PARATHYROID

SCINTIGRAPHY

1989

Dr. PA JENNINGS

IN FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF MASTER OF MEDICINE

IN THE DEPARTMENT OF NUCLEAR MEDICINE

AT THE

UNIVERSITY OF CAPE TOWN

ACKNOWLEDGEMENTS

My sincerest thanks to:

Dr J.A.Smith, Head of the Department of Nuclear Medicine, for his support and confidence.

Professor R.E.Kottler, Head of the Department of Radiology, for his persistence, persuasion and above all his understanding.

Dr B.H.Ascott-Evans, Consultant in the Department of Endocrinology, for his valuable guidance and criticism.

Mr J.Boniaszczuk, Senior Radiographer in the Department of Nuclear Medicine, for his invaluable help both with content and technical aspects.

The staff of the Department of Nuclear Medicine for their genuine concern and support.

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Chapter 1

Introduction

INTRODUCTION

The classical presentation of hyperparathyriodism with bones, stones, abdominal groans and psychic moans is today almost entirely preceded by routine biochemical detection of hypercalcaemia for both hospitalized as well as ambulatory patients and the subsequent serum assay for parathyroid hormone (PTH) levels.[1,2]

Routine serum analysis:The impact of:

Incidence: According to Heath et al[3] the average annual incidence of primary hyperparathyroidism in a representative community, has increased from 7,8 cases per 100 000 to 51 cases per 100 000 of the population.

Age: The increase is predominantly in persons over the age of forty and is attributable to routine serum calcium analysis.

Clinical characteristics: In addition they show that the distribution of clinical characteristics among cases of primary hyperparathyroidism have also changed. The patients are older and the criteria of clinical diagnosis is shifting. Urolithiasis, renal failure and hyperparathyroid bone disease, are now uncommon, and the more subtle signs and symptoms of hypertension, osteopenia and psychological problems are to be sought.

The asymptomatic patient: In addition more than 50% of the patients now presenting with raised serum

calcium and PTH have no symptoms or obvious adverse effects of the disease.[3]

The significance of this study is that primary hyperparathyroidism is shown to be a relatively common disease of the middle-aged and elderly, and a potential source of great health care expense particularly as the accepted means of treatment is surgical.

The question arises as to the cause and treatment of hypercalcaemia in an asymptomatic patient. Despite the sophisticated biochemical criteria for the prediction of parathyroid glandular involvement the ultimate confirmation of the diagnosis and cure of the condition is still that of surgical exploration for parathyroid adenoma or hyperplasia. Surgical management is required in a symptomatic patient but is not necessarily indicated for the asymptomatic patient. With this issue controversy still reigns.

Management: Surgical or medical?

At present the management of primary hyperparathyroidism is in a similar situation as the treatment of mild hypertension was a few years ago. That is, how to treat patients with mild to moderate primary hyperparathyroidism who have relatively minor attributable symptoms. There are controversial opinions in the literature with regard to this dilemma.[4-12]

Conservative treatment: Scholz et al[4] attempted to determine the risks of judicious observation of 147

patients with mild asymptomatic and uncomplicated hyperparathyroidism. Suprisingly their results indicate that progression of the condition is uncommon rather than inevitable, with only 8-22% ultimatly requiring surgical treatment. However they are unable to determine any predictive criteria to indicate when surgery is needed. What they also show is that medical follow up is fraught with problems of patient cooperation, time wasted with keeping track of the patients and expense, estimating that 5,5 years of annual medical treatment costs as much as initial diagnosis and surgical treatment. Thus their overall recomendation is surgical treatment although they do conclude that those patients who refuse surgery or have other contraindications can be followed up medically with minimal risk.[4]

Renal impairment: In a similar vein Coe et al[5] consider what is more dangerous to the asymptomatic patient, parathyroidectomy or the untreated disease? They show concern with regards to renal damage from hypercalcaemia. They point out that this frequently fails to heal and can progress to renal failure. Their worry is that this may occur in some patients who are left untreated. However a 10 year study on 13 patients by Paterson et al[6] shows little obvious harm from not having surgery, and more specifically serum calcium does not rise over the ten year period and progressive renal impairement is not evident.

Survival: Palmer et al[7] are in agreement with there being no change in renal function but they also assess the problem in terms of survival. Their study points to a critical age of seventy. Those patients under the age of seventy with increased serum calcium have a lower survival than the general population, while those seventy and above do not. Unfortunatly the lower survival is satistically related to the degree of hypercalcaemia. In essence while recognising that hypercalcaemia is a risk factor for premature death, they maintain that it is not an argument for operating on symptomless patients under the age of seventy because parathyroid surgery has not been shown to reduce this risk.

Morbidity: Lafferty et al[8] look at the problem from the other side of the spectrum and review the longterm surgical morbidity. They assess aspects of negative exploration, persistent hypercalcaemia, recurrent hypercalcaemia, permanent hypoparathyroidism and recurrent laryngeal nerve damage. Of interest is that they show that surgical morbidity occuring in 19% of surgically corrected patients is almost as poor as the 8-22% progression of disease in medically treated patients. Another significant finding is that there is no improvement in hypertension, peptic ulcer disease or renal function following successful parathyroid surgery. There is also no clearcut evidence that mild hyperparathyroidism causes spinal osteoporosis or that

the surgical correction of mild hyperparathyroidism will improve it.[9] Surgery does however improve the extent of osteitis fibrosa cystica and the recurrent passage of renal calculi. The authors do mention some improvement in neuropsychiatric complaints.[8]

Neuropsychiatric spectrum: On the theme of psychiatric symptoms Joborn et al[10] are advocates for surgical correction maintaining that if not specifically questioned for, neuropsychiatric problems will not be found and many of these patients will be considered as "asymptomatic". Using the Comprehensive Psychopathological Rating Scale their work demonstrates some very important concepts. The majority of their fifty nine patients with "asymptomatic" hyperparathyroidism had considerable psychiatric symptoms of fatiguability, lassitude, failing memory, concentration difficulties, sadness and inner tension. In addition the majority of these symptoms are reversed by parathyroid surgery despite the fact that the severity of symptoms is not related to the degree of hypercalcaemia. A more objective finding of their work is that hyperparathyroidism is associated with changes in the CNS turnover of monoamines, which may have some importance to the symptomatology.

In summary the treatment of "asymptomatic" primary hyperparathyroidism is still in a state of uncertainty and the criteria for that decision are also changing from the importance of renal function, hypertension and

osteopenia to more emphasis now being placed on the neuropsychiatric symptoms.

Surgical treatment: In experienced hands neck exploration, with the removal of the source of excess PTH production, leads to a 90-95% cure.[11] This is even without any preoperative localization procedure. The operation is, at times, painstakingly difficult and long and may carry significant complications. Even with the best technique there is a 5-10% failure rate, usually related to aberrant or ectopically located glands or recurrent hyperplasia. Reexploration is technically more difficult because of scarring and fibrosis and the resultant loss of anatomical planes. Morbidity increases with a higher risk of nerve injury and other complications. Moreover, the success rate of finding an adenoma at the second operation is only 65-70%.[12]

Dissension: There is at present dissension in the ranks not only whether to utilise a localization imaging technique prior to virginal neck exploration, but also the issue of surgical treatment versus medical management in what today is the majority of patient's who now present with very little in the way of symptoms. There is thus a need for an imaging technique to not only localize the parathyroid adenoma anatomically but to localize it on the basis of excess PTH production. There are five principal ways that such

a technique could assist both the physician and the surgeon:

1.**Diagnosis:** The diagnosis of primary hyperparathyroidism can usually be confirmed with certainty by the combination of elevated serum calcium and immunoreactive PTH levels. However an imaging technique could play a minor diagnostic role in those exceptional problematical cases such as familial hypocalciuric hypercalcaemia. Positive identification of a site of excess PTH production would favour against such a diagnosis while a negative study would be more in favour.

2.**Management:** Such a technique could play a role in the dilemma with "asymptomatic" patients. To cut or not to cut? A technique with a high predictive sensitivity could sway the decision.

3.**Localization** both in terms of lateralization and also to demonstrate ectopic parathyroid tissue. Such localization would enable the lesion to be immediately sought and exposed, limiting surgery to the site of the pathology. Operating time would be shortened and with less extensive dissection the risk of injury to important structures would be diminished. The nett result being surgical intervention with greater confidence, more speed and less complications.

4.**Recurrence:** The 5-10% post surgical failure rate and the complications of reexploration. Its importance

in patients first presenting with primary hyperparathyroidism should not be underestimated as there is evidence to suggest that preoperative localization reduces the incidence of and necessity for reexploration.

5.**Reexploration:** Localization is of paramount importance in patients who have previously undergone surgery due to the loss of anatomical planes.

Techniques: Current localizing techniques in use with some degree of success are ultra sound (US), computerized tomography (CT) and magnetic resonance (MR). These approaches rely on anatomical localization and the assumed direct relationship between glandular size and hyperfunction, which is not always the case.

Scintigraphy: Radionuclide scintigraphy studies emphasise physiological function as well as anatomic position. This appears to be a more promising approach to the problem of accurate localization of excess PTH production .

Aim: The purpose of this study is not only to describe scintigraphy in parathyroid imaging and the results obtained but also to discuss the merits and limitations of the technique so that its role in today's climate of cost containment, may better be defined.

Chapter 2

The Parathyroids

Historical

Historically the parathyroid glands have a fascinating record, being first identified in the dissection of an Indian rhinoceros! In 1898, tetany was first noted in dogs and cats following removal of the parathyroid glands. In 1903, a relationship was noted between the parathyroid glands and disease of bone. In 1914, it was discovered that parathyroid hyperplasia developed in response to a low calcium diet. An important advance was made in 1921 when a convenient measure of serum calcium concentration became available. In 1924 and 1925, Collip[16] demonstrated that extract of parathyroid tissue relieved tetany in dogs. In 1926, Mandl[17] performed the first parathyroid surgery in humans, removing an adenoma. Rasmussen and Craig[18], in 1959, isolated purified parathyroid hormone and found it to be an 84 chain amino acid polypeptide. In the 1960s, radioimmunoassays of PTH were first developed.[19]

Embryologic and anatomic considerations:

The parathyroid glands originate from the endodermal epithelium lining the third and fourth pharyngeal pouches. The inferior glands from the third pouch and the superior glands from the fourth.[13]

The inferior glands: During foetal development the inferior parathyroids and the thymus are intimately related. Both originate from the third pharyngeal pouch. Communication between the pouch and the pharynx is soon lost, but the connection between the thymic and parathyroid rudiments persists with the parathyroid epithelium later passing caudally with the developing thymus.[13]

The superior glands: The superior parathyroid glands develop, in a similar manner, from the dorsal recess of the fourth pharyngeal pouch. They come into relation with, and are anchored by, the lateral lobes of the thyroid gland and thus remain cranial to the parathyroid glands derived from the third pouch.[13]

Variations in number, size and position appears to be a feature of the parathyroid glands.[14]

Number: The common number of glands is four, two superior and two inferior. Numbers can vary from as few as a total of two to as many as six. There may even be many minute islands of parathyroid tissue scattered in

the connective tissue and fat in the region of the usual position of the glands.[14]

Size: Wang's[14] cadaveric study of one hundred and sixty postmortem subjects demonstrates the variation in size of the normal glands with average dimentions of 6mm longitudinally, 3-4mm transversly and 1-2mm anteroposteriorly. The range for the longitudinal measurement being from a minimum of 2mm to a maximum of 12mm. Understandably the weight is also variable from 10mg (0,018ml) to 70mg (0,048ml) with an average weight of 40mg (0,033ml) each.

Position: The superior parathyroid glands are more constant in position than the inferior glands with 77% at the cricothyroid junction posteriorly and 22% at a higher location behind the upper poles of the thyroid lobes. Retropharyngeal and retroesophageal positions account for only one percent. Rarely, a parathyroid gland can reside entirely within the thyroid. In such circumstances it is most frequently an upper gland.[14]

The inferior parathyroid glands show more variation of position than the upper glands and are more likely to be in an aberrant position. Normally they migrate only as far as the lower poles of the thyroid, but they may descend with the thymus into the thorax, or they may not descend at all and remain above their normal level, near the bifurcation of the common carotid artery. They are most commonly located

anteriorly, on the lateral posterior surface of the lower pole of the thyroid (42%), in the thymic tongue (39%), or lateral to the lower pole of the thyroid (15%), when the inferior parathyroid drops into the mediastinum (2%), it is almost always situated anteriorly. Ectopic positions account for 2% and can be located anywhere from below the mandible to the level of the pericardium, within the thymus, in the vagus nerve or even within the submucosa of the oesophagus.[14]

Arterial supply to the parathyroids is via the inferior thyroid arteries or from the anastamoses between the superior and inferior thyroid arteries. A mediastinal gland can be supplied by either the inferior thyroidal artery or the internal mammary artery. [15]

Venous drainage is ultimately into the internal jugular and innominate veins via the superior, middle and inferior thyroid veins. The inferior thyroid veins often unite to form a common trunk which drains into the left innominate vein. The thymic vein, draining mediastinal structures, also drains into the left innominate vein.[15]

Lymphatics: In a similar trend to the arterial and venous systems the lymph vessels are associated with those of the thyroid and thymus glands.[13]

Nerve supply to the parathyroids is sympathetic, either directly, from the superior or middle cervical

ganglia, or indirectly through a plexus in the fascia on the posterior surface of the lobes of the thyroid gland.[13]

Physiology:

Calcium:

Extracellular calcium exists in three states:[23]

Protein-bound constituting 40% of the total extracellular calcium. Ninety percent of this fraction is bound to albumin and 10% to globulin. Total serum calcium concentration is thus a reflection of the serum albumin. Awareness of this is demonstrated in venous stasis and hypoalbuminaemic states. In addition various factors may affect the shape of the albumin molecule exposing more or fewer binding sites. Alkalosis exposes more sites with a resultant drop in ionised calcium. Hyponatraemia increases binding while hypernatraemia can decrease it.

