, investigated the risk of congenital hypothyroidism (CH) in twin (multiple) pregnancies versus single pregnancies in Italy between 1987 and 2000. The incidence of overall CH was 1:3130 live births. The prevalence of twin (multiple) pregnancies among CH twins was 3% being about 3-fold higher than the frequency of twin (multiple) pregnancies in the normal population. The proportion of affected pairs concordant for CH was 7.1% (pairwise concordance rate) while the probability of having an affected twin, given that his/her co-twin is affected, was 15.7% (probandwise concordance rate). They also found a higher prevalence of eutopic gland in twin- versus singletons CH (51% vs 26%), while, after re-evaluation at 2–3 years of age, the prevalence of twins with permanent CH was 1.7% and with transient CH was 10.5%. The authors concluded that twin pregnancies result in a higher risk of CH and that transient hypothyroidism was more prevalent in twins than in singletons. *(Comment:* It would be interesting to know what factors would be responsible for the transient hypothyroidism in twins, such as circulating thyroid antibodies and if mothers of twins had a higher prevalence of these antibodies than mothers of single pregnancies). ***Persani et al.,*** Milan, Italy, analyzed TSH receptor gene mutations in 10 young (one month – 25 years) unrelated patients with non-autoimmune subclinical hypothyroidism i.e. slight (6,6–14,9 mU/l; n = 7) to moderate (24–46 mU/l; n = 3) elevation of TSH associated with normal free T_4 and free T_3 serum levels. They found in 4/10 familial settings germline loss-of-function mutations of the TSH receptor gene. The authors conclude that this type of subclinical hypothyroidism is probably less rare than thought so far. ***Perri et al.,*** Pisa, Italy, sequenced genomic DNA for mutations in the TSH receptor gene and the Gsα gene in 8 patients with subclinical hypothyroidism without the presence of autoimmunity. In 6 sporadic cases no genetic alterations were found in both genes. However, in 2 patients being mother and son, a mutation was found in the TSH receptor gene for which the mother was homozygous and the son heterozygous. *(Comment:* so far it is understood

that subclinical hypothyroidism is a condition secondary to thyroid disease, mostly based on thyroid autoimmunity. However these previous 2 reports show that other causes may be operative as well. It would be important to know if in these cases there is indeed subclinical- or mild hypothyroidism present, like in the cases secondary to thyroid disease, or that full compensation of thyroid function is reached. If the latter is not the case, T_4 treatment is maybe an option as well in these patients). ***Dedecjus et al.,*** Lódz, Poland, and Dijon, France, measured cholesteryl ester transfer protein (CETP) concentrations in patients during hypothyroidism and after replacement therapy and compared levels with controls. CETP is considered to be a key protein in reverse cholesterol transport, a protective system against atherosclerosis and its deficiency leads to an increased risk for coronary sclerosis. The authors found low levels of CETP during hypothyroidism that normalized after T_4 replacement therapy. Furthermore CETP mass and activity levels correlated positively with free concentrations of serum T_3 and T_4 and negatively with serum TSH. ***Dagre et al.,*** Athens, Greece, who previously showed that flow mediated vasodilatation of the brachial artery is impaired in hypothyroidism, evaluated the duration and degree of reactive hyperemia in patients with hypothyroidism of different severity: 29 patients had low-normal TSH 0,3–2,0 mμ/ml, group 0; 26 had TSH 2,1–4, 0, group 1; 19 had TSH 4,1–10,0 and normal T_4 levels, group 2; and 24 patients with overt hypothyroidism TSH >10 mU/ml, group 3. Baseline forearm blood flow (FBF) was similar in all groups. However, the duration of reactive hyperemia (after release of an occluding cuff) was shorter in groups 2 and 3 as compared to the other two groups. Thus, not only in overt hypothyroidism but also in subclinical hypothyroidism endothelial function is impaired in the microvasculature. ***Caraccio et al.,*** Pisa, Italy, measured the lipoprotein profile in stable subclinical hypothyroidism in 53 patients (6 men) before and after treatment with T_4 or placebo. At baseline, triglycerides, LDL cholesterol, Apo B and LP(a) were significantly higher than in controls and were significantly positively related to serum TSH. After 6 months of treatment, T_4 patients showed a decrease in triglycerides and LDL cholesterol without a change in Apo B and LP. No changes occurred during placebo treatment. The findings of this study are that subclinical hypothyrodism results in an atherogenic lipoprotein profile that is reversible by T_4 treatment. It appeared furthermore that the LP(a) levels that were elevated, were significantly correlated with a familiar disposition for diabetes mellitus and/or coronary heart disease. *(Comment:* more and more investigations show that even in subclinical hypothyroidism secondary to thyroid disease (see above), different parameters point to an increased risk of developing atherosclerosis. However, the clinical relevance of these associations has not been shown so far. Despite this, my personal opinion is that replacement therapy with T_4 is certainly an option in such patients, for instance when there are other risk factors present for cardio-vascular disease or when patients have complaints compatible with hypothyroidism, but should be decided on an individual basis). ***Calvo et al.,*** Madrid, Spain, London, UK, and Brussels, Belgium, measured thyroid function parameters in coelomic- and amniotic fluids (CF and AF) and fetal serum (FS) from 27 normal women/fetuses undergoing termination of pregnancy. CF between 5.8 and 17 wks. of gestational age, FS from 12 to 17 wks., AF from 5.8 to 17 wks. Maternal serum was also obtained. Overall results were that a decrease in maternal T_4, even within the euthyroid range, would lead to a decrease of FT_4 in CF and FS, being the source of T_4 for the ontogenically-regulated intracellular generation of T_3 and nuclear receptor T_3 occupancy. The authors suggest that the end result of such a situation could be theloss of opportunity for an orderly cerebral development in the fetus. For the latter they foundevidence, as reported in another communication at this meeting by ***Lavado et al.,*** Madrid and Alicante, Spain, in developing rat fetuses made hypothyroxinemic whenever there was an

inadequate supply of maternal T_4, even when serum T_3 was normal. From both these studies the authors conclude that the results support the convenience that maternal hypothyroxinemia in human pregnancy should be prevented.

