



Surgical Significance of Supernumerary Parathyroid Glands in Renal Hyperparathyroidism

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Abstract. In secondary hyperparathyroidism (2HPT) fundamentally all parathyroid glands, including supernumerary glands, become hyperplastic, and stimulation of parathyroid glands continues after parathyroidectomy (PTx). Therefore supernumerary glands have special significance during surgery for 2HPT, whether persistent or recurrent HPT. In the present study 570 patients underwent initial total PTx with a forearm autograft. The frequency, type, location, histopathology, and clinical significance of the supernumerary glands were evaluated. At the initial operation 90 supernumerary glands were removed from 82 of 570 patients (14.4%); 12 patients (2.1%) required extirpation of supernumerary glands for persistent/recurrent HPT. Altogether 104 supernumerary glands were identified at operation in 94 of the 570 patients (16.5%). Among these 104 glands, 25 (24.0%) were of the rudimentary, or split, type and 79 (76.0%) of the proper type. Supernumerary glands were most frequently identified in the thymic tongue (53/104, 51.0%); 32 (60.4%) of these 53 glands were identified only microscopically. In 6 of the 570 cases (1.1%), reoperation was required for persistent HPT due to supernumerary glands located in the mediastinum, and 6 patients underwent neck reexploration for recurrence. Histopathologically, 61 of 104 (58.7%) supernumerary glands, including 36 glands recognized only microscopically, showed diffuse hyperplasia, and 43 (41.3%) displayed nodular hyperplasia. Residual small supernumerary glands with diffuse hyperplasia have the potential to be transformed to nodular hyperplasia during long-term hemodialysis. Therefore all parathyroid glands including supernumerary glands should, if possible, be removed at the initial operation. Routine removal of the thymic tongue and careful examination of the regions surrounding the lower poles of the thyroid, especially on the left side, are important steps in the surgical treatment.

Despite recent therapeutic advances, severe secondary hyperparathyroidism (2HPT) due to uremia is refractory to medical treatment and necessitates parathyroidectomy (PTx) [1]. It is well known that one of the histopathologic characteristics of both primary and secondary parathyroid hyperplasia is asymmetric glandular enlargement [2, 3]. With 2HPT, however, all parathyroid glands, including small supernumerary glands (parathyroid nests), may be histopathologically hyperplastic. Therefore patients with 2HPT pose a special threat for PTx, given the risk of persistent/recurrent HPT. The risk of recurrent HPT due to remaining parathyroid tissue is not negligible, especially in pa-

tients who require long-term maintenance hemodialysis (HD) after PTx [4]. Surgeons then must remove all parathyroid glands including supernumerary glands to avoid persistent/recurrent HPT [5], so surgeons have to be familiar with the anatomic characteristics of parathyroid glands for successful outcome of the treatment.

Detailed studies about human parathyroid glands have previously been done, and knowledge about their location and number has accumulated in autopsy and surgical series [6–12]. In this study we evaluated the frequency, location, pathologic findings, and clinical significance of supernumerary glands in our large surgical series of patients with 2HPT due to uremia.

Materials and Methods

Between March 1981 and August 1996, a total of 570 patients underwent initial total PTx with forearm autograft for advanced 2HPT at the Departments of Transplant Surgery of Nagoya Second Red Cross Hospital and Kakegawa City General Hospital. Among the patients were 236 women and 334 men. Their ages (mean \pm SE) were 48.4 ± 0.3 years (range 19–76 years), and the duration of HD (mean \pm SE) was 11.7 ± 4.6 years (range 0–25.6 years).

Our surgical indications for 2HPT are described in detail elsewhere [13]. In summary, the following concomitantly existing factors were regarded as indications: (1) a high (>500 pg/ml) serum parathyroid hormone (PTH) (intact PTH, measured by Allegro kit; normal range <60 pg/ml); (2) enlarged parathyroid glands (weighing >500 mg) detected by imaging diagnosis; (3) positive findings of osteitis fibrosa on radiography or high bone turnover detected by bone scintigram or bone metabolic markers; and (4) patients refractory to medical treatment.

