

BODY IRON EXCHANGE IN MAN *

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The present studies were undertaken to measure total body iron turnover in man. The assumptions were made: *a*) that the adult is in iron equilibrium, and *b*) that it is possible by the intravenous injection of iron to label body iron uniformly to the extent that blood sampling will reflect iron exchange. Such studies had previously been carried out in animals and the premise was shown to be generally valid (1). This report indicates the approximate period of time required for uniform labeling of miscible iron, and characterizes the total iron turnover in normal men, in nonmenstruating and in menstruating women.

MATERIALS AND METHODS

Patients in the Northern State Hospital were selected for study because of their good health and normal hematologic findings, and absence of history of abnormal blood loss or anemia. They were divided into three groups. Group I was composed of 6 adult men, Group II of 12 adult nonmenstruating women and Group III of 6 adult menstruating women. Pertinent hematologic data are summarized in Table I.

Hematocrit, plasma iron and reticulocyte determinations were performed initially and at the end of the study on venous blood samples from these patients. The plasma iron method employed was that of Bothwell and Mallett (2). Radioiron was injected intravenously as Fe^{59} citrate in dosage of 100 μc . (60 μg . of iron) per patient. Samples were drawn on the second month after injection and at 4 month intervals thereafter over a period of from 46 to 54 months. On each occasion the red cell hematocrit was determined, and duplicate samples of blood were pipetted with a calibrated pipette for radioactive analysis. At the end of the study all samples were wet-ashed, precipitated, electroplated and counted as previously described (3).

In calculation of data, average figures of red cell activity for each group were plotted on semilog paper. Employing these figures after the first year, a line was fitted by the method of least squares and extrapolated to zero time. The slope of this line appeared constant over

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a three year period and was taken to represent external loss of iron. Turnover rate was then calculated from this slope according to the formula:

$$\text{Turnover rate (per cent per year)} = \frac{0.693}{T \frac{1}{2} \text{ (in years)}} \times 100 \quad (1).$$

Red cell mass was estimated on the basis of an assumed blood volume of 64 ml. per Kg. and the determined red cell hematocrit. The factor 1.1 was used to convert red cell volume (ml.) to iron content (mg.). The formula employed was:

$$\text{Red cell iron (mg.)} = \text{body weight (Kg.)} \times \text{hematocrit} \times 64 \times 1.1.$$

The estimation of miscible tissue iron was derived from two sources: *a*) The initial distribution of radioiron in the normal subject at 60 days was assumed on the basis of other studies¹ to be 10 per cent in tissues other than circulating red cells. Thus, early tissue localization of iron would be represented by the formula:

$$\text{Red cell iron (mg.)} \times \frac{10}{90}.$$

b) There was an indication from the plot of red cell activity that the fall during the first year was excessive. The magnitude of this initial component was obtained by extrapolating the latter slope to zero time and subtracting this value from 100 per cent. This was interpreted as due to mixing of radioiron with tissue iron and its amount in mg. of iron was calculated from:

$$\text{Red cell iron (mg.)} \times \frac{\text{initial component (per cent)}}{100 \text{ per cent} - \text{initial component (per cent)}}.$$

It was assumed that a uniform specific activity was attained in the course of these studies between red cell and miscible tissue iron. Total miscible body iron then was represented by the addition of these two fractions of labeled tissue iron to red cell iron. Turnover rate was applied to this total miscible iron figure in the calculation of daily iron absorption and excretion. It was assumed that the subjects studied were in a steady state; that is, that iron absorption and excretion were equal over the period of study.

RESULTS

Radioiron data obtained in individual subjects are shown in Figure 1, and average data in the

¹ This is based on the determination of the amount of radioiron in circulation in five normal subjects at 60 days, employing Cr^{51} to estimate red cell mass (4).

