that might prove advantageous is the substitution of 5% dextrose for 0.9% saline in those patients who are initially hypernatraemic.

The values for salicylate clearance given in Table II and Fig. 2 cannot be compared with those of other authors as they are based on total serum salicylate concentrations—as measured by the method of Trinder (1954)—and not on the unbound fraction only. They are presented, nevertheless, because they provide the clinician with a rough estimate of the rate of salicylate excretion that he may obtain with acetazolamide and sodium bicarbonate infusion at any given serum salicylate level. In Fig. 2 creatinine clearance values are also shown, since the glomerular filtration rate is sometimes low in salicylate overdose and may be further depressed by acetazolamide (Milne, 1963). The effectiveness of the treatment regimen might be limited by this, and also by competition for tubular secretion between acetazolamide and salicylate (Weiner *et al.*, 1959).

Although this paper lays greater emphasis on a very high urine pH than a very high urine flow, it is clear that the rate of flow must still be a factor limiting salicylate clearance. When rehydration is not promptly followed by a brisk diuresis the use of an osmotic diuretic may therefore still be of value. We have unpublished data to show that the addition of mannitol to the present treatment regimen can further increase salicylate clearance. It should, however, be borne in mind that mannitol may cause complications of its own (Morgan *et al.*, 1968).

It is not suggested that acetazolamide and sodium bicarbonate treatment will replace haemodialysis in the severest cases of salicylate intoxication, for in these there may be other indications for dialysis than the serum salicylate concentration. However, the concentration itself may often be brought down to a safer level during the time required to transfer a patient to a dialysis unit. We have recently treated two such patients prior to dialysis, reducing the serum salicylate in one from 136 to 107 mg./100 ml. in two hours, and in the other from 104 to 69 mg./100 ml. in three hours.

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Strontium-85 Scanning of Suspected Bone Disease

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Summary: Strontium-85 scanning of suspected bone lesions in 81 patients has added to the criteria for the diagnosis of malignant and other lesions of bone. Of 46 patients with a previous history of malignant disease and skeletal symptoms negative radiological findings were recorded in 19, but nine of these had positive scans, eight of which when followed up over periods of up to four years proved to be metastatic. A similar prevalence of positive scans occurred in patients without a previous history of malignancy. Because of the anatomical localization of lesions made possible by this technique a tissue diagnosis was made in six patients, while fields of radiotherapy were altered in another seven. This technique can improve the management of patients with suspected bone disease.

Introduction

Patients with back pain present difficulties in diagnosis when the radiological features are normal or show changes which can be interpreted in more than one way. It has been estimated that at least a 30% alteration in bone density must take place before changes can be detected by conventional radiological techniques (Lachman, 1955). Tomography may improve the delineation of the lesion, but some idea of the area involved must be given first.

Normal bones accumulate radioisotopes by a variety of processes which involve simple exchange diffusion, active transport, and incorporation into bone mineral (Bauer, Carlsson, and Lindquist, 1958). Increased uptake in a particular area of bone may be due to increased blood flow, altered exchange processes, or new bone formation. These changes arise in the repair processes involved in traumatic, inflammatory, and neoplastic lesions, micro-fractures probably occurring in most of the vertebral diseases of this nature. In neoplastic lesions a variety of causes may lead to an increased uptake, including osteolysis opening up a large area for exchange, new bone formation in sclerotic deposits, and, on occasion, osteomalacia (Folles, 1950). Bone biopsy of areas which had shown increased ⁸⁵Sr uptake

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demonstrated a qualitative relationship between bone formation and isotope uptake (Charkes, Sklaroff, and Young, 1966). At the present time there is no simple way of distinguishing these lesions from the degree of uptake or turnover, but a variety of patterns may emerge indicating metastatic disease rather than traumatic or inflammatory lesions.

