BNL 6925

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THE STUDY OF MENSTRUAL AND OTHER BLOOD LOSS, AND CONSEQUENT IRON DEFICIENCY BY Fe^{59} WHOLE BODY COUNTING.*

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* Research supported by the U. S. Atomic Energy Commission. Presented in part to the Canadian Society for Clinical Investigation, Toronto, Canada, January 17, 1962.

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DISCLAIMER

Menstrual blood loss provides a normal mechanism of iron loss from the female body which can vary greatly in quantity. Several studies have shown normal menstrual loss to range from 7 to 180 ml of blood, for the most part some 20 to 70 ml of blood per period[1,2,3,4,5]. The resulting iron loss from the body ranges from 2 to 79 mg per period[2,8]. Menorrhagia, however, can produce losses as great as 900 or more ml of blood, or 220 mg of iron[6,7]. Although the average diet contains 12 to 15 mg of iron daily, and thus readily supplies the additional 1.0 to 1.5 mg of iron per day needed to make up normal menstrual loss[9], menorrhagia of sufficient degree and chronicity can lead to marked iron deficiency. Recognition of this pathogenesis of iron deficiency may be particularly difficult because of the patient's subjective impression of average menstrual flow, and existing problems in accurately quantitating the blood lost.

Early methods of menstrual assessment by iron or hemoglobin assays on collected pads were tedious, unpleasant and inaccurate. The more recent use of both Fe^{59} [4] and Cr^{51} [4,5,7] as red cell labels has undoubtedly simplified such assays, but they are still far from being utilized as a routine clinical procedure. Simple inspection of the pads can give a fair assessment of menstrual loss[7]. In the presence of anemia a trial of oral iron therapy has also been advocated, provided no other possibility of blood loss exists[10]. There remains a definite place, however, for a simple but effective clinical test to assess the significance of menorrhagia in the investigation of hypochromasia in menstruating females.

The recent development of human whole body counters offers a simple yet unique method for the study of excessive menstrual blood loss and its

resulting iron deficiency. The iron deficient state can be readily demonstrated by increased tracer Fe^{59} absorption as measured with a whole body counter[11]. With almost 100 per cent radioiron incorporation into circulating red cells, any significant fall in total body Fe^{59} activity during the next few months will quantitatively reflect blood loss in the menses or elsewhere. The present study outlines such a method for investigating menstrual blood loss and iron deficiency as applied to seven menstruating women, six of whom presented with hypochromic anemia. In addition, two further patients studied demonstrate the usefulness of the method in assessing other forms of blood loss.

MATERIALS AND METHODS

The steel room whole body counter presently in use at Brookhaven National Laboratory, and the protocol for each radioiron absorption study, have been described in detail elsewhere[11]. The counter consists of an 8" by 4" NaI(Tl) crystal detector suspended in fixed geometry 0.5 meters above a flexed cot in a 42-ton laminated steel room. Impulses from the crystal after linear amplification are fed to a Penco (Model PA-4) 100-channel pulse height analyser. Each patient after an overnight fast and a background body count is given orally 1-10μc Fe^{59} in 250 μg carrier iron, food being withheld an additional hour. Several body counts over the next 4-10 hours establish the patient's own 100 per cent activity level[12]. Total body Fe^{59} activity followed to day 20, compensated for decay and expressed as percentage of the 4-10 hour activity, represents the patient's tracer radioiron retention (ie. -absorption). Subsequent weekly body counts are similarly expressed as percentage of the 4-10 hour activity, and any fall

in body activity is correlated with the menses and interpreted as per cent total blood volume lost.

On the day of isotope administration the patient's hemoglobin, microhematocrit, red blood count and red cell indices are determined as previously described[11]. In addition, the plasma iron[13] and the unsaturated iron binding capacity (UIBC)[14] are measured the same day*. Several 3.0 ml hemolysed samples of the patient's blood between days 10 and 30 are counted in a crystal well counter (Packard Model 410 Autogamma Spectrometer) against a retained standard of the administered Fe^{59} to determine the red cell radioiron uptake[11]. For this purpose the total blood volume is estimated as 64.0 ml/kg body weight[15]. In the presence of a hemoglobin less than 10.0 g %, the blood volume is corrected for an equivalent diminution in red cell mass. The same blood volume is then used to quantitate menstrual blood loss from the percentage of total blood volume lost per period, as determined above.

