termination of one nerve, the optic, can be seen within the eye. Some of the nerve trunks in the limbs can be felt; a few, as the ulnar, in the normal state; others only when enlarged by disease." Another 50 years were to pass after Moniz's discovery before the dark continent was further illuminated by Godfrey Hounsfield's non-invasive procedure, computed tomography.

Charcot was the third personality depicted—and further enhanced by an excellent paper from Dr Capildeo. Charcot was the real giant of neurology of the nineteenth century, who correlated clinical signs with necropsy appearances, gaining his enormous experience at the Salpêtrière with its more than 5000 inmates. Doctors from all over the world flocked to his clinical demonstrations, which set the pattern for posterity.

Last came Ramon y Cajal, perhaps the most dramatic life study of the four. Born of humble stock in 1852 in a small,

almost inaccessible village in the barren mountains of Aragon (beautifully filmed in colour) he qualified in medicine at the local University of Saragossa, having in adolescence been a cobbler's assistant for a year. He was a talented painter, a superb dissector, and a self-taught microscopist. He was appointed to the chair of anatomy at Valencia, and wrote a thesis on cholera after an epidemic there in the 1880s. Then he moved to Madrid, where he became world famous for his work on the microscopical anatomy of the cortex and retina. Like Moniz he won the Nobel prize.

Some 50 speakers from many countries took part, and the proceedings are to be published as a book. It is very appropriate that the meeting was so international, as no one has travelled the world more in furthering neurology internationally than Dr Critchley. It was a fitting tribute to a man whose name is known wherever neurology is practised.

Regular Review

The role of skeletal scanning in clinical oncology

JAMES H MCKILLOP, I ROSS McDOUGALL

As long ago as 1942 Treadwell and colleagues¹ used an external probe and radiotracers to study the metabolism of bone metastases. Then in 1961 the first scintigraphic images of bone metastases were reported by Fleming and co-workers² using strontium-85 and a rectilinear scanner. Only since the early 1970s, however, which saw the introduction of the technetium-99m labelled phosphate agents,^{3,4} has radioisotope bone scanning become widely used in clinical practice. At present the most frequent indication for bone scanning is the study of patients with malignant disease.

Technically reliable bone scanning is possible in any hospital with a nuclear medicine department. The optimum imaging device is a gammacamera with a wide field of view, but acceptable results may be obtained with other instruments. Whole-body scans are simpler to evaluate than multiple spot views and are aesthetically more pleasing, but they may not necessarily detect more lesions. The radiopharmaceuticals can be prepared simply by the addition of sterile technetium-99m to commercial kits. Of the compounds used for bone imaging, the diphosphonates give the best clinical results, in that they may show lesions that are not seen with pyrophosphates. Methylene diphosphonate (MDP) is pharmacokinetically superior to hydroxyethylidene diphosphonate (HEDP), but these differences do not seem clinically important.⁶ The technique requires only a single intravenous injection and then the imaging procedure some hours later and may be performed in outpatients or critically ill patients; there are no known systemic side effects. The total body radiation is about 0.1 rad.

Bone scanning in malignant disease—Bone disease is apparent on conventional x-ray films only when there is considerable structural alteration, with loss of some half of the mineral

content.⁷ Patients may have normal skeletal radiographs despite the presence of histologically proved metastatic disease.^{8,9} The precise mechanism of the uptake of the bone-scanning agents is uncertain, but it appears to be related to bone blood flow and to some aspect of bone metabolism, possibly osteoblastic activity.¹⁰⁻¹³ Because the bone scan reflects bone function rather than bone structure it will become abnormal in many diseases before there are radiographic changes.¹⁴ In a few patients the result of the scan may be negative when the patient has evidence of bone marrow metastases from biopsies or aspirates¹⁵; but in general it seems to be more sensitive than conventional biochemical investigations, such as serum alkaline phosphatase, for detecting bone metastases.¹⁶

Unfortunately bone scanning is not only more sensitive than x-ray studies in detecting metastases; it is also less specific, and many bone disorders, both benign and malignant, may alter bone function to produce abnormalities on scanning. Poor specificity is particularly a problem when a solitary abnormality is found on scanning in a patient with a primary cancer who is thought to be free of metastases on all other grounds.¹⁷ Multiple abnormalities which mimic metastases may also arise from benign disease,¹⁸⁻²⁰ though the scan pattern may suggest a non-malignant aetiology. Bone scan abnormalities must always be correlated with the history and with other studies (figure). Radiographic evidence of a benign lesion at the site of an abnormal appearance on the bone scan makes malignant disease highly unlikely. A normal bone radiograph associated with an abnormal scan is highly suggestive of malignant disease, especially if there is no history to suggest local trauma or osteitis due to infection or secondary to radiation. The probability of malignant disease is further

