The Use of FE$^{59}$ and CR$^{51}$ for Estimating Red Cell Production and Destruction: An Interpretive Review

By Frederick Stohlman, Jr.

IN RECENT YEARS use of radioactive sodium chromate to determine red cell lifespan and of radioactive iron to estimate red cell production has gained widespread acceptance both as an experimental and diagnostic aid. The desirability of quantifying both of these parameters is obvious but whether Cr$^{51}$ and Fe$^{59}$ provide us with such a quantitative tool is open to question. In this review we will consider the uses of these isotopes, their quantitative limitations and their role in clinical medicine. It is beyond the scope of this review to cover all uses of these isotopes in clinical investigation and other research.$^{1,2}$ These isotopes have permitted important extensions of knowledge of red cell physiology, but their application to clinical practice is more limited.

The Steady State

Consideration of whether the red cell mass is in a steady state is critical in interpreting data derived from studies with iron and chromium. A steady state exists when the red cell mass is constant. Red cell production must equal red cell destruction to maintain a constant red cell mass. Under these circumstances, it is necessary to measure only one parameter, the other being equal. When a steady state is not present, changes in production rates, occurring chiefly as the result of changes in hemoglobin and red cell levels, must be taken into account.

Clinically, the non-steady states, in which Cr$^{51}$ and Fe$^{59}$ technics would be used, are usually those in which destruction is greater than production. Hemolysis, suppression of red cell production or ineffective erythropoiesis may be responsible. In these cases maintenance of hemoglobin by transfusion cannot be considered a steady state. Transfusions affect production rates and hence iron turnover except in the patient with an aplastic marrow. A patient does not make as many red cells at 10 Gm. as at 7 Gm. of hemoglobin. In sickle cell anemia, transfusion above 11–12 Gm. of hemoglobin may completely suppress red cell production.$^{3}$ Even in patients with erythroid hyperplasia and ineffective erythropoiesis, transfusions alter the production rate.$^{4}$ When the rate of erythropoiesis is fluctuating, the average survival rate measured over several weeks or months cannot be compared with the production rate measured over a few hours or perhaps days.

Practically, red cell mass cannot be measured daily. Consequently, the specific activity of Cr$^{51}$ and Fe$^{59}$ are measured rather than the total circulating radioactivity. The specific activity can be measured by assuming either a
constant red cell mass or a constant blood volume. In a steady state, the red cell mass is constant, whereas the blood volume may be subject to fluctuation. Accordingly, measurement of cpm/cc. of red cells is more desirable. This is true only when the red cell mass is in a steady state. When the hemoglobin is falling, when production rates are altered by transfusion, or when the hemoglobin is rising, due either to transfusion or increased production, specific activity based on a constant red cell mass (cpm/cc. of packed cells) is unreliable. In this case one can gain better estimates by measuring the specific activity of whole blood, changes in red cell mass being to a large extent offset by changes in plasma volume (table 1). This consideration is particularly important in Cr51 studies, where survival curves measured as cpm/cc. of packed cells are only valid if the death of a labeled cell is followed by replacement with an unlabeled cell. In the absence of red cell production, for example, the ratio of tagged to untagged cells will not change except from elution, so that in measuring the fall in the cpm/cc. of cells rather than estimating survival one would be estimating elution. Here measurement of cpm/cc. of whole blood would give a better estimate of survival although it would be no better than the hematocrit.

**The Use of Radioactive Sodium Chromate for Estimating Cell Survival**

One of the main problems in measuring red cell destruction with Cr51 arises from the loss of more Cr51 than can be accounted for by cell death. In man

