



Unilateral Parathyroidectomy in Hyperparathyroidism Due to Single Adenoma

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As a general principle in the treatment of primary hyperparathyroidism due to single adenoma, unilateral parathyroidectomy was applied to 50 patients and compared with another group of 50 conventionally explored patients. Twenty-five patients were explored only on the "adenoma" side. The other 25 patients were explored on both sides, avoiding biopsies at the first. In the conventionally explored patients, the adenoma was removed and one to three normal glands were biopsied. Oil-red-O technique was used in the intraoperative microscopical examination. The patients in whom the operation could be limited to the "adenoma" side had a statistically more favorable situation concerning early postoperative hypocalcemia, length of operation time, and need for calcium and vitamin D substitution. The principle of unilateral parathyroidectomy in conjunction with intraoperative oil-red-O staining technique is advocated in hyperparathyroidism due to single adenoma because it offers more reliable preoperative distinction between uni- and multi-glandular involvement, reduced operation time, decreased risk for complication, reduced early hypocalcemia, and more favorable technical conditions for reoperation.

THE AIM OF THE SURGICAL procedure in hyperparathyroidism due to single adenoma is to remove the tumor and as little as possible of the remaining normal glandular tissue. A major diagnostic dilemma during operation, is to decide whether the macroscopical tumor really represents a solitary lesion or if it is part of a multiglandular disease, in which case a more extensive surgical procedure is required. To cope with this dilemma, microscopic investigation of grossly normal parathyroid tissue is necessary.

Various surgical approaches to this problem have

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been advocated from removal of the adenomatous gland²² to an obligatory 3.5 gland excision.¹⁷ In multiglandular disease, either with or without connection to MEN syndrome, most authors agree that at least a subtotal parathyroidectomy should be performed. However, if the choice of surgical procedure is based solely on the macroscopic appearance of the glands, unpleasant surprises may occur at the microscopic examination, indicating that the grossly normal-looking gland really shows microscopic signs of nodular hyperplasia.

In the case of a single adenoma, removal of this and bioptic identification of the other glands is the procedure used most frequently.^{2,10,12,19} The extirpation of the tumor-bearing gland, leaving two or three glands identified but intact, is preferred by others.^{8,9,22}

The introduction of a preoperative fat-staining method on frozen sections by Roth and Gallagher²¹ in 1976 and later, the oil-red-O modification as described by Ljungberg et al,¹⁴ have offered improved possibilities to distinguish between single adenoma and multiglandular hyperplastic involvement of the parathyroid organ. This method adds a functional dimension to the morphologic examination because the accumulation of intracellular fat droplets indicates suppressed parathyroid function and reduction of fat droplets hyperactivity as seen in adenoma or hyperplasia.

As a consequence of this improved diagnostic procedure, a new surgical strategy implying unilateral parathyroidectomy has been applied in the treatment

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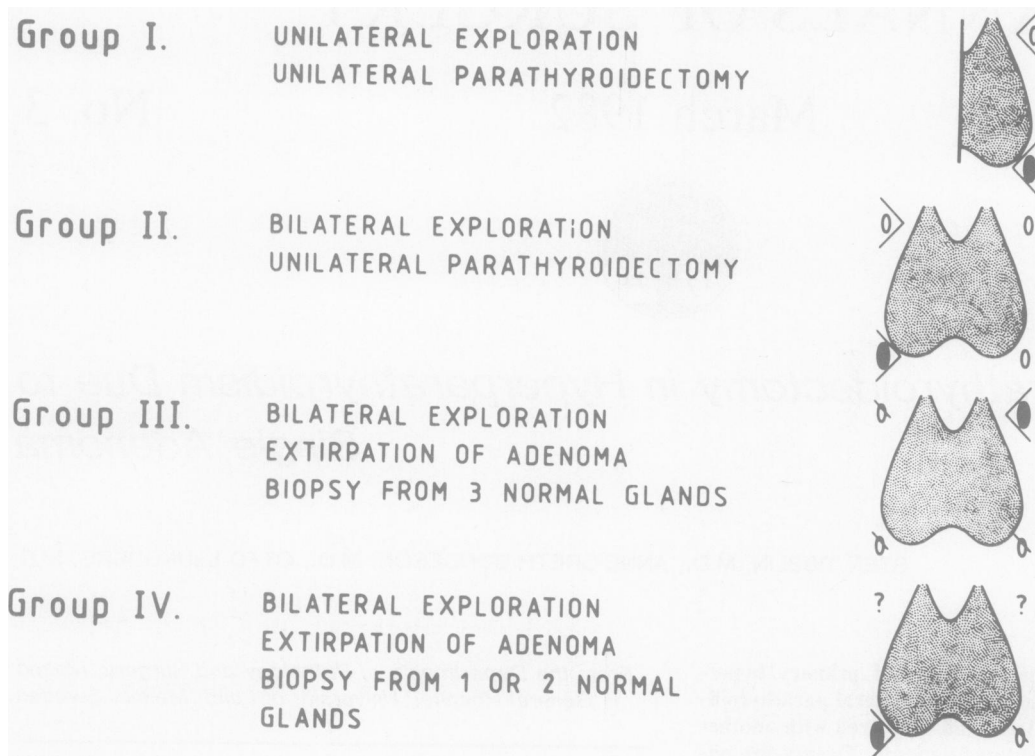


