Thyroid autonomy: sensitive detection in vivo and estimation of its functional relevance using quantified high-resolution scintigraphy

Manfred Bähre, Reinhard Hilgers¹, Corinna Lindemann and Dieter Emrich

Division of Nuclear Medicine, Department of Radiology, and Division of Medical Statistics¹, University of Göttingen, Göttingen, FRG

Abstract. This study is concerned with 236 euthyroid individuals living in an area of iodine deficiency, 227 of whom had endemic goitres. In these subjects, autonomy could be suspected owing to an inhomogeneous activity distribution on the thyroid scintigram or a subnormal TSH response to TRH. They complete a total number of 426 investigated individuals. Previously, in 190 separated controls without evidence of autonomy, the reference ranges for the thyroid 99mTc pertechnetate uptake under suppression (TcUₙ), a measure for the non-suppressible thyroid iodide clearance, and for suppressibility of circumscribed thyroid regions, had been determined. These two parameters obtained by high-resolution quantified scintigraphy were used for an accurate detection of thyroid autonomy among the 236 individuals. Suppression scintigraphy revealed autonomy in 171 patients. ΔTSH after TRH was subnormal in 40% of the subjects with abnormal thyroid suppressibility. Prevalence of abnormal suppression was dependent on three factors: patient age, goitre type and estimated thyroid weight. In the total investigated collective, the prevalence of autonomy was 77% in patients with a goitre weight above 50 g. The individuals with abnormal suppression were grouped into four classes of TcUₙ. In these classes, free thyroxine index (FT₄I) and total triiodothyronine (TT₃) increased with increasing TcUₙ, whereas ΔTSH decreased. This finding indicates a continuum of different extents of autonomous thyroid function, whereas in the individual patient, the extent can be determined using the pertechnetate uptake under suppression. In addition, FT₄I, TT₃ and ΔTSH in each of the TcUₙ classes depended on the individual iodine supply. It is concluded that, in patients with thyroid autonomy, actual thyroid hormone concentrations and TSH stimulation are determined by two major factors: the extent of autonomy and the individual iodine supply. Therefore, in iodine deficiency, the TRH test may be normal, although autonomy is present. This relationship explains the reduced sensitivity of the TRH test to detect autonomy in iodine-deficient goitres.

To this day, iodine deficiency is still present in numerous countries (Hetzel 1983; Report of the subcommittee for the study of endemic goitre and iodine deficiency of the European Thyroid Association 1985). In iodine-deficient goitres, functional thyroid autonomy is frequently found (Miller & Block 1970; Gensenjäger et al. 1976; Dige-Petersen & Hummer 1977; Emrich & Bähre 1978; Joseph et al. 1980). Since autonomy can cause thyrotoxicosis after iodine contamination (Fradkin & Wolff 1983), it is of clinical importance in areas of iodine deficiency. On the cellular level, pathophysiological aspects of thyroid autonomy in patients with endemic goitres have been extensively investigated using autoradiography (Miller & Block 1970; Peter et al. 1985; Studer et al. 1985). Systematical in vivo investigations of autonomy have been performed to a lesser extent.
This might result from the methodical difficulties in detecting thyroid autonomy in vivo. Suppression scintigraphy, combined with measurement of the thyroid trapping of radioiodine (Burke 1967) or $^{99m}$Tc pertechnetate as a substitute for the thyroid iodide clearance (Dige-Petersen et al. 1976; Joseph et al. 1980), is suited to detect and to localize autonomous tissue in vivo. When determining the reference range of the trapping function under suppression, it is important to exclude individuals with evidence of increases in total or partial thyroid function. In addition, the sensitivity to detect autonomy depends on the investigation technique applied. Therefore, our investigation is based on two main sections:

First, a strictly defined reference range of the total thyroid uptake of $^{99m}$Tc pertechnetate under suppression (TcU$_4$), as an equivalent of the non-suppressible iodide trapping of the thyroid, had been defined in 190 individuals without evidence of autonomy (Bähre et al. 1987).