HYPERTHYROIDISM

Hammer et al., Bochum, Germany, measured thyroid function parameters in 177 consecutive patients with first manifestations of atrial fibrillation in 1999 and 2000 and compared results with 336 matched controls without a history of atrial fibrillation. They found a serum TSH < 0.01 mU/l in 7.3 % of patients and in 3.3 % of controls. These results indicate a 2.5-fold increased risk for atrium fibrillation in patients with subclinical hyperthyroidism as serum T_4 and T_3 were normal in subjects with low TSH. *(Comment:* The results of this study confirm earlier results published several years ago by Sawin et al., NEJM 1944;331: 1249. Furthermore, in a recent report Parle et al., Lancet 2001;358:861, showed that in persons ≥ 60 year, mortality from all causes is increased in particular mortality due to circulatory and cardiovascular diseases. In my mind there is no doubt that (elderly only?? I don't think so!) persons with subclinical hyperthyroidism should be treated effectively). ***Czarkowski et al.,*** Warsaw, Poland, measured non-invasively arterial resistance in hyperthyroid patients with Graves' disease. They used a technique based on ultrasound that could measure vascular input impedance. Twenty-four patients were investigated and results were compared with 22 controls. They found that arterial resistance is depressed not only by a lowered tone of the arterioles but also a lowered resistance of the arteries. Changes in peripheral resistance were closely related to plasma thyroid hormone concentrations. ***Plazinska et al.,*** Warsaw, Poland, studied the effect of lithium carbonate on thyroid uptake and biological- and effective half-life of administered ^{131}I, in 128 patients with hyperthyroidism and a 24h ^{131}-I uptake of <30 %. They found that administration of lithium carbonate, started 3 days before uptake measurement and continued for 5 days, did increase ^{131}I uptake in 106/128 patients, but irrespective of the effect on uptake, increased the biological- (5.8 to 267 days, $p < 0.001$) and effective half-life of ^{131}-I (6 to 7.8 days, $p < 0.001$) in all 128 subjects. They found this effect to be present in subjects with Graves' disease, toxic adenoma and toxic multinodular goiter. The authors suggest that especially in patients with hyperthyroidism and low iodine uptake, administration of lithium carbonate enhances efficacy of iodine of ^{131}-I treatment. ***Ogilvie et al.,*** Cape Town, South Africa, randomly allocated 58 patients with untreated Graves' disease to treatment with carbimazole alone in reducing titrated doses and 48 patients to combined treatment of 40 mg carbimazole and thyroxine sufficient to suppress TSH. Both groups were treated for 12 months. In both treatment groups the relapse rate after one year was high (around 50 %) and also in both groups risk to relapse was especially great if thyroid volume did not decrease during treatment. ***Zimmermann-Belsing et al.,*** Copenhagen, Denmark, evaluated prospectively the insulin-like growth axis before and after 12 months of treatment of 24 female patients with Graves' hyperthyroidism. They did the study as patients with Graves' disease often complain of cognitive impairment, depression, severe fatigue and changes in body composition several months or years after obtaining euthyroidism, while these symptoms are often also seen in patients with growth hormone deficiency. They found that IGF-1, IGF-2 en IGFBP-3 decreased from levels in the high normal range before treatment, to the lower end of the normal range after treatment. Both total lean body mass

and total bone mineral content were positively related to these parameters in the thyrotoxic state but not so after 12 months of antithyroid drug treatment. The authors conclude that the activity of the insulin-like growth axis is decreased in patients with Graves' disease after treatment resembling mild growth hormone deficiency *(Comment:* obviously it would be interesting to know if this decreased activity persist in subjects remaining euthyroid after treatment).

THYROID CARCINOMA

Fatemi et al., Los Angeles, CA, USA, retrospectively studied the prognostic value of a 2 year post-thyroidectomy (Tx) serum Tg (during TSH-suppressive T_4 treatment) using a threshold of 2 μg/l, to indicate risk of recurrence/persistence (R/P) in patients with treated papillary thyroid carcinoma. A group of 285/1419 patients from a large multi-center health plan met the study criteria (papillary ca, initial Tx, no Tg antibodies, .4 years of Tg measurements). Of these patients 245/285 (86.6 %) had a 2 year post-Tx serum Tg <2 μg/l . The <2 μg/l group had a lower percentage R/P at 5 and 10 years (2.8% and 4% respectively), $P < 0.001$ compared with the >2 μgTg group (77.5% and 82.5% respectively. When in the <2 μgTg patients, no-, low dose- or high dose ^{131}I treatment was related to R/P, no effect of ^{131}I was detected. The authors conclude that using a threshold of a Tg 2 μ/l, is an excellent parameter for risk stratification and therapeutic decision-making when found 2 years after thyroidectomy in patients with papillary thyroid carcinoma. *(Comment:* This is an excellent study and helps a lot in risk stratification and decision-making in patients thyroidectomized for papillary thyroid carcinoma. It should be noted that the 2 year post-thyroidectomy Tg threshold is obtained during TSH suppressive T_4 treatment. In patients having a Tg ≤ 2 μ/l, according to this study, treatment with ^{131}I is not necessary). ***Santini et al.,*** Pisa, Italy, studied the effect of endogenous TSH stimulation (by partially withdrawing T_4 treatment) or exogenous TSH stimulation (recombinant human TSH) in two groups of patients (7 in each group) suffering from advanced poorly differentiated thyroid carcinoma with demonstrated metastases, when treated with a combination of carboplatinum and epirubicin administered at 4–6 weeks interval for 6 courses. When a positive response was defined as stable disease or reduction of metastases, 11/14 patients had a positive response. Serum Tg dropped significantly after chemotherapy in 9 patients. No differences were seen in response rate between the two groups. The authors speculate that the relatively favorable response may be at least in part caused by TSH stimulation allowing cytotoxic drugs to enter carcinoma cells. At present, mean survival from start of chemotherapy is 7.5 months in these 11 patients. *(Comment:* No control group, i.e. without TSH stimulation, was studied at the same time). ***Toubert et al.,*** Paris, France, evaluated the sensitivity of high resolution ultrasound (HRUS) + color flow-Doppler (CFD) in three groups of patients with persistent or recurrent differentiated thyroid carcinoma (DTC). Group 1 (n = 85) comprising of patients with high risk DTC, group 2 (n = 13) discordant Tg/WBS, and group 3 (n = 10) present circulating anti-Tg antibodies. All tissues considered suspect with HRUS + CFD were biopsied. Out of 47 patients with suspected recurrence or persistence, 43 had positive cytology. The authors conclude that HRUS + CFD is a reliable method to detect cervical persistent or recurrence of DTC. ***Pacini et al.,*** Pisa, Italy, compared the performance of 5 prognostic scoring systems for patients with differentiated thyroid carcinoma (DTC) in a series of 1053 patients. They tested the following systems:

