Radiology in the Management of Cancer

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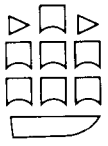

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Preface

In the last twenty years there has been an enormous increase in the range of imaging techniques available to investigate the patient with cancer. New techniques like radioisotope imaging, ultrasound, X-ray computed tomography and magnetic resonance imaging have often been developed by specialist groups who have assessed their value in patients with benign or malignant tumours. These techniques are then employed in other departments or offered on a restricted basis to colleagues. The effect is a patchy introduction and further development without analysis of their relative value. Some may have limited application in common diseases or only be useful in rare tumours and confusion can arise about the role and value of these newer techniques.

The result is that patients are sometimes referred for oncological opinion without having had simple investigations on which major treatment decisions can be made. In other situations they may have been subjected to inappropriate investigations, incomplete studies which need to be repeated or multiple unnecessary investigations. This creates extra work, wastes finite resources and may delay treatment. The patient with cancer should have the relevant investigations carried out as quickly and efficiently as possible. Different techniques are appropriate in initial assessment, staging, monitoring the response to treatment and in the management of relapse. This requires the radiologist to understand the particular relevance of all techniques to the patient's management, at any time in the course of their illness.

This book aims to improve understanding of the role radiology has to play in the management of cancer. It is not a standard textbook illustrating the radiological appearances of cancer and only limited space is given to the role of radiology in the initial diagnosis. The main thrust of the text relates to the integration and limitations of available imaging modalities in staging patients and assessing the response to treatment or the complications of therapy. In addition to the chapters on tumours at specific sites there are chapters dealing with radioisotope and magnetic resonance imaging and one on the use of radiology in radiotherapy treatment planning.

Whilst primarily intended for Radiologists and Oncologists the text should also be of value to all clinicians who treat patients suffering from cancer.

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R.J.J
B.E.
R.D.H

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K. E. Britton

INTRODUCTION

Imaging using the techniques of conventional radiology, computed tomography (CT) and ultrasound shows the structural changes which occur with tumour growth. The techniques show the site, size, shape, density, space occupation and what the presence and effects of metastases look like in other tissues. Nuclear medicine techniques depend on the emission of gamma rays arising from the nuclei of atoms from within a patient who has received a particular radiopharmaceutical. They show how the presence of the tumour or metastasis affects one or other of the metabolic functions of the organ or system under study.

Nuclear medicine is thus pertinent to the assessment of the patient with cancer, not to its primary diagnosis. The question 'Has this patient a renal tumour?' is appropriately answered by the structural techniques of ultrasound and radiology, whereas the question 'How much renal function will the patient lose as a result of nephrectomy?' is the province of nuclear medicine. Nevertheless, alteration of function may be an exquisitely sensitive, if not very specific way of detecting the presence of metastases; an example is the widespread use of the whole body 'bone scan'.

A new approach in nuclear medicine is to demonstrate the presence of cancer more specifically, not by its position or dimensions, but by tissue characterization: firstly through the identification of the presence of tumour associated antigens, and secondly through a tumour's receptor binding status. The oncogene/anti-oncogene hypothesis of cancer indicates that there are specific deoxyribonucleic acid chains in cancer tissue which alter its growth characteristics. The hope is that specific oncoproteins related to these gene alterations will be identified so that cancer tissue characterization may be performed by in vivo imaging using radiolabelled antibodies specific to such oncoprotein antigens. This technique, termed radioimmunoscintigraphy, has a long way to progress before meeting this requirement. It also holds out the hope for specific unsealed source radiotherapy and chemotherapy by the binding of alpha or beta particle emitting radionuclides or cellular toxins to the antibody to target them to the malignant tissue. Experimental work in this field is under way.

The presence on cancer cells of receptors for active molecules is well recognized. The most encouraging recent development in this approach is the use of the noradrenaline analogue *meta*-iodobenzyl guanidine, MIBG, which is taken up by the neurosecretory granules of many neural crest tumours, particularly benign and malignant phaeochromocytoma and neuroblastoma where its use in both staging and therapy is being exploited.

MATERIALS AND EQUIPMENT

Radiopharmaceuticals

It is often difficult for the diagnostic radiologist, who is used to receiving contrast material sterile, pyrogen free and conveniently packaged in an ampoule, to appreciate the recent complexity in providing routine radiopharmaceuticals for nuclear medicine. For the UK the combined requirements of the Medicines Act, the Administration of Radioactive Substances Advisory Committee (ARSAC) and the Ionising Radiations Regulations, make the production and dispensing of radio-

pharmaceuticals, particularly when distributed to more than one department, a matter for the professional radiopharmacist and a highly trained technical staff.

Dispensing demands a fully aseptic technique in a positive pressure room by a gowned, masked and capped technician taking the necessary precautions against radiation hazard and calculating and measuring the appropriate activity for the time of administration. To meet the logistics of having the right patient at the right time so that activity is not wasted by decay, the nuclear medicine department should have its own designated porter.