In this present study, the reference ranges of the pertechnetate uptake of the whole thyroid under suppression (TcU$_3$) and, in addition, the suppressibility of thyroid regions were used to detect autonomy with a high rate of accuracy in 236 individuals. They either exhibited an irregular activity distribution in the suppression scintigram or had a subnormal TSH response to TRH. The correlations between TcU$_3$, iodine excretion, the concentrations of the thyroid hormones and ATSH were studied in individuals with abnormal suppression.

**Subjects and Methods**

**Subjects**

This study is concerned with 236 of 426 consecutively investigated individuals, with and without euthyroid endemic goitre, living in an area of iodine deficiency. The 426 subjects fulfilled the following criteria:

1. No history of hyper- or hypothyroidism, no destructive therapy, and no thyroid treatment during the last three months prior to the investigation.
2. Euthyroidism according to physical examination.
3. No evidence of iodine contamination as determined by iodine excretion in the urine (iodine excretion lower than 89 µmol/mol creatinine).

**Subject grouping**

First, in the 426 investigated individuals, a control group of subjects without evidence of autonomy (group C) had been defined according to the following criteria to determine the reference range of TcU$_4$:

Group C (controls) consisted of 190 individuals with a normal TSH response to TRH and with an entirely homogeneous activity distribution on the thyroid scintigrams before as well as under suppression (Bähre et al. 1987).

After having separated the controls, 236 subjects with an irregular activity distribution in at least one of the two scintigrams or a subnormal TRH test remained. Their ages ranged from 15 to 76 years. Thirty-nine of them were males, 31 of the 197 females took oestro gens, mostly contraceptives. No goitre was found in 9 individuals; 151 had a grade I goitre, 73 a grade II goitre, and 3 a grade III goitre.

Using the reference ranges for global and regional suppressibility, according to the result of suppression scintigraphy and the result of the TRH test, these 236 subjects were classified as follows:

Group N (normals): Individuals with normal suppressibility of the whole thyroid gland (TcU$_4$ below 1.6%, no circumscribed areas of insufficient suppression) and normal ATSH after TRH (N = 52).

Group A (autonomy): Individuals with abnormal suppressibility of the whole thyroid (TcU$_4$ above 1.6%) or insufficient suppressibility of circumscribed regions within the gland, independent of a normal or subnormal ATSH after TRH (N = 171).

Group S (subnormal TSH response): Individuals with normal thyroid suppressibility (TcU$_4$ below 1.6%, no circumscribed areas of insufficient suppression), but a subnormal ATSH after TRH (N = 13).

**Protocol**

**Before suppression.** Thyroid weight was estimated according to palpation. Free thyroxine index (FT$_4$I), total triiodothyronine (TT$_3$), and TSH response (30 min after 552 nmol [200 µg] TRH iv) were determined using commercially available kits: Thyroxine binding index (TB1): Byck Mallinckrodt, St. Louis, MO; total T$_4$ (TT$_4$) and TT$_3$: Corning, Medfield, MA, and TSH: Biorad, Richmond, CA. Iodine excretion in the urine was measured by a Technicon autoanalyzer. Reference ranges were: FT$_4$I: 5.3–10.4; TT$_3$: 1.54–3.08 nmol/l (100–200 ng/dl); ATSH: 3–26 mU/l, and iodine excretion: 8.9–45 µmol/mol creatinine (10–50 µg/g creatinine (Emrich et al. 1982)). Five minutes after 19–74 MBq (0.5–2 mCi) of $^{99m}$Tc sodium pertechnetate were injected iv, thyroid scintigraphy was performed with a present time of 10 min using an improved technique which has been published by our group (Bähre et al. 1985). Total $^{99m}$Tc pertechnetate thyroid uptake (TcU$_4$) was determined by a program described by Mahlstedt & Csirik (1981).

