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From the Orthopaedic Research Laboratories (Head: Göran C.H. Bauer, M.D.) of the Orthopaedic Clinic, Malmö, (Head: Sophus von Rosen, M.D.), Lund University, Sweden.

MINERAL METABOLISM OF FRACTURES OF THE TIBIA IN MAN STUDIED WITH EXTERNAL COUNTING OF Sr^{85}

by

BO WENDEBERG

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INTRODUCTION

The orthopaedic surgeon every day witneses the remoldeling capacity of the skeleton. He knows that this capacity is stronger in childhood than in adults, and that it is particularly strong during healing of fractures. He does not know, however, the rates of the two processes of remodeling, bone formation and resorption. The reason for this is simply that he cannot measure them. He cannot trace the origin of the organic matrix or the inorganic bone salt which build up the fracture callus. Hence he cannot measure the rate of bone formation in the callus. With the aid of X-ray techniques it is well known that the metaphyseal ends of a fractured bone shaft lose mineral. It is not known whether this condition is due to a diminished rate of bone formation or an increased rate of bone resorption, or if, perhaps, both possibilities obtain.

Animal experiments have shown that use of radioactive isotope tracer techniques should make it possible to measure the gross rates of the anabolic and katabolic processes involved in bone healing. Such techniques have now been developed to a point where they are safe and convenient for use in man.

Therefore it was decided to study the mineral metabolism of fractures in man with the aid of a radioactive isotope tracer method.

CHAPTER I

TRACER METHODS FOR STUDY OF MINERAL METABOLISM IN FRACTURES

1. Choice of tracer

Tracer methods have been fundamental for bone physiology since the days of Belchier, Duhamel, and Hunter around 1750 (see Bick, 1948). Two factors hampered the use of pre-isotope tracers: they lacked specificity and were difficult to measure quantitatively. The organic molecule of alizarin in madder, which was used for bone studies by the above authors, for example, does not follow the metabolic pathways of any single component of the bone tissue, and is hard to measure quantitatively even with modern equipment.

Alizarin, porphyrins, tetracyclines, and other materials which stain forming bone are valuable tracers because they identify bone formed since the administration of the tracer. Autoradiography following administration of β-emitting isotopes such as Ca^{45} or P^{32} gives a picture similar to that obtained with alizarin; the autoradiographic image permits higher resolution and is somewhat less difficult to quantitate. Cortical bone is remodeled by interstitial replacement of Haversian systems. Planimetry of newly formed as compared to old Haversian systems permits calculation of the fraction of the bone replaced (formed) per unit time, as has been recently shown by Frost, Villanueva and Roth (1960). Such methods are difficult to apply to cancellous bone because of its distorted structure. In the fracture callus this difficulty is particularly evident.

With radioactive isotopes of calcium, sodium, strontium, or any other

component of the bone salt the problem of quantitation is easy; the amount of tracer per unit bone tissue can be measured in, for example, ashed specimens of the bone. In the same way stable strontium or lead may be used as tracers for the bone salt; relative to radioactive tracers they are difficult to measure unless given in large doses.

In experimental animals it is not a problem that stable elements or β-emitting isotopes can be assayed practically only in biopsy or autopsy specimens of the skeleton. In man it is necessary to make serial measurements *in vivo*. During recent years γ-emitting isotopes of calcium (Ca^{47}, half-life 4.9 days) and strontium (Sr^{85}, half-life 65 days) have become available. Their half-lives are sufficiently short to make them safe for use in man. It is now a routine procedure to measure γ-emitting isotopes in the body with the aid of scintillation counters located on the body surface.

The metabolic fate of strontium injected into the circulation is not identical with that of calcium (Bauer, Carlsson and Lindquist, 1961). The main difference is that strontium is cleared from the plasma by urinary and faecal excretion more efficiently than is calcium (Spencer, Laszlo and Brothers, 1957). However, studies in animals (Bauer, Carlsson and Lindquist, 1955 a) and in man (Dow and Stanbury, 1960) have failed to demonstrate any difference in the rates at which the skeleton cleares plasma from the two elements when given in tracer dosage. As Ca^{47} has not been routinely produced until quite recently, Sr^{85} has been the tracer of choice for studies of fracture metabolism in man. Owing to its longer half-life it is still preferable for long-term studies.

Owing to the bulk of the shielding of the scintillation crystal, external counting techniques are more suitable for larger animals and man than for small experimental animals.

2. Applications of radioactive tracers

a. *Studies in experimental animals.* — The mineral metabolism of fractures has been studied in animals with the aid of radioactive isotopes of calcium, phosphorus, strontium, and other components of the bone salt. These studies have shown that the uptake of tracer from the circulation is more rapid in a fracture than in comparable, normal bone. Bauer (1954) found that the amount of tracer in a one-week-old fracture of the femoral shaft in adult rats was higher than normal within hours after parenteral injection of Ca^{45} and increased

for the following five days. The ratio of the activity in the fracture to that in the intact shaft increased for 3—4 days, and then dropped.

The rate of the uptake varies with the age of the fracture: in rats the uptake in a fractured femoral shaft measured 24 hours after parenteral injection increases for 1—2 weeks and then slowly drops (Karsher, 1953; Cartier, DeBernard and Lagrange, 1956). Bohr (1955) found that even 6 months after fracture the uptake of P^{32} in femoral fractures in rats was still higher than normal. Falkenberg (1961) found an increased uptake of Sr^{85} in fractures of the radius in rabbits for 4 months after fracture.

Following fracture of the femoral shaft in rats, the uptake of P^{32} or Ca^{45} *per unit bone ash* was higher than normal also in adjacent bone, for example in the metaphyseal ends of the femur and tibia, and in the tibial shaft (Bohr and Sörensen, 1950; Wilkinson and Leblond, 1953). On the other hand, Bauer (1954) found that the *absolute* uptake of tracer in adjacent bone was not higher than normal; the shaft fracture had induced a loss in ash weight in adjacent metaphyseal bone. However, in subsequent experiments Bohr (1955) found that also the absolute uptake of P^{32} in the entire fractured leg was higher than normal. Lacroix and Ponlot (1956) have presented autoradiographic evidence that the absolute uptake of Ca^{45} is higher than normal in areas of post-traumatic loss of bone tissue in dogs.

Karsher (1953) and Bohr (1955) found in rats that the uptake of tracer in poorly healing fractures did not differ from that in normally healing fractures.

External counting techniques for measurement of $RI^{131}SA$, Sr^{85}, Na^{22} and other γ-emitters were used by MacDonald (1958) in his studies of fractures in rabbits.

b. *Studies in man.* — With external counting Dudley, Markowitz and Mitchell (1956) found higher uptake of Ga^{72} in human fractures than in intact bone; the uptake varied with the age of the fractures. However, only rarely did the activity over a fracture exceed a value which was two fold that recorded over intact bone, due probably in part to the poor selective affinity of gallium for bone tissue (Coste, Layani, Guérin and Guérin, 1959). In 1959 Bauer and Wendeberg described the use of external counting of Ca^{47} and Sr^{85} in the evaluation of mineral metabolism in various localized bone lesions in human subjects. The uptake of these tracers in human tibial and femoral fractures was found to be several times that in normal bone tissue. Bauer and Scoccianti (1961) made similar findings in studies of vertebral fractures in man.

3. Interpretation of tracer data

Radioactive isotopes of calcium and strontium present in the body fluids are incorporated into the skeleton by irreversible deposition (accretion) as a part of formation of bone mineral (Bauer, Carlsson and Lindquist, 1955 b; 1961). Under certain conditions a correlation was found, in experiments in rats, between "the amount of activity recovered from different portions of bone and the amount of bone salt formed in these bones in the course of bone growth and repair" (Bauer, 1954). An increased uptake of labelled calcium or strontium in fractured, as compared to intact, bone may thus indicate an increased accretion rate in fractured bone. In man it has been shown how the externally recorded activities following intravenous injection of Ca^{47} or Sr^{85} may be interpreted as an index of the accretion rate (Bauer and Wendeberg, 1959).

On the basis of the general consideration above, data from tracer studies in animals may be interpreted as follows:

Shortly after fracture the accretion rate in a fractured bone shaft is increased. It reaches a peak value within weeks in rats and stays higher than normal for several months. The calcium of the callus is derived from the general circulation. The accretion rate in poorly uniting fractures does not differ from that in normally healing fractures. The mineral loss in adjacent bone induced by a fracture is not caused by a decrease in the accretion rate but by a rise in the rate of bone salt resorption (Bauer and Carlsson, 1955). Some data indicate that the loss of bone mineral in adjacent bone is accompanied also by increased accretion. On this point the data conflict.

Bauer and Ray (1958) on the basis of a four-compartment model for strontium kinetics in man were able to simulate external counting curves over the knee and thigh in normal human subjects during five days from the moment of injection of Sr^{85}. On the basis of a two-compartment model similar simulations were made during the interval 1—10 days following injection of Ca^{47} or Sr^{85} in man under normal conditions and in general metabolic bone disease (Wendeberg, 1961).

4. Purpose of this investigation

The purpose of this investigation was to study the mineral metabolism in fractures of the tibial shaft in man by means of external counting of intravenously injected Sr^{85}. The tibia was selected for this investigation because it lends itself well to external measurements over the fracture as well as over adjacent bone. The intact leg served as control.

On the basis of a two-compartment model for strontium metabolism the results of the tracer study were interpreted to give information on changes in the accretion rate induced by the fracture.

CHAPTER II INVESTIGATION

A. CLINICAL MATERIAL

The present investigation was based on 53 isotope studies in 51 patients with a fracture of the shaft of one tibia. There were 38 males and 13 females ranging in age between 19 and 77 years. One patient without fracture was included for comparison with the fracture cases. Six patients were hospitalized during the investigation period.

With only two exceptions the patients had no other lesions in their lower limbs: one had a fracture of the contralateral patella 4 months prior to the investigation, and one had an osteoma of the ipsilateral femoral shaft. The material does not include any cases of fractures through localized bone lesions.

Forty-three fractures were classified as normally healing. At the time of the isotope investigation they were healed or were subsequently found to have healed within six months after fracture. Eight fractures showed delayed or non-union and/or osteitis. Pertinent data of the individual cases are given in Table I (normally healing fractures) and Table II (delayed healing, pseudarthrosis and/or osteitis). Case numbers in the following refer to these tables.

In 30 cases the fracture was located in the lower third of the tibia, in 19 cases in the middle third of the tibia and in 2 cases in the upper third of the tibia.

Twelve of the fractures were transverse, 18 fractures were oblique, and 21 fractures were comminute. In 11 cases the fracture was open.

The cause of the fractures were: traffic accidents (25 cases), falls (14 cases), sport accidents (4 cases), or crush injuries (8 cases).

The fractures were treated by osteosynthesis with Lane's or Egger's plate (17 cases), osteosynthesis with one or more screws (17 cases), osteosynthesis with Rush pin (1 case), sliding tibial graft (2 cases), transfixation (2 cases), and immobilization in plaster only (11 cases). In all of the cases the fractured leg had been immobilized in a plaster cast from groin to toes for a period ranging from 2 to 5 months for the group of normally healing fractures.

The interval between the fracture and the isotope study varied between 2 days and 106 months. Twenty-two patients, selected to observe the later stages of fracture repair, were obtained from a group of cases under follow-up in a clinical investigation to be reported in detail later (Bauer and Widmark, 1962).

B. METHOD

1. *Dose and administration of* Sr^{85}. — Each patient received an intravenous injection of 25—50 μC carrier-free Sr^{85} (γ-emitter with half-life of 65 days). The amount of radiation delivered to the skeleton by this dose was calculated to be less than the maximal permissible dose recommended by the International Commission on Radiological Protection (Bauer and Wendeberg, 1959).

2. *External counting measurements.* — At specific intervals of time after the injection of the isotope, activity measurements were performed with scintillation detectors over various locations of the fractured leg and over corresponding locations of the intact leg. Measurements were made over (a) the thigh, (b) the knee, and (c) at 5—7 points 5 cm apart from each other over the tibia. Duplicate measurements were made at each location on each occasion. The detector was repositioned between the two duplicate measurements. In order to ensure exact repositioning of the detector in duplicate measurements and in measurements at various intervals after the injection each area to be measured was marked with red ink. Marks were thus made (a) over the

femoral shaft 20 cm proximal to the base of the patella, (b) over the patella and (c) over the fracture and as many points as possible 5 cm apart from one another and on both sides of the fracture.

During the external counting the patient was in the supine position with the legs slightly abducted and the patella facing upwards. The legs were held in position by sand bags. The scintillation detector was placed with its outer aperture horizontal and close to the skin over the location marked with red ink. Care was taken to adjust the detector exactly over the mark. For measurements of patients still having plaster, this was removed or reduced to a posterior plaster splint.

The examination period covered 14 days. In most cases measurements were made only at 1 week and 2 weeks after the injection; in some also on intermediate occasions. In the latter group, then, the activities over the fracture and over the corresponding location of the intact tibia were measured every 1 to 5 minutes during the first hour after injection using two similar counting equipments. About 1 hour after the injection, activity measurements were made over the thighs, knees, fracture and intact tibia. The detector used for these measurements was also employed for repeated measurements over a period of 2 weeks after the injection. Measurements over all counting locations of the tibia (scanning) were performed only at 1 and 2 weeks after injection.

The results of the activity measurements are given as:

1) *Activity,* which means the externally recorded counting rate given as fraction of the counting rate of a Sr^{85} standard sample measured under standard conditions. This unit was used to describe the changes with time in counting rate recorded over one and the same location.

2) *Activity ratio,* which means the ratio between the counting rate over two anatomically corresponding locations, such as the knees. The activity ratio thus differs from unity if the two locations differ from one another in activity. In the following, the abbreviations (a) *thigh/control ratio,* (b) *knee/control ratio,* and (c) *fracture/control ratio* will be used for external counting rate ratios (a) thigh of fractured leg/thigh of intact leg, (b) knee of fractured leg/knee of intact leg, and (c) fracture/intact tibia, respectively.

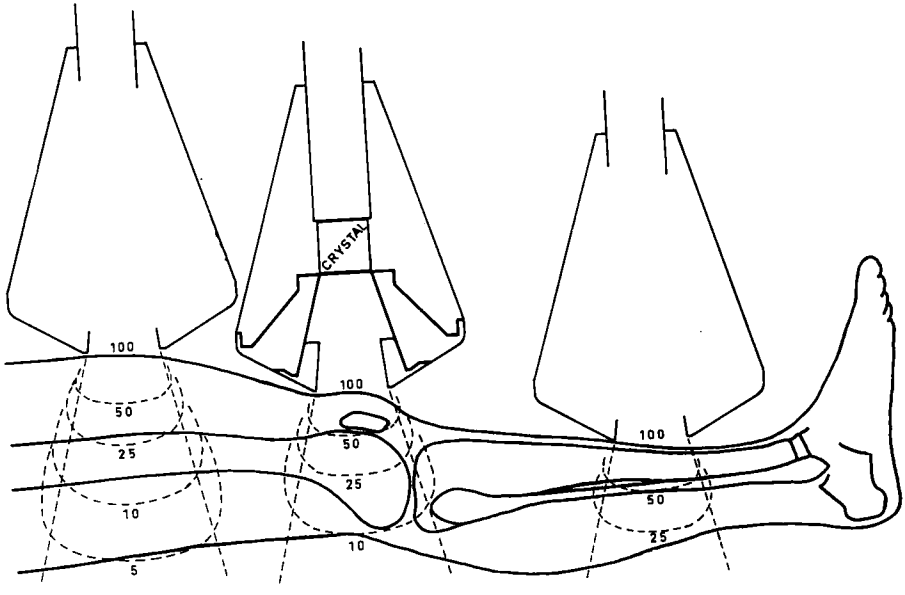

Fig. 1. Figure shows isoactivity curves projected over the three main counting locations. The curves were obtained by measurements of the activity of a point source of 10 μC Sr^{85} in different positions of a vertical plane through the crystal center. The measurements were performed with the Sr^{85} source placed in water assuming the radiation absorption in water being about equal to that in the body tissues. The counting equipment was the same as that used for external counting in the patients. The lower margin of the 12° wide-angle collimator was placed at the surface of the water. The figures give the activity as fraction of the activity recorded with the Sr^{85} source placed centrally in the outer aperture of the collimator. The counting efficiency of the activity retained in bone tissues thus differs between the counting locations. This may be part of the explanation of the different activity curves obtained over the thigh, the knee and the tibia and stresses the importance of anatomical identity between counting locations to be compared.

The influence on the external counting rate of anatomical factors, *e.g.* the proportions between the amounts of soft tissues and bone tissues and the position of these tissues in regard to the detector, is indicated in Fig. 1. It must be realized that even small differences in anatomy between two locations may make the activity ratio deviate from unity. Thus, for example, atrophy of the thigh muscles in the fractured leg, oedema in the fracture region, or increased amounts of bone tissue (callus) under the detector will increase the counting rate over the fractured leg. In the patients studied atrophy of thigh muscles was observed, but the difference between the circumference of the thigh in the two legs never exceeded 2 cm. Excessive amounts of callus were not observed in the patients studied. These sources of error must be taken into account in the interpretation of activity ratios which deviate only slightly from unity.