Most routine work is undertaken using ^{99m}Tc technetium. It has a halflife of six hours and a gamma ray energy of 0.140 MeV, which is ideal for the modern gamma camera. Each morning technetium is 'milked' from its parent ^{99}Mo molybdenum 'cow' – a sterile lead-encased generator containing ^{99}Mo bound to a solid matrix from which its daughter decay product ^{99m}Tc is eluted using a saline solution into a shielded sterile ampoule. After determining the activity in an ionization chamber, appropriate aliquots of the ^{99m}Tc pertechnetate solution are added to sterile ampoules of the various 'kit' preparations following the manufacturer's instructions: MDP (methyldiphosphonate) for bone imaging; DTPA (diethylene triamine penta-acetate) for kidney and brain studies; HMPAO (hexamethylpropylene amine oxime) for brain and white cell labelling; tin colloid for liver Kupffer cell uptake; microspheres for lung or nanocolloids for marrow imaging etc. Some materials may be bought in ready prepared such as ^{131}I-MIBG (*meta*-iodobenzyl guanidine). Many have been synthesized and radiolabelled in the radiopharmacy before becoming commercially available, such as ^{123}I-MIBG for imaging neuroblastoma. The radiolabelling of monoclonal antibodies with ^{123}I (halflife 13 h, gamma ray energy 0.159 MeV) or ^{111}In indium (halflife 67.4 h, gamma ray energies 0.171 and 0.250 MeV) is another example.

The gamma camera computer system

The technical problems consist essentially of determining the quantity and distribution of radioactivity in an organ or tissue under study at a particular time and of measuring how this changes with time. When a radionuclide such as ^{99m}Tc is combined in a radiopharmaceutical and distributed in the tissues after intravenous injection, its gamma rays penetrate the body. Some interact with the tissue and are scattered, travelling with a lower energy at different angles (Compton scattering), others pass through and may be detected by their interaction with the camera's crystal of sodium iodide, which contains a small proportion of thallium impurity. Flashes of light are emitted, which pass from the crystal to a light sensitive photomultiplier tube, so they are detected as pulses of electricity in this 'scintillation detector'. A gamma camera consists of a single large crystal, for example, 37 cm in diameter and 1 cm thick, to which is applied a large array of photomultiplier tubes, 37 or more. In front of the face of the camera is fixed a lead sheet (collimator) 4 cm thick, in which many thousands of parallel holes reduce the entry of gamma rays other than those travelling perpendicular to the face of the detector. The design of the collimator depends on the energy of the gamma rays emitted by the radionuclide; the higher the gamma ray energy, the thicker must be the lead septa around each hole to prevent their penetration by gamma rays coming in at an angle. The more lead there is in the collimator, the lower the sensitivity of the camera. A 'low energy' collimator is used for ^{99m}Tc and ^{123}I, whereas a heavier 'medium energy' collimator must be used for ^{111}In and ^{131}I.

Beyond the photomultiplier tube is an analyser which may be set so that only pulses equivalent to the original energy of the gamma rays are registered; thus the scattered lower energy gamma rays are not recorded. This is achieved by setting a 'window' of e.g. 20% around the photopeak, which represents the particular energy of unscattered gamma rays. This allows the acceptance of gamma ray energies 10% higher and lower than that from the particular radionuclide in use. ^{111}In has two important gamma rays of different energies so two photopeaks have to be chosen in this 'pulseheight analyser' when imaging with ^{111}In-labelled compounds. Checking that the correct collimator is being used, and the setting of the photopeak(s) are important initial steps before imaging is undertaken.

A complex electronic network determines the position at which each gamma ray struck the crystal and this is displayed as a dot on a cathode ray tube. The number of gamma rays detected determines the brightness of the display. The distribution of dots may be viewed using a 'persistance' scope, which is used to check the positioning of the gamma camera over the patient. Once this is decided the image recording is made. The distribution of gamma rays may be summed on transparent film to give the conventional image of scan. In addition, this distribution is transferred electronically on line through an interface directly into the computer, where it is stored in a matrix of picture elements (pixels), usually a 128 × 128 matrix, for display in black and white or colour on a visual display unit (VDU). Sophisticated data manipulation is undertaken and, depending on the nature of the programs, includes, for example, region of interest (ROI), selection, image translation and rotation and image comparison or subtraction.

