Bone Marrow Imaging with $^{59}$Fe


SUMMARY
Commercially available collimators are not suitable for the visual demonstration of the kinetics of $^{59}$Fe, because of its physical properties. A locally designed collimator, that provides integral visual information of the whole body distribution of erythropoietic marrow, is discussed. Whole-body scans of 4 individuals are also included to demonstrate the capabilities of the collimator.


Kinetic studies of $^{59}$Fe in plasma and red cells or external counting of radioactivity to localise sites of red cell production and destruction and to determine rates of erythropoiesis do not provide integral visual information of the whole body distribution of erythropoietic marrow. Such visual information is important in understanding the function and distribution of haematopoietic tissue in patients with haematological disorders.

The in vivo marrow distribution has been determined by means of $^{59}$Fe and a positron camera. The rapid physical decay of $^{59}$Fe (T1/2 8 h) makes it unsuitable for determining the effectiveness of erythropoiesis and the sites of sequestration of the newly formed erythrocytes. The other disadvantage of this procedure is that cyclotron-produced $^{59}$Fe and positron cameras are not readily available.

$^{99m}$Tc-sulphur colloid and $^{111}$In-chloride have also been used for marrow scanning. They provide an indication of reticulo-endothelial and erythropoietic marrow distribution respectively, but do not reflect a true picture of iron deposition, since the kinetics of these radiopharmaceuticals differ significantly from those of iron.

The physical half-life of $^{59}$Fe (45 days) makes it suitable for sequential scanning, but this technique has not been widely used owing to the difficulties of collimation and detection of its high-energy $\gamma$-rays (1.098 and 1.289 keV), and because presently available commercial high-energy collimators allow excessive $\gamma$-ray septal penetration.

Special collimators, such as the 7-hole collimator for a 20-cm diameter crystal described by Chaudhuri, have been designed for whole-body scanning with $^{59}$Fe. However, for our dual probe, 12.5-cm diameter, scintillation crystal Ohio Nuclear Scanner, 3-hole collimators with additional guard rings were built locally in order to obtain acceptable bone marrow scans with 10 $\mu$Ci of $^{59}$Fe.

In this article we describe the design of the collimators and the use of the scanner in 4 patients with haematological disorders.

MATERIALS AND METHODS

Theoretical Considerations

Beck showed that, for the same value of the radius of view (taken at the focal plane) and the focal distance, a tapered-hole collimator is geometrically more efficient than one with parallel holes. It has also been shown that the optimum geometrical efficiency of a tapered-hole collimator is given by the equation

$$ G = \frac{N \pi R^4}{64F^3 (1 + \frac{F}{L})^2} = \frac{N \pi R^4}{64F^3 (1 + \frac{R}{2r_{opt}})^2} \ldots (1) $$

$$ r_{opt} = \frac{RL}{2F} \ldots \ldots \ldots (2) $$

where $R$ = radius of view at the focal point
$F$ = focal distance
$L$ = length of the collimator
$N$ = number of holes in the collimator
$r_{opt}$ = hole radius at crystal for optimum geometrical efficiency.

In order to construct a collimator with maximum geometrical efficiency, the optimum hole size at the crystal should be determined for specified values of $R$, $F$ and $L$. Although the use of multichannel collimators increases the geometrical efficiency, septal penetration results in a degradation of the geometrical resolution. Attention should therefore be given to septal penetration when multihole collimators are designed.

The septal penetration fraction is given by

$$ P = \frac{G_b - G}{G} \frac{M}{\text{geometrical fraction}} \ldots \ldots (3) $$

where $G_b$ = geometrical efficiency of a single large hole when the septum is removed.
\[ G = \text{geometrical efficiency with the septum in position.} \]
\[ M = \text{mean probability of septum penetration.} \]
\[ M = e^{-\lambda L(1 - \tau)} \quad \cdots \quad (4) \]
where \( \lambda = \text{linear attenuation coefficient} \)
\[ L(1 - \tau) = \text{effective mean length through the septum material.} \]
\[ 2rF \]
\[ L = \frac{2rF}{R} = \text{length of the collimator} \]
\[ \tau = \frac{8\pi r^2}{3\sqrt{3}D} = \text{transmission ratio} \]
\[ D = \text{diameter of the crystal.} \]

The expression for \( M \) in equation 4 is only approximate, although accurate enough for high-energy photons. The above expression has already been used for the design of many collimators.\(^5\)

### Design and Physical Determinations

For specified values of \( R, L \) and \( F \), it was necessary to determine \( r_{\text{opt}} \). The values chosen for \( L \) and \( F \) were 8.4 cm and 7.0 cm respectively, which is, to a certain extent, within the range of the values specified for the commercially available collimators of the Ohio Nuclear rectilinear scanner. The value of \( R \) is specified from the fact that the optical resolution (diameter of a spherical distribution) for anatomical localisation in ferrokinetic studies is approximately 4.5 - 5 cm.

