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MINERAL METABOLISM IN PRIMARY BONE TUMORS STUDIED BY EXTERNAL COUNTING OF ^{85}Sr

By

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INTRODUCTION

Mulry & Dudley (1951) reported increased uptake of ^{72}Ga in 15 of 18 primary or secondary bone tumors, and that skeletal tumor metastasis could be detected by isotope technique before being visible on roentgenograms.

Gynning et al. (1961) and *Corey et al.* (1962) have also shown the advantages of isotope techniques in addition to roentgenography for early detection of bone metastasis.

Previous communications have described the technique of body surface activity measurements of intravenously injected ^{47}Ca and ^{85}Sr (*Bauer & Wendeborg* 1959, *Wendeborg* 1961). The results suggested that the method may be valuable for localisation and delineation of bone lesions such as fractures, infections and tumors. Subsequent reports have been made concerning external counting over fractures (*Wendeborg* 1961), bone infections (*Dymling & Wendeborg* 1965, *Fel-länder & Lindberg* 1964) and osteoarthritis of the hip (*Danielsson, Dymling & Heripret* 1964).

The present report deals with the uptake of intravenously injected ^{85}Sr in primary bone tumors assayed by means of the external counting technique.

CASE MATERIAL

The report is based on studies of 22 cases of primary bone tumor: osteogenic sarcoma (3 cases); chondrosarcoma (2 cases); eosinophilic granuloma (3 cases); osteoclastoma (4 cases); solitary bone cyst (4 cases); osteofibroma (4 cases); Ewing's sarcoma (1 case) and Letterer-

TABLE

Case no.	Fig. no.	Age	Sex	Diagnosis	Localisation
I	1, 2, 3	10	♀	Osteogenic sarcoma	Large tumour destruction of distal, lateral femur
II	4, 5	13	♀	Osteogenic sarcoma	Large tumour destruction of distal, lateral femur
III	6, 7	50	♂	Osteogenic sarcoma	Massive tumour involvement around prox. femur
IV		57	♀	Chondrosarcoma	Large tumour destruction of the upper part of femoral diaphysis
V	8, 9	45	♂	Chondrosarcoma	Tumour localised to lateral, femoral condyle. Size 5 × 5 × 4 cm
VI	10, 11	3	♂	Eosinophilic granuloma	Large tumour in the middle part of femur
VII		12	♂	Eosinophilic granuloma	Tumour localised to the diaphysis of humerus
VIII		9	♀	Eosinophilic granuloma	Rather large destruction of prox. tibia
IX		16	♀	Osteoclastoma	Large destruction of caput humeri
X		48	♀	Osteoclastoma	Large destruction of distal femur
XI		55	♀	Osteoclastoma	Large destruction of caput humeri
XII	12, 13	23	♂	Osteoclastoma	Total destruction and compression of vertebral body L III
XIII		6	♂	Solitary bone cyst	Large cyst in trochanteric region of femur
XIV		11	♂	Solitary bone cyst	Large cyst in prox. humerus
XV		10	♀	Solitary bone cyst	Small cyst in prox. fibula
XVI		17	♂	Solitary bone cyst	Small cyst in distal humerus
XVII		11	♂	Osteofibroma	Small fibroma in distal femur
XVIII		18	♀	Osteofibroma	Small fibroma in prox. tibia. Size 1 × 1 × 2 cm