Single photon emission computed tomography (SPECT)

Single photon emission computed tomography (SPECT) is a technique for reconstructing sections through the body of the distribution of uptake from the collection of all the data from a region by rotating the gamma camera full circle around the patient. The filtered back projection computer algorithm which performs the reconstruction is complex and similar to that used for X-ray computed tomography (CT), although SPECT predated CT by over ten years. The sections are usually transverse axial, but coronal and sagittal sections may be reconstructed. The advantage is the increased contrast of the target in the plane of the section and particularly the ability to separate objects from in front of and behind the target, e.g. the bladder from a pelvic tumour, which may overlap on a conventional view. Another practical advantage is the ability to quantitate the amount of activity in a region of the transverse section, for example, for dosimetry; however, this is much more difficult than expected. Errors occur due to less than perfect rotation and linearity of response of the camera, Poisson's statistical noise, algorithm noise, artefacts due to overlapping tissue activities, the partial volume effect, patient and organ movement and difficulties in correcting for tissue attenuation. Accuracy is thereby considerably reduced and the anatomical relationships of tissues and target may be difficult to visualize and to interpret. SPECT sections, once created, cannot be repositioned. The technique is a potentially useful adjunct to, but not a substitute for, planar imaging.

Positron emission tomography (PET)

This technique is designed to image radiopharmaceuticals labelled with a positron-emitting radionuclide. The annihilation of a positron gives two 511 keV gamma photons which travel in opposite directions. PET uses a ring of opposing detectors and the technique of coincidence counting to determine positional information. The advantage is that the net attenuation of the gamma ray pair is independent of the location of their source and constant. Thus attenuation correction can be made accurately using data from a transmission measurement taken from an external radiation source before imaging commences. This means that quantification with PET is much more accurate than with SPECT and resolution has been made greater by improved detector development. Only the elements of life, carbon, nitrogen and oxygen, have positron-emitting radionuclides. Thus PET is the key to precise physiology and most advances have been in the quantitative characterization of a variety of neuroreceptors in the brain. The disadvantage is that these have very short halflives (^{11}C, 20 min; ^{13}N, 11 min; ^{15}O, 2 min), making the radiochemistry and radiopharmacy complex. Even though the cyclotrons for producing these radionuclides have been automated and reduced in size to fit into a room 19 × 22 feet, the capital cost of a PET, hot cell, cyclotron complex is of the order of two million pounds with staff and revenue costs of about a quarter of a million per year. In oncology, the main application has been in the grading of the malignancy of brain tumours (Di Chiro et al 1984) and the demonstration of viable brain tumour recurrences (La France et al 1986).

BONE IMAGING

Introduction

The use of whole body bone imaging in the management of patients with cancer is well documented (McNeil 1984). The osteoblastic response to the presence of a bone metastasis increases the blood flow to and the metabolic activity of the bone at the site of invasion and thus the uptake of bone-seeking radiopharmaceuticals such as ^{99m}Tc technetium-labelled methyldiphosphonate (MDP) is increased at the site. Multiple unevenly distributed focal areas of increased uptake with an emphasis on the axial skeleton are the typical features of bone metastases (Fig. 1.1a and b). Whereas a metastasis may need to cause a more than 30% loss of bone in a vertebra for it to be evident on a plain radiograph, a very small metabolically provocative metastasis may be easily detectable by radionuclide imaging. It is necessary to understand that size is *not* the main criterion for detectability; a radioactive pinhead in the body would be visualized if it were sufficiently radioactive. It would appear as a spot apparently two centimetres across due to the limitations of resolution of the gamma camera. Conversely, a larger tumour causing no reaction in the surrounding bone may not be detected at all. As a generalization, tumours of tissues to which the bone is accustomed, i.e. the cells of bone marrow, cause much less reaction than tumours of tissues external to the skeleton. Hodgkin's and non-Hodgkin's lymphomata and myeloma are therefore best imaged using a conventional radiographic skeletal survey when investigating such patients for bone involvement, whereas for all adenocarcinoma the bone scan is a more sensitive and cost-effective method of detecting bone metastases before treatment. Metabolic activity, occasionally after an initial 'flare', typically decreases with successful treatment and so positive lesions on the bone scan become less evident and may disappear, whereas the skeletal radiograph may become more evident with treatment. As the cells in a previously undetected site of bone metastasis die, they are replaced by fibrous tissue and often calcify, thereby becoming more radiologically evident. In patients with adenocarcinomatous metastases to bone, the radiologically positive, bone scan negative finding usually indicates a patient who has received chemotherapy or radiotherapy previously. Focal loss of normal bone uptake may also be a feature of some bone metastases (Fig. 1.2).