Our preferable, routine operative procedure for 2HPT was total PTx with forearm autograft [13], and all 570 patients underwent this procedure initially. To identify the parathyroid glands, including supernumerary glands, at the operation, the following procedures were performed routinely. To certify the diagnosis and localization, preoperative noninvasive image diag-

nosis, including computed tomography (CT), ultrasonography (US), $^{201}\text{TlCl}$ and $^{99\text{m}}\text{TcO}_4^-$ double scintigraphy or $^{99\text{m}}\text{Tc}$ MIBI scintigraphy, and magnetic resonance imaging (MRI) were performed. At the operation, all parathyroid glands were sought carefully, and their removal was based on the imaging diagnostic findings. Thymic tissue was excised through the cervical incision, as supernumerary glands are most frequently located in the thymic gland. To identify supernumerary glands, the carotid sheath was opened bilaterally, and fat lobules covering the glands were extirpated. Some parts of each removed gland were transferred to the pathologist for histopathologic identification during operation.

The glandular size and weight were estimated, and all specimens were fixed in buffered neutral formalin and embedded in paraffin. The sections were stained with hematoxylin-eosin for histopathologic examination. Semiquantitatively, the number of parenchymal cells in relation to fat cells, pattern of hyperplasia (nodular or diffuse), and dominant cell type were determined.

Definition and Classification of Supernumerary Glands

Based on previous reports, supernumerary glands are classified into two types: rudimentary (split) type and proper type [8, 9]. The rudimentary, or split, glands are divided glands lying close to the other glands and usually clearly delineated. The proper-type glands are located well away from the other four glands. When there are more than five parathyroid glands, it is sometimes difficult to determine which gland is supernumerary. For this paper we defined supernumerary glands on the basis of glandular location and size. Rudimentary, or split, glands lay close to the other glands and are defined as small glands; the proper-type glands are represented by glands with a more unusual location.

Using this definition, the following items were examined: (1) number of glands removed at the initial operation and reoperation; (2) frequency of supernumerary glands recognized at the initial operation and suggested by the clinical course; (3) type and location of these glands; (4) glandular weight and histopathologic findings; and (5) preoperative identification by imaging diagnosis.

Clinical Course

Because the serum calcium level is influenced by the postoperative treatment in patients with 2HPT, we defined persistent and recurrent renal HPT as follows. In patients with persistent HPT, the postoperative minimal level of PTH should be higher than the upper normal limit (60 pg/ml), and in patients with recurrent 2HPT the PTH level should be normalized (<60 pg/ml) after surgery and reelevated first after more than 6 months postoperatively.

Among nine patients in whom only two or three glands were removed at the initial operation, three patients had persisting high PTH levels, and so neck reexploration was performed. In each case a fourth gland was removed at the second operation. High PTH levels were persistent in 19 of the 561 patients (3.4%) in whom more than four parathyroid glands were resected at the initial operation. Of these 19 patients, 6 (31.5%) required reoperation because of persistent clinical findings of HPT; and in all of these patients supernumerary glands were resected from the mediastinum. Six (1.1%) patients with recurrent 2HPT induced by

Table 1. Parathyroid glands removed at initial operation (March 1981 to August 1996, $n = 570$).

No. of glands	No. of cases	%
7	1	0.2
6	6	1.1
5	75	13.2
4	479	84.0
3	8	1.4
2	1	0.2
Total	570	

Table 2. Parathyroid glands removed at initial operation and reoperation (March 1981 to August 1996, $n = 570$).

Total no. of glands	No. of cases	%
7	3	0.5
6	6	1.1
5	83	14.6
4	472	82.8
3	5	0.9
2	1	0.2
Total	570	

Table 3. Frequency of supernumerary parathyroid glands ($n = 570$).