FIG. 1. The four surgical procedures for hyperparathyroidism due to single adenoma that were studied.

of primary hyperparathyroidism due to single adenoma. The present investigation was undertaken to assess the clinical significance of the new surgical principle.

Diagnostic Criteria

Single adenoma means that the microscopic demonstration of one tumor containing chief cells shows lack of suppression with oil-red-O technique, *i.e.*, intracytoplasmic fat droplets are absent or sparse. In the same gland, a rim of normal suppressed chief cells, *i.e.*, chief cells filled with intracytoplasmic fat droplets, is present.

The diagnosis of multiple adenomata is characterized by the presence of adenoma as described above in more than one gland, and the concomitant demonstration of one whole macroscopically normal gland that microscopically shows chief cells filled with intracellular fat droplets as an indication of suppression.

Nodular hyperplasia is defined as a state in which multiple nodules of chief cells, devoid of intracellular fat droplets, occur intermingled with areas containing chief cells with an abundance of intracellular fat droplets as an indication of suppression. Macroscopically normal glands with a uniform picture of suppressed chief cells are not found.

Diffuse hyperplasia is characterized by chief-cells that uniformly are devoid of intracellular fat droplets. Macroscopically normal glands with signs of suppression are not found.

Material and Methods

Four groups, each consisting of 25 patients with primary hyperparathyroidism due to single adenoma were compared as to postoperative S-Calcium level, postoperative need of substitution treatment, operation time, and late results. All patients had a single adenoma removed. None had previously undergone either thyroid or parathyroid surgery. Indication for surgical treatment was based on clinical characteristics and conventional diagnostic means, elevated S-calcium, S-PTH, and increased urinary output of cyclic AMP. The patients did not belong to families with hyperparathyroidism nor were any of them afflicted with multiple endocrine neoplasia. The mean age was 61.5 and did not differ significantly between the various groups. Twenty-three were male (8, 4, 5, and 6 respectively of each group).

The patients were selected consecutively from the clinical material: the individuals of group I and II from the beginning of the period during which the unilateral parathyroidectomy was applied; the individuals of group III and IV from the time preceding and partly overlapping this period.

In group I the exploration was limited to the first side to be explored. Both the adenoma and the normal gland of this side were removed. The contralateral side was not explored (Fig. 1). Group II comprised patients in whom the side explored first revealed two grossly nor-