Clinical Class, MACIS, EORTC, OHIO, TNM. Their final results show that these five systems have similar prognostic values. The OHIO system is better in defining risk groups. The Clinical Class is the easiest to work with and the MACIS has the greatest overlap in low-risk categories. ***Gubala et al.,*** Gliwice, Poland, performed reverse transcription polymerase chain reaction (RT-PCR) to detect Tg mRNA in 75 lymph nodes from 66 patients with suspected DTC recurrence. Classical cytology confirmed lymph node metastases in 22/75 (29%) of lymph nodes while Tg mRNA was positive in 20/22 (92%). Additionally 3 positive Tg mRNAs were found in initially negative lymph nodes on cytology but positive after re-examination of cytology. The authors conclude that with a sensitivity of 86% to histo-pathology examination and a specificity of 100%, Tg mRNA determination in suspected lymph nodes is a useful technique. *(Comment:* Apparently these authors had a maximal specificity of Tg mRNA evaluation in tissue of lymph nodes whereas other authors, see next 2 reports, find much lower specificity when tested in serum of patients with DTC). ***Fugazzola et al.,*** Milan and Rozzano, Italy, measured serum Tg and blood Tg mRNA at days 1–6 after administration of recombinant human TSH (rhTSH) in 37 patients treated by total thyroidectomy and radio-ablation for differentiated thyroid carcinoma (DTC). They tested 2 Tg kits (Immulite and Delfia). Immulite having a functional sensitivity of 1.0 ng/ml lacked sensitivity resulting in a predictive value of 62%. Delfia (functional sensitivity 0.1 ng/ml) performed much better and was highly sensitive, predictive value 86% after rhTSH stimulation. Blood Tg mRNA determinations in basal and stimulated conditions were concordant with clinical status in only 68% of patients, mainly due to false positive cases, i.e low specificity. ***Vivaldi et al.,*** Pisa, Italy, assessed performance of RT-PCR measurement of serum Tg mRNA in 63 patients treated by total thyroidectomy for DTC. Blood was collected while off LT_4 suppressive therapy. Four groups were studied:

1). patients definitely cured (negative WBS and undetectable Tg), n = 16;
2). patients with thyroid remnant, n = 32 (21/32 with detectable Tg);
3). patients with local or distant metastases, n = 15, Tg high in all patients;
4). normal controls, n = 10, Tg within normal range.

The results show no differences in Tg mRNA between groups 1, 2, and 3. Unfortunately 62.5% of definitively cured patients still showed positive Tg mRNA. Although sensitivity was high, the low specificity found, invalidated this technique for the follow-up of patients with DTC. ***Elisei et al.,*** Pisa, Italy, analyzed Na+/I-symporter (NIS) gene expression in human thyroid carcinoma tissues. They found expression in 9/19 primary papillary carcinoma (PTC) and in 21/26 PTC node metastases. Remarkable is that NIS expression was positive in 8/18 PTC thyroid tumors and 6/7 PTC positive lymph nodes that were cold at ^{131}-I scanning before surgery. A dissociation of NIS expression between primary tumors and their corresponding lymph nodes was observed in 28% of cases. From these and other data the authors conclude that

1) undifferentiated tumors and undifferentiated tumor cell lines do not express NIS,
2) there is a poor correlation between iodine uptake in vivo and NIS expression and
3) NIS expression in metastatic tissues can not predict NIS expression in the primary tumor.

(Comment: The absence of iodine uptake in tissues that still express NIS may be explained on the basis that gene expression in these studies was done at the messenger RNA level so that no information is present about protein expression and furthermore that it is not known if tissues were cold due to absent NIS protein or to other abnormalities such as absent incorporation of radioactive iodine in thyroglobulin or even absence of Tg itself). ***Orgiazzi et al.,*** Lyon, France, studied the efficacy of somatostatin receptor scintigraphy (SRS) in 22 patients with recurrence of DTC without iodine concentrating characteristics. They found SRS positive in 16/22 patients. SRS dif-

fered according to metastatic sites. SRS was positive in 7/13 patients with lung metastases in 1 of 4 patients with bone metastases, all 13 patients with mediastinal localizations. On the basis of these and other results the authors conclude that SRS is valuable when tumor metastases do not concentrate iodine. It is especially valuable in patients with mediastinal lesions but underestimates lung metastases. *(Comment*: It is hoped that radioactive somatostatin may also be useful for the treatment of this type of SRS-positive lesions).