**Under suppression** with 97 nmol (75 µg) of thyroxine per day for two weeks, followed by 194 nmol (150 µg) of thyroxine for another two weeks, thyroid scintigraphy...
and determination of total $^{99m}$Tc pertechnetate thyroid uptake ($\text{TcU}_2$) were repeated. The upper limit of the reference range for the $\text{TcU}_2$ used was 1.6% of the tracer activity applied (Bähre et al. 1987).

To evaluate the suppressibility of circumscribed regions of the thyroid, the regional $\text{TcU}_2$ was determined before and under suppression. The decrease of uptake of the suspicious region was compared with that of an adjacent reference area without evidence of autonomy. When determining the normal variation, methodical aspects were considered, for example the regional counting statistics and the feasibility of marking identical regions with a light pen. The normal variation of regional suppressibility measured in controls was below 10%. Therefore, suppression of thyroid regions was considered insufficient, if their decrease in uptake was 10% less than that of adjacent tissue.

**Evaluation**

According to the result of suppression scintigraphy, the 236 subjects were classified into groups N, A, and S. The prevalence of abnormal suppression was calculated for the total collective of 426 individuals referring to patient age, goitre type, and estimated thyroid weight.

Subjects with abnormal suppression (A) were grouped according to the distribution of areas with insufficient suppression as follows:

a) focal (one to three regions of insufficient suppression, adjacent tissue suppressed),

b) multifocal (more than three focal areas of insufficient suppression, multiple foci which could not be completely separated from each other or circumscribed regions of insufficient suppression which were associated with incomplete suppression of the adjacent tissue),

c) disseminated (insufficient suppression of the total thyroid uptake, but absence of circumscribed regions of insufficient suppression; individuals with clearly defined cold areas were allowed, those with irregular activity distribution including 'hot' areas were classified as multifocal).

The median values of $\text{FT}_{\delta 1}$, $\text{TT}_3$ and $\text{ΔTSH}$ for the three groups (N, A and S) determined before suppression, were compared with those of 141 individuals of the control group (individuals taking oestrogens had to be excluded for this purpose). Individuals of group A were further subdivided into four classes according to the range of their $\text{TcU}_2$: group $A_1$: $\text{TcU}_2 < 1.6$%; group $A_2$: $\text{TcU}_2 1.6-3.2$%; group $A_3$: $\text{TcU}_2 3.3-4.8$%, and group $A_4$: $\text{TcU}_2 > 4.8$%.

In each of these four subgroups, the medians of the hormone concentrations were determined. The dependency of $\text{FT}_{\delta 1}$, $\text{TT}_3$ and $\text{ΔTSH}$ on $\text{TcU}_2$ as well as on the individual iodine supply, as measured by the iodine excretion in three ranges ($< 18$, $18-45$, $46-89$ $\mu$mol/mol creatinine), was studied. Eight subjects of group A with a missing value of iodine excretion below suppression, but who had no evidence of iodine contamination, when considering the iodine excretion under suppression, were excluded from the latter evaluation.

**Statistics**

The statistical distribution of the $\text{TcU}_b$, $\text{TcU}_s$ (Bähre et al. 1987) and of $\text{ΔTSH}$ were skewed to the right. Because it is incorrect to characterize such distributions of parameters statistically using means and standard deviations, in this study we present all values as medians. Statistically, one cannot definitely presuppose that the values of the parameters have a certain distribution. Therefore, differences were evaluated statistically using the distribution-free rank test of Wilcoxon-Mann-Whitney.