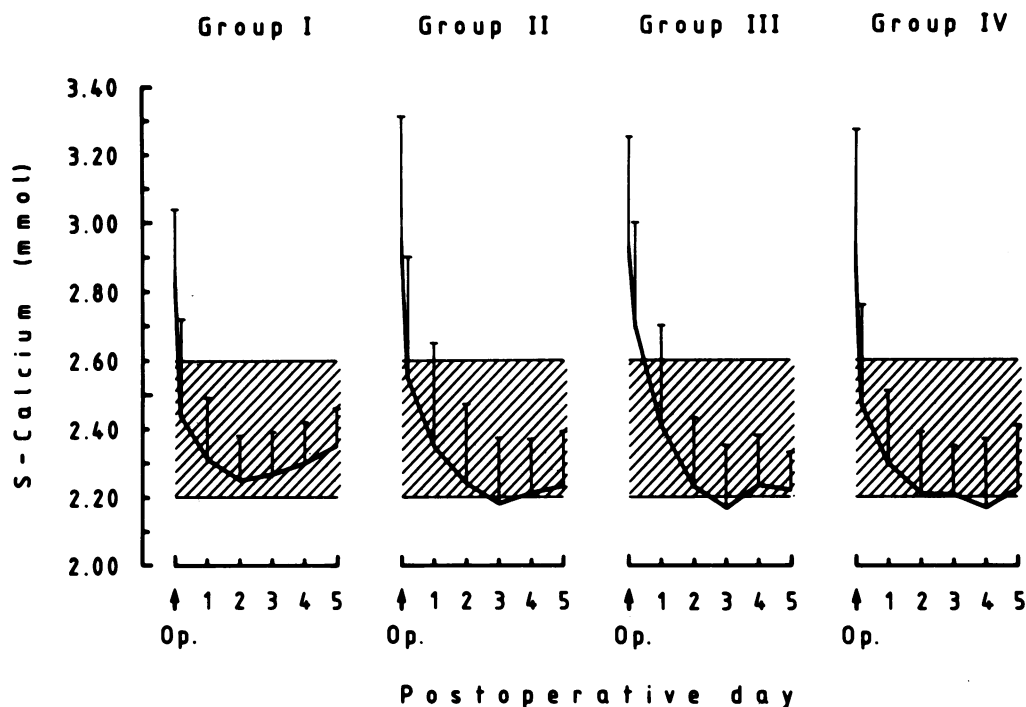


FIG. 2. Early postoperative S-calcium response to various surgical procedures for hyperparathyroidism due to single adenoma. Mean values \pm SD.

mal parathyroids. These were left intact. The adenoma and the fourth normal gland were found at the other side in which unilateral parathyroidectomy was performed. Group III comprised patients who were explored bilaterally and in whom extirpation (of the adenoma and identification by incisional biopsy) of three normal glands were performed. Group IV comprised patients in whom a parathyroid adenoma was extirpated and identification by incisional biopsy of all three normal glands was attempted, but was successful in only one or two glands.

Biopsy Techniques

Excisional biopsy. The gland was dissected free, and the hilar vessels were isolated, divided, and ligated. Surrounding fat tissue was removed, and the normal gland was weighed immediately after removal. The weight of the removed normal glands varied between 18 and 62 mg. Following the weighing procedure, the gland was delivered in saline for pathologic examination.

Incisional biopsy. Part of the gland, usually one of the poles, was dissected free, and an incision of less than $\frac{1}{4}$ of the gland was performed by use of eye-scissors. Immediately following the incision, the incised part of the gland was weighed. The weight of the specimen never exceeded 10 mg. Immediately following the weighing procedure, the specimen was delivered in saline to the pathology department for frozen section examination.

In groups I and II the removed specimens were investigated before operation with conventional hematoxylin-eosin method and the oil-red-O staining technique performed on frozen sections.¹⁴ In groups III and IV, the tissue was studied with hematoxylin-eosin only.

S-calcium determinations were performed four hours after operation and during the following postoperative days. The blood samples were withdrawn under fasting conditions in the morning before the patients had received any peroral or intravenous calcium treatment.

Peroral calcium treatment was given as fervescent calcium tablets of 0.5 g. The patients were informed of the early signs and symptoms of hypocalcemia and were instructed to take peroral calcium whenever subjective symptoms appeared. If hypocalcemia was prolonged for more than two weeks or calcium treatment was insufficient, vitamin D treatment was instituted.

The follow-up period was two to four years in groups I and II and four to seven years in groups III and IV. Wilcoxon's rank sum correlation test was used for the statistical analysis.

Results

The postoperative S-calcium response is depicted in Figure 2. The mean postoperative calcium levels of the groups were 2.86, 2.95, 2.94, and 2.95 respectively (normal range 2.20–2.60 mmol). These mean values did not differ significantly. Hypercalcemia was eliminated in all groups during the first postoperative day.

