DISCUSSION ABOUT THE LIMIT BETWEEN NORMAL THYROID AND GOITER: MINIREVIEW

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Although the goitre seems to be well defined at least from clinical point of view, it is virtually impossible to find the precise definition of the opposite side of what should be the normal thyroid as concerns its size, histological structure and namely the level of growth stimulation by the external factors (such as TSH) and intrinsic tissue growth factors. Theoretically, the normal thyroid should be able to cover the requirements of the organism for the hormone in a reasonably large range without being stimulated to grow by any external or internal factors.

So far, the search for normal thyroid has been conducted by several ways: 1. by post mortem thyroid weight, 2. by palpation, 3. by ultrasound. As based on post mortem thyroid weight, until the middle of this century a typical thyroid gland was considered to be about 20-25 g with the accepted upper normal size of 30 g, while more recent studies in iodine replete population have reported mean weights of about 10 g and an upper normal size 20 g. According to several classifications for thyroid palpation the unpalpable thyroid should be allotted to the Grade 0 which is defined as "normal gland", "no goiter at all", "absence of goiter" etc.

The first recommendation of normal thyroid volume for children and adolescents as estimated by ultrasound has been developed by GUTEKUNST and TEICHERT (1994). However, this was later challenged by the findings of considerable number of thyroid volumes which were higher than the upper limit of that recommendation as found in the countries with satisfactory values of urinary iodine (DELANGE et al. 1997). Nevertheless, recently it appeared that about 10-15 percent of adolescent thyroids show increased thyroid growth rate which significantly differs from the majority and which might be related to different tuning of molecular growth mechanism presumably of genetic origin (TAJTAKOVA et al. 1998; LANGER et al., in press). From, this follows that a certain number of enlarged thyroids apparently should not be included into a normal range.

Key words: Goiter – Normal thyroid – Thyroid and sex – Ultrasound – Iodine

The definition of normal thyroid is still needed

From sophisticated pathophysiological view the goiter has been defined as "slowly developing diffuse or nodular enlargement of thyroid gland due to an excessive replication of follicular epithelia with subsequent generation of new follicles of widely differing structure and function" (STUDER 1982). Another more clinically adjusted definition says that "goiter is simply an enlargement of the thyroid gland and may result from hormonal or immunological stimulation of gland growth or the presence of inflammatory, proliferative, infiltrative, or metabolic disorders" (SIMINOSKI 1995). In contrast, it is virtually impossible to find somewhere the precise definition of the opposite side of such coin – i.e. the definition of what should be the normal thyroid as concerns its size, histological structure and namely the level of growth stimulation by the external factors (such as TSH) and intrinsic tissue growth factors.

Search for normal thyroid by post mortem thyroid weight

Actually, the most objective information on the thyroid size may be obtained by weighing the gland after death. There are two large scale observations on the thyroid weight in the population after 50 years of age which was subjected to iodine deficiency for first 3-4 decades of life. Thus, Gerber (1980) collected the data from 4865 subjects of various age in Switzerland and found that in 1949-50 (i.e. after 30 years of salt iodination) the average thyroid weight in women over 50 was in a range of 80-90 g, while that in men was 55-75 g. However, if they evaluated such data from subjects of the same age as obtained 30 years later (which means that they spend the whole life under the influence of iodized salt) the average thyroid weight in both sexes was the same, the range being 20-30 g which was about a half of that obtained in 1949-50.

In another report from former Czecho-Slovakia (Silink and Reisenauer 1966) 2365 males and 2020 females over 50 were examined in 1958 (i.e. after 10 years of salt iodination) and the average thyroid weight found was 33.69 g and 36.03 g, respectively.

Furthermore, several authors from various countries reported the data on thyroid weight obtained under not clearly defined iodine intake by the population of the appropriate area. Thus, Pankow et al. (1985) reviewed 10 reports on the thyroid weight from the literature between 1926 and 1963, among them one from Switzerland and 9 from the United States. The average values for what they called normal thyroid as reported in those papers ranged from 16.7 to 28.0 grams, the average female thyroid being about 3 grams less than that of males.