Bone scanning with radioisotopes has been used for several years in the early diagnosis of bone pain and lesions, particularly of the spine and pelvis. The first isotopes used were ^{45}Ca and ^{85}Sr (Bauer and Wendebergh, 1959; Corey and Kenny, Greenberg, Pazianos, Pearson, and Laughlin, 1961; Corey, Kenny, Greenberg, and Laughlin, 1962; Bauer and Scoccianti, 1961; Gynning, Langeland, Lindberg, and Waldskog, 1961). Those authors reported use of these isotopes in detecting malignant disease in bone and a variety of vertebral lesions and limb fractures. The introduction of short-lived cyclotron-produced isotopes $^{87\text{m}}\text{Sr}$ and ^{18}F increased the use of this technique. Large activities could be given to the patient, enabling the overall scanning time to be short and at the same time reducing the radiation dose by a factor of 200; the dose to bone giving 500 μCi . Strontium-87m is 200 mrad, while 70 μCi of ^{85}Sr gives 2.6 rads (Blau, Laor, and Bender, 1963; Charkes, Sklaroff, and Bierly, 1964; French and McCready, 1967; Spencer, Herbert, Rish, and Little, 1967; Moon, Dworkin, and Lafuer, 1968).

There are, however, disadvantages associated with these short-lived isotopes. They cannot be stored for use on demand; they are produced only intermittently; the source of production must be close to their site of use; the scans must be made within hours of injection, and serial scans over days or weeks are impossible. In the case of a doubtful initial scan serial scans can be a valuable adjunct, as the uptake ratio of diseased to normal bone may increase over several days (Greenberg, Rothschild, DePalo, and Laughlin, 1966). Pelvic scans made soon after ^{18}F administration are complicated by high count rates over the renal tract which can obscure certain lesions, though faecal collection of ^{85}Sr provides a similar problem.

The present study had several objectives.

(1) The detection of bone lesions in patients with a past history of neoplastic disease where the symptoms suggested a bony metastasis.

(2) The detection of possible bone metastases in patients presenting with bone pain as the first symptom of spread from a primary site, often undetected.

(3) The detection of the extent of bony metastatic spread beyond that already delineated by a radiological survey where fields of radiotherapy might be extended or the whole therapeutic approach altered (Sklaroff and Charkes, 1967).

(4) Where the situation of the primary neoplasm was uncertain, scanning was used to detect the optimum site for biopsy of the metastasis.

(5) A few patients were suspected of having either inflammatory or neoplastic lesions of the spine, producing fever and pain, with doubtful radiological features. These were scanned after appropriate antibiotic or antitumour therapy to see if any changes in uptake had taken place (Kampffmeyer, Dworkin, Carr, and Bull, 1967).

Methods

Patients were referred from various departments of the hospital and seen by a physician or radiotherapist (Table I). Appropriate radiological studies had been made. Serum chemistry for calcium (MacIntyre, 1961), phosphorus (Fiske and Subbarow, 1925), alkaline and acid phosphatase (King and Armstrong, 1934), and 24-hour excretion of calcium and hydroxyproline (Prockop and Udenfriend, 1960) in the urine had been estimated in the majority of patients.

About 1 μCi of ^{85}Sr /kg. was given intravenously as strontium chloride in aqueous solution (U.K.A.E., U.K.A.E.A., Amersham

code SOS.1P) and the patient was recalled at varying times up to 90 days after administration.

TABLE I.—Reasons for Referral of 81 Patients for Radioisotope Scanning

Group		No. of Cases	Positive Scans
1. Patients with past history of malignant disease with symptoms suggestive of a recurrence of metastasis	Carcinoma of breast Carcinoma of bronchus Carcinoma of prostate Other conditions	15 9 2 9	35 9 6 2 5
2. Patients presenting with skeletal pain as first evidence of malignant disease	Carcinoma of bronchus Carcinoma of breast Other conditions	9 3 7	19 7 2 3
3. Patients with metastatic pain where scans changed portals of radiotherapy or changed therapy to be given	Carcinoma of breast Carcinoma of bronchus Carcinoma of prostate	7 1 1	9 6 1 1
4. Patients known to have bony involvement where a scan was used to pick out an area likely to contain altered bone	Carcinoma of prostate Paget's disease	6 1	7* 6 1
5. Patients where scans were used to detect the possible cause of skeletal pains and effects of therapy on bone disease	? Vertebral inflammatory disease Paget's disease Obscure skeletal pains	4 3 4	11 3 0

* All biopsies positive.