The most marked depression of S-calcium was ob-

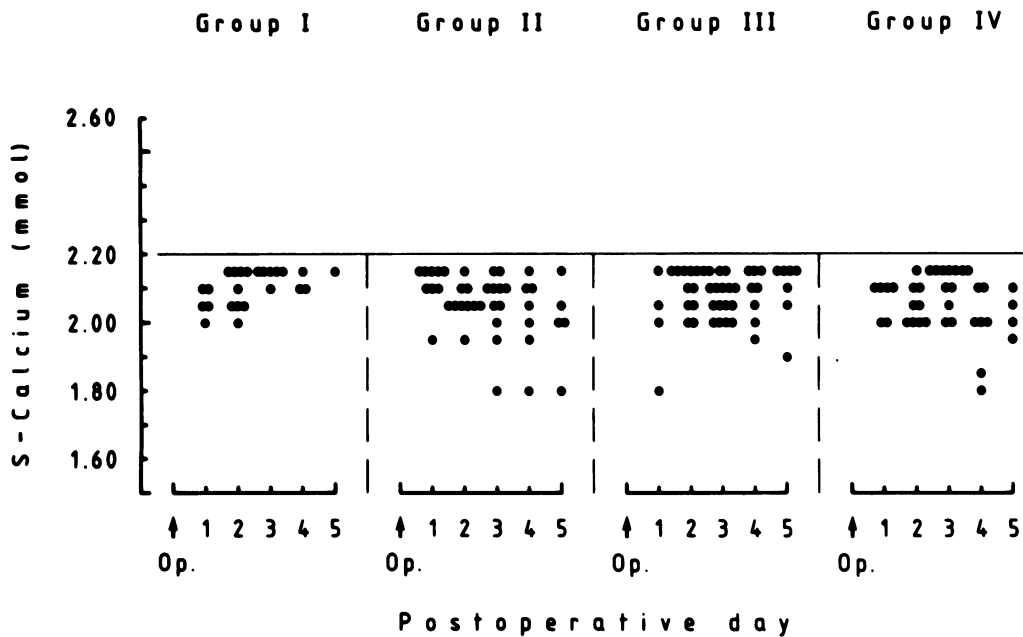


FIG. 3. Individual occurrence and degree of early postoperative hypocalcemia following various surgical procedures for hyperparathyroidism due to single adenoma.

served at the second postoperative day in group I, at the third day in groups II and III, and at the fourth day in group IV. The lowest mean value for group I was 2.24 and in the other groups 2.19, 2.17, and 2.18 respectively. At the fifth postoperative day, mean S-calcium was 2.34 in group I and 2.23, 2.22 and 2.23 respectively in the other groups.

The frequency of hypocalcemic days related to the degree of hypocalcemia in the four groups is depicted in Figure 3. In group I 19% of the postoperative days with available S-calcium determinations was hypocalcemic. The corresponding figures for the other groups were 34, 38, and 36% respectively. S-calcium values below 2.00 mmol/l were not recorded in group I. In the other groups such values were observed at seven, three, and three days respectively. Mean values for the hypocalcemic deviation are depicted graphically in Figure 4. The degree of hypocalcemia was the same in all treatment groups in the initial postoperative phase. At the fifth day, the hypocalcemia was significantly less in group I.

All patients were normocalcemic at the examination four weeks after the operation. Two to seven years follow-up is available in all patients. No case of recurring hyperparathyroidism has been reported. Neither has any instance of late hypocalcemia been observed. Vocal cord function was normal in all patients at the one-year follow-up.

Transient peroral calcium treatment was given to two of the patients in group I (Table 1). In the other groups, where both sides were explored, peroral calcium was given to eight, nine, and nine patients respectively. In

addition, one patient in each group III and IV had a permanent need of vitamin D at the follow-up.

The length of the surgical procedure comprehended time from skin incision to the final stitch, including the frozen section examination (Table 2). Mean length was 93 minutes for the patients explored unilaterally as compared to 115 and 116 minutes for groups II and III. The incompletely explored patients in group IV had a mean length of operation time of 164 minutes. A statistical comparison between the groups showed significantly shorter operation time for group I. The postoperative care period had a mean length of 5.6 days. There were no significant differences between the groups.

Discussion

Preoperative histopathologic examination is important for the identification of parathyroid tissue and the distinction between uni- and multi-glandular involvement. Hematoxylin-eosin staining is a reliable method for the identification of parathyroid tissue. For the distinction between various types of parathyroid pathologic involvement it is sometimes inadequate. As this distinction is important for the choice of surgical procedure, the addition of the oil-red-O technique to the preoperative diagnosis represents a considerable improvement. In addition to the morphologic dimension of the examination, the oil-red-O technique adds a functional dimension. Occurrence of intracytoplasmic fat droplets indicates suppressed chief cells and absence of intracytoplasmic fat droplets signifies hyperfunction.