PERCUTANEOUS ETHANOL INJECTION (PEI) OF THYROID NODULES

Swider and Grzywa, Rzcszów, Poland, evaluated the effect of percutaneous ethanol injection (PEI) in group A: 17 patients with a benign solid thyroid nodule, mean volume 17.3 ml, and group B: 19 patients with benign nodules that were predominantly cystic, mean volume 24.9 ml. Patients from group A received a mean of 5 injections and group B of 2 injections. After 12, 36, 48 months mean nodule decrease in group A was 68%, 73%, and 85% respectively. These values were for group B 89%, 94%, and 94% respectively. No serious complications were observed and the authors conclude that PEI is an efficacious and safe method in the treatment of non-autonomous thyroid nodules. ***Monzani et al.,*** Pisa, Italy, reported their results of 10 years experience with PEI in 247 patients; 140 with autonomous thyroid adenoma (89 toxic and 51 pre-toxic) and 107 with a benign cold nodule. The mean number of injections was 5 and although PEI was well tolerated, transient local pain was present in 30% of sessions. Transient vocal cord palsy occurred in 6 patients and in 10% of sessions in patients with toxic nodules a transient temperature increase to 38 °C occurred. A positive functional effect in hyperthyroid nodules was seen in 81% and in 92% in "pretoxic" autonomous nodules. The authors suggest that PEI could be considered as a first choice of treatment in the case for thyroid cysts and is certainly suitable for benign cold solid nodules. It may also be the first choice for "pretoxic" nodules and is very effective in toxic nodules when < 3 cm in diameter. *(Comment:* It would be nice to know if the number of clinics that select PEI as a first choice of treatment for benign thyroid nodules is increasing).

AUTOIMMUNITY

Bülow Pedersen et al., Aalborg and Glostrup, Denmark, did a cross-sectional comparative population study in 4649 subjects randomly selected from the general population of two geographical areas with mild (median urinary iodine 61 µg/l) and moderate (45 µg/l) iodine deficiency. They found no difference in the prevalence of TPO-Ab and Tg-Ab between the two areas. In both populations the 2 types of antibodies were more frequently measured in females than in males of the same age group and increased in females with increasing age. Tg-Ab was more often measured in non-smokers than smokers, but the prevalence of TPO-Ab was independent from smoking. The authors conclude that the distribution of thyroid autoantibodies in moderate and mild iodine deficiency is similar, is more frequent in females than males and increases with age in females. A negative association was found between smoking and Tg-Ab. *(Comment:* As in Graves' disease smoking is related to a higher prevalence of ophthalmic disease (OD) whereas smoking is apparently also

associated with a decreased prevalence of Tg-Ab, it would be interesting to know if the presence of Tg-Ab suppresses the development of OD. In this respect one wonders if the prevalence and/or concentration of Tg-Ab is higher in Graves' patients without OD than with OD?? Who takes this up??). ***Mazziotti et al.,*** Naples, Italy, evaluated thyroid- autoimmunity and function in 112 patients (84 males, mean age 50 years), 7 years after a 12 months period of treatment with recombinant IFN-α for hepatitis C. They found that autoimmunity (presence of circulating thyroid autoantibodies) had developed in 32 % of patients. Further analysis showed that absence of antibodies at the end of therapy indicated that no autoimmunity would develop in the years thereafter. However when present, there was an increased risk for development of subclinical or overt thyroid hyper/hypo function. *(Comment:* This study is of practical value in that it seems to tell us that when thyroid autoantibodies are absent after treatment, frequent follow-up for thyroid function seems to be less mandatory). ***Gasnier et al.,*** Munich, Germany, argued that mild selenium deficiency may contribute to the development and maintenance of thyroid autoimmunity and therefore performed a blinded, placebo controlled prospective study in 72 female patients with autoimmune thyroiditis and presence of circulating TPO-Ab and/or Tg-Ab, both > 350 U/ml. The treatment group (36 patients) received 200 μg sodium selenite orally/day for 3 months and the other group of 36 patients a placebo. After 3 months of treatment 9/36 patients in the treatment group had completely normalized antibody titers versus 2/36 in the placebo group ($p = 0.02$). In these 9 patients ultrasound of the thyroid showed a normalized pattern. In the treatment group the mean TPO-Ab concentration decreased by 49 % versus 9 % in the placebo group. *(Comment:* These are provocative results and if confirmed, selenium treatment to prevent or suppress autoimmunity may become an option). ***Gärtner et al.,*** Munich, Germany, tested the frequency of autoimmune thyroiditis in 58 patients with polycystic ovary (PCO) syndrome and compared results with 106 age matched female control subjects. In the control population 10 % had TPO-Ab and/or Tg-Ab, whereas in the patients group this figure was 43.1 % ($p = 0.0001$). In 20/58 of the PCO group, hypoechogeneity of the thyroid ultrasound was present, 8 patients were substituted with LT_4 and 2 were operated in the past for Graves' disease. The results of this study demonstrate a 4-fold higher prevalence of autoimmune thyroiditis in females having PCO. As a possible mechanism the authors suggest that this increased risk might be caused by the elevated estrogen-/low progesterone levels in this patients group.

Several reports were on the ***relationship between thyroid autoimmune disease and diabetes mellitus.*** Thus, ***Bjøro et al.,*** Oslo and Verdal, Norway, analyzed 1972 persons with diabetes mellitus type I or II and found that hypothyroidism was present in females in type I DM, type II DM, and controls in, 10.3 %, 8.1 %, and 4.7 % respectively, while these figures for males were 7.1 %, 1.8 %, and 0.8 %. All these values are significantly higher as compared to controls for both sexes. A significantly increased prevalence of hyperthyroidism in both type I and type II diabetes was present in females: 3.7 %, 3.5 %, and 2.4 % respectively, but for males only in type I DM: 2.9 %, 0.7 %, and 0.6 % respectively. ***Belinchón et al.,*** Canary Islands, Spain, detected thyroid autoimmunity in 14.9% of a group of 101 subjects (52 males) with type I DM, with or without clinical thyroid symptoms. The ratio female to male was 3 : 1 and thyroid autoimmunity was 4 times more frequent in subjects with islet cell antibodies versus absence of islet cell antibodies. ***Karlovich et al.,*** Minsk, Belarus, measured TPO-Ab in 95 patients (46 males) with type I DM. In the total group, TPO-Ab were found in 34.7 % of subjects, with a female to male ratio of 2 : 1.

