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The Challenge of the Middle Mediastinal Parathyroid

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In most cases of persistent or recurrent hyperparathyroidism (HPT), the pathological parathyroid (PT) will be in the neck or accessible through the cervical approach, and in only a small percentage will median sternotomy be required. We present 3 cases of persistent HPT where the PT tissue was in the middle mediastinum. We acknowledge that this is a rare occurrence and that it cannot be explained adequately by standard embryological teaching. In cases requiring formal mediastinal exploration, the mediastinal exploration is not complete unless the middle mediastinum is carefully explored to exclude ectopic PT tissue.

The treatment of primary hyperparathyroidism is surgical and the initial operation for this condition may be successful in 95–98% of cases [1–5]. Reexploration for persistent or recurrent hyperparathyroidism, however, remains a difficult and demanding surgical exercise with a diminished chance of success accompanied by a significant increase in morbidity [6, 7].

It is firmly established that in the majority of cases of persistent or recurrent hyperparathyroidism requiring reexploration, the "missing" parathyroid tissue will lie within or be accessible from the neck. Even though only 1–3% of initial cervical explorations fail due to the adenoma residing in the mediastinum, up to 30% of reoperations require sternotomy [8].

When formal mediastinal exploration is required, the parathyroid tissue is usually found in the anterior mediastinum either within the thymic capsule or in close relationship to this organ as would be expected from the common embryological origin of these tissues [7, 9, 10]. Additionally, many adenomas have been located in close proximity to the aortic arch vessels. There have only been isolated case reports of ectopic parathyroid tissue lying within the pericardium or other aberrant mediastinal positions [5, 11].

We present 3 cases of persistent primary hyperparathyroidism in which the abnormal parathyroid tissue was found in the

middle mediastinum, posterior to the aortic arch but anterior to the tracheal carina and main bronchi.

Case Histories

Case 1

A 69-year-old, morbidly obese, black male with active nephrolithiasis of 20 years' duration and a history of hypertension presented to the Department of Surgery, Ann Arbor, Michigan, U.S.A. with persistent hypercalcemia (calcium, 11.5 mg/dl) and an inappropriately raised immunoreactive parathyroid hormone level following a previous cervical exploration at another institution for hyperparathyroidism in 1976 in which one normal parathyroid gland was removed.

Cervical and mediastinal explorations were undertaken and one further normal parathyroid gland was found in the neck. The thymus and anterior mediastinal fat were excised at mediastinal exploration but no mediastinal parathyroid tissue was found. The patient remained hypercalcemic (calcium, 11.2 mg/dl). Selective venous sampling demonstrated a significant "step-up" in midterminal PTH assay in the region of the left innominate vein. Selective arteriography of the left internal mammary artery showed a 0.9 × 2.0 cm vascular tumor in the left aortopulmonary window (Fig. 1). A left anterior thoracotomy was performed and a parathyroid adenoma 1.0 × 2.0 cm was located deep in the aortopulmonary window, posterior to the aortic arch (Fig. 2). The patient was rendered normocalcemic (calcium, 9.2 mg/dl) after the excision of this gland and remains so 2 years after this event.

Case 2

A 35-year-old white female was referred to the Mayo Clinic, Rochester, Minnesota, U.S.A. with symptomatic hyperparathyroidism and active nephrolithiasis on a background of MEN I syndrome. The diagnosis of MEN I was supported by a family history of a father with hyperparathyroidism and thymic carcinoid and a brother with hyperparathyroidism and an islet cell
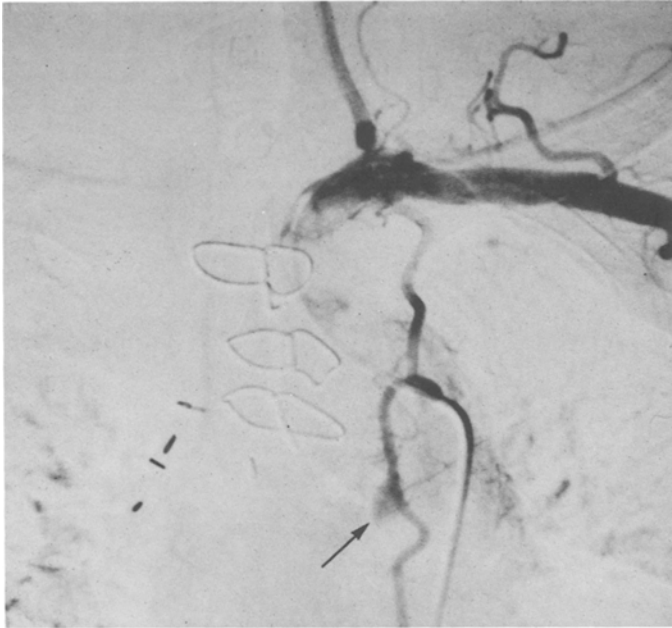
Fig. 1. Selective arteriogram of the left internal mammary artery showing a vascular tumor: 0.9 × 2.0 cm (Case 1).