Time of diagnosis	No. of cases	Total frequency of supernumerary glands (%)
Initial operation	82	82 (14.4)
Reoperation	12 ^a	92 (16.1)
Clinically diagnosed without reoperation	13	105 (18.4)

^aIn two cases supernumerary parathyroid glands were removed at the initial operation.

residual supernumerary glands in the neck underwent reexploration.

Statistical Analysis

All the data were expressed as the mean \pm SE. Statistical analysis was performed by Welch's nonparametric method. A p value <0.05 was considered significant.

Results

The number of removed glands at initial operation and the total number at the initial surgery and reoperation are shown in Tables 1 and 2. In 98.5% of the cases four or more glands were extirpated at the initial PTx. The frequency of supernumerary glands in our series is summarized in Table 3.

Altogether 104 supernumerary glands removed at the initial surgery and reoperation were examined. The frequency of rudimentary, or split, glands was 25 of 104 (24.0%). The location of rudimentary (split) glands is shown in Figure 1. The remaining 79 (76.0%) glands were of the proper type. Almost half of the proper-type glands (48/79, 60.8%), were found in the thymic

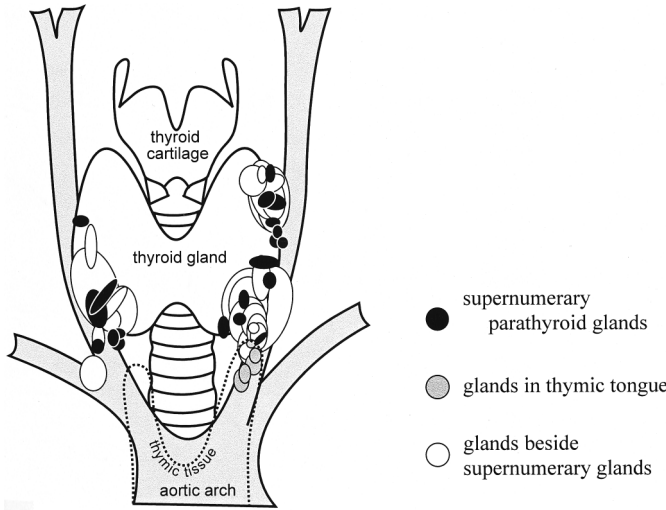


Fig. 1. Location of rudimentary, or split, type supernumerary glands removed at the initial operation in 25 cases. The black shading represents rudimentary, or split, type glands located around the thyroid gland. The gray shading indicates the rudimentary glands located in the thymic tongue. The nonshaded areas indicate the parathyroid glands closest to the rudimentary glands. The size of the area represents the size of the glands. Glandular weight in supernumerary glands (black and gray areas) ranged from 31 to 843 mg, and that of those next to the glands (nonshaded areas) was 51 to 2828 mg.

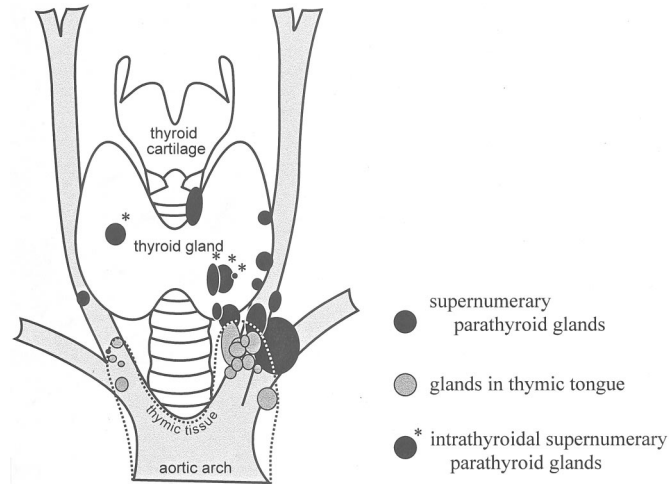


Fig. 2. Location of the proper type supernumerary glands identified macroscopically at the initial operation in 28 cases. The black-shaded areas without an asterisk represent glands located around the thyroid gland, and gray shaded areas indicate the sites of the glands located in the thymic tongue. Asterisks in the black shading show the intrathyroidal supernumerary glands. The size of the shaded areas represents the size of the glands. Glandular weight ranged from 17 to 2425 mg.