GRAVES' OPHTHALMOPATHY (GO)

Wakelkamp et al., Amsterdam, The Netherlands, determined orbital expression and TSH-R mRNA in orbital fat and connective tissue obtained during decompressive surgery of 6 untreated patients with active GO and 11 patients with inactive GO. They found that TSH-R mRNA was present in 5/6 active GO and 2/11 inactive GO. Furthermore in active GO, mRNA levels of pro-inflammatory cytokines (IL-1 β, IL-6, IL-8, and IL-10) were higher than in inactive GO while Th1 cytokine expression IFN α and IL-12 also tended to be higher in active GO. Th2 cytokine expression was similar in both groups and TSH-R mRNA was almost exclusively found in active GO. The authors conclude that expression of the TSH receptor at the transscriptional level is only observed in the active stage of the disease and lost in the inactive stage. Cytokine expression in both GO stages is different and may be used for selection of immunomodulatory treatment. *(Comment:* The temporary expression of TSH-R is remarkable and its significance as to the cause of the disease warrants further study). ***Simonetta et al.,*** Pisa, Italy, studied the distribution of thyroglobulin in orbital tissues from patients with OG. 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 GO. The present authors took this issue up again and found that in extracts of orbital tissues from patients with a GO in 3/7 cases using immunoprecipitation, and in 4/7 cases using ELISA, Tg was found in retrobulbar fibroadipose tissue and in inflamed palpebral skin. In addition, ELISA Tg was also found in extraocular muscles. The authors feel that these results support the previously forwarded hypothesis by Kriss et al, in that Tg may act as a co-antigen in the pathogenesis of GO *(Comment:* Is Tg also present in the same tissues of control patients?).

GOITER

Bonnema et al., Odense, Denmark, assessed the effect of I^{-131} therapy in 23 patients with very large goiters on the reduction of intrathoracic goiter and measured inter- and intraobserver variation of MR images of the thyroid and upper airways and the validity of ultrasound goiter size estimation by planimetry. They found that radioiodine treatment has a similar reductive effect on intrathoracic and cervical goiter tissue. MR evaluation of goiter volume has a high intra- as well as interobserver precision but is less precise for calculation of tracheal dimensions. Ultrasound as compared to MR underestimates goiter volume when goiters are large. This underestimation increases with increasing goiter volume. *(Comment:* The results of these authors and of others on treatment of patients (even very old ones) with large goiters, are very favorable in that therapy is very effective and well tolerated. It is my opinion that in patients with large goiters, even if partially intrathoracic, treatment with radioactive iodine is, in general, the first option). ***Knudsen et al.,*** Aalborg, Denmark, studied the effect of iodine intake, smoking and parity on goiter formation in 3.712 women randomly selected from the general population in Denmark. People were selected from 2 areas, one with mild and one with moderate iodine deficiency. They answered questionnaires concerning previous thyroid disease, parity, and smoking habits. Thyroid volume was assessed by ultrasound. Mean thyroid volume was 12.5 ml among parous women and 11.8 ml among nulliparous women ($p = 0.007$). Thyroid volume was strongly associated with parity among smokers, but not in non-smokers. This association was most pronounced

in combination with iodine deficiency and young age. *(Comment:* Cigarette smoke contains thiocyanate that enters the blood and subsequently the thyroid and has antithyroid activity leading to goiter formation. It has also been shown that cigarette smoking is associated with GO in patients with Graves' disease. Here however the mechanism was suggested to be related to direct ocular damage by smoke and/or hypoxia-mediated ischaemic orbital injury).

MISCELLANEOUS

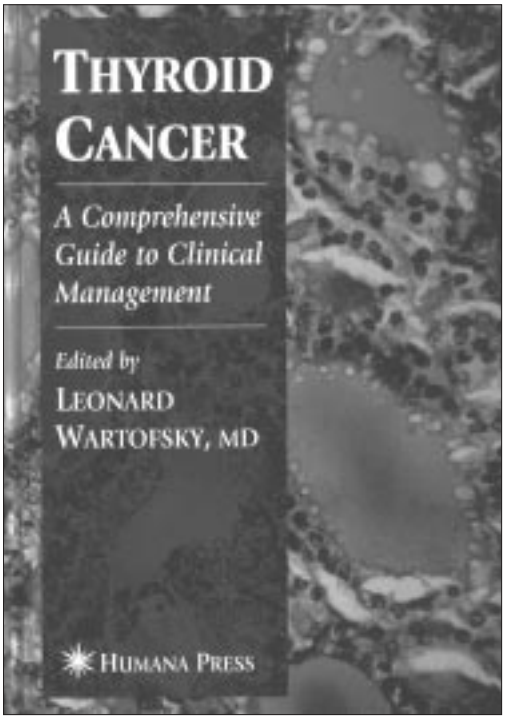
Smyth et al., Dublin, Ireland, investigated possible associations between ***iodine status, thyroid dysfunction and breast cancer.*** In 529 patients with breast cancer and asymptomatic for thyroid disease it was shown that thyroid volume was increased (>18.0 ml) in 32 % as compared to 10.5 % in matched controls ($p < 0{,}001$). In the whole group of breast cancer patients elevated TSH (>4.0 mU/l) was found in 8.0 % vs. 2.8 % ($p < 0.02$) respectively and TPO-Ab positivity in 33.2 % vs. 18.3 % ($p < 0.05$) respectively. Although iodine status between the two groups did not differ, tissue iodine levels were significantly lower in breast cancer tissues than in benign (fibro-adenoma) breast tumors, corresponding to a lower expression of NIS in malignant- versus benign breast tumors. *(Comment:* Apparently patients with breast cancer have significantly higher prevalence of thyroid autoimmunity. The same authors showed previously that prognosis in breast cancer patients who also have circulating thyroid autoantibodies is better than without these antibodies). ***Duntas et al.,*** Athens, Greece, measured circulating levels of ***oxidized-LDL in thyroid disease.*** They found in 33 acute hyperthyroid-, 29 hypothyroid patients, and 57 controls that hypothyroidism is accompanied by enhanced levels of oxidized-LDL while in hyperthyroidism levels are not different from controls. The highest concentrations of oxidized-LDL are however found in smokers irrespective of thyroid function. *(Comment:* Oxidized-LDL is a well known atherogenic factor). ***Faber et al.,*** Frederiksberg, Denmark, measured the relationship between ***mood and the TSH response to TRH in bipolar affective disorder.*** In 19 patients who were followed for 3 years, it was found that ΔTSH was negatively correlated to changes in mood in either direction. In other words, worsening of mood correlated with a reduction in the TSH response to TRH. These changes in TSH response occurred already in minor changes in mood suggesting that the test can be used to detect beginning of mood changes in patients with bipolar affective disorder. ***Obuobie et al.,*** Cardiff, Wales, UK, assessed central ***arterial stiffness in patients with hyper- and hypothyroidism.*** They studied 20 untreated hyperthyroid patients vs. 20 matched controls and 10 hypothyroid patients vs. 12 matched controls and found decreased central arterial stiffness in untreated hyperthyroidism and increased in stiffness in untreated hypothyroidism. After treatment central arterial stiffness moved towards control values in both groups. Before as well as after treatment, central arterial stiffness correlated with age being the major predictor of altered central arterial stiffness. ***Bourdoux et al.,*** Brussels, Belgium, measured serum ***thyroid function parameters and urinary iodine in 818 school children in an area of iodine prophylaxis*** in Central African Republic in June '99 and December '99. Urinary iodine was 18.8 μg/dl and 31.8 μg/dl respectively. Serum T_3 and T_4 values were normal but median TSH was elevated at the two time points, 2.62 and 2.67 mU/l. The authors suggest that excessive iodine prophylaxis might be the cause of the increased TSH and emphasize the crucial need to monitor iodine intake by collecting biochemical data. *(Comment:* It has been shown earlier that, especially in the