3. *Equipment.* — The equipment described by Bauer and Wendeberg (1959) was used in this investigation. Activity measurements were thus made with a lead shielded collimated scintillation detector with a 1.5″×1″ or a 2″×2″ NaI(Tl) crystal. A 12° wide-angle collimator (diameter of outer aperture 65 mm) was used throughout the investigation and in one case (Case II-6) also a 10 mm slot aperture insert. The distance from the center of the crystal to the outer aperture of the collimator was about 15 cm. The pulses from the photomultiplier were fed into a scaler via a linear amplifier and a pulse height analyzer. With the exception of the measurements made during the first hour after the injection of Sr^{85}, at least 1,000 impulses were counted on each occasion within a 7.5 or 10 volt discrimination window over the 0.51 MeV energy peak of S^{85}.

4. *Statistics.* — The counting rate was corrected for background activity and for physical decay of the Sr^{85}. The background activity was recorded with the detector placed over the examination table and with the apparatus adjusted as for measurements of the patients. The background activity was about 0.5 and 1.2 counts per second for the 1.5″×1″ and 2″×2″ crystals, respectively. Correction for physical decay was made by expressing the counting rate over the patient as fraction of the counting rate of a Sr^{85} standard.

The stability of the apparatus was checked daily by measuring the activity of a Na^{22} standard (half-life 2.5 years).

The lowest counting rates in this investigation were recorded on measurements over the tibia 14 days after injection of Sr^{85}; they were never

found to be less than twice the background activity. This implies that the standard deviation of the single observation due to random decay was less than ± 2 %.

Calculated on the basis of 150 duplicate measurements over fractures, knees and thighs the difference between the two measurements over the same area with intermediate repositioning of the detector was 2.7 ± 1.8 % of the mean value of the two counting rates.

In 50 patients without local bone lesions in the lower legs the activity ratios between the two knees at 1 and 2 weeks after injection of Sr^{85} were 1.06 ± 0.06 (mean ± S.D.) and 1.09 ± 0.09, respectively. The activity ratios between the two thighs at 1 and 2 weeks after injection were 1.05 ± 0.06 and 1.06 ± 0.09, respectively. The activity ratios were calculated by division of the higher counting rate with the lower one.

5. *General mineral metabolic studies.* — In four hospitalized patients (Cases I-3, II-4, II-6 and II-7) the urinary and faecal excretion of Sr^{85} and the serum activity were determined during a 14 day post-injection period. Based on these data the accretion rate of the total skeleton, the size of the exchangeable calcium pool in the body, the excretion rate and the body distribution of Sr^{85} were calculated according to Wendeberg, 1961. The data thus obtained were used for the interpretation of external counting measurements.

C. RESULTS

1. Intact bone

In the subject without fracture (Fig. 2) the activity over the knee rose from the moment of the injection to reach a maximum value at about 24 hours and then gradually dropped throughout the 14-day period studied. The activity over the thigh reached an activity peak as early as 10 minutes after the injection and then decreased continuously throughout the period of the investigation. The activity over the tibia reached an activity maximum within 24 hours of the injection and then decreased. The counting rate over the knee region was higher than over the thigh and tibia and somewhat higher over the thigh than over the tibia. The activity curves given in Fig. 2 are representative for the normal activity pattern observed in a large number of patients with or without metabolic bone disease.

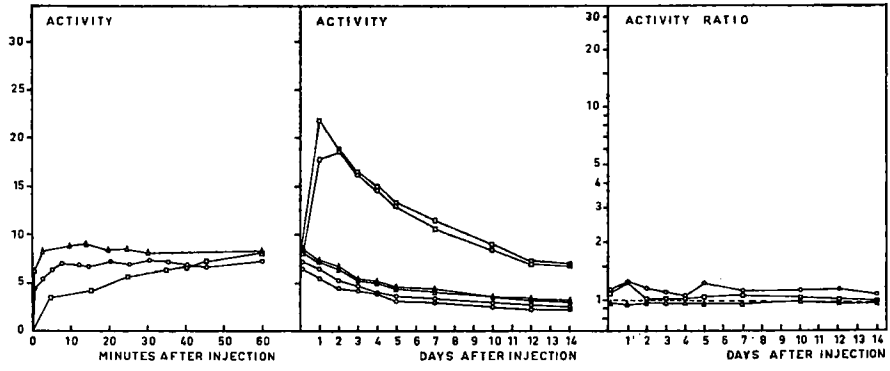

Fig. 2. Activity curves obtained by external counting over the thigh (△), the knee (□) and the tibia (○) at various intervals following injection of 40 μC Sr^{85} to a *normal man, aged 42, without bone injury.*

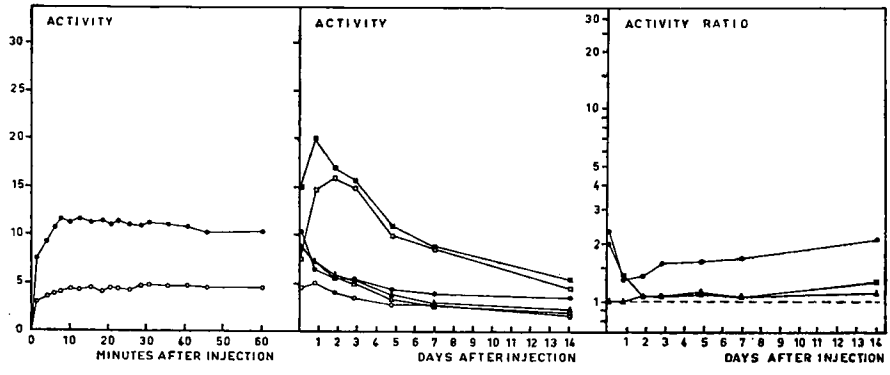

Fig. 3. Activity curves in a man, aged 37, given 40 μC Sr^{85} intravenously *two days* after he sustained a closed, comminute fracture of the middle third of his right tibia. (Case I-1).

Explanations of symbols for Figs. 3—10 and 18—20:

- ● fracture and activity ratio fracture/intact tibia
- ○ intact tibia
- ■ knee of fractured leg and activity ratio knee of fractured leg/knee of intact leg
- □ knee of intact leg
- ▲ thigh of fractured leg and activity ratio thigh of fractured leg/thigh of intact leg
- △ thigh of intact leg.

2. Normally healing fractures

a. *Variation in pattern of uptake of Sr^{85} with age of fracture.* — The activities over the lower limbs during a 14 day period following injection of Sr^{85} at increasing intervals of time following fracture of the tibia are shown for 8 patients in Figs. 3—10.

day-old acture.

In a patient, who received Sr^{85} 2 days after he sustained a fracture of the tibia (Fig. 3), the activity recorded over the fracture reached a maximum at about 8 minutes after injection, and thereafter decreased but stayed above that recorded over the control tibia throughout the 14 days of investigation. The fracture/control ratio thus dropped from 2.6 at 10 minutes to 1.3 at Day 1. The fracture/control ratio then increased to 2.1 recorded at Day 14. During the first few days after the injection the activity of the knee of the fractured leg was higher than that of the control knee with a knee/control ratio of 2.0 at 1 hour. This ratio decreased later to about unity. No difference in activity was noted between the two thighs.

day-old acture.

The pattern of the activity curves recorded in a patient who received the Sr^{85} 4 days after the fracture (Fig. 4) was found to be about the same as that of the patient described above.

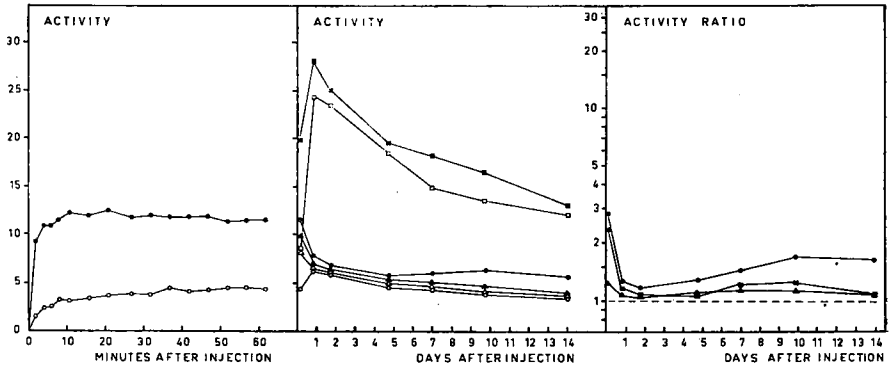

Fig. 4. Activity curves in a man, aged 19, given 30 μC Sr^{85} intravenously *four days* after he sustained a closed, transverse fracture of the middle third of his right tibia (Case I-2). The fracture was reduced and immobilized in plaster. For explanation of symbols, see Fig. 3.

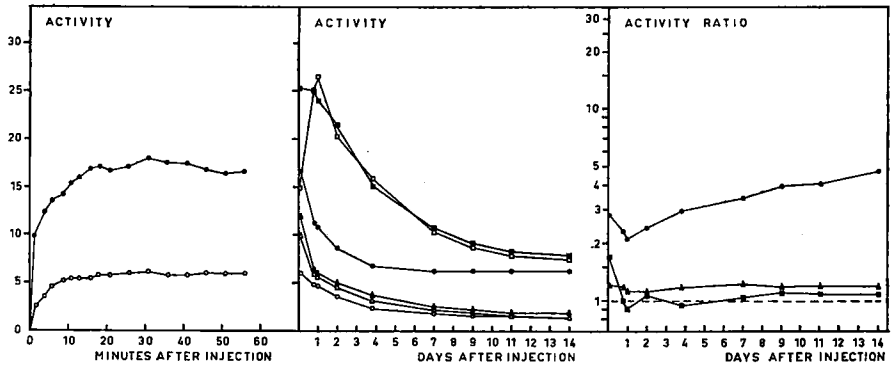

Fig. 5. Activity curves in a woman, aged 29, given 40 μC Sr^{85} intravenously *ten days* after she sustained a closed, oblique fracture of the middle third of her left tibia (Case I-3). The fracture was reduced and immobilized by an intramedullary Rush pin and plaster. In this case the externally recorded activity curves were simulated on the basis of a kinetical model, see Fig. 25. For explanation of symbols, see Fig. 3.

10-day-c
fracture

One patient (Fig. 5) received an injection of Sr^{85} 10 days after the fracture. The activity curves obtained over the fractured and the intact legs differed initially. These differences between the knees and thighs disappeared within 24 hours of the injection. The fracture/control ratio decreased during the initial 24 hours and then increased to 4.8 recorded at Day 14.

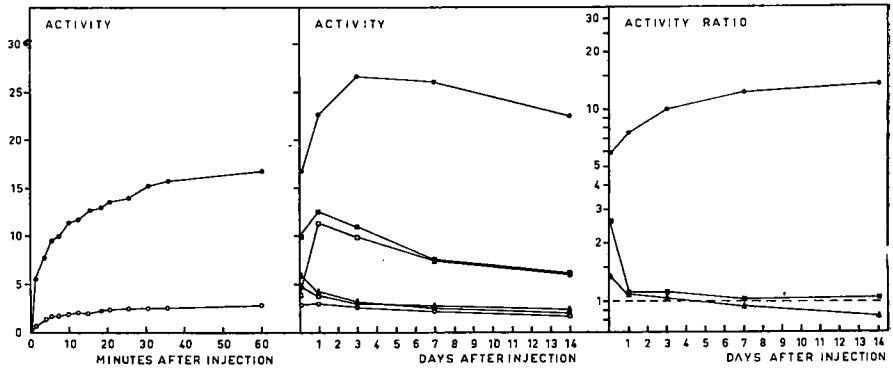

Fig. 6. Activity curves in a man, aged 19, given 30 μC Sr^{85} intravenously *five weeks* after he sustained a closed, oblique fracture of the distal third of his right tibia (Case I-5). The fracture was reduced and immobilized in plaster. Radiographs of the knee regions in this patient are shown in Fig. 39. For explanation of symbols, see Fig. 3.

week-old icture.

Five weeks after the fracture (Fig. 6) the pattern of the activity curves differed from those recorded earlier. The activity over the fractured increased for 3—4 days from the moment of injection and then gradually decreased. The fracture/control ratio increased throughout the 14-day-period: it was 12.3 at 1 week and 13.6 at 2 weeks after injection. In the knees and in the thighs activity differences were found 1 hour after the injection (knee/control ratio 2.6 and thigh/control ratio 1.3) but not at later intervals.

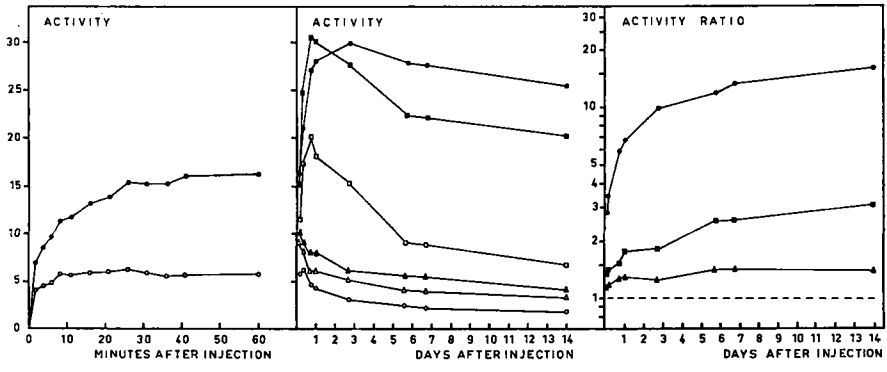

Fig. 7. Activity curves in a man, aged 19, given 30 μC Sr^{85} intravenously *five and a half* months after he sustained a closed, comminute fracture of the distal third of his right tibia (Case I-7). The fracture was reduced and immobilized by Egger's plate and plaster. This is the same case as in Fig. 11. A radiograph of the fractured tibia is shown in Fig. 27. For explanation of symbols, see Fig. 3.

:-month-old icture.

Five and a half months after the fracture (Fig. 7) the activity over the fracture increased until the third day after the injection and thereafter decreased. The fracture/control ratio increased throughout the 14 days of investigation; it was 12.8 at 1 week and 16.2 at 2 weeks after the injection. In this case activity differences were recorded also between the two knees and between the two thighs during the entire investigation: the knee/control and thigh/control ratios 14 days after injection were 3.1 and 1.4, respectively.

:nonth-old icture.

At 10 months after the fracture (Fig. 8) the activity pattern was largely the same as that observed five and a half months after the fracture.

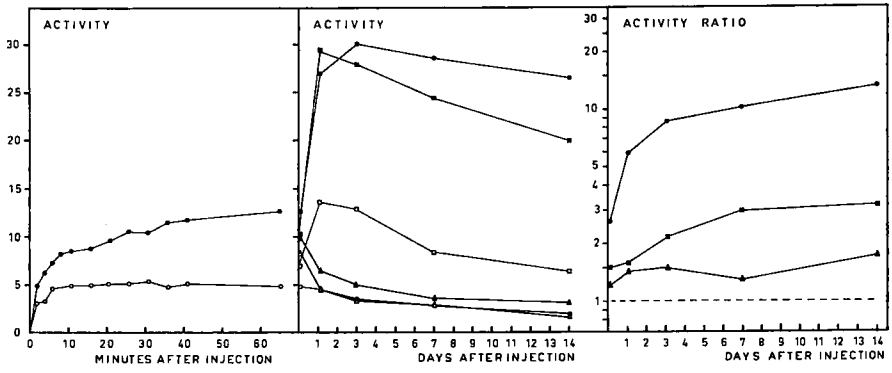

Fig. 8. Activity curves in a man, aged 32, given 40 μC Sr^{85} intravenously *ten months* after he sustained a closed, oblique fracture of the middle third of his right tibia (Case I-19). The fracture was reduced and immobilized by Egger's plate and plaster. For explanation of symbols, see Fig. 3.

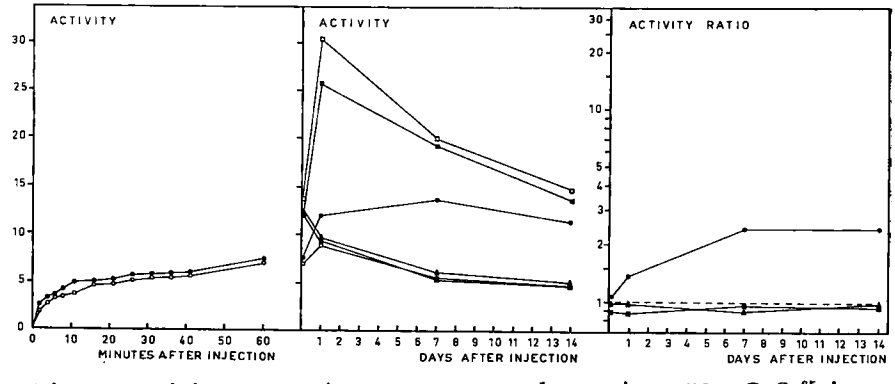

Fig. 9. Activity curves in a woman, aged 75, given 50 μC Sr^{85} intravenously *20 months* after she sustained a closed, oblique fracture of the distal third of her left tibia (Case I-24). The fracture was imobilized by screws and plaster. For explanation of symbols, see Fig. 3.

20-month-o fracture.

At 20 months after the fracture (Fig. 9) the activity over the fracture region was the same as over the control tibia during the first hour after the injection, but later the activity over the fractured tibia was higher than over the normal tibia. The fracture/control ratio was 2.4 both 1 and 2 weeks after the injection. The activities over the thighs and over the knees were lower in the fractured leg than in the control leg.