TABLE I
Hematological data on subjects

Subject	Age	Sex	Weight	RBC iron	Hematocrit			Reticulocytes		Plasma iron		Blood volume
					Initial	Average	Final	Initial	Final	Initial	Final	
			Kg.	mg.	%	%	%	%	%	µg. %	ml.	
Group I (Men)												
J. A.	82	M	65	2,015	42	44	44	0.4	0.7	88	116	4,160
P. A.	84	M	64	1,805	39	40	39	1.4	1.5	73	98	4,100
A. B.	61	M	59	2,040	50	49	47	0.1	0.1	112	66	3,780
P. B.	70	M	86	2,895	46	47	49	1.9	1.1	56	156	5,600
O. O.	64	M	57	1,685	42	42	41	1.0	0.4	112	75	3,650
T. O.	57	M	63	2,080	46	47	50	0.8	0.6	68	100	4,030
Average values			66	2,085	44	45	45	0.9	0.7	85	102	4,220
Group II (Nonmenstruating women)												
J. A.	75	F	57	1,685	42	42	44	0.6	0.9	82	82	3,650
S. A.	77	F	77	2,385	43	44	45	0.8	0.3	66	67	4,930
M. B.	76	F	57	1,765	44	44	46	0.1	0.5		110	3,650
A. B.	67	F	43	1,210	38	40	41	0.3	0.5		59	2,750
F. B.	70	F	52	1,610	44	44		1.3		100		3,330
I. B.	56	F	62	1,830	42	42	42	0.3	0.9	100	77	3,970
E. B.	63	F	68	1,965	38	41	43	0.7	0.4		108	4,350
A. Bo.	74	F	58	1,875	47	46	45	1.7	1.0	70	128	3,710
H. G.	68	F	73	2,155	43	42	42	0.3	0.8	106		4,670
F. G.	64	F	50	1,690	46	48		0.2				3,200
B. S.	50	F	64	2,115	48	47	47	0.6	1.0	75	105	4,100
A. G.	49	F	45	1,300	40	41	40	0.6	0.9	39	75	2,800
Average values			59	1,799	43	43	44	0.6	0.7	80	90	3,759
Group III (Menstruating women)												
D. C.	37	F	55	1,590	43	41	41	1.5	0.4	154	177	3,520
E. C.	39	F	67	2,170	46	46	42	1.2	1.1	75	261	4,290
A. O.	40	F	59	1,785	44	43	40	0.8	1.2	89	122	3,775
E. P.	44	F	57	1,605	39	40		0.7		115	130	3,648
E. B.	33	F	59	1,910	45	46	46	1.7	1.0	97	128	3,775
L. R.	32	F	66	1,950	41	42	41	1.1	1.2	81	97	4,225
Average values			61	1,835	43	43	42	1.2	1.0	102	153	3,872

three groups are shown in Figures 2a, b and c. In all instances the blood value at two months after initial injection was taken to represent 100 per cent and subsequent values are plotted as a fraction of this value. An excessive fall was observed during the first year of 15 per cent in men and 9 per cent in women. The slope of decreasing red cell radioactivity over the following 3 years in these three groups indicated a half-life of 8.3 years in men, 6.4 in nonmenstruating women and 3.4 years in menstruating women. This is equivalent to yearly decreases in red cell radioactivity of 8.3, 10.8 and 20.1 per cent in these three groups.

The miscible tissue (or non-red cell) iron in the three groups, derived from an assumed 10 per cent tissue distribution at the time of injection and from the excessive fall in activity during the first year,

was 600 mg. in men and 380 mg. in women (Table II). Daily turnover of total miscible iron was calculated to be 0.61 mg. per day in men, 0.64 mg. per day in nonmenstruating women and 1.22 mg. in menstruating women.

DISCUSSION

Assuming the normal adult to be in iron balance, it should be possible to determine iron turnover by measuring quantitatively either absorption or excretion. There are serious limitations in the use of absorption measurements. Chemical balance studies have the advantage of measuring the total intake of iron in its dietary form, but are of insufficient precision. Isotopes of iron, which have the advantage of more accurate quantitation, do not allow one to administer iron in its various forms as they occur in food. However, studies

done in which radioiron was added to food (5) or in which various foodstuffs were biosynthetically labeled (6-8) suggest an absorption of about 5 per cent or 0.75 mg. per day from a normal diet.