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Dose μ C	Collimator	Interval after injection	Activity ratio	Comments
25	12°	2 days	7.6	Act. measurem. on bone spec. post mortem
50	12°	20 days	7.3	
50	10 mm	20 hours		Amputation
50	12°	7 days	5.8	See <i>Bauer-Wendeberg</i> 1959, Case 9
	12°	14 days	7.5	
50	12°	7 days	11.9	
	12°	14 days	12.1	
50	12°	5 days	7.3	
	12°	14 days	11.0	
50	12°	9 days	11.4	
	12°	14 days	11.7	
50	12°	9 days	11.0	
	12°	14 days	12.6	
50	12°	7 days	8.6	
15	24 mm	5 days	9.3	
	24 mm	10 days	9.4	
30	24 mm	7 days	6.3	
	24 mm	12 days	4.8	
20	12°	6 days	11.2	See <i>Bauer-Wendeberg</i> 1959, Case 10
30	12°	14 days	2.2	
50	12°	10 days	3.9	Marked activity peak over bone lesion See <i>Bauer-Wendeberg</i> 1959, Case 11
40	12°	7 days	4.3	
	12°	14 days	4.1	
35	12°	7 days		
		14 days		
20	12°	11 days	1.8	
	12°	18 days	1.8	
30	12°	14 days	3.7	
30	12°	7 days	1.1	
	12°	14 days	1.0	
30	12°	7 days	1.0	
	12°	14 days	1.0	
30	12°	7 days	1.2	
	12°	14 days	1.2	
35	12°	7 days	1.2	
	12°	14 days	1.2	

TABLE

Case no.	Fig. no.	Age	Sex	Diagnosis	Localisation
XIX		13	♂	Osteofibroma	Fibroma of distal tibia. Size $2 \times 2 \times 4.5$ cm
XX		12	♀	Osteofibroma	Small fibroma of distal tibia. Size $1 \times 1 \times 2.5$ cm
XXI		9	♀	Ewing's sarcoma	Tumour localized to lumbo-sacral region of the spine
XXII	14a+b	2	♀	Letterer-Siwe's disease	Large bone destruction of prox. tibia and prox. femur.

Siwe's disease (1 case). Patient age ranged from 2 to 55 years. The diagnoses were based on clinical appearance, roentgenography and in most cases microscopy of biopsy specimens. The localisation and relative size of the tumors with other pertinent data of the patients are given in Table 1. The case numbers used in the text refer to this table.

METHOD

The patients were given less than $1 \mu\text{C}$ carrierfree ^{85}Sr per kilogram body weight by intravenous injection. External counting was performed with a collimated scintillation detector. Three sets of collimators were alternatively used; a 12° wide angle collimator, a 24 mm cylindrical collimator and a 10 mm slot aperture collimator. The positioning of the detector in relation to the bone lesion was made with the aid of roentgenograms and palpation. The collimator was placed with its outer aperture close to the skin over the area to be counted. The activity measurements were made at irregular time intervals after injection of ^{85}Sr , usually at about 1 and 2 weeks. For further details of the method see *Bauer & Wendeborg* (1959).

The results were, when possible, expressed as *activity ratio*, i.e. counting rate over bone tumor to counting rate over corresponding normal bone. In two cases of tumors of the spine the activity values were compared to activity values of normal persons (*Bauer & Scoccianti* 1961). Absolute activity measurements were made in a well crystal scintillation counter on bone ash dissolved in concentrated nitric acid, and were expressed as per cent of dose per gram ash weight.

1 (cont.)

Dose μC	Collimator	Interval after injection	Activity ratio	Comments
15	12°	6 days	2.0	
10	24 mm	4 days	1.9	
	12°	4 days	1.3	
15	12°	7 days		{ Slightly increased activity compared to normal values
		14 days		
10	12°	14 days		
		tibia	0.5	
		femur	0.8	

RESULTS

The three cases of osteogenic sarcoma all showed significantly higher uptake of ^{85}Sr in the tumor area than in corresponding normal bone tissue (Figs. 1, 2, 4, 6). The activity ratios 14 days after injection were

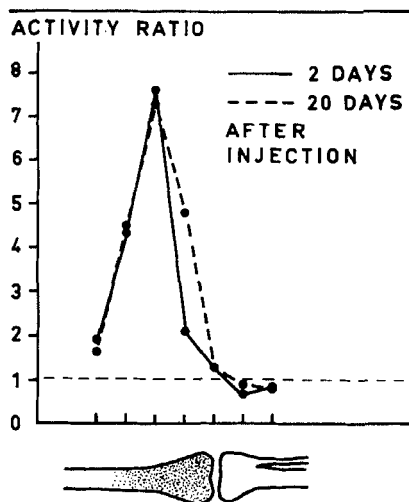


Fig. 1.