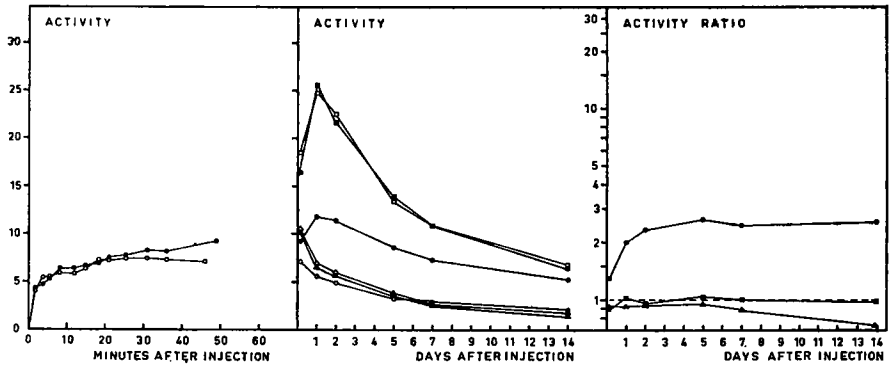

Fig. 10. Activity curves in a man, aged 54, given 50 μC Sr^{85} intravenously *55 months* after he sustained a closed, comminute fracture of the distal third of his left tibia (Case I-30). The fracture was immobilized by screws and plaster. This patient was studied also 41 months after fracture, see p. 30. For explanation of symbols, see Fig. 3.

-month-old acture.

At 55 months after the fracture (Fig. 10) the activity pattern was largely the same as that observed at 20 months.

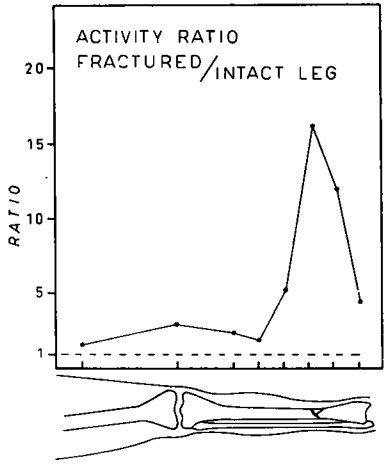

Fig. 11. Activity ratios fractured/control leg obtained by external counting two weeks after injection of 30 μC Sr^{85} to a man, aged 19, with a *5½-month-old* tibia fracture (Case I-7). A radiograph of the fractured tibia at the time of the isotope investigation is shown in Fig. 27. Activity curves of this patient are given in Fig. 7.

b. *Activity ratios fractured/intact leg 14 days after injection of Sr^{85}.* — Fig. 11 shows the external counting rate ratio fractured/control leg obtained 2 weeks after injection of Sr^{85} into a patient with a 5½-month-old tibial fracture. The activities in all locations of the fractured leg were higher than in corresponding control locations. The largest difference was noted between the fracture and the normal tibia as shown by the peak in the figure. Similar peaks were noted for all the patients examined with the scanning technique. The peaks tended to vary in height with the age of the fracture at the time of the isotope study (compare Figs. 11 and 12, see also Fig. 15) and in width with the anatomical type of the fracture

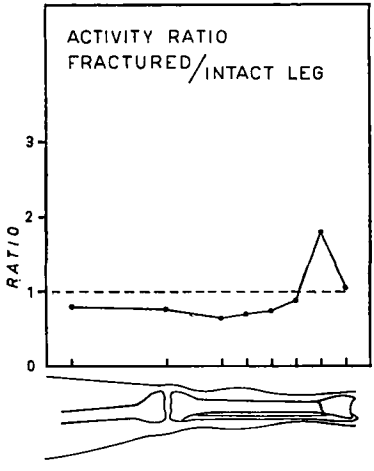

Fig. 12. Activity ratios fractured/control leg obtained by external counting two weeks after injection of 40 μC Sr^{85} to a woman, aged 39, with a *58-month-old* tibial fracture (Case I-33). A radiograph of the fractured tibia at the time of the isotope investigation is shown in Fig. 28.

(Fig. 13). The peaks were thus more broad-based when the fractures were spiral than when they were transverse. Additional, less marked peaks were noted over fibular fractures at levels other than that of the tibial fracture. An increased activity uptake was observed also over the donor site of a tibial graft proximal to the fracture (Fig. 14).

The activity ratios recorded 2 weeks after the injection are summarized in Fig. 15. The *fracture/control ratio* was above unity in all patients studied. It increased rapidly during the first few months after the fracture (Fig. 15, insert). The highest values were recorded about 6—8 months after the fracture; activity ratios fracture/control up to 30 were observed with a mean of 15.5 ± 7.2 for 14 patients studied at 5—10 months after the fracture, With increasing time after the fracture the ratios decreased. However, in the ten patients studied more than five years after fracture the fracture/control ratio still was significantly higher than unity (mean value 2.0 ± 0.59).

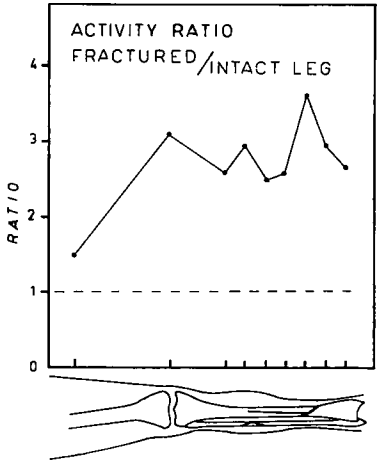

Fig. 13. Activity ratios fractured/control leg obtained by external counting two weeks after injection of 50 μC Sr^{85} to a man, aged 35, with a *15-month-old* tibial fracture (Case I-23). There was a comminute fracture of the distal third of tibia and a longitudinal fracture through the middle third of tibia. Fibula was fractured through its upper third. Radiographs of the fractured leg after injury, after reposition and fixation with screws and at the time of isotope investigation are shown in Fig. 29.

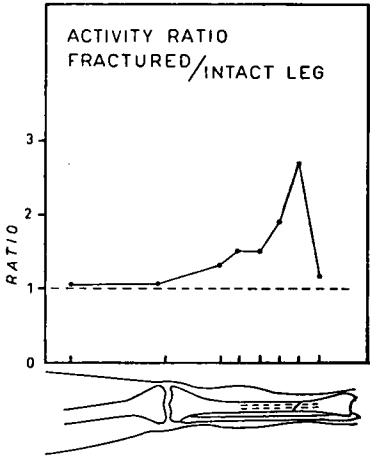

Fig. 14. Activity ratios fractured/control leg obtained by external counting two weeks after injection of 40 μC Sr^{85} to a woman, aged 46, with a *64-month-old* tibial fracture primarily treated by sliding bone graft operation (Case I-35). Note the broad peak including the donor site of the graft. A radiograph of the fractured tibia at the time of the isotope investigation is shown in Fig. 30.

No significant differences were observed between the fracture/control ratios obtained over fractures of the proximal, middle and distal third, respectively, of the tibia.

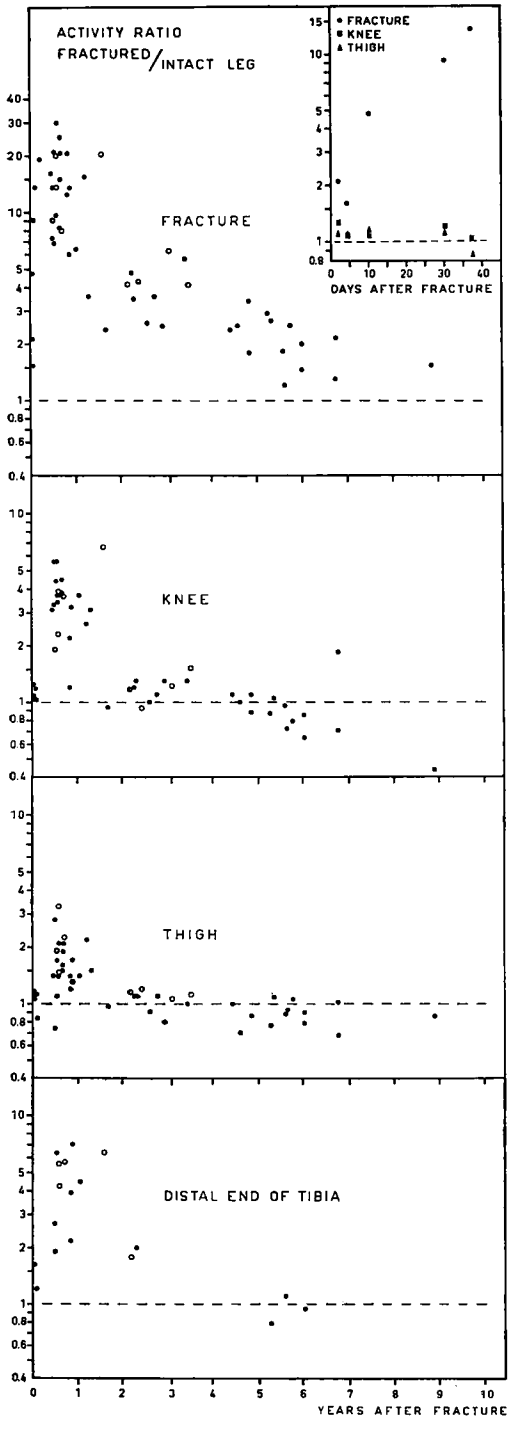

Fig. 15. Activity ratios fractured/intact leg obtained two weeks after injection of Sr^{85}. The figure includes activity ratios obtained one week after injection for three patients (Cases I-20, II-6 and II-7), who were not measured later. Knee/control and thigh/control ratios have been omitted for two patients who suffered from a fracture of the patella and an osteoma of the femoral shaft, respectively (Cases I-6 and I-32). The activity ratios given for the distal end of the tibia include only cases with fractures of the middle or proximal third of the tibia to exclude influence from activity in the fracture region.

● normally healing fractures

○ pseudarthrosis, delayed healing or osteitis.

During the first month after the fracture the *knee/control ratio* was normal. Thereafter it increased to a peak about 6 months after the fracture with a mean of 3.8 ± 1.3 for 14 patients studied at 5—10 months after fracture; it then decreased at roughly the same rate as the fracture/control ratio. Up to 4—5 years after the fracture the knee/control ratio was *above* unity and later *below* unity.

The *thigh/control ratio* varied with time in roughly the same way as the knee/control ratio; the peak activity ratios were lower, however. The mean of the activity ratios for 14 patients studied at 5—10 months after fracture was 1.6 ± 0.5. During the first 2—3 years after the fracture, the thigh/control ratio was *above* unity and later *below* unity.

The activity ratios obtained over the *distal tibia* are given in Fig. 15 only for patients with fractures of the middle or proximal third of tibia in order to exclude any influence of activity in the fracture region on the measurements. The change in the activity ratio with time after the fracture was found to be largely the same as that recorded over the knee region.

Two patients were examined twice. One of those (Case I-4) was studied 1 month and 8 months after the fracture. Between the two investigations the fracture/control ratio at Day 14 decreased from 9.1 to 8.3, the knee/control ratio increased from 1.2 to 4.5, and the thigh/control ratio increased from 1.1 to 1.5. The other patient (Case I-30) was examined 41 and 55 months after the fracture. During this interval the fracture/control ratio at Day 14 decreased from 5.7 to 2.5, the knee/control ratio from 1.3 to 1.0 and the thigh/control ratio from 1.0 to 0.70. The variation in the activity ratios with time after fracture in these two patients thus fitted the pattern observed for the material as a whole.

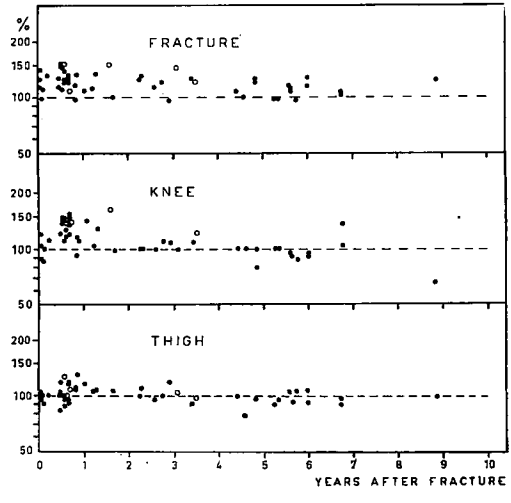

Fig. 16. Activity ratios recorded at two weeks in per cent of those recorded at one week following intravenous injection of Sr^{85}. For explanation of symbols, see Fig. 15.

Fig. 16 gives the activity ratios obtained two weeks after injection in per cent of the activity ratios obtained one week after injection. In most cases the fracture/control ratios rose between the two measurements. This was also noted for the knee/control ratios and the thigh/control ratios during the first years after fracture. Later, when most of these ratios were below unity, they tended to drop from 1 to 2 weeks after injection.

3. Fractures with delayed or non-union

Eight patients had pseudarthrosis, delayed healing and/or osteitis. Clinical data and radiographs of the fractures of these patients are given in Table II and Figs. 31—38.

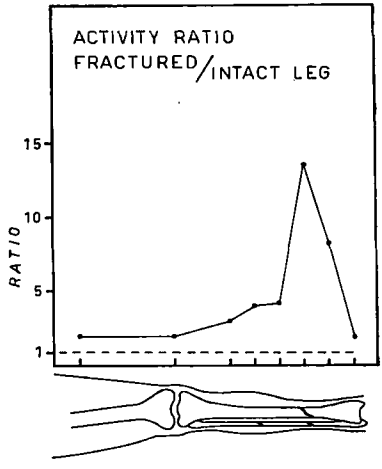

Fig. 17. Activity ratios fractured/control leg obtained by external counting two weeks after intravenous injection of 50 μC Sr^{85} to a man, aged 58, with *six-month-old*, slowly uniting fractures of his tibia and fibula (Case II-1). Radiographs of these fractures at the time of the isotope investigation are shown in Fig. 31

Fig. 17 gives activity ratios fractured/control leg obtained two weeks after injection of Sr^{85} in Case II-1. A marked peak was found over the fracture of the tibia and a less marked peak was found over the non-uniting fracture of the fibula.

Figs. 18 and 19 show the activity curves for two patients (Cases II-3 and II-4) with delayed healing of fractures of the tibia. The fractures were 7 and 8½ months old, respectively, at the time of investigation. The activity patterns in these cases did not differ from those obtained in normally healing fractures of corresponding age.

For one patient with a 26-month-old tibial pseudarthrosis (Case II-6) the activity pattern was largely the same as those of normally healing fractures of corresponding age (Fig. 20—A). Eight days after the injection of Sr^{85} the lower leg of this patient was amputated. Immediately before

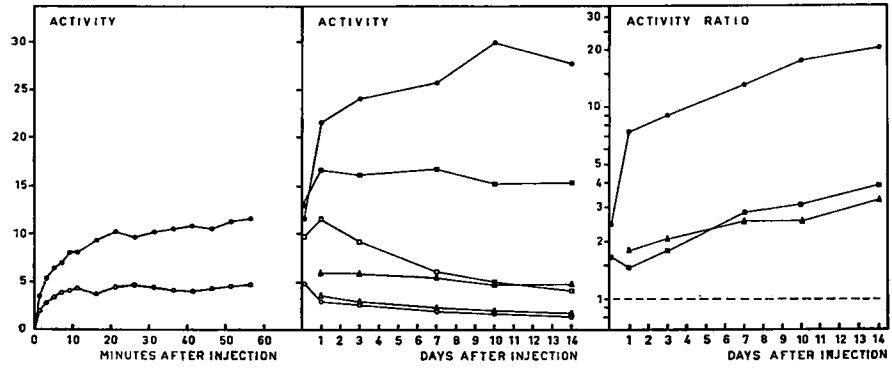

Fig. 18. Activity curves in a man, aged 22, given 40 μC Sr^{85} intravenously *7 months* after he sustained an open, transverse fracture of the middle third of his right tibia (Case II-3). The fracture was treated primarily with Egger's plate and plaster. At the time of the isotope injection he had delayed healing caused by infection. Radiographs of his tibia are shown in Fig. 33. For explanation of symbols, see Fig. 3.