Changes in total serum calcium as a result of changes in globulin concentration is of minor significance but have been described in myeloma.

Ionised: Fifty percent of the extracellular calcium is in the ionised diffusible form. It is this fraction that is both homeostatically regulated and physiologically active and thus a true indicator of the patients calcaemic state.

Complexed making up the remaining 10% of the extracellular fraction. This is also a diffusible form of calcium but non-ionised and complexed to bicarbonate, citrate and other organic ions.

The maintance of a narrow range of serum calcium concentration is vital to a variety of biological functions. This is well illustrated by only a cursory look at the role of calcium:[20]

Structural: Calcium is essential for its structural role in the composition of bones and teeth.

Cofactor: It is a cofactor in enzymatic reactions allowing the functioning of adenylate cyclase, guanilate cyclase, thrombokinase, and many others.

Muscle contraction: It regulates muscle contraction with particular reference to striated and cardiac muscle; the excitability of the latter being particularly sensitive to concentrations of calcium.

Membrane permeability depends upon the correct serum calcium concentration, affecting both nerve excitability and the renal tubular concentrating mechanism.

Foetal development: Calcium also plays a vital role in foetal muscular, skeletal and CNS development.

An understanding of the multifacetted role of calcium adds more perspective to the actions of PTH.

Parathyroid hormone (PTH):

Chemistry: PTH is an 84 amino acid single-chain polypeptide containing no cysteine. Only the amino terminal region of the molecule is required for biological activity.[19] This emphasizes the importance of having antibodies against the amino-terminal of the molecule to demonstrate the biological significance of radioimmunoassays.

Function: There is an intimate interaction between PTH, vitamin D and calcitonin in the regulation of serum calcium. The primary role of PTH, in conjunction with Vitamin D, is to increase the serum calcium level when it drops below the "set point". This is achieved in three main interactions:[21]

Bone: PTH acts on bone by direct membrane receptor binding to osteoclasts. This stimulates, through the action of cyclic AMP, the resorption of bone with the consequent release of calcium into the extracellular fluid.

Vitamin D (cholecalciferol): Vitamin D is essential for the intestinal absorption of calcium. Its source is dietary or from the skin through the action of sunlight. Vitamin D must undergo two hydroxylation reactions to develop into its most active form. The first hydroxylation takes place in the liver with the formation of 25,Hydroxy D. The second reaction is in the kidney forming $1,25(OH)_2D$. This latter hydroxylation is under PTH regulation. Therefore PTH

has an indirect action upon calcium intestinal absorption.[22]

Renal: PTH also has a direct positive effect upon renal tubular cell reabsorption of calcium as well as negative effects on phosphate and bicarbonate.

The net result of these actions is that increased levels of PTH generally cause increases in the serum calcium concentration, while decreased levels will be associated with a decrease in serum calcium. A feedback mechanism on the parathyroid glands establishes a "set point" for serum calcium concentration. Values above that level turn off the secretion of PTH by the parathyroid glands, and below that level stimulate secretion of PTH to maintain serum calcium within a narrow concentration range.

Pathology:

The regulatory role of PTH on serum calcium concentration explains why any pathology of the parathyroid glands is invariably reflected by changes in the serum calcium. Care must be taken to ensure that the serum calcium measurement is a true reflection of the patients physiologically active condition by measurement of the ionised fraction of serum calcium.

Hypercalcaemia:

The two most common conditions to consider when presented with a patient with hypercalcaemia are:

Malignancy: The raised serum calcium is usually due to metastatic spread to bone. The primary tumour being most commonly breast, lung or kidney. Bony metastatic deposits associated with hypercalcaemia carries a poor prognosis.

Several tumours have been described that secrete PTH-like substances. These substances although initiating hypercalcaemia are often not identified by the PTH assay due to immunological differences with parathyroid PTH and are not picked up on newer sensitive IRMA double antibody PTH assays.

Hyperparathyroidism is a condition characterized by excess secretion of PTH. It is usually , but not inevitably, associated with elevations of serum calcium concentration.

Between 80% and 90% of patients with primary hyperparathyroidism have a solitary **adenoma** of the parathyroid glands[24] in which there is proliferation of chief cells. These adenomas range from 100mg to more than 20g. In some cases (1%), more than one adenoma is present and responsible for the hyperparathyroidism. In 5% to 15% of cases, hyperparathyroidism is caused by **diffuse hyperplasia** of chief cells in all four glands. Histological distinction between adenoma and hyperplasia is often not clear. **Carcinoma** of the parathyroid gland is rare accounting for less than four percent of parathyroid tumours. These are always functionally active and are often palpable.

Hyperparathyroidism is divided into three classes:

Primary hyperparathyroidism implies autonomous, unregulated secretion of PTH by adenomatous or hyperplastic glands, usually associated with hypercalcaemia.

Secondary hyperparathyroidism is not associated with hypercalcaemia as the PTH production is a physiological response to low serum calcium. Most commonly it is found in patients with renal failure or intestinal malabsorption states. In both conditions there is reduced calcium absorption from the gut. In the former the failing kidney is unable to manufacture 1,25-dihydroxy vitamin D.

Tertiary hyperparathyroidism occurs in the setting of chronic renal failure as well. However, in the tertiary form , the parathyroid glands become autonomous with a consequent rise in serum calcium and is diagnosable only by prior awareness of the state of secondary hyperparathyroidism.

Other less common causes of hypercalcaemia are listed in Table I.[239]

Clinical features of primary hyperparathyroidism

The concept of image localization of pathology is of prime significance in primary hyperparathyroidism. The reason being that the autonomous production of PTH in 90% of cases is as a result of a single parathyroid adenoma. In addition, 21% of the patients with hypercalcaemia in the local South African environment

TABLE 1. CAUSES OF HYPERCALCAEMIA

Malignancy
- Secondary bone deposits
- Tumour secretion of osteoclast-stimulating factor, prostoglandins and PTH-like peptides

Hyperparathyroidism
- Primary adenoma
- Primary diffuse hyperplasia
- Multiple endocrine adenopathy syndrome
- Tertiary

Hyperproteinaemia
- Venous stasis
- Dehydration
- Myeloma

Other endocrine causes
- Hyperthyroidism
- Acromegaly
- Phaeochromocytoma
- Addison's disease

Other causes due to bone resorption
- Thiazides
- Immobilisation
- Vitamin A excess

Decreased urine loss
- Hypocalciuric hypercalcaemia
- Thiazides

Increased gut absorption
- Granulomatous disease, eg. sarcoidosis, berylliosis, tuberculosis
- Vitamin D overdose
- Milk alkali syndrome

have primary hyperparathyroidism as the causative factor.[25]

Excess PTH results in a raised serum calcium concentration with mobilisation of calcium predominantly from bone. The manifestations of primary hyperparathyroidism are thus a direct result of both the high levels of PTH and the resultant hypercalcaemia. The spectrum of clinical presentation is wide, varying from biochemical evidence of raised serum calcium and PTH only, with an absence of symptoms, to gross forms of the conditions listed in table 2. Interestingly, although there is an association between the conditions listed and primary hyperparathyroidism there is not always a direct relationship between either the PTH or serum calcium concentrations and the clinical severity of the condition.

Management:

Surgical or medical?: When the diagnosis is certain, the serum calcium above 2.90 mmol/litre, and the patient fit for operation , surgery represents the best therapeutic approach. Many asymptomatic patients with lesser degrees of hypercalcaemia are managed conservatively over several years, and do not develop any apparent complication other than debatable slightly accelerated osteoporosis.[3-7] Such management may include advice on fluid intake and perhaps oral

TABLE 2. MANIFESTATIONS OF PRIMARY HYPERPARATHYROIDISM

Renal
- Stones(25% to 35% of symptomatic primary hyperparathyroidism)
- Nephrocalcinosis

Skeletal
- Bone pain,pathological fractures,"brown" tumours
- Nonspecific joint pain
- Osteitis fibrosa cystica

Gastrointestinal
- Increased incidence of peptic ulcer disease and pancreatitis

Neurological
- Emotional lability
- Decreased mentation
- Easy fatiguability
- Muscle weakness

Other
- Ectopic calcification
- Electrocardiographic changes
- Pruritis
- Anaemia
- Hypertension

phosphate; beta-blockers and H_2-antagonists have not been established as being of value.

It appears, however, that up to 15% of concervatively managed patients do experience problems with increasing hypercalcaemia, urolithiasis, decreasing renal function, loss of bone mass, hypertension or emotional disturbance, and careful follow-up is necessary.[4-10]

Chapter 3

Scintigraphy

PARATHYROID SCINTIGRAPHY

Historical

Imaging by functional analysis, as compared to exclusively anatomic or structural tissue differences, has particular relevance in endocrine pathology. This is no less so with parathyroid gland localization. In this situation a relatively tiny anatomical structure has widespread systemic effects solely on the basis of hyperfunction.

Vitamin B12 labelled with Co-57 (Co-57B12): The whole concept of parathyroid imaging on the basis of localizing the site of excess PTH production, probably originated with the work of Sisson and Beierwaltes in 1962.[26] They noted that Co57B12 when injected into dogs had an affinity for the parathyroid glands compared to other tissue. They proposed the possibility of using Co57B12 as an imaging pharmaceutical. However on attempting to do so, Beierwaltes with DiGuilo found that the specific activity of Co57B12 was too low to achieve a good target to background ratio. The idea of functional imaging of the parathyroid gland was however concieved.

Selenium-75 methionine: Potchen et al[27] continued with the concept of parathyroid imaging expanding on their discovery that tritiated methionine accumulated in calcium depleted rat parathyroids. Being an amino

acid, methionine is incorporated into protein within cells and possibly even into PTH directly. Thus all that was needed was to label the methionine with a radioactive marker. This was achieved by using selenium-75 (Se^{75}) which substitutes for sulphur in methionine with complete retention of biological function. This work resulted in the creation of ^{75}Se-Selenomethionine as a possible parathyroid imaging agent. However methionine incorporates into both thyroid and parathyroid tissue. To inhibit thyroid uptake exogenous L-thyroxine was administered to suppress pituitary secretion of TSH. With no TSH, thyroglobulin synthesis ceases and therefore uptake of the methionine by the thyroid is prevented. Parathyroid uptake of methionine is not under TSH control. Thus the use of both L-thyroxine and in addition subjecting the patient to a low calcium diet resulted in inhanced parathyroid accumulation of ^{75}Se-Selenomethionine.[28]

Unfortunatly by 1968 two independent groups reported on poor results with ^{75}Se selenomethionine.[29,30]

In 1975 revival of the pharmaceutical appeared imminent with the work of Arkles and Ell who both used a computer generated subtraction technique to overcome the problem of ^{75}Se methionine accumulation in the thyroid.[31,32]

Waldorf et al[33] finally brought an end to the ^{75}Se era by concluding that the technique should be abandoned after their work showed a sensitivity of only 40% and a specificity of 51%. Due to its poor imaging characteristics, of a half life of 120 days and multiple energy peaks ranging from 136-560 keV, ^{75}Se did not reach the expectations required.

Cesium-131: Serendipidy played it's role in a chance discovery by Ferlin et al. They discovered that the isotope ^{131}Cs concentrated in a parathyroid adenoma.[34] They had reasonable success with other patients but because of the long half-life and high gamma emissions, they substituted thallium-201(^{201}Tl) for ^{131}Cs. This was the initiation of the thallium era, which is still in continuance.

Thallium Parathyroid Scintigraphy

At about the same time as the work of Ferlin et al, case reports were emerging from Japan on the use of ^{201}Tl chloride as an agent to visualise parathyroid glands.[35]

Physical characteristics: Tl-201 has a physical half-life of 73 hours and decays by electron capture. While its photon energies are not ideal, being 90% abundant in the 69 to 83 keV range, this is superior to the characteristics of both ^{75}Se and ^{131}Cs.

Biological distribution: Tl-201 appears to behave as an analog of potassium, the most abundant intracellular cation in the body. Thallium in the +1 valence state mimics potassium in that its uptake is inhibited (1) competitively by K^+ and (2) by poisoning the Na^+-K^+ adenosine triphosphatase (ATP'ase) dependent membrane pump.[36,37] Consequently, Tl^+ is concentrated by all the cells of the body when administered in tracer doses. In macroscopic doses, thallium is,of course, a heavy metal and as such is poisonous. No toxic effects of thallium are noted in the tracer quantities used for radionuclide studies.

Being an analog of K^+ the intensity of ^{201}Tl accumulation in body tissue is dependent upon the cellularity and vascularity of that tissue. After ^{201}Tl administration a scinti-image in the region of the neck will demonstrate both parathyroid and thyroid tissue. The sternocleidomastoid muscles in the neck also concentrate ^{201}Tl and provide background activity. Generally, this is of a lower intensity of activity than thyroid and parathyroids because the latter are much more vascular.

Subtraction study: In an attempt to differentiate parathyroid activity from thyroid activity the computer generated subtraction work of Arkles and Ell was revived. These workers independently had some encouraging results when ^{75}Se methionine was combined with ^{131}I or technetium subtraction studies. The poor

imaging characteristics of ^{75}Se were the downfall of such a manipulation. Now with the better characteristics of thallium such a subtraction technique holds more promise.