Fig. 1. Case 1. Osteogenic sarcoma of distal femur. The roentgenogram is given in Fig. 3.

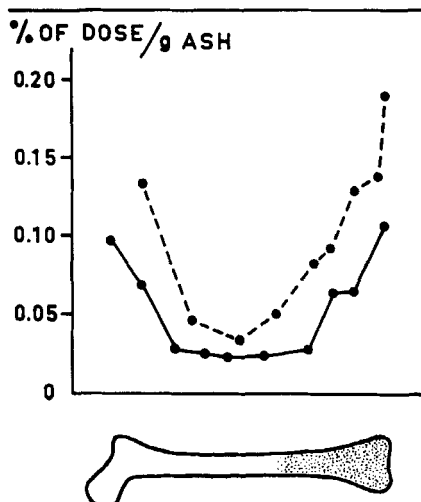


Fig. 2.

Fig. 2. Case I. Osteogenic sarcoma of distal femur. 50 μC of ^{85}Sr was given 2 days before the patient died of pulmonary metastasis. Graph shows absolute activities expressed as per cent of dose gm ash weight in bone specimens taken from tumor femur (-----) and normal femur (———).

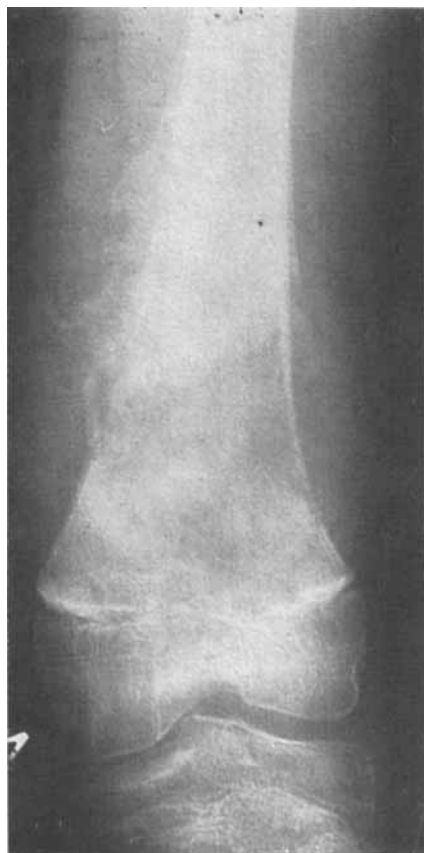


Fig. 3.
Case I. Osteogenic sarcoma.

found to be as high as 12 in case III, where the ratio increased from 7.5 to 12.1 during the four month interval between the two investigations performed in this case (Fig. 6). Activity measurements were made on bone ash from the affected and the normal femur of case I, who was given a second injection of ^{85}Sr two days before she died from pulmonary metastasis. In all bone specimens taken from the affected femur in this case the activity per gram ash weight was higher than the activity of corresponding specimens from the normal femur (Fig. 2). In case II measurements were made with the 10 mm slot aperture collimator over the bone specimen dissected free from soft tissues after thigh amputation. The activity curve given in Fig. 4 shows the delinea-

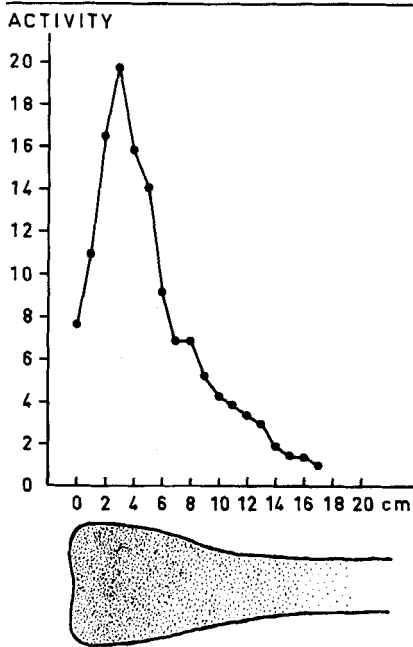


Fig. 4.