**Results**

Among the 236 subjects, 52 had a normal $\text{ΔTSH}$ and a normal thyroid suppressibility; they were classified in group N. A total of 171 individuals showed abnormal suppression (group A), 43 of them exhibited circumscribed regions of the thyroid with insufficient suppression, but had a normal overall uptake under suppression ($\text{TcU}_s$

**Table 1.**

| Frequency of insufficient suppression referring to patient age, goitre type and estimated thyroid weight. |
|--------------------|-----------------|-----------------|------------------|
| Age (years)        | <= 25           | 26-35           | 36-45            | > 45             |
| % of patients      | 14              | 37              | 39               | 65               |
| Goitre type        | diffuse         | single nodule   | multinodular     |
| % of patients      | 32              | 61              | 76               |
| Estimated thyroid weight (g) | <= 30 | 31-50          | > 50             |
| % of patients      | 18              | 37              | 77               |

**Table 2.**

| Frequency of three distribution patterns of non-suppressible areas within the thyroid in 171 subjects. |
|-----------------|-----------------|-----------------|------------------|
| Group            | Focal           | Multifocal      | Disseminated     |
| N                | 42              | 84              | 45               |
| % of patients    | 25              | 49              | 26               |
Three distribution patterns of autonomous tissue on thyroid scintigrams before (upper row) and under suppression (lower row): a) strictly focal (TcU₅ increased, complete suppression of tracer uptake in the tissue adjacent to the 'hot' area), b) multifocal (TcU₅ increased, whereas multiple focal areas of increased tracer uptake are depicted), c) disseminated (TcU₅ increased, but absence of circumscribed areas of increased uptake).

< 1.6%), and 128 of them had an insufficient suppression of the whole gland (TcU₅ > 1.6%). Of these 171 individuals in group A, 69 had a subnormal TRH test. In 13 subjects normal suppression and a subnormal TSH response were found (group S).

The frequency of abnormal suppression among the 426 patients increased with age and with the estimated weight of the thyroid (Table 1). Furthermore, abnormal suppression was more frequent in individuals with nodular and even more pronounced in those with multinodular goitres than in individuals with diffuse goitres (Table 1). Among the 426 individuals, there were 54 without goitre. Only 3 of these 54 subjects showed an abnormal suppression.

The frequency of three distribution patterns of thyroid tissue which exhibited reduced suppression is presented in Table 2. Scintigrams of three patients with focal, multifocal and disseminated distribution patterns of autonomous tissue before and under suppression are shown in Fig. 1.

The medians of FT₄I, TT₃, ΔTSH, and iodine excretion in the range below 89 µmol/mol creatinine measured in the four groups before suppression are presented in Table 3. When compared with the controls, the medians of FT₄I were significantly lower in subjects with normal suppression and normal ΔTSH (group N). In group A, the increase in TT₃ and the decrease in ΔTSH were significant. By definition, ΔTSH was significantly lower in group S. In the groups classified according to increasing ranges of TcU₅, the FT₄I decreased significantly in A₁, but did not change in groups A₂–A₄, when compared with the control group (Table 4). With the increase of TcU₅, which indicates enhanced non-suppressibility, TT₃ increased and ΔTSH decreased significantly.
Table 3.
FT₄I, TT₃, ΔTSH, and iodine excretion (medians) measured before suppression in 205 individuals (31 taking oestrogens were excluded) compared with 141 controls (C). N: subjects with normal suppression and normal ΔTSH; A: subjects with abnormal suppression; S: subjects with normal suppression, but subnormal ΔTSH.

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>N</th>
<th>A</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>141</td>
<td>44</td>
<td>149</td>
<td>12</td>
</tr>
<tr>
<td>FT₄I (nmol/l)</td>
<td>8.2</td>
<td>7.6</td>
<td>8.0</td>
<td>8.2</td>
</tr>
<tr>
<td>TT₃ (nmol/l)</td>
<td>2.19</td>
<td>2.16</td>
<td>2.39</td>
<td>2.16</td>
</tr>
<tr>
<td>ΔTSH (mU/l)</td>
<td>7.3</td>
<td>6.4</td>
<td>3.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Iodine excretion (µmol/mol creatinine)</td>
<td>27</td>
<td>30</td>
<td>28</td>
<td>22</td>
</tr>
</tbody>
</table>

Significant differences: FT₄I: C—N P < 0.05. TT₃: C—A P < 0.001; N—A P < 0.05. ΔTSH: C—A, N—A P < 0.001; (C−S, N−S P < 0.001; A−S P < 0.05 — by definition).