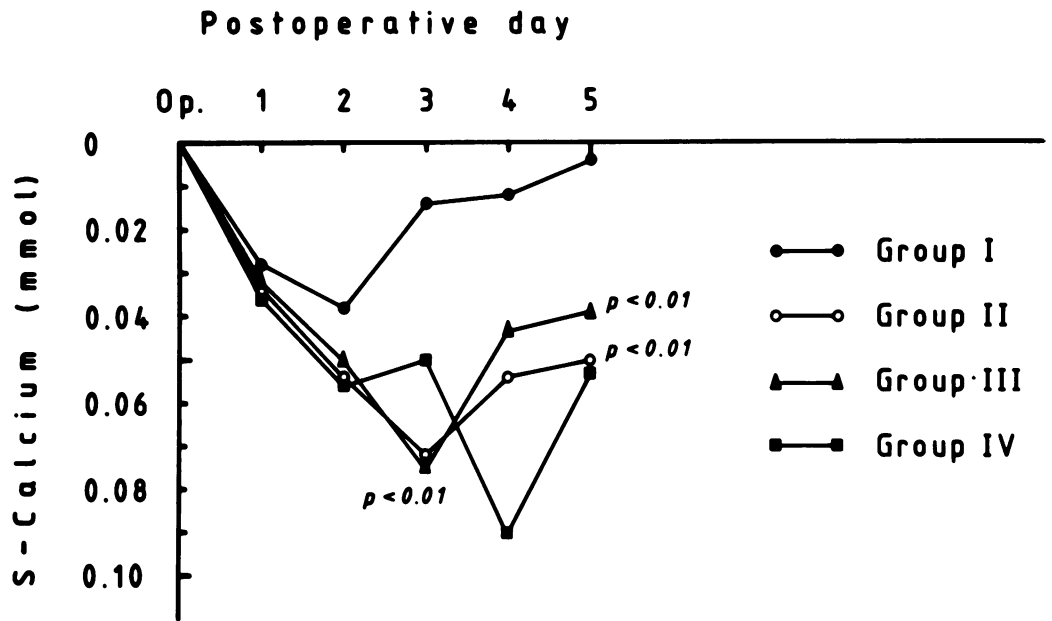


FIG. 4. Mean hypocalcemic deviation in the early postoperative period following various surgical procedures for hyperparathyroidism due to single adenoma.

The rim of normal parathyroid tissue with suppressed chief cells found in an adenomatous gland is of great value for the diagnosis of adenoma. The characteristic picture of a mixture of hyperfunctioning nodules intermingled with areas of normal suppressed chief-cells is a strong diagnostic indication for nodular hyperplasia. In macroscopically normal glands, the finding of minute hyperfunctioning nodules suggests the presence of nodular hyperplasia. Particularly useful is the technique in the diagnosis of diffuse hyperplasia in macroscopically normal glands. The chief cells of these glands are devoid of intracellular fat droplets. In a previous report, Ljungberg et al.¹⁴ could demonstrate that of 39 cases with adenoma 38 showed the typical picture of adenoma chief cells devoid of fat droplets in combination with a rim of normal chief cells with an abundance of fat droplets.

Chief cell hyperplasia was first recognized as a cause of primary hyperparathyroidism by Cope et al.⁵ in 1958. They stressed the generalized involvement of all parathyroid glands as opposed to the adenoma disease. Still, in nodular hyperplasia only one gland may appear grossly abnormal whereas the remaining normal-looking glands at microscopic examination reveal minute hyperplastic foci indicating hyperfunction. So called "true recurrences" of hyperparathyroidism may represent such cases where only the grossly abnormal gland has been removed, whereas in the remaining glands areas of nodular hyperplasia have been allowed to develop into a clinical recurrence later on. The microscopic examination of one whole macroscopically normal gland should reduce the risk to oversee minimal nodular changes.

Since the introduction of the oil-red-O technique, 32 cases of primary hyperparathyroidism due to hyperplasia were diagnosed. They were all treated with subtotal parathyroidectomy. In 20 of these cases an enlarged gland was found together with a grossly normal gland at the first explored side, simulating single adenoma disease macroscopically. In these cases, however, the preoperative microscopic examination revealed involvement of the grossly normal gland, indicating hyperplastic disease. Subsequent exploration of the other side showed additional abnormal glands.