Fig. 5.

Fig. 4. Case II. Osteogenic sarcoma of distal femur. Thigh amputation was performed 20 hours after isotope injection. The distal femur was dissected free from soft tissues. Activity measurements were made with a 10 mm slot aperture collimator. The roentgenogram of the tumor is given in Fig. 5.

Fig. 5. Case II. Osteogenic sarcoma.

tion of the tumor in the distal femur and will be compared to the roentgenographically visualized tumor of Fig. 5.

In the cases of the chondrosarcomas (Fig. 8 and case 9 in *Bauer & Wendeborg* 1959), the eosinophilic granulomas (Fig. 10) and the osteoclastomas (Fig. 12) the activity ratios were significantly higher than normal. This was true even in those cases of osteoclastoma where bone destruction was advanced.

In the series of solitary bone cysts and osteofibromas the activity ratios varied. In some cases the ratios approximated 1 but were in others significantly higher. The higher values were found in cases with relatively large cysts or fibromas.

The case of Ewing's sarcoma of the spine was found to have slightly increased activity uptake over the tumor area compared to normal cases. In the case of Letterer-Siwe's disease the activity ratio was lower

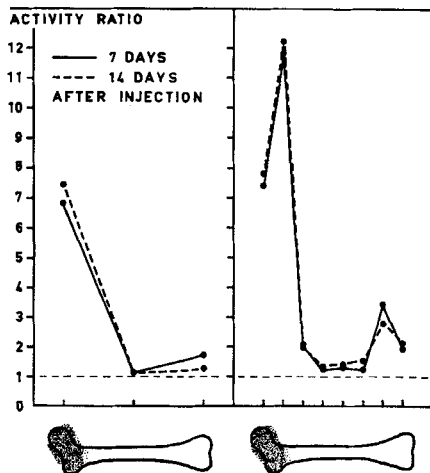


Fig. 6.



Fig. 7.

Fig. 6. Case III. Osteogenic sarcoma of proximal femur. The first investigation (left) was made four months prior to the second (right). The roentgenogram is given in Fig. 7.

Fig. 7. Case III. Osteogenic sarcoma.

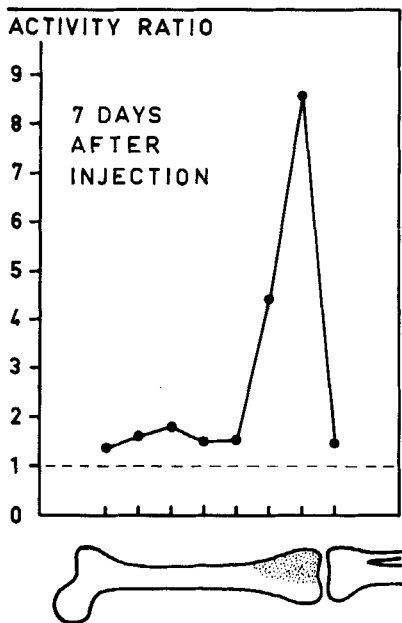


Fig. 8.



Fig. 9.

Fig. 8. Case V. Chondrosarcoma of distal femur. The roentgenogram is given in Fig. 9.

Fig. 9. Case V. Chondrosarcoma.