Once the radioisotope has been given the detection of increased uptake over suspect lesions is made in one of two ways. A scintillation crystal-collimator assembly with a large field of view—for example, 5-cm. circle—may be used, and the total number of counts obtained in a fixed time at 5-cm. intervals along the spine recorded. This was the method used at the Royal Sussex County Hospital, where the first patients reviewed here were investigated. Alternatively, a crystal-collimator assembly with a small field of view—for example, 1-cm. circle—and designed to show maximum sensitivity to a source placed some distance in front of the system may be used, and the crystal-collimator assembly scans automatically over the spine. In the latter method the count rate is recorded continuously during the scan, via light pulses on to film and/or by mechanical print-out as numbers or coloured dots. The design of the collimating system depends on the energy of the radiation being measured. Calcium-47 requires heavy shielding provided by instruments such as the high-energy scanner at the Sloan Kettering Institute (Laughlin, Kenny, Corey, Greenberg, and Weber, 1964; Greenberg *et al.*, 1966). Conventional scanning machines, such as the Picker Magna Scanner V, used for the more recent studies reported above, are suitable for ^{85}Sr . This is the machine in use at King's College Hospital.

The first scan was usually carried out within three days of the injection, depending on the urgency of the problem. Patients in pain were often taking analgesics which slowed bowel emptying, so that suspicious areas in the pelvis needed to be rescanned after bowel evacuation. One major disadvantage of the low count rates inevitable with ^{85}Sr is the slow rate of scanning, but a complete vertebral and pelvic scan could be completed in two sessions of 45 minutes. Reference points were marked out both on the scans and on the patients, so that matching of future scans was made more easily.

Because of variations in patients, such as age and degree of pain or discomfort, often aggravated if the subject has to lie prone, the overall scanning time imposed had to be varied. This meant that other scan conditions, such as the speed of movement of the detector and the distance between adjacent scan lines, were not the same for all patients. A width of 10 or 12 cm. was scanned along the spinal column, and 6 cm. of this was consistently used as the width which adequately covered all vertebrae. The total number of dots printed out over a spinal segment could be counted on the completed scan and the count rate calculated from this number. The vertebrae were fitted into the scanning scheme as shown in Table II.

Discontinuities in the numbers of dots counted were obviously expected between each of the groups. All scans were normalized

to fit into this scheme, so that they could reasonably be compared. The dots per vertebra were counted on this scheme and plotted out for each patient, and from the number of dots, knowing all the other scanning conditions, the average count rate over a vertebra could be calculated. This was done only for the vertebrae which gave the highest count rate in each of the four categories for each patient, to see whether there was any correlation between absolute count rate in a vertebra with the final diagnosis, with or without a raised uptake relative to neighbouring vertebrae. Without reference to any other information a scan was classified as positive if the counts in one vertebra were more than 20% higher than those in adjacent vertebrae. Similar criteria were applied when sides of the pelvis, ribs, or femur were compared. Rosenthal (1964, 1965), reviewing 200 bone scans, made use of an ankle/spine count ratio and determined this ratio for 32 normal patients; two standard deviations outside these limits had been accepted as evidence for bone disease.

TABLE II

Vertebrae	No. of Scan Lines, 0.5 cm. Apart and 6 cm. Long	Length of Vertebrae (cm.)	Total Scan Path Length (cm.)
C 1-7	3	1.5	18
D 1-9	4	2	24
D 10-12	5	2.5	30
L 1-5	6	3	36

Results

A typical normal scan showing the variation in the number of counts per vertebra over the length of the column is shown in Fig. 1; this was taken from a patient with back pain, persistent pyrexia, and a raised sedimentation rate for over six months, whose diagnosis remained unknown and who was followed up for two years with complete recovery and no sequelae. The discontinuities of the number of dots per vertebra between the vertebral groups from lumbar to cervical spine are inherent in the scheme adopted for assessing the scans, which takes no account of the geometry involved in scanning in a single plane with the patient prone or the varying amount of bone mass in various parts of the spine. All the proved normal scans to date had a similar pattern, as shown by the range of dots counted for each group of vertebrae superimposed on the normal curve (Fig. 2), though these points may represent different count rates (Table III).