elderly, moderate to mild iodine excess may result in hypothyroidism, see Laurberg et al Thyroid 11,457, 2001). ***Ostapenko et al.,*** Minsk, Belarus and Bethesda and New York, USA, measured Tg in 9334 Belarusian subjects, living in an area of moderate iodine deficiency, who were aged 0–18 years at the time of the ***Chernobyl accident .*** The subjects included 4671 without thyroid and laboratory abnormality (normals), 53 with carcinoma all but one papillary, 496 with solitary nodules and 198 with multiple nodules. Compared to the normal group the other three groups had significantly elevated Tg. Tg concentrations were also significantly elevated in subjects with WHO grade 2 diffuse goiter or with ultrasound volumes > 200 % as compared to unexposed matched controls. It appeared that Tg was higher in those subjects that had urinary iodine excretion less than 100 μg/l. Despite these data, the authors conclude that although the average Tg was significantly elevated in carcinoma subjects and subjects with nodules, its sensitivity was too low to be useful as a screening parameter for detection of thyroid carcinoma and nodule formation after ^{131}I exposure in areas of moderate iodine deficiency.

Book Review

By Prof.Ian D. Hay, M.D., Ph.D, F.A.C.E, F.A.C.P., F.R.C.P.(E,G & L).

Dr. Wartofsky, past president of the American Thyroid Association, has dedicated this new textbook to "all our patients who struggle under the cloud of an uncertain future with their malignancies". It is his hope that his comprehensive guide will serve the "needs of practicing physicians for clinically relevant information about thyroid cancer", a disease which Dr. Mazzaferri, in his extensive foreword, describes as "a neglected orphan among human cancers". Dr. Wartofsky has assembled a cast of 22 American authors, 13 from Washington D.C., to produce 52 chapters, organized into nine parts, of which 6 are de-voted to the specific histotypes of thyroid malignancy, with papillary thyroid cancer taking the lion's share at 82 pages. The first part of the book considers the thyroid nodule from the viewpoint of the endocrinologist, nuclear medicine specialist, cytologist or histopa-thologist, and endocrine surgeon. From the standpoint of these three latter disciplines, Wartofsky has been fortunate to have enlisted the expertise of Yolanda and James Oertel, and Orlo Clark, whose contributions are collectively responsible for 25% of the chapters in the text. The main body of the text (269 pages) is devoted to the specific tumor types, and the individual parts for the papillary (PTC) and follicular cancers (FTC) are similarly organized, with chapters devoted to clinical aspects by the editor, followed by considerations from pathology, pediatrics, surgery, nuclear medicine, medical oncology, and radiation therapy. Under "general considerations", and preceding the chapters on the differentiated tumors, is a section that takes up more than a quarter of the whole text, and en-compasses molecular pathogenesis, epidemiology, and radiation effects, but also includes a timely contribution from Matt Ringel on rhTSH, and perhaps a less clinically relevant contribution on immunologic aspects of follicular neoplasms from Jim Baker. The text concludes with a "future directions" section, which includes 6 paragraphs devoted to new approaches to chemotherapy and radiotherapy, but consists principally of a 35 page scholarly review on DNA ploidy, tumor markers, and cancer-causing genes, accompa-nied by an "exhaustive" list of 236 references. The lack of current relevance of 34 of these pages to "practicing physicians who are managing patients with thyroid cancer" does not seem lost on Dr. McDermott, who readily admits in his concluding remarks that such studies of oncogenes and tumor suppressor genes have provided "extremely valuable insights into pathophysiology", and optimistically hopes that "many of these discoveries have or will soon have important clinical applications". In the meanwhile, the practicing physician, who is strapped for time, might want in this overlong chapter to concen-



THYROID CANCER: A COMPREHENSIVE GUIDE TO CLINICAL MANAGEMENT.
Editor: Leonard Wartofsky M.D.
Humana Press, Totowa, N.J.

trate on the final section devoted to possible clinical applications! Although the text has a publication date of 2000, it is disappointing to note that most of the recent references seem to be from the 1996–98 period, many abstracts are cited from presentations at international meetings during 1996, and only a handful of references in the entire book are derived from the literature published during 1999.