A collimator (Fig. 1) with 3 tapered holes 8.4 cm in length, with a focal distance of 7 cm and a channel radius at the crystal of 1.2 cm, was constructed out of a solid lead block.

With the constructed collimator in position, the scan showed no contrast. Oblique penetration and rays penetrating the space between the collimator and its container were to a certain extent responsible for the lack of contrast (Fig. 2(A)). Penetration was largely eliminated by covering the container of the collimator as well as the space between the collimator and its container with lead shield rings (Fig. 2(B)).

### Ferrokinetic Studies and Bone Marrow Imaging

Ferrokinetic studies were performed as described by Finch et al.\(^11\) Ten \( \mu \)Ci of \(^{59}\)Fe were incubated with either the patient's own, or with compatible plasma. Free \(^{59}\)Fe
was removed by column chromatography. Bone marrow scanning was done 5 hours after administration of the radionuclide.

Patients

Three patients with hyperplastic, hypoplastic and aplastic erythropoietic bone marrow respectively and one with extramedullary erythropoiesis were selected as illustrative material for the \(^{59}\)Fe scans. The diagnoses of these patients were further substantiated by clinical evaluation, full blood counts, bone marrow analysis and serum iron determination.

Patient 1, a 30-year-old White woman, with a clinical diagnosis of idiopathic splenomegaly and the haematological features of hypersplenism, was investigated.

A haemoglobin estimation of 11.0 g/dl, a leucocyte count of \(3.0 \times 10^9/\) and a reticulocyte count of \(0,2\%\) were obtained. The aspirated bone marrow was normocellular with a myeloid-erythroid ratio of \(1.5 - 1\).

Patient 2, an 8-year-old White girl with a final clinical diagnosis of hypoplastic anaemia of the Fanconi type, was investigated. A peripheral blood count showed a haemoglobin of 8.8 g/dl, a leucocyte count of \(3.0 \times 10^9/\) with neutrophils \(0.48 \times 10^9/\), a platelet count of \(25 \times 10^9/\) and a reticulocyte count of \(0.2\%\). The aspirated and biopsied bone marrow was hypocellular with inactive erythropoiesis, myelopoiesis and reduced numbers of megakaryocytes.

Patient 3 was a 10-year-old Black boy, with a short history of bleeding and increasing weakness. The clinical diagnosis was that of bone marrow failure. The haematological findings were as follows: haemoglobin 3.3 g/dl, leucocyte count \(2.5 \times 10^9/\) with neutrophils \(0.675 \times 10^9/\), platelet count \(64 \times 10^9/\) and a reticulocyte count of \(0.3\%\). The bone marrow, on aspiration and biopsy, was found to be hypocellular, with nearly total absence of myeloid precursors. The patient did not respond to therapy with anabolic steroids and 2 months later the features of acute myeloblastic leukaemia were present.

Patient 4, a 60-year-old White man, was admitted to hospital with complaints of increasing weakness. A diagnosis of idiopathic myelofibrosis was made. The spleen was palpable 5 cm below, and the liver 1 cm below the costal margin. No fibrosis or sclerosis of the skeleton was evident on X-ray examination.

A peripheral blood haemoglobin estimation of 6.1 g/dl, a leucocyte count of \(32.7 \times 10^9/\) with a shift to the left, a leuco-erythroblastic reaction and a platelet count of \(200 \times 10^9/\) were obtained. The red cell morphology was that seen in bone marrow infiltration. No bone marrow could be aspirated. A bone biopsy showed a hypercellular marrow with striking megakaryocytic hyperplasia and the presence of markedly increased reticulin fibres.

RESULTS

Characteristics of the Collimator

In Fig. 1 the longitudinal section of the constructed tapered-hole collimator is shown. The geometrical efficiency and the septal penetration fraction of the collimator, totally shielded, are 0.02 and 0.18 respectively.

The geometrical resolution of the collimator, with and without shielding, was compared by determining the modulation transfer function (MTF). The MTF is a function of the spatial frequency as well as the line spread function. The improvement in the geometrical resolution is clearly illustrated in Fig. 4.

![Fig. 4. A comparison of the geometrical resolution, using the MTF as a criterion, with and without shielding of the collimator.](image-url)

Fig. 4. A comparison of the geometrical resolution for (optical and septal) and (optical and septal and shielding) penetration.
for the cases (optical + septal) and (optical + septal + shielding) penetration. It is clear from this figure that better geometrical resolution could be achieved if the response is only due to optical and septal penetration.