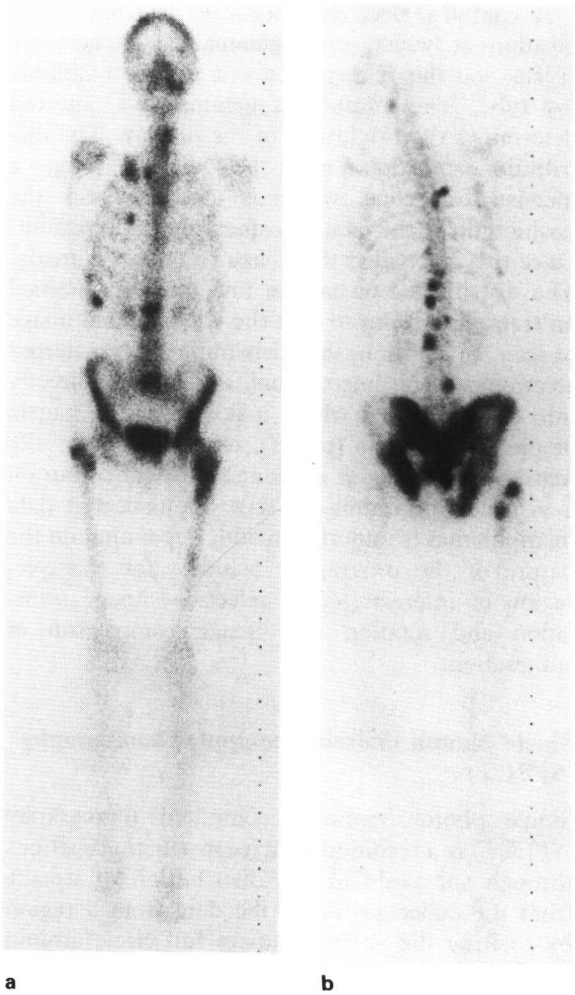

Fig. 1.1 (a) Bone metastases from breast carcinoma. An anterior view of the whole body bone scan shows multiple focal areas of increased uptake in the skull, sternum, ribs, spine, pelvis and proximal femora, a typical distribution. (b) Bone metastases from prostatic carcinoma. A posterior view of the whole body bone scan shows multiple focal areas of increased uptake in the spine, pelvis, proximal right femur and some ribs, a typical distribution.

Bone-imaging is undertaken 2–3 hours after the intravenous injection of 600 MBq (15 mCi) ^{99m}Tc methyldiphosphonate, MDP, or equivalent radiopharmaceutical. During the period before

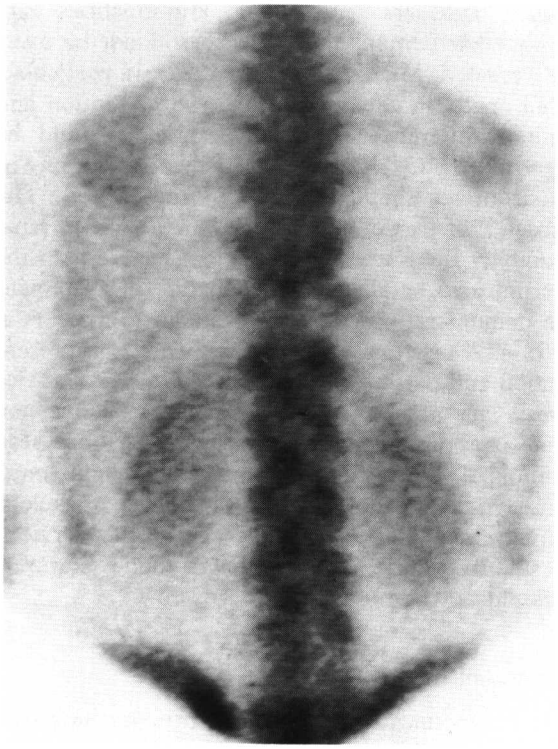

Fig. 1.2 Bone metastases from bronchial carcinoma. A posterior view of the thoraco-lumbar spine showing a focal defect in the eleventh thoracic vertebra. ^{67}Gallium scan was positive at this site, and bone biopsy confirmed metastasis.

imaging the patient should be encouraged to have a high fluid intake since increased renal clearance of the ^{99m}Tc MDP improves bone image contrast. The bladder must be emptied before imaging starts in order to improve the view of the pubic bones and should be emptied again after the imaging has been completed to reduce the small gonadal radiation dose. Some workers advise giving 400 mg potassium perchlorate orally at the time of the injection to reduce thyroid and stomach uptake of any free ^{99m}Tc pertechnetate, but adequate radiopharmaceutical preparation and quality control should obviate the need for this.

The lack of specificity of the bone scan must be remembered. The simple bunion at the base of the big toe will show as a focal area of increased activity, as will the commonly found increased osteophytosis around the fifth lumbar vertebra, and osteoarthritis of the knee, hip and base of the thumb in the elderly. The increased uptake in the region of the right shoulder as compared to the left in a right-handed patient and increased uptake in one or both sternoclavicular joints is often noted. These normal or common findings are not to be confused with metastatic disease. The lack of specificity means that a single focal area of increased uptake in a bone such as a vertebra or rib should not be considered as evidence of a metastasis and a local radiograph will usually help determine the nature of the lesion if it is due to a benign cause. In infants and children the epiphysiseal plates, the sites of bone growth, show high symmetrical uptake.

