sensations becoming the cue and precipitant for further anxiety leading to hyperventilation and recurrence of panic attacks. Patients with panic disorders who also have respiratory or cardiac disease (whose symptoms might be the cue for an initial panic attack) and who consequently experience abnormal somatic sensations may repeatedly respond to them with panic. This is also consistent with the effects of administration of beta adrenergic agonists and beta adrenergic blockers. Because hyperventilation must be mediated by central processes clearly these processes can be activated either "reactively," as a response to an awareness of threat, or "endogenously," as a result of some pathological process. Either way these processes might be influenced pharmacologically, thus accounting for the apparent effect of antidepressants.

Plainly hyperventilation deserves further consideration and it should be included in the differential diagnosis of all cases of panic disorder whether or not there appear to be other sources of frightening somatic sensations.

G A HIBBERT

Research Psychiatrist and Honorary Senior Registrar,
University Department of Psychiatry,
Oxford OX3 7JX

- ¹ Marks IM, Lader M. Anxiety states (anxiety neurosis): a review. *J Nerv Ment Dis* 1973;**156**:3-18.
- ² American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 3rd ed. Washington, DC: American Psychiatric Association, 1980.
- ³ Tyrer P, Candy J, Kelly D. Phenelzine in phobic anxiety: a controlled trial. *Psychol Med* 1973;**3**:1204.
- ⁴ Mountjoy CQ, Roth M, Garside RF, Leitch IM. A clinical trial of phenelzine in anxiety depressive and phobic neuroses. *Br J Psychiatry* 1977;**131**:486-92.
- ⁵ Zitrin CM, Klein DF, Woerner MG. Behavior therapy, supportive psychotherapy, imipramine, and phobias. *Arch Gen Psychiatry* 1978;**35**:307-16.
- ⁶ Sheehan DV, Ballenger J, Jacobsen G. Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. *Arch Gen Psychiatry* 1980;**37**:51-9.

- ⁷ Ko GN, Elsworth JD, Roth RH, Rifkin BG, Leigh H, Redmond DE. Panic-induced elevation of plasma MHPG levels in phobic-anxious patients: effects of clonidine and imipramine. *Arch Gen Psychiatry* 1983;**40**:425-30.
- ⁸ Marks IM, Gray S, Cohen D, et al. Imipramine and brief therapist-aided exposure in agoraphobics having self-exposure homework. *Arch Gen Psychiatry* 1983;**40**:153-62.
- ⁹ Easton JD, Sherman DG. Somatic anxiety attacks and propranolol. *Arch Neurol* 1976;**33**:689-91.
- ¹⁰ Frohlich ED, Tarazi RC, Dustan HP. Hyperdynamic β -adrenergic circulatory state. Increased β -receptor responsiveness. *Arch Intern Med* 1969;**123**:1-7.
- ¹¹ Stampfer FM. Panic disorder: description, conceptualisation and implications for treatment. *Clinical Psychology Review* 1982;**2**:469-86.
- ¹² Snaith P. Panic disorder. *Br Med J* 1983;**286**:1376-7.
- ¹³ Lewis BI. Chronic hyperventilation syndrome. *JAMA* 1954;**155**:1204-8.
- ¹⁴ Clark DM. Therapeutic aspects of increasing pCO₂ by behavioural means. University of London, 1979. Dissertation.
- ¹⁵ Mora JD, Grant L, Kenyon P, Patel MK, Jenner FA. Respiratory ventilation and carbon dioxide levels in syndromes of depression. *Br J Psychiatry* 1976;**129**:457-64.
- ¹⁶ Dudley DL, Martin CJ, Holmes TH. Psychophysiological studies of pulmonary ventilation. *Psychosom Med* 1964;**26**:645-60.
- ¹⁷ Lum LC. Hyperventilation and anxiety states. *J R Soc Med* 1981;**74**:1-4.
- ¹⁸ McCaul KD, Solomon S, Holmes DS. Effects of paced respiration and expectations on physiological and psychological responses to threat. *J Pers Soc Psychol* 1979;**37**:564-71.
- ¹⁹ Clark DM, Salkovskis PM, Chalkley J, Hemsley D. Role of hyperventilation in panic attacks. [Abstract.] *Bulletin of the British Psychological Society* 1983;**36**, May:50.
- ²⁰ Salkovskis PM, Clark DM, Chalkley J. The use of respiratory control in the behavioural treatment of panic attacks. [Abstract.] *Biological Psychiatry* 1983;**16**:293.
- ²¹ Lowenstein H. A clinical investigation of phobias. *Br J Psychiatry* 1968;**114**:1196.
- ²² Goldstein AJ, Chambless DL. A reanalysis of agoraphobia. *Behaviour Therapy* 1978;**9**:47-59.
- ²³ Cohen M, White P. Life situations, emotions, and neurocirculatory asthenia (anxiety neurosis, neurasthenia, effect syndrome). *Association for Research in Nervous Disease Processes* 1950;**29**:832-69.
- ²⁴ Winokur G, Holemon E. Chronic anxiety neurosis: clinical and sexual aspects. *Acta Psychiatr Scand* 1963;**39**:384-412.
- ²⁵ Pfeffer JM. The aetiology of the hyperventilation syndrome, a review of the literature. *Psychother Psychosom* 1978;**30**:47-55.
- ²⁶ Breggin PR. The psychophysiology of anxiety with a review of the literature concerning adrenaline. *J Nerv Ment Dis* 1964;**139**:558-68.