Thallium nonspecifically accumulates in both thyroid and parathyroid tissue and by itself cannot distinguish these two. Therefore, a second radiopharmaceutical is simultaneously or sequentially administered to demarcate the thyroid tissue. This is usually ^{99m}Tc pertechnetate, although some authors have used ^{123}I. The process is analagous to the subtraction of the "mask" image in digital subtraction angiography, wherein the technetium thyroid image is subtracted from the thallium image, resulting in an image depicting any areas of excess thallium. If there is no patient motion and the images are correctly registered, sites of thallium excess are usually presumed to be due to parathyroid adenomas or hyperplasia. The technique can be performed in various fashions, most commonly either with ^{99m}Tc first followed by thallium[38,39] or with thallium first followed by ^{99m}Tc.[40,41] Both methods are technically demanding and require attention to detail and careful processing.

Recent refinements: Recent refinements in acquisition, processing and image interpretations have evolved parathyroid scintigraphy into an effective screening test that should be the first modality used in patients with confirmed primary

hyperparathyroidism.[42] These refinements include the use of cobalt markers for accurate position and reregistration of images if motion has occured. Image re-registration software is becoming more available for the correction of patient motion. The use of a variable or graded normalized subtraction, as described by Blue et al,[42] and the use of ultrasound for equivalent or negative radionuclide scans are additionally helpful refinements. Single photon emission computed tomography(SPECT) has been of limited usefulness in the neck; however, SPECT can be useful to locate intrathoracic adenomas.[43]

Efficacy of the technique: The technique should identify greater than 90% of adenomas that are at least 500mg (0,5ml) in size and a majority of those 300 to 500mg in size, while most of those under 300mg are not seen. An adenoma as small as 60mg, which is in the normal range, has suprisingly been detected.[40] The technique is less sensitive for the detection of secondary parathyroid hyperplasia. An intrathyroidal parathyroid adenoma[44] and parathyroid adenomas in the neck and mediastinum have been successfully localized.[43] The technique is useful in the postoperative patient, in whom ultrasound and CT encounter difficulties. Parathyroid scintigraphy has been demonstrated to reduce the operative time and the number of nonparathyroid tissue biopsies at initial neck exploration.[45]

Pitfalls of the technique: Despite its value, the technique is not ideal, largely due to thallium's limited imaging characteristics, fast washout, and relatively poor counting statistics. The nonspecificity of the uptake of thallium has led to an ever increasing list of false positive studies, which range from a sarcoid lymph node[38] to primary thyroid carcinoma, metastatic carcinoma,[46] and Hodgkin's lymphoma.[47] The most frequent source of false positives encountered in routine imaging is that of the thyroid adenoma, which often accumulates thallium to a greater degree than technetium. This cause of false positivity could be reduced by taking care with the interpretation of studies on those patients with palpable thyroid abnormality or known nodular thyroid disease.

Despite its limitations, the benefits of localization that the scans provide should be of more aid to the surgeon in comparison to a blind exploration.

Chapter 4

Imaging

OTHER IMAGING MODALITIES

Other imaging modalities in current use today for the localization of parathyroid adenomas are really divided into noninvasive and invasive. The division between the two is not so clearly defined. The noninvasive techniques include ultrasound(US), computed tomography(CT), and magnetic resonance(MR). The invasive procedures encompass such techniques as angiography, selective catheterization and venous sampling for PTH and digital subtraction angiography(DSA).

Ultrasound:[51]

Advantages: This technique has the advantages of being totally noninvasive, constituting no radiation dose to the patient and the least expensive of all the investigations.

Technique: Today US is performed by making transverse and parasagittal scans through both lobes of the thyroid, with the patients neck hyperextended. With high-resolution real-time equipment this is simply a matter of making sweeps with the transducer. A 10mHz tranducer is focused to 1,5cm from the skin surface and a waterbath incorporated into the scanning head.

Most parathyroid adenomas can be detected by either static or real-time techniques, the latter is routine at Groote Schuur. Adenomas that lie inferior to

the thyroid may be visible only during swallowing. Demonstration of an adenoma that rises from behind the clavicle with swallowing is possible only with real-time equipment.

Features: A parathyroid adenoma is shown as an area of low echogenicity, hypoechoic when compared to the overlying thyroid gland, usually lying behind the thyroid in the angle between the trachea and oesophagus.

The cervical adenomas not located by ultrasonography tend to be less than 200mg, lying more medially behind the trachea or inferiorly behind the clavicular heads.

Efficacy: The reported sensitivities are 29% for adenomas less than 100mg; 69% for those 500-1000mg and 96% for those greater than 2000mg. In patients following unsuccessful surgical exploration ultrasonography can be valuable in demonstrating the missed adenoma in some 80% of cases.[48]

The solitary low echogenic follicular thyroid adenomas or rare thyroid cyst can well present a diagnostic problem if present in a case of hyperparathyroidism. This can generally be resolved by needle aspiration estimations of PTH levels.

Ultrasound is of limited use in the mediastinum as a result of the air and bone interface and consequent absence of an acoustic window.

Computed tomography:[52]

Computed tomography has become more successful in locating parathyroid adenomas using the new faster fourth generation scanners. Five millimetre cervical and one centimetre thick upper mediastinal sections are done back to back with contrast enhancement. The use of IV contrast to improve performance unfortunately increases morbidity.

CT is best for suspected mediastinal adenomas as there is some difficulity in the neck and shoulder regions due to swallowing and bone artifacts.

Despite the high resolution of the new scanners the sensitivity of CT is no better than that for US.[49] In addition it constitutes a high local radiation dose to the patient and is considerably more expensive.

US and CT both depend upon anatomic or structural tissue differences to detect pathologically enlarged glands. Neither depend on function for localization. Therefore, abnormalities visualized may not be the source of PTH excess. Each has advantages and disadvantages that determine their utility in individual situations. Sonography is limited in

examinations of the mediastinum but has good anatomical resolution in the neck and is best used for identifying pathology close to the thyroid. On the other hand CT is best for mediastinal adenomas.

Of interest is that neither CT nor US have been shown to reduce the incidence of reoperaion when used for preoperative screening and localization.[50]

Magnetic resonance:[53]

Of all the imaging techniques for parathyroid localization the most interesting today is MR. Developmentally it is still in its infancy and probably has the greatest potential for improvement in refinement.

Advantages: The advantages of MR imaging are its definition of anatomy with high spatial resolution, tomographic imaging in multiple planes with a wide contrast scale among soft tissues. MR is also completely noninvasive with no ionizing radiation and no contrast material.

Image quality has substantially improved with the introduction of surface coils. These allow for thin sections (5mm).

T1- and T2- weighting: Acquisition is of both T1- and T2- weighted images. The T1- weighted images provide good contrast between the enlarged gland and the fat in which it is usually embedded. The T2-

weighted image is also important because most adenomas show a marked increase of intensity on T2- weighted images. However, T2- weighted images cannot be used exclusively because some adenomas become isointense relative to fat, and therefore poorly visible on T2-weighted images.

Efficacy: The ability of MR to localise parathyroid adenomas is promising. The reported studies with MR encompass fewer patients than those for other imaging studies but the overall sensitivity is 64-79% and appears to be at least as good as that of other imaging modalities.

Pitfall: As with the other techniques a potential pitfall in the detection of parathyroid adenomas is the presence of concurrent thyroid disease, and distinction between the two at present is not possible.

Development: Despite its present limitations there is still immense potential for MR. It is a technique that is able to use more tissue-specific factors in the detection of disease and it is possible that future pulse sequences will be determined that will be more optimal for parathyroid imaging. Additionally, paramagnetic enhancing agents such as gadolinium-DTPA may be helpful. Thus localization is tending towards function for differentiation to enhance its inherent high spatial resolution.

At present the high cost of magnetic resonance and its relatively low specificity reduces its usefulness as a routine screening test. However with refinement it may eventually prove to be the modality of choice.

Venous sampling:[53,55]

A more invasive technique but probably the most useful for the difficult case. It is generally not used for routine screening.

Technique: This procedure consists of introducing a venous catheter, usually through the femoral vein, sampling blood under fluoroscopic control from the small veins in the neck, and using radioimmunoassay to build up a picture of the PTH concentration throughout the region. Samples are taken as selectively as possible from the inferior, middle and superior thyroid veins, as well as from the larger veins such as the jugular, subclavian, innominate and azygos veins. Thymic and left superior intercostal samples are also taken if possible. Hormone production may fluctuate even during the course of a procedure and it may be necessary to take simultaneous arterial and venous samples and express the result as a ratio.

The procedure is relatively safe. A good knowledge of the normal venous anatomy is essential to recognise variations in flow patterns. Such variations are a common source of error as is the distortion resulting from previous surgery.

Efficacy: The accuracy of the technique in predicting the site of a tumor ranges from 50-90% in different series. However it is a useful tool and often reserved for those patients with persistent hypercalcaemia despite previous surgical exploration.

Arteriography:[53,55]

Arteriography occasionally reveals a tumour on an arch aortogram, but bilateral selective superior and inferior thyroid arteriography is usually required. The technique is time consuming and not without hazard since the thyro-cervical trunk gives branches of supply to the spinal cord. This vessel may be injured by high local concentrations of contrast medium such as occur during superselective injections.

Digital subtraction angiography:[56]

This technique provides an accurate but nonspecific method for the localization of small vascular tumours. Being an intravenous procedure it can be carried out on an outpatient basis.

The sensitivity of DSA, although low at 40%, enables the display of relatively small lesions, provided they are vascular enough to create a blush. The anatomical location of the blush coupled with the clinical presentation allows estimation of the nature of the lesion.

The advantage of DSA as a technique is that it does not depend on differences in tissue density and planes of cleavage around a lesion in order to identify its morphological appearance as is required for US and CT, since the lesion betrays its presence simply by its vascular blush.

In view of its invasive nature, nonspecificity and low sensitivity, DSA is not an imaging modality in common use for the localization of parathyroid tumours.

The localization sensitivities of the noninvasive techniques appear to be remarkably similar. Each technique has its advantages and disadvantages. Circumstances determine which technique is best. In addition differences in institutional expertise with each imaging modality will also play a role in selection.

Chapter 5

Method

METHOD

Patients

A total of 74 patients, from 1984 to June 1989, were referred preoperatively to the nuclear medicine department for parathyroid scintigraphy. All patients had clinical and biochemical evidence of hyperparathyroidism. Three studies were technically unsatisfactory. Two because of patient movement and one due to a mandibular tumor which accumulated most of the injected thallium. Tweleve patients refused consent for surgery. In nine patients some other cause for their hypercalcaemia was found. In eight the decision was to treat conservatively due to poor operative risk or because the patient was over seventy and asymptomatic.

Thus only 42 patients ultimatly had surgical confirmation of their condition. Of these patients four had had previous surgery, one a total thyroidectomy and the other three were recurrences from previous surgery. Four patients underwent surgery twice having parathyroid scintigraphy prior to each surgical procedure.

Diagnosis: A confident diagnosis is invariably made with a clinical history, physical examination and elevated serum calcium and PTH levels.

PTH measurement: A radioimmunoassay up until 1988 since then a double antibody "Sandwich" Immuno

Radiometric Assay (IRMA) with antibodies against both the amino-terminal and carboxy-terminal of the molecule. This has greatly simplified the diagnosis of hyperparathyroidism. Problems in interpretation may still arise when the elevated calcium is associated with a PTH level within the normal range. Such levels are usually "inappropriately high" and consistent with the presence of an adenoma.

Surgery: All 42 patients underwent subsequent surgery including bilateral neck exploration with removal of the abnormal parathyroid gland and , in most cases, biopsy of the normal parathyroid glands.

Standard: The surgical and histological findings were the gold standard against which scintigraphic performance was judged.

RADIONUCLIDE PARATHYROID IMAGING AT GROOTE SCHUUR HOSPITAL

DESCRIPTION OF IMAGING TECHNIQUE

(01) EQUIPMENT

General Electric Starcam (either Mobile or LFOV);

Collimator: Pinhole with 4 mm aperture for thyroid area images;

Low energy general purpose parallel hole for chest image.

(02) RADIOPHARMACEUTICALS

Tc-99^m pertechnetate - 80 MBq

Tl-201 chloride - 110 Mbq

(03) CAMERA SETUP:

Use was made of the camera's ability to produce two separate images from two separate windows simultaneously.

Two energy windows were set: a 20% window centered at 72 keV and a 20% window centered at 140 keV (for Technetium).

The following images were then defined using a 64 X 64 word matrix and termination set for 5 minutes:

Ant thyroid 1

Ant thyroid 2

(It should be noted that because of the dual windows used, each of the above defined images actually produced two images - one for each energy).

At this stage the camera energy setting was changed such that only one window remained - the one centered about the 72 keV energy.

Further images also using a 64 X 64 word matrix and 5 minutes preset termination were then defined as follows:

Ant thyroid 3

Ant thyroid 4

Ant chest

All images were then queued in the above order ready for acquisition.

The pinhole collimator was fitted to the camera.

(04)PROCEDURE:

A small intra-cath (Jelco) was inserted into either an antecubital or hand vein of the patient. This intra-cath was connected to a three way tap.

The Tc-99m was then injected through this line and the line flushed with 10 ml of heparinised saline.

After waiting 10 minutes, the patient lay supine on the SPECT imaging bed with the arms secured alongside the body and the head secured and immobilized with tape and sandbags.

The neck was slightly extended to facilitate imaging.

The patient's thyroid area was then positioned under the pinhole aperture. The collimator to patient

distance was set such that the thyroid and some surrounding tissue was seen.

The first image (Ant thyroid 1) was then acquired.

(As was noted above, because of the dual windows in effect at this stage, actually 2 images were acquired).