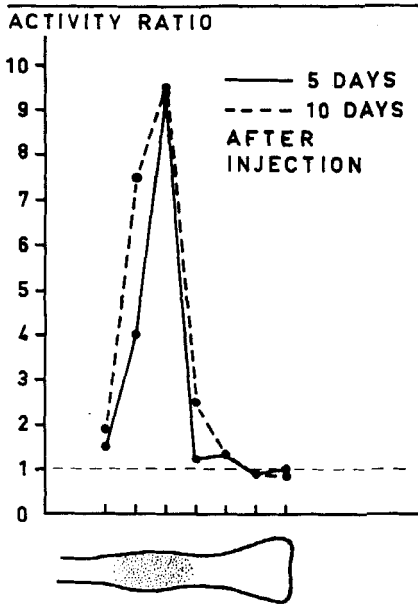


Fig. 10.

Case VI. Eosinophilic granuloma of middle femur. The roentgenogram is given in Fig. 11.

Fig. 11.

Case VI. Eosinophilic granuloma.



than normal over the affected areas of the hip and knee despite evidence of periosteal reaction on roentgenogram (Figs. 14 a and b).

DISCUSSION

The validity of the external counting method for differentiating bone lesions is limited because skeletal reaction to various lesions (tumor, infection or fracture) is non-specific and because of certain technical difficulties.

Increased uptake of bone seeking isotopes in a localised bone lesion is presumptive evidence of increased bone formation rate. The activity observed by the external counting method represents values based on integration of activity present in tumor, in bone reacting to tumor and in bone not reacting to tumor, since the limits of these three sources

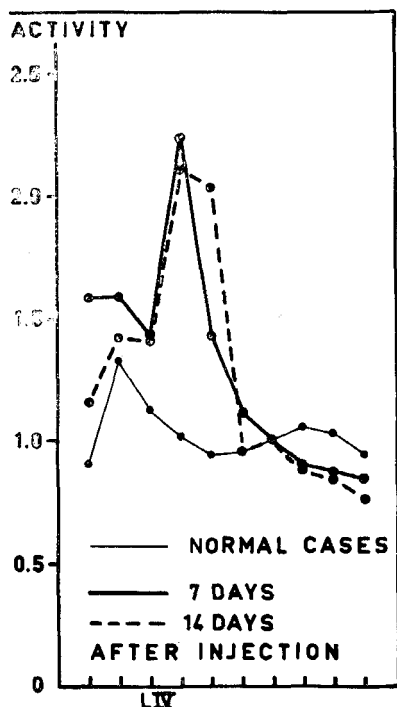


Fig. 12.

Case XII. Osteoclastoma with destruction and compression of the body of L III. Normal cases represent values obtained by Bauer & Scozzianti (1961). The roentgenogram is given in Fig. 13.



Fig. 13.

Case XII. Osteoclastoma.

cannot be defined. The bone structure itself of a tumor area is also qualitatively and quantitatively different from normal bone tissue.

The activity ratios do not express *absolute* indices but may under standardized conditions (of time intervals and collimators) be used as *relative* indices of differential of bone formation rates in a tumor area compared with normal bone tissue. The measurements must be taken when most of the tracer has left soft tissues and body fluids by excretion or incorporation in skeleton. Earlier studies from this laboratory suggest that for this purpose 1–2 weeks after injection constitutes a suitable interval and therefore most of the measurements reported here were done within these time limits. Furthermore, a definitive ratio between the size of the tumor and the aperture of the collimator must be established before valid comparisons of activity data from patients