tumor of the pancreas. The patient had undergone 2 previous surgical explorations with removal of 4 normal parathyroid glands prior to her referral, yet she remained persistently hypercalcemic (calcium, 11.3 mg/dl), with a raised parathyroid hormone of 63 μLEq/mL (normal, 0–50). Investigations, which included a computed tomography (CT) scan to the aortic arch together with a high-resolution, real-time, ultrasound scan of the neck and thallium-technetium subtraction scan failed to localize the pathological parathyroid gland. Combined cervical and mediastinal exploration finally identified hyperplastic parathyroid tissue in the middle mediastinum, just to the right of the carina, anterior to the right main bronchus and posterior to the right pulmonary artery (Fig. 3). Removal of this tissue rendered the patient normocalcemic (calcium, 9.6 mg/dl), although she has, again, developed recurrent, mild hypercalcemia.

Case 3

A 50-year-old white female with symptomatic hyperparathyroidism (calcium, 12.8 ng/dl and PTH, 0.8 ng/ml; N-terminal assay: normal, 0–1 ng/ml) and nephrolithiasis underwent cervical exploration and identification of 4 normal parathyroid glands in the neck. She remained hypercalcemic (calcium, 12.6 mg/dl) postoperatively. CT scan was normal, but selective venous sampling showed a significant "step-up" in N-terminal PTH in the azygos vein. Several months later, mediastinal exploration was performed with total thymectomy and excision of anterior mediastinal fat, but no parathyroid tissue was found. She continued with persistent hypercalcemia and, 3 months later, developed florid signs of hyperthyroidism due to Graves' disease. This was treated with radioactive iodine and she was

rendered euthyroid, but the hypercalcemia continued (calcium, 13.6 mg/dl) with the development of proximal limb myopathy. Further combined cervical and mediastinal exploration was performed and a 2.0 × 2.0 cm parathyroid adenoma was located and excised from deep in the middle mediastinum, just to the right of the carina, anterior to the right main bronchus, posterior to the right pulmonary artery (Figs. 4, 5). The serum calcium returned to normal (9.5 mg/dl) following a period of postoperative hypocalcemia that required replacement therapy for 4 months.

Discussion

All 3 cases presented with persistent hyperparathyroidism having previously undergone one or more failed cervical explorations for primary hyperparathyroidism. In each case, the initial cervical exploration(s) had been unsuccessful because the pathological tissue lay deep within the mediastinum. Previous reports of failed cervical explorations emphasize that, in the majority of cases requiring reexploration, the "missing" gland is in the neck or accessible from the cervical incision [6, 7, 12]. Edis et al. suggested that the reason for the unsuccessful initial exploration is "failure on the part of the surgeon to appreciate the nuances and variations of normal parathyroid anatomy" [13]. This point of view is supported by several reported series of reexploration where the missing gland was subsequently located in a normal anatomical position in up to 60% of cases [7, 14, 15]. This simple comment, however, understates what most surgeons regard as a complex problem. The reasons for failure of initial cervical exploration in parathyroid surgery are multifactorial. These include: variation in the position, size, and shape of the parathyroids, the presence of supernumerary glands and double adenomas, the presence of intrathyroidal glands, and the presence of multiglandular disease, especially in association with MEN syndrome [8, 16, 17]. Also, despite one's best diagnostic efforts, failure may occur if the hypercalcemia is actually due to nonparathyroidal causes.