The study group consisted of six parous females with hypochromasia and hemoglobins ranging from 8.8 to 11.8 g %, all with a history of heavy menses, and a seventh unmarried woman with normal menses and a normal hematologic picture. For comparison of total body Fe^{59} retention, an eighth, post-menopausal patient was included with marked iron deficiency due to treatment of polycythemia vera by phlebotomy, but no blood loss during the period of study. In those patients overtly anemic, thorough medical investigation including repeated stool guiacs and gastrointestinal x-rays where indicated revealed no source of blood loss other than menses. Two patients were found

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* We are indebted to Dr. L. R. Wasserman, Mt. Sinai Hospital, New York, for these determinations.

clinically to have fibroids. To illustrate other types of blood loss, radioiron studies are included of a patient with hereditary hemorrhagic telangiectasia and hypochromic anemia due to steady intestinal blood loss, and a patient with untreated stress polycythemia but two subsequent severe epistaxes.

RESULTS

In Figure 1 is seen the curve of total body Fe^{59} activity in the iron-deficient, non-menstruating patient CT, with 87.4% absorption of the tracer and a subsequent rate of Fe^{59} loss of only 0.012% per day. Normal radioiron absorption by this method has been found to be 5.7-24.7%, and excretion over days 20-100 to be 0.103-0.182% per day[11].

In contrast to patient CT, patient AY in Figure 2 demonstrates a step-like fall in total body Fe^{59} activity with each menstrual period. Her excessive menses had produced iron deficiency to the extent of a hemoglobin of 10.0g%, hypochromic indices (MCH-25γγ), and a radioiron absorption of 53.7%. Loss of labeled red cells during the four periods studied ranged from 6.41% to 13.28% of her total blood volume, equivalent to 270-550 ml of blood. In Figure 3, a similar study in patioent BR revealed 66.4% radioiron absorption with a menstrual blood loss of 250-550 ml of blood per period.

Normal menstruation, shown in patient RO in Figure 4, was associated with a radioiron absorption of only 19.6% and an estimated menstrual blood loss of 33 ml and 59 ml in the two periods studied. As described in previous studies with the whole body counter[11], in the absence of iron deficiency the falling total body activity up to day 20 invalidates patient RO's first period for accurate assessment of menstruation. In addition, with only 72% radioiron uptake in circulating red cells, we have noted[16] an increase in the loss of Fe^{59}

from the body at the 100 to 130 day period due to recycling of hemoglobin-released Fe^{59} through a more labile iron pool. This additional loss of Fe^{59} in patient RO results in an erroneously high estimattion for her fourth period of 260 ml. Counting of menstrual pad Fe^{59} activity estimated this period to be only 99 ml of blood.

Chart I summarizes the hematologic and tracer data from the seven menstruating patients studied. Comparison may be made of the various parameters of iron deficiency found in the one normal and the six iron deficient subjects. Previous pregnancies are also noted as an additional factor in the pathogenesis of the iron deficiency found.

DISCUSSION

The data summarized in Chart I demonstrate well the coexistence of menorrhagia and iron deficiency. Although menorrhagia can come as a consequence of iron deficiency, the failure here to demonstrate any other source of blood loss incriminates the menses as the cause of the iron deficiency found in these patients. Although all six patients were tried on a course of oral iron therapy (ferrous gluconate 300 mg tid and ascorbic acid 100 mg tid), one patient quickly developed gastric intolerance and two patients could not be satisfactorily followed for hematologic response. The remaining three patients, however, all demonstrated return to normal of the hemoglobin and the red cell indices.

Recognition of this pathogenesis of iron deficiency through menorrhagia is important both in guidance for adequate therapy, and in avoidance of unnecessary transfusion therapy where the possibility of surgery may be entertained[17,18]. Previous methods of assessing menstrual blood loss by collection

of pads