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Autotransplantation of human parathyroid glands

P J BILLINGS FRCS*
Registrar
E MILROY FRCS
Consultant Urologist
The Middlesex Hospital

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Summary

Six patients with primary hyperparathyroidism have had glands autotransplanted into their forearm or deltoid region immediately after presumed total parathyroidectomy. Five hyperplastic glands were transplanted; two patients are normocalcaemic, two are hypercalcaemic and one is hypocalcaemic. The one normal transplanted gland did not show any evidence of function. We conclude that immediate transplantation of parathyroid tissue following total parathyroidectomy may not be the procedure of choice.

Introduction

The parathyroid gland was first described by Professor Richard Owen in the Indian Rhinoceros in 1862 *(1)* but it was not until 1925 that Mandl in Vienna *(2)* performed the first parathyroidectomy for primary hyperparathyroid disease. Cristiana and Ferrari *(3)* are credited with the first experimental parathyroid autotransplants in animals in 1897, but Lahey did not publish the first account of human autotransplantation until 1926 *(4)*.

Interest in parathyroid autotransplantation has increased over the past 20 years. Several centres in Britain carrying out parathyroid surgery now have experience of this technique. We have carried out a series of six autotransplants for primary hyperparathyroidism over the past 6 years and we review our results here. All calcium estimations are corrected for an albumin of 41 g/l (normal 2.22–2.55 mmol/l) and an amino-terminal assay *(5)* is employed for parathyroid hormone (PTH) estimations (normal 120 pg/ml).

Patients

S A is a 32 year old Indian lady with the Multiple Endocrine Adenoma type 1 syndrome. She has had an insulinoma of her pancreas removed and has also recently been diagnosed as having a pituitary microadenoma that has been responsible for hyperprolactinaemia. She was first noted to be hypercalcaemic in 1975, when her insulinoma was diagnosed, but parathyroidectomy was not performed until 1978. At operation 4 hyperplastic glands were removed and one third of one of the glands was minced and implanted into her left forearm according to the technique described by Wells *et al. (6)*. Her postoperative calcium dropped to 1.6 mmol/l and she was started on 1,25-dihydroxycholecalciferol (1,25-DHCC) (calcitriol, Rocaltrol) with slow release calcium (Calcium-Sandoz) supplements. In 1982 an attempt was made to wean her off all supplements but her calcium fell to 1.6 mmol/l and they had to be restarted. Her parathyroid hormone gradient was measured at this time and found to be 75 pg/ml in the left (transplanted) arm and 105 pg/ml in the right arm. These results suggest that there is no graft function.

D G, a 36 year old man, presented in August 1977 with ureteric colic and was found to be hypercalcaemic. In May 1978 four hyperplastic parathyroid glands were removed from his neck. A minced portion of one gland was implanted into his left deltoid muscle. His postoperative calcium fell to 2.08 mmol/l and he was started on 1,25-DHCC and calcium supplements. By October 1982 his serum calcium had risen to 2.14 mmol/l and all supplements had been stopped. His last recorded calcium in March 1984 was 2.25 mmol/l, off all supplements and asymptomatic.

The first symptom that A A, a 64 year old lady, had of hypercalcaemia was an attack of ureteric colic in 1951. In 1965 she suffered from a peptic ulcer but it was not until 1976 that she was found to be hypercalcaemic. Her serum calcium has risen to 2.91 mmol/l by 1981 and 3 hyperplastic glands were found at neck exploration and removed. Following her first operation she remained hypercalcaemic (3.00 mmol/l). She was referred to The Middlesex Hospital where her remaining gland was localised and subsequently removed in February 1982. At re-exploration about one-third of this hyperplastic gland was minced and implanted into her right forearm, both into pockets within brachioradialis and by injection into the muscle. We finely chop the parathyroid tissue in chilled Waymouth's tissue culture medium and then inject the suspension through a 19 gauge needle superficially into a marked 5 cm × 5 cm area of brachioradialis muscle. Postoperatively her calcium fell to 1.91 mmol/l, but by December 1982, 10 months after her second operation, her calcium had risen to 2.90 mmol/l. The PTH level in the right (implanted) antecubital fossa was greater than 2000 pg/ml but only 195 pg/ml in the left antecubital fossa. On 14th January 1983 parathyroid tissue was excised under local anaesthetic from the right forearm. However, her calcium remained raised at 2.71 mmol/l and the PTH gradient remained the same as preoperatively. Further excision of muscle and parathyroid tissue down to the depth of the radius and behind the median nerve was performed on 21st January. Histological examination showed hyperplastic

Correspondence to Mr E Milroy, The Middlesex Hospital, Mortimer Street, London W1N 8AA.
* Present appointment: Research Registrar, University Department of Surgery, Bristol Royal Infirmary.

parathyroid tissue within muscle. After this second excision of tissue her calcium dropped to 1.96 mmol/l and 1,25-DHCC supplements had to be started. When last seen, in May 1984, she was off supplements and her calcium had crept back up to 2.79 mmol/l. She undoubtedly represents an overactive arm implant.

