THE ROLE OF FLUORINE-18 AND STRONTIUM-87m SCINTIGRAPHY IN THE MANAGEMENT OF INFECTIVE SPONDYLITIS*

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Radioactive isotopes have only recently been used diagnostically in clinical orthopaedics, despite the fact, well recognised for many years, that it is possible to label bone with a variety of radionuclides. The earliest report of a clinical application for bone scanning was by Bauer and Wendeberg (1959). They employed Calcium-47 and Strontium-85, which have certain clinical and technical disadvantages. Calcium-47 has a high energy gamma emission of 1.31 MeV, which made it difficult to collimate, and in consequence gave inadequate resolution. Strontium-85 has a 0.513 MeV gamma emission, which makes it practicable for use with the majority of scanners. However, both nuclides have relatively long half-lives, 4-7 and 64 days respectively.

Several reports have recently been published of screening techniques for the investigation of inflammatory and other non-malignant conditions of bone (Dymling and Wendeberg 1965, Felländer and Lindberg 1966, Kettunen and Rekonen 1968). These followed the introduction of Fluorine-18 by Blau, Nagler and Bender (1962) and of Strontium-87m by Charkes, Sklaroff and Bierly (1964), which provide more suitable materials for scintiscanning of bone. For clinical purposes, Fluorine-18 is produced in a cyclotron. It is a positron emitter with a 0.65 MeV \( \beta^+ \) emission, and associated 0.51 MeV annihilation gamma radiation; it has a short half-life of 112 minutes. Strontium-87m has a gamma energy of 0.338 MeV and a half-life of 168 minutes.

Blau et al. (1962) calculated that, if an even distribution of Fluorine-18 throughout the skeleton was assumed, the radiation dose would be 0.23 rads per millicurie. That is approximately 200 times less than that produced by one millicurie of Strontium-85. The amount of radiation received by the patient would be approximately equivalent to that of a routine radiological examination of the thoracic spine (Hand-book of Radiological Protection 1971).

The mechanism of the fixation of these nuclides in bone is not exactly known. Selective concentration occurs rapidly after administration. It appears to involve ion exchange between the circulating blood and the exposed bone matrix. Neuman and Neuman (1958) have shown that fluoride ions replace hydroxyl or bicarbonate ions at the surface and in the interior of the hydroxyapatite crystal lattice of the bone. Calcium-45 ions exchange with the stable calcium ions. Bauer and Ray (1958) suggest that strontium can be substituted for calcium because the skeleton cannot differentiate between the two cations.

According to Chaudhri, Gartside and Ranicar (1970), the uptake of Fluorine-18 after intravenous injection in rats reached a maximum in thirty minutes and remained almost constant at 4 per cent of the dose per gramme for a further ninety minutes. The bone/blood ratio was high—10 : 1 at one hour and 50 : 1 at two hours. This confirmed the work of French and McCready (1967), who showed that there was a rapid uptake of this isotope in man. They demonstrated that the activity of the isotope in the circulation decreases to 25 per cent one minute after injection and to 6 per cent at one hour. Approximately 5 per cent is excreted in the urine in the first hour and 10 per cent by two hours. Strontium-87m has a slower rate

* Based on a paper read to the British Orthopaedic Association at Aviemore in April 1972.
of uptake; according to Blau, Laor and Bender (1969) the percentage remaining in the blood is 11 per cent at one hour and 8.5 per cent at two hours, compared with values of 8 and 4 per cent for Fluorine-18. Weber, Greenberg, Dimich, Kenny, Rothschild, Myers and Laughlin (1969) made a detailed study of the uptake of the various bone-seeking isotopes. They found that Fluorine-18 gave the highest ratios and had the most rapid clearance.

This paper reports the use of Fluorine-18 and Strontium 87m bone scanning techniques in the investigation of patients with infections of the spine. An evaluation is made of this technique for diagnosis, and the relation between the scintigraphic and the operative findings is considered.