In addition, Mortensen et al. (1955) from Mayo Clinic found the weight of a great majority of 821 thyroids between 20 and 40 g. Agerbaek (1974) in Denmark reported the average weight of 25.5 g in 156 males and 22.9 g in 61 females. Berghout (1987) reviewed the thyroid weight indicated in five fundamental textbooks published in 1973-85 which ranged between 15 and 30 g, while DeGroot and Stanbury (1986) in their textbook indicated normal weight of 15-20 g. At the same time, Solomon (1986) reported that "one generally estimates normal male gland at 15-20 g and the normal female gland at 20-25 g". In addition, Matovinovic (1983) in his review indicated 20-25 g as normal thyroid weight.

Theoretically, the normal thyroid should be able to cover the requirements of the organism for the hormone in a reasonably large range without being stimulated to grow by any external or internal factors.

Thus, such thyroid should be of normal size. Such conditions are very likely to be reached under optimal iodine intake existing for several generations or at least since early childhood (in this respect the requirement of a regular daily optimal intake should be stressed) which may be the case in such countries like Japan, Iceland or perhaps some small Pacific islands. Such view may be supported by the report of Sigurjonsson (1961) who found in Iceland the average thyroid weight of 14 g in men and 11.6 g in women. Pankow et al. (1985) reported the data from 1400 normal thyroids taken at autopsy in state of Washington between 1979 and 1981 showing the average weight of 16.4 g for 20-29 year old males, 18.5 g for 30-69 year old males and 14.4 g for 20-69 year old females. It appears that the values reported in last two papers are remarkably lower than the previous ones. Thus, considering the high iodine intake in the US namely during last 3-4 decades, these values together may be considered as close to what may be called the normal thyroid.

Thus, until the middle of this century a typical thyroid gland was considered to be about 20-25 g with the accepted upper normal size of 30 g, while more recent studies in iodine replete population have reported mean weights of about 10 g and an upper normal size 20 g.

Considering the specific weight of the thyroid tissue of about 1 g, such view on the normal limit of thyroid size may be supported even by several ultrasonographic data which will be presented bellow. Actualy, the correlation of the ultrasound assessments of thyroid weight with true gland weight was found to be very close (r=0.88 to 1.00) by Tannahill et al. (1978), Berghout et al. (1988) and Hegedus (1990).

Search for normal thyroid size by palpation

Until the early eighties, the size of the thyroid *in vivo* has been evaluated exclusively by palpation.

From such point of view several classifications of thyroid size were suggested (reviewed by THILLY et al. 1980). The common feature of such classifications is that the unpalpable thyroid is being allotted to the Grade 0 which, by various authors, is defined as "normal gland", "no goiter at all", "absence of goiter" etc.

In contrast, goiter Grade I is defined as "visible goiter", "visibly enlarged", "visible with head in normal position" etc. Thus, using the palpation, the main problem to be solved appears to consist in defining at which degree of thyroid enlargement there may be sufficient pathological alteration of the gland justifying to speak about goiter, as defined e.g. by STUDER (see above). Nevertheless, from epidemiological view the distinction between Grade 0 and Grade I is still unsettled. On one hand, some small thyroid hypertrophies are considered not to have sufficient pathological significance to be classified as goiter, but they should not be recorded as normal. On the other hand, several classification systems (including that of WHO) ask to record all palpable thyroids as goiter. From these and other reasons HEGEDUS et al. (1990) stated "we do not believe that palpation of the thyroid as an estimate of its size can be used in goitre epidemiology studies".

Search for normal thyroid volume by ultrasound

However, within a recent decade such problems have been seriously challenged by ultrasonographic volumetry as described by RASMUSSEN and HJORT (1974) and namely by BRUNN et al. (1981). One of the first papers turning attention to the problem of discrepancy between the thyroid size obtained by simple palpation and ultrasound was perhaps that by OLBRICHT et al. (1985) who examined by ultrasound the volume of non-palpable thyroids in 217 men and 325 women and found the range from 5 to 40 ml with maximum frequency between 10 and 25 ml. Today such discrepancy between the data obtained by weighing or palpation on one side and by ultrasonography on the other is well known and generally accepted (GUTEKUNST et al. 1986; HEGEDUS 1990).