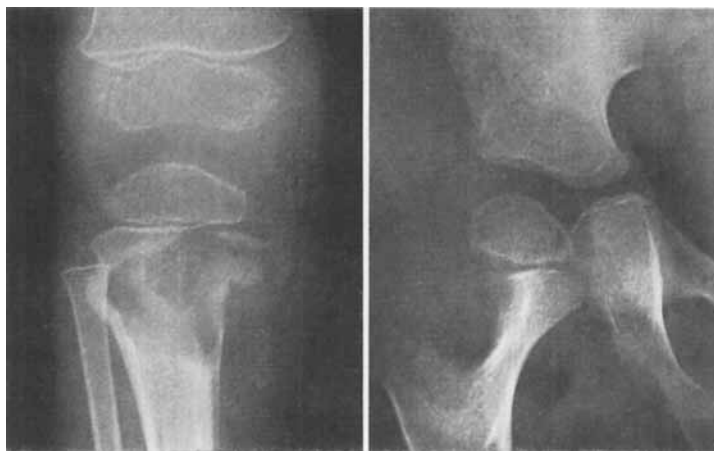
*Fig. 14 a.**Fig. 14 b.*

Fig. 14a. Case XXII. Letterer-Siwe's disease. Large tumor destructions of the proximal part of tibia and femur (Fig. 14b).

Fig. 14b. Case XXII. See legend of Fig. 14a.

with different kinds of tumors of varying sizes can be made. The areas "seen" by the detector must contain comparable proportions of tumor tissue, bone reacting to tumor and bone not reacting to tumor in the different patients. Otherwise, when using a large aperture collimator for measurements of small tumors, for example, a large portion of low-specific activity bone not reacting to tumor will dilute the minor portion of high-specific activity bone reacting to tumor. The activity ratio in such a case will be lower than if a more "close" collimation was used (compare activity ratios obtained with 12° wide angle and 24 mm cylindrical collimator in case XX). From a practical point of view such individual collimation cannot be performed. The choice of aperture of the collimator used in this study constitutes a compromise between a very wide aperture and a very narrow one.

In the series presented here the tumors were of varying sizes. The largest tumors were the osteogenic sarcomas, the chondrosarcomas, the eosinophilic granulomas and the osteoclastomas. These tumors also produced the highest activity ratios. In some cases of small bone cysts and osteofibromas the activity ratios were slightly above normal, while in others they were normal. These differences in activity ratios between large and small tumors must not be interpreted as varying bone formation rate in different kinds of tumor but may be caused by unsuitable collimation. In the case of Letterer-Siwe's disease with extensive bone

destructions of the proximal tibia and the proximal femur in one extremity the activity ratio was lower than normal despite roentgenological evidence of periosteal reactions. This may have been due to differences in bone mass of the two extremities.

The technique used in this investigation does not distinguish tracer in bone from tracer in tumor. *Corey et al* (1961) have presented autoradiographic evidence that in osteogenic sarcomas the tumor itself may incorporate tracer calcium or strontium. On the other hand, they also found that skeletal metastasis of mammary carcinoma do not incorporate tracer calcium in tumor tissue but only in adjacent bone. Hence the increased rate of bone formation observed by external counting over bone tumors without osteogenic properties is not a measure of tumor activity *per se* but rather of a skeletal repair reaction to bone destruction. The method thus does not seem to be applicable to differentiating different types of tumor.

In case II (Fig. 6) activity ratios higher than unity was found throughout the involved extremity. The peak activity ratio corresponds to the location of the osteogenic sarcoma in the proximal femur. Another minor peak was found over the ipsilateral knee region. This latter peak did not reflect tumor involvement but probably a phenomenon observed by *Wendeborg* (1961) in tracer studies of fractures of the shaft of the tibia, *i.e.* increased bone formation distal and proximal to a skeletal lesion in the extremities. This reaction which is especially pronounced in metaphyseal bone apparently involves the entire extremity and should not be confused with the area of tumor involvement.

Attempts were made to correlate the degree of roentgenologically evident periosteal reaction and sclerosis to the activity ratios but no conclusive results were obtained.

SUMMARY

The external counting studies of primary bone tumors have shown increased uptake of ^{85}Sr in the tumor area indicating increased bone formation rate, probably representing adjacent skeletal reaction to tumor bone destruction. The external counting technique seems to give no further information concerning differential diagnosis of bone tumors already visible on roentgenograms. Yet as has been shown previously the technique lends itself to early detection of bone lesions as tumor or infection not visible or questionable on roentgenograms. The extent of a tumor involvement may be estimated by scanning over the lesions.