In his foreword, Mazzaferri describes that "thirty years ago the main diagnostic tests to identify a malignant nodule were thyroid hormone suppression and radionuclide, imaging". It seemed therefore quite remarkable that the first figure *(page 8)* in this text written for the 21 st century, was a suggested algorithm for nodule evaluation that included both of these ancient techniques. Frustratingly, the relevant text to accompany this algorithm consisted of only one sentence on page 5, and the interested reader has to wait until the summary on page 44 in Chapter 4 to learn more about Dr. Wartofsky's justification for this proposed algorithm. By contrast, Dr. Blum's contribution on nonisotopic imaging is authoritative and well illustrated, while Dr. Oertel's guide to FNAB is concise, practical, and reflects her extensive personal experience in performing aspirations, including her use of an ice cube for mild anesthesia. In Dr. Clark's initial chapter on surgical management of thyroid nodules and cancer risk, he summarizes his reasons for favoring total thyroidectomy, and makes the point that in removing a thyroid cancer adequately, a surgeon should remove all nodes in the central compartment, and consider modified radical neck dissection in patients with palpable nodes in the lateral neck. His initial discussion of the surgery of follicular cell-derived cancers is so comprehensive that one wondered what more would be said later for the individual histotypes, a point to which this reviewer will return.

In the "general considerations" section, there are three chapters by James Figge and his collaborators. The chapter on epidemiology is concise and well written, while that on molecular pathogenesis could well have been abbreviated from its 19 pages and 118 references. The chapter on radiation consists of two parts: the first, devoted to 1949–85, is comprehensive but readable, while the second, devoted to Chernobyl, is perhaps more detailed than the practicing clinician requires, with its accompanying 95 references. The Oertels' chapter on classification of thyroid cancer is derived from the 1988 WHO Monograph and the 1992 AFIP Fascicle. Given that widely accepted classification, it is somewhat surprising to find medullary thyroid carcinoma (MTC) treated in this text under "un-differentiated cancers", taking its place after anaplastic carcinoma, and lymphoma. The Oertels make clear what they consider to be "miscellaneous and unusual cancers of the thyroid", and describe their pathology in Chapter 48. It seems unfortunate that, in the accompanying clinical aspects chapter, the atypical histologic variants (tall cell, columnar cell, solid, and diffuse sclerosing) of PTC are not considered under that heading, and even more extraordinary that Hurthle cell carcinoma (HCC), instead of being considered in the FTC section, finds itself relegated to the end of Chapter 49, after embryologic thyroid remnants and metastatic cancers in the thyroid gland. The two chapters by Johnston and Sweeney on radioiodine therapy seem to this reader inappropriately placed in the text at this point. It would seem unusual to consider arguments for routine remnant ablation even before one has read about the presentation and initial operative therapy of PTC and FTC. A similar argument might be made about the present position in the text of the second chapter, which lists all possible short- and long-term radiation side effects and complications.

As noted above, the PTC section, encompassing Chapters 16 through 26, represents almost 20 % of the text, and the quality of its content varies considerably. Chapter 17 by the Oertels is an author-

itative, well illustrated "gem". By contrast, Clark's Chapter 18 on the surgical approach to PTC, gives new meaning to the term "rampant redundancy", since all but 2 sentences in this chapter are identical to the 6 paragraphs previously published on pages 51–53 in Chapter 5! I personally was delighted to read about the pTNM system of staging in PTC in Dr. Wartofsky's clinical aspects chapter, but was saddened to see that, for patients aged 45 years and older, stages II and III are wrongly described. Stage II should include both T_2 and T_3 node-negative cases, while stage III implies either T_4NOM^0 or Any T,N^1M^0 disease. In contrast to most other contemporary references on this subject, there was no mention of AGES, AMES, or even EORTC prognostic systems. Dr. Wartolsky inaccurately describes recurrences at nodal, distant, and local sites as "three varieties of presentation that reflect a different prognostic category", and states that these factors have been incorporated into the "MACIS" scoring system, which is certainly not the case. The chapters devoted to I^{-131} therapy, external irradiation, and chemotherapy in PTC are informative, as is Dr. Burch's chapter on Tg monitoring in follow-up. Chapter 24 on Dr. Wartofsky's approach to the whole body scan-negative, Tg-positive patient will be familiar to readers of the previously published and non-referenced JCEM 83: 4195–4203 of 1998. In my opinion, the chapter devoted to prognosis in PTC is inadequate. Much is quoted from a 1990 report from the Mayo Clinic on 1,500 consecutively treated PTC patients, but, like Wartofsky's chapter 16, there is no mention of the many prognostic scoring and risk-group schemes that have been derived since 1987 from large multivariate analyses. This is an unfortunate omission in a text that is claiming to be a comprehensive guide for the practicing physician. Lastly, with regard to the PTC section, the approach to pediatric cases advised by Dr. Poth, in terms of routine administration of 80 to 150 mCi of I^{-131} for remnant ablation, seems remarkably aggressive, and perhaps foolhardy in view of the potential for long-term morbidity, and even mortality, consequent to such an approach.