A 41 year old farm labourer, H B, presented in 1979 with acute pancreatitis, he was subsequently found to be hypercalcaemic with values up to 3.37 mmol/l. Three parathyroid glands were removed in 1980 which were initially thought to be normal but at later review a diagnosis was made of lipoadenomatous hyperplasia *(6)* in all three glands. Postoperatively he remained hypercalcaemic with calcium estimations up to 2.80 mmol/l. He was referred to The Middlesex Hospital and in February 1982 re-exploration of his neck was performed. The remaining gland was removed and one-third implanted into the left forearm by a combination of inserting minced fragments into pockets and injection into the muscle. Since his second operation his calcium has ranged up to 2.62 mmol/l as an outpatient but the maximum value on inpatient investigation is only 2.33 mmol/l. We wondered if using his arm muscles during his work has stimulated PTH production. During subsequent admission his arms were exercised. The PTH values in the arm with the transplant went up to 1600 ng/ml from a basal level of 500 ng/ml but the maximum value in the other, non-transplanted, arm did not change from the basal level of less than 40 ng/ml. His serum calcium did not rise over the period of the test. We think that his transplant should be regarded as having normal function.

M P presented aged 20 in 1975 with a child who had neonatal hypocalcaemic tetany, her calcium estimations ranging up to 2.95 mmol/l at that time. She was referred to The Middlesex Hospital in 1979 when her calcium was 3.30 mmol/l. Her neck was explored in August 1979, 4 histologically normal glands were found and 3 were removed. Following this operation she remained hypercalcaemic (3.07 mmol/l). One week later her neck was re-explored and a block dissection performed removing three-quarters of the thyroid gland, the fourth parathyroid gland and removing the thymus down to the innominate vein. The whole of the fourth parathyroid gland was finely chopped and injected into the right forearm. She remained hypercalcaemic with a calcium of 3.82 mmol/l. She was reinvestigated in 1980 when further localisation studies were performed. Parathyroid venous sampling showed a 'hot-spot' in the innominate vein indicating a mediastinal tumour and computerised tomography indicated a retrosternal soft tissue mass. Her mediastinum was explored in July 1980 and a parathyroid adenoma removed. Postoperatively her calcium fell to 1.90 mmol/l and she has had to be maintained on 1,25-DHCC with calcium supplements with no recovery of parathyroid function. This lady also illustrates the need to exercise extreme caution when removing normal parathyroid tissue.

In 1964 an enlarged parathyroid gland was removed from M M's neck following a diagnosis of primary hyperparathyroidism. Between 1965 and 1967 she had multiple episodes of ureteric colic, a horseshoe kidney was found and a diagnosis of renal osteodystrophy was made. Intermittent hypercalcaemia was again noted in 1968. In 1980, aged 35, she was referred to The Middlesex Hospital where the diagnosis of primary hyperparathyroidism was confirmed. In October 1980 her neck was re-explored and 3 hyperplastic glands were removed, a pathological diagnosis of nodular hyperplasia was made. At operation half of the smallest gland was finely chopped and injected into the right brachioradialis muscle. After her second operation her calcium dropped to 2.02 mmol/l and calcium supplements had to be started. Her supplements were discontinued in April 1981 and in October of the same year she was again found to be hypercalcaemic at 2.6 mmol/l. Three paired PTH estimations were taken from both antecubital fossae in October 1983 with the results in pg/ml as follows, the right arm containing the transplant:

Right	*Left*
1100	1000
1000	400
640	425

The results of the above tests were interpreted as being due to overactive transplanted parathyroid tissue. In May 1983 histologically proven parathyroid tissue was removed from right forearm but her postoperative calcium remained raised at 2.79 mmol/l. Two further operations were performed in quick succession but no further parathyroid tissue was found on histology and her calcium was still elevated at 2.72 mmol/l. Two further paired samples of blood for PTH assay have been taken since her last series of operations, neither having shown a significant difference between the two sides. The most likely explanation of this lady's continuing hypercalcaemia is that she has a missed fifth gland, probably within the mediastinum. Residual hyperactive transplanted tissue within her forearm is a much less likely explanation of her hypercalcaemia.

Discussion

Autotransplantation of parathyroid glands is now a well recognised procedure in parathyroid surgery and enthusiastically advocated by some authors. Our, admittedly small, series shows that it is not an operation without problems. Only two of our six patients are normocalcaemic, one has recurrent graft-dependent hypercalcaemia, one a presumed fifth supernumerary gland and two are permanently hypocalcaemic.

Saxe has recently reviewed the world literature on the subject *(8)* and records a total of 369 fresh parathyroid autografts with 83% functioning. However, the majority of these were performed after total thyroidectomy or for secondary hyperparathyroidism. Wells *(9)* has published the largest series of patients who have had total parathyroidectomy and an immediate forearm autotransplant for primary hyperparathyroidism due to 4 gland hyperplasia. He found that only 18 of the 30 patients were normocalcaemic. Ten of his patients developed graft-dependent hypercalcaemia which was cured by partial excision under local anaesthetic, one patient suffered from persistent hypercalcaemia probably due to an undetected supernumerary parathyroid gland and one other patient became permanently hypocalcaemic.