R E S U M E

Les études par comptage externe des tumeurs osseuses primaires ont montré un accroissement de ^{85}Sr dans la région de la tumeur indiquant un taux accru de formation osseuse, représentant probablement une réaction squelettique adjacente à la destruction osseuse provoquée par la tumeur. La technique du comptage externe ne semble pas donner de plus amples renseignements concernant le diagnostic différentiel des tumeurs osseuses déjà visibles sur les radiogrammes. Comme on l'a démontré antérieurement, cette technique tend en soi à une détection précoce des lésions osseuses comme les tumeurs ou les infections qui ne sont pas visibles ou qui douteuses sur les radiogrammes. L'étendue d'une tumeur doit être établie par l'examen des lésions.

Z U S A M M E N F A S S U N G

Die externen Zählungsstudien von primären Knochentumoren haben eine gesteigerte Aufnahme von ^{85}Sr in der Tumorregion aufgewiesen und damit eine Steigerung der Geschwindigkeit der Knochenneubildung angezeigt, die wahrscheinlich eine Reaktion des angrenzenden Skelettes gegenüber der Knochendestruktion des Tumors darstellt. Die externe Zählungstechnik gibt anscheinend keine weitere Auskunft hinsichtlich der Differentialdiagnose von Tumoren, die bereits im Röntgenbilde sichtbar sind. Wie jedoch früher gezeigt wurde ist die Technik behilflich bei der frühzeitigen Entdeckung von Knochenschäden wie z. Bsp. Tumoren oder Infektionen, die in Röntgenbilde entweder nicht sichtbar sind oder fragwürdig erscheinen. Das Ausmass der Tumorausbreitung kann mittels Szintigraphie über der Erkrankungsstelle geschätzt werden.

R E F E R E N C E S

- Bauer, G. C. H. & Wendeborg B.:* External counting of Ca^{47} and Sr^{85} in studies of localized skeletal lesions in man. *J. Bone Jt Surg.* 41-B: 558, 1959.
- Bauer, G. C. H. & Scoccianti, P.:* Uptake of Sr^{85} in non-malignant vertebral lesions in man. *Acta orthop. scand.* 31: 90, 1961.
- Corey, K. R., Kenny, P., Greenberg, E., Pazianos, A. & Pearson, O. H.:* The use of Ca^{47} in diagnostic studies of patients with bone lesions. *Am. J. Roentgenol.* 85: 955, 1961.
- Corey, K. R., Kenny, P., Greenberg, E. & Laughlin, J. S.:* The use of Ca^{47} and Sr^{85} in diagnosis of bone tumors. In "Medical Uses of Ca^{47} " p. 95. International Atomic Energy Agency, Vienna, 1962.
- Dymling, J. F. & Wendeborg, B.:* External counting of ^{85}Sr and ^{47}Ca in localized bone infections. *Acta orthop. scand.* (this issue), 1965.

- Danielsson, L., Dymling, J.F. & Heripret, G.:* Coxarthrosis in man studied with external counting of Sr^{85} and Ca^{47} . Clin. orthop. 31: 184, 1964.
- Felländer, M. & Lindberg, L.:* Studies on the uptake of ^{85}Sr in inflammatory spinal lesions. Presented at the IXth SICOT Congress in Vienna, 1963. To be published. 1965.
- Gynning, I., Langeland, P., Lindberg, S. & Waldeskog, B.:* Localisation with Sr^{85} of spinal metastasis in mammary cancer and changes in uptake after hormone and roentgen therapy. Acta radiol. 55: 119, 1961.
- Mulry, W. C. & Dudley, H. C.:* Studies of radiogallium as a diagnostic agent in bone tumours. J. Lab. Clin. Med. 37: 239, 1951.
- Wendeborg, B.:* Mineral metabolism of fractures of the tibia in man studied with external counting of Sr^{85} . Acta orthop. scand. Suppl. 52, 1961.