When applying the surgical strategy of unilateral parathyroidectomy, it is crucial to exclude the possibility of a multiglandular disease before operation. For that reason a one-sided parathyroid operation should not be performed with less than the microscopic identification of one whole normal gland.

In order to test the principles of unilateral parathyroidectomy against the conventional "four gland exploration" procedure, four groups of patients with hyperparathyroidism due to single adenoma were compared. In groups I and II the principle of unilateral parathy-

TABLE 1. Postoperative Treatment for Hypocalcemia after Various Surgical Procedures for Hyperparathyroidism. Each Group Includes 25 Patients

Surgical Procedure	Transient Peroral Calcium	Permanent Vitamin D
Group I	2	0
Group II	8	0
Group III	9	1
Group IV	9	1

TABLE 2. Length of Surgical Procedure (Min)

Surgical Procedure	Mean Operation Time
Group I	93
Group II	115
Group III	116
Group IV	164

roidectomy was applied; in groups III and IV the principle of exploring all four glands was used.

Removal of the parathyroid adenoma resulted in a prompt elimination of the hypercalcemia in all groups. The drop of the postoperative S-calcium was more marked in groups II, III, and IV, suggesting that the approach in group I in which only one side had been explored was less traumatic. Also the number of postoperative hypocalcemic days were fewer, and the absolute level of hypocalcemia was less pronounced following the unilateral exploration. The increased need for peroral calcium medication or vitamin-D substitution in groups II, III, and IV also indicates that the damage is reduced by restricting the exploration to one side. Particularly notable is that the mere identification of the glands without biopsies as in group II resulted in a similar frequency of postoperative hypocalcemia as seen in group III, where incisional biopsies of all three normal glands were performed. This clearly demonstrates that even an atraumatic identification procedure carries a risk of at least a transient hypofunction of the healthy parathyroid glands. The lack of difference in the frequency of hypocalcemia between groups II and III supports the opinion that the identification procedure is equally traumatic as the biopsies. Removal of one whole normal gland did not seem to influence negatively the postoperative S-calcium level. The chief cell mass in one normal gland should be approximately the same as biopsies from three glands.

In the present material the frozen sections were studied both with conventional hematoxylin-eosin and the intracellular fat staining technique. In spite of the somewhat increased time consumption for the mere staining procedure the operation time for the unilateral exploration was less than in the other groups. The fourth group in which the exploration was incomplete because of lack of identification of one or two normal glands the operation time was significantly prolonged.

In 12 of the 25 patients in group I, no hypocalcemic postoperative days occurred. This suggests that the normal glands of these patients retained a sufficient functional capacity to avoid hypocalcemia already during the first postoperative days.

The variation in intracellular fat droplet content recently reported¹⁴ possibly reflects a varying degree of

suppressed chief cell function. The correlation between grade of hypocalcemia after operation and degree of suppression as reflected in the appearance of intracytoplasmatic fat droplets is presently studied. Dekker et al.⁸ recently reported on the therapeutic impact of the oil-red-O, and they concluded that the surgically more conservative approach is justified in patients with primary hyperparathyroidism.

Roth, Wang, and Potts²⁰ have previously described a unilateral approach in hyperparathyroidism. If one abnormal and one normal gland is found on the first side to be explored, they advocate the removal of the adenoma and a 0.1–0.2 cm biopsy of the normal gland. In our opinion, the removal of one whole gland facilitates the evaluation of hyperplasia for the pathologist, particularly if the oil-red-O staining technique is used as it allows a functional evaluation of the normal chief cells. We agree with these authors that the exploration should continue on the contralateral side if any signs of multiglandular involvement are revealed at the histopathologic examination of the glands from the first explored side. We also agree that the exploration should be extended to the contralateral side if one or two normal glands are found on the first side. In this situation we do not biopsy the macroscopically normal-looking glands of the first explored side if the adenoma and a macroscopically normal gland are found at the contralateral side. If only one adenomatous gland is found, one whole gland from the contralateral side is removed provided there are two identified. We thus try to leave the glands of one side without biopsies and remove all parathyroid tissue at the "adenoma side."

Postoperative hypocalcemia, even of mild degree, is a miserable state not only because of tetany but also as a result of the anxiety that accompanies it. The rapidly increasing extent of parathyroid surgical activity necessitates the formulation of simple and safe surgical methods. A more conservative approach to the parathyroid neck exploration has recently been advocated by Edis et al.⁹ They compared neck explorations in which biopsies were used extensively with operations in which the enlarged gland was removed with or without biopsy of one normal-sized gland.