Increases in FT₄I and TT₃ dependent on Tc₃ were also found under suppression. The medians of FT₄I and TT₃ increased not only with the increase in Tc₃, but also with the increase in iodine excretion in each of the Tc₃ classes; conversely, ΔTSH decreased (Table 5). Probably owing to the low number of subjects, some changes in the hormone concentrations were not statistically significant.

Table 4.
FT₄I, TT₃, ΔTSH, and iodine excretion (medians) of 149 individuals with abnormal suppression (22 subjects taking oestrogens were excluded from the 171 individuals) compared with 141 controls (C). A₁: subjects with normal Tc₃ (<1.6%), but regions of insufficient suppression; A₂: Tc₃ 1.6−3.2%; A₃: Tc₃ 3.3−4.8%; A₄: Tc₃ > 4.8%.

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>A₁</th>
<th>A₂</th>
<th>A₃</th>
<th>A₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>141</td>
<td>37</td>
<td>75</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Before suppression FT₄I</td>
<td>8.2</td>
<td>7.2</td>
<td>8.0</td>
<td>8.8</td>
<td>8.7</td>
</tr>
<tr>
<td>TT₃ (nmol/l)</td>
<td>2.19</td>
<td>2.28</td>
<td>2.36</td>
<td>2.45</td>
<td>2.54</td>
</tr>
<tr>
<td>ΔTSH (mU/l)</td>
<td>7.3</td>
<td>6.1</td>
<td>3.3</td>
<td>2.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Iodine excretion (µmol/mol creatinine)</td>
<td>27</td>
<td>30</td>
<td>29</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

Under suppression FT₄I | 12.3 | 13.8 | 13.9 | 14.0 | 14.3 |
| TT₃ (nmol/l)            | 2.33 | 2.76 | 2.70 | 2.85 | 3.08 |

Significant differences: Before suppression: FT₄I: C−A₁ P < 0.01; A₁−A₃ P < 0.01; A₁−A₄ P < 0.05.
TT₃: C−A₂ P < 0.05; C−A₃, C−A₄ P < 0.01; A₁−A₄ P < 0.05.
ΔTSH: C−A₁ P < 0.01; C−A₂, C−A₃, C−A₄ P < 0.001; A₁−A₂ P < 0.01; A₃−A₄ P < 0.05; A₁−A₄ P < 0.001; A₂−A₄ P < 0.001.
Iodine excretion: C−A₄ P < 0.05; A₁−A₄ P < 0.01; A₂−A₄ P < 0.01.
Under suppression: FT₄I: C−A₁, C−A₂ P < 0.01; C−A₃, C−A₄ P < 0.05.
TT₃: C−A₁, C−A₂, C−A₃ P < 0.001; C−A₄ P < 0.01.

Discussion
Detection of thyroid autonomy in vivo
In the euthyroid state, a subnormal TRH test may be due to thyroid autonomy (Gemsenjäger et al. 1976; Dige-Petersen & Hummer 1977; Emrich & Bähre 1978). However, the sensitivity of TRH-tests is limited in this regard, especially in areas of iodine deficiency (Pickardt et al. 1973; Ribka et al.
Table 5.
Medians of hormone concentrations before suppression in the subgroups A₁–A₄ with respect to the iodine excretion in three classes. Individuals taking oestrogens or in whom a value of iodine excretion was missing, were excluded.