The main conclusion to be drawn from these and other findings to be presented bellow is that the upper limit of normal thyroid volume should be shifted down and more or less deeply into the range of what was used to be called "unpalpable thyroid".

If we take the above presumption on the normal thyroid existing only in the territories with long-term and regularly optimal iodine intake, we should first consider the sonographic data from such countries. Thus, in Japan YOKOYAMA et al. (1986) found the average thyroid volume in adults about 10 ml which was similar to that reported by UEDA (1990) for Japanese adolescents over 160 cm of body height. Moreover, about the same volume in adults was reported by BERGHOUT et al. (1987) from non-iodine deficient area of Netherlands (average of 12.7 ml in 25 men and 8.7 ml in 25 women) and by GUTEKUNST et al. (1986) from Sweden (average of 11.1 ml in man and 7.7. ml in women out of a total of 303 subjects). In Slovakia, TAJTAKOVA and LANGER (unpublished) found median thyroid volume of 10.4 ml in 558 adult women (age 21 to 74 years) and no difference between these of 21-40 years of age (median 10.7 ml, N=218) and 41-74 years of age (median 10.3 ml, N=340). Such values are very close to those presented above which were found by weighing the thyroid in Iceland (SIGURJONSSON 1961) and USA (PANKOW et al. 1985).

It may be suggested that such thyroid size is presumably approaching to what might be defined as normal thyroid for the species homo sapiens.

Male and female thyroid

One of the special problems to be discussed seems to be the relationship between the thyroid size and sex which appears to be still a matter of controversy. Actualy, several recent reports showed larger thyroids in adult men than in adult women as estimated by sonography. Such reports originated mostly from iodine sufficient countries like Japan, Denmark, Sweden and Netherlands (YOKOYAMA et al. 1986; HEGEDUS et al. 1983, 1990; GUTEKUNST 1986; BERGHOUT et al. 1987; resp.), but also from the countries with marginally deficient iodine intake such as former West Germany (OLBRICHT et al. 1985; STRUVE and HINRICHS 1989).

In contrast, there are extensive observations on thyroid weights in adults subjected to iodine deficiency for a majority of their life (for more details see above) definitely showing larger thyroids in wom-

en than in men either in Switzerland (Gerber 1980) or in former Czecho-Slovakia (Silink and Reisenauer 1966).

In addition, even some recent ultrasound data showed larger thyroids in adolescent girls than in boys in some areas of iodine deficient former West Germany (Leisner et al. 1985; Gutekunst et al. 1985; Mueller-Leisse et al. 1988; Menken et al. 1992) and Poland (Golkowski et al. 1993). Finally, there are still some general opinions about the female thyroid being larger than the male one (e.g. Solomon 1986; see above) which are apparently reflecting the past experience obtained during the period of prevailing iodine deficiency in a majority of countries.

Our recent data from iodine replete Slovakia (Tajtakova and Langer, unpublished) showed no difference in mean values of thyroid volume between 13 year old boys (4.47 ml/m^2 of body surface; N = 346) and girls (4.19 ml/m^2; N = 411) as well as between 17 year old boys (4.80 ml/m^2; N = 260) and girls (4.94 ml/m^2; N = 372). Similar data showing the same thyroid volume in boys and girls

aged 6-14 years were reported from the area of mild iodine deficiency in Italy (Vitti et al. 1994) and from northern Finland (Takalo et al. 1991). In mild iodine deficient South Tirol (northern Italy) Oberhofer et al. (1992) found slightly higher thyroid volume in girls between 10 and 13 years of age, but they examined different subjects in each age group. Only slightly higher thyroid volumes in girls were observed in iodine replete Sweden (Gutekunst et al. 1985) and recently in Berlin after the normalization of iodine supply (Liesenkoetter et al. 1997).