The image obtained from the 72 keV window reflects the scatter of the Tc-99m into this (the Thallium) window; (scatter image).

The image obtained from the 140 keV window shows the distribution of the Tc-99m in the thyroid.

On completion of the first image, the Tl-201 was then administered through the line, followed by a saline flush.

Care was taken not to move the patient during the Tl-201 administration.

One minute after Tl-201 administration, the second image (Ant thyroid 2) was initiated.

The image obtained from the 72 keV window now reflects the scatter of the Tc-99m into this window plus the distribution of the Tl-201 in the thyroid and parathyroids.

The image obtained from the 140 keV window still shows the distribution of the Tc-99m in the thyroid.

When the above image was completed, the images Ant thyroid 3 and Ant thyroid 4 were then acquired.

It should be noted, that for these two images, only the window at 72 keV was in use.

It was not always possible to acquire the image Ant thyroid 4 due to the inability of the patient to lie supine and still for the whole imaging period.

After all thyroid/parathyroid imaging was completed, the pinhole collimator was removed, and replaced with the low energy, general purpose, parallel hole collimator.

An image of the chest, using the 72 keV window, was then acquired.

The Jelco was removed.

(5)PROCESSING:

Image processing was accomplished using General Electric software on either the Starcam or Starview system.

Firstly, a check was performed to see if any significant patient movement had occurred during the imaging procedure.

Two irregular regions of interest (ROIs) were drawn on the Tc-99m thyroid image; one around each lobe.

These ROIs were then superimposed on each Tl-201 thyroid image, thus allowing the operator to see if movement had occurred.

If any Tl-201 thyroid image did not fit well within the defined ROIs, then that image was reorientated such that a good fit was obtained.

After correcting for patient movement, the scatter image, (mentioned above), was subtracted from each of

the Tl-201 thyroid images (Ant thyroid 3 and Ant thyroid 4).

All Tl-201 thyroid images were then added together to form one composite image.

In order to compensate for the different activities of Tc-99m and Tl-201 used and for their differing degrees of uptake in the thyroid, the following normalization procedure was adopted:

Using the Tc-99^m thyroid image (Ant thyroid 1), four small, rectangular ROIs were constructed, one at each pole of the two thyroid lobes (probe regions).

The total counts in each of these ROIs was ascertained.

These ROIs were then superimposed, in exactly the same locations, on the composite Tl-201 thyroid image (Ant thyroid 3), and the total counts obtained.

Four Tl-201 to Tc-99^m ratios were then calculated by dividing the Tl-201 counts by the Tc-99^m counts in corresponding regions.

These ratios were then averaged to produce one Tl-201 to Tc-99^m ratio.

The Tc-99^m thyroid image was then multiplied by this factor producing a normalized image.

The normalized Tc-99^m image was then subtracted from the composite Tl-201 thyroid image, thus eliminating the thyroid component of the Tl-201 image.

Hardcopies of all relavent images were then made.

(6)POINTS OF INTEREST:

(a) Controversy exists as to whether the Tc-99^m or the Tl-201 should be administered first.

In this study we elected to give the Tc-99^m first.

It takes several minutes for the Tc-99^m to localise in the thyroid; this localisation is taking place while the patient is seated before imaging begins and movement is not a problem.

Only after twenty mintues, once localisation has taken place, does imaging begin.

The energy of the Tl-201 emissions is +/- 72 keV and those of Tc-99^m 140 keV.

In general, if one is going to image with two radionuclides of differing energies, it is better to start with the lower energy one and then image with the higher energy one. This avoids the problem of downscatter from the higher energy radionuclide into the window used for the lower energy one.

However, if the patient is not moved between radionuclide administrations and the higher energy radionuclide is used first, a correction for downscatter can be made.

This is simply accomplished by acquiring an image in the lower energy window after the higher energy radionuclide has been administered but before administration of the lower energy one.

Thus the image produced will reflect the downscatter of the higher energy emissions into the lower energy window.

Thus after the lower energy radionuclide has been administered, this 'scatter image' is then subtracted from all subsequent lower energy images.

(b) It is very important that no patient movement takes place during imaging. Small degrees of movement can be corrected for as described in processing above, but gross movement renders the image useless.

In order to minimise the results of patient movement, several short acquisitions rather than one long one are done.

Thus the patient may remain still for the first two images but move on the third; the third image can then be reorientated or discarded as required, leaving two good images.

If one long acquisition was done, and movement occurred, then the whole acquisition would be useless.

(c) The placing of the probe regions (see page 50) for image normalization is important.

The probe regions are never placed in any region that is obviously abnormal; eg. 'cold or hot' area. If necessary only three or two probe regions are used.

Placing probe regions in obviously abnormal regions may give unrealistic normalization factors.

Image evaluation:

The results were assessed by a single observer (PJ), who had no information as to the surgical or histological results. Inevitably the observer had some information about the high prevalence of parathyroid abnormalities in the sample of patients involved in the study.

The images were assessed with regards to the presence or abscence of thallium accumulation in the subtracted image for each of the four quadrants of the thyroid area. The findings were recorded as being positive, negative, or indeterminate where thyroid pathology was such that it could not be differentiated from parathyroid pathology.

Sensitivity was calculated as the ratio of adenomas of the parathyroid gland accurately identified by the localizing procedure (true-positive); to the entire group of parathyroid adenomas identified at operation (true-positive plus false-negative).

True-positive (TP) / TP + False-negative (FN)

Specificity was calculated as the ratio of parathyroid glands accurately identified as normal by a negative localization procedure (true-negative) to the entire group of normal parathyroid glands identified at operation (true-negative plus false-positive).

True-negative (TN) / TN + False-positive (FP)

Accuracy was calculated as the ratio of normal and abnormal parathyroid glands accurately identified by the localizing procedure (TP + TN) to the entire group of both normal and abnormal parathyroid glands identified at operation (TP + TN + FP + FN).

TP + TN / TP + TN + FP + FN

The predictive value of a positive test was calculated as the ratio of abnormal parathyroid glands accurately identified by the localizing procedure (TP) to the entire group of positive procedures (TP + FP).

TP / TP + FP

The predictive value of a negative test was calculated as the ratio of normal parathyroid glands accurately identified by a negative localizing procedure (TN) to the entire group of normal and abnormal glands not identified by the procedure (TN + FN).

TN / TN + FN

Chapter 6

Results

RESULTS

Twenty eight of the 42 patients who had bilateral neck exploration had a single parathyroid adenoma. Interestingly there were no cases of multiple adenomas. Of the twenty eight adenomas Tl/Tc scintigraphy identified twenty four(86%), correctly localising the tumours in all cases. There was no positive study which gave the wrong position. Sometimes the anatomical site was difficult to interpret owing to the inherent poor resolution of the technique. This was understanderably the situation with the eight ectopic (29%) and three intrathyroidal (11%) adenomas identified. Seventy five percent of the adenomas were situated at one or other of the lower poles of the thyroid. The majority (50%) being located at the right inferior pole.

Size: The mean volume of the parathyroid adenomas accurately identified was 2,2ml, the smallest being 0,5ml. The mean volume of the adenomas not visualized was 1ml, the largest being 2ml, thus demonstrating considerable overlap.

Biochemical: There were no discernible differences in the mean preoperative serum **calcium** elevations in patients with adenomas correctly identified (3,05mmol/l) and with adenomas not identified (3,02mmol/l).

Comparison of the mean preoperative serum **PTH** was not technically possible because of the two different types of assay utilized.

Hyperplasia of the parathyroid glands demonstrated in five patients, was associated with chronic renal failure. Most of these hyperplastic tumours were too small to measure at operation despite showing histological evidence of hyperplasia. In addition, with hyperplasia multiple parathyroid gland involvement was more the rule than the exception.

Two patients were found to have parathyroid carcinoma. One was missed on the study and the other was reported as an indeterminate result as differentiation between parathyroid pathology and thyroid pathology could not be made.

Thyroid pathology: There were seven studies on patients who had coexisting thyroid pathology, usually a multinodular goitre but in one case chronic thyroiditis. In five such conditions it was not possible to differentiate between thyroid pathology or parathyroid pathology as both the thyroid nodules and the parathyroid adenomas take up thallium to a greater degree than technetium. Such a situation was classified as an indeterminate study (fig 1). Of importance there were two patients where a correct interpretation of parathyroid adenoma could be made despite the underlying thyroid pathology. This was shown in a

patient with a multi nodular thyroid goitre (fig 2) and in a patient with a coexisting thyroid adenoma (fig 3).

The results are summarised in **Table 3.** The operative confirmation of the localizing procedure results is given in **Table 4.** The efficacy as a diagnostic modality is given in **Table 5.**

There were twenty four true positive studies (fig 4, fig 5). Ninety five true negative studies (fig 6), and only two false positive results. The false negative results were assessed from those normal parathyroid glands found at surgery and not demonstrated by thallium accumulation. The lower number of false positives compared to the litrature is a reflection of the use of the indeterminate calling.

False negatives: The false negative studies were high at 14 (33%), with the majority (7) being associated with parathyroid hyperplasia secondary to chronic renal failure. All seven were less than 0,4ml. Two adenomas that were missed could also be explained on the basis of small volume of gland.

In patient number 12 (see table 3) a tumour was found at surgery at the left superior pole of the thyroid. This was not identified on the Tl/Tc study and the histology was that of an atypical parathyroid adenoma, suggestive of malignancy.

Patients 15 and 16 are the same patient having a repeat surgical exploration (table 3). This patient was an unusual case, who on inital surgery had five normal parathyroid glands. On prior scintigraphy only an area of decreased activity consistent with and reported as a thyroid cyst was present in the right thyroid lobe (fig 7). The patients symptoms persisted post surgery and neither CT or MR could identify a possible site of excess PTH production. Selective venous sampling at this time demonstrated increased PTH from the right brachiocephalic vein. Again only the cyst was shown on scintigraphy. On rexploration the cyst was aspirated and the aspirate tested for PTH. A right hemithyroidectomy was also carried out and sent for histology. Suprisingly the aspirate was negative for PTH but the histology of the cyst was compatible with a parathyroid adenoma.

On retrospective analysis this particular case should have been recorded as an indeterminate study. It is a case such as this that confirms again that differentiation between parathyroid and thyroid pathology, particularly when the parathyroid gland is intrathyroidal, cannot be made scintigraphically with certainty.

The false negative result obtained with patient number one (table 3) is more difficult to interpret. This was one of the first patients of the Tl/Tc study and the technique differed in that the Tl was injected

first. In addition there was an obvious hot dominant thyroid nodule demonstrated on the Tc image. Again in retrospect, on subtraction there could be an arguement for a focus of increased activity at the right superior pole (fig 8), a more acceptable decision in this case would have been an indeterminate result.

Intrathyroid: The number of intrathyroid parathyroid glands was interesting (11%) and differs from the litrature·[14] These included patient 15 as already discussed (fig 7) but also patient number 20. This case also demonstrated apparent thyroid pathology on the Tc image and marked Tl accumulation (fig 9), which are features favouring thyroid rather than parathyroid pathology. However, as again demonstrated by histology , only an indeterminate call could be made.

Case number 23 was the only intrathyroid parathyroid adenoma correctly localized scintigraphically (fig 10). At surgery a right thyroidectomy was performed as no adenoma was isolated. However on histology parathyroid adenoma tissue was identified in the right inferior lobe of the thyroid. In addition this patient also demonstrated poor Tc uptake by the thyroid gland (fig 10) which on histology was shown to be the result of a mild lymphocytic thyroiditis.

Ectopic: The majority of ectopically situated parathyroid adenomas were situated either within the thyroid tissue (intrathyroid) or around the vicinity of the thyroid lobe. Those adenomas in the neck in close proximity to, but not within, the thyroid were all correctly localized. Positions ranged from three of the six being in the right carotid sheath, well demonstrated and shown to be completely separate from the thyroid gland (figs 11,12,13), to medial to the right thyroid lobe (fig 14). This adenoma, at surgery, was found to be adjacent to the pharynx displacing the recurrent laryngeal nerve.

The only mediastinal parathyroid adenoma in the study was in the thymus (patient 31). The only imaging modality to correctly localize this was selective venous sampling.

Hyperplasia: The poor results in terms of positive localization of parathyriod gland hyperplasia can be explained on the basis of gland size. Despite the high PTH levels the glands tended to be small and on gross examination at surgery many were indistinguishable from normal glands. Acute change in pathology also appears to be an interesting aspect of hyperplasia. This was demonstrated with case number 39. This patient had parathyroid surgery without prior localization in 1984 and remained normocalcaemic until march 1989. On this admission prior localization demonstrated a tumour at the right inferior pole of the thyroid (fig 15). This

was confirmed as hyperplasia at surgery and was removed. the other glands on biopsy were normal. The patient improved once again but only for three months. Prior localization again showed features of a tumour, but this time at the left inferior pole of the thyroid (fig 16). This was again confirmed to be parathyroid hyperplasia on reexploration.