The superior parathyroid gland (embryologically, PT IV) is relatively constant in position with 92% of normal glands found in a juxtathyroidal, juxtacricoidal position posterior to the upper pole of the thyroid gland [16, 17]. In pathologically enlarged glands, however, more than one-third (36–39%) of adenomas of the superior glands migrate, presumably under the influence of gravity, deglutition, and negative intrathoracic pressure and come to lie in the posterior superior mediastinum [8]. These abnormal glands are always accessible from the neck at operation.

The inferior parathyroid glands (embryologically, PT III), because of their embryological association with the thymus, are more widely distributed and can be found from the angle of the mandible (the undescended "parathymus") to the level of the diaphragm [18]. In spite of this potential for a wide distribution, 70% of the inferior glands are associated with the inferior pole of the thyroid gland or the thyrothymic tract [13, 16, 17].

When the inferior parathyroid glands are situated in the mediastinum, they are intrathymic or in relationship to the great vessels of the anterior mediastinum, posterior to the thymus [7, 9]. Even when situated in the anterior mediastinum, most
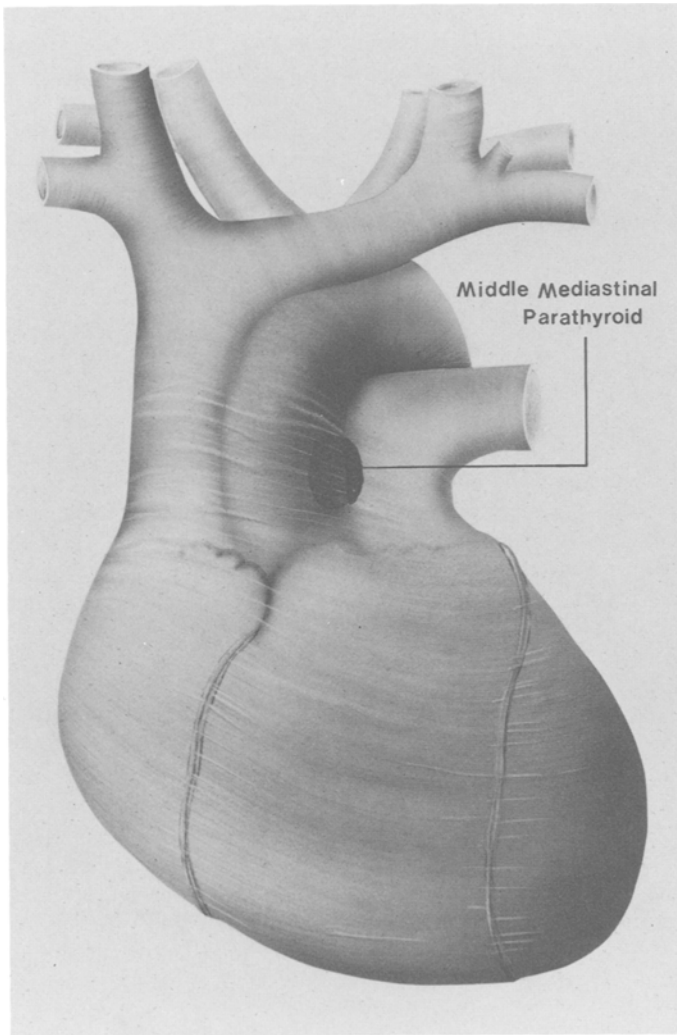
Fig. 2. Location of parathyroid adenoma in Case 1: deep in the aortopulmonary window, posterior to the aortic arch.

inferior parathyroid glands are accessible from the cervical incision [10]. In several recent large series of reexploration for persistent or recurrent hyperparathyroidism, only 18–20% of cases required median sternotomy to remove the mediastinal parathyroid. Of the total of 72 deep mediastinal glands reported in these combined series, only 1 gland was found in the middle mediastinum and this is Case 2 reported in our article [6, 7, 10]. Cohn and Silen [19] successfully removed a middle mediastinal adenoma 4 cm in diameter in the aortopulmonary window between the aorta and pulmonary artery in a patient who had undergone 10 previous cervical explorations and 3 mediastinal operations. Recently, there has been a further case report of a middle mediastinal parathyroid adenoma in an identical position to the parathyroid tissue in Cases 2 and 3 reported here [11].