A second approach to the quantitation of iron balance is the measurement of iron loss. Chemical measurements are not feasible, but losses of radioiron, measured by periodic collections of urine, feces and sweat over a period of 140 days have been reported by Dubach, Moore and Callender (9). Daily losses of 0.38 to 0.52 mg. of iron were calculated in three male and one female subjects.

In the present study body iron turnover was determined by sampling red cell iron over a period of three to five years. Calculations of the daily turnover of red cell iron after the first year gave values of 0.47, 0.53 and 1.0 mg. per Kg. in men, nonmenstruating and menstruating women, respectively. After allowance was made for mix-

ing with other body iron, the calculated daily exchange of body iron was 0.61, 0.64 and 1.22 mg. in three groups of subjects (Table II). Since the possibility of further gradual mixing of radioiron in circulation with tissue iron cannot be excluded, it should be emphasized that these calculated rates of iron excretion represent maximal values.

Dubach and co-workers (9) obtained evidence that iron losses were decreased in iron deficiency and increased with hemolytic anemia. Similar results indicating a direct correlation between amount of body iron and excretory losses were obtained by us in the mouse (1). It is known as well that both the state of iron stores and the rate of erythropoiesis influence absorption. Thus the data here which apply only to iron turnover in the normal subject may well be appreciably modified in pathologic states.

Of additional interest was the evaluation of miscible tissue stores by this technique. In all three groups the time required to reach a constant

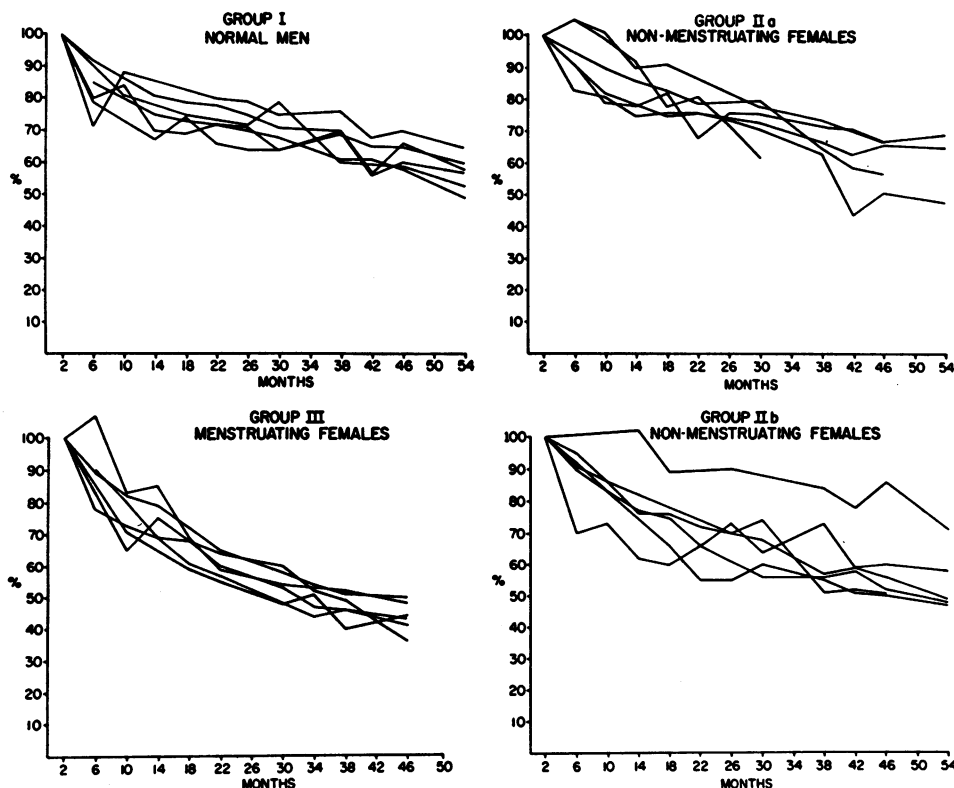


FIG. 1. Fe^{55} ACTIVITY OF CIRCULATING BLOOD

Levels of red cell activity over a period of 54 months are plotted. The value at 60 days in each instance is taken as 100 per cent.