TABLE # 3 SUMMARY OF RESULTS IN PATIENTS WITH PARATHYROID ADENOMA/HYPERPLASIA

Pat. #	Age/Sex	Calcium	Phosphate	PTH	Surgical Result		Gland Identification				Complicating Factors
		Normal: 2,1-2,6 mmol/l	Normal: 0,8-1,4 mmol/l	Normal: 10-55 pg/ml	Gland vol (ml)						
					Adenoma	Hyperplasia	Tp	Tn	Fp	Fn	
01	64/F	3,44	0,60	50,0	RS/1,7			3		1	Problem - Tl-201 inj. first
02	70/F	3,12	0,78	20,0	RI/1,1		1	3			
03	50/F	2,18	0,83	45,0	RI/2,0		1	3			
04	73/F	3,30	0,86	55,0	LI/2,0		1	3			
05	63/M	4,60	1,02	1220	LS/3,5		1	3			Parathyroid adenoma within a multinodular goitre
* 06	63/F	2,63	0,80	65.0				4			Initial surgery & scan negative. Rt. thyroid lobectomy.
* 07	63/F	2,70	0,74	64,0	LI/0,5		1				Subsequent surgery - adenoma behind remnant of Lt thyroid
08	66/F	3,35	0,80	50,0	LI/4,0		1	3			Large trilobed lipo-adenoma
09	66/F	2,83	0,70	75.0	RI/3,0		1	2			Ectopic situation - between the Rt common carotid artery and internal jugular vein

RS - Right superior ; RI - Right inferior ; LS - Left superior ; LI - Left inferior
TP - True positive ; TN - True negative ; FP - False positive ; FN - False negative
? - Indeterminate studies
* - Same patient with surgery X 2

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					Adenoma	Hyperplasia	Tp	Tn	Fp	Fn	
10	65/F	2,70	0,83	50,0	RI/0,7		1	3			On the anterior surface of the Rt lobe
11	67/F	2,88	0,77	63,3	RI/0,4			3		1	
12	22/F	3,03	0,99	7,3	LS/0,5			3		1	Histology atypical and suggestive of malignancy
13	51/F	3,08	0,70	74,8	LS/20		?				Multinodular goitre
14	52/F	2,73	0,83	110,1				3	1		No adenoma - 3 normal glands only
* 15	61/F	3,29	0,58	150,0				5			Initial surgery - 5 normal parathyroids found
* 16	61/F	3,40	0,58	269,4						1	Intrathyroidal cystic parathyroid adenoma
17	67/F	3,03	0,86	19,7		LI		3		1	
18	58/F	2,60	0,77	10,1	RS/0,4			3		1	

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					Adenoma	Hyperplasia	Tp	Tn	Fp	Fn	
19	31/M	3,35	0,74	64,8	RI/3,0		1	3			
20	55/F	2,83	0,90	59,6	RI/1,4		?				Intrathyroidal - unable to differentiate between thyroid or parathyroid
21	53/F	2,90	0,80	90,0	LS/0,4		?				
22	69/M	3,38	0,77	230,8	RI/1,0		1	3			
23	42/M	2,85	0,93	128,0	RI/		1	3			Intrathyroidal
24	55/M	3,20	0,70	345,5	LI/1,4		1	3			Ectopic - below the superior thyroid artery within the tracheo-oesophageal groove
25	55/F	3,10	0,65	80,5	RI/2,0			3		1	
26	67/M	3,03	0,90	58,0	RI/3,0		1	3			Ectopic - adjacent to the pharynx displacing the recurrent laryngeal nerve Pat. died of cardiac failure

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					Adenoma	Hyperplasia	Tp	Tn	Fp	Fn	
27	64/M	3,88	0,90	1150,0				4			Negative surgery despite a Rt thoracotomy plus re-exploration of neck and a median sternotomy. Pat. died
28	56/F	4,38	0,61	236,0	LI/1,0		1	3			
29	75/F	3,00	0,83	262,0	RI/4,5		1	3			
30	43/F	2,83	0,93	75,0	LI/2,4		1	1			
31	69/F	2,93	0,64	104,0						1	Intrathymus - only localised with venous sampling
32	54/F	2,93	0,74	138,0	RI/29,0		?				
33	63/F	2,95	0,74	82,0	LI/1,0		1	3			
* 34	34/M	2,98	0,74	222,0		RI & LI	1	2	1	1	
* 35	34/M	2,75	0,67	88,0		LI		3		1	

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					Adenoma	Hyperplasia	Tp	Tn	Fp	Fn	
36	52/M	2,53	2,05	450,0		4 gland hyperplasia				4	
37	24/M	3,20	0,80	100,0	RS/4,5		1	3			Ectopic - within the Rt carotid sheath
38	41/F	2,30	1,98	702,0		RI & LI/2,0	2	2			
* 39	44/F	2,90	1,67	156,0		RI/1,0	1	3			3/3/89 - Hyperplasia RI localised and removed
* 40	44/F	2,65	1,39	184,0		LI/2,0	1				12/6/89 - Hyperplasia LI localised and removed
41	21/F	1,08	1,44	463,0	Papillary Ca		?				Papillary carcinoma - identified scintigraphically but indeterminate
42	35/F	3,80	0,64	41,0	RI/0,5		1	3			Ectopic

RS - Right superior ; RI - Right inferior ; LS - Left superior ; LI - Left inferior
TP - True positive ; TN - True negative ; FP - False positive ; FN - False negative
? - Indeterminate studies
* - Same patient with surgery X 2

	Tl-201 / Tc-99m
TRUE POSITIVE	24
TRUE NEGATIVE	95
FALSE POSITIVE	2
FALSE NEGATIVE	14
INDETERMINATE	5

Table 4: **CONFIRMATION OF LOCALIZING PROCEDURE RESULTS WITH OPERATIVE FINDINGS**

	Tl-201 / Tc-99m	
	No. of patients	Percent
SENSITIVITY (Tp / Tp + Fn)	24/38	63
SPECIFICITY (Tn / Tn + Fp)	95/97	98
ACCURACY (Tp + Tn / Tp + Tn + Fp + Fn)	119/135	88
PREDICTIVE VALUE OF POSITIVE TEST (Tp / Tp + Fp)	24/26	92
PREDICTIVE VALUE OF NEGATIVE TEST (Tn / Tn + Fn)	95/109	87
FALSE POSITIVE RATE (100 - Specificity)	100-98	2
FALSE NEGATIVE RATE (100 - Sensitivity)	100-63	37

Table 5: **EFFICACY OF LOCALIZATION OF PARATHYROID ADENOMAS**

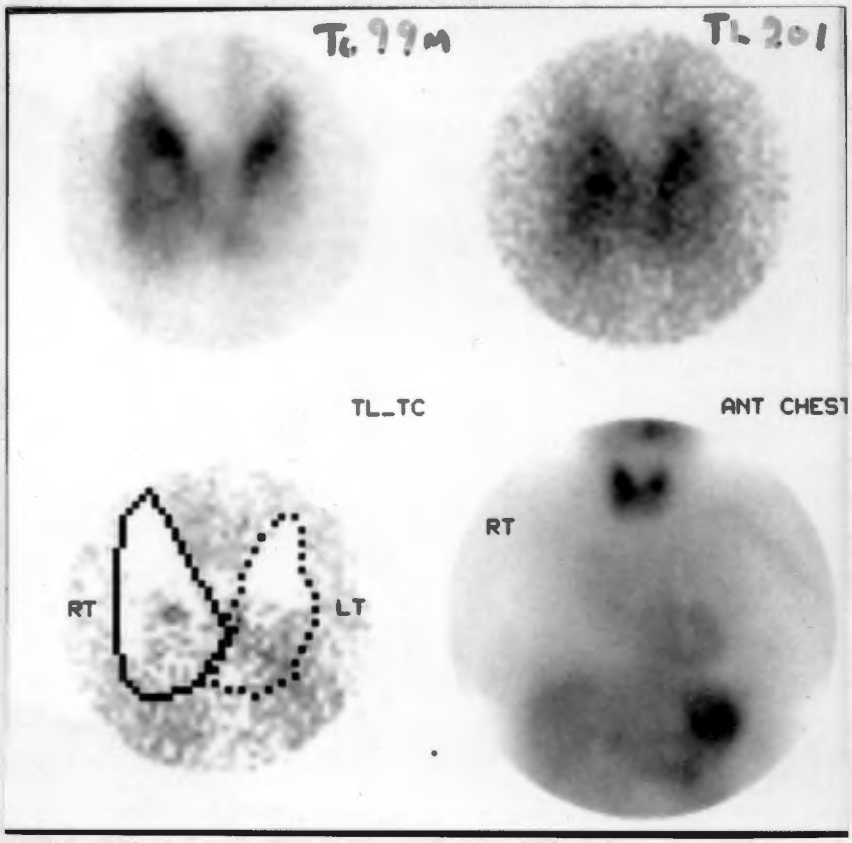

Fig.1 Thallium/Technetium subtraction parathyroid image.
An indeterminate study.
Left upper image: Tc-99m pertechnetate image showing inhomogeneous uptake consistent with a multinodular goitre.
Right upper image: Tl-201 image.
Left lower image: computer subtraction image revealing thallium activity at both lower poles of the thyroid.

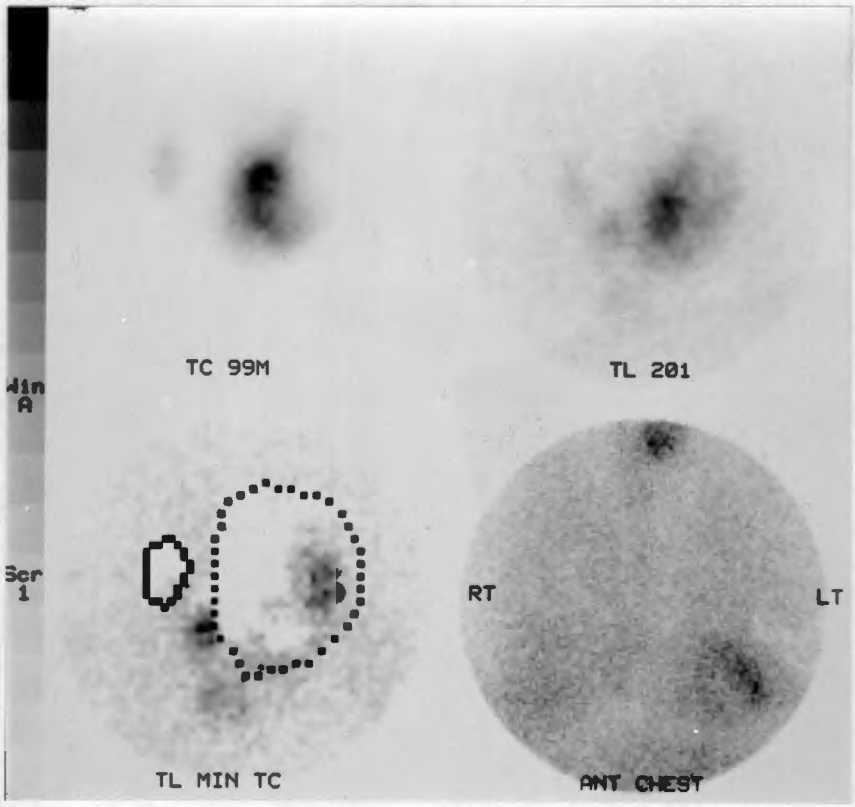

Fig.2 A positive thallium/technetium study in a multinodular thyroid goitre.
Tl-201 Image: Increased activity at the medial aspect of the left lower lobe (arrow). This is accentuated on the subtraction image.

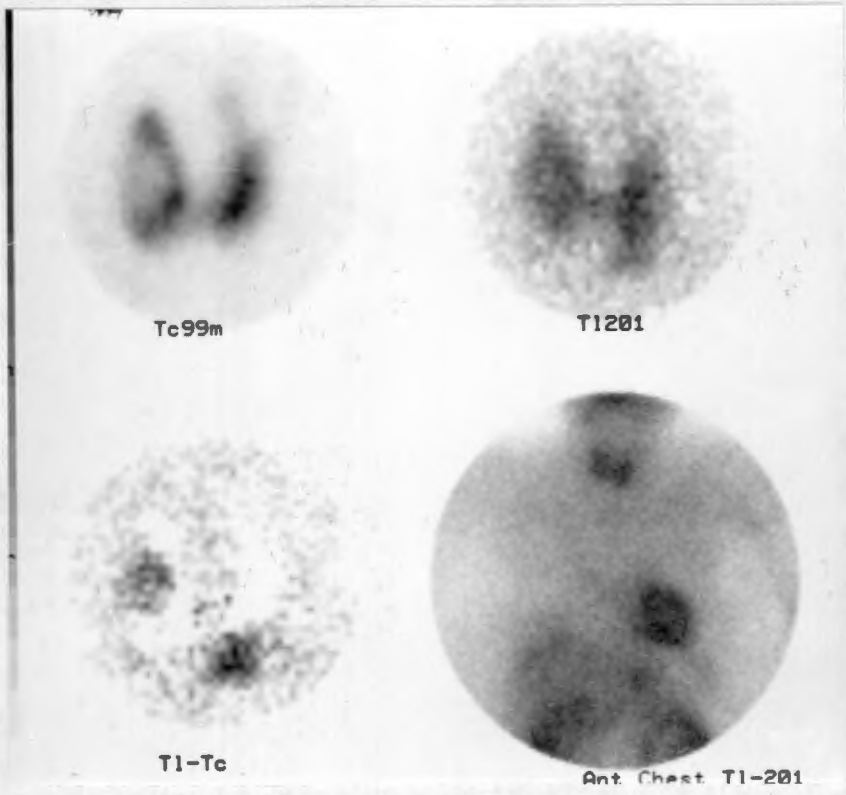

Fig.3 A positive thallium/technetium study:
Demonstrating a parathyroid adenoma at the left lower pole and a co-existing adenoma in the right lobe.