It is interesting to note that the higher minimum count rates in all patients with skeletal bone disease reflect the generalized increase in uptake, even when disease is localized to one part of the skeleton, confirmed by tracer studies with ⁴⁷Ca in similar patients.

FIG. 1.—Count rates per vertebra 24 hours after injection of ⁸⁵Sr in a normal patient.

Patients were referred for the reasons outlined above; their diagnoses and the incidence of positive scans are shown in Table I. All the patients are grouped together in Table IV to show the incidence of positive and negative scans for the main clinical, radiological, and biochemical criteria. For the latter the patient should have a serum calcium concentration

TABLE III.—Variations in Maximum Count Rate per Vertebral Group in Patients with Negative and Positive Scans

Vertebral Group	Negative Scans (Counts/Minute)		Positive Scans (Counts/Minute)	
	Highest	Lowest	Highest	Lowest
C 1-7	520	130	924	314
D 1-9	640	165	1,260	292
D 10-12	574	98	1,040	244
L 1-5	654	109	1,580	378

greater than 10.8 mg./100 ml., or an alkaline phosphatase greater than 15 King-Armstrong units in the absence of other abnormal liver function tests, or a hydroxyproline peptide output greater than 50 mg./24 hours on a ward diet not containing excess gelatin. Radiological data include radiographs of the spine, chest, and pelvis, and were recorded as negative when they indicated no bony disease beyond degenerative changes. Biochemical data are not available for some patients, and where absent or incomplete they are assumed to be negative for the sake of preserving main divisions in this relatively small series.

FIG. 2.—Mass plot of normalized dot density, showing the range along the vertebral column in eight patients followed with no abnormality.

TABLE IV.—Breakdown of All the Patients Scanned to Show Incidence of Positive and Negative Scans for Each Criterion

	Past History of Malignant Disease (46)				No Past History of Malignant Disease (35)			
	With Radiological Signs (27)		Without Radiological Signs (19)		With Radiological Signs (24)		Without Radiological Signs (11)	
	Biochemistry		Biochemistry		Biochemistry		Biochemistry	
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
Positive scans	13	11	3	6	11	8	3	2
Negative scans	0	3	2	8	2	3	2	4
Total	13	14	5	14	13	11	5	6

False-positive Scans.—The majority of patients with negative radiology and positive scans eventually showed evidence of neoplastic erosion, and this was regarded as confirmation. In very few was a thorough histological examination of the spine made at necropsy, gross inspection of a cut strip being regarded as giving sufficient information. One patient, aged 61 with carcinoma of the breast, had collapse of the lower dorsal vertebrae, seen on the radiographs, and a positive scan, but metastases were not seen on examining the spine at necropsy.

The coexistence of osteoporotic collapse and metastatic disease outside the spine may lead to confusion, but this was the only occasion in the series.

False-negative Scans.—All the 20 negative scans were followed for a sufficient period and remained clinically and radiologically negative save for the six in Table V. The finding that multiple myeloma deposits do not induce such increased new bone formation as do other malignant diseases is paralleled by the normal values of alkaline phosphatase in these patients. It may be explained by the extent of the destruction of the vertebrae so that no remaining bone-forming elements were retained; in Case 5 the count rate over the affected vertebrae was significantly below that in neighbouring vertebrae. The patient with carcinoma of the breast (Case 2) has so far shown no evidence of a recurrence of her pain following radiotherapy, and the presence of deposits is still open to doubt.

TABLE V.—Six Patients in Whom the ^{85}Sr Scan was Negative

Case No.	Age Sex		Radiology	Bio-chemistry	Result
1	75 F	Ca. bladder	Neg.	Neg.	Died with meta-stases
2	65 F	Ca. breast	Neg.	Neg.	Alive and well after deep x-ray therapy
3	61 M	Multiple myeloma	Pos.	Neg.	Died, renal failure
4	58 F	Ca. uterus	Neg.	Neg.	Died of metastases (necropsy not carried out)
5	48 F	Hypernephroma	Pos.	Pos.	Biopsy of vertebrae positive
6	60 F	Multiple myeloma	Pos.	Neg.	Under treatment

The following illustrative cases show where scans have contributed to their diagnosis and management.