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<thead>
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<th>Table 1.—Effect of Changes in Steady State on Cr51 Specific Activity*</th>
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<td>(a) Steady State</td>
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<td>(d) Regeneration (production &gt; destruction)</td>
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<td>(e) Effect of transfusion</td>
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<td>cpm/cc. RBC</td>
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*These hypothetical examples were constructed assuming a shortened red cell life span except in the case of transfusion, a normal cell age distribution, and a constant total blood volume except for minor daily fluctuations; chromium elution was omitted for the sake of simplicity.
this excess loss of Cr$^{51}$ takes the form of a distinct two component curve. Roughly 5 per cent of the tag is lost in the first 24 hours;\textsuperscript{5} thereafter Cr$^{51}$ is lost at a rate of 0.5–1.5 per cent per day in excess of that expected from cell death.\textsuperscript{6} Frequently the second component appears exponential, but in some instances, particularly with mild to moderate hemolysis, this is not the case. This excess loss may be explained equally well by elution, selective destruction, or selective tagging, but since the concept of elution is so well established, it will be retained. Correction terms for elution have been established using average values derived from a group of normal individuals. In correcting for Cr$^{51}$ elution one assumes that the rate of elution corresponds to the normal and that any disease process affecting red cell survival will not also affect elution. Unless these conditions are met, correction for Cr$^{51}$ elution is not valid. Unfortunately, the elution rate in most patients is not that of the observed normal mean. Since the value for elution may vary by 0.5 per cent, one may underestimate (or overestimate) red cell loss in a 70 kg man with a 5000 cc. blood volume by as much as 25 cc. per day.

When hemolysis is severe, Cr$^{51}$ elution is less important provided the chromium itself does not influence red cell survival and the red cell defect responsible for hemolysis does not affect elution. If the observed Cr$^{51}$ apparent half-time is 5–10 days, correction with either of the extremes reported for the average T/2 for chromium elution (46–77 days)\textsuperscript{6,7} changes the "corrected Cr T/2" very slightly (1–2 days). With milder rates of hemolysis the value one assigns for correcting chromium elution becomes important. Thus in the absence of senescent loss and with an observed 50 per cent apparent Cr$^{51}$ half-time of 20 days one gets a figure of 27 days for the corrected T$_{1/2}$ of Cr$^{51}$ survival using a 77-day elution and 35.5 days with the 46-day figure; this results in a difference of 12 days in the mean cell life span.

We have seen changing rates of chromium elution in dog and man.\textsuperscript{8,9} This problem is exemplified by a patient with hemolysis resulting from insertion of a ball valve prosthesis into the descending aorta.\textsuperscript{9} Here, red cells are trapped and destroyed by the lucite ball as it seats in its rigid housing. This should lead to pure random loss in addition to the normal senescent loss. Survival was measured by differential agglutination of homotransfused cells obtained from a donor who had not been bled for any reason in the preceding 5 years (fig. 1). An aliquot of these cells was tagged with Cr$^{51}$. In figure 2 the loss of Cr$^{51}$, as measured directly and corrected with a figure of 0.9 per cent/day, is compared with the loss of cells measured by differential agglutination. The measurements with differential agglutination showed the expected random loss of cells, 1.5 per cent being destroyed daily in addition to those lost from senescence. In contrast, the corrected chromium curve overestimated destruction during the early part of the study and underestimated it thereafter. It is not certain whether this discrepancy was due to a change in elution, or, more likely, the selective destruction of a relatively small number of heavily labeled cells.

A skewed age distribution of red cells may obscure mild hemolysis. In a patient with long-standing mild hemolysis, the age distribution of cells be-
RED CELL DESTRUCTION AFTER INSERTION OF HUFNAGEL PROSTHESIS

![Graph showing post-transfusion survival of normal red cells in a patient with a Hufnagel prosthesis in the descending aorta.](image)

Fig. 1.—The post-transfusion survival of normal red cells in a patient with a Hufnagel prosthesis in the descending aorta. Measurements of cell survival by differential agglutination are on the left; the ratio of differential agglutination to expected senescent loss is plotted on the right. The latter gives an estimate of the loss of cells other than from senescence. The straight line plot on a semilogarithmic scale indicates pure random loss; the rate was 1.5 per cent per day.

comes skewed (fig. 3) so that few, if any cells, survive 100 days. In such a patient one could not consider as normal a daily loss of 2 per cent of the chromium from autotransfused cells. The normal senescent loss is replaced by random loss, so that the chromium curve may look quite similar to the normal. For this reason mild hemolysis may be difficult if not impossible to detect with the Cr²¹ technic. Patients receiving repeated transfusions will also have a distorted age distribution of cells, the degree of distortion depending on the frequency of transfusion and survival of donor cells. Here, interpretation of data gained from autotransfusion is unreliable. Indeed from a diagnostic standpoint, it may be questioned that the added body burden of isotope can be justified by the limited information obtained in the above circumstances.