When a supernumerary gland is the cause of persistent or recurrent hyperparathyroidism, the offending gland is located in the mediastinum in approximately 50% of cases [20–22]. In 2 of our cases, it would appear that the mediastinal was, indeed, a fifth gland.

The occurrence of parathyroid tissue in the middle mediastinum is difficult to explain by standard embryological teaching. It is unlikely that, in our 3 cases, there was migration of pathological glandular tissue from the anterior mediastinum to their final position in the middle mediastinum although, in Case 1, the blood supply to the gland arose from the internal mammary artery.

In Cases 2 and 3, it is probable that the parathyroid tissue came to lie in the middle mediastinum early in the embryological development rather than by migration of pathological glands. These mediastinal ectopic parathyroid III glands usually lie in the line of the embryological descent of the thymus.

Fragmentation of parathyroid III occurs when the ductus pharyngobrachialis III separates from the pharynx in the 13 mm embryo-forming accessory parathyroids and thymic remnants. These usually migrate with the main thymic component into the anterior mediastinum. At an early stage of embryological development, the fused intrathoracic thymus is dorsal to the pericardium [23]. It is possible that the accessory parathyroid III tissue may retain this dorsal relationship with the pericardium and come to lie in the middle mediastinum. It is significant that there was no thymic tissue found in relationship to the parathyroid in our 3 cases nor in the other recently reported middle mediastinal parathyroid [11].

This absence of thymic tissue raises the possibility that the ectopic parathyroids of the middle mediastinum arose from parathyroid IV. Gilmour noted that parathyroid IV is in contact with the pericardium in the 3 mm embryo and it is possible that some parathyroid precursor cells may retain this relationship and develop in the middle mediastinum [24]. It is of note that, in Cases 2 and 3, and in the recently reported similar case of Stocks et al. [11], not only was there absent thymic tissue, but there was also a constant relationship to the right pulmonary artery which, embryologically, is derived from the VIth branchial artery.

Parathyroid IV develops from the dorsal area of the "caudal pharyngeal complex," which is derived from the fusion of IVth and Vth pharyngeal pouches. The absence of the Vth branchial artery brings the "caudal pharyngeal complex" into relationship with the VIth branchial artery in the 7.5–11 mm embryo [23]. If fragmentation of the parathyroid IV component occurs at this stage, parathyroid tissue may remain to develop in the proximity of the future right pulmonary artery and remain in the middle mediastinum. Although this is speculation, we tend to favor the last theory of development because of the constancy of position of the glands and the absence of thymic tissue.