<table>
<thead>
<tr>
<th>TcU₃ (%)</th>
<th>Iodine excretion (µmol/mol creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 18</td>
</tr>
<tr>
<td>A₁ &lt; 1.6%</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>FT₄I</td>
</tr>
<tr>
<td></td>
<td>TT₃ (nmol/l)</td>
</tr>
<tr>
<td></td>
<td>ΔTSH (mU/l)</td>
</tr>
<tr>
<td></td>
<td>Iodine excretion (µmol/mol creatinine)</td>
</tr>
<tr>
<td>A₂ 1.6–3.2%</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>FT₄I</td>
</tr>
<tr>
<td></td>
<td>TT₃ (nmol/l)</td>
</tr>
<tr>
<td></td>
<td>ΔTSH (mU/l)</td>
</tr>
<tr>
<td></td>
<td>Iodine excretion (µmol/mol creatinine)</td>
</tr>
<tr>
<td>A₃ 3.3–4.8%</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>FT₄I</td>
</tr>
<tr>
<td></td>
<td>TT₃ (nmol/l)</td>
</tr>
<tr>
<td></td>
<td>ΔTSH (mU/l)</td>
</tr>
<tr>
<td></td>
<td>Iodine excretion (µmol/mol creatinine)</td>
</tr>
<tr>
<td>A₄ &gt; 4.8%</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>FT₄I</td>
</tr>
<tr>
<td></td>
<td>TT₃ (nmol/l)</td>
</tr>
<tr>
<td></td>
<td>ΔTSH (mU/l)</td>
</tr>
<tr>
<td></td>
<td>Iodine excretion (µmol/mol creatinine)</td>
</tr>
</tbody>
</table>

Significant differences:
FT₄I: Class of iodine excretion 18–45: P < 0.01*.
TT₃: Class of iodine excretion 18–45: P < 0.01*; class of TcU₃ > 4.8%: P < 0.01*.
ΔTSH: Class of iodine excretion < 18: P < 0.05*; class of iodine excretion 18–45: P < 0.001*;
class of TcU₃ < 1.6 group 1 vs 3 P < 0.05, class of TcU₃ 1.6–3.2*: groups 1 and 2 vs 3: P < 0.05.

* Overall comparison statistic.

1979; Joseph et al. 1980). Suppression scintigraphy allows one to detect and localize autonomous tissue and has been available as a routine investigative procedure for years (Burke 1967; Dige-Petersen et al. 1976; Joseph et al. 1980).

When performing suppression tests, the appropriate parameter should be used to determine the degree of thyroid suppression. The ratio of the radioiodine or ⁹⁹mTc pertechnetate uptake under suppression to the uptake before suppression is inadequate because of two reasons. First, suppressibility defined by the uptake-ratio depends to a large extent on the baseline thyroid uptake, which is inversely correlated with the individual iodine supply (Bähre et al. 1987). In severe iodine deficiency, reduction of uptake by suppression can be normal, although a considerable extent of autonomy is present. Second, according to statistical rules, this parameter is unsuited for use in an unknown sample, since frequency distributions of ratios of random variables generally have poor statistical properties. Consequently, the parameter of greatest clinical relevance to characterize autonomous function is the non-suppressible thyroid iodide trapping function, rather than reduction of the trapping func-
tion by suppression. $^{99m}{\text{Tc}}$ pertechnetate is a satisfactory substitute for measuring the trapping function (Alexander et al. 1969; Atkins 1971; Burke et al. 1972; Hays & Wesselsky 1973; Hilditch & Alexander 1980; Fragu et al. 1982). The pertechnetate uptake under suppression substitutes for the non-suppressible iodide clearance. We preferred $^{99m}{\text{Tc}}$ pertechnetate to $^{123\text{I}}$ because it is inexpensive and permanently available.

The result of suppression scintigraphy was used to detect individuals with autonomous tissue and to classify its extent among the 236 subjects in whom autonomy could be suspected owing to a subnormal TSH response to TRH or an irregular activity distribution on the thyroid scintigrams before or under suppression. The investigation technique applied provided a high sensitivity and specificity for detecting autonomous tissue in vivo. Some individuals with normal TcU$_{5}$ showed circumscribed areas of increased uptake on the scintigram under suppression. Thus, two criteria had to be used to classify the 236 subjects: the TcU$_{5}$ and the suppressibility of thyroid regions.