Studies with Cr²¹ can give useful clinical information. We recently studied a patient with a severe hemolytic process; his reticulocyte count was 1 x 10⁶/mm³; his fecal urobilinogen excretion, 700 mg. per day. Clearly he was destroying his own cells. Was this confined to destruction of the patient’s own cells or would he destroy donor cells? One might approach this problem (a) by measuring the rate of fall of hemoglobin following transfusion of normal cells; or (b) by measuring the survival of a few chromated normal cells. Technic (a) appears straightforward but is not. In this patient, transfusion of 4 units of compatible red cells raised the hemoglobin from 10 to 14.5 Gms. Within 30 days the hemoglobin had returned to 10–11 Gms. Did this indicate a 30-day
Fig. 2.—The post-transfusion survival of red cells measured by differential agglutination (Ashby) (from fig. 1) is compared with survival measured with Cr$^{51}$. A 5 cc. aliquot of cells was labeled with Cr$^{51}$, the remainder of the unit of transfused blood was not exposed to Cr. Correction for Cr elution was made using the value of 0.9 per cent per day for elution.

survival of the infused cells? Not at all. The measurement after infusion of a small number of chromated normal cells indicated normal survival. Raising the hemoglobin to a normal level by transfusion suppressed erythropoiesis below that previously needed to maintain the hemoglobin at 10 Gms. Destruction of the recipient's cells continued unabated, and this, together with decreased production constantly reduced the proportion of the patient's circulating cells. The rapid fall in hemoglobin was due not to destruction of donor cells but rather to failure of the bone marrow to replace recipient cells. Thus, in any patient in whom maintenance of hemoglobin following transfusion is used as an index of red cell survival, one must also consider changes in production rates.

Measurement of intravascular red cell survival will not permit the distinction between loss of cells from hemolysis and that from internal bleeding. In patients with thrombocytopenia, there is always appreciable occult internal hemorrhage, so that survival studies are of little value. In a young patient with severe thrombocytopenia there was sufficient "internal" hemorrhage for the resultant hemoglobin breakdown to increase the indirect bilirubin to 3.5 mg. per cent. When the bleeding was controlled, the bilirubin fell to less than 1 mg. per cent. Clearly it would have been impossible to decide with Cr$^{51}$ labeled cells whether the patient was hemolyzing in addition to bleeding. In
Fig. 3.—A hypothetical curve of the age distribution of cells in a patient with chronic mild hemolysis compared with the normal age distribution.

spite of this we see patients with thrombocytopenia in whom Cr¹⁰ survivals have been done in an effort to determine whether hemolysis existed.

Chromium labeling has been particularly useful in establishing the clinical significance of rare blood group antibodies. Can A₁B blood be given safely to a patient of type A₂B, who has an anti-A₁ antibody? It was possible to show with chromium, using less than 1 cc. of blood, that this antibody was hemolytic and A₁B blood could not be used.¹¹

The experimental study of survival characteristics of cells preserved under different conditions of storage has been facilitated by the use of chromium. This isotope requires smaller amounts of blood than previously needed with the Ashby technic. A short term study of survival usually suffices, since it has been demonstrated that most cells damaged by storage will be eliminated in the first 24 hours after transfusion. Those cells surviving this interval usually survive normally.¹²,¹³

Jandl¹⁴ suggested surface scanning after injection of chromated cells for locating sites of hemolysis. At present this method holds promise of being a useful clinical and experimental tool. If the spleen is a major site of red cell destruction, there should be a substantial increase in splenic radioactivity with time. This technic may complement other clinical and laboratory observations used as criteria for splenectomy and may turn out to be helpful in questionable cases; however, further experience with this method and its correlation with the results of splenectomy are required. The method offers no additional informa-
tion, however, in a disease such as hereditary spherocytosis, known to be controlled by splenectomy.

The Use of Radioactive Iron to Estimate Red Cell Production

Huff and associates suggested that hemoglobin synthesis could be estimated by measuring iron turnover. In theory, if one injects radioiron bound to the plasma iron binding protein (siderophilin, transferrin), the rate of plasma iron turnover can be determined from:

\[
\text{Plasma iron turnover/24 hours} = \frac{0.693}{\text{Fe}^{59} \times \text{serum Fe/mL} \times \text{plasma T/2 (hrs)}} \times \text{vol. x 24.}
\]

Measurement of radioiron appearing in peripheral cells 7–10 days after injection of radioiron gives an estimate of the proportion of iron used for hemoglobin synthesis. The hemoglobin content of red cells permits conversion from hemoglobin synthesis to red cell production.