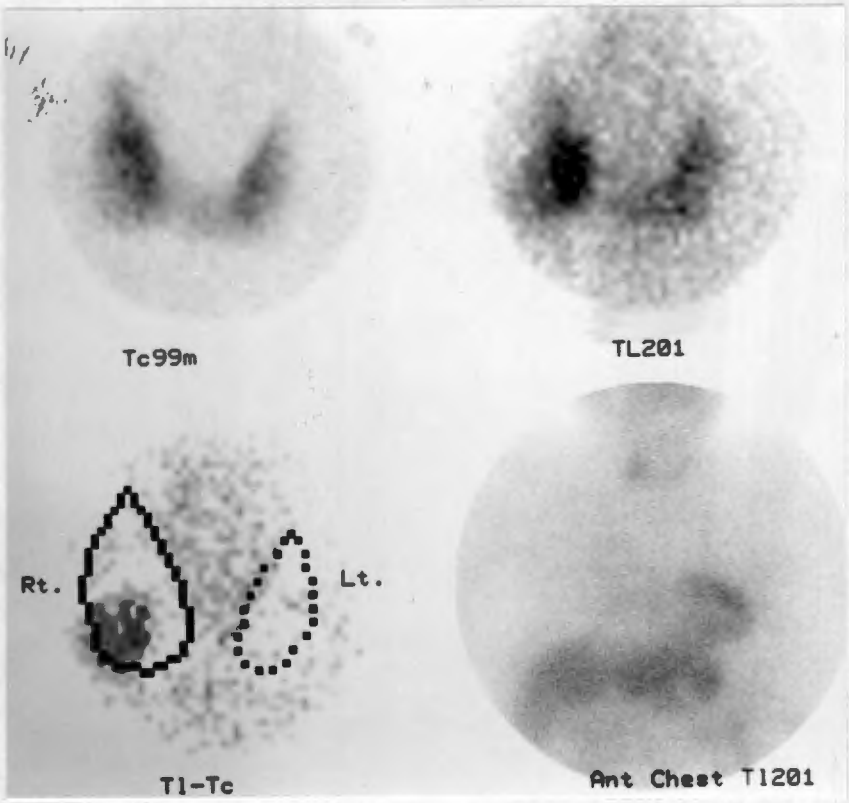

Fig.4 True positive thallium/technetium study.
Demonstrating a parathyroid adenoma at the right lower lobe of the thyroid.

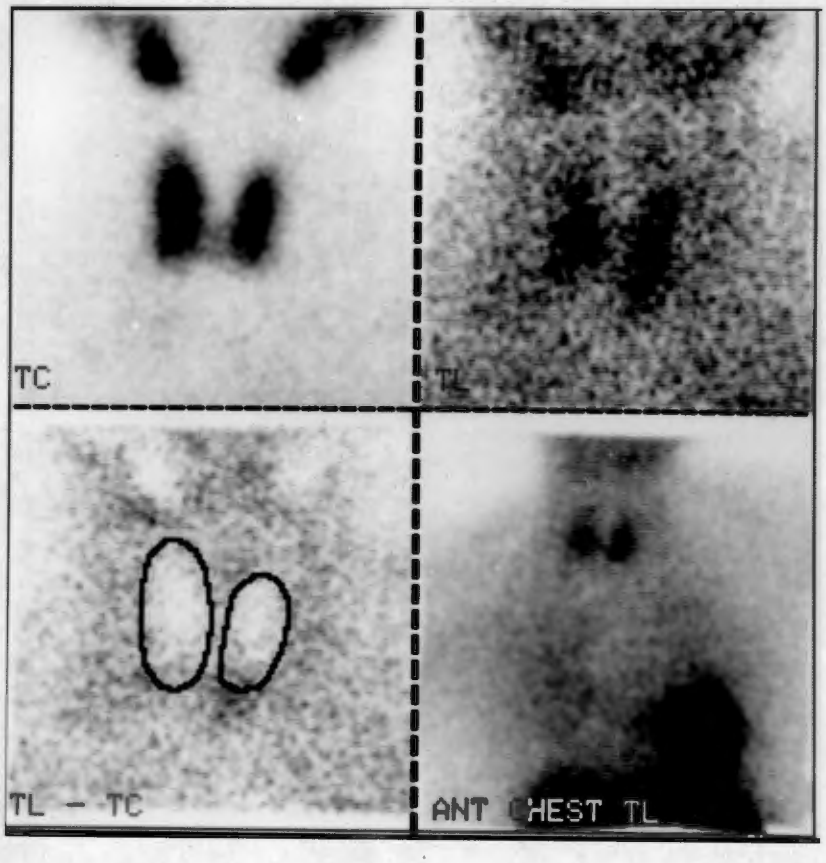

Fig.5 True positive thallium/technetium study.
A confirmed tri-lobed parathyroid lipoadenoma at the left lower pole.

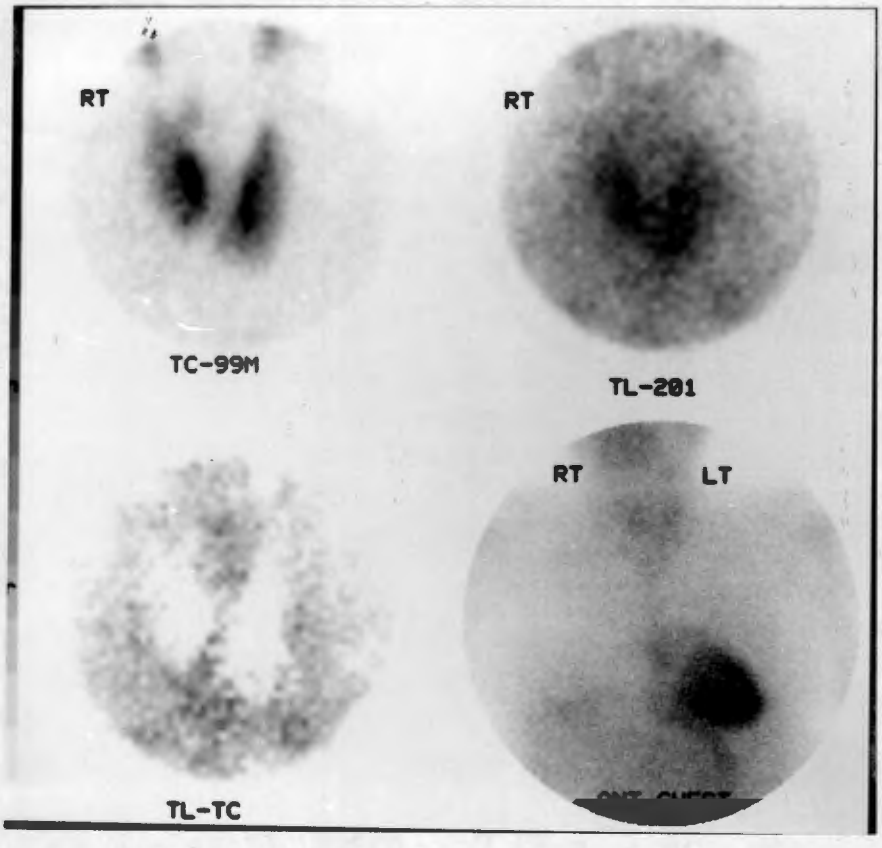

Fig.6 A true negative thallium/technetium study.

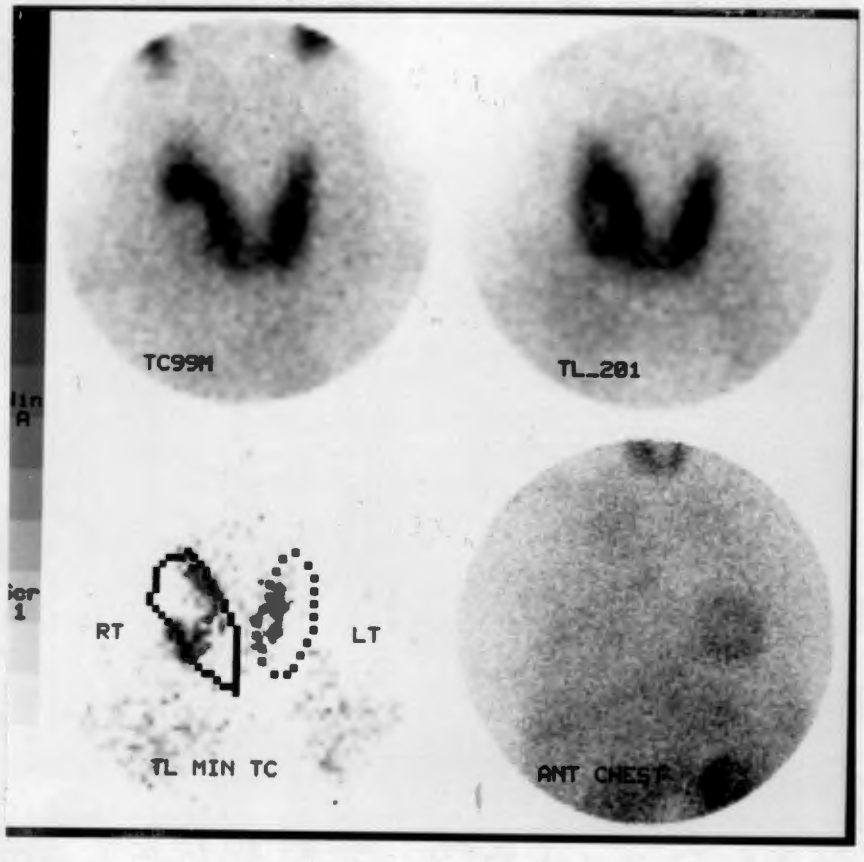

Fig.7 A false negative study.
The images demonstrate the cystic nature of the lesion in the right thyroid lobe. Features of a thyroid cyst but shown histologically to be an intrathyroidal cystic parathyroid adenoma.

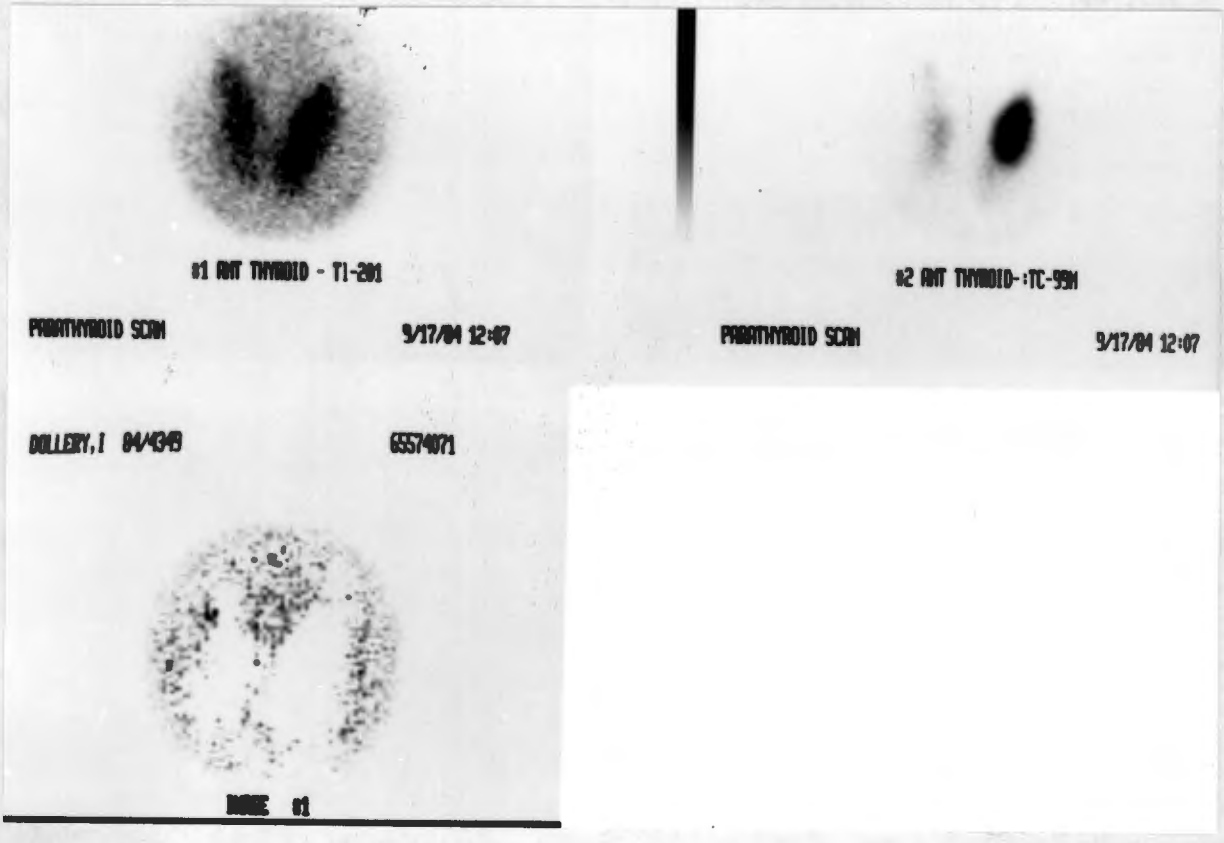

Fig.8 False negative study.
Accumulation of activity in a single nodule on the technetium image. No definate area of retained thallium activity on the subtraction image.