### TABLE I
**DETAILS OF THE SERIES**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>16</td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
</tr>
<tr>
<td>Total number of scans</td>
<td>57</td>
</tr>
<tr>
<td>Fluorine-18</td>
<td>47</td>
</tr>
<tr>
<td>Strontium-87m</td>
<td>10</td>
</tr>
</tbody>
</table>

### TABLE II
**DETAILS OF THE FLUORINE-18 SCANS IN FORTY-TWO PATIENTS**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Positive scan</th>
<th>Negative scan</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 new lesions</td>
<td>24</td>
<td>9</td>
<td>Tuberculosis 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6 single, 3 repeats)</td>
<td>S. pyogenes 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gumma 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neoplasia 2</td>
</tr>
<tr>
<td>12 old lesions</td>
<td>8</td>
<td>6</td>
<td>Tuberculosis 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4 single, 2 repeats)</td>
<td>See Table IV</td>
</tr>
</tbody>
</table>

### MATERIALS AND METHODS

The Fluorine-18 used was supplied by the Medical Research Council Cyclotron Unit at Hammersmith Hospital. The Strontium-87m was supplied by the Radiochemical Centre, Amersham, as a generator column containing the parent isotope Yttrium-87, from which the isotope Strontium-87m was obtained by elution.

The patients reported in this paper were those referred to the Spinal Unit of the Royal National Orthopaedic Hospital with a provisional diagnosis of infective spondylitis between November 1968 and December 1971. There were fifty-two patients (Table I). Their ages ranged from twelve to seventy-one years, with an average of forty-three. The operation findings, the isotope employed and the scintigraphic findings are shown in Tables II to IV.

In the establishment of the diagnosis, it is standard practice to carry out comprehensive investigations so that the appropriate chemotherapy can be given before operation.
Haematological investigations include the sedimentation rate and the differential leucocyte count. Serological investigations include the antistaphylococcal-alpha haemolysin, the antistaphylococcal Panton Valentine leucocidin and the anti-streptolysin-0 titres; the Widal test, typhoid and paratyphoid titres, and agglutinin levels for brucellosis; the Venereal Disease Reference Laboratory and Reiter protein complement fixation tests.

In addition, serum electrophoresis and liver function tests are carried out. The Mantoux test is routine. If the results of cytological examination of sputum and urine are positive, bacteriological investigations follow. Standard radiological investigations include anterior and lateral films of spine and chest, lateral tomography of the lesion and pyelography.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Positive scan</th>
<th>Negative scan</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9</td>
<td>1</td>
<td>S. pyogenes 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. proteus 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E. coli 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tuberculosis 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radiologically, healed tuberculous lesion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New lesions (9)</th>
<th>Old lesions (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 healed tuberculous lesions</td>
<td>3 healed tuberculous lesions. Negative operation findings</td>
</tr>
<tr>
<td>3 degenerative disease of the spine</td>
<td>1 healed tuberculous lesion. Radiological findings accepted</td>
</tr>
<tr>
<td>1 haemangioma of vertebral body</td>
<td>2 late scans after treatment of recurrent tuberculosis</td>
</tr>
<tr>
<td>1 active tuberculous lesion (steroid therapy)</td>
<td></td>
</tr>
</tbody>
</table>

The management of these patients has been described by Jackson (1971) and by Kemp, Jackson, Jeremiah and Cook (1973). Unless there were contra-indications to surgery, all lesions were explored by an anterior approach. This permitted an accurate comparison between the disease process and the scintigrap.

The isotope studies were performed either at the Radiotherapy Department of University College Hospital or in the Isotope Department of St Bartholomew’s Hospital. At the former, a Picker Magnascanner Mark 3 was initially used, but in 1970 a Magnascanner 500 became available. At St Bartholomew’s Hospital an Isotope Developments Ltd. Dual Detector Scanner has been used throughout. Either one or two thallium-activated sodium iodide crystals are employed as the scintillator in conjunction with a focusing collimator. The distribution of radioactivity is displayed as a print of arbitrary coloured marks on a paper sheet; the spacing and colour varies with the intensity of the radiation over the area investigated.

No special preparation of the patient is required before scanning, except when Fluorine-18 is used. Because a high concentration of this isotope in the renal tract may obscure pelvic or sacral lesions, the patients are required to void urine immediately before the scanning.
1.6 mCi Fluorine-18 or 2.0 mCi Strontium-87m were injected intravenously and scanning started one and a half hours later, usually with the patient prone and one detector above the couch (Fig. 1). For pelvic scanning at St Bartholomew's Hospital, two counters have been aligned co-axially, one above and one below the couch, with outputs summated to obtain a uniform depth response. The area scanned includes the suspect area and a wide margin on either side for comparison with normal bone. Before starting the scan it is important to examine both patient and radiographs carefully to ensure that false positives are not reported; gross deformities of the spine can influence the results. The effect of such factors can often be reduced by careful positioning, and by performing a parallel lateral scan using the two detectors as well as the routine posterior-anterior scan.