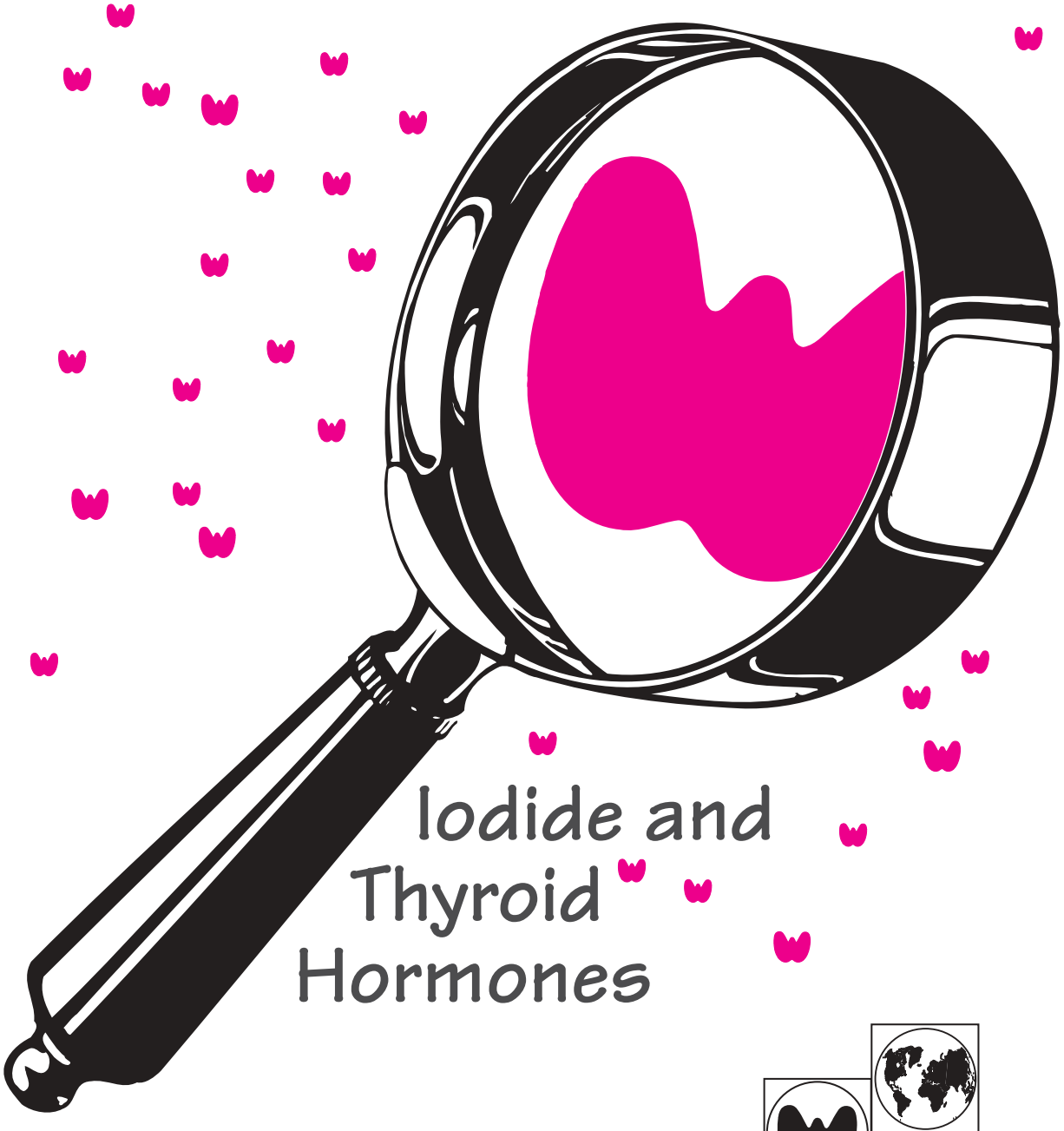
The section devoted to FTC, like that on PTC, varies in quality. The Oertels are again right on target with their chapter on pathology. Dr. Clark does address the problems he encounters both with follicular and Hurthle cell cancers (HCC), and suggests that in his particular surgical setting frozen section is "a waste of time and money". Some might differ from him in his personal interpretation of "minimally, regular, and widely" invasive in terms of involvement of the thyroid capsule. Again, the chapter on prognosis in FTC seems suboptimal, and the table of poor prognostic factors incomplete by the exclusion of older patient age, which is the first factor mentioned in the accompanying text. Incidentally, the inclusion of age would make the tables for PTC and FTC identical, which probably represents an over-simplification, which would be clarified by consideration of the plentiful data derived from many multivariate analyses in series of both histotypes. The clinical aspects chapter again has some unusual features, some irritating, and others misleading. The first reference cited in Chapter 27 is numbered 15, and it transpires that references 1 through 14 are contained in the summary, which consists of the last 2 paragraphs of the chapter. The chapter talks of staging and prognostic indicators, but the data cited refers to patients with PTC, not FTC. Two paragraphs are devoted by Wartofsky to the particular problems faced by patients with HCC, but as noted above, the reader has to wait another 158 pages of the text to get to the real HCC section! Dr. Poth does have 5 paragraphs devoted to pediatric FTC, although in her first sentence she freely admits to "an almost total lack of definitive data". This presumably underscores Dr. Wartofsky's stated intent "to present evidence-based recommendations where possible, and to indicate clearly where evidence is lacking".

In contrast to the PTC and FTC sections, the parts V through VIII, devoted to "undifferentiated can-

cers", and miscellaneous unusual cancers, are of generally high standard. The four pathology chapters are very well presented and illustrated. Dr. Sherman has done an excellent job with both anaplastic carcinoma and thyroid lymphoma. His contribution on prognosis in anaplastic cancer is appropriately short, bot adequate. The chapter by Donglas Ball on medullary thyroid cancer (MTC) is of a high standard, but I have a problem with his discussion of initial clinical stage. The cited work of Bergholm in Sweden used the internationally accepted pTNM stages, which I think should have been shown in his table 2. Instead, he shows a system attributed to the NTCTCS group, which considers stage I as being only C-cell hyperplasia, in contrast to pTNM where stage I would be in-trathyroid microcancer ($T_1N^0M^0$). Lastly, although I believe that the PTC variants, and both insular and HCC should have been considered under the PTC and FTC sections, respectively, I think that Ringel and associates are to be complimented for the way that they have identified from the literature 45 cases of squamous cell cancer, 228 insular cancers, 163 tall cell variants, 24 columnar cells, 63 diffuse sclerosing variants, and 31 mucoepidermoid cancers. Moreover, they have given the reader accurate references with one exception! In their tables 2 and 3, they refer to data "adapted from Burman and Ringel (ref. 210) with permission". However, their list of references stops at number 188! For those who want to read more about these unusual tumors, I would guess that the reference is by Burman, Ringel, and Wartofsky from the Endocrinology and Metabolism Clinics of North America 25:49-68 in March of 1996.

Well, would I recommend that individual clinicians go out to purchase a personal copy of this rather expensive text? No, I would rather they spend the money on a more general endocrine text, or maintain their dues to their respective thyroid association. However, I do think that this book should grace the library shelves of every significant Division of Endocrinology. It is not an easy task to attempt to create a timely and comprehensive guide for managing thyroid cancer, and Dr. Wartofsky should be applauded for his making such an attempt. In concluding, I am sure that this important text will provide a resource for many years to come for our clinical and lab-based colleagues, who, like myself, have an interest in trying to provide answers for relevant questions posed by concerned patients with differentiated thyroid cancer.

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