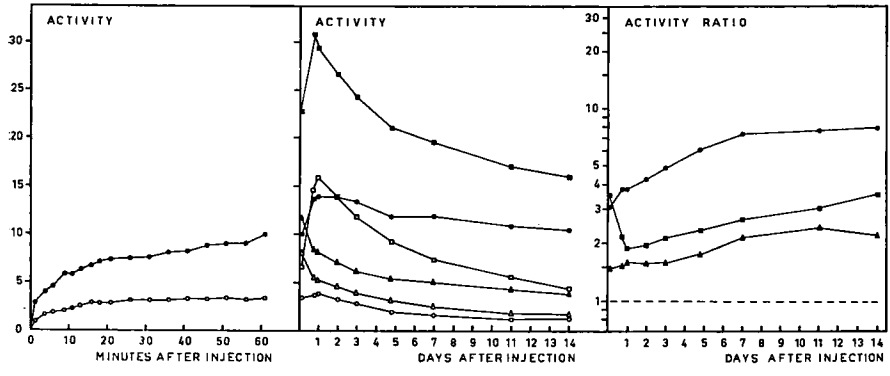

Fig. 19. Activity curves in a man, aged 38, given 40 μC Sr^{85} intravenously *8½ months* after he sustained an open, comminute fracture of the middle third of his left tibia (Case II-4). At the time of the isotope investigation he had delayed healing of the fracture. Radiographs of his tibia are shown in Fig. 34. For explanation of symbols, see Fig. 3. In this case the externally recorded activity curves were simulated on the basis of a kinetical model, see Fig. 24.

the amputation scanning was performed over the fracture and its surroundings and over the intact tibia with a 10 mm slot aperture insert. These measurements showed a well defined activity peak over the tibial fracture and a less marked peak over the fibular fracture (Fig. 20—B). The activity

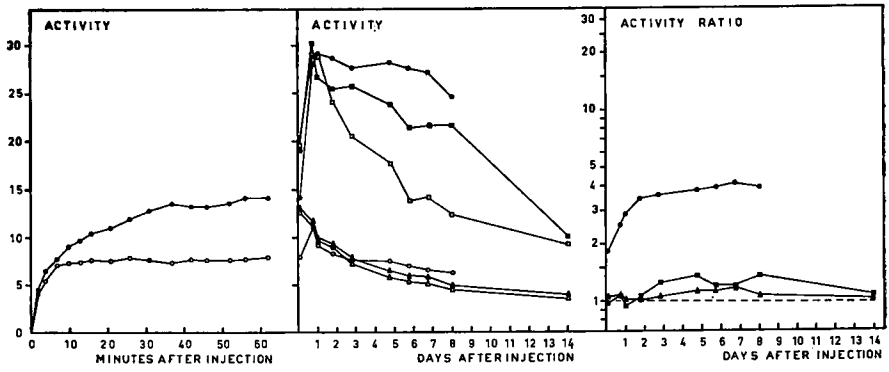

Fig. 20—A. Activity curves in a man, aged 58, given 50 μC Sr^{85} intravenously *26 months* after he sustained an open, transverse fracture of the middle third of his right tibia (Case II-6). Because of pseudarthrosis a lower leg amputation was decided on. The isotope injection was made 8 days prior to amputation. Immediately before amputation scanning with a 10 mm slot aperture insert was performed over the fracture, adjacent parts of tibia and fibula and over the intact left leg ("in vivo" of Fig. 20—B). After the amputation the tibia was dissected free from soft tissues and the fibula, cut transversly into 10 mm slices, which were ashed, dissolved in nitric acid and individually counted in a well scintillation counter ("in vitro" of Fig. 20—B). The most active slice included the pseudarthrosis and contained 0.2 % of the given dose of Sr^{85} (see Table III). A radiograph of the pseudarthrosis is shown in Fig. 36. For explanation of symbols, see Fig. 3.

ratio fracture/intact tibia was 5.8. After the amputation the tibia was dissected free from soft tissues and from the fibula and sawn into 10 mm thick slices corresponding to the areas covered by the collimator during external measurements. Measurements were then performed with the same equipment as used for in vivo measurements with the bone slice containing the pseudarthrosis placed vertically and centrally under the 10 mm slot aperture insert and with its upper margin 1 cm from the outer aperture of the insert. The counting rate recorded over this single bone piece (1.9 counts/second) was lower than the in vivo counting rate over the pseudarthrosis (2.6 counts/second). By adding the two bone slices adjacent to the pseudarthrosis the counting rate was about 25 % higher than earlier (2.4 counts/second) but still somewhat lower than in in vivo measurements (fibula was removed). No further increase in the counting rate was observed by placing more bone pieces at the side of the others. Thereafter the bone slices were ashed and dissolved in nitric acid and the activity

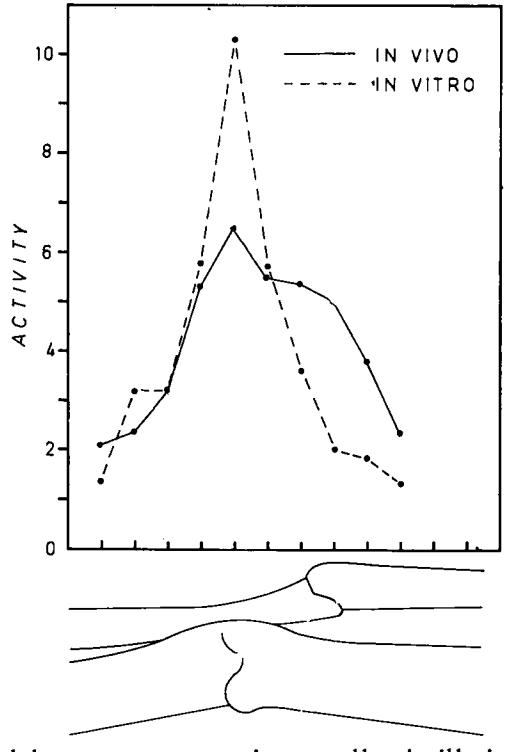

Fig. 20—B. See legend of Fig. 20—A.

was determined by measurements in a well scintillation counter (Table III and Fig. 20—B). The activity of the pseudarthrosis area was found to be higher than that of adjacent bone. Agreement was thus found between measurements made *in vivo* and *in vitro*.

The activity ratios obtained 2 weeks after the injection in the poorly healing cases are given in Fig. 15 together with those obtained in normally healing fractures. The activity ratios were of the same order in both groups. Thus no significant differences in the uptake of Sr^{85} was found between fractures in which healing was complicated and those in which healing was normal.

TABLE III.

Distance from pseudarthrosis (mm)	50	40	30	20	10	0	10	20	30	40	50
	proximal										distal
Activity (% of dose)	0.027	0.033	0.040	0.070	0.111	0.200	0.112	0.061	0.060	0.025	0.018
Ash weight (g)	1.73	1.77	1.80	2.22	1.29	1.27	1.39	1.51	1.79	1.54	1.16

Absolute activities and ash weights of 10 mm bone slices of tibia obtained from case II-6 after lower leg amputation because of a pseudarthrosis. Fifty uC of Sr^{85} was given intravenously 8 days before operation. See also legend of Fig. 20-A.

CHAPTER III DISCUSSION

A. KINETICS OF STRONTIUM IN MAN

In the interpretation of external measurements of Sr^{85} kinetical, anatomical, counting-geometrical and technical factors must be taken into account (Bauer and Wendeberg, 1959).

The kinetics of strontium in man was described by Bauer and Ray (1958) on the basis of an open four-compartment system drained by excretion and accretion (Bauer, Carlsson and Lindquist, 1955 b; 1961) (Fig. 21). The rate of exchange between three of the four compartments was so rapid that within about two hours of the injection of Sr^{85} they behaved kinetically largely as a single compartment (Figs. 21 and 22). After this time the kinetical model may be described as an open two-compartment system where one of the compartments (*S*) represents strontium in plasma, extra- and intracellular fluid and probably also a rapidly exchangeable fraction of bone mineral and where the other compartment (*E*) represents a less rapidly exchanging fraction of the bone mineral strontium.

After intravenous injection of Sr^{85} the isotope is thus, according to this concept, (a) mixed among the different compartments by *exchange* processes, (b) deposited in bone by irreversible *accretion*, or (c) lost from the body by *excretion* with urine and faeces. Calculated on the basis of this model, as described by Wendeberg (1961), the distribution of Sr^{85} during a 14 day post-injection period is shown for two patients (cases I-3 and

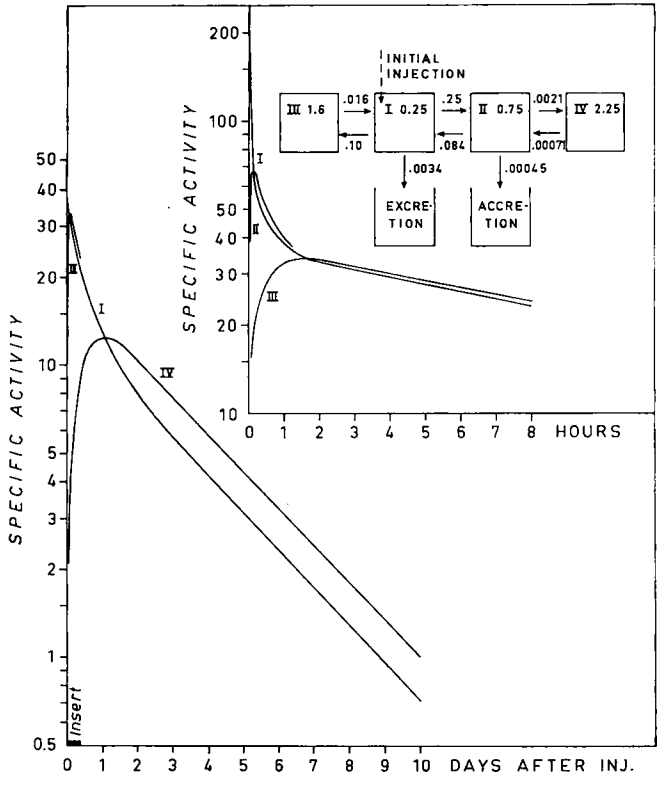

Fig. 21. Graph showing the kinetical four-compartment model for strontium metabolism given by Bauer and Ray (1958) and the specific Sr^{85} activities in the different compartments during a ten day post-injection period. The activity values were calculated by the electronic computer SMIL of Lund University using the values of the sizes of the compartments and the fractional removal rates given by Bauer and Ray. By definition compartment I represents intravascular strontium. Compartment IV was found to represent exchangeable strontium of the bone mineral. Compartments II and III were found to represent strontium of the extravascular body fluids and probably also represent a minor, rapidly exchangeable fraction of bone mineral strontium. Figures within the boxes indicate compartment sizes in units of g Ca. Bauer and Ray used 2.5 liters of plasma as unit. The fractional removal rates (units per minute) are indicated in the model. The figure shows that a few hours after injection compartments I, II and III may be treated as a single compartment.

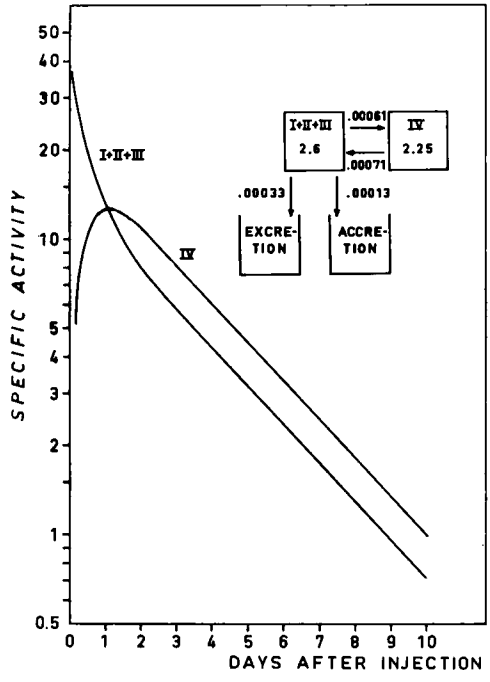

Fig. 22. Graph showing the two-compartment model, used for the analysis of external counting curves in this study, and the specific Sr^{85} activities in the two compartments during a ten day post-injection period. The size of the compartments and the fractional removal rates were derived from the four-compartment model given in Fig. 21 by lumping of compartments I, II and III. These three compartments are later referred to as compartment *S* and compartment IV is referred to as compartment *E*. The specific activity curves were calculated by the electronic computer SMIL of Lund University, Lund. A comparison of the curves given in this figure with those given in Fig. 21 reveals that a few hours after injection no differences in specific activity are obtained between the two models. This stresses the validity of the two-compartment model (Wendeberg, 1961).

II-4) in Fig. 23. The activity in the *S*-compartment dropped continuosly after the injection. The activity in the *E*-compartment increased to a maximum about 24 hours after the injection and then decreased almost linearly with the plasma activity. The activity in the accretion and excretion fractions increased cumulatively with the time after the injection.

It should be pointed out that the model used for this analysis does not take into account resorption of labelled strontium incorporated into the skeleton by accretion during 14 days following injection of the tracer.

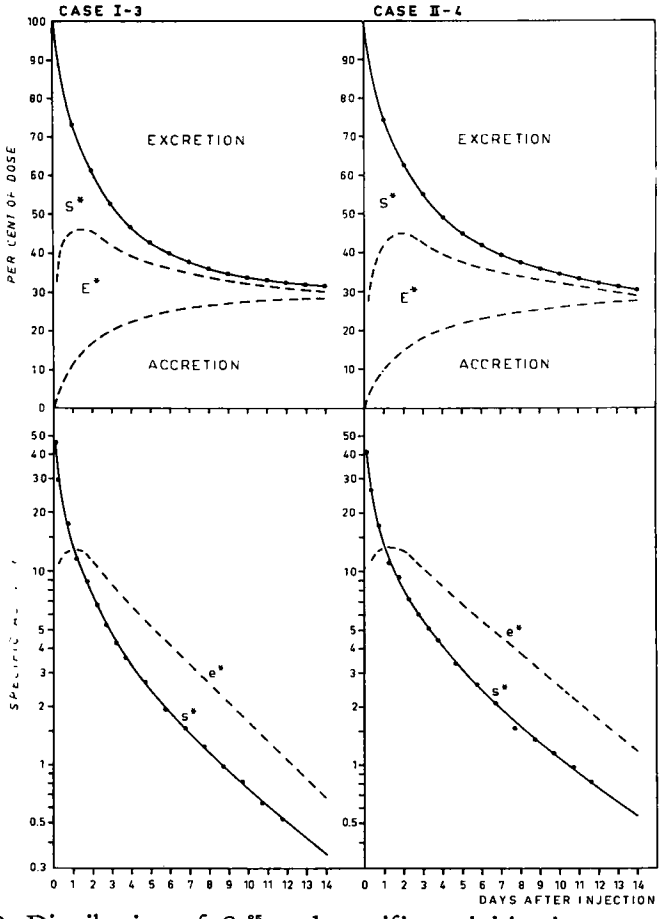

Fig. 23. Distribution of Sr^{85} and specific activities in compartments *S* and *E* (*s** and *e**, respectively, in per cent of dose/g Ca) during a 14 day period after single intravenous injection of Sr^{85} to Case I-3 and Case II-4. The black dots indicate experimentally determined serum activity values. The calculation of the distribution was based on the two-compartment model given in Fig. 22 and was made as follows:

Excretion by direct measurement of urine and faeces.

Accretion is the accretion rate *times* the intergrated specific serum activity.

S (amount of activity in compartment S)* is the size of compartment *S times* the specific serum activity (*s**).

E (amount of activity in compartment E)* is the size of compartment *E times* specific activity in compartment *E* (*e**).

The accretion rate, the sizes of compartments *S* and *E*, and the specific activity in compartment *E* were calculated according to Wendeberg (1961).

	Accretion rate (g Ca/day)	*S* (g Ca)	*E* (g Ca)
Case I-3	0.52	2.2	2.6
Case II-4	0.45	2.4	2.3

The reason for this is that at present all available data suggest that the minimum life span of normal bone tissue in man is longer than 14 days (Bauer, Carlsson and Lindquist, 1961). Frost, Villanueva and Roth (1960) found that the turnover time of normal cortical bone is 7—24 years.

B. INTERPRETATION OF EXTERNAL COUNTING OF Sr^{85}

Bauer and Ray (1958, on the basis of the four-compartment model were able to simulate external counting curves over the knee and thigh in normal human beings during the first 5 days after the injection of Sr^{85}.

In the present investigation externally recorded activities over the lower

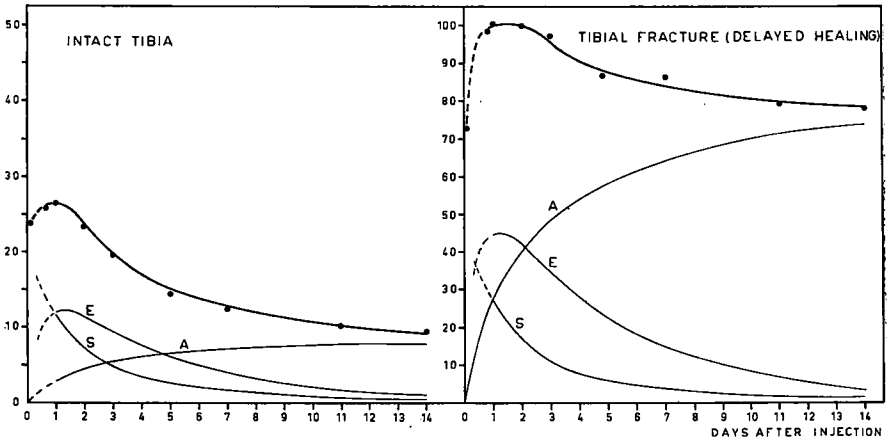

Fig. 24—A. Graphs representing simulation (on the basis of model shown in Fig. 22) of externally recorded activity values over the control right tibia and over the 8 ½-month-old fracture of the left tibia with delayed healing in Case II-4. Activity curves and radiographs of this case are given in Figs. 19 and 34, respectively. Body distribution of Sr^{85} after injection is given in Fig. 23.