**Prevalence of autonomy**

Suppression was abnormal in 171 subjects (43 of these 171 exhibited regions of reduced suppression, but they had normal values of the TcU$_{5}$), corresponding to 40% of all 426 individuals investigated and 45% of those with euthyroid goitres. This was a surprisingly large share when compared with previous studies and can be explained by the sensitive in vivo investigation technique used. Such a high prevalence of autonomy is relevant in pathophysiological and clinical respects. The prevalence of abnormal suppression increased with patient age, goitre size, and goitre type. This is in agreement with earlier studies in which the result of the TRH test served as an indicator for autonomy (Emrich & Bähr 1978) and it again indicates the increase in frequency of autonomy with the length of goitre presence. Using the method applied, the prevalence of abnormal suppression was 77% in patients with an estimated thyroid weight over 50 g and it was still 37% in subjects with an estimated weight of 30–50 g (Table 1). Thus, in clinical routine, the use of suppression scintigraphy can be focussed on individuals with a high prevalence of autonomy to provide cost-effective detection of patients with autonomy which means an increased risk of hyperthyroidism.

In this study, the relative rarity of a strictly focal distribution pattern of autonomous regions in the thyroid (25%) could be documented in vivo. Similar findings were reported on the basis of autoradiographic studies (Miller et al. 1964; Miller & Block 1970; Studer & Ramelli 1982; Peter et al. 1985; Studer et al. 1985). A multifocal distribution pattern was observed in 49% of the individuals with evidence of autonomy, a disseminated pattern in 26%. Disseminated autonomy can only be detected by means of increased TcU$_{5}$, not by changes in regional activity distribution. Therefore, the necessity of an adequate in vivo investigation technique has to be emphasized.

**Interdependencies between iodine excretion, TcU$_{5}$, FT$_{4}$I, TT$_{3}$, and ΔTSH**

The frequency of autonomous tissue was not overestimated using the method applied as indicated by the hormone concentrations measured in group A. Individuals with evidence of autonomy showed a significantly increased median of TT$_{3}$, together with a decreased median of ΔTSH when compared with the controls. However, more than half of the patients with evidence of autonomy still showed a TSH stimulation within the normal range. In other words, the sensitivity of suppression scintigraphy in detecting autonomy was 2.5 times higher than that of the TRH test which meets results of Joseph et al. (1980).

The question arose, whether there might be different extents of autonomous function and how they could be differentiated. The increases in the medians of FT$_{4}$I, TT$_{3}$ and a corresponding decrease in ΔTSH from subgroup A$_{1}$ to A$_{4}$, i.e. the range of TcU$_{5}$ (Table 4), demonstrate a direct correlation between the non-suppressible iodide clearance of the thyroid and the hormone secretion of autonomous tissue. In the subgroup A$_{1}$, the extent of autonomy has to be estimated low, higher in A$_{2}$ and A$_{3}$, and at a maximum in A$_{4}$. In A$_{1}$ the FT$_{4}$I was lower than in the controls. Since the TSH reserve was still rather high, this was possibly due to compensation of the increased secretion of TT$_{3}$ via the normal feedback mechanisms.

The medians of FT$_{4}$I and TT$_{3}$ in group N and group S and the median of ΔTSH in group N were not statistically different from those in the controls (C). These parameters confirmed the absence of autonomy in group N, which was in agreement with the results of quantified suppres-
sion scintigraphy. The existence of group S could not be precisely explained by the present data. A partial paravenous injection of TRH might have occurred in these cases.