Regular Review

Bone scintigraphy in benign bone disease

JAMES H MCKILLOP, IGNAC FOGELMAN

The introduction of phosphates labelled with technetium-99m in the early 1970s led to wide use of isotope bone scanning in the evaluation of patients with malignant disease.¹ The principle of the bone scan is that the tracer that is injected intravenously is incorporated into the bone crystal matrix; the main determinants of regional deposition are thought to be osteoblastic activity and blood flow.² So bone scans reflect bone function rather than structure, and areas of abnormal function have an increased uptake of the tracer—"hot spots." Disease often changes bone function before structure so that the bone scan is usually more sensitive than radiographic studies of the skeleton. Many disorders produce changes in osteoblastic activity, however, so that though an abnormal pattern may suggest a particular diagnosis, changes in a bone scan are non-specific and often have to be correlated with the

results of other investigations, including x ray films of abnormal areas or bone biopsy.

In recent years there has been growing awareness that bone scanning may be valuable in non-malignant bone diseases. This review considers the application of the technique in trauma, osteomyelitis, metabolic bone disease, aseptic necrosis, Paget's disease, and arthritis.

Trauma

A bone scan is unnecessary in most cases of skeletal trauma, since x ray films usually provide adequate information. A scan may be of value in radiologically difficult areas such as the wrist, hips, ribs, and sternum; a fracture is highly unlikely

if the scan is persistently normal. An abnormal scan is not, however, completely diagnostic of fracture as it may occur because of subperiosteal haematoma. Scintigraphic abnormalities will be seen in over 95% of patients studied three days after the development of the fracture.³ Soft tissue trauma and hyperaemia may be difficult to differentiate from fracture in early scintiscans, but abnormalities seen seven to 10 days after trauma make a bony lesion likely.⁴ The bone scan may remain abnormal for some time after a fracture, but lesions persisting more than 18 months are often associated with incomplete union or healing with malalignment. Despite much investigation, no generally accepted scan technique has emerged to allow separation of normal and complicated fracture healing.^{3,5} Recent studies in animals suggest that scans may be valuable in assessing viability of bone grafts, but this remains to be proved in clinical work.⁶

The bone scan is of particular value in assessing stress fractures, where the bone scan is often abnormal two to three weeks before changes are seen in the film.⁷ This may be very helpful in advising athletes on whether a painful limb should be rested. The bone scan has also been used to evaluate suspected cases of the "battered baby" syndrome.^{8,9}

Osteomyelitis

In acute osteomyelitis radiographic abnormalities may not be seen for 10 days to several weeks after the onset of symptoms. Handmaker and Leonards showed that in many cases the bone scan is abnormal within 24 to 48 hours of the onset of symptoms,¹⁰ and it is recommended that a scan should be obtained in all patients with suspected osteomyelitis and normal bone *x* ray appearances.¹¹ The characteristic scan abnormality in osteomyelitis is a hot spot, but early in the disease the only finding may be an area of decreased uptake of tracer.¹⁰ This is thought to reflect thrombosis of small blood vessels caused by the acute inflammatory process. The scan abnormalities may be subtle in osteomyelitis,¹² a particular problem being encountered in neonates, in whom the bone scan is not reliable for diagnosing acute disease.¹³ A further problem is in differentiating acute osteomyelitis from overlying cellulitis. A comparison of standard delayed images with immediate views after injection reflecting vascular flow may help in this dilemma.¹⁴

Chronic osteomyelitis causes bone scan abnormalities, so that the technique cannot be used to diagnose acute exacerbations. Locally increased uptake of either gallium-67 citrate¹⁵ or indium-111 labelled leucocytes¹⁶ may be a useful indicator of an acute exacerbation.