Fractions of the amounts of activity in *S*, *E* and *A* (accretion) in the total body distribution were chosen so that their sum simulated the observed external counting measurements. The ratios of the *S*, *E* and *A* fractions in the fracture over those in the intact tibia were 2.4, 3.7 and 9.2, respectively. The external counting rate ratio fracture/control tibia at Day 14 was 8.0. Note the difference in activity scales in the two graphs.

The observed activity values are shown as black dots.

legs were analysed on the basis of the two-compartment model described above. The total body distribution of Sr^{85} in the two cases selected for this analysis is shown in Fig. 23. Fractions of the amounts of activity in

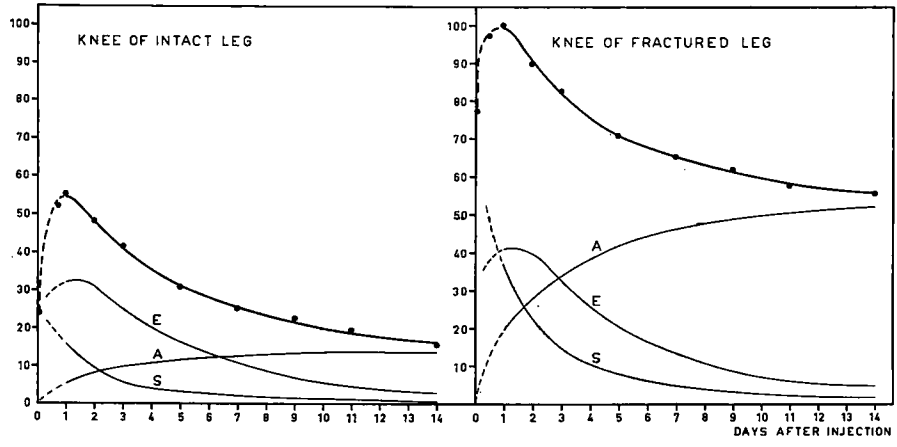

Fig. 24—B. Graph showing simulation of external counting measurements over knee of intact leg and knee of fractured leg in the same case as in Fig. 24—A. The ratios of *S*, *E* and *A* fractions in the knee of the fractured leg over those in the knee of the intact leg were 2.4, 1.3 and 3.7, respectively. The external counting rate ratio at Day 14 was 3.6.

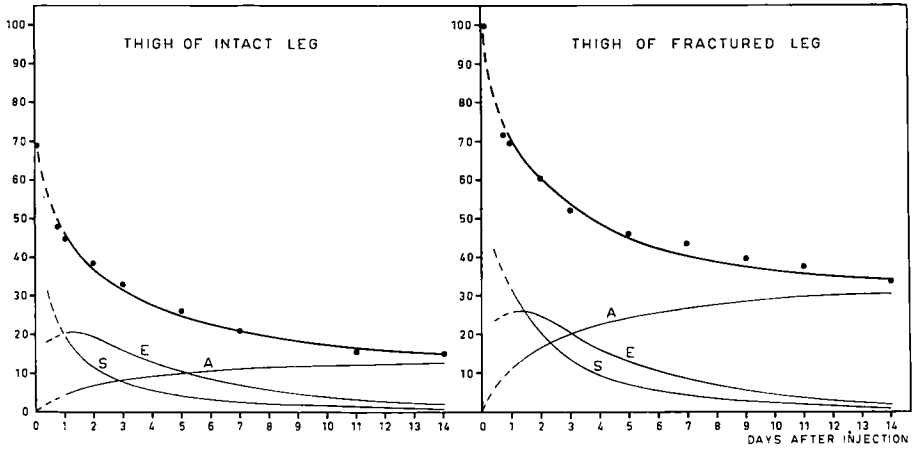

Fig. 24—C. Graphs showing simulation of external counting measurements over the thigh of the intact leg and the thigh of the fractured leg in the same case as in Fig. 24—A. The ratios of the *S*, *E* and *A* fractions in the thigh of the fractured leg over those in the thigh of the intact leg were 1.7, 1.3 and 2.5, respectively. The external counting rate ratio at Day 14 was 2.3.

compartments S and E, and of the amount of activity accreted (A) were chosen so that the sum simulated the externally recorded activities during the interval 1 to 14 days after injection. These simulations are shown in Figs. 24 and 25. All of the curves, except the one recorded over the fresh tibial fracture in Case I-3, who received the Sr^{85} already 10 days after fracture, could be simulated in this way. The cause of the deviation of the fracture curve from the simulated curve may probably be explained by the fact that the accretion rate in a 2—3 weeks old fracture increases rapidly during the investigation period (Fig. 15, insert).

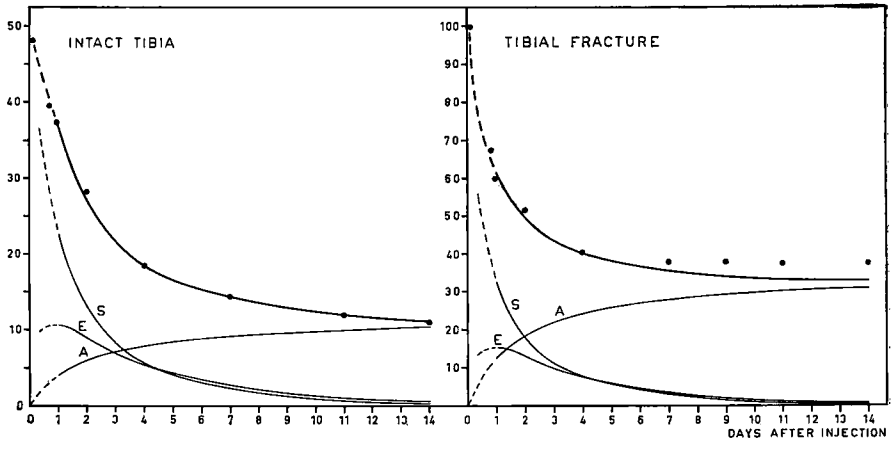

Fig. 25—A. Graphs representing simulation of externally recorded activity values over intact, left tibia and fractured, right tibia. The fracture was ten days old at the time of the isotope injection. The activity curves of this case are also given in Fig. 5. Body distribution of Sr^{85} after injection is seen in Fig. 23. No fit could be found for the fracture curve. The ratios of the S, E and A fractions in the fracture and the intact tibia was 1.4, 1.4 and 3.0, respectively. The external counting rate ratio at Day 14 was 4.8. Note different activity scales in the two graphs.
The observed activity values are shown as black dots.

The strontium in the regions studied — fractures, intact tibia, knees and thighs — would thus be composed of three, kinetically different, fractions. The shapes of the activity curves are determined by the relative proportions

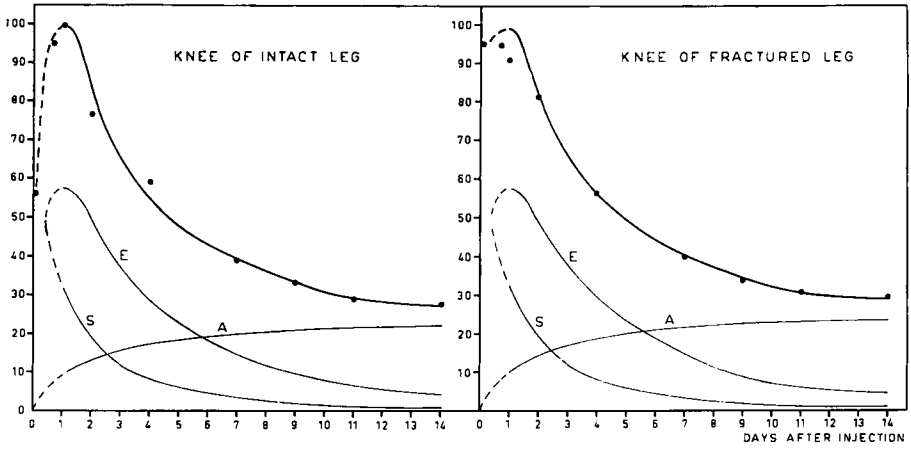

Fig. 25—B. Graphs showing simulation of external counting measurements over knee of intact leg and knee of fractured leg in the same case as in Fig. 25—A. The ratios of *S*, *E* and *A* fractions in the knee of the fractured leg over those in the knee of the intact leg were 1.0, 1.0 and 1.1, respectively. The external counting rate ratio at Day 14 was 1.1.

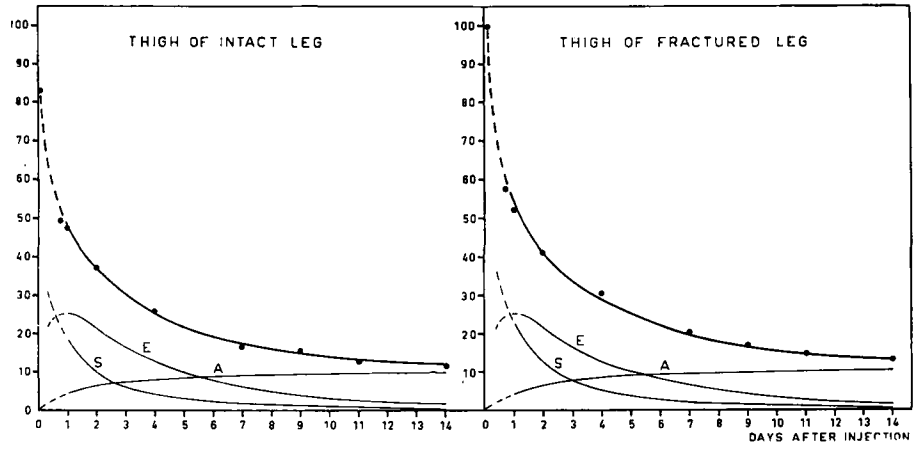

Fig. 25—C. Graphs showing simulation of external counting measurements over the thigh of the intact leg and the thigh of the fractured leg in the same case as in Fig. 25—A. The ratios of the *S*, *E* and *A* fractions in the thigh of the fractured leg over those in the intact leg were 1.3, 1.1 and 1.1, respectively. The external counting rate ratio at Day 14 was 1.2.

of these three fractions as is shown in Fig. 26. In the present investigation three types of activity curves were observed: (a) the activity continuously decreased after an early peak value, (b) the activity increased during the

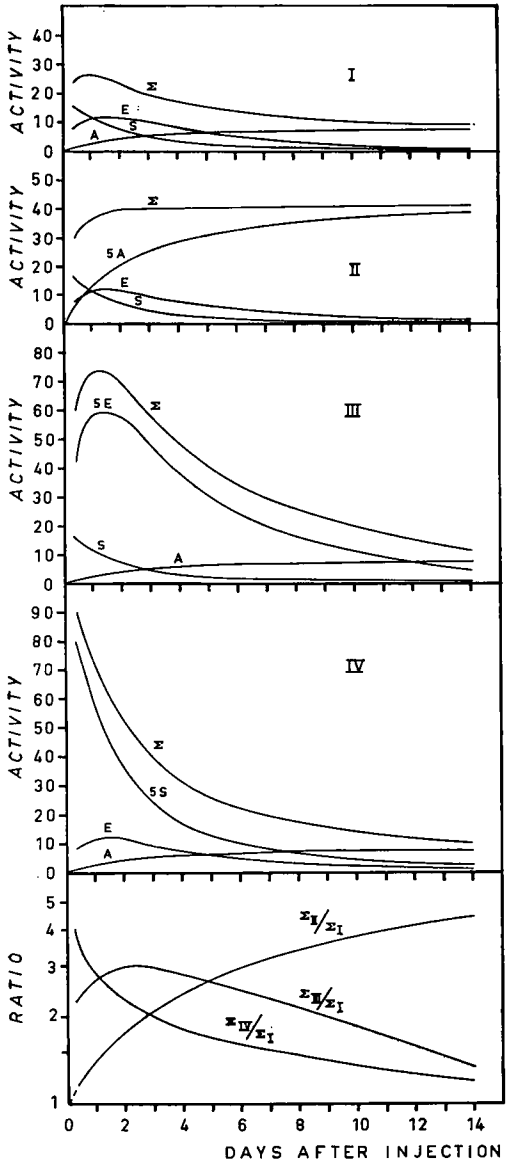

Fig. 26—A. Graphs showing a theoretical analysis of the shape of activity curves and of activity ratios related to the relative proportions of fractions *A*, *E* and *S* of the model shown in Fig. 22. Starting from a normal tibia curve (I=Fig. 24) the *A*, *E* and *S* fractions have separately been increased by a factor of five (II, III and IV, respectively). In V and VI (Fig. 26—B) fractions *A* and *S*, and *A* and *E*, respectively, have been increased giving activity curves and changes in activity ratios roughly similar to those observed by external counting as shown in Figs. 3—5 and 18, respectively.

first day or the first few days after the injection and then decreased, and (c) the activity continuously increased during the entire 14-day period studied. Examples of (a) were regularly *observed* over the thigh and over

fresh fractures (Figs. 3—5) and are *interpreted* as due to a relatively large fraction of soft tissue activity (Figs. 24—C, 25—A and C, and 26, IV and V). Examples of (b) were regularly *observed* over the knee region and in most fractures (Figs. 6—10 and 19—20). The activity peak of these curves is *interpreted* as due mainly to a relatively large exchangeable skeletal fraction (Figs. 24—A and B, 24—B and 26, III). An example of (c) was *observed* in the fracture of Fig. 18 and is *interpreted* as an effect of a relatively large fraction of accreted activity (Fig. 26, VI).

The change in the external counting rate ratio fractured/intact leg with time after injection is an effect of different proportions of *A*, *E* and *S* in the two counting locations compared (*cf.* Bauer and Wendeberg, 1959). It is clear from Fig. 26 that an increase of either *A*-, *E*- or the *S*-fraction causes changes in the activity ratios with time after the injection which are characteristic of the fraction that has increased. The increase from 1 to 2 weeks following injection observed in most fracture/control, knee/control, and thigh/control ratios (Fig. 16) thus indicates a larger accretion fraction in the fractured leg than in the intact leg. Conversely, the activity ratios below unity observed over the knee and thigh 5—9 years after the fracture and which decreased between measurements 1 and 2 weeks after the injection suggest a smaller accretion fraction in these locations of the fractured bone than in corresponding locations of the intact bone.

The initially increased and then falling activity ratios recorded for cases with fresh fractures suggest an increased soft tissue fraction (*S*) in the fractured leg .

It would thus seem that the externally recorded activity curves, as well as the change in the activity ratios with time after injection, can be analyzed and interpreted kinetically on the basis of the simplified two-compartment model illustrated in Fig. 22.

The continuous redistribution of Sr^{85} from exchangeable to non-exchangeable mineral fractions with time after the injection provides a basis for the interpretation of the activity ratios obtained at different intervals after the injection of the isotope. During the earlier intervals after the injection most of the activity injected is distributed in exchangeable compartments (*S* and *E*) and only a minor portion has become accreted. External counting during the first hour after the injection therefore does not give any direct information of the accretion rate but only of the relative magnitude of the exchangeable compartments under the detector. A closer analysis of this part of the curve cannot be made on the basis of the two-compartment model used for analysis of the curves during the later period after

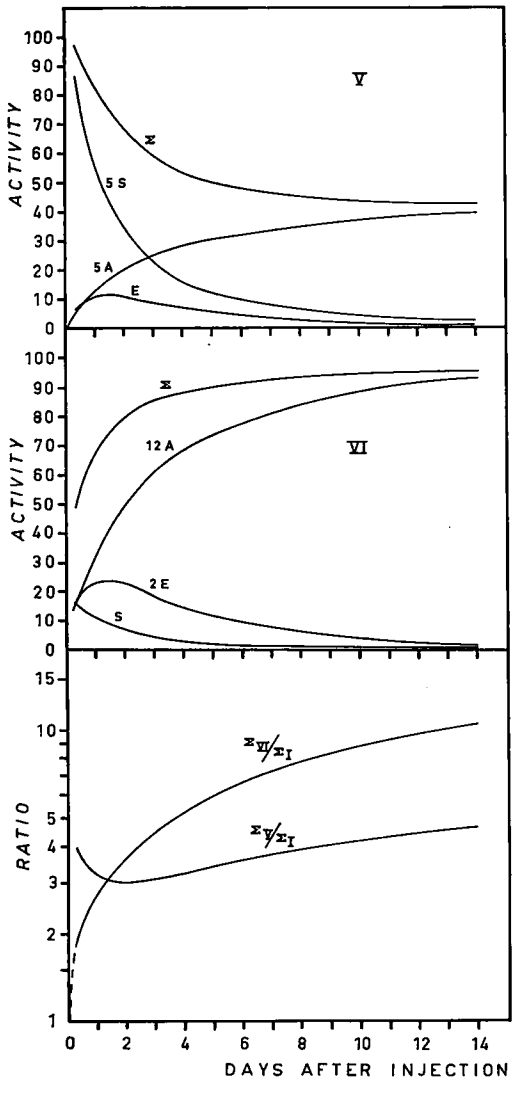

Fig. 26—B. See legend of Fig. 26—A.

the injection (1—14 days) because the model is not valid for short intervals after injection. The activity differences observed between the fractured tibia and the intact tibia during the first hour after the injection and between the knees and thighs of the fractured and the intact leg at measurements about one hour after injection may be ascribed to (a) the hypervascularization and the increased blood flow demonstrated in a fractured

leg by angiographic studies in human beings and experimental animals both in normally healing fractures and in pseudarthrosis (Lexer, 1934; Baumgarthl, Gremmel and Willmann, 1958; Judet, Judet and Roy-Camille, 1958; Wray and Lynch, 1959; Göthman, 1960), and (b) the positive correlation between the accretion rate and the size of the exchangeable mineral pool of the skeleton, found in studies of the mineral metabolism of the entire skeleton (Bauer, Carlsson and Lindquist, 1955 b; Heaney and Whedon, 1958; Bauer and Wendeberg, 1961). It seems reasonable that the vascular factors predominate in fresh fractures in which accretion is still slow, and that the larger exchangeable bone mineral fractions predominate in fractures with a high accretion rate.