Recently a cluster of 3265 children aged 6-15 years from four European countries (European Thyromobil Study) considered to be iodine replete as based on a single urinary iodide estimation in all of them has been evaluated and significantly higher values were found in girls between 9 and 14 years of age (Delange et al. 1997). Comparing these data with ours as obtained in iodine replete Slovakia (Tajtakova and Langer, unpublished), it may be suggested that the whole cluster defined above from a single urinary iodine estimation may not originate from definitely iodine replete areas.

From the above observations it may be suggested that the female thyroid tends to be smaller than the male one under relatively sufficient iodine intake, while it appears to be more vividly responding to either absolute or relative (puberty, pregnancy) iodine deficiency under which it tends to become larger than that of males.

Fundamentals on thyroid growth

Several recent comprehensive reviews by Dumont et al. (1991, 1992) showed the complex role of numerous tissue growth factors, local hormones, cytokines, oncogenes, neurotransmitters etc. in the proliferation and differentiation of thyrocytes and thus in thyroid growth. In spite of some previous temporary doubts the decisive role of pituitary TSH (in cooperation with insulin, IGF, EGF and other growth factors) in the stimulation of thyroid growth via several cell proliferation cascades (from hormone receptor to adenylate cyclase, tyrosine protein kinase or phospholipase C) appears to be well defined and conclusively demonstrated. In contrast, the thyroid growth is known to be inhibited by iodine (Dugrillon et al. 1990).

In addition, it should be kept in mind that the thyroid cells are polyclonal and functionally heterogenous (Studer and Ramelli, 1982) which generates an individual growth program and widely varying basal and TSH stimulated cAMP activity of different clones (Huber et al. 1990). This further results in a fine tuning of the activity of whole gland by responding of more and more clones to the increasing level of TSH.

Some fractions of cells with shorter cell cycle may generate progenies that tend to overgrow their neighboring cells. In nonneoplastic endocrine hyperplasia such as iodine deficiency goiter these processes may be accelerated by systemically acted growth-promoting factors. In such progenies, the chances for the acquisition of various mutations are increasing with shorter interdivision times (Studer and Derwahl 1995).

Finally, the problem of autoimmunity and thyroid growth cannot be overlooked in some thyroid abnormalities (Drexhage 1996). This concept is currently based on the findings of IgG fractions of Graves sera that are capable to stimulate thyrocyte proliferation *in vivo* and *in vitro* by stimulating 2nd messenger cascades other than cAMP. Since such antibodies to the TSH-receptor are polyclonal, there is increasing

evidence that some of their varieties are against distinct isoforms of TSH-receptor coupled to distinct G proteins. These findings support possible participation of such interrelations in influencing the thyroid growth mechanism.

Adolescent goitre as a possible background of thyroid disorders in adulthood

It is well known that the thyroid during the childhood and adolescence is growing together with the organism. However, the question appears which growth rate would be still physiological and where should be the threshold of pathological growth. Actualy, Gutekunst and Teichert (1993) obtained ultrasound data from children and adolescents with optimal iodine intake and indicated 50 and 97 percentile limits of what they called normal thyroid volume. This appears to be a first sophisticated attempt to delineate the normal thyroid, although it might be not definitely confirmed and accepted in the future. Actualy, the upper limit of their data which are now called "Gutekunst norm" has been recently challenged by the group conducting European Thyromobil Study (Delange et al. 1997). In brief, in 12 European countries they examined thyroid volume by ultrasound in 7599 schoolchildren and iodine in 5709 urine samples. From such amount of data, they selected a cluster of 3265 children from 23 sites located in Netherlands, Slovakia, Austria and France where the median urinary iodine was at least 10 g/dl in groups of at least 50 children each and claimed the thyroid volume in these sites to be normal. After computing the thyroid volumes for individual age groups between 6 and 15 years, they claimed such thyroid volumes to be normal. Since the 97 percentile of the obtained data was higher than the previous "Gutekunst norm", they suggested to increase the level of 97th percentile by 2-5 ml depending on the age. This conclusion was apparently based on the presumption that all thyroids in adolescents represent a single compact homogenous group. However, recently it appeared that a certain number (i.e. at least about 10-15 percent) of adolescent thyroids shows increased thyroid growth rate which significantly differs from the majority and which might be related to different tuning of molecular growth mechanism presumably of genetic origin (Tajtakova et al. 1998; Langer et al., in press). From, this follows that the adolescent thyroids do not represent any homogenous group and thus it may be suggested that a certain number of enlarged thyroids should not be included into a normal range.