In concert with other units on undertaking a mediastinal exploration, we recommend total thymectomy and excision of mediastinal fat followed by skeletonization of the aortic arch and great vessels [6, 9]. In view of the 3 cases presented, we believe mediastinal exploration is not complete unless the middle mediastinum and aortopulmonary window are carefully explored to assure that parathyroid tissue is excluded from these sites. The middle mediastinum is particularly inaccessible when approached from the median sternotomy, but may be approached by gentle retraction of the great vessels and, as was necessary in Case 3, by ligation and division of the left innominate vein. This allows free access to the area posterior to the aortic arch to the level of the carina, posterior to the pulmonary arteries. This region is richly endowed with lymph
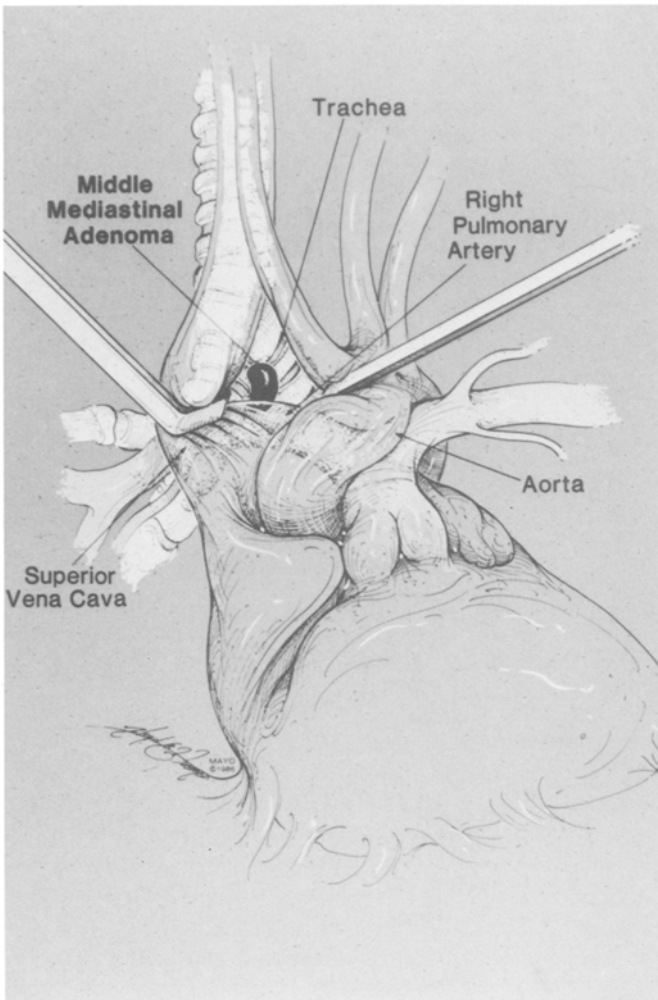
Fig. 3. Middle mediastinal parathyroid gland, anterior to the right main bronchus and posterior to the right pulmonary artery (Case 2).
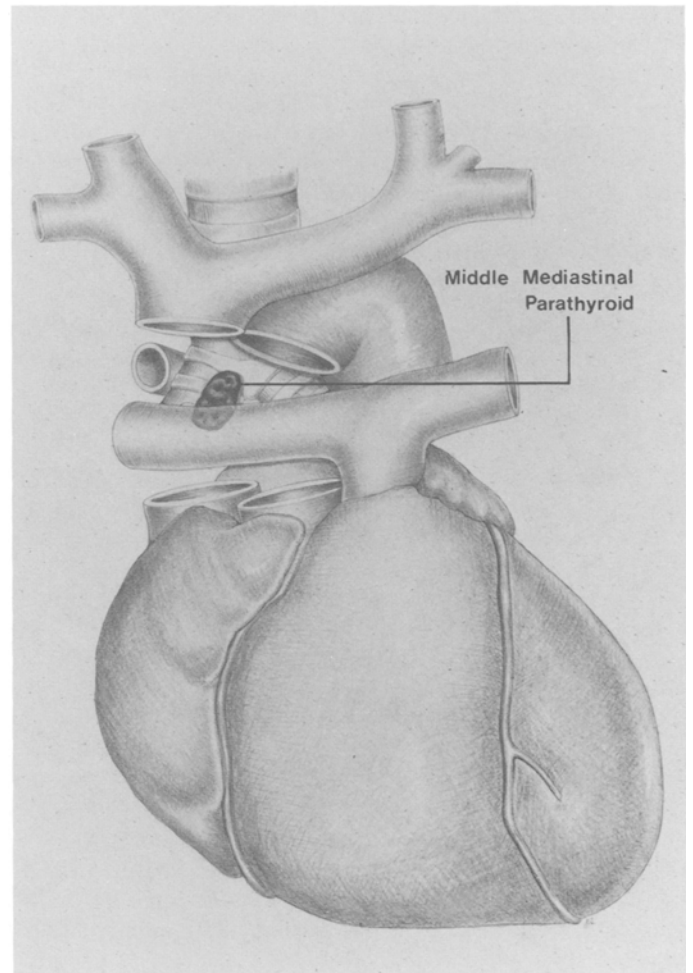
Fig. 4. Middle mediastinal parathyroid adenoma: 2 cm in diameter, located to the right of the carina, anterior to the right main bronchus, posterior to the right pulmonary artery (Case 3).
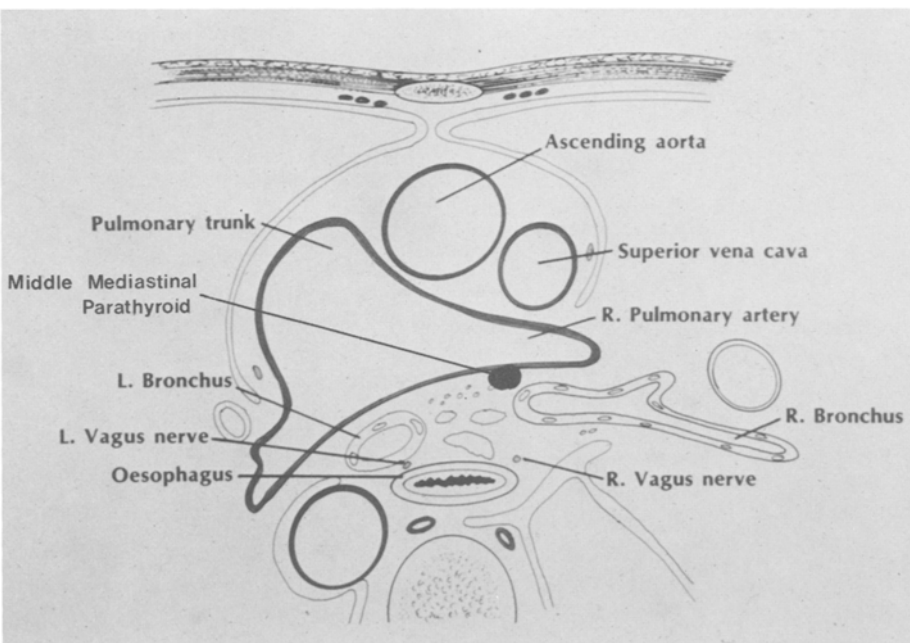
Fig. 5. Transverse section of thorax showing location of the parathyroid adenoma in Case 3: posterior to the right pulmonary artery.