The rapid uptake of Sr^{85} in the fracture region during the first hour after the injection and the high fracture/control activity ratios observed subsequently both in normally healing fractures and in cases of delayed and non-union indicate an adequate blood supply to the fracture region and a rapid exchange of mineral between body fluids and the callus. These studies, as well as earlier experimental isotope studies of fracture healing, thus provide evidence that the humoral source of bone salt is essential for the normal progress of healing as claimed by Urist (1942). It is seen in Fig. 20—B that the major part of the activity recorded by external counting over a fracture really is located in the actual region of the fracture.

Fourteen days after the injection most of the activity retained in the body has been incorporated in the skeleton by accretion (Fig. 23). The ratio between two externally recorded activities may then be interpreted as an index of the difference in the amount of Sr^{85} accreted within two body locations measured. The amount of activity accreted is a function of the accretion rate and the concentration of tracer in the serum (Bauer, Carlsson and Lindquist, 1955 b, 1961). The concentration of Sr^{85} in the serum may be regarded as equal in both legs. The activity ratios at Day 14 may thus be interpreted as indices of differences in accretion rates (Bauer and Wendeberg, 1959). For two reasons, however, these differences are not absolute but relative: (a) the activity recorded by external counting 14 days after the injection of Sr^{85} is not exclusively accreted activity but contains a minor fraction of exchangeable activity (Figs. 24 and 25), and (b) a wide-angle collimator was used in this investigation.

The size of the collimator is of importance mainly for measurements over skeletal lesions which are small in relation to the aperture of the collimator, such as fractures. The use of a wide-angle collimator will then give a lower activity ratio than will a narrow-angle collimator because bone tissue of a high specific activity in the actual fracture region, seen by

the detector, is "diluted" with bone tissue of a lower specific activity adjacent to the fracture (Bauer and Wendeberg, 1959). These two factors imply that the activity ratio observed 14 days after the injection is somewhat smaller than the absolute difference in the accretion rate between the two areas studied.

The external counting technique has been used by MacDonald (1958) for studies of tibial fractures in rabbits. By external counting of Na^{22} and $RI^{131}SA$ an increased vascularity was demonstrated in the fractured leg. External counting curves recorded over tibial fractures in rabbits during the first hour after injection of Sr^{85} are similar to those found for human beings in this study. Thus, the activity peak was reached earlier in fresh fractures than in older fractures.

MacDonald (1958) also made external counting over fractured and normal tibias in rabbits up to 100 days after parenteral injection of Sr^{85}. During later intervals of time the Sr^{85} activity in the fracture decreased at a faster rate than did that in the normal control tibia, presumably because of the progressive resorption of labelled callus. In the present investigation activity measurements were made only during 14 days after injection of Sr^{85}. During this interval the activity in the normal tibia decreased at a faster rate than did that in the fracture. However, it is evident that at later intervals of time the activity ratio fractured/intact leg will decrease because the life-span of the mineral in the fracture region is shorter than that in normal bone.

C. CHANGES IN THE ACCRETION RATE INDUCED BY THE FRACTURE

1. Accretion rate in the fracture region

a. Normally healing fractures. — An increased accretion rate in the fracture region was observed as early as within a week of the fracture (increasing fracture/control ratio from Day 1 after injection of Sr^{85} in Case I-1). The accretion rate increases rapidly during the first months, it is high during the first year after the fracture and then decreases gradually. The most rapid accretion rate in the fracture region was observed 6—8 months after fracture and was found to be up to 30 times that in the normal tibia. For 14 patients studied 5—10 months after fracture the mean accretion rate was at least 15.5 ± 7.2 times that in the intact tibia. Signs of increased bone formation in the fracture region were observed in the present investigation as late as 9 years after the fracture. This shows that

the reorganization of the bone tissue in the fracture region continues long after healing has ensued. No correlation was found between clinical healing and the rate of accretion. This is apparent also from the fact that no differences were observed in accretion rate between normally healing fractures and fractures with established non-union.

The pattern of uptake of Sr^{85} in human tibial fractures (Fig. 15) is largely the same as that observed for Ca^{45}, P^{32} and Sr^{85} in animal experiments (Copp and Greenberg, 1945; Bohr and Sörensen, 1950; Karsher, 1953; Bauer, 1954; Bohr, 1955; Cartier, DeBernard and Lagrange, 1956; MacDonald, Lorick and Petriello, 1957; MacDonald, 1958; Falkenberg, 1961). However, the maximal uptake of tracer is reached earlier and the difference in uptake between fracture and intact bone is less marked in small animals than in man. Thus, for example, the uptake of P^{32} and Ca^{45} in fractures of the tibia or the femur in rats showed a peak 9—15 days after fracture and then was about twice that in intact bone (Karsher, 1953). Falkenberg (1961) found maximal uptake of Sr^{85} in fractures of the radius in rabbits 2—3 weeks after fracture; it was about 6 times that in normal bone. By external counting of Sr^{85} in rabbits Mac Donald (1958) found 8 times higher activities over fractures of the tibia than over intact tibias 10—25 days after fracture. The experimental investigations referred to above do not show how long an increased bone formation rate can be demonstrated in the fracture area, but 6 months following a femoral fracture in the rat, the uptake of P^{32} was found to be increased compared with normal bone tissue (Bohr, 1955).

b. Fractures with delayed or non-union and/or osteitis. — No difference was found between the accretion rate in a pseudarthrosis or in a fracture complicated in some other way and normally healing fractures. Neither was any difference noted between these two groups regarding the changes in accretion rate in adjacent bone. This is in accordance with histopathological investigations by Urist, Mazet and McLean (1954). The authors concluded that "there is never an end to the process and effort of healing" in human tibial pseudarthrosis, and that "osteogenesis progressed steadily all around the fracture gap but never across it". In addition, there was also agreement with the data of Karsher (1953) and Bohr (1955), which indicate the same accretion rate values in poorly healing fractures as in normally healing fractures. Also in pseudarthrosis of the femur, the radius and the humerus of human subjects the accretion rate is rapid (Wendeberg, 1962). However, the increased accretion rate observed in patients in whom non-union was caused by osteitis may be partly due to the infection (Bauer and Wendeberg, 1959).

Thus, a rapid accretion rate was noted in non-uniting fractures in which roentgen examination indicated that the net increase in mineral content in the region of the fracture was slight. This shows that the rate of bone salt accretion is counterbalanced by a rapid rate of resorption of bone salt in poorly healing fractures. This explanation is supported experimentally by the work of Bohr (1955) who found a lower ash weight in poorly healing fractures than in normally healing fractures.

c. Absolute accretion rate. — In Case II-6 in whom lower leg amputation was performed 8 days after injection of Sr^{85} the absolute accretion rate in the fracture region may be calculated. On the basis of excretory and serum activity data the accretion rate of the total skeleton and the size of the exchangeable calcium fraction in the skeleton (*E*) were calculated according to Wendeberg (1961). The accretion rate and the *E*-fraction were found to be 0.57 g Ca/day and 1.7 g Ca, respectively. At Day 8 40 % of the given dose of Sr^{85} was calculated to be incorporated in the skeleton by accretion and about 10 % was in the exchangeable fraction. From the 10 mm bone slice including the pseudarthrosis 0.2 % of the dose was recovered (Table III). As the accretion rate and the size of the exchangeable calcium fraction in the skeleton are positively correlated (Bauer, Carlsson and Lindquist, 1955 b; Heaney and Whedon, 1956) it may be assumed from the figures given above that 4/5 of the activity recovered from the bone piece was accreted, *i. e.* 0.16 % of the dose. These figures thus indicate that 0.4 % of the amount of calcium laid down by accretion in the total skeleton was laid down in the pseudarthrosis, *i. e.* 0.0023 g Ca/day. Bauer (1954) found that in one-week-old fractures of the femur in rats 0.001 g Ca was laid down per day.

The ash weight of the bone piece was 1.27 g, which equals 0.50 g Ca. The turnover time of the bone tissue in the fracture region may thus be calculated to be about 220 days. From P^{32} data and bone biopsy (Bauer, Carlsson and Lindquist, 1957) the turnover time of bone tissue in the proximal part of tibia in a normal man was calculated to be about 1100 days. From studies with tetracyclines even longer turnover times have been described (Frost, 1960). The turnover time of the bone tissue in the pseudarthrosis thus was found to be at least 5 times shorter than that in normal tibial bone. This figure may be compared to the activity ratio fracture/intact tibia obtained 8 days after injection in this case with the 10 mm slot aperture insert, which was 5.8 (see page 00). Assuming that the total skeleton of this patient contained 1000—1500 g Ca the mean turnover time of the skeleton was calculated, from the accretion rate of 0.57 g Ca/day, to be

between 1800 and 2600 days or some ten times longer than that of the fracture specimen.

2. Accretion rate in bone adjacent to the fracture

External measurements over bone adjacent to the tibial fracture showed that some months after the fracture an increased accretion rate is induced in the entire ipsilateral leg (Fig. 15). The activity ratios noted over the tibial shaft, knee and thigh in the two legs thus differed from unity according to a pattern similar to that of the fracture. Signs of increased accretion rate were, however, observed to start in these areas later than in the fracture (Fig. 15, insert) and were less marked than in the fracture. For 14 patients studied 5—10 months after fracture the mean accretion rate in the knee was at least 3.8 ± 1.3 and in the thigh 1.6 ± 0.5 times higher than the corresponding values of the intact leg. The increased accretion rate disappeared in the knee region 4—5 years and in the thigh region 2—3 years after the fracture. In most cases signs of decreased accretion rate were later seen (activity ratios below unity). The increased accretion rate found in bone adjacent to a fracture was in agreement with the experimental findings of Karsher (1953), Bohr (1955), Cartier, DeBernard and Lagrange (1956 and Lacroix and Ponlot (1956), who found an increased uptake of P^{32} and Ca^{45} in the metaphyseal portions of a fractured bone and in the tibia in fracture of the femur, for example.

The cause of the increased accretion rate observed in bone adjacent to the fractured tibia is not known. Post-traumatic osteopenia of the bones of the foot, distal tibia, and knee region form a common, roentgenologically demonstrable phenomenon some months after a tibial fracture. This osteopenia is due to an increased rate of bone resorption as has been shown experimentally by Bauer (1954) and Bauer and Carlsson (1955). This is apparent also from the present investigation; normal accretion rates were observed in bone in which osteopenia developed. The increased loss of mineral observed in a fractured leg is mainly due to the injury and only to a minor degree to immobilization (Burdeaux and Hutchinson, 1953). Loss of mineral was observed in the knee region of a fractured leg (Fig. 39) before any signs of increased accretion rate could be demonstrated (Fig. 6), and in patients with extreme decalcification a marked increase in uptake of Sr^{85} was noted (Fig. 40). Perhaps the increased accretion rate in the surroundings of a fractured bone is induced by the increased bone salt resorption as a process of repair.

The intact leg served as control. Roche and Mourgue (1939) and Falkenheimer (1955) have claimed that a fracture initiates an increase in mineral metabolism throughout the skeleton in animals. Studies of Bohr and Sörensen (1950), Bauer (1954) and MacDonald, Lorick and Petriello (1957) do not give support to this opinion. The data of these authors fail to show any change in the accretion rate in bone contralateral to a fracture (see for example Fig. 8, p. 187 in Bauer, 1954). Also in the present investigation the shapes of the activity curves obtained over the control leg were largely similar to those obtained in non-fractured cases.

CHAPTER IV SUMMARY AND CONCLUSIONS

1. Fifty-one adult patients with fractures of one tibia were studied by external counting with scintillation detectors over the thighs, the knees and the tibias during a 14 day period after intravenous injection of 25—50 μC Sr^{85}. At the time of injection the fractures ranged in age from 2 days to about 9 years. Forty-three fractures were classified as normally healing fractures and eight fractures showed delayed or non-union and/or osteitis.

2. The pattern of the activity curves recorded over the fractured leg compared to those recorded over the control leg varied significantly with the age of the fracture.

3. In the *fracture region* as compared to the intact tibia an increased uptake of Sr^{85} was observed in all cases studied. In fresh fractures this was most marked during early intervals after injection. The activity ratio fracture/control tibia obtained 14 days after injection rose during the first months after fracture to reach a peak value 6—8 months after fracture. The mean of the 14 Day fracture/control ratios obtained in 14 patients studied 5—10 months after fracture was 15.5 ± 7.2. The 14 Day activity ratios then subsequently dropped. Even 6—9 years after fracture the counting rate over the fracture was higher than that over the intact tibia.

4. In the *knee region* of the fractured leg as compared to the knee region of the intact leg an increased activity uptake was found some months after fracture. About 6 months after fracture a peak value

was reached. The mean 14 Day activity ratio knee of fractured leg/knee of intact leg for 14 patients studied 5—10 months after fracture was 3.8 ± 1.3. Thereafter the knee activity dropped to reach values which were equal to or lower than that of the control knee at about 4 years and later after fracture.

In the *thigh* of the fractured leg and the *tibia adjacent to the fracture* the uptake of Sr^{85} varied according to a pattern similar to that in the knee region of the fractured leg. The mean 14 Day activity ratio thigh of fractured leg/thigh of intact leg for 14 patients studied 5—10 months after fracture was 1.6 ± 0.5.

5. No differences in activity uptake were observed between normally healing fractures and fractures showing delayed or non-union.

6. The activity curves obtained over the thigh, the knee and the tibia of the fractured and intact legs during the interval 1—14 days after injection of Sr^{85} could be simulated on the basis of a two-compartment model for the kinetics of strontium in the body.

7. Based on this kinetical analysis the externally recorded Sr^{85} activity values may be interpreted as follows:

(a) The activity ratios fractured/intact leg obtained during early intervals after injection are mainly related to differences in the size of the exchangeable mineral spaces under the detector.

(b) The 14 day activity ratio of two anatomically comparable locations may be used as a relative index of the difference in the accretion rate (rate of irreversible deposition of bone mineral) in these locations, but is somewhat lower than the absolute difference in the accretion rate.

(c) The bone salt laid down in the fracture callus is derived from the body fluids.

(d) The accretion rate in the fracture region is increased within a week of the fracture. It rapidly increases during the first months after fracture to reach a peak value at 6—8 months after fracture. Thus for the 14 patients studied 5—10 months after fracture the mean accretion rate in the fracture region was at least 15.5 ± 7.2 times that in the control tibia. Thereafter the accretion rate drops but still 6—9 years after fracture the accretion rate in the fracture region may be higher than normal.

(e) The accretion rate in the entire fractured leg is increased some months after fracture. This reaction, however, appears later, is less marked and disappears earlier than in the fracture region. Thus in the knee and thigh region of the fractured leg the mean accretion rate for 14 patients studied

5—10 months after fracture was at least 3.8 ± 1.3 and 1.6 ± 0.5, respectively, times that in corresponding locations of the control leg.

(f) The traumatic osteopenia is caused by increased resorption and not by decreased accretion.

(g) The accretion rate in fractures showing delayed or non-union does not differ from that in normally healing fractures.

(h) The turnover time of bone tissue in a 26-month-old pseudarthrosis of the tibia was calculated to be about 220 days, which is at least 5 times shorter that in the normal tibia. The accretion rate in the actual region of the pseudarthrosis was calculated to be 0.0023 g Ca/day.

ZUSAMMENFASSUNG

1) Es wurden 51 erwachsene Patienten mit einseitigen Tibiabrüchen durch äussere Messung mit Scintillations-Detektoren über den Oberschenkeln, den Knien und den Schienbeinen während eines 14-tägigen Zeitraumes nach der intravenösen Injektion von 25—50 μC Sr^{85} untersucht. Zur Zeit der Einspritzung waren die Brüche 2 Tage bis etwa 9 Jahre alt. Dreiundvierzig Brüche wurden als normal heilende bezeichnet, acht zeigten verzögerte oder keine Heilungstendenz mit oder ohne Osteitis.

2) Die Aktivitätskurven, die über dem gebrochenen Bein ermittelt wurden, zeigten im Vergleich zu denen über der Kontrollextremität einen bemerkenswerten Unterschied entsprechend dem Alter der Frakturen.

3) Über dem *Knochenbruch* wurde, verglichen mit der unversehrten Tibia, in allen Fällen eine gesteigerte Aufnahme von Sr^{85} beobachtet. Bei frischen Brüchen war diese während der ersten Zeit nach der Injektion am meisten augenfällig. Der Aktivitätsquotient Fraktur-Stelle: Kontroll-Tibia, ermittelt 14 Tage nach der Injektion von Sr^{85}, erhöhte sich während der ersten Monate nach der Fraktur, um sechs bis acht Monate danach einen Höchstwert zu erreichen. Der Mittelwert der 14-tägigen Aktivitätsquotienten, der bei der Untersuchung von 14 Patienten während der ersten 5—10 Monate nach der Fraktur ermittelt wurde, war 15.5 ± 7.2. Danach verminderte sich der Wert der 14-Tage-Quotienten laufend. Auch 6—9 Jahre nach dem Knochenbruch war der Messwert über dem gebrochenen Bein höher als über der unversehrten Tibia.