Symptomatic hypocalcemia requiring treatment occurred in 24% of the more extensively explored patients, as compared to 4% in the more conservatively treated group. The more extensive explorations did not yield any higher cure rate.

In a Scandinavian survey of parathyroid surgical activity during 1975, 652 patients, operated upon in various hospitals around Scandinavia, were studied. The best results were obtained when only the adenoma was removed. In this group 9% were hypocalcemic at the

discharge from the hospital. If biopsy was done on one or more glands, the corresponding figure was doubled.¹¹ These figures indicate that the principle of identifying and biopsying all glands should be critically reconsidered.

Unilateral parathyroidectomy should be reserved for patients with primary hyperparathyroidism due to a single adenoma who previously have not undergone a neck exploration. In re-explorations either after previous parathyroid surgery or thyroid surgery, the exploration should be adjusted to the individual situation. In these patients, removal of one whole normal gland might be hazardous as healthy parathyroid tissue might have been removed with or without intention at previous operations. Also, in patients with familial hyperparathyroidism as well as in patients with multiple endocrine, adenopathy unilateral parathyroidectomy should not be used. If these different types of hyperparathyroidism are excluded, the majority of cases still remains, *i.e.*, patients with hyperparathyroidism due to a single adenoma. In the clinical material of our institution from the latest six years, it would have been possible to employ the surgical principle of unilateral parathyroidectomy in 70% of all cases with primary hyperparathyroidism.

Since the introduction of the oil-red-O method in 1976, 186 patients undergoing various forms of parathyroid surgery have been investigated. Multiple adenomata fulfilling the criteria given above have not been found in any patient. In the 50 patients included in the present study, no case of hypercalcemia could be demonstrated at the follow-up two to four years after the operation.

Multiple parathyroid adenomata have been reported in several series of patients with primary hyperparathyroidism. A review of eight patient-materials after 1958 gives a frequency of 1.9%–5%.^{1-4,7,15,18,23} Harness *et al.*¹³ reports a 1.7% incidence of double adenomas. In a recent report on 199 patients with primary hyperparathyroidism, Block *et al.*³ noted seven patients with enlargement of only two parathyroid glands. In the first 200 patients treated surgically for hyperparathyroidism at the Massachusetts General Hospital, 5% of double adenomas were found. Wang and Rieder²³ reported in 1978 that of 13 of the patients with double adenomas found at the Massachusetts General Hospital through 1958, six eventually proved to be primary chief cell hyperplasia, and the diagnosis has not been conclusively substantiated in the other seven. Since 1958, they were not able to find a single case of double adenomata. Cope⁶ has stated that "it is such a biological feat to make one hyperfunctioning adenoma that a coincidental second hypersecreting neoplasm is highly unlikely."

None of these reports have used the strict diagnostic criteria of the present study. The demonstration of one whole, macroscopically normal gland with a uniform picture of suppressed chief-cells as indicated by abundance of fat droplets must be considered a necessary prerequisite for the diagnosis of multiple adenomata. Moreover, the glands in which the adenomata are found must exhibit a rim of normal suppressed chief cells.

Even if no case could be found in the present material, multiple adenomata might exist, although in a frequency probably less than 1%. As the chance of having two adenomata at the same side is as big as finding one at each side, the risk of missing a second adenoma by applying unilateral parathyroidectomy is reduced by 50%. Further, should it occur, the reoperation can be performed in previously unexplored tissue.

The elimination of hypercalcemia and the absence of recurrence during the follow-up after unilateral parathyroidectomy indicates that this method can be used safely with regard to curability. Moreover, even if the differences were small between the groups explored according to different surgical strategies the postoperative hypocalcemia was less pronounced in the patients in whom only one side had been explored.

In conclusion, the data of the present report suggest that unilateral parathyroidectomy as a surgical principle based upon preoperative functional and morphologic evaluation by oil-red-O technique is a good choice in the treatment of hyperparathyroidism due to single adenoma. It offers:

1. More reliable preoperative distinction between uni- and multi-glandular involvement.
2. Reduced hypocalcemia in the early postoperative course, both as to frequency and degree.
3. Decreased risk for complications in terms of nerve damage and persisting hypoparathyroidism.
4. Reduced operation time.
5. More favorable technical conditions if a reoperation should be necessary.

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