Bone imaging in specific cancers

Breast cancer

The incidence of a positive bone scan indicating metastasis at the time of presentation in stage I and stage II breast cancer is low, probably under 5%. When radical surgery to the breast was regularly undertaken, it was crucial to avoid such operations on anyone with a possibility of metastatic disease and therefore logical to undertake a bone scan before such surgery was contemplated in all patients with a clinical diagnosis of breast cancer. The less radical surgical approach and the lower incidence of bone metastases than previously thought has altered this rationale. It should be performed if there are symptoms referable to the axial skeleton, if there is locally advanced disease or if a 'base line' is required for follow-up purposes and prognosis. There is general agreement that a bone scan is essential in patients with stage III disease where the incidence of bone metastases is between 15 and 40%, and in stage IV disease (McKillop 1987).

A bone scan will typically be performed before commencing chemotherapy or undertaking local radiotherapy (Kunkler et al 1985). How frequently should the scan be repeated? Either an 'active' approach is pursued with regular bone scanning at six-monthly intervals, or a 'passive' approach is adopted with bone scanning being performed on some clinical indication, usually axial skeleton pain. The incidence of bone metastases is about five times greater in those scanned using a passive approach than an active one (Derimanov 1987) but

the conversion rates of 2% to 10% per year in stage III suggest an active approach is appropriate if early treatment is to be instituted. The average time for appearance of bone metastases in a stage II patient who goes on to develop them is 51 months, and in stage III, 32 months (Derimanov 1987). The typical sites are the vertebral column and pelvis. Due to the limitation of the field of view of the gamma camera the arms and hands are often omitted on a routine whole body bone scan and so a particular request should be made if the upper limbs are thought to be involved.

The assessment of the effects of therapy may be undertaken by serial bone scanning at three-monthly intervals provided that certain precautions in interpretation are taken. In the first three months after instituting effective therapy for bone metastases the 'flare' phenomenon may sometimes be seen where the scan shows more active uptake at the sites of known metastases and additionally small 'new' metastases may appear due to their increased metabolic activity in response to effective treatment. Such a finding should not be interpreted as progression of disease, and many avoid performing the next bone scan until at least four months after starting therapy. Loss of previously demonstrated metastases may be taken as a sign of regression but reduction in activity of known metastases, even after allowing for different photographic settings, is a less reliable indicator of response. Many semiquantitative approaches have been tried but none has been found reliable in practice because of the variability of the biological response to treatment.

Genito-urinary cancer

Prostatic cancer has so frequently metastasized to bone at presentation (5% in stage I, 10% in stage II and 20% in stage III) that a bone scan is indicated on diagnosis, and regular follow-up at three to six-monthly intervals during chemotherapy or hormonal treatment is usual. The so-called 'super scan' is where there is a high bone uptake with a rather uniform appearance which may occur due to wide involvement of the vertebral column, but usually small asymmetries in uptake, particularly in the ribs, point to the diagnosis of prostatic metastases rather than active metabolic bone disease. Bladder and renal abnormalities are frequently demonstrated but should not be over-interpreted (Mlodkowska et al 1985). In particular, 'hot spots' in calyces, minor pelvic retention and minor differences in relative uptake should be ignored, but clear severe pelvic retention or hydroureter should be further investigated. The absence of part of one kidney may be due to renal tumour. Bone scanning is more sensitive than the serum acid or alkaline phosphatase measurement in demonstrating bone involvement (Merrick et al 1985). A negative bone scan in patients at presentation and particularly a negative bone scan at two years are good prognostic signs; the conversion rate is approximately 10% per year. A bone scan should also be performed in patients demonstrated to have renal cancer since the incidence of skeletal involvement is high. However, in uterine, cervical, testicular and ovarian cancers bone scanning should not be routinely undertaken.

Lung cancer

Since the surgical treatment of primary lung cancer is a major procedure, the bone scan is required in the initial evaluation. In this way the 5–20% of patients who will have bone metastases will be demonstrated and surgery can be avoided (McNeil et al 1977). An 'active' follow-up is not usually undertaken and the 'passive' approach is usual. A positive bone scan is associated with a significantly reduced survival (Merrick & Merrick 1986). The peri-osteal reaction of hypertrophic pulmonary osteoarthropathy, in forearms and legs, shows up dramatically on the bone scan and should not be misinterpreted.

Primary bone tumours

Primary osteosarcoma gives the typical 'inverted fir tree' appearance of high uptake at the expanded end of a long bone, and demonstrates the extent of the disease (Fig. 1.3). However, increased activity in the involved and related bones as compared to the contralateral side are evidence of generally increased vascularity 'in sympathy' and should not be taken to indicate extension of the tumour. A bone scan is useful in the assessment of the extent of the tumour and in detecting