4) Über dem *Knie* des gebrochenen, verglichen mit dem Knie des unversehrten Beines, wurde einige Monate nach der Fraktur eine gesteigerte Aktivitätsaufnahme gefunden. Etwa 6 Monate nach dem Bruch liess sich ein Höchstwert erreichen. Der Mittelwert der 14-tägigen Aktivitätsquotienten Knie des gebrochenen Beines: Knie der unversehrten Extremität war bei 14 Patienten, die 5—10 Monate nach dem Bruch untersucht wurden, 3.8 ± 1.3.

Danach nahm die Knieaktivität ab und erreichte Werte, die gleich denen oder niedriger als diese des Kontrollknies zu einem Zeitpunkt von vier oder mehr Jahren nach der Fraktur, waren.

Im *Oberschenkel* des gebrochenen Beines und in dem der Fraktur benachbarten Teil der Tibia war die Aktivitätsaufnahme von Sr^{85} etwa die gleiche wie im Knie der gebrochenen Seite. Der Mittelwert der 14-Tage-Aktivitätsquotienten Oberschenkel des gebrochenen Beines: Oberschenkel des unversehrten Beines war bei 14 Patienten, die 5—10 Monate nach dem Bruch untersucht wurden, 1.6 ± 0.5.

5 Es wurde kein Unterschied in der Aktivitätsaufnahme zwischen normal heilenden und solchen Brüchen beobachtet, die verzögerte oder keine Heilung zeigten.

6) Die Aktivitätskurven, die über dem Oberschenkel, dem Knie und der Tibia des gebrochenen und des unbeschädigten Beines während eines Zeitraumes von 1—14 Tagen nach der Verabreichung von Sr^{85} ermittelt wurden, könnten auf der Basis eines Zwei-"compartment" Modelles der Kinetik von Strontium im Körper vorgetäuscht werden.

7) Nach Zugrundelegung dieser kinetischen Analyse können die oberflächlich aufgezeichneten Sr^{85}-Aktivitätswerte wie folgt gedeutet werden:

a) Die Aktivitätsquotienten gebrochenes: intaktes Bein, ermittelt während der ersten Zeit nach der Injektion, sind hauptsächlich von Grössenunterschieden der austauschbaren Mineralräume unter dem Detektor abhängig.

b) Der 14-tägige Aktivitätsquotient zweier anatomisch vergleichbarer Stellen kann als relativer Index des Unterschiedes der "accretions"-Geschwindigkeit (=Geschwindigkeit der irreversiblen Ablagerung von Knochen-Mineralien) an diesen Stellen gebraucht werden, ist aber etwas niedriger als der absolute Unterschied der "accretions"-Geschwindigkeit.

c) Die Knochensalze, die im Frakturcallus abgelagert sind, stammen aus den Körperflüssigkeiten.

d) Die "accretions"-Geschwindigkeit des Frakturgebietes vergrössert sich innerhalb einer Woche nach dem Bruch. Sie steigt währen der ersten

Monate nach einer Fraktur rasch an, um etwa 6—8 Monate danach einen Höchstwert zu erreichen. Somit war bei den 14 Patienten, die während 5—10 Monate nach der Fraktur untersucht wurden, der Zuwachsanteil des Frakturgebietes mindestens 15.5 ± 7.2 mal grössers als der der Kontrolltibia. Danach nimmt der "accretions"-Geschwindigkeit wieder ab, kann aber noch 6—9 Jahre nach der Fraktur in eigentlichen Bruchgebiet noch immer höher als normal sein.

e) Die "accretions"-Geschwindigkeit des unversehrten Teiles des gebrochenen Beines ist einige Monate nach der Fraktur erhöht. Diese Reaktion jedoch tritt erst später in Erscheinung, ist weniger augenfällig und verschwindet früher als im Frakturgebiet. Somit war die "accretions"-Geschwindigkeit im Knie und Oberschenkel des gebrochenen Beines bei 14 Patienten, die während 5—10 Monate nach der Fraktur untersucht wurden, mindestens 3.8 ± 1.3, beziehungsweise 1.6 ± 0.5 mal grösser als die der entsprechenden Stellen des Kontrollbeines.

f) Die traumatische Osteopenie wird durch erhöhte Resorption und nicht durch verminderten Anbau verursacht.

g) Die "accretions"-Geschwindigkeit bei Frakturen mit verzögerter oder keiner Heilungstendenz unterscheidet sich nicht von der bei normal heilenden Frakturen.

h) Die Umbauzeit von Knochengewebe bei einer 26 Monate alten Pseudarthrose der Tibia wurde auf etwa 220 Tage geschätzt, ein Wert, der mindestens einem Fünftel des Wertes der normalen Tibia entspricht. Die absolute "accretions"-Geschwindigkeit der eigentlichen Pseudarthrose wurde auf etwa 0.0023 g Ca pro Tag geschätzt.

RESUMÉ

1. Cinquante et une personnes adultes, atteintes de fracture d'un tibia, ont été étudiées par comptage externe avec un détecteur à scintillation. Le comptage a été pratiqué sur le tibia, le genou et la cuisse pendant une période de 14 jours aprés une injection intra-veineuse de 25 à 50 μC de Sr^{85}. Au moment de l'injection, l'âge des fractures s'étalait sur une periode de 2 jours à 9 ans.

Quarante-trois fractures ont été classées comme ayant une consolidation normale et huit fractures ont présenté un retard ou une absence de consolidation, ou une ostéite soit isolée surajoutée a l'un ou l'autre des deux premiers cas.

2. L'aspect des courbes d'activité relevées sur le membre fracturé, comparé à celui des courbes relevées sur la jambe de contrôle a varié de façon significative suivant l'âge de la fracture.

3. Dans tous les cas étudiés, une augmentation du taux de Sr^{85} fut observé dans la région de la fracture par rapport au tibia intact. Dans les fractures fraîches, cette augmentation fut la plus marquée durant les intervalles de temps proches de l'injection. Le rapport d'activité tibia fracturé/tibia de contrôle, obtenu 14 jours aprés l'injection augmenta durant les premiers mois aprés la fracture pour atteindre un sommet à 6—8 mois aprés la fracture. La moyenne des rapports fracture/contrôle au 14^{éme} jour aprés l'injection, moyenne obtenue chez 14 cas étudiés de 5 à 10 mois aprés la fracture, fut de 15.5 ± 7.2. Alors, passé cette période, les

rapports d'activité au 14^{éme} jour baissérent. Même 6 à 9 ans aprés une fracture, le taux de comptage sur la fracture fut encore plus élevé que sur le tibia sain.

4. Dans la région du genou du membre fracturé, comparativement à celle du genou du membre intact, on trouva une augmentation du taux d'activité quelques mois aprés la fracture. Une valeur-sommet fut atteinte environ 6 à 8 mois aprés la fracture. La moyenne des rapports d'activité au 14^{éme} jour du genou côté-fracture/genou côté-intact, relevée chez 14 cas examinés 5 à 10 mois aprés la fracture fut de 3.8 ± 1.3. Ensuite l'activité du genou, côté fracture, diminua jusqu'à atteindre des valeurs qui furent égales ou inférieures du genou de contrôle, environ 4 ans et plus aprés la fracture.

Dans la région de la cuisse du membre fracturé et dans les regions tibiales adjacentes à la fracture, le taux de Sr^{85} évolua de la même façon que dans le région du genou. La moyenne des rapports d'activité, au 14^{éme} jour aprés l'injection, de la cuisse côté-fracture/cuisse côté-sain, relevée ches 14 malades examinés 5 à 10 mois aprés la fracture, fut de 1.6 ± 0.5.

5. Aucune différence des taux d'activité n'a été observée entre les fractures consolidant normalement et les fractures montrant un retard de consolidation ou une pseudarthrose.

6. Les courbes d'activité, obtenues sur le tibia, le genou et la cuisse des membres fracturés et intacts pendant la période de 1 à 14 jours aprés l'injection de Sr^{85} peuvent être représentées, en ce qui concerne les mouvements du strontium dans le corps, sur la base d'un modéle à deux compartiments.

7. Basées sur cette analyse cinetique, les valeurs d'activité du Sr^{85} relevées par comptage externe, peuvent être interprétées comme suit:

a) Les rapports d'activité du membre fracturé/membre intact, obtenus à des intervalles de temps rapprochés aprés l'injection, ont concerné surtout des différences dans la dimension de l'espace minéral échangeable placé sous le détecteur.

b) Le rapport d'activité au 14^{éme} jour de deux localisations anatomiquement comparables peut nous servir comme un index relatif des différences dans la vitesse d"accrétion" (taux de dépôt irréversible des sels minéraux dans l'os) de ces localisations, mais il est quelque peu inférieur à la différence absolue de la vitesse d"accrétion".

c) Le sel osseux déposé dans les cals de fracture provient des fluides du corps.

d) La vitesse d"accretion" dans la région de la fracture augmente en moins d'une semaine aprés la fracture. Elle augmente rapidement durant les premiers mois aprés la fracture pour atteindre une valeur-sommet à 6—8 mois aprés la fracture. Ainsi pour les 14 cas étudiés de 5 à 10 mois aprés leur fracture, la vitesse moyenne d"accrétion" dans la région de la fracture fut au moins 15.5 ± 7.2 fois celle relevée dans le tibia de contrôle.

Puis la vitesse d"accrétion" baisse, mais 6 à 9 ans aprés la fracture elle est encore plus elevée que normal.

e) La vitesse d"accrétion" dans le membre entier côté-fracture augmente quelques mois aprés la fracture. Cette réaction, cependant, semble plus tardive, est moins marquée et disparaît plus precocement que dans la région même de la fracture. Ainsi dans les régions du genou et de la cuisse du membre fracturé, la vitesse moyenne d"accrétion" pour 14 cas étudiés sur 5 à 10 mois aprés la fracture, fut respectivement au moins 3.8 ± 1.3 et 1.6 ± 0.5 fois celui des localisations correspondantes du membre de contrôle.

f)L'osteopénie traumatique est causée par une augmentation de la résorption et non par une "accrétion" diminuée.

g) La vitesse d"accrétion" dans les fractures montrant un retard ou une absence de consolidation ne différe pas de celle des fractures consolidant normalement.

h) La durée de vie du tissu osseux dans une pseudarthrose du tibia vieille de 26 mois a été estimée à environ 220 jours, ce qui est au moins 5 fois plus court que dans un tibia normal. La vitesse absolue d"accrétion" dans cette pseudarthrose a été calculee être de: 0,0023 g Ca/jour.

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TABLES

TABLE I

Normally healing fractures.

Case	Fig.	Age (years)	Sex	Type and localization of tibial fracture	Cause of injury	Treament[1]	Plaster (months)	Dose of Sr^{85} (uC)	Months between fracture and isotope injection	Activity ratios: Fracture/control 1 week	Fracture/control 2 weeks	Knee/control 1 week	Knee/control 2 weeks	Thigh/control 1 week	Thigh/control 2 weeks
1.	3	37	M	Closed, comminute, middle third of tibia	Fall	Screws	3	40	$^{2}/_{30}$	1.7	2.1	1.1	1.3	1.1	1.1
2.	4	19	M	Closed, transverse, middle third of tibia	Sport	Plaster	2½	30	$^{4}/_{30}$	1.4	1.6	1.2	1.1	1.1	1.1
3.	5, 23 25 A—C	29	F	Closed, oblique, middle third of tibia	Traffic	Rush pin	2½	40	$^{10}/_{30}$	3.4	4.8	1.0	1.1	1.2	1.2
4.		58	M	Closed, transverse, middle third of tibia	Fall	Transfixation	5	50	1	9.2	9.1	1.4	1.2	1.1	1.1
		59	M	Closed, transverse, middle third of tibia	Fall	Transfixation	5	50	8	6.3	8.3	3.3	4.5	1.3	1.5
5.	6, 39	19	M	Closed, oblique, distal third of tibia	Traffic	Plaster	3	30	1¼	12.3	13.6	1.0	1.0	0.94	0.84
6.[2]		52	M	Closed, oblique, distal third of tibia	Traffic	Transfixation	3½	50	2½	14.5	19.2	0.68	0.76	0.90	0.90
7.	7, 11 27	29	M	Closed, comminute, distal third of tibia	Crush	Egger's plate	3½	30	5½	12.8	16.2	2.6	3.1	1.4	1.4
8.		25	M	Closed, transverse, middle third of tibia	Sport	Plaster	3½	30	6	6.4	7.3	3.9	5.6	2.7	2.8
9.		53	M	Closed, oblique, proximal third of tibia	Fall	Egger's plate	2½	50	6	6.1	9.2	2.4	3.3	0.92	0.74
10.	40	26	M	Closed, transverse, middle third of tibia	Traffic	Egger's plate	4½	25	6½	4.7	6.9	3.8	5.6	1.1	1.1
11.		39	M	Closed, oblique, distal third of tibia	Traffic	Screws	5	50	6½	19.0	21.0	4.0	4.4	1.7	1.7

12.		37	M	Closed, transverse, middle third of tibia	Traffic	Plaster	4	35	7	23.6	30.0	2.9	3.4	2.2	2.1
13.		74	M	Closed, comminute, distal third of tibia	Traffic	Screws	4	50	7	6.9	9.7	2.9	3.7	1.6	1.4
14.		33	M	Open, oblique, distal third of tibia	Traffic	Egger's plate	2	40	8	20.5	25.2	2.5	3.7	2.3	2.1
15.		35	M	Closed, oblique, distal third of tibia	Traffic	Lane's plate	4½	35	8	16.4	20.9	5.0	6.0	1.6	1.9
16.		53	M	Closed, comminute, distal third of tibia	Crush	Screws	4	50	8	12.4	15.0	2.5	3.8	1.7	1.6
17.		19	M	Closed, comminute, middle third of tibia	Traffic	Egger's plate	3	25	10	21.1	20.5	1.3	1.2	1.3	1.4
18.		38	M	Closed, comminute, middle third of tibia	Crush	Egger's plate	2½	50	10	10.7	12.5	1.9	2.2	1.1	1.2
19.	8	32	M	Closed, oblique, middle third of tibia	Sport	Egger's plate	3	40	10	10.2	13.6	2.9	3.2	1.3	1.7
20.		50	M	Closed, oblique, distal third of tibia	Traffic	Egger's plate	5	50	10	6.0		2.2		1.3	
21.		26	M	Closed, oblique, middle third of tibia	Sport	Egger's plate	4½	35	12	5.9	6.4	2.6	3.7	1.2	1.4
22.		44	M	Open, comminute, distal third of tibia	Traffic	Screws	4½	50	14	14.2	15.7	2.5	2.6	2.1	2.2
23.		35	M	Closed, comminute, distal third of tibia	Crush	Screws	2½	50	15	2.7	3.6	2.4	3.1	1.4	1.5
24.		75	F	Closed, oblique, distal third of tibia	Fall	Screws	2½	50	20	2.4	2.4	0.96	0.94	0.90	0.97
25.		45	M	Closed, transverse, distal third of tibia	Crush	Egger's plate	3	50	27	3.8	4.8	1.2	1.2	1.1	1.1
26.		21	M	Closed, transverse, middle third of tibia	Traffic	Plaster	4	30	27	2.7	3.5	1.3	1.3	1.0	1.1
27.		22	M	Open, transverse, distal third of tibia	Traffic	Plaster	3	35	31	2.3	2.6	1.0	1.0	0.95	0.91
28.		25	M	Closed, comminute, distal third of tibia	Traffic	Plaster	2½	50	33	3.0	3.6	1.0	1.1	1.1	1.1

TABLE I (continued)

Case	Fig.	Age (years)	Sex	Type and localization of tibial fracture	Cause of injury	Treament[1])	Plaster (months)	Dose of Sr^{85} (uC)	Months between fracture and isotope injection	Activity ratios: Fracture/control 1 week	Fracture/control 2 weeks	Knee/control 1 week	Knee/control 2 weeks	Thigh/control 1 week	Thigh/control 2 weeks
29.		50	F	Closed, oblique, distal third of tibia	Fall	Screws	3	50	35	2.6	2.5	1.2	1.3	0.70	0.83
30.		54	M	Closed, comminute, distal third of tibia	Fall	Egger's plate	5½	50	41	4.5	5.7	1.2	1.3	1.1	1.0
		55	M	Closed, comminute, distal third of tibia	Fall	Screws	5½	50	55	2.5	2.5	1.0	1.0	0.90	0.70
31.		48	F	Closed, oblique, distal third of tibia	Fall	Screws	1	50	53	2.2	2.4	1.1	1.1	1.0	1.0
32.[3]		42	F	Closed, comminute, distal third of tibia	Fall	Screws	3½	50	58	2.7	3.4	1.4	1.1	2.3	3.0
33.		39	F	Closed, oblique, distal third of tibia	Fall	Screws	4	40	58	1.5	1.8	0.90	0.88	0.90	0.86
34.		26	M	Closed, transverse, middle third of tibia	Traffic	Sliding tibial graft	4	35	63	2.9	2.9	0.87	0.87	0.85	0.77
35.		46	F	Closed, oblique, distal third of tibia	Traffic	Sliding tibial graft	9	50	64	2.8	2.7	1.1	1.1	1.1	1.1
36.		50	F	Closed, oblique, middle third of tibia	Fall	Screws	3	50	67	1.6	1.8	1.0	1.0	0.84	0.88
37.		62	F	Closed, comminute, distal third of tibia	Traffic	Plaster	3	50	67	1.1	1.2	0.79	0.72	1.0	0.9
38.		70	M	Closed, comminute, distal third of tibia	Fall	Screws	3	50	69	2.6	2.5	0.90	0.79	0.99	1.1

39.	62	F	Closed, oblique, proximal third of tibia	Traffic	Lane's plate	5	50	72	1.3	1.5	0.94	0.85	0.86	0.79
40.	77	F	Closed, comminute, distal third of tibia	Traffic	Plaster	5	50	72	1.6	2.0	0.68	0.64	0.83	0.90
41.	55	F	Closed, comminute, distal third of tibia	Fall	Plaster	2½	50	81	1.3	1.3	0.68	0.70	0.76	0.68
42.	70	M	Open, comminute, distal third of tibia	Fall	Plaster	8	50	81	2.1	2.2	1.4	1.8	1.1	1.0
43.	68	F	Closed, oblique, distal third of tibia	Fall	Screws	3½	50	106	1.3	1.6	0.69	0.43	0.87	0.87

[1] All types of treatment included plaster.