Bone scans have also been used in patients with painful prosthetic joints to differentiate loosening from periprosthetic infection.¹⁷ Others have found the technique to be less reliable, however.¹⁸ Gallium-67 imaging may help, as very intense uptake of tracer or discrepancy between its uptake and that of a standard bone scan agent usually indicates infection.^{18,19} Labelled white cell imaging is less helpful in these patients.²⁰

Aseptic necrosis and infarction

Bone scanning may be used to evaluate suspected avascular necrosis of bone. In the early stage of the disease the affected area shows decreased uptake of tracer followed later by increased uptake.²¹ Children with recent onset Legg-Perthes' disease show a characteristic "cold notch" on the superior and lateral aspects of the femoral head, allowing differentiation

from infection or tumour.²² The bone scan may also be used for early detection of steroid induced osteonecrosis after renal transplantation, with scan changes usually preceding *x* ray abnormalities.²³ Bone scan abnormalities are also seen in sickle cell disease²⁴ and caisson disease.²⁵

Paget's disease

The bone scan appearances in Paget's disease are usually characteristic, with intense uptake of tracer throughout the affected bones.²⁶ It is important to recognise Paget's disease, as it will often be an incidental finding in scans performed for other reasons, such as in the search for tumour or infection. While neither the bone scan nor radiography will detect all sites of pagetoid disease, clearly the bone scan is the more sensitive technique.²⁶⁻²⁸ Furthermore, those sites that are occasionally missed in the bone scan are metabolically inactive.^{27,28} Indications for performing a bone scan in Paget's disease include the investigation of a patient with raised serum alkaline phosphatase activity and any patient in whom Paget's disease is suspected clinically. Even when the diagnosis is established a bone scan is of value to document the extent and activity of disease and serves as a baseline for future reference.

Metabolic bone disease

A bone scan image provides a functional display of skeletal metabolic activity, and we have suggested that certain patterns of scan abnormality (metabolic features) are commonly found in the metabolic bone disorders.²⁹ Their recognition, however, essentially depends on an awareness of increased uptake of tracer throughout the skeleton. With the newer bone scanning agents there is higher absolute uptake of tracer by the normal skeleton, and recognition of abnormality against this "higher" background may be difficult.² Absent kidney images in the bone scan will always suggest high skeletal avidity for tracer but the other metabolic features are less reliable. We do not consider that subjective evaluation of bone scan images will consistently identify patients with conditions such as primary hyperparathyroidism or osteomalacia, and more accurate quantitative techniques are required.³⁰

In osteoporosis the bone scan appearances are usually normal and the scan does not have real diagnostic value.³¹ The bone scan may be of value as an initial screening test to detect coexistent disease, however, particularly when bone pain is a predominant feature. In vertebral collapse linearly increased uptake of tracer suggests a benign aetiology, and also that the collapse has occurred relatively recently.

Arthritis

In inflammatory synovitis the blood flow to the synovium and periarticular bones is increased. This hyperaemia must contribute to the positive bone scan in rheumatoid arthritis, but local bone remodelling is probably of greater importance.³² Whatever the precise mechanism of tracer uptake in rheumatoid arthritis, areas of appreciably increased uptake are seen in the bone scan at sites of activity. The appearances are non-specific and may be seen in a wide variety of conditions including psoriatic and gouty arthritis, ankylosing spondylitis, seronegative polyarthritis, reflex sympathetic dystrophy syndrome, and regional migratory osteoporosis.²¹

In rheumatoid arthritis the bone scan may antedate clinical and radiological manifestations of inflammatory synovitis.³³ Once a diagnosis has been established, however, a bone scan will not provide any additional information and therefore its role in the routine management of patients with rheumatoid arthritis is limited.²¹ It has been suggested that the bone scan may prove to be an accurate means of monitoring a patient's response to treatment, but any advantage in clinical practice over simpler techniques remains to be established.