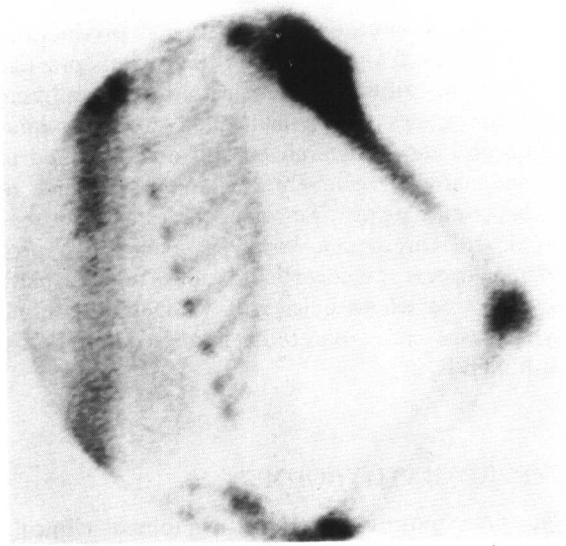

Fig. 1.3 Primary osteosarcoma of the humerus. An anterior view of the left upper chest and humerus showing an area of uniform and intense uptake in the head and proximal shaft extending outside the line of the normal bone, a typical distribution. Note the 'active' elbow joint 'in sympathy'.

synchronous or metastatic tumours. Although there are case reports of chest metastases being seen only on the bone scan and not on the chest X-ray, this is rare. Chondrosarcoma in a long bone typically gives a rather irregular pattern with local soft tissue activity, focal areas of increased uptake and focal defects (McLean & Murray 1984). The bone scan cannot be used to decide whether a lesion is benign or malignant, but high and/or irregularly increased uptake and increased vascularity are features more typical of malignant disease.

Paget's disease may provide difficulties in the presence of multiple metastases, but the characteristic uniformity of the hemipelvis, or long bone involvement and the 'trilobed' appearance of the vertebra with Paget's disease involving the spine as well (unusual for metastases), should help in the differentiation.

Bone imaging in other tumours

Neuroblastoma, primary and soft tissue metastases will often take up the bone imaging agent as well as bone metastases. Local involvement of bone may be demonstrable in the context of malignant tumours of the head and neck, particularly those of the eye, the maxillary sinus and the parotid. SPECT may be very useful in this context. Focally increased uptake local to the site is characteristic of meningioma and may demonstrate more widespread involvement than the skull X-ray. No help is given, however, in the evaluation of pituitary adenoma. In parenthesis it should be noted that many vascular or calcifying cerebral tumours and recent cerebral infarcts take up the bone imaging agents. Bone scanning should be performed in thyroid cancer in conjunction with ^{131}I surveys.

In conclusion, bone imaging is an essential service for the management of many cancer patients, having a higher sensitivity but lower specificity in the detection of metastases, and being cheaper and giving a lower radiation dose than conventional skeletal radiology.

ADRENAL CORTICAL IMAGING

The adrenal cortex is functionally at least two organs: the outer cortex producing the minerocorticoid aldosterone and the inner cortex producing the glucocorticoid cortisol.

Primary hyperaldosteronism is associated with Conn's syndrome of hypertension and hypokalaemia and may be due to hyperplasia, which may be micronodular, macronodular or adenoma. Adenocarcinoma is very rare. The prime reason for imaging is to lateralize the adenoma once the clinical, biochemical and endocrinological diagnosis has been confirmed. Using ^{75}Se selenocholesterol, the findings in a unilateral adenoma are an increased uptake than normal in the gland with adenoma and a normal uptake in the contralateral gland (normal range 0.07–0.3% of the injected dose). In bilateral macronodular hyperplasia, uptake in both glands is increased above normal but some overlap with the normal range may occur (Shapiro et al 1981).

A quantitative approach is essential since adrenal depth varies from person to person and on each side so a planar image may cause a false interpretation whereby a gland closer to the skin surface may be mistaken for a gland that has

increased uptake. Adrenal depth is therefore determined approximately from true lateral images of a prior ^{99m}Tc DTPA renal study (Britton et al 1979a), then 10 MBq (250 μCi) of ^{75}Se selenocholesterol are injected and imaging is carried out 7 and 14 days later. The correction factor for attenuation at different depths determined from a phantom study is used to obtain the true count rate from the adrenal. The adrenal count rate is also corrected for tissue background activity using a circumferential background region of interest and the uptake is expressed as a percentage of the activity administered (Hawkins et al 1980).

When ^{131}I norcholesterol is used some authorities recommend dexamethasone suppression, so that only aldosteronomas are seen (Seabold et al 1976). However, a normal result is no image at all and early imaging at 3–4 days is necessary since 'dexamethasone escape' occurs at about 5 days. At these early stages, tissue background, liver, biliary and gut uptake are high, making for difficulties in interpretation. The combination of X-ray CT and ^{75}Se selenocholesterol imaging should make the diagnosis of a functioning aldosteronoma in the majority of cases, thereby avoiding the need for the potentially difficult and traumatic technique of adrenal venous sampling.

Many hypertensive patients are now having X-ray CT of the adrenals and an enlargement may be shown. It is essential to use a functional technique to demonstrate that such masses are functionally significant through adrenal radionuclide imaging (radiolabelled cholesterol and radio-iodine-labelled *meta*-iodobenzyl guanidine (MIBG) before invasive investigations or surgery are contemplated.