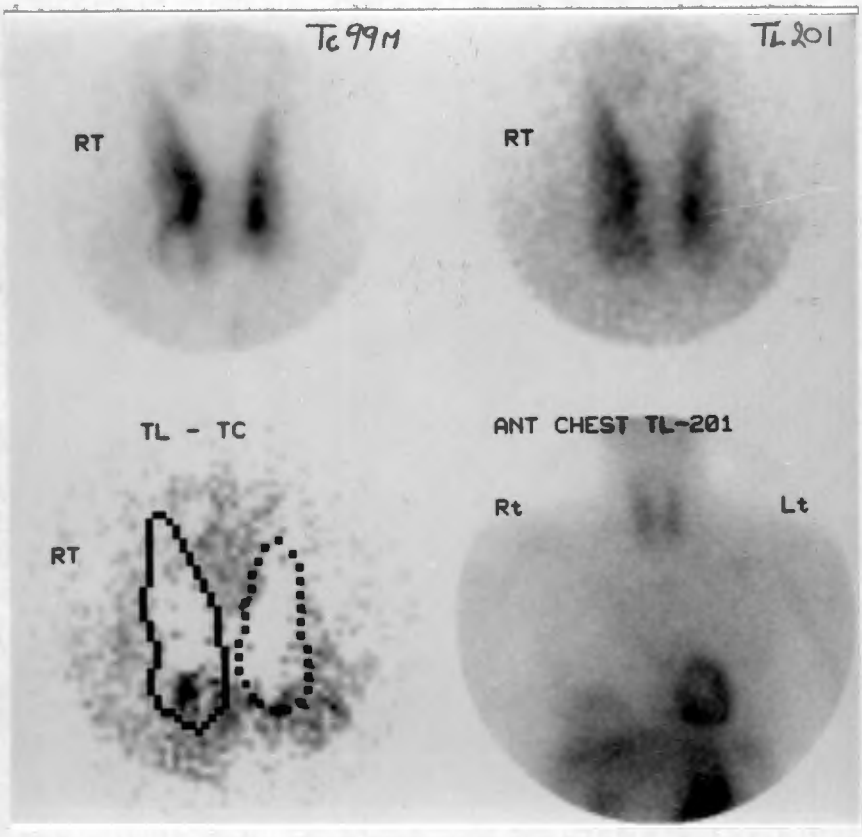

Fig.9 An indeterminate study.
An intrathyroidal parathyroid adenoma in the right inferior pole.

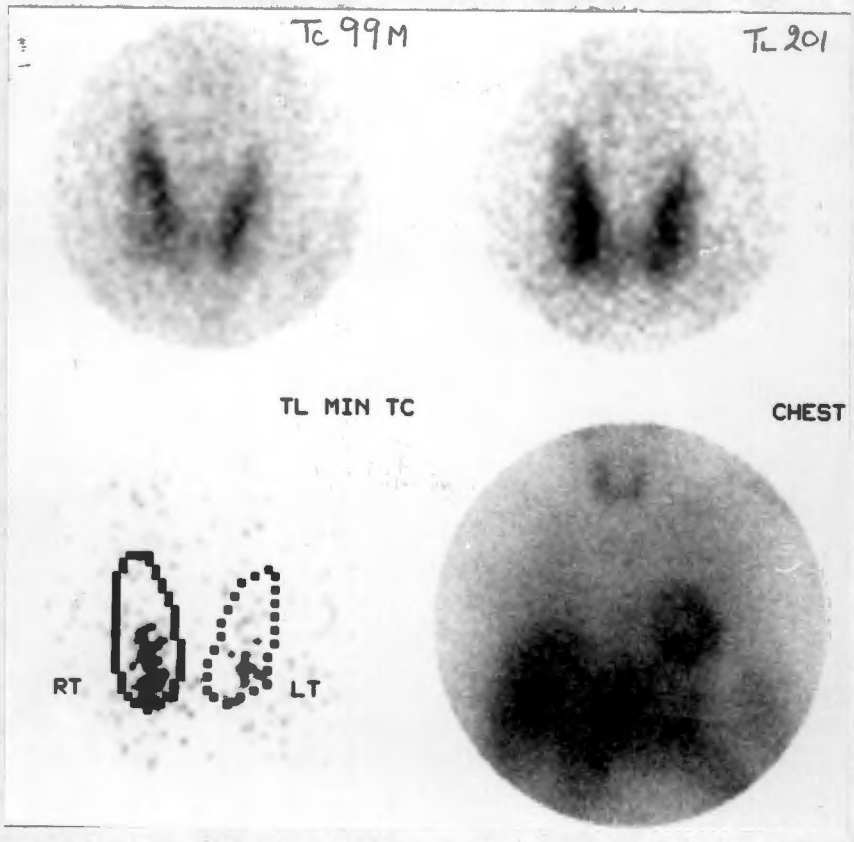

Fig.10 A positive study.
An intrathyroid parathyroid adenoma in the right inferior pole.

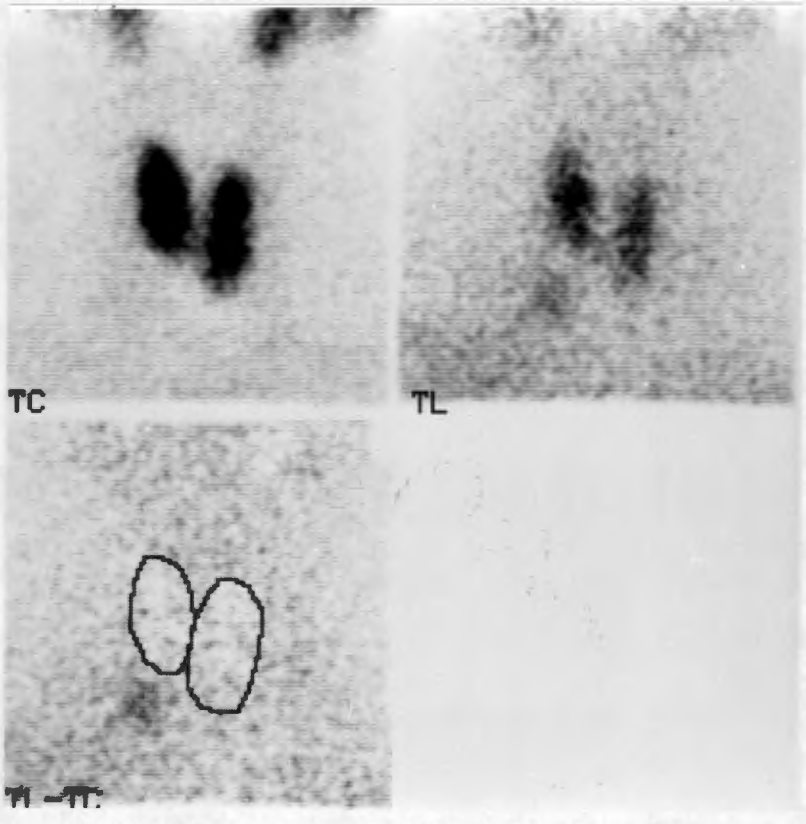

Fig.11 An ectopic parathyroid adenoma in the right carotid sheath lying on the internal jugular vein.

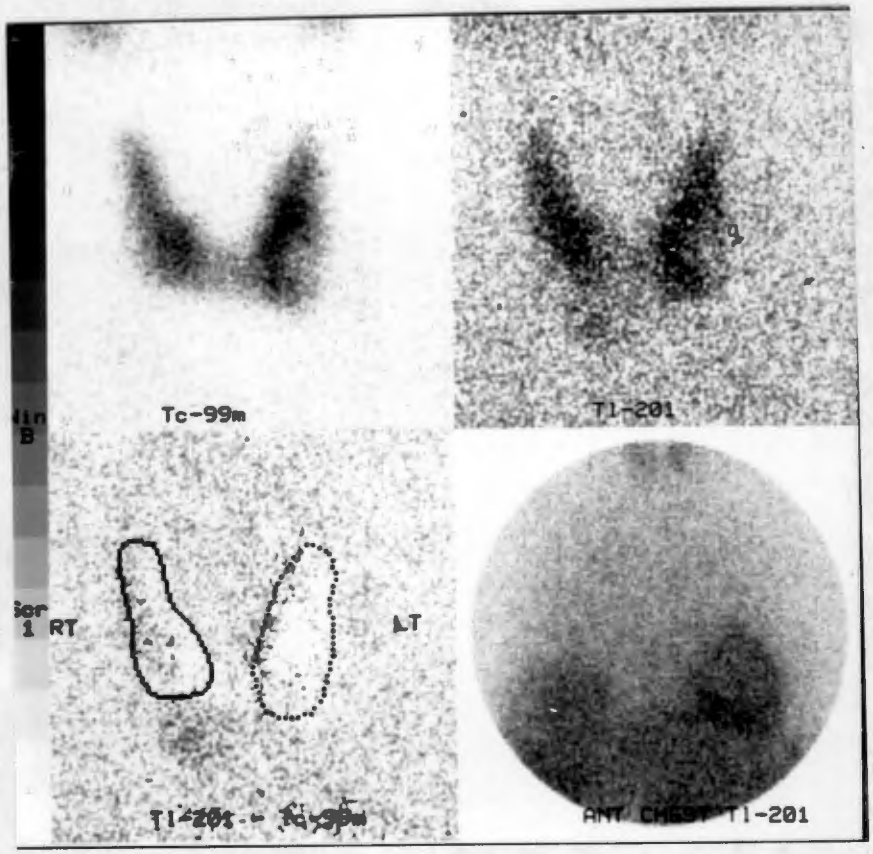

Fig.12 An ectopic parathyroid adenoma in the right carotid sheath.

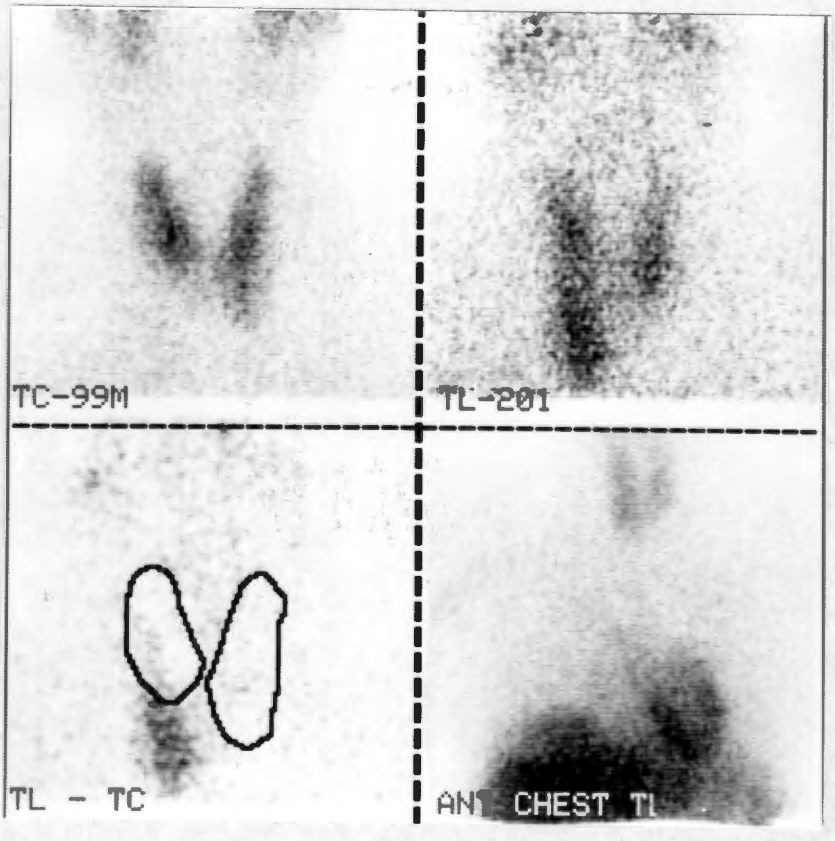

Fig.13 Ectopic parathyroid adenoma medial to the right carotid sheath.

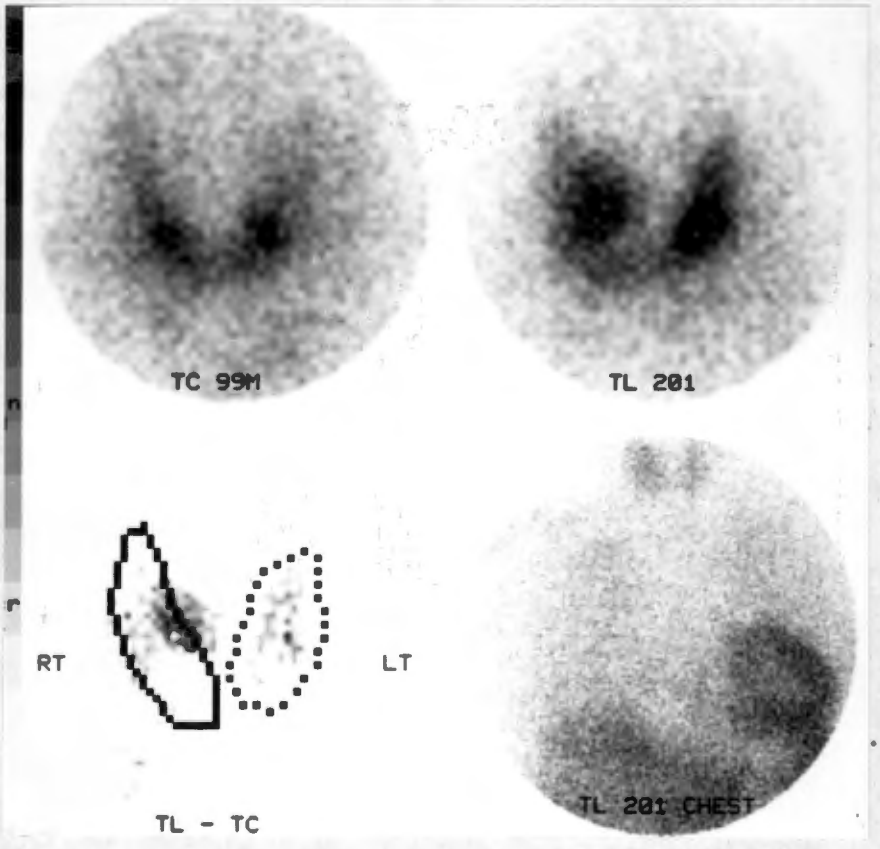

Fig.14 Ectopic parathyroid adenoma adjacent to the pharynx.