![Fig. 1](image)

To show the equipment used. The scintillation detector (A) is positioned above the patient who normally lies prone. Occasionally the supine position is used for scanning the pelvis and lumbo-sacral region. A second detector (B) is in position below the table and can be used synchronously. The electronic acquisition equipment and the control modules are housed in a single unit (C). The colour print-out is recorded at the side of the unit (D).

When a positive scan is obtained, the area of increased uptake is localised in the following way. The scanner is moved so that it is centred over the active area. A corresponding mark is made on the scintigraph and a central lead marker is taped to the skin at that site. Four other marks are made on the scan “framing” the lesion and corresponding lead markers are taped on (Fig. 2). A radiograph is then taken with the beam vertically centred over the central marker at a standard distance of six feet (Fig. 3). The resulting radiograph can then be orientated in relation to the scintigraph by aligning the markers (Fig. 4). In order to obtain an accurate comparison it is occasionally necessary to correct for magnification on the radiograph. The centre of the active area is determined by this method and its extent can be assessed.

In addition to the use of scintiscanning as a pre-operative diagnostic aid, further scans were performed on a small group of patients in order to assess the influence of treatment on the uptake of isotope in the diseased area. Scans were also performed on patients in whom there was clinical evidence of reactivation of disease.
RESULTS

Fluorine-18 and Strontium-87m scintigraphs appear to have no advantage over orthodox radiological examination in establishing the diagnosis in typical inflammatory lesions of the spine arising de novo. However, the scintigraph does depict the site and extent of the infective process with considerable accuracy. It is of academic interest that the scintigraph occasionally
indicates a greater extent than the radiographic examination. Although there is an approximate relationship between the concentration of isotope at the site of infection and the response of the tissues in terms of repair, at the present time there is no satisfactory method of quantitative assessment. The findings in the present series agree with those of Felländer and Lindberg (1966), namely, that it is not possible to differentiate between tuberculous and pyogenic spondylitis by this technique.

The pattern of uptake of isotope in infections of the spine shows the greatest concentration at the site of maximal radiological involvement; there is a gradual decline in uptake proximally and distally, while laterally this gradation is more sharply defined by the margins of the vertebral bodies. Increased uptake is not observed in relation to soft-tissue lesions such as paravertebral abscess.

The importance of this investigation is that a negative scan virtually excludes infection. In all patients with new lesions, except one, the scan was positive and the findings were confirmed surgically (Tables II and III). The only exception was the patient in Case 40.

Case 40—A man aged thirty-six had previously been diagnosed as a case of sarcoidosis and had been treated for six months with prednisone. Radiologically there was a destructive lesion of the bodies of the fifth and sixth cervical vertebrae and a retropharyngeal abscess. A feature was the absence of any evidence of attempted repair. Although the Mantoux test was positive at 1 in 5,000, the erythrocyte sedimentation rate was only 15 millimetres in the first hour (Westergren). The scan was negative. At operation it was observed that the normal repair response was diminished. The lesion was shown histologically to be tuberculous. A possible explanation was that the steroid therapy had suppressed the mechanism of repair and that in the absence of enhanced bone metabolism, increased isotope uptake could not occur.

Scintigraphy aids the diagnosis of atypical lesions of the spine. Occasionally spinal metastases resemble inflammatory lesions. Galasko (1969), investigating mammary cancer, showed that skeletal metastases can frequently be detected by scintigraphy before radiological changes become manifest. He also demonstrated that such lesions are often multifocal and, by inference, that the scintigraph pattern is usually circumferential while the lesions remain discrete.

In general, as in this series, it has been observed that secondary deposits produce a positive scan only if they stimulate an osteoblastic response, and a negative scan if the lesion is essentially osteolytic. Two patients with a provisional diagnosis of tuberculous spondylitis were subsequently shown to be suffering from neoplastic disease.