At first sight, there was no close correlation between TcU₃ and thyroid hormone concentrations in subgroups A₁–A₄ in the individual patient, although autonomous function could be presumed according to suppression scintigraphy. Even in three patients of group A₄ who were suspicious of severe autonomy, ΔTSH was still normal. In these three patients, iodine excretion was very low (<18 µmol/mol creatinine). In addition, increases in FT₄I, TT₃ and decreases in ΔTSH were found in all classes of TcU₃, dependent on the extent of iodine excretion (Table 5). The change in ΔTSH was clearer than the changes in FT₄I and TT₃, since the TSH concentration is more sensitive to slight increases in thyroid hormone secretion than the thyroid hormone concentrations in the plasma. The TRH test was subnormal in about half of the subjects in subgroup A₁ when the iodine excretion was in the range between 46–89 µmol/mol creatinine, in A₂ when it was 35–50 µmol/mol creatinine, and in A₃, when it was still lower (the small number of patients in A₃ hinders interpretation). In group A₄, even the majority of subjects with the lowest iodine excretion showed subnormal TSH responses.

These data suggest two main conclusions:

First, considering also the findings in the control group (Bähre et al. 1987), there is a continuum ranging from very discrete TSH independent thyroid function in subjects without primary evidence of autonomy, and slight extents of autonomy (subjects of A₃) to severe autonomous function in the 426 patients.

Second, as earlier anticipated, the study proved that actual thyroid hormone concentrations of individuals with autonomy are determined by two major factors: the extent of autonomy and the iodine supply. Consequently, the sensitivity of the TRH test to detect autonomy decreases with decrease of iodine intake and is especially low in areas of iodine deficiency where autonomy is most frequent.

Conclusions for patient care
Provided that TcU₃ estimates the functional potency of autonomy directly, individuals could be classified into high or low risk groups for developing hyperthyroidism. Although the present study cannot provide definite information in this respect because it was not prospective, two observations support the conclusion. First, the considerable TSH stimulus on the thyroid in most of the subjects in subgroups A₁ and A₂ indicates a kind of functional reserve which can be occupied by autonomous hormone secretion. There is no such reserve in individuals of group A₄. It is plausible that a slight increase in thyroid iodine intake could cause a transition into a hyperthyroid state in subgroup A₄, whereas the reserve in A₁ and A₂ might prevent immediate transition into an increased hormone secretion after a moderate increase in iodine intake. Especially in the case of iatrogen iodine contamination with large doses, e.g. iodine-containing X-ray contrast media, individuals of subgroup A₃ and A₄ would be at a considerable risk of developing hyperthyroidism. Second, considering the observed frequencies of patients with an iodine excretion between 46 and 89 µmol/mol creatinine in subgroups A₁ and A₂, the estimated frequency of patients in the subgroups A₃ and A₄ would be in the range of 10. However, no such patients were observed in the collective investigated. This might be due to the selection of clinically euthyroid subjects for the study. Subjects with an iodine excretion >46 µmol/mol creatinine and a TcU₃ >3.3% might already be hyperthyroid and then they would have been excluded.

To a large extent, the data presented are based on the improved technique of thyroid scintigraphy used (Bähre et al. 1985). In combination with quantification of the scintigrams, this technique allows a sensitive detection of even slight increases in thyroid trapping function in vivo under suppression as an evidence of autonomy. Therefore, with respect to the role of scintigraphy in investigating autonomy in vivo, one can hardly agree with Studer et al. (1985) who considered the contribution of scintigraphy to be insignificant and not decisive for the management of goitre patients. An adequate technique of quantified scintigraphy makes it possible to detect thyroid autonomy and classify precisely its extent, which is a prerequisite for making therapeutic decisions. In patients with a large extent of autonomy suppression, scintigraphy is especially valuable, because it offers the opportunity to eliminate autonomy before hyperthyroidism develops.
Acknowledgment

The authors wish to thank Mrs Gerbatsch-Bornemisza for carefully correcting the manuscript.

References


Received May 7th, 1987.

Accepted September 15th, 1987.

Dr Manfred Bähr,
Institut für Nuklearmedizin,
Medizinische Universität zu Lübeck,
 Ratzeburger Allee 160,
 D-2400 Lübeck, FRG.