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IRON KINETICS

Part I: Clinical Considerations — Part II: Methodology

ANDREW TEN PAS, M.D.*, DAVID M. LEAHY, M.S.**, AND ELLIS J. VAN SLYCK, M.D.*

PART I: CLINICAL CONSIDERATIONS:

A DYNAMIC PICTURE of the transport and utilization of iron in normal and disease states can be obtained by adding small amounts of radioactive iron to the circulation. Normally when tracer iron (59Fe) is injected intravenously, roughly a quarter of the dose disappears in ten minutes. The remainder is bound to a beta globulin (transferrin) and clears exponentially from the plasma. At first it leaves the plasma rapidly, approximately 50 per cent leaving in 90 minutes. After 4-8 hours the decrease of 59Fe diminishes progressively, and after two days a second slower exponential rate of decrease is established which persists for 8-10 days. This pattern indicates a continuous "feedback" of iron from an available source (bone marrow and/or liver) to the plasma: the so-called "labile iron pool".

The iron movement after it leaves the plasma can be followed by serial counting over the liver, spleen, and marrow (sacrum). The marrow counts rise to a peak in about four hours, stay at this level for two days and then decrease rapidly in the next four days. As the iron leaves the marrow, the counts over liver and spleen increase and approach the original blood level, indicating that iron is being incorporated into new red blood cells circulating through these organs.

The 59Fe appears in the circulating red blood cells in increasing quantities. In seven to ten days 75 to 85 per cent of the injected iron is found in the red blood cells and will remain there for about 100 days.

Small quantities of iron added to the circulation by intestinal absorption or by intravenous injection are used preferentially for red blood cell formation. This implies that iron is not uniformly mixed throughout the body, and that recently added iron is more readily available for the metabolic needs than storage iron. This has led to the concept of the labile iron pool, which has a constant, slow exchange with the storage iron (ferritin and hemosiderin).

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To summarize, the following parameters can be studied with $^{59}$Fe: The rate of clearance from the plasma, the rate of appearance and degree of incorporation in the newly formed red blood cells, and the rate of appearance and disappearance in the liver, spleen, and marrow. Together they elucidate the pathways of iron transportation and iron metabolism (Figure 1).

**Plasma Iron Clearance Rate ($T_{1/2}$)**

The $^{59}$Fe clears exponentially from the plasma in the first few hours. When the counts are plotted on semilogarithmic paper, it will give a straight line. In the first two to five hours, there will be no interference from the "feedback" mentioned before. When followed for more than two days, a second, slower exponential rate of disappearance slope appears. In the period of study used clinically (five to six hours), about 90 per cent of the radioactivity is cleared without deviation of the slope.

![Figure 1](image)

Scheme of the iron cycle with the location where the iron exchange can be studied with radioiron ($^{59}$Fe).

The clearance rate is expressed as the length of time required for one half of the injected $^{59}$Fe to disappear from the circulation. Normally, this half time ($T_{1/2}$) is 80 to 120 minutes. It is accelerated in iron deficiency anemia, hemolytic anemia, polycythemia vera, pernicious anemia, and in the anemia associated with infection and malignancy. The plasma iron clearance rate is decreased in hypoplastic and myelophthisic marrow states (Figure 2). Under normal circumstances, the $T_{1/2}$ in minutes roughly equals the plasma iron concentration.

**Plasma Iron Transport Rate (P.I.T.)**

The P.I.T. utilizes the rate of plasma clearance, as well as an estimate of the total transport iron (transferrin) to give a measure of the total amount of iron leaving the plasma per unit time. Thus, a rapid clearance in the presence of low circulating iron might yield a transport rate no greater than a much slower clearance in a subject with a high total plasma iron. The P.I.T. does not measure the rate of utilization of iron in erythrocyte hemoglobin. This is a separate determination to be discussed later. Normally, about one third of the iron leaving the plasma returns from the marrow unused.
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The slope constant of the plasma iron clearance is determined as follows:

\[
\log_2 \frac{T_{1/2}}{2\text{ hrs.}} = \frac{0.693}{2} = 0.346,
\]

indicating that 34.6 per cent of the total plasma iron is removed per hour. But, as mentioned before, the P.I.T. also depends on the total iron content of the plasma: a low value if the plasma iron is low, a high value if the plasma iron is high.

Two methods of calculating the plasma iron transport rate are as follows:

1) \[
P.I.T. = 0.693 \times 24 \times \text{serum iron (mg/liter)} \times \text{plasma volume (liter)} = \text{mg. Fe/day} \\
\frac{T_{1/2} \text{ (in minutes)}}{2}
\]

or \[
P.I.T. \frac{(\text{mg.Fe/day})}{\text{Weight (kg)}} = \text{mg. Fe/kg/day}
\]

2) \[
P.I.T. = \frac{\text{Serum iron (\(\mu\text{g}/100 \text{ ml}\)) \times 100 \times \text{hematocrit}}}{\text{mg. Fe/day/100 ml. blood} \times T_{1/2} \text{ (minutes)}} \times \frac{100}{100}
\]

Normal values for the plasma iron transport rate (P.I.T.) may be expressed in the following ways:

0.61 mg. Fe/day/100 ml. blood.
0.31 - 0.75 mg. Fe/kg./day
40 mg. Fe/day for a 70 kg. man (32-52)

Figure 2

Plasma clearances of an intravenous tracer dose of radioiron (59Fe).
FACTORS INFLUENCING THE PLASMA IRON TRANSPORT RATE

1. **Red cell destruction:**

   Increased red cell destruction per se will raise the plasma iron, but does not significantly affect the plasma iron transport rate unless there is an associated marrow hyperactivity (see 3c.)

2. **Increased body stores of iron:**

   In hemachromatosis the plasma iron transport rate may be increased as much as 70 per cent above the normal value. It does not reflect increased red cell production, but rather reflects accumulation and increased turnover in the liver.

3. **Marrow activity:**

   a) **Complete arrest of bone marrow:** The P.I.T. will be decreased, but not less than half of the normal rate, reflecting that the turnover in other organs is about 50 per cent.

   b) **Decreased erythropoiesis:** The P.I.T. will be decreased.

      Example: hypoplastic anemia.

   c) **Increased erythropoiesis:** The P.I.T. will be increased.

      Example: hemolytic disorders.

   d) **Ineffective erythropoiesis:** As an example, the P.I.T. is increased in pernicious anemia, but the reticulocyte count is low. There is increased heme formation out of proportion to the rate of blood formation. The P.I.T. reflects this so-called "ineffective erythropoiesis" or "heme shunt". This parameter, along with the reticulocyte count, can give a good indication of an existing block in erythropoiesis.

   Ineffective erythropoiesis can also be demonstrated in the sideroachrestic anemias which show acceleration in the plasma iron clearance with a marked increase of the plasma iron transport rate. Values as high as 135 mg. Fe/day have been reported.

4. **Diurnal variations in plasma iron:**

   The P.I.T. may be influenced by a diurnal rhythm for obscure reasons. In general, it has been found that, in about 50 per cent of the cases, the hemostatic mechanism keeps the P.I.T. constant. In the other 50 per cent, variability in the P.I.T. has been demonstrated, especially in cases with a rapid turnover.

THE APPEARANCE OF $^{59}$Fe IN THE ERYTHROCYTES (R.B.C. UTILIZATION)

The appearance of $^{59}$Fe in the erythrocytes involves three phases of iron kinetics: 1) plasma iron transport 2) mobility and quantity of iron stores and 3) marrow function. About 80 per cent of the plasma iron transport serves for immediate red
blood cell production. Therefore, a high proportion (75-85 per cent) of a given dose of $^{59}$Fe will soon appear in the circulating red blood cells. This can be used to measure the efficiency of erythropoiesis by calculating the “red cell turnover rate” as follows:

\[
\text{Plasma iron transport rate (P.I.T.) (mg/day) } \times \text{ maximal uptake tracer in RBC(%) } \times \frac{100}{100} = \text{ mg. Fe/day.}
\]

Normal values are 30-50 mg. Fe/day (0.43-0.72 mg. Fe/kg./day). However, there may be some error in measuring the maximal uptake of tracer in the red blood cells. The plateau is usually reached in 7-10 days, but this is not always true. Also, there is evidence that after the fifth day tracer from the extramedullary pool also contributes to the result. It is clear, then, that the fraction utilized for red blood cell formation cannot be calculated with accuracy under normal conditions. Under pathological conditions the situation is even more complicated by reutilization from short-lived erythrocytes or by altered pool kinetics.

These difficulties can be partly avoided by collecting blood samples daily or every other day for seven to ten days, to determine the radioactivity in the red blood cells, and to draw up an “appearance curve” (Figure 3). This will indicate not only the fraction of the original tracer dose appearing (although not very accurately), but also the rate of appearance which may be helpful under pathological conditions.

Figure 3
Patterns of appearance of intravenously injected tracer iron ($^{59}$Fe) in newly formed red blood cells.

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INTERPRETATION OF THE RED BLOOD CELL APPEARANCE CURVE

Two components are of importance: the size of iron stores and the bone marrow function. The curve will be depressed when the iron stores are increased even when the erythropoiesis is normal, and conversely, the curve will be elevated when the iron stores are low. Therefore, with a normal blood production, it reflects the state of iron storage. When the storage iron is normal, it reflects the rate and degree of erythropoiesis. Usually, in iron deficiency, the initial utilization is more rapid than in normals. However, in our experience, the utilization curve is often depressed. This paradox may be explained by the fact that the amount of $^{59}$Fe used in the procedure is too small to stimulate the marrow's erythrocyte production from its dormant state, present in many cases of severe iron deficiency.

The flatness of the curve in infection, malignancy, or uremia is roughly proportional to the severity of these conditions and is an indication of depressed erythropoiesis. On the other hand, in hemolytic anemia there is a prompt appearance of $^{59}$Fe in the red blood cells, but the total utilization is low. This suggests that in hemolytic anemia the serum iron binding protein is highly saturated with iron from the lysed erythrocytes, and the injected radioiron is partly deposited in the inactive tissue stores. In some instances the radioiron is deposited in the spleen, and after splenectomy the utilization improves. The increased red cell production may show itself by an initial sharp rise of the appearance curve, only to fall off rapidly because of the short life span of the erythrocytes (Figure 3).

IN VIVO COUNTING OVER BODY SITES

In practice, the counters are placed over liver, spleen, and sacrum (marrow), and the recorded activity is expressed as counts per minute per mc $^{59}$Fe injected. No great accuracy can be expected. The rate of blood flow through the organs, anatomical variations, and placement of the counter, all influence the results. For investigational use the method can be applied as an adjunct to the plasma iron clearance and the red blood cell appearance of $^{59}$Fe.

Normally, there will be a sharp rise over the marrow within a few hours after injection, reaching its peak at about 12 hours. Radioactivity will start to fall off after one or two days, with a concomitant rise in the counts over the liver and spleen, approaching the original blood levels.

Several patterns have been described:

Pattern M = hyperfunction of the marrow with erythroid hyperplasia, resulting in an earlier and higher marrow peak.

Pattern O = hypofunction of the marrow with erythroid hypoplasia, resulting in a low marrow count with high counts maintained over the liver and spleen.

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Pattern E.M. = extramedullary erythropoiesis, which gives an initial temporary high count over liver and spleen and a low marrow peak. The curve characteristic of marrow, in this case, appears over liver and spleen.

The iron kinetic patterns in several clinical conditions are outlined in Table I, and the following brief case reports serve to show the value of this technique in unusual clinical circumstances. (Also see Figure 4).

CASE 1: D. B. (#115 94 28). This 23 year old woman received 1500 mg. of chloramphenicol intravenously after an operative procedure (uterine suspension). Two weeks later she developed pallor and was found to have widespread petechiae.

Pertinent laboratory data were as follows: Hemoglobin 9.8 gm. per 100 ml., white blood cell count 150 per cu. mm., reticulocyte count 0.2 per cent, platelet count 67,500 per cu. mm., serum iron 131 µg. per 100 ml. and total iron binding capacity 314 µg. per 100 ml. The bone marrow showed few developing cells and was markedly hypocellular. The M:E ratio was 4:1. The findings suggested aplastic anemia induced by chloramphenicol.

Iron kinetic studies showed an accelerated plasma iron clearance (T½ = 62 minutes) and a high normal plasma iron transport rate (48.6 mg. Fe/day). The red blood cell utilization was almost normal (72.3 per cent). These findings were not those of aplastic anemia, and indeed the patient showed a rapid spontaneous recovery. Within two weeks the white blood count rose to 6,000 per cu. mm., the platelet count to 617,500 per cu. mm., and the reticulocyte count to 5.4 per cent. The serum iron dropped to 51 µg. per 100 ml.

In this instance the results of the iron kinetic studies were the earliest indication of the subsequent marrow recovery.

CASE 2: M.S. (#085 27 81). This 64 year old woman was admitted on August 20, 1964, for investigation of a persistent refractory anemia, present for about 6 months. In 1962, she underwent splenectomy for idiopathic thrombocytopenic purpura, with a good result.
<table>
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<th>Table I The Iron Kinetic Patterns Under Normal and Pathological Conditions</th>
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Admission laboratory data showed: Hemoglobin 6.8 gm. per 100 ml., white blood cell count 4,250 per cu. mm., platelet count 305,000 per cu. mm., reticulocyte count 7.7 per cent, serum iron 188 μg. per 100 ml. and serum iron binding capacity 235 μg. per 100 ml. A peripheral smear showed predominantly macrocytic red blood cells. The bone marrow was hypercellular with an increased normoblastic erythropoiesis (34 per cent).

Iron kinetic studies were as follows: a rapid plasma iron clearance (T½ = 49 minutes) with an increased plasma iron transport rate (70 mg. Fe/day). The red blood cell utilization (87.1 per cent) showed a steeper than normal curve with a short plateau. These findings suggested a hemolytic process.

Further investigations revealed a plasma hemoglobin of 60 mg. per 100 ml. and a positive test for urine hemosiderin. The diagnosis of paroxysmal nocturnal hemoglobinuria was confirmed by a positive Crosby test and a positive Hegglin heat resistance test.

CASE 3: A. S. (#088 15 57). This 57 year old man was found to have massive hepatosplenomegaly in 1958. A diagnosis of agnogenic myeloid metaplasia was made. In August, 1964, splenectomy was considered because of evidence of hemolysis due to hypersplenism.

Laboratory data showed: Hemoglobin 6.3 gm. per 100 ml., reticulocyte count 5.9 per cent, platelet count 250,000 per cu. mm., serum iron 133 μg. per 100 ml., and total iron binding capacity 332 μg. per 100 ml.

Iron kinetic studies were done prior to splenectomy. They showed a normal plasma iron clearance (T½ = 86 minutes) and a high normal plasma iron transport rate (50 mg. Fe/day), but the red blood cell utilization was markedly decreased (35 per cent). These findings were in keeping with the original diagnosis of myeloid metaplasia.

CASE 4: E. B. (#109 82 03). This 60 year old man was followed since April, 1963, for a refractory anemia with a hemolytic component. Laboratory data in 1963 showed: Hemoglobin 8.6 gm. per 100 m., white blood cell count 3,650 per cu. mm., reticulocyte count 1.5 per cent, total bilirubin 2.4 mg. per 100 ml., serum iron 163 μg. per 100 ml., and total iron binding capacity 247 μg. per 100 ml. The Coombs' test was negative. The marrow was hypercellular with an intense normoblastosis, many macronormoblasts, and a few megaloblasts. 51Cr studies showed a mean red cell life of 51.9 days (normal 120 days).

Treatment with hemopoietic agents was unsuccessful. Corticosteroids did not decrease the rate of hemolysis. Two short courses of 6-mercaptopurine had to be stopped because of severe leukopenia.

The clinical picture remained unchanged, and the laboratory studies in February, 1965, showed: Hemoglobin 6.7 gm. per 100 ml., white blood count 2,300 per cu. mm., and reticulocyte count 0.9 per cent. The red blood cell morphology was pleomorphic with a moderate hypochromasia. The serum iron was 248 μg. per 100 ml., and the total iron binding capacity, 282 μg. per 100 ml. Marrow studies showed marked hypercellularity with increased erythropoiesis, incompletely megaloblastic. The M:E ratio was 1:2.

Iron kinetic studies revealed a rapid plasma iron clearance (T½ = 45 minutes) with an enormously increased plasma iron transport rate (197.3 mg. Fe/day). In contrast the red blood cell appearance curve was delayed, and the utilization extremely poor (16.3 per cent).

These findings can be explained by the concept of “ineffective erythropoiesis”; in other words, a rapid iron turnover with a hyperactive marrow, but without the production of an adequate number of erythrocytes. It supports the diagnosis of erythremic myelosis in this case.

**PART II: METHODOLOGY**

*Production of 59Fe*

$$^{59}\text{Fe} \xrightarrow{(B,\gamma)} ^{59}\text{Co}$$

The above is the (n,γ) reaction for the production of 59Fe by neutron activation.
Physical Characteristics

\(^{59}\)Fe has an approximate half-life of 45 days.

1. Beta radiation:
   a) B of 0.271 mev. maximum energy occurring 46%
   b) B of 0.462 mev. maximum energy occurring 54%
   c) B of 1.560 mev. maximum energy occurring 0.3%

2. Gamma radiation:
   a) \(\alpha\) of 0.191 mev. maximum energy occurring 2.8%
   b) \(\alpha\) of 1.098 mev. maximum energy occurring 57%
   c) \(\alpha\) of 1.289 mev. maximum energy occurring 43%

Dosage

The usual tracer dose is 10 µc. of the radioiron, in the chemical form of ferous citrate.* The radioactivity is contained in 10 ml., with a specific activity of approximately 16 mc./mg. iron.

Radiation Dosimetry

Assuming counter efficiency for \(^{59}\)Fe to be 0.25 and administered dose of approximately 10 µc.:

1. \(2.5 \times 10^4 = 1.0 \times 10^6 \text{ dis./ min. in whole marrow} \div 0.25\)
   dividing by weight of marrow in grams.
2. \(1.0 \times 10^6 = 3.85 \times 10^2 \text{ dis./gm./min. or,}\)
3. \(3.85 \times 10^2 \times 0.12 \times 10^4 \text{ ev.} = 4.61 \times 10^7 \text{ ev./gm./min. or,}\)
4. \(4.61 \times 10^7 \times 1.44 \times 10^9 = 6.64 \times 10^{16} \text{ ev./gm./day or,}\)
5. \(6.64 \times 10^{16} \div 35 \times 10^{12} = 0.0013 \text{ roentgens equivalent physical per day}\)
   for \(^{59}\)Fe, if all activity in erythropoietic areas = 0.013 rep./day. Then, if one assumes much of the activity is stored in liver and spleen, and assuming an even distribution in all three organs, multiply the calculated bone marrow radiation dose given above by 0.13.

*Ferrutope — E. R. Squibb and Sons, New Brunswick, New Jersey.
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Procedure

Prior to administration of the radioiron, a fasting blood sample is taken, to be used as a control and background count. The $^{59}$Fe is slowly injected into a large vein in the patient's arm. In order to determine the plasma radioiron disappearance curve for the patient, 4 ml. of blood are withdrawn at the following time intervals after injection: 15 minutes, 45 minutes, 75 minutes, and 105 minutes. In order to determine the total red blood cell utilization of the patient, blood samples are taken from day 1 to day 10, according to the physician's discretion. These blood samples are later counted against a standard, prepared from a properly diluted aliquot of $^{59}$Fe.

Counting Techniques

The blood samples taken to determine plasma iron clearance undergo centrifugation, to separate the plasma from the red blood cells. One ml. of plasma is then accurately pipetted into a screw cap glass vial (1 dram, 15 x 45 mm.). The five samples, 15 minutes, 45 minutes, 75 minutes, and 105 minutes, and the background sample are then ready for the direct counting procedure. The blood samples taken to determine red blood cell utilization are centrifuged, to separate the blood components.

The plasma is then pipetted off and discarded, and one ml. of packed red blood cells is drawn up and transferred into a glass vial, preparatory to counting.

An $^{59}$Fe standard is prepared by taking 1 ml. containing 1 $\mu$C./ml. on a known date, from a standard vial of radioiron. This is then diluted to 100 ml. with distilled water. One ml. is then taken from this primary dilution and is pipetted into a screw cap glass vial. This standard is then equal to 0.01 $\mu$C./ml. on a known date. Decay for the standard is calculated from the date that it was 0.01 $\mu$C. to the day of injection. The count rate obtained from this standard is used to determine, in an equation, the amount of radioactivity in the patient's total red blood cell mass.

Instrumentation

The 1 ml. plasma and red blood cell samples containing $^{59}$Fe are counted using a scintillation detection system, composed of a NaI(T1) well crystal for counting the gamma radiation, used in conjunction with a Tracerlab SC-71 Compu/Matic scaler and automatic read-out system. The samples are counted for 10 minutes each, and a background count is also taken. When the patient's blood is known to contain radioactive chromium ($^{51}$Cr), an isotope used in blood volume work, a spectrometer is interconnected with the detection system. The window width of the spectrometer is set to discriminate against the $^{51}$Cr gammas, picking up only the $^{59}$Fe photons.
Calculations

In determining the plasma-iron disappearance curve, the net counts obtained from the 1ml. plasma samples of 15 minutes, 45 minutes, 75 minutes and 105 minutes are plotted on semilogarithmic paper with time in minutes on the horizontal axis, and net count rate per 10 minutes on the vertical axis. An extrapolation is made to time zero from the linear function obtained. The T\(^{1/2}\) plasma iron clearance value is the time required for the plasma count rate to reach one half of the extrapolated count rate at time zero. Examples of plasma iron clearance curves are illustrated in Figure 2.

In determining the total red blood cell utilization, the hematocrit and normal blood volume figures must be available, since only 1 ml. of packed red blood cells counted. Having subtracted the background, the net counts for the packed red blood cell samples collected over 7-10 days are obtained. The rates now have to be changed to yield a value for the per cent of iron utilized by the total red cell mass for that particular day after injection of the radioiron. This value is calculated by utilizing the following 4 factors: 1) the net count rate of the standard, with its accurate microcurie level at day of injection (accounting for decay) 2) the net count rate for the sample, representing the activity in 1 ml. of packed red blood cells 3) the patient's hematocrit and 4) blood volume. A sample calculation of per cent iron utilization is as follows:

**Day of Injection: 9/23/64**

**Standard** = 0.01 μc./ml. on 9/23/64

**Blood Volume** = 4835 ml.

**Hematocrit** = 31%

**Sample Net Count** = 48135 c/10 min.

**Standard Net Count** = 9080 c/10 min. (4 days after injection)

**Step 1:**

\[
\frac{0.01}{48135} = \frac{X}{9080}
\]

\[= 0.0010 \text{ μc./ml. packed red blood cells}\]

**Step 2:**

\[4835 \times 0.31 = 1499 \text{ ml. packed red blood cells}\]

**Step 3:**

\[1499 \times 0.0019 = 2.85 \text{ μc.}\]

**Step 4:**

\[2.85 = 28.5\% \text{ utilized by 9/27/64 (4 days after injection)}\]

Examples of red blood cell appearance curves are shown in Figures 3 and 4.
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REFERENCES