Case 36—A man aged sixty-one was referred with a provisional diagnosis of tuberculosis of the bodies of the sixth and seventh thoracic vertebrae. He was paraplegic below that level. The relevant findings were a negative Mantoux at 1/1,000 and a sedimentation rate of 30 millimetres/hour. He had an intercurrent coliform urinary infection. Radiographs revealed lesions of the bodies of the sixth and seventh thoracic vertebrae with diminution of the intervening disc space. The scintigraph showed increased uptake at the site of the lesion and, in addition, areas of increased uptake by radiologically normal vertebral bodies. In view of the scintigraphic findings, an exhaustive search was made for a primary lesion but without success. At operation extensive secondary deposits were found; histologically they were metastases from a round-cell carcinoma. Subsequent necropsy confirmed the osteoblastic nature of the lesion, but still the primary lesion could not be found.

Case 52—A man aged sixty-one with pain in the thoracic spine for six months was diagnosed elsewhere as a case of tuberculous spondylitis. He had pulmonary tuberculosis with a positive sputum. Radiographs showed collapse of the seventh thoracic and fourth lumbar vertebral bodies. The scintigraph was negative. The patient died before he had been fully investigated. Necropsy revealed extensive osteolytic metastases from a primary renal carcinoma.

Increased isotope uptake was not generally observed in lesions other than infection and malignant disease, although a slight general increase was detected in patients with ankylosing spondylitis and associated disorders. Consequently a negative scan is of considerable significance in that it virtually excludes such disorders, and can therefore aid the diagnosis of atypical lesions of the spine.
Case 34—A man aged twenty-nine presented with a history of progressively severe thoraco-lumbar pain for two years. This was associated with loss of appetite, night sweats and loss of weight. He also complained of vague low back pain for the previous eight years. The Mantoux test was negative, as were all other serological and clinical investigations. Radiologically, there was a lytic lesion of the first lumbar vertebra with collapse of the body. The adjacent disc spaces were relatively unaffected. The scintigraph was negative, a finding that was considered to exclude infection. A diagnosis of haemangioma was made and confirmed at operation.

Case 22—A woman aged twenty-four presented with a vague history of pain at the lumbo-sacral level, present for several years and increasingly severe over the previous three months. All serological and clinical investigations were normal. A routine chest radiograph revealed a paravertebral shadow to the left of the thoracic spine and erosion of the lateral margins of the bodies of the seventh and eighth thoracic vertebrae (Fig. 5). The scan was negative. However, because of uncertainty regarding the nature of the lesion, it was decided to explore the mediastinum. The appearances were found to be due to reduplication of the foregut forming a fusiform swelling next to the vertebral bodies.

In cases of reactivation of infection, scintigraphy may often be the only certain method of supporting the clinical diagnosis. In patients in whom there is extensive destruction and cavitation, particularly when associated with soft-tissue calcification and deformity, accepted radiological techniques may not only be misleading but may fail completely to reveal an area of reactivation. The following examples illustrate the value of the technique.

Case 16—A woman aged twenty-two presented with a history of increasing pain in the mid-thoracic spine for three months. She complained of night sweats, lethargy, loss of weight and loss of appetite. Nine years previously a tuberculous lesion of the fifth thoracic vertebra with a paravertebral abscess had been successfully treated by costo-transversectomy and antibiotics. After discharge from hospital she defaulted and the chemotherapy was not completed. On examination, the patient was cachectic. There was a tender angular kyphosis at the level of the fourth thoracic vertebra and a paravertebral...
Case 10—The lateral radiograph and the lateral tomograph of the lower thoracic spine show a chronic tuberculous lesion involving several bodies. Because of the extensive soft-tissue calcification it was not possible to find evidence of reactivation.

FIG. 7

Case 16—The antero-posterior radiograph shows a funnel-shaped paravertebral abscess. The destructive lesion involving the fourth and fifth thoracic vertebral bodies was considered to be active.

FIG. 6

Case 16—The antero-posterior radiograph shows a funnel-shaped paravertebral abscess. The destructive lesion involving the fourth and fifth thoracic vertebral bodies was considered to be active.