Scheme for clarification of abnormal bone scan in the patient with malignant disease

increased if there is local pain.²¹ Bone biopsy may be valuable in confirming metastases in these circumstances.²¹

The most common abnormality on bone scanning consists of areas of increased uptake ("hot spots"), but areas of reduced uptake of the tracer have also been reported to be due to metastatic disease,²²⁻²⁴ primary neoplasms of bone,²⁴ and a variety of benign bone disorders.²⁵ Apparent cold areas on the bone scan may also result from overlying objects—for example, a breast prosthesis—when lesions may be overlooked.²⁶

The central skeleton is the most common site of metastatic disease, accounting for some 80% of the lesions. Solitary metastases may, however, occur in the skull or the long bones of the limbs,^{27, 28} and a total body bone scan is essential when screening for metastases. Uptake of the bone scan agent in soft tissues should also be evaluated, as this may occur in a variety of malignant disorders,^{29, 30} including cerebral tumours,³¹ hepatic metastases,^{32, 33} and primary breast cancer.³⁴ Uptake of bone-scanning agents has also been reported in normal breast,³⁵ in cerebral infarction,³⁶ and in hepatic amyloid³⁷ and hepatic necrosis.³²

Some 50-60% of the dose of bone-scanning agents is excreted through the kidneys by the time of imaging. The presence of radioactive urine in the bladder may obscure details of the bony pelvis, and patients should empty their bladder before imaging. In some cases 24 hours may need to elapse before adequate pelvic images are obtained. Un-suspected abnormalities in the renal tract can be detected from the bone scan,^{38, 39} including renal carcinoma, which usually gives rise to a filling cold defect on the renal image but may also show increased tracer uptake.⁴⁰ Evaluation of the renal tract is especially important in patients with tumours which may cause urinary tract obstruction, such as carcinoma of the uterine cervix.⁴¹ The combination of the absence of the renal image and diffusely intense skeletal uptake of the tracer is usually due to metabolic bone disease, but may result occasionally from widespread metastases.⁴²

Indications for bone scanning in patients with cancer—There are six main indications for bone scanning in patients with malignant disease.³⁰

Firstly, staging of disease before treatment is valuable when the patient has no symptoms of metastatic disease but has a primary tumour which frequently produces bone metastases. The bone scan rather than skeletal radiography is then the investigation of choice. Secondly, the bone scan may be used to document the development of clinically occult metastases. Thirdly, it is valuable in the investigation of radiologically "difficult" areas, such as the sternum, scapula, or faciomaxillary region. Fourthly, bone scanning is the investigation of choice to confirm clinical suspicion of bone metastases. Fifthly, the bone scan may be valuable in identifying the site of metastases which are producing referred pain or in showing more extensive metastases than are to be seen on the radiographs. This is of value when looking for biopsy sites or when

planning radiation portals. Finally, bone scans are valuable in monitoring the effects of treatment. In a patient with known bone metastases the scan may be used as an objective assessment of the response to systemic treatment—though a diffuse increase in skeletal uptake of tracer may be a normal response to chemotherapy.⁴³

Cancer of the breast—Bone scanning is widely used in patients with breast cancer, but some of the indications remain controversial. Patients with abnormal scans at presentation and those in whom the bone scan result becomes positive during follow-up have a very poor prognosis, and most die from metastatic breast cancer.⁴⁴

One of the areas of contention is the incidence of bone metastases detected on scan in patients with early (stage I or II) disease. Most reports quote an incidence of 5-15%, but the range from British centres has been as low as 2% and as high as 20%.⁴⁵ Those who find a low positive rate claim that routine bone scanning is not cost-effective.⁴⁶ Patients with positive scans which are due to metastases will not be cured by local treatment, so that if as many as 10% of patients with early breast cancer have bone metastases which can be detected only on scan, the investigation is justified. About 2% of scans, however, will give a false-positive result (due to benign disease), so in patients with stages I and II cancer metastases should be proved to be present before systemic treatment is given. Follow-up scans at intervals of six months will show new metastases in about 20% of patients, but if scan results are persistently negative up to two years the prognosis is excellent⁴⁷ and sequential scans after that time have a low pick-up rate. Given a cost of \$200 per scan (the cost in Britain would be lower but has to cover instrumentation, radio-pharmaceutical, technologist, and doctor) the cost of finding a new lesion over the next three years, if all normal patients were scanned twice yearly, would be about \$30 000.

Stage III breast cancer is more frequently associated with skeletal metastases (about 30%) and scans are clearly indicated, since a positive result will almost certainly dictate systemic treatment and the findings on scanning may then be used as an objective method of judging whether the treatment is effective.