Acute sacroiliitis, such as occurs in ankylosing spondylitis, will produce a positive bone scan image, and the bone scan may detect radiologically negative sacroiliitis.^{21 34} The difficulty in assessing the sacroiliac joints in the bone scan is that they normally appear hotter than the surrounding pelvis and sacrum, and even more so in young patients, in whom sacroiliitis is most frequently seen. Furthermore, while sacroiliitis may be unilateral, it is often bilateral and the abnormality may be difficult to detect on subjective evaluation of a bone scan image. To overcome such difficulties a quantitative technique, using a computer, has been used to relate tracer uptake by each sacroiliac joint to that in the sacrum.³⁴ This ratio is abnormally high early in the disease when x ray findings are often minimal or absent but tends to

approach normal as end stage fusion of the joints develops.

Ankylosing spondylitis may be associated with a peripheral arthropathy, which will be seen in the bone scan. The bone scan will often fail clearly to illustrate the normal segmental anatomy of the spine because of bony ankylosis.

In osteoarthritis increased mechanical stresses occur at altered joint surfaces, with reactive new bone formation, and this may be readily shown by bone scanning. The typical scan findings are of asymmetrical tracer uptake in the weight-bearing joints and distal joints of the hands and feet. Focal or patchy uptake of tracer is often seen in the lower lumbar spine. As degenerative disease of the spine is common, such appearances may on occasion lead to diagnostic difficulty when metastatic disease is suspected. Hence any such area of abnormality should be examined radiographically to confirm the presence of degenerative change.