Recently, several reports accumulated on the ultrasound findings namely in children 13 years old from various countries which show the long-term effects of the iodine intake and complex antithyroid influences perhaps much better than any other examination (e.g single estimation of urinary iodine etc.). Thus, the average thyroid volume in the countries with optimal iodine intake such as Sweden (Gutekunst et al. 1985 – 224 cases), Japan (Ueda 1990 – 45 cases) or Slovakia (Langer et al. – 702 cases) and city of Berlin (Liesenkoetter et al. 1997) was 4-5 ml, while in those with marginally deficient such as Finland (Takalo et al. 1994 – 76 cases), Belgium (Chanoine et al. 1991 – 32 cases), Austria (Oberhofer et al. 1992 – about 100 cases) and some areas of Italy (Aghini-Lombardi et al. 1997 – several hundred cases) was about 7 ml.

In addition, in some countries with clearly deficient iodine intake, at least until recently, the thyroid volume in the same age group was 7-12 ml (e.g. in Germany; several papers reviewed by Menken et al. 1992 – about 2500 cases), former East Germany (Meng and Schindler 1997 – 207 cases), Poland (Golkowski 1993 – several thousand cases) Hungary (Szecsenyi-Nagy et al. 1992 – 183 cases) and some areas of Italy (Aghini-Lombardi et al. 1997 – number of cases for 13 year old unknown).

The above data show that the long-term influence of different iodine intake results in considerable differences in thyroid volume as early as in childhood. It should be recalled that iodine is known as important intrathyroidal modulator of TSH effect on the growth and endocytosis which is increasing under iodine deficiency and vice versa (Studer and Ramelli 1982; Pisarev 1985).

From this follows that the effective iodine prophylaxis should be predominantly applied since early childhood with the special aim to keep molecular growth mechanisms quiet and thus to prevent the expression of appropriate growth factors which is under TSH control. Actualy, at the level of serum thyroxine below 5 mg/dl the level of TSH in the euthyroid subjects below 15 years of age was about

twice as high as that in those between 16 and 25 years (Delange 1985). It has been also reported that the iodine prophylaxis, if applied after adolescence, does not reverse the hyperplastic changes in the thyroid any more (Correa 1980). From this viewpoint it appears that the molecular background of various thyroid disorders manifesting themselves in adult age may originate during childhood and adolescence, if the activity of local growth factors is being inappropriately stimulated and, in contrast, that the best chance to counteract the pathological thyroid growth and thus to prevent a certain percentage of thyroid disorders is particularly during that period of life.

References

Agerbaek H: Weight and iodine content of the thyroid gland in Jutland. Acta Med Scand **96,** 505-506, 1974

Berghout A, Wiersinga WM, Smits NJ, Touber JL: Determinations of thyroid volume as measured by ultrasonography in healthy adults in a non-iodine deficient area. Clin Endocrinol **26,** 273-280, 1987

Berghout A, Wiersinga WM, Smits NJ, Touber JL: The value of thyroid volume measured by ultrasonography in the diagnosis of goitre. Clin Endocrinol **28,** 409-414, 1988

Brunn J, Block U, Ruf G, Bos I, Kunye WP, Scriba PC: Volumetrie der Schilddruesenlappen mittels realtime Sonographie. Dtsch Med Wschr **106,** 1138-1340, 1981

Chanoine JP, Toppett V, Lagasse R, Spehl M, Delange F: Determination of thyroid volume by ultrasound from the neonatal period to late adolescence. Eur J Pediatr **150,** 395-399, 1991