tongue. Of these 48 glands, 32 (66.7%) were recognized microscopically during histopathologic examination of the thymic tongue, which was resected routinely. Another four glands were identified microscopically outside of thymic tissue. Except for glands microscopically identified, the locations of proper-type glands removed at the initial operation are shown in Figure 2. Of the 104 glands, 6 (5.8%) were located in the mediastinum. In our series all mediastinal parathyroid glands were supernumerary and were removed at reoperation for persistent HPT. The locations of the mediastinal supernumerary glands are shown in Figure 3. Figure 4 shows eight supernumerary glands from six patients who underwent neck reexploration because of recurrent HPT.

All supernumerary glands, including those identified microscopically, were histopathologically hyperplastic. The mean weights and hyperplastic patterns are summarized in Table 4. All patients who developed persistent/recurrent HPT had at least one nodular hyperplastic supernumerary gland.

Only 7 of 90 (7.8%) glands removed at the initial operation were recognized by preoperative imaging, and so persistent HPT could be avoided. The weight of these glands was more than 500 mg. In all patients who required reoperation, at least one gland could be identified before reoperation. The detection of ectopic glands by various localizing modalities is summarized in Table 5.

Discussion

Analysis of autopsy examinations of normal parathyroid anatomy indicated that supernumerary glands occur in 2.5% to 12.7% of patients [6–10]. In our 2HPT series, supernumerary glands were found more frequently, perhaps due to the fact that hyperplastic glands are easier to recognize [10].

It was relatively easy to recognize the rudimentary, or split, type

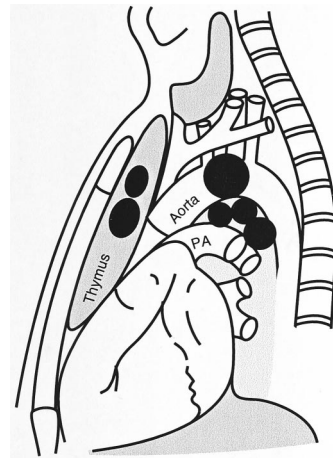


Fig. 3. Location of the mediastinal supernumerary glands removed at reoperation in six cases because of persistent hyperparathyroidism. Glandular weight ranged from 1160 to 8165 mg.

supernumerary glands, so it seems reasonable to assume that the rudimentary, or split, type glands are not of clinical significance. The proper-type supernumerary glands, which are frequently at ectopic sites, seems to be of importance for persistent/recurrent HPT. In our series 45.6% glands of the proper type were identified microscopically mainly in the thymic tongue, which explains the higher frequency of proper-type glands in our study compared with that found in autopsy series [8–10].

In our series the incidence of persistent HPT diagnosed clinically was 22 of 570 (3.9%), and in 9 patients (1.6%) reoperation was required. The reason the incidence of persistent HPT was lower in our series than in reports of others could be explained by the fact that in our series more than four glands were resected in 98.5% at the initial operation [14, 15], although we could not avoid persistent HPT induced by supernumerary glands located in the mediastinum.