All spinal movements were painful. The Mantoux test was positive and the sedimentation rate was 70 millimetres/hour. All other serological and clinical investigations were normal. No evidence of infection at other sites was detected and the level of protein-bound iodine was normal. The radiographs suggested active disease of the bodies of the fourth and fifth thoracic vertebrae with involvement of the fourth left pedicle. A bilateral paravertebral shadow was observed, of typical "funnel" shape (Fig. 6). The Fluorine-18 scan was negative, but this was disregarded and the lesion was explored by a left transthoracic approach. The paravertebral shadow was found to be due to unresolved pleural thickening. There was no evidence of active disease and several biopsies from representative areas showed normal or reparative tissue. Routine histology and culture revealed no evidence of tuberculosis. No therapeutic measures were instituted. The patient was discharged when she had recovered from the operation, and has remained symptomless for the past three years.
Case 10—This woman aged sixty-one was originally diagnosed, at the age of eighteen, as a case of tuberculosis of the lower thoracic spine and lung. Three episodes of incomplete paraplegia were treated conservatively before the onset of the episode which caused her admission. There were symptoms and signs of incomplete paraplegia below the level of the eighth thoracic vertebra. All investigations were negative apart from the Mantoux test, which was positive at 1 : 5,000. Because of the excessive calcification it was impossible to determine reactivation from radiographic examination, including lateral tomography (Fig. 7). Myelographic examination was also inconclusive. An isotope scan was performed. This indicated active disease at the level of the eighth, ninth and tenth thoracic vertebrae (Fig. 8). This region was explored and the area of reactivation was cleared. The patient was treated with antituberculous drugs and made an uneventful recovery. The sedimentation rate returned to normal four months after operation.
Case 21—A man aged fifty-three had been treated conservatively twenty-four years earlier for tuberculosis of the lower thoracic spine. Five years later he developed paraplegia. This was treated by antero-lateral decompression, spinal fusion and antibiotics. After being symptomless for seventeen years, he presented complaining of pain at the site of the original lesion, rigors and fever. On examination, the apex of the kyphosis was tender. Radiographs indicated that the graft was soundly incorporated and gave no evidence of reactivation. The sedimentation rate was 90 millimetres/hour. A scintigraph demonstrated increased uptake in the tenth and eleventh thoracic vertebrae. The patient refused further operation, but was successfully treated by chemotherapy.

Repeated scintigraphs at intervals of three months on patients with tuberculous disease who have been adequately treated by grafting and chemotherapy reveal that the isotope uptake is within normal limits after an average period of three to six months. The incidence of reactivation in such patients is about 1 per cent, and is regarded as due to inadequate clearance. The value of repeated scintigraphy is shown in the following case.

Case 6—A man aged sixty-five with a history of spinal tuberculosis forty years previously presented with reactivation and impending paraplegia after a road traffic accident. Investigations, including a scintigraph, indicated active disease. This was treated by clearance of the lesion from the seventh to the tenth thoracic vertebrae, grafting and chemotherapy. Convalescence was uneventful and the paraplegia resolved. Nine months later he complained of recurrent back pain, which became steadily worse. By one year the sedimentation rate had risen to 32 millimetres/hour. A further scintigraph showed an increased uptake at the lower end of the grafted area. Re-exploration revealed incorporation of the graft proximally but active disease distally, which had led to non-union of the graft. Further clearance and grafting were successful. The sedimentation rate returned to normal three months after operation. The patient has remained symptomless for two years and resumed work fifteen months ago.

CONCLUSIONS

The advantages of Fluorine-18 and Strontium-87m over isotopes previously used in the assessment of bone lesions are that both have a relatively short half-life, 112 and 168 minutes respectively. This makes it possible to administer enough isotope to give maximal definition, while at the same time the radiation dose is held at a minimal and acceptable level. The technique of scintigraphic examination is relatively simple and causes only slight inconvenience to the patient. The results are reliable and are reproducible. Consequently a negative scan in association with negative serological investigations virtually excludes a diagnosis of infective spondylitis arising de novo. Scanning is an important aid in the detection of reactivation of an inflammatory lesion, indeed it is often the only certain method of diagnosis. Scintigraphy is also of value in assessing the progress of inflammatory disease and in the differential diagnosis of atypical lesions.

The disadvantages of Fluorine-18 are, firstly, that the high concentration in the urine can interfere with pelvic and lumbo-sacral scans; this is partly prevented by emptying the bladder immediately before scanning is commenced. Secondly, because of the short half-life the department using this isotope must have easy access to the site of production. Strontium-87m, which is slightly less effective because of the lower bone/blood ratio, will probably be more used because the Yttrium-87 generator can be housed in a suitably equipped radioisotope department.

SUMMARY

1. An ancillary diagnostic technique using Fluorine-18 or Strontium-87m is described, and has assisted in the correct diagnosis of fifty-two patients admitted with the provisional diagnosis of infective spondylitis.
2. The technique is of particular value in the assessment of reactivation of chronic spinal infections and in the differential diagnosis of atypical lesions.

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REFERENCES