Lung cancer—The presence of distant metastases in patients with lung cancer is a clear indication that surgical cure is impossible. Such patients have a dismal prognosis: in one recent study 40 out of 46 patients died within six months and a further four in the next six months.⁴⁸ A major surgical procedure, with a substantial mortality, should not be inflicted on patients with a short survival, and bone scanning should be an integral part of the evaluation of patients who appear to be candidates for surgery. Kelly *et al*⁴⁹ found occult bone metastases in eight of 59 asymptomatic patients. Forty out of a series of 88 patients had abnormal bone scintigrams, but most of these had other evidence of skeletal lesions. Defining the presence of metastases reduces the immediate surgical morbidity and mortality,⁵⁰ but it may not provide any additional benefit until chemotherapy becomes more effective.

Cancer of the prostate—Again, bone scanning will detect metastases when other investigations are normal. Schaffer and Pendergrass⁵¹ showed that the lesion in one-quarter of 219 patients who had abnormal scans proved to be metastases from cancer of the prostate, though there was neither clinical evidence of bone disease nor raised activities of acid or alkaline phosphatase. Similar results were reported by Shafer and Reinke.⁵² Though only about 10% of patients with stage I or II

disease have abnormal bone scans due to metastases, identification of this small group is important, since treatment of early cancer of the prostate differs considerably from treatment of widespread disease.

Cancer of the cervix—Carcinoma of the cervix spreads to bone infrequently (about 4% of patients). In one study 24 out of 100 patients had abnormal bone scans but only four were due to metastases; none of 79 patients with stage 0, I, or II disease had an abnormal scan.⁴² Skeletal scintigraphy is of little value in early cervical cancer but has a place in patients with invasive disease or bone pain. Attention should be paid to the appearance of the urinary tract on the scan, since otherwise unsuspected obstruction may be diagnosed.

Miscellaneous cancers—Some patients with other cancers will have bone lesions which are detected only by scintigraphy. For example, in 59 patients with urogenital cancer, seven had lesions on the scan but normal x-ray appearances.⁵³ Similar findings occur in patients with pancreatic and bowel cancer.⁵⁴ A recent study in patients with advanced melanoma showed that 30% had positive bone scans but frequently they also had bone pain.⁵⁵ Since, however, only half of those patients with bone pain had bone metastases, the result of the scan is important in making clinical decisions: bone scans may also be superior to radiological investigations in detecting metastases from neuroblastoma,⁵⁶ and in this group of patients they will often also show abnormalities of the urinary tract. The bone scan is less effective than skeletal radiology for detecting bone lesions in multiple myeloma.⁵⁷ The choice between the bone scan or x-ray studies is still uncertain for showing skeletal spread of thyroid cancer,⁵⁸ while in lymphoma both techniques give some false-negative results.⁵⁹

Primary bone cancer—Bone scanning offers no real advantage over skeletal radiographs in the study of the primary tumour in osteogenic sarcoma. In particular, "skip" metastases, which are common in this tumour,⁶⁰ were not shown in a careful study using ^{99m}Tc-polyphosphate.⁶¹ The

result of the bone scan may even be misleading, since the limb bearing the tumour often shows diffusely increased uptake owing to hyperaemia,⁶² and this may result in an overestimation of the extent of the primary lesion.⁶¹ All children with osteosarcoma, however, should have a bone scan at presentation to detect distant bone metastases.⁵⁰

Metastatic osteogenic sarcoma in non-bony sites such as lymph nodes or lung may show uptake of phosphate compounds,⁶³ but lung metastases detected in this way are usually visible in the chest x-ray film. There are no published studies to show that information obtained from bone scanning in osteogenic sarcoma allows the outcome to be influenced favourably.

Skeletal scintigraphy appears to be clinically indicated in Ewing's sarcoma. A recent report⁶⁴ described bone metastases in three out of 28 patients (11%) at the time of presentation, and in 45% of the remainder after a follow-up of three to 37 months.

Because of increased sensitivity, radionuclide imaging rather than radiology is usually the investigation of first choice in patients who have clinical evidence of possible bone metastases, since in most cancers a normal scan result virtually excludes the presence of metastases. The non-specific nature of the scan abnormalities makes it essential to correlate them with clinical information and other studies. In cancers which have a high predilection for spreading to bone (notably, cancer of the breast, lung, and prostate, and osteogenic sarcoma) a good case may be made for scanning asymptomatic patients at presentation, as this may identify individuals in whom extensive surgery is contraindicated. Moreover, though this remains to be proved, if the result is positive starting systemic treatment earlier may improve prognosis.

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