Group 1

A 57-year-old man had had a right upper lobectomy for a squamous-cell carcinoma of the lung in 1957. He had chest pain along the thoracotomy site for some time after surgery, and this recurred infrequently until 1964, when the pain became more persistent. Radiology of the upper thoracic vertebrae did not show any erosion or sclerosis, alkaline phosphatase was within normal limits, but a scan was positive over the vertebrae near his scar. Radiotherapy was applied to this area with some relief, but more generalized symptoms of metastases developed and seven months later he died of metastatic disease, originating probably from a site in the right lung shown in subsequent pathological surveys.

A 58-year-old woman had had a sarcoma of the uterus removed two years previously and was being seen for treatment of obesity when she complained of acute pain in the right shoulder together with pain and tenderness over the humerus. Radiology showed a cystic area in the humeral head, raising suspicion of a secondary deposit. The symptoms persisted, and before biopsy and radiotherapy was suggested a scan was carried out; this did not reveal any abnormality of uptake. Further action was delayed; after a few weeks her pain eased and no other features emerged, and a second opinion on the x-ray changes reported the changes as within normal limits. A scan in this situation was helpful in delaying therapy, which proved unnecessary.

Group 2

A 57-year-old tobacconist presented with diffuse pelvic pain and urinary symptoms at another hospital. Full radiological and cystoscopic examination showed nothing beyond an infected urine and a tender prostate. A diagnosis of cyst prostatitis was made and treatment instituted. Three months later his pain persisted and he was referred for physiotherapy. Further radiology of the pelvis, including tomography, was unrewarding, and the alkaline but not the acid phosphatase was raised. He was referred for a scan, which showed lesions in the left iliac crest and in two lumbar vertebrae separated by a normal vertebra. This type of "spotty" uptake is typical of carcinoma of the prostate. Punch biopsy of the gland proved positive for a poorly differentiated adenocarcinoma. Stilboestrol has controlled his symptoms for over a year.

Group 3

A 68-year-old man had carcinoma of the prostate diagnosed and treated with stilboestrol in 1963. He later developed skeletal pain

while on this therapy, and radiology suggested disease confined to the lumbar spine, which was amenable to local radiotherapy. A scan, however, showed up scattered deposits throughout the vertebral column, and radiotherapy was thought inadvisable; instead he was given courses of ^{32}P with some relief before he died a year later.

Group 4

A 69-year-old man had many of the symptoms of a carcinoma of the colon—changed bowel habit, pelvic pain, and loss of weight. Sigmoidoscopy and two barium enemas had failed to show any abnormality. Radiological survey of the pelvis and lumbar spine did not suggest metastasis, but a raised alkaline phosphatase led to a scan being carried out. This showed a raised uptake in the left iliac bone. A biopsy specimen from this area showed Paget's disease at an early stage. Reassured, and with appropriate analgesics, this patient began to recover.

Group 5

A 65-year-old married woman was admitted for investigation of weakness, fever, and high thoracic pain. Radiology delineated a benign angioma of D 4, which was assumed to be an unlikely cause of her pain. A scan revealed an 85% increased uptake of this vertebra, which persisted for 90 days and was not thought to be a simple increase in blood flow. On the basis of this finding and tenderness over the area a diagnosis of osteomyelitis was made, and appropriate treatment with lincomycin led to an immediate cessation of her symptoms, fever, and pain. The scan was thought to add to the radiological findings in indicating an added disturbance in an abnormal vertebra.