nodes and, in the adult, these nodes are heavily laden with pigment, which may make the identification of parathyroid tissue difficult.

These 3 cases add a further dimension to the challenge of reoperative parathyroid surgery by extending the potential areas of the mediastinum from which the parathyroid tissue must be excluded if a satisfactory outcome is to be achieved.

Résumé

Dans la plupart des cas d'hyperparathyroïdie (HPT) persistante ou récidivante, la glande parathyroïdienne (PT) pathologique responsable se trouve souvent dans le cou ou est au moins accessible par une incision cervicale. Il est rare qu'une sterno-tomie médiane soit nécessaire. Nous présentons 3 cas d'HPT persistante dans lesquels la glande PT restante se trouvait dans le médiastin moyen. Nous reconnaissons qu'il s'agit d'une éventualité rare qui ne peut être expliquée par l'embryologie classique. Dans les cas où une exploration médiastinale réglée est nécessaire, il faut, pour être complet, ne pas oublier d'explorer le médiastin moyen pour exclure toute possibilité d'existence de tissu PT ectopique.

Resumen

En la mayoría de los casos de hiperparatiroidismo persistente o recurrente la glándula patológica se encuentra en el cuello o es accesible por un abordaje cervical, y sólo en un mínimo porcentaje se hace necesario realizar esternotomía. Presenta-mos 3 casos de hiperpartiroidismo persistente en los cuales el tejido paratiroideo anormal fue hallado en el mediastino medio, posterior al arco aórtico pero anterior a la carina y a los bronquios principales. Reconocemos que este es un hallazgo raro y que no puede ser adecuadamente explicado a la luz de los conocimientos embriológicos ordinarios. En casos que requi-eran exploración mediastinal formal, la exploración no puede ser considerada como completa a menos que el mediastino medio sea cuidadosamente inspeccionado a fín de excluir la presencia de tejido paratiroideo ectópico.