Correa P: Pathology of endemic goiter. In Endemic Goiter and Endemic Cretinism (Eds. JB Stanbury and BS Hetzel), pp. 303-332, John Wiley, New York 1980

DeGroot L, Stanbury JB: The Thyroid and its Diseases. John Wiley, New York 1986

Delange F: Adaptation to iodine deficiency during growth. In Pediatric and Adolescent Endocrinology (Ed. Z Laron), pp. 295-326, Karger, Basel 1985

Dugrillon A, Bechtner G, Uedelhoven WM, Weber PC, Gaertner R: Evidence that an iodolactone mediates the inhibitory effect of iodide on thyroid cell proliferation but not on adenosine 3',5'-monophosphate formation. Endocrinology **127,** 337-343, 1990

Dumont JE, Maenhaut C, Pirson I, Baptist M, Roger PP: Growth factors controlling the thyroid gland. Bailliere's Clin Endocrinol Metab **5**, 727-754, 1991

Dumont JE, Lamy F, Roger P, Maenhaut C: Physiological and pathological regulation of thyroid cell proliferation and differentiation by thyrotropin and other factors. Physiol Rev **72**, 667-697, 1992

Gerber D: Schilddruesengewichte and Jodsalzprophylaxe. Schweiz med Wochenschr **110,** 2010-2016, 1980

Golkowski F, Szybinski Z, Huszno B, Stanuch H, Zarnecki A: Ultrasound measurement of thyroid volume in the nation-wide epidemiological survey on iodine deficiency in Poland. Endokrynologia Polska **44,** 351-358, 1993

Gutekunst R, Smolarek H, Wachter W, Scriba PC: Strumaepidemiologie. IV. Schilddruesenvolumina bei deutschen und schwedischen Schulkindern. Dtsch med Wschr **110,** 50-54, 1985

Gutekunst R, Smolarek H, Hasenpusch U, Stubbe P, Friedrich H-J, Wood WG, Scriba PC: Goitre epidemiology: thyroid volume, iodine excretion, thyroglobulin and thyrotropin in Germany and Sweden. Acta Endocrinologica (Copenh) **112,** 494-501, 1986

Gutekunst R, Teichert HM: Requirements for goitre surveys and the determination of thyroid size. In Iodine deficiency in Europe: A continuing Concern (Eds. F Delange, JT Dunn and D Glinoer), pp. 109-115, NATO ASI, Series A: Life Sciences vol. 241, Plenum Press, New York 1993

Hegedus L: Thyroid size determined by ultrasound. Danish Med Bull **37,** 249-263, 1990

Hegedus L, Perrild H, Poulsen LR, Andersen JR, Holm B, Schnohr P, Jensen G, Hansen JM: The determination of thyroid volume by ultrasound and its relationship to body weight, age, and sex in normal subjects. J Clin Endocrinol Metab **56,** 260-263, 1983

Huber G, Derwahl M, Kaempf J, Peter H-J, Gerber H, Studer H: Generation of intercellular heterogeneity of growth and function in cloned rat thyroid cells (FRTL-5). Endocrinology 126, 1639-1645, 1990

Langer P, Tajtakova M, Podoba J, Kostalova Ł, Gutekunst R:
Thyroid volume and urinary iodine in school children and adolescents in Slovakia after 40 year of iodine prophylaxis. Exp Clin Endocrinol 102, 394-398, 1994

Langer P, Tajtakova M, Bohov P: Possible role of genetic factors in thyroid growth rate and in the assessment of upper limit of normal thyroid volume in iodine-replete adolescents. Thyroid, in press

LEISNER B, HUTTER G, KNORR D: Schilddruesenvolumen euthyreoter Kinder und jugendlicher. Münchn med Wschr **127,** 909-911, 1985

LIESENKOETTER KP, KIEBLER A, STACH B, WILLGEROT H, GRUETERS A: Small thyroid volumes and normal iodine excretion in Berlin schoolchildren indicate full normalization of iodine supply. Exp Clin Endocrinol Diabetes **105,** Suppl. 4, 46-50, 1997