Based on histopathologic and pathophysiologic investigations,

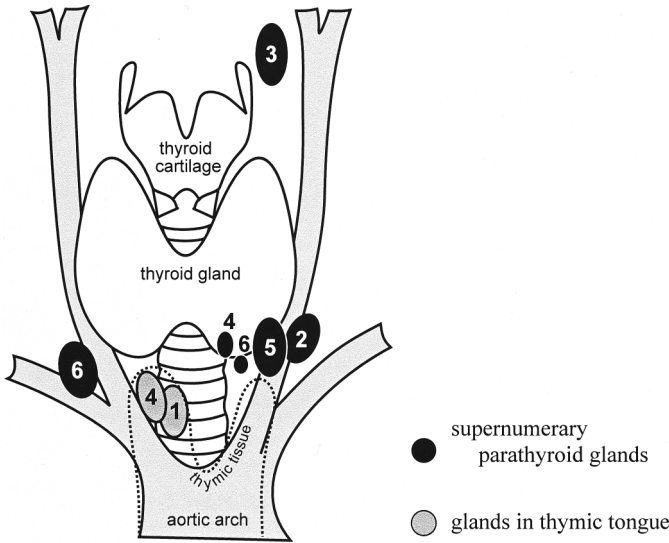


Fig. 4. Location of supernumerary glands extirpated at reoperation from six patients for recurrent hyperparathyroidism. The numbers in this figure reflect the patient number. Two supernumerary glands were resected from patients 4 and 6 at reoperation. Glandular weight ranged from 98 to 1383 mg.

Table 4. Glandular weight and hyperplastic pattern of supernumerary glands at initial operation.

Type of supernumerary glands	Weight (mg), mean and range	No. (%) of glands, by hyperplastic pattern	
		Diffuse	Nodular
Rudimentary, or split, type (n = 25)	173 ± 172* (31–843)	11/90 (12.2)	14/90 (15.6)
Proper type (n = 65)	357 ± 526*,** (17–2425)	52/90 (57.8)	13/90 (14.4)
Macroscopic (n = 29)		16/90 (17.8%)	13/90 (14.4)
Microscopic (n = 36)		36/90 (40.0)	0
Total (n = 90)		63/90 (70.0)	27/90 (30.0)

* < **, p < 0.01.

it is suggested that when a patient has at least one nodular hyperplastic gland 2HPT is refractory to medical treatment and PTx is required [16]. In our investigation 30.0% of the supernumerary glands resected at the initial operation showed nodular hyperplasia. Particularly if these glands are missed, persistent HPT may develop, and the patients may require reoperation. Considering our patients who required reoperation for recurrent HPT, the PTH level dropped under normal levels, and it was strongly suggested that the residual parathyroid tissue was small and diffusely hyperplastic. The tissue may have been transformed to nodular hyperplasia due to stimulation of the uremia during long-term HD, and so re-PTx was required. Because in some cases recurrent HPT may be induced by residual small pieces of parathyroid tissue, surgeons should have a radical attitude about the initial operation [4].

Preoperative diagnosis to identify supernumerary glands in ectopic sites is helpful for preventing persistent/recurrent HPT,

Table 5. Detection of ectopic parathyroid glands by various imaging diagnostic procedures.

Location	CT	US	MRI	²⁰¹ TlCl scintigram
Mediastinum	+	–	+	++
Intrathyroidal	+	+	+	–
Undescended	+	+	+	+
Thymic tongue	+	–	+	++
Carotid sheath	+	+	+	+

++: very useful; +: useful; –: not useful.

CT: computed tomography; US: ultrasonography; MRI: magnetic resonance imaging.

but it is difficult to identify ectopic glands of less than 500 mg by any preoperative imaging procedure. When persistent HPT is suggested, we initially perform ²⁰¹TlCl single photon emission computed tomography (SPECT) to recognize any missed supernumerary glands in the mediastinum [17–19]. Many reports have indicated that ^{99m}TcMIBI scintigraphy is more sensitive for identifying parathyroid glands than ²⁰¹TlCl and other imaging techniques [20–22]. Therefore MIBI may be “the first” examination, at least for reoperation.

Conclusions

In our large group of renal HPT patients the frequency of supernumerary glands was about 20%. The main reason for persistent HPT was missed nodular hyperplastic glands, especially those located in the mediastinum. Residual small supernumerary glands showing diffuse hyperplasia have the potential to be transformed to nodular hyperplasia during long-term HD after initial PTx. Therefore all parathyroid glands, including small supernumerary glands, should be removed at the initial operation. Routine removal of the thymic tongue, careful checking of the paraesophageal area especially on the left side, and routine preoperative image diagnosis are useful for identifying supernumerary glands, thereby avoiding persistent/recurrent renal HPT.