Discussion

The grouping of patients reflects immediately both the commonest malignancies—carcinoma of the breast, bronchus, and prostate—and their tendency to metastasize to bone. The Registrar General's ratio of death rates for these three types of carcinoma is 6:3:2; in our small series the ratio is 10:4:3, suggesting that this is not a particularly selected population in that carcinoma of the lung presents with distant metastases giving rise to bone pain as an initial symptom more often than carcinoma of the breast. Clearly, the group in which biopsy localization has been helped most is where the pelvis has been scanned, because in this area biopsy is easiest; vertebral biopsy is becoming commoner but is still an orthopaedic or neuro-surgical procedure where bronchoscopy, lymph-node biopsy, liver biopsy, and location by means of barium studies of the gut and the intravenous pyelogram have proved negative.

Positive scans were a help in approximately one in six patients in whom the radiological findings were essentially negative. In 104 cases of scanning a very similar rate of better detection was recorded, and in a further 17 patients monostotic radiological findings were polystotic on scanning (Bessler, 1968). When a particular tumour such as carcinoma of the prostate is selectively studied, the incidence of positive scans with negative radiological findings rises from 27% (Sanguineti, 1968) to as high as 48% (DeNardo and Volpe, 1966; Williams and Blahd, 1967).

In this analysis of the patients the tendency is for the positive scans to follow the criteria of history, radiology, and biochemistry; there are more positive scans in those with all criteria positive than in those with a negative history or negative radiology or biochemistry. At the outset of this screening programme there was a tendency to investigate patients in whom the diagnosis was in little doubt, and our experience now is to expect positive scans where the history, radiology, and biochemical changes all point in the direction of metastatic disease. The use of scanning in these patients would now be confined to the delineation of radiotherapy fields. With increasing use of scanning to outline particular areas of suspicion in the vertebral column, better radiological views and tomography

have revealed the presence of bony changes which had been barely visible in previous radiographs. This may reflect the clinicians' poor prediction rather than radiological technique. On occasion, while scanning one area under suspicion another, totally unexpected, area will appear active, and when this is examined radiologically the bony changes are apparent. In this situation scanning has supplemented but in no way replaced radiology.

Because of the limited areas scanned in this group of patients, coupled with the frequent occurrence of crush and healing fractures, the biochemical indices of overall bone diseases are difficult to compare with the scanning results. In three patients increased excretion of hydroxyproline containing peptides was the only positive biochemical finding which correlated with a positive scan, and this finding needs to be confirmed in a larger series.

Malignancy was suspected in three patients, but biopsy in one showed a tuberculous abscess and in the other two the symptoms receded with antibiotic therapy—a reminder that not all vertebral disease in patients with a past history of malignant disease need be metastatic.

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Post-partum Hypercalcaemia in Treated Hypoparathyroidism

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Summary: Two patients with post-thyroidectomy hypoparathyroidism were observed throughout three pregnancies. Their normal maintenance treatment with vitamin D remained unaltered. Serum calcium levels remained normal until shortly before delivery but rose rapidly in the immediate postpartum period to peak levels of 7.8, 6.0, and 6.8 mEq/l. while still on normal or reduced maintenance treatment. This apparent increased sensitivity to vitamin D after delivery persisted for as long as three months.

Introduction

This report concerns three pregnancies in two treated well-established hypoparathyroid patients in whom there was an unexpected and significant rise in serum calcium levels post partum.

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Treated hypoparathyroidism in pregnancy has not previously been noted to require any alteration in maintenance therapy (Anderson and Musselman, 1942; Graham *et al.*, 1964; O'Leary *et al.*, 1966). The level of serum calcium in these reported cases was carefully followed during the pregnancy and again at varying intervals afterwards, but not immediately post partum.

Case 1

Hypoparathyroidism became evident in this patient 24 hours after a nine-tenths thyroidectomy for juvenile thyrotoxicosis in 1957. Since then maintenance treatment with calciferol 100,000 units daily together with calcium Sandoz (57 mEq of calcium daily) has kept the serum calcium within the normal range (4.5–5.5 mEq/l., venepuncture performed without stasis). Since 1957 she has remained euthyroid (normal neck uptake of radioiodine) and in good general health.

First Pregnancy

The first pregnancy occurred in 1964–5, when she was aged 23 years. No change was made in the maintenance therapy during this pregnancy, and frequent serum calcium levels showed no trend upwards or downwards, varying between 4.9 and 5.5 mEq/l.