Secondary hyperaldosteronism and Barrter's syndrome usually show bilaterally increased adrenocortical uptake.

In confirmed Cushing's syndrome due to adenoma, the production of cortisol suppresses pituitary adrenocorticotrophic hormone, ACTH, so that the normal adrenal is *not* visualized. The adenoma has high uptake and is easily lateralized. In bilateral hyperplasia one or both adrenals have uptake which is above the normal range and usually asymmetrical. The visualization of both adrenals indicates hyperplasia even if uptake on one side is not increased. The cause of hyperplasia, a pituitary adenoma or ectopic ACTH production, cannot be determined. After the previous practice of bilateral subtotal adrenalectomy, the adrenal remnant grows under continued ACTH stimulation and can be lateralized and demonstrated to be the cause of recurrent Cushing's syndrome in such patients using ^{75}Se selenocholesterol. Adrenal cortical carcinoma, however, even when producing excess glucocorticoids does not usually take up ^{75}Se selenocholesterol. Congenital adrenal hyperplasia causes markedly increased uptake by both glands.

HYPERPARATHYROIDISM

The first requirement is a combined clinical, biochemical and endocrinological diagnosis of hyperparathyroidism. The difficulties in demonstrating adenoma or hyperplasia before surgery are well known. Thallium ^{201}Tl is the latest non-specific radiopharmaceutical to be used for localization of adenoma based on its increased uptake at sites of increased flow and metabolism. Since it is also taken up by thyroid tissue and particularly by thyroid adenoma, care must be exercized in interpreting the results of imaging and of any subtraction technique. Normal parathyroids are not seen, hyperplastic glands are identified in about 50% and adenoma in about 85% of cases. The smallest adenomas detectable are generally over 400 mg, and benign and malignant tumours are not distinguishable (Young et al 1983, Gimlette & Taylor 1985, Gimlette et al 1986, Blake et al 1986).

The subtraction technique used at St Bartholomew's Hospital is given in Appendix 1 (page 456).

THE PANCREAS

The pancreas is well visualized using ^{75}Se selenomethionine (SM) when a composite liver pancreas scan has a conventional liver colloid scan subtracted from it (Kaplan et al 1966).

The problem of tumour identification is that one

is seeking a defect of uptake in an organ whose normal variation in position and thickness makes interpretation difficult (Cotton et al 1978). If a pancreatic tumour is found using X-ray CT or ultrasound, the SM scan will show the extent of normally functioning tissue: the more normal the image, the more likely the tumour operability. After a Whipples operation, an SM scan will show if the pancreatic remnant is functioning.

THE RETICULO-ENDOTHELIAL SYSTEM

Liver, spleen and bone marrow

Imaging of deposits in the liver, spleen and bone marrow is undertaken using the phagocyte properties of the cells of the reticulo-endothelial system in these organs. For the conventional liver colloid scan, ^{99m}Tc-labelled tin colloid with a particle size of 2–4 microns is used which is appropriate for the Kupffer cells. At least four views are taken: anterior with a costal margin flexible lead strip marker; anterior, right lateral and posterior views with additional views; right posterior oblique, standing and supine views; left lateral and left posterior oblique for the spleen where appropriate. SPECT increases the accuracy of detection of small deep deposits (Khan et al 1981, Brendal et al 1984). The presence of a metastasis is demonstrated by a focal defect or defects in one or more views at sites away from regions of high normal variation: the gall bladder fossa, the porta hepatis and the exit of the hepatic veins superiorly (Lunia et al 1975). Well circumscribed defects are typical of gastro-intestinal metastases, including carcinoid, whereas those from breast or lung tend to be smaller with less distinct margins (Sears et al 1975). Focal defects in the liver scan are not specific as to aetiology, for an area of decreased or absent Kupffer cell function has many causes including cyst, abscess, congenital abnormalities and areas of liver necrosis or fibrous replacement in hepatitis or cirrhosis, and its routine use in the evaluation of possible metastases has given way to ultrasound which is more specific. However, ultrasound may miss liver metastases in some circumstances particularly when air in the bowel or lung prevents an adequate view, or if the lesion is isoechoic. In colorectal and stomach cancer a combined use of ultrasound and the liver colloid scan has been recommended to maximize tumour detection (Taylor et al 1977, Clarke et al 1986).