[2] Fracture of the contralateral patella 4 months prior to the isotope investigation.

[3] Osteoma of the ipsilateral femoral shaft.

TABLE II

Delayed healing pseudarthrosis and/or osteitis.

Case	Fig.	Age (years)	Sex	Type and localization of fracture	Cause of injury	Treatment[1]) (Figures show time in months after fracture)	Clinical state at time of isotope investigation	Dose of Sr^{85} (uC)	Months between fracture and isotope injection	Activity ratios: Fracture/control 1 week	Fracture/control 2 weeks	Knee/control 1 week	Knee/control 2 weeks	Thigh/control 1 week	Thigh/control 2 weeks
1.	17, 31	57	M	Open, comminute, distal third of tibia	Traffic	Screws	Delayed healing	50	6	9.2	13.6	1.3	1.9	1.6	1.9
2.	32	19	M	Closed, comminute, middle third of tibia	Traffic	Screws	Delayed healing Osteitis	25	7	11.1	13.7	1.6	2.3	1.5	1.5
3.	18, 33	22	M	Open, transverse, middle third of tibia	Traffic	Egger's plate	Delayed healing Infection	40	7	13.2	20.3	2.8	3.9	2.6	3.3
4.	19, 23 24 A—C 34	38	M	Open, comminute, middle third of tibia	Traffic	Transfixation with Steinman pins	Delayed healing	40	8½	7.4	8.0	2.6	3.6	2.1	2.3
5.	35	47	M	Open, transverse, middle third of tibia	Crush	Egger's plate Extr. of plate (5) Sequestrectomi (9)	Pseudarthrosis Osteitis	40	19	13.6	20.6	4.1	6.8		
6.	20 A—B 36	58	M	Open, transverse, middle third of tibia	Traffic	Egger's plate Extr. of plate (2) Skin transpl. (3) Transfixation (15) Osteotomy of fibula (20) Amputation (26)	Pseudarthrosis	50	26	4.2		1.2		1.2	
7.	37	67	M	Open, comminute, distal third of tibia	Crush	Egger's plate Extr. of plate and only bone graft (6)	Pseudarthrosis	50	29	4.3		0.94		1.2	
8.	38	61	M	Open, comminute, distal third of tibia	Crush	Screws and wires Extr. of wires and screws (5) Curretage (14)	Osteitis	50	42	3.4	4.2	1.3	1.5	1.1	1.1

[1] All types of treatment included plaster.

RADIOGRAPHS

Fig. 27. Radiograph of the fractured leg at the time of isotope investigation 5 ½ months after injury of Case I-7.

Fig. 28. Radiograph of the fractured leg at the time of the isotope investigation 58 months after injury of Case I-33.

Fig. 29 A—C. Radiographs of the fractured leg immediately after injury (A), after reposition of the fracture (B) and at the time of isotope investigation 15 months after injury (C) of Case I-23.

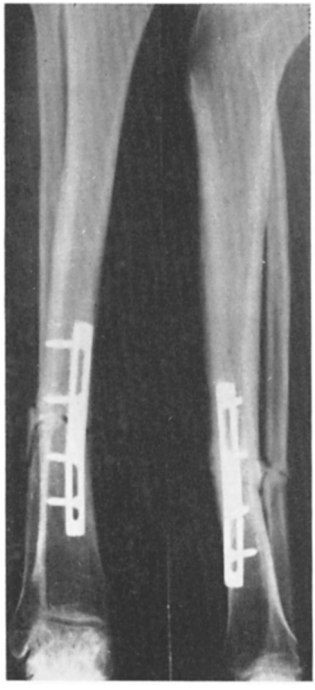


Fig. 27

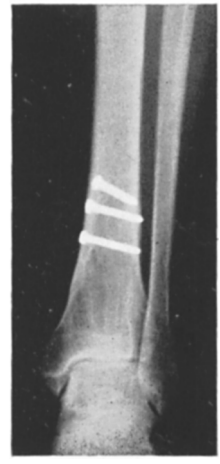


Fig. 28

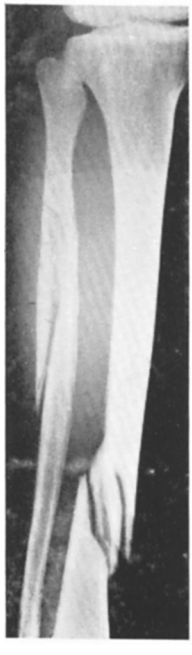


Fig. 29—A

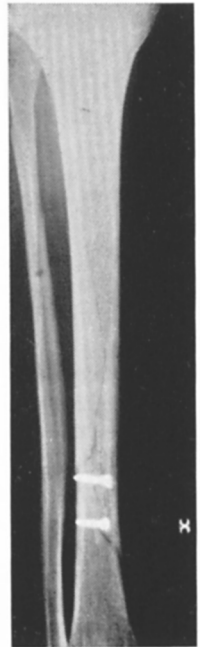


Fig. 29—B

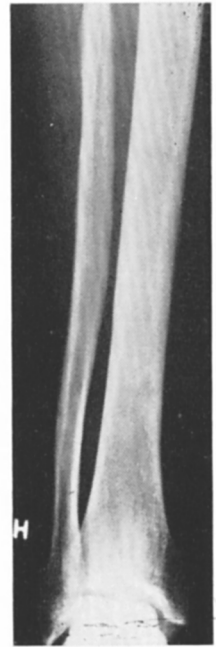


Fig. 29—C

Fig. 30. Radiograph of the fractured leg at the time of isotope investigation 64 months after injury of Case I-35. A sliding bone graft has been taken proximal to the fracture.

Fig. 31. Radiograph of the fractured leg at the time of isotope investigation 6 months after injury of Case II-1. The tibial fracture showed delayed healing and the proximal fibular fracture non-union.

Fig. 32. Radiographs of the fractured leg at the time of isotope investigation 7 months after injury of Case II-2. This case had osteitis in the fracture region.

Fig. 33. Radiograph of the fractured leg at the time of isotope investigation 7 months after injury of Case II-3. The fracture showed delayed healing and was later operated with only bone graft.

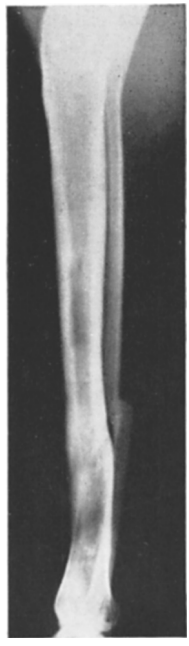


Fig. 30

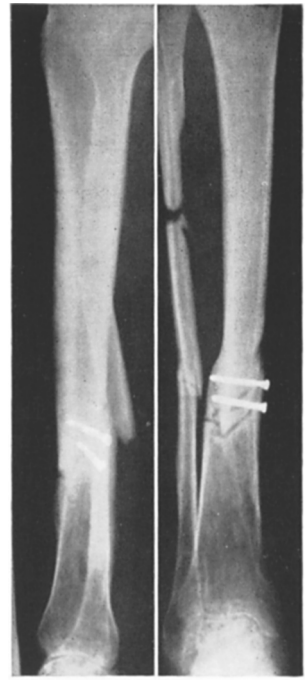


Fig. 31

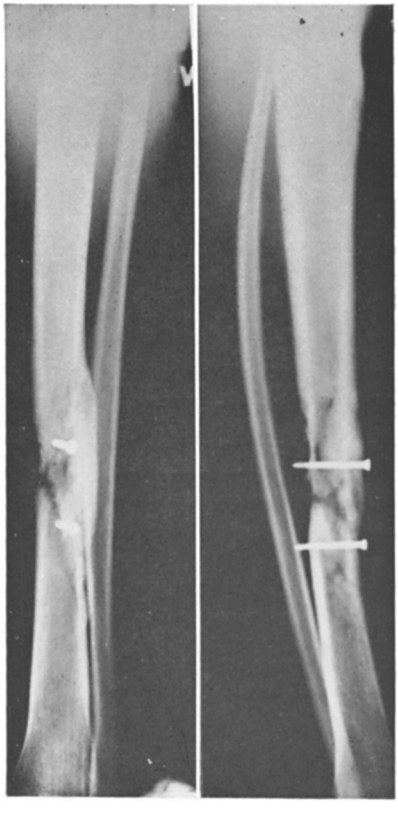


Fig. 32

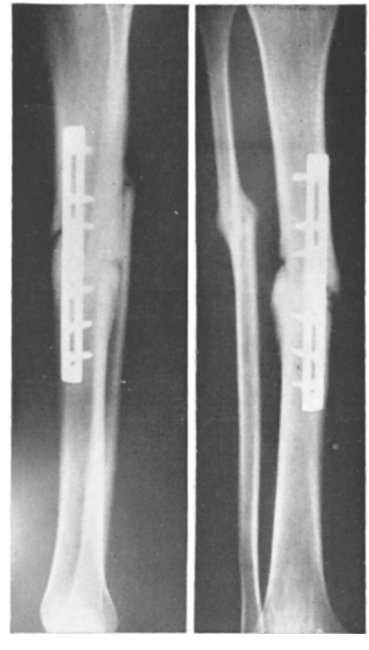


Fig. 33

Fig. 34. Radiograph of the fractured leg at the time of isotope investigation 8 ½ months after injury of Case II-4.

Fig. 35. Radiograph of the fractured leg at the time of isotope investigation 19 months after injury of Case II-5. This case had a pseudarthrosis and osteitis.

Fig. 36. Radiograph of the fractured leg at the time of isotope investigation 26 months after injury of Case II-6. This case had a pseudarthrosis of tibia and lower leg amputation was performed.

Fig. 37. Radiograph of the fractured leg at the time of isotope investigation 29 months after injury of Case II-7. This case had a pseudarthrosis of tibia.

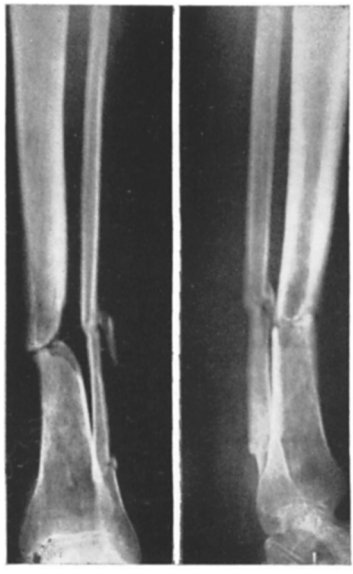


Fig. 34

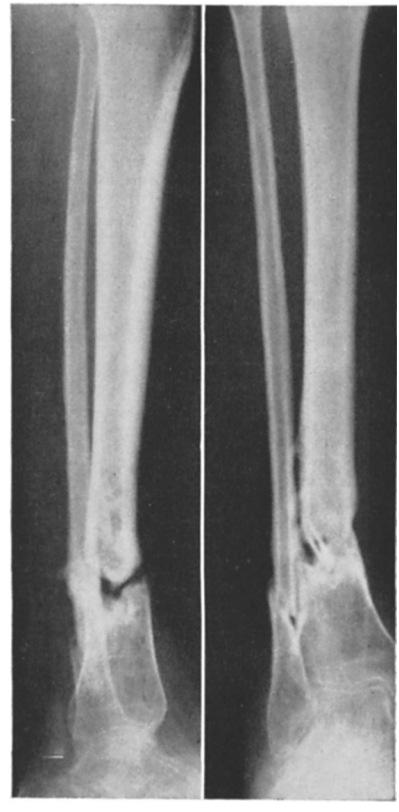


Fig. 35

Fig. 36

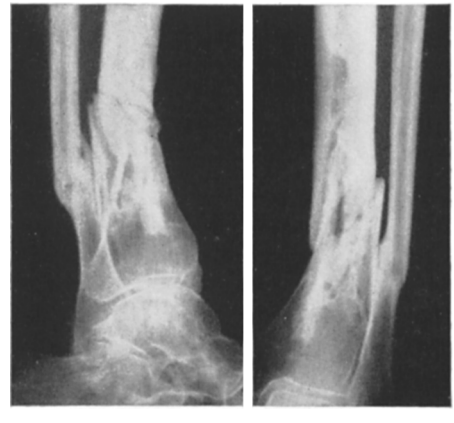


Fig. 37

Fig. 38. Radiograph of the fractured leg at the time of isotope investigation 42 months after injury of Case II-8. The tibial fracture was healed but osteitis was present.

Fig. 39. Radiograph of the knees of a patient who had a five-week-old fracture of his right tibia (Case I-5). A slight loss of density was observed in the knee region of the fractured leg but the accretion rate in this knee did not differ from that in the other knee (see Fig. 6 which shows the activity values in this patient).

The reproduction of this radiograph is hazardous but may be justified because separate interviews with five roentgenologists gave unequivocal evidence for loss of density in the right as compared to the left knee region.

Fig. 40. Radiographs of the knees of a patient with a 6 ½-month-old fracture of his right tibia (Case I-10). An advanced loss of density was observed in the knee region of the fractured leg as compared to that of the intact leg. The externally recorded Sr^{85} activity in the right knee region at Day 14 was 5.6 times higher than that in the knee of the intact, left leg.

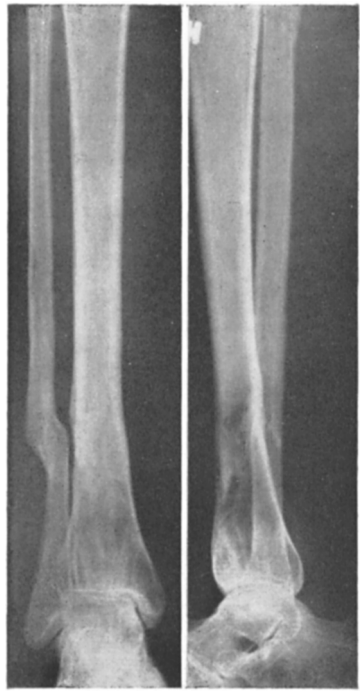
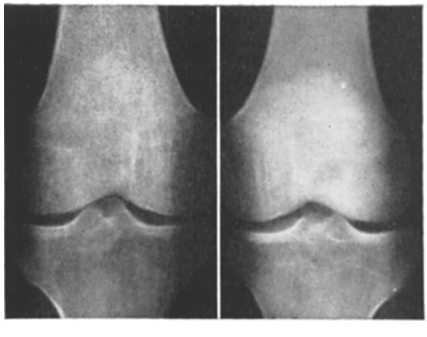
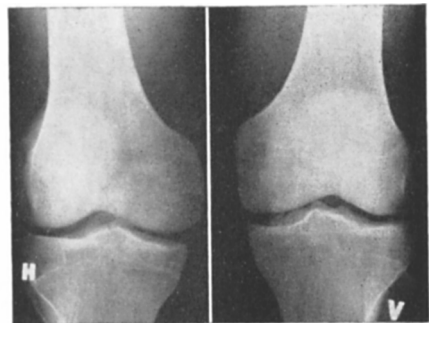


Fig. 38



RIGHT (fractured leg) LEFT (intact leg)

Fig. 39



RIGHT (fractured leg) LEFT (intact leg)

Fig. 40

ERRATA

Page 63, line 6: LV 5 cases; *should read:* LV+SI 5 cases
LV 3 cases

Page 63, line 29: 14; *should read:* 4

Page 68, fig. 3: Black fields indicating the occurrence of denervation potentials m. exst. dig. brev. are missing for cases: 407/58, 443/58, 546/58, 560/58 and 241/59.

Page 69, fig. 4: Black fields indicating the occurrence of denervation potentials in case number 1638/58 are missing for the muscles from m. tensor fascia lata to m. erector trunchi.

Page 106, in the table below: Other SI—: 5.7 $\%_2$; *should read:* 5.7 $\%_4$
affection
LV—SI

Page 113, line 12: myelography showed abnormalities; *should read:* myelography showed no abnormalities.

Page 121, line 7: 78.6 %; *should read:* 78.3 %.