Résumé

Puisque dans l’hyperparathyroïdie (HPT2), toutes les glandes parathyroïdes, y comprises les glandes surnuméraires, deviennent hypertrophiées et que la stimulation des glandes parathyroïdes continue bien après la parathyroïdectomie (PTx), les glandes surnuméraires ont une importance particulière dans la chirurgie pour HPT2 en ce qui concerne l’hyperparathyroïdie persistante ou récidivante. Dans cette étude de 570 patients qui ont eu une PTx totale avec autogreffe dans l’avant-bras, on a évalué la fréquence, le type, le site, l’histopathologie et la signification clinique des glandes surnuméraires. A l’intervention initiale, on a enlevé 90 glandes surnuméraires chez 82 des 570 patients (14.4%), et 12 patients (2.1%) ont eu besoin d’une excision de glande surnuméraire en raison de la persistance ou d’une récurrence d’HPT. Au total, on a identifié 104 glandes surnuméraires chez 94 des 570 cas (16.1%) au moment de l’intervention. Vingt-cinq (24.0%) de ces glandes étaient de type rudimentaire alors que 79 (76.0%) de type normal. Le plus souvent, les glandes surnuméraires étaient localisées dans le thymus (53/104 = 51.0%), et 32 (60.4%) de ces glandes ont été identifiées uniquement au microscope. Dans six cas (1.1%), une réintervention a été nécessaire

pour HPT persistante en rapport avec des glandes surnuméraires dans le médiastin et dans six cas, une exploration du cou a été nécessaire pour contrôler la récurrence. Du point de vue anatomopathologie, on a retrouvé une hyperplasie diffuse dans 61 des 104 (58.7%) glandes surnuméraires, y comprises 36 reconnues uniquement au microscope, alors que 43 (41.3%) avaient une hyperplasie de type nodulaire. Des petites glandes surnuméraires résiduelles avec une hyperplasie diffuse peuvent se transformer en hyperplasie nodulaire après hémodialyse chronique. Toutes les glandes parathyroïdes, y comprises les glandes surnuméraires, doivent être enlevées chaque fois que possible, pendant l'intervention initiale. L'ablation systématique du thymus et un examen soigneux des régions autour du pôle inférieur de la thyroïde, surtout à gauche, sont importants dans le traitement chirurgical.

Resumen

Puesto que en el hiperparatiroidismo secundario (HPT2) fundamentalmente todas las glándulas paratiroides, incluso las supernumerarias, se hacen hiperplásicas y el estímulo de las paratiroides continúa luego de la paratiroidectomía (PTx), resulta que las glándulas supernumerarias poseen una significación especial en la cirugía por HPT2 en lo concerniente a HPT persistente/recurrente. En el presente estudio se hizo la evaluación de 570 pacientes sometidos a PTx inicial con autoinjerto en el antebrazo, en lo pertinente a la incidencia, tipo, ubicación, histopatología y significación clínica de glándulas supernumerarias. En la operación inicial se removieron 90 glándulas supernumerarias en 82/570 casos (14.4%), y 12 (2.1%) requirieron su extirpación por HPT persistente/recurrente. En total se identificaron 104 glándulas supernumerarias en 94/570 casos (16.1%) durante la operación. Veinticinco (24.0%) de estas glándulas fueron del tipo rudimentario o dividido y 79 (76.0%) del tipo ordinario. La ubicación más frecuente de las glándulas supernumerarias ocurrió en la lengüeta tímica, en 53/104 (51.0%), y 32 (60.4%) de ellas fueron identificadas sólo en el microscopio. En 6 casos (1.1%) se requirió reoperación por HPT persistente debido a glándulas supernumerarias ubicadas en el mediastino y 6 casos fueron sometidos a re-exploración cervical por recurrencias. En el examen histopatológico, 61/104 (58.7%) de las glándulas supernumerarias, incluso las 36 que sólo fueron microscópicamente identificadas, exhibieron hiperplasia nodular. Glándulas supernumerarias residuales pequeñas con hiperplasia difusa poseen el potencial para transformarse en hiperplasia nodular en el curso de hemodiálisis a largo plazo. Es entonces cuando todas las glándulas supernumerarias, en lo posible, deben ser extirpadas con la primera operación. La resección rutinaria de la lengüeta tímica y un examen meticuloso de las regiones que rodean los polos inferiores de la glándula tiroidea, especialmente en el lado izquierdo, constituyen pasos importantes en el tratamiento quirúrgico.