References

1. Bruining, H.A., van Houten, H., Juttman, J.R., Lamberts, S.W.J., Birkenhäger, J.C.: Results of operative treatment of 615 patients with primary hyperparathyroidism. World J. Surg. 5:85, 1981
2. Martin, J.K., van Heerden, J.A., Edis, A.J., Dahlin, D.C.: Persist-ent postoperative hyperparathyroidism. Surg. Gynecol. Obstet. 151:764, 1980
3. Mundy, G.R., Cove, D.H., Fisken, R.: Primary hyperparathyroid-ism: Changes in the pattern of clinical presentation. Lancet 1:1317, 1980
4. Satava, R.M., Beahrs, O.H., Scholz, D.A.: Success rate of cervical exploration for hyperparathyroidism. Arch. Surg. 110:625, 1975
5. Thompson, N.W.: Discussion on Results of reoperation for hyper-parathyroidism with evaluation of preoperative localization studies. Surgery 84:384, 1978
6. Brennan, M.F., Marx, S.J., Doppman, J.L., Costa, J., Saxe, A., Spiegel, A., Krudy, A., Aurbach, G.: Results of re-operation for persistent or recurrent hyperparathyroidism. Ann. Surg. 194:671, 1981
7. Grant, C.S., van Heerden, J.A., Charboneau, J.W., James, E.M., Reading, C.C.: Clinical management of persistent and/or recurrent primary hyperparathyroidism. World J. Surg. 10:555, 1986
8. Thompson, N.W., Eckhauser, F.E., Harness, J.K.: The anatomy of primary hyperparathyroidism. Surgery 92:814, 1982
9. Norton, J.A., Schneider, P.D., Brennan, M.F.: Median sternotomy in reoperations for primary hyperparathyroidism. World J. Surg 9:807, 1985
10. Wang, C.-A.: Surgical management of primary hyperparathyroid-ism. Curr. Prob. Surg. 22:1, 1985
11. Stocks, A.E., Hartley, L.C.J.: Hypercalcaemia: The case of the missing adenoma. Med. J. Aust. 145:92, 1986
12. Rossi, R.L., Re Mine, S.G., Clerkin, E.P.: Surg. Clin. North Am. 65:187, 1985
13. Edis, A.J., Sheedy, II, P.F., Beahrs, O.H., van Heerden, J.A.: Results of reoperation for hyperparathyroidism with evaluation of preoperative localization studies. Surgery 84:384, 1978
14. Beazley, R.M., Costa, J., Ketcham, A.S.: Reoperative parathyroid surgery. Am. J. Surg. 130:427, 1975
15. van Vroonhoven, J.J., Muller, H.: Causes of failure in surgical treatment of primary hyperparathyroidism: Lessons from 51 suc-cessful reoperations. Br. J. Surg. 65:297, 1978
16. Åkerström, J.R., Malmaeus, J., Bergstrom, R.: Surgical anatomy of human parathyroid glands. Surgery 95:14, 1984
17. Wang, C-A.: The anatomic basis of parathyroid surgery. Ann. Surg. 183:271, 1976
18. Edis, A.J., Purnell, D.C., van Heerden, J.A.: The undescended "parathymus": An occasional cause of failed neck exploration for hyperparathyroidism. Ann. Surg. 190:64, 1979
19. Cohn, K.H., Silen, W.S.: Lessons of parathyroid reoperations. Am. J. Surg. 144:511, 1982
20. Russell, C.F., Grant, C.S., van Heerden, J.A.: Hyperfunctioning supernumerary parathyroid glands: An occasional cause of hyper-parathyroidism. Mayo Clin. Proc. 57:121, 1982
21. Scholz, D.A., Purnell, D.C., Woolner, L.B.: Mediastinal hyper-functioning parathyroid tumours: Review of 14 cases. Ann. Surg. 178:173, 1954
22. Wang, C.-A., Mahaffey, J.E., Axelrod, L., Perlman, J.A.: Hyper-functioning supernumerary parathyroid glands. Surg. Gynecol. Obstet. 148:711, 1979
23. Hamilton, W.J., Mossman, H.W.: Human Embryology, 4th edi-tion, Cambridge, W. Heffner & Sons, 1972, chapters X (pp. 228–290), XI (pp. 291–376)
24. Gilmour, J.R.: Embryology of the parathyroid glands and thymus and certain associated rudiments. J. Pathol. 45:507, 1937

Invited Commentary

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This article by Curley et al. describes 3 patients with persistent hyperparathyroidism. The first 2 patients had 2 negative para-thyroid explorations and the third one failed parathyroid oper-ation before the elusive solitary parathyroid "adenomas" were removed from the middle mediastinum near the aortopulmon-ary window. This article briefly describes the pertinent clinical histories of these 3 patients and emphasizes that a "mediastinal exploration is not complete unless the middle mediastinum and aortopulmonary window are carefully explored to ensure that parathyroid tissue is excluded from these sites." The authors also give an excellent discussion of the embryological reasons