**Demonstration Cases**

The whole-body scans reflect the clinical prediction of marrow distribution in the 4 demonstration cases reported. The hyperplastic erythropoiesis with normal distribution in the vertebral and pelvic marrow is illustrated in demonstration case 1 (Fig. 6).

The 2 patients with a clinical picture of bone marrow failure had hypoplasia with reduced activity in the bone marrow (Fig. 7), and almost total aplasia with activity in the liver and none in the bone marrow (Fig. 8), as was expected in demonstration cases 2 and 3 respectively.

Patient 2 responded favourably to anabolic steroid therapy. Patient 3 did not respond to therapy and is an example of a person suffering from the well-described phenomenon of preleukaemic aplastic anaemia. The characteristic pattern of extramedullary erythropoiesis in the liver and spleen with no activity in the bone marrow (Fig. 9) was found in the patient with idiopathic myelofibrosis (case 4).

**DISCUSSION**

The necessity of additional shielding for the constructed collimator has been demonstrated in this investigation. The physical characteristics of "Fe, such as high energy and restricted dose, are responsible for low count rates. The integrated counts from both detectors as well as the counts obtained in the range of the two photo-peaks of "Fe provide a higher count rate response.

Optimum adjustment of the image enhancement module is of great importance, because detail is lost if the preset value is too high, while too low a value reduces the contrast.
From a clinical point of view, marrow scanning with $^{59}$Fe provides an acceptable resolution, and the distribution of erythropoietic marrow is readily perceptible, since sites of effective erythropoiesis are characterised by a rapid accumulation of radio-iron. Abnormal extramedullary sites of $^{59}$Fe deposition are readily demonstrated.

Frequently, the examination of peripheral blood samples, bone marrow aspirates and biopsies is not sufficient to establish the diagnosis and to evaluate certain haematological disorders. Although ferrokinetic studies provide valuable quantitative data on erythropoiesis, whole body scanning with $^{59}$Fe adds useful supplementary visual information. Knowledge of the existence of residual erythropoietic tissue in patients with features of aplastic anaemia may be a useful prognostic sign and may provide a reference point in assessing progressive bone marrow failure or response to therapy. This procedure may prove useful in determining the prognosis of idiopathic myelofibrosis and for the selection of patients for splenectomy.

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REFERENCES

Nutrition Research

The Effect of Protein Energy Malnutrition on Plasma Renin and Oedema in the Pig

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SUMMARY

Five litter-mate male pigs, aged 7 days and fed a standard Pig Industry Board diet containing 190 g/kg dry mass of digestible protein, were compared with 10 male pigs from two litters fed a protein-deficient diet (50 g/kg) for a period of 70 days. The 10 experimental animals developed oedema between the 42nd and 70th days of the study and 4 of them became lethargic. Although the 10 experimental animals showed the typical biochemical changes characteristic of protein energy malnutrition (PEM), including changes in muscle electrolytes, liver fat and plasma albumin, the 4 lethargic animals showed a significant increase in effective plasma renin activity (EPRA) only by the 70th day of the study. Since oedema preceded any increase in EPRA in some pigs and developed in others without any change in EPRA, it is suggested that the increased renin activity is not responsible for the initial fluid retention and oedema.


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Previous work on children and experimental animals suggests that the development of oedema during protein energy malnutrition (PEM) may be the result of increased activity of the renin-angiotensin system. The increased renin activity may explain the increased plasma aldosterone, decreased glomerular filtration rate, and the consequent retention of sodium and water found in patients with kwashiorkor. However, it has not been established whether this increased renin is a primary cause of water retention and consequent oedema, or whether the increase is due to other changes which occur during PEM. Therefore, an experiment was designed to examine the time relationship between the onset of oedema and the increase in plasma renin activity, using the pig as the experimental model.

MATERIALS AND METHODS

Fifteen male pigs from 3 litters, aged 7 days (3.0 ± 0.2 kg), were studied over a period of 70 days. The pigs were assigned at random to two groups: a control group of 5 pigs fed a standard Pig Industry Board diet containing 190 g/kg dry mass digestible protein, and an experimental group of 10 pigs fed a protein-deficient diet based on whole-wheat flour and maize starch and containing 50 g/kg digestible protein. Both groups received antibiotics, and mineral and vitamin supplements.

The pigs were examined daily for lethargy and oedema, which was first observed in the neck and at the base of the tail. On the 1st, 14th, 28th, 42nd and 70th days the glomerular filtration rate was determined by using 3H-