Cryopreservation of excised parathyroid tissue after parathyroidectomy for multigland disease with delayed transplantation into the forearm has been advocated *(8)*. The advantage of this technique is that it allows any remaining parathyroid tissue to declare itself before an arm implant is made. Most methods of cryopreservation of parathyroid tissue employ a programmed freezing unit *(10)*, but the relative rarity of these units limits the application of the technique. We have recently used a simplified technique, placing the parathyroid tissue in the vapour phase of a liquid nitrogen freezer for 10 minutes before transferring it to the liquid nitrogen freezer. This method yields tissue on thawing that, when tested *in vitro*, produces PTH. This technique should make cryopreservation of parathyroid tissue more widely available.

Saxe and Brennan have followed a policy of total parathyroidectomy and cryopreservation followed by delayed transplantation in re-operative parathyroid surgery *(11)*. Their results indicate how difficult it is to remove totally all parathyroid tissue as 10 of their 26 patients were normocalcaemic without either transplantation or calcium and vitamin D supplements. They performed autografts in 4 of their patients and found that 2 were rendered normocalcaemic. The other 2 were permanently hypocalcaemic. Saxe *et al.* have also reported their total experience of transplanting cryopreserved parathyroid tissue and have an overall success rate of 7 grafts out of 12 attempted *(12)*. One interesting observation is that neither Saxe and Brennan nor

Wells *(9)* have reported graft-dependent hypercalcaemia following autotransplantation of cryopreserved tissue.

The forearm is the site favoured by most authors for transplanting parathyroid tissue. Blood may be taken from both antecubital fossae and a gradient established between the two sides. This enables a relatively easy assessment of graft function to be made.

We have used a combination of the original Wells technique *(7)* placing small pieces of the parathyroid tissue into discrete muscle pockets and our own variant of injecting finely minced tissue into the belly of brachioradialis. The 3 patients who have had tissue injected have all had graft function which may be a reflection of the small size of the fragments and more intimate contact with the muscle bed. However, it is easier to locate and remove tissue when placed within discrete muscle pockets.

In view of the difficulties that we have experienced we feel that autotransplantation of fresh hyperplastic parathyroid tissue is not a procedure to be undertaken without caution. Long-term maintenance of patients on calcium and vitamin D supplements is relatively easy in patients without functioning parathyroid tissue. Cryopreservation of excised tissue and later transplantation allows assessment of any undetected remaining parathyroid activity to be made. It may now be the precedure of choice after total parathyroidectomy for primary hyperparathyroidism.

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Notes on books

Postgraduate Nephrology edited by Frank Marsh. 646 pages, illustrated. William Heinemann Medical, London. £40.

All aspects of modern renal medicine are covered in this comprehensive, scientifically based and clinically orientated treatise. The contributors are leading British authorities in nephrology and the volume will surely become a standard reference work.

Prevention of Perioperative Infections edited by H Schönfeld. 208 pages, illustrated. S Karger, Basel. $89.25.

All surgeons should find this review volume of interest. Each chapter covers an individual operative site, is fully referenced and succinctly discusses the prevention of perioperative infections by chemoprophylaxis.

Pocket Manual of Surgical Nutrition by Frank B Cerra. 210 pages, illustrated, paperback. C V Mosby, St Louis. £21.

As the title suggests this book is intended for the houseman's pocket and should be used at the bedside. It is a practical manual and contains very few references.

Diagnostic Ultrastructural Pathology by Feroze N Ghadially. Illustrated, paperback. Butterworths, London. £9.95.

This book comprises 50 full page high quality electron photomicrographs. Each is fully discussed in the form of questions and answers. A book that is primarily of interest to surgical pathologists.

Problems in Otolaryngology by Padman Radnesar. 112 pages, illustrated. MTP Press, Lancaster. £7.95.

This book aims to give a short and practical account of diseases of the ear, nose and throat. It is didactic and written in short note style with many lists. Although primarily intended for general practitioners, many others will find it of value—particularly Casualty Surgeons.

Cardiac Problems of the Adolescent and Young Adult edited by Desmond G Julian and Nanette K Wenger. 282 pages, illustrated. Butterworths, London. £45.

An extensively referenced volume which reviews the current state of knowledge of cardiac disease in the young. Although principally of interest to physicians this book will also appeal to cardiac surgeons.

Spinal Cord Injury by Vickie Nixon. 233 pages, illustrated. William Heinemann Medical, London. £27.50.

Written by a physiotherapist this book covers in detail the rehabilitation of a patient who has sustained a spinal cord injury. It is in loose-leaf format and copiously illustrated.

Arthroscopy of the Knee: a Diagnostic Colour Atlas by David J Dandy. Illustrated. Butterworth, Kent. £39.50.

This magnificent folio atlas comprises large numbers of high quality colour photographs taken through an arthroscope with adjacent line diagrams explaining the appearances. There is a detailed text. The volume is beautifully produced and published on high quality paper and will no doubt be required reading of all orthopaedic surgeons who practise this technique. Those who don't will also find it of interest and may perhaps be tempted to learn.