JAMES H MCKILLOP

Senior Lecturer in Medicine,
Royal Infirmary,
Glasgow G31 2ER

IGNAC FOGELMAN

Consultant Physician in Nuclear Medicine,
Guy's Hospital,
London SE1 9RT

- ¹ McKillop JH, McDougall IR. The role of skeletal scanning in clinical oncology. *Br Med J* 1980;**281**:407-10.
- ² Fogelman I. Diphosphonate bone scanning agents—current concepts. *Eur J Nucl Med* 1982;**7**:506-9.
- ³ Matin P. Bone scintigraphy in the diagnosis and management of traumatic injury. *Semin Nucl Med* 1983;**13**:104-22.
- ⁴ Merrick MV. Fractures and benign bone tumours in bone scintigraphy. In: Pauwels EKJ, Schutte HE, Taconis WK, eds. *Bone scintigraphy*. The Hague: Leiden University Press, 1981:59-80.
- ⁵ O'Reilly RJ, Cook DJ, Gaffney RD, Angel KR, Paterson DC. Can serial scintigraphic studies detect delayed fracture union in man? *Clin Orthop* 1981;**160**:227-32.
- ⁶ Dee P, Lambruschi PG, Hiebert JM. The use of Tc-99m MDP bone scanning in the study of vascularised bone implants: concise communication. *J Nucl Med* 1981;**22**:522-5.
- ⁷ Roub LW, Gumerman LW, Hanley EN Jr, Clark MW, Goodman M, Herbert DL. Bone stress: a radionuclide imaging perspective. *Radiology* 1979;**132**:431-8.
- ⁸ Haase GM, Ortiz VN, Sfakianakis GN, Morse TS. The value of radionuclide bone scanning in the early recognition of deliberate child abuse. *J Trauma* 1980;**20**:873-5.
- ⁹ Sty JR, Starshak RJ. The role of bone scintigraphy in the evaluation of the suspected abused child. *Radiology* 1983;**146**:369-75.
- ¹⁰ Handmaker H, Leonards R. The bone scan in inflammatory osseous disease. *Semin Nucl Med* 1976;**6**:95-105.
- ¹¹ Nelson HT, Taylor A. Bone scanning in the diagnosis of acute osteomyelitis. *Eur J Nucl Med* 1980;**5**:267-9.
- ¹² Sullivan D, Rosenfield NS, Ogden J, Gottschalk A. Problems in the scintigraphic detection of osteomyelitis in children. *Radiology* 1980;**135**:731-6.
- ¹³ Ash JM, Gilday DL. The futility of bone scanning in neonatal osteomyelitis: concise communication. *J Nucl Med* 1980;**21**:417-20.
- ¹⁴ Gilday DL, Paul DJ, Paterson J. Diagnosis of osteomyelitis in children by combined blood pool and bone imaging. *Radiology* 1975;**117**:331-5.
- ¹⁵ Lisbona R, Rosenthal L. Observations on the sequential use of ^{99m}Tc-phosphate complex and ⁶⁷Ga imaging in osteomyelitis, cellulitis and septic arthritis. *Radiology* 1977;**123**:123-9.
- ¹⁶ Propst-Proctor SL, Dillingham MF, McDougall IR, Goodwin D. The white blood cell scan in orthopedics. *Clin Orthop* 1982;**168**:157-65.
- ¹⁷ Williamson BRJ, McLaughlin RE, Wany G-J, Miller CW, Teates CD, Bray ST. Radionuclide bone imaging as a means of differentiating loosening and infection in patients with a painful total hip prosthesis. *Radiology* 1979;**133**:723-6.
- ¹⁸ Horoszowski H, Ganel A, Kamhin M, Zaltman S, Farine I. Sequential use of technetium 99m MDP and gallium 67 citrate imaging in the evaluation of painful total hip replacement. *Br J Radiol* 1980;**53**:1169-73.
- ¹⁹ Rosenthal L, Lisbona R, Hernandez M, Hadjipavlou A. ^{99m}Tc-PP and ⁶⁷Ga imaging following insertion of orthopedic devices. *Radiology* 1979;**133**:717-21.
- ²⁰ McKillop JH, Cuthbert GF, Gray HW, McKay I, Sturrock RD. A comparison of gallium-67 citrate scintigraphy and indium-111 labelled leukocyte imaging for the diagnosis of periprosthetic joint infection. In: Raynaud C, ed. *Nuclear medicine and biology*. Oxford: Pergamon Press, 1982:877-80.
- ²¹ Rosenthal L, Lisbona R. Role of radionuclide imaging in benign bone and joint disease of orthopedic interest. In: Freeman LM, Weissman HS, eds. *Nuclear medicine annual 1980*. New York: Raven Press, 1980:267-301.
- ²² Danigelis JA, Fisher RL, Ozonoff MB, Sziklas JJ. ^{99m}Tc-polyphosphate bone imaging in Legg-Perthes disease. *Radiology* 1975;**115**:407-13.
- ²³ Hull A, Hattner RS, Vincente R. Prospective scintigraphic evaluation of avascular necrosis (AVN) of the femoral head in renal transplant recipients. [Abstract.] *J Nucl Med* 1979;**20**:646.
- ²⁴ Sain A, Sham R, Silver L. Bone scan in sickle cell crises. *Clin Nucl Med* 1978;**3**:85-90.
- ²⁵ Gregg PJ, Walder DN. A study of old lesions of caisson disease of bone by radiography and bone scintigraphy. *J Bone Joint Surg* 1981;**63B**:132-7.
- ²⁶ Serafini AN. Paget's disease of bone. *Semin Nucl Med* 1976;**6**:47-58.
- ²⁷ Shirazi PH, Ryan WG, Fordham EW. Bone scanning in evaluation of Paget's disease of bone. *CRC Critical Reviews in Clinical Radiology and Nuclear Medicine* 1974;**5**:523-58.
- ²⁸ Fogelman I, Carr D. A comparison of bone scanning and radiology in the assessment of patients with symptomatic Paget's disease. *Eur J Nucl Med* 1980;**5**:417-21.
- ²⁹ Fogelman I, Citrin DL, Turner JG, Hay ID, Bessent RG, Boyle IT. Semiquantitative interpretation of the bone scan in metabolic bone disease: definition and validation of the metabolic index. *Eur J Nucl Med* 1979;**4**:287-9.
- ³⁰ Fogelman I, Bessent RG, Turner JG, Citrin DL, Boyle IT, Greig WR. The use of whole-body retention of Tc-^{99m}diphosphonate in the diagnosis of metabolic bone disease. *J Nucl Med* 1978;**19**:270-5.
- ³¹ Fogelman I, Carr D. A comparison of bone scanning and radiology in the evaluation of patients with metabolic bone disease. *Clin Radiol* 1980;**31**:321-6.
- ³² Bekerman C, Genant HK, Hoffer PB, Kozin F, Ginsberg M. Radionuclide imaging of the bones and joints of the hand. *Radiology* 1976;**118**:653-9.
- ³³ Hoffer PB, Genant HK. Radionuclide joint imaging. *Semin Nucl Med* 1976;**6**:121-37.
- ³⁴ Lentle BC, Russell AS, Percy JS, Jackson FI. Scintigraphic findings in ankylosing spondylitis. *J Nucl Med* 1977;**18**:524-7, 8.

Correction

Chest pain in patients with normal coronary arteriograms

An error occurred in the leading article by Professor Sydney Brandon (19 November, p 1491). In the ninth paragraph mianserin is said to be a tricyclic antidepressant; it is in fact a tetracyclic antidepressant.