The liver colloid scan has been modified to attempt the early detection of gastro-intestinal metastases in the following way. Liver metastases derive their blood supply almost exclusively from the hepatic artery and it has been demonstrated by Leveson et al (1983) that the hepatic to total liver blood flow ratio increases with such metastases before focal defects are detectable. Since an intravenous bolus arrives about five seconds before that travelling to and returning from the gut and spleen by the portal vein, the hepatic artery contribution can be obtained by careful analysis of the early part of the activity–time curve from a region of interest over the liver. The choice of the region of interest is performed retrospectively after viewing all the dynamic images so that areas of overlap with lung, kidney and spleen are excluded. A typical arterial curve is obtained from a region of interest over the left kidney where it is free of overlap from the spleen and a typical portal venous curve is obtained from the spleen. These curves are used to help define the time limits of the arterial and portal venous phases of the hepatic activity–time curve, in techniques developed by different authors (Fleming et al 1981, Wraight et al 1982). The normal hepatic artery to total liver blood flow ratio as a percentage is less than 30%. Definite metastases are present when the percentage exceeds 45% with a borderline range below this. 50% of patients with colorectal cancer with a value over 45% with normal liver colloid scan and liver ultrasound at that time developed overt liver metastases within six months of follow-up (Gough et al 1985).

Hepatoma shows a vascular blush during dynamic scintigraphy followed by a defect in the colloid scan. This may be contrasted with the increased uptake of ^{67}Ga gallium citrate scan in hepatoma, but many liver metastases also take up gallium. Neither the liver scan nor the spleen scan are reliable in determining involvement of these organs in Hodgkin's disease (Lipton et al 1972, Silverman et al 1972, Ell et al 1975). Spleen

scanning with denatured labelled red cells is only required when looking for splenunculi.

^{67}Ga gallium

^{67}Ga gallium citrate scanning has a long track record of use in lymphoma (Hoffer 1978), but has never been sufficiently specific nor reliable to come into routine use. Whole body imaging at the time of staging of Hodgkin's disease will show focally increased uptake only in a percentage of the involved nodes present. The demonstration of uptake in previously normal nodes on follow-up indicates progression. Use of the whole body longitudinal section scanner or SPECT with coronal sections is advantageous for the reliable demonstration of para-aortic nodes, particularly under the left lobe of the liver which normally takes up gallium (Turner et al 1978). This technique also aids the interpretation of abdominal images since gallium is excreted by the large bowel. ^{67}Ga with ultrasound may have a rôle prior to staging laparotomy (White et al 1984). ^{111}In bleomycin which is not bowel-excreted had a brief vogue as an alternative agent. In the chest, focal uptake of ^{67}Ga in the mediastinum may help to elucidate the nature of a mediastinal mass, for example in distinguishing recurrence from post-therapy fibrosis, but it cannot differentiate between a soft tissue metastasis, an involved lymph node or a site of infection. A negative gallium scan does not exclude active disease. Use of high dose ^{67}Ga is advocated by some to overcome the inherent disadvantages of ^{67}Ga as an imaging agent (Anderson et al 1983). ^{67}Ga is no longer routinely used in oncology and is only applicable in a highly selected lymphoma population. Imaging of lymphoma by radio-immunoscintigraphy using lymphoma specific monoclonal antibodies is under development (see subsequent section).

Bone marrow imaging is being used more frequently due to the introduction of ^{99m}Tc-labelled nanocolloids. This provides a method of demonstrating bone scan negative metastases as focal defects in the marrow distribution in the skull, vertebral column, ribs and pelvis. In this way previously undetected metastases from carcinoma of the breast and lung are being revealed. The technique is not specific since fat infiltration and non-malignant conditions will cause defects. Marrow imaging also has a rôle in patients with therapy-induced bone marrow suppression to determine the presence of islets of functioning marrow from which recovery can occur.

Lymphoscintigraphy

Conventional lymphoscintigraphy relies on the uptake of an appropriate radiolabelled colloid injected subcutaneously into a region of skin drained by the lymph node group under evaluation. Visual evidence of uptake by the nodes is taken to indicate their normality and filling defects or lack of uptake to indicate involvement. Although it may be appreciated that in principle it is neither a very sensitive nor a very specific technique because lack of visualization may be due to absence of a normal node, previous damage to a node or non-malignant as well as malignant infiltration, nevertheless it has benefit in certain defined contexts where it is more accurate than clinical examination or biopsy studies. Most work has been done in visualizing lymph node involvement in the internal mammary chain and axillary group in patients with breast cancer, where it has been of value in staging the disease (Ege 1980, Osborne et al 1983, Ege & Clark 1985, Mazzeo et al 1986). The detection of metastatic involvement of the axillary nodes in breast cancer is of great prognostic importance (Fisher et al 1983). Clinical examination of the axillary nodes is prone to error in the assessment of the presence or absence of metastases: 38% of nodes with metastases were clinically negative and 37% of nodes without metastases were called clinically positive in one study (Cutler et al 1970). In another study axillary node biopsy showed that due to sampling error 42% of nodes with metastases were biopsy negative, and that only 24% of nodes with metastases were correctly identified (Davies et al 1980). The technique is of some benefit in evaluating the internal iliac chain after peri-anal injection of colloid in patients with seminoma (Kaplan 1983) but has not found favour in the routine evaluation of other pelvic malignant disease, or melanoma.