MATOVINOVIC J: Endemic goiter and endemic cretinism at the dawn of third millennium. Ann Rev Nutrit **3,** 341-412, 1983

MENKEN KU, ENGELHARDT S, OLBRICHT T: Schilldrüsenvolumina und Jodurie bei Kindern im Alter von 2-16 Jahren. Dtsch med Wschr **117,** 1047-1051, 1992

MORTENSEN JD, WOLLNER LB, BENNET WA: Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab **15,** 1270-1280, 1955

MUELLER-LEISSE C, TROEGER J, KHABIRPOUR F, POECKLER C: Schilddruesenvolumen-Normwerte. Dtsch med Wschr **113,** 1872-1875, 1988

OBERHOFER R, OBER A, SEEBER A, AMOR H: Struma-Epidemiologie in Suedtirol, Dtsch med Wschr 117, 1508-1512, 1992

OLBRICHT T, BENKER G, REINWEIN D: Ultrasound: A novel tool for the diagnosis and follow-up of simple goitre. In Treatment of Endemic and Sporadic Goiter (Eds. D Reinwein and PC Scriba), pp. 175-189, Schattauer, Stuttgart 1985

PANKOW BG, MICHALAK J, MCGEE MK: Adult human thyroid weight. Health Physics, December 1985

RASMUSSEN SN, HJORTH L: Determination of thyroid volume by ultrasound scanning. J Clin Ultrasound **2,** 143-148, 1974

SIGURJONSSON J: Studies on the human thyroid gland in Iceland. In: Advances in Thyroid Research (Ed. R Pitt-Rivers), pp. 279-282, Pergamon Press, Oxford 1961

SIMINOSKI K: Does this patient have a goiter? JAMA **273,** 813-817, 1995

STRUVE C, HINRICHS J: Schilddruesenvolumina und Haufigkeit herdfoermiger Veraenderungen bei Schilddruesengesunden Maennern und Frauen verschiedener Alterklassen. Dtsch med Wschr **114,** 283-287, 1989

SILINK K, REISENAUER R: Geographical spread of endemic goiter and problems of its mapping. In: Endemic Goitre and Allied Diseases (Eds. K Silink and K Cerny), pp. 33-47, VEDA, Bratislava 1966

SOLOMON D: Clinical examination of the thyroid. In: The Thyroid Gland (Ed. L van Middlesworth), pp. 19-34, Year Book Medical Publishers, Chicago 1986

STUDER H, RAMELLI F: Simple goiter and its variants: Euthyroid and hyperthyroid multinodular goiters. Endocrine Rev **3,** 40-61, 1982

TAJTAKOVA M, LANGER P, GONSORCIKOVA V, BOHOV P, HANCINOVA D: 1998 Recognition of a subgroup with rapidly growing thyroids under iodine-replete conditions: seven year follow-up. Eur J Endocrinol **138,** 674-680, 1998

TAKALO RM, MAKARAINEN HP, JAAKKOLA RK: Thyroid gland volume and echo structure in 13-year-old children in northern Finland. Acta Endocrinologica (Kbh) **79,** 600-603, 1994

THILLY CH, DELANGE F, STANBURY JB: Epidemiologic surveys in endemic goiter and cretinism. In: Endemic goiter and endemic cretinism (Eds. JB Stanbury and BS Hetzel), pp. 157-184, John Wiley, New York 1980

UEDA D: Normal volume of the thyroid gland in children. J Clin Ultrasound **18,** 455-462, 1990

VITTI P, MARTINO E, AGHINI-LOMBARDI F, RAGO T, ANTONANGELI L, MACCHERINI D, NANNI P, LOVISELLI A, BALESTRIERI A, ARANEO G, PINCHERA A: Thyroid volume measurement by ultrasound in children as tool for the assessment of mild iodine deficiency. J Clin Endocrinol Metab **79,** 600-603, 1994.

YOKOYAMA N, NAGAYAMA Y, KAKEZONO F, KIRIYAMA T, MORISA S: Determination of the volume of the thyroid gland by a high resolutional ultrasonic scanner. J Nucl Med **27,** 1475-1479, 1986

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