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Invited Commentary

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The authors of this paper present an outstanding experience with parathyroid surgery in patients with hyperparathyroidism (HPT) secondary to uremia. The extraordinary number of patients and the obviously advanced parathyroid disease in their series obviously relates to management by long-term hemodialysis rather than an active kidney transplantation program. The advanced parathyroid disease should also relate to the adopted indications for surgery, implying requirements of rather high parathyroid hormone (PTH) values (>500 pg/ml), the presence of radiologically visualized enlarged parathyroid glands prior to surgery, the demonstration of osteitis fibrosa, or disease refractory to medical therapy. Most authors also consider high serum calcium as an important indication, reflecting probably most appropriately the degree of secretory autonomy of the abnormal parathyroid glands. It should also be required that the patients have been adequately managed medically with phosphate binders, appropriate dialysis calcium, and vitamin D₃ suppressive therapy.

By demonstrating an overall supernumerary gland incidence of 16% within their series the authors provide the ultimate proof of the significance of such glands [1] and thereby strongly support previous suggestions on the management of patients with parathyroid hyperplasia. Autopsy studies have demonstrated that at least 13% of all normal persons have one or several supernumerary glands, half of which should be proper ones and the others rudimentary islets of parathyroid tissue lying either close to the normal parathyroids or within the thymus [1–3]. The continuous growth stimulation in both primary and secondary parathyroid hyperplasia may obviously stimulate also the rudiments of parathyroid glands to grow, and many of them may thus appear as proper supernumerary ones [1, 4–6]. Gilmour [2] reported supernumerary parathyroid glands in 21% of human embryos, and scattered islets of minute parathyroid tissue have been reported as a fairly common finding if the thymus is subjected to serial sectioning. Similar parathyroid gland rudiments can often also be found in the fat pad that normally surrounds the parathyroid glands.

The authors report excellent surgery. They have obviously performed the initial neck exploration well aware that the patients are likely to harbor supernumerary glands, an important message to any surgeon dealing with secondary and possibly also primary parathyroid hyperplasia. It is no disgrace that they were sometimes unable to avoid persistence due to enlarged supernumerary

glands in the mediastinum, which subsequently required reoperation. This type of failure has obviously stimulated efforts to locate supernumerary glands prior to the initial surgery. The methods used in this respect are apparently of limited value, and perhaps sestamibi scintigraphy would have been more efficient in locating mediastinal glands. However, routine introduction of this method prior to the initial operation emphasizes that persistence due to mediastinal supernumerary glands occurred in only approximately 1% of the patients in the presently reported series. Although not discussed by the authors, it appears from the presentation that almost one-third of the supernumerary mediastinal glands were located in the aortopulmonary window, a location easily missed at reoperation. Moreover, the possibility that the patients might harbor intrathyroidal glands, as did four of the present patients, could support liberal use of preoperative ultrasonography.

In summary, the present contribution substantiates previous recommendations about the surgical strategy for HPT and the need to extend neck exploration in parathyroid hyperplasia to routinely include removal of thymic tissue and to clear fat around the parathyroid and the thyroid glands [1]. It is obvious that such recommendations are particularly important in patients with parathyroid hyperplasia, where marked extrinsic stimulation can be expected to remain as in patients with HPT secondary to uremia kept for substantial time periods on maintenance hemodialysis. The same recommendations should apply to patients with genetic alteration expected to stimulate parathyroid growth, as in patients with HPT associated with multiple endocrine neoplasia type I [8, 9].

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