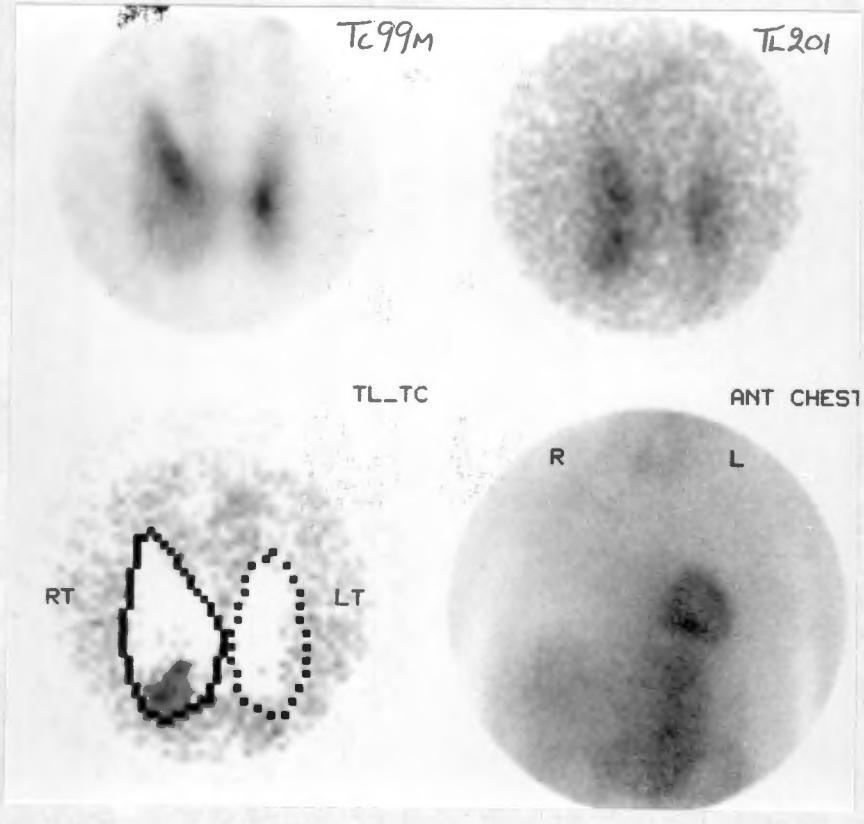

Fig.15 Parathyroid hyperplasia.
The right inferior gland.

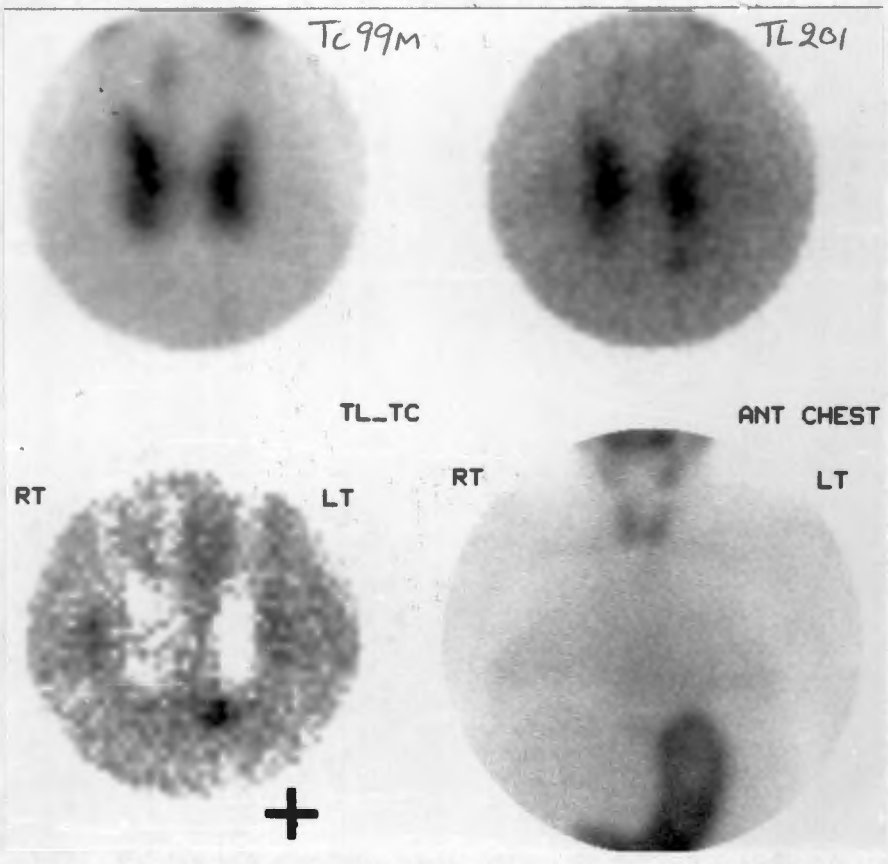

Fig.16 Parathyroid hyperplasia.
The left inferior gland three months later in the same patient as fig.15.

Chapter 7

Discussion

DISCUSSION

Early success in the scintigraphic localization of parathyroid adenomas was limited. The initial enthusiasm in ^{75}Se and ^{131}Cs was short lived, mainly as a result of their poor imaging properties. The work on these earlier isotopes was in no way wasted as the concepts and imaging techniques paved the way to the current Tl/Tc subtraction imaging.

Success with Tl/Tc subtraction imaging for the localization of parathyroid pathology has had reasonable appeal. However the original concept of imaging sensitivity being indepent of size appears to be limited. Despite this the actual process of scintigraphic imaging is still a concept of gland function thus enhancing the specificity of the technique.

Earlier work utilising Tl/Tc scintigraphy is confusing and difficult to assess in terms of the efficacy of the technique. There are disparities in results and in the methods of assessing these results. The main criterion in these studies is the ability to localize the pathology. The surgical relevance in the evaluation of a localizing procedure depends on:

1. Whether all patients who had the procedure subsequently went for surgery, and not only those with a positive finding.

2. Whether or not the procedure accurately predicted a precise site for an enlarged parathyroid gland, lateralization alone is not good enough.

3. Whether the localization results were made prior to the surgical finding.

The first reports on the success of Tl/Tc imaging for parathyroid adenoma localization came from Ferlin et al.[39] They reported a 92% success rate by correctly localizing 24/26 parathyroid adenomas. However a major flaw in this study is that the 22 patients with negative studies did not have surgical exploration. In another study by Gooding et al[57] a sensitivity rate of 74% was reported using Tl/Tc scintigraphy to identify 23 parathyroid adenomas. This study was prospective and evaluated all patients having bilateral exploration of the neck after these localizing procedures. Manni et al[58] reported correct localization in 82% of patients. However these rates were determined only for patients successfully explored. Reported sensitivities of 86% (Okerlund et al[59]) and 94% (Young et al[38]) were found. But again this latter report was based on a series of 34 patients with preoperative localization and only 22 going for surgery. Thus disparity in these earlier studies makes comparison difficult.

An excellent study with a more realistic finding was carried out by Roses et al.[49] They compared the imaging modalities of US, CT and Tl/Tc scintigraphy on

36 patients with a collective number of 41 abnormal parathyroid glands. The study was prospective. None of the patients had had previous surgery to the neck. All reports on the different imaging modalities were carried out by three consultants, each specialized in his particular modality. All patients imaged went to surgery and were operated on by the same surgeon. All patients had bilateral neck exploration. Their results for the three different modalities were remarkably similar. In particular the sensitivity and specificity for Tl/Tc scintigraphy was 49% and 92% respectively.

The Groote Schuur study: The results of this Groote Schuur study on 42 patients who had preoperative parathyroid localization are similar to those of Roses et al. The local findings also depict a low sensitivity of 63% as a result of a high false negative rate. A high percentage of these false negatives is a consequence of parathyroid hyperplasia, and although morphologicaly similar to adenomas, one wonders whether their functional ability to trap thallium is different. The use of ^{123}I in place of technetium pertechnetate has been suggested as pertechnetate has been reported to accumulate in a parathyroid adenoma where iodine has not.[60] This could result in fewer false negatives. On the other hand, discordant thyroid nodules that accumulate pertechnetate (but not iodine) would be a more frequent source of false positives when radioiodine is used!

Ideally, a successful localization technique should be able to facilitate the identification of ectopically located parathyroid adenomas, multiple adenomas or small adenomas. These are presentations that might elude the surgeon, whereas a single, clearly enlarged parathyroid gland in a normal location adjacent to the thyroid gland should not present the surgeon with any difficulty.

In this study the majority of ectopically situated glands were in and around the thyroid. However the prior localization was of definite assistance with regards to those glands unassociated with the thyroid but was of limited success with those glands that were intrathyroidal. Unfortunatly there was only one mediastinal ectopic parathyroid adenoma in the series and this was not localized scintigraphically. The imaging modality was also of little assistance with multiple and small lesions the majority of the former also being small.

In view of the low sensitivity and high number of false negative studies Roses et al concluded that the routine use of parathyroid localization prior to surgery was not warranted.

Despite the similarity of findings to Roses results I disagree with their conclusion because I believe that there is more latitude in the use of this procedure than solely localization of pathology. Even

in this respect the low sensitivity rate is not prohibitive in that the specificity is excellent at 98%, and the predictive value of a positive test is 92%. If the procedure is undertaken with the knowledge of these limitations in mind and the necessary precautions taken, the technique is extremely valuable. At least a positive biochemical indication of hyperparathyroidism with raised serum calcium and PTH must be made and in addition, an assessment for underlying thyroid pathology. With such evidence no patient should be denied surgery on the basis of a negative Tl/Tc study.

In this study Tl/Tc scintigraphy played a definite role in the following:

1.**Diagnosis:** Of the original 74 patients who underwent Tl/Tc scintigraphy nine patients did not proceed to surgery because the diagnosis of hyperparathyroidism could not be substantiated or some other cause for their hypercalcaemia was found. Of these nine patients eight had a normal Tl/Tc study and although surgery was not undertaken to varify the results the imaging procedure had some influence on the decision to look for another cause of hypercalcaemia and to withhold surgery.

2.**Management:** In eight patients the decision was to treat them conservatively due to poor operative risk or because the patient was over seventy and/or

asymptomatic. In three of these patients the Tl/Tc study was normal adding additional criteria to the eventual decision of conservative management.

Unfortunatly it is not possible with the patient data available to assertain to what extent a positive study influenced the decision to operate on "asymptomatic" patients.

3.**Localization:** As already discussed, despite the high rate of false negative results the corresponding high positive accuracy makes this study invaluable, providing unquestionable assistance particularly with the ectopic parathyroid glands around the thyroid.

4.**Recurrence:** With no previous recurrence rates of hyperparathyroidism at Groote Schuur it is not possible to assess the impact of scintigraphy in this respect. The current literature is however positive in this respect.[45]

5.**Reexploration:** Eight patients had had previous neck surgery, one a total thyroidectomy and the other seven were recurrences. Of these eight the Tl/Tc study was positive in seven,making this an accurate technique under such difficult anatomical circumstances.

The usefullness of Tl/Tc scintigraphy in the Groote Schuur setting has been assessed and despite limitations its value as a routine procedure prior to surgery cannot be denied. Consideration must be given

to biochemical evidence of pathology and the presence of thyroid disease.

Refinement of technique as discussed by Blue[42] appears to improve sensitivity to as much as 91%. More emphasis must be placed on improving the detection of ectopic parathyroid adenomas in the mediastinum with the possible use of SPECT facilities for better anatomical positioning. As for the future, the limitation of the resolution of thallium as well as the nonspecificity of its uptake will result in it being replaced with another radiopharmaceutical with better imaging characteristics or more specific parathyroid uptake. Hayward et al[41] reported the uptake of I-131 metaiodobenzylguanidine (MIBG) in a parathyroid adenoma suggesting with further development an alternative to thallium. I-131 toluidine blue, a radiolabled histologic dye, has been reported to accumulate in parathyroid adenomas.[42] On a histologic basis, it appears that this radiopharmaceutical will offer more selective uptake in parathyroid tissue than thallium. Then there is always the research on monoclonal antibodies with the possible development of a specific antiparathyroid antibody.

In summary, despite its limitations, Tl/Tc scintigraphy is an accurate routinely available noninvasive procedure for the detection of parathyroid adenomas in patients with primary hyperparathyroidism. Ultrasound can be complementary and is a useful

adjunctive test for those negative or indeterminate cases. CT is useful for mediastinal adenomas. MRI, while still promising, is relatively expensive and impractical as a routine screening test. Refinement in all modalities is likely to lead to improved resolution and lesion detection. Future investigation may lead to the development of a more specific radiopharmaceutical. The final endpoint should be a reliable, specific, noninvasive test that indicates to the surgeon the location of any and all sites of excess PTH secretion, whether adjacent to the thyroid bed or ectopic. In addition the predictive value should be high enough for the result to be of assistance in both diagnosis and management. Once this is achieved, there will be clear benefits to the patient.

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APPENDIX

DOSIMETRY

EXAMINATION	FORM	ACTIVITY ADMINISTERED (MBq)	ABSORBED DOSE cGy / MBq			ABSORBED DOSE / PROCEDURE (cGy)		
			THYROID	GONADS	TOTAL BODY	THYROID	GONADS	TOTAL BODY
Tc-99m	Sodium Pertechnetate	80	0,0035	0,0005	0,0005	0,28	0,04	0,04
Tl-201	Chloride	110	0,0278	0,0159	0,0056	3,06	1,75	0,62
Chest Radiograph						0,01	0,002	0,005