To obtain meaningful estimates from this formulation certain conditions must be fulfilled:
1. It is necessary to accurately separate initial clearance and recycling;
2. red cell precursors should be labeled during the period when plasma iron clearance is being measured;
3. plasma iron turnover and hemoglobin synthesis should remain constant during the study;
4. there should be no overlap between production and destruction of cells;
5. plasma and red cell volumes should be known and relatively constant.

The plasma iron clearance curve normally is not a true first order reaction (i.e., simple exponential removal). Usually after several hours there is definite curvilinearity. In certain instances a third component may be present. These deviations from an exponential do not represent multiple removal mechanisms each of which is itself a first order reaction; this would result in a curve described by the expression \[e^{-\left(a + b + c \cdots n\right)t}\] which reduces to \[e^{-(n)t}\], a simple exponential expression in which the multiple rate constants are not separable. Curvilinearity only results from reentry of Fe \[^{59}\] into plasma after its initial removal. It has been suggested that the reticuloendothelial system removes iron from plasma, part of this iron being recycled back to plasma. If, in addition, this iron is in equilibrium with a storage compartment, a second pool of re-entry and a third component to plasma clearance results. This notion is supported by the recent studies of Noyes and associates on the fate of iron derived from non-viable, labeled transfused cells.

Pollycove has suggested that the curvilinearity results from an equilibrium between plasma and a labile bone marrow iron pool, associated with the developing red cell compartment. He suggests that the first component of the iron curve represents an exchange between plasma and the labile pool, and the second component is due to iron incorporation into hemoglobin. Experimental evidence for the existence of this rather large labile marrow pool has yet to be obtained. Final evaluation of this interesting concept therefore must await further experimental study.

In normal subjects the second and third components are small and even
though disregarding this fraction one may obtain a "reasonable" estimate of hemoglobin production. One cannot disregard these considerations when there is significant curvilinearity early in the clearance. Here recycling of Fe\(^{59}\) maintains the plasma radioactivity and leads to an underestimate of the clearance rate. To handle such cases models have been proposed based on two or three pools in equilibrium with the plasma iron pool.\(^1\)\(^{16}\)\(^{18}\) These models undoubtedly provide a better estimate of plasma iron clearance than does the simple expression given earlier; that it is the correct value may be disputed. In our experience multiple components to iron clearance curves are frequent in pathologic conditions. Some of the variations are shown in figure 4.

In patients with suspected hemolysis, care should be taken to determine whether there is destruction of labeled red cells during the measurement of plasma clearance. If hemolysis is present this introduces still another pool of labeled iron feeding into the plasma, for which a satisfactory mathematical model has not been devised. Moreover, it is difficult if not impossible to measure accurately the fraction of iron taken up by erythropoietic tissue, since some emerging red cells are destroyed and others contain recycled radioiron. Consequently only the roughest estimate of cell production can be made. In fact it is doubtful if the iron turnover would give as much information as the reticulocyte count, transfusion requirements and cell survival.

In measuring plasma clearance of iron, it is assumed that the rate of iron clearance is constant over a 24-hour period. In the steady state the total iron cleared during each 24-hour interval may be constant, but it seems unlikely that iron clearance does not change from hour to hour within that period. Not

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**Fig. 4.—Variations in the shape of Fe\(^{59}\) plasma clearance curves.** E. R. had normal red cell production; F. D. had lymphatic leukemia with reduced red cell production and anemia; N. G. had refractory anemia with a hyperplastic marrow.
only does the serum iron fluctuate rather substantially during the course of 24 hours19,20 (fig. 5), but the pattern may differ among individuals. These variations suggest fluctuations in plasma iron clearance. The alternative explanation that the input from tissue varies but that clearance remains constant seems less likely. These variations raise several questions; (a) does a clearance curve in which the T/2 is measured over 4–6 hours have meaning in terms of a 24-hour period; (b) if the serum iron is changing should an average serum iron value be used in the calculations; (c) are models valid in which the rate constants are considered to be nonvariable or should a stochastic model be developed? No matter what the cause of the change in serum iron, it implies that one or more of the rate constants involved in iron turnover is changing. If the second component of iron clearance represents an equilibrium between non-erythropoietic tissue and plasma, then the changing pattern of serum iron must be reflected in this component. In certain pathologic states where the second component is large this may produce large errors.

The factors influencing the movement of iron to tissue are unknown. Blood flow may be one possible determinant. To look at this aspect of the problem we studied the effects of an intravenous infusion of adrenalin on iron clearance in the dog. Figure 6 shows the results of such an experiment. Adrenalin roughly halved the plasma iron clearance rate. It seems likely that adrenalin, by diverting much of the blood flow to the periphery, reduced the amount of iron to the bone marrow and splanchnic area. This may not be the correct explanation. It suffices to say, however, that plasma clearance of iron was altered drastically for a few hours by an effect which appears totally unrelated to hemoglobin synthesis. In patients who are not in a steady state, changes in blood flow may be important, being particularly worthy of consideration when there is significant splenomegaly or congestive failure.

The recycling of iron from extramarrow sites or intramarrow turnover of iron from death of cells (ineffective erythropoiesis) may result in labeling of red cells several hours or days after injection of radioiron. When this occurs, the peripheral iron uptake cannot be used as an estimate of the proportion of iron removed for erythropoiesis during measurement of plasma iron turnover. The magnitude of this secondary labeling varies with the pathologic state. Lamerton and associates studied the effect of giving Imferon 24 hours after radioiron in normal and irradiated animals (fig. 7). In both groups the Imferon

![Graph showing the effect of adrenalin on Fe59 plasma turnover rate in the dog. Adrenalin was given in a constant I.V. infusion; serum iron 113 γ before and 124 γ after adrenalin; plasma volume 740 cc. before and 615 cc. after.](image-url)
reduced the total iron incorporation. A greater difference was noted in animals with altered erythropoiesis, where not only the magnitude but also the shape of the curve was changed by blocking the recycling of radioiron with a "flooding dose" of non-radioactive iron. Rubin et al.\textsuperscript{27} reported an excellent example of the importance of recycling of iron in man. One patient with a drug-induced red cell aplasia was given Fe\textsuperscript{59} 6 days prior to discontinuing the drug. Only a small amount of the injected Fe\textsuperscript{59} emerged within the first 15 days but over 55 per cent of the injected dose emerged between the 15th and 25th day. This can only be explained by recycling of iron to a regenerating marrow. Qualitative analyses of cell proliferation have been made using radioiron emergence curves. These have been discussed elsewhere.\textsuperscript{21,22}

The values for heme synthesis and mean corpuscular hemoglobin content (MCH) have been used to derive total red cell production. If the mean hemoglobin content of red cells produced over the preceding 120 days (i.e., life span of circulating red cells) has been constant, this gives a good estimate. However, if there has been a gradual change in the red cell hemoglobin content over the preceding several months as in developing iron deficiency anemia, then

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**Fig. 7.**—The influence of "flooding doses" of non-radioactive iron on Fe\textsuperscript{59} uptake in the rat (from Lamerton, L. F., Belcher, E. H., and Harriss, E. B.: Blood uptake of Fe\textsuperscript{59} in studies of red cell production. In The Kinetics of Cellular Proliferation. Stohlmann, F., Jr., Ed. New York, Grune and Stratton, pp. 301–311, 1959.
the younger cells undoubtedly contain less hemoglobin than those produced 60-90 days previously. Transfusion also may alter the mean cell hemoglobin. Under these circumstances one cannot calculate accurately red cell production from the values for heme synthesis and mean red cell hemoglobin content.

The uncertainty of the nature of iron clearance and extraneous factors, which may influence it, the observed variation in serum iron, and the uncertainty of the proportion of final uptake of iron by red cells, occurring during measurement of iron clearance, preclude quantitative measurement of iron turnover. The best estimates are made in normal subjects, when in a steady state. Total hemoglobin synthesis can only be crudely estimated in a patient not in a steady state. Until the determinants of iron turnover and red cell production are better understood and a stochastic model evolved, precise measurement of heme synthesis will not be possible.

Radioactive iron studies are most useful clinically when there is question of extramedullary erythropoiesis or in refractory anemia associated with erythroid hyperplasia. Surface scanning to measure the proportion of injected radioiron going to bone marrow as compared with liver and spleen may be helpful in establishing the presence of extramedullary red cell production. In anemia characterized by erythroid hyperplasia and reticulocytopenia, radioiron incorporation may help to give a better idea of the extent of red cell production, particularly when blood loss or hemolysis obscures estimates of production from transfusion requirements. In these cases delayed red cell release from the marrow may negate the value of peripheral reticulocyte counts. In anemia, associated with an aplastic marrow, measurement of iron incorporation offers little diagnostic help.

**Summary**

In surveying some of the limitations of studies with Cr$^{51}$ and Fe$^{59}$ my purpose has been not to deny their usefulness but to put them in perspective. These technics have made possible many extensions of the fundamental understanding of red cell physiology and iron metabolism. They will continue to be valuable experimental tools. It is hoped that if some of the limitations of isotope technics are considered, the non-experimental use of these isotopes will be confined to situations in which otherwise unavailable information of diagnostic or therapeutic importance can be obtained. Unfortunately isotope technics are used when more conventional means would be adequate or even preferable. An extreme example is the suggestion that repeated Fe$^{59}$ turnover studies might be used to determine the total dose of parenteral iron (as Imferon or saccharated iron oxide) to be given in iron deficiency anemia, pointing out that in so doing the possibility of iatrogenic hemochromatosis could be avoided. The usual calculations for determining dose however are not only safer but more accurate.

The use of Fe$^{59}$ and Cr$^{51}$ entails some risk, the main hazards being hepatitis, with the use of donor plasma or cells, and the possibility of untoward effects from radiation. An estimate of the risk of hepatitis can be gained from its incidence after transfusion. The radiation hazard is more difficult to assess. Leukemia has occurred after large doses of radiation but the extent of the radia-
tion hazard is unknown from the much smaller doses of radiation employed in the usual isotopes studies. Certainly the risk is not such as to preclude the use of isotopes to obtain information essential for diagnosis. However, when such information can be obtained by other means or when results cannot be adequately interpreted, the use of isotopes in clinical medicine appears unwarranted. In considering the use of isotopes in the doubtful case, the dose of radiation to be delivered should not be thought of as an isolated event but rather as adding to a total radiation dose, which as shown by the British survey may be appreciable.

SUMMARIO IN INTERLINGUA

In presentar un revista de certe limitationes de studios con Cr⁵¹ e Fe⁵⁹, mi objectivo non es negar le utilitate de tal studios sed de poner los in un perspective appropriate. Iste technicas ha rendite possibile multe extensiones del comprehension fundamental del physiologia erythrocytic e del metabolismo de ferro. Illos va continuar esser precioso instrumentos de recerca. Es sperate que si certes del limitationes del technicas a isotopos es prendite in consideration, le usos non-experimental de illos va esser restringite a situationes in que alteremente non obtenibile informaciones de importancia diagnostic o therapeutic pote esser obtenite per medio de illos. Infortunatemente, technicas a isotopos es currentemente usate quando medios plus conventional esserea adequate o mesmo preferibile. Un exemplo extreme es le proponimento que repetite studios de transito de Fe⁵⁹ poterea esser usate pro determinar le dose total de ferro parenteral (como Imferon o saccharate oxydo de ferro) a administrar in casos de anemia a deficitia de ferro, con le commento que per iste procedimento le possibilitate de hemochromatosis iatrogenic pote esser evitate. Tamen, le calculationes usual pro determinar le doses es non solmente plus secur sed etiam plus accurate.

Le uso de Fe⁵⁹ e Cr⁵¹ porta con se certe riscos. Le plus significative de istos es hepatitis, con le uso de plasma o cellulas ab donatores, e le possibilitate de effectos adverse ab radiation. Un estimato del risco de hepatitis pote esser derivate ab le incidentia de hepatitis post transfusiones. Le hasardo del radiation es plus difficile a evalutar. Leucemia ha occurrite post grande doses de radiation, sed le magnitude del risco radiatori non es cognoscite in le caso del multo plus micre doses de radiation emplete in le usual studios a isotopos. Certo, le risco non es tal que on deberea abandonar le uso de isotopos pro obtenire informaciones que es essential pro le diagnose. Tamen, quando ille information pote esser obtenite per altere medios o quando le resultatos non pote esser interpretate adequatemente, le uso de isotopos in le medicina clinic non pare justificate. In considerar le uso de isotopos in casos dubitose, le dose de radiation que va esser applicate non debe esser reguardate como un evenimento isolate sed plus tosto como un magnitude addite al total dose de radiation le qual, como le enquete britannic lo monstra, pote esser appreciable.

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RED CELL PRODUCTION AND DESTRUCTION


Frederick Stohlm, Jr., M.D., Senior Investigator, National Institutes of Health, Bethesda, Md.
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