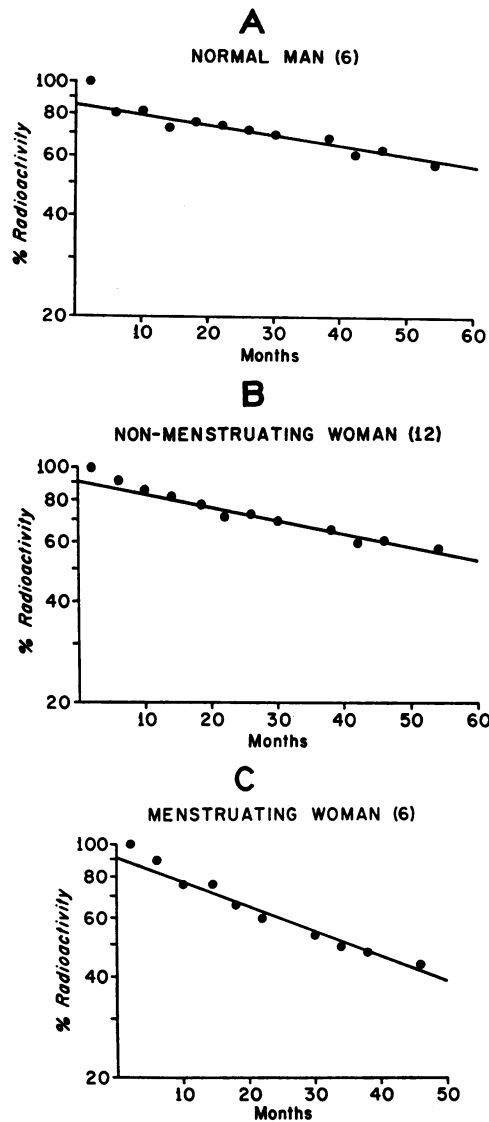


FIG. 2. RADIOIRON LOSS FROM CIRCULATING ERYTHROCYTES OF NORMAL MAN (A, SIX SUBJECTS), NONMENSTRUATING WOMAN (B, 12 SUBJECTS) AND MENSTRUATING WOMAN (C, SIX SUBJECTS)

Average values for each group of subjects are plotted. The line expresses the slope of fall in red cell radioactivity after the first year.

daily loss was approximately one year. The average size of body stores calculated from the size of this original mixing component, and with allowance for an initial tissue iron labeling by about 10 per cent of the injected activity, was from 377 to 600 mg. The figure of 600 in men is about half of that previously shown to be available for hemoglobin synthesis by phlebotomy experiments (10). Thus it seems likely that only a portion of storage iron (ferritin and hemosiderin) is miscible in the normal individuals over prolonged periods, despite the fact that it may all be mobilized from tissues if needed for red cell production.

SUMMARY

Red cell iron turnover as measured by the radioactivity of the circulating red cell iron over a four year period was found to represent 0.47 and 0.53 mg. per day in a group of 6 men and 12 nonmenstruating women. The amount of miscible tissue iron was identified by an exaggerated fall in the first year. This miscible pool is appreciably smaller than estimates of nonhemoglobin body iron. Iron turnover of total miscible body iron is calculated to be 0.61 mg. per day in men, 0.64 mg. per day in nonmenstruating women and 1.22 mg. per day in menstruating women.

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TABLE II
Iron metabolism of the experimental subjects

Group	Red cell iron	Miscible tissue iron	Total miscible iron pool	Pool turnover		Daily absorption or excretion
				%/year	mg./year	
I Men	2,085	600	2,685	8.3 ± 1.1	223	0.61 ± 0.08
II Nonmenstruating women	1,799	377	2,176	10.8 ± 0.8	235	0.64 ± 0.05
III Menstruating women	1,835	385	2,220	20.1 ± 1.7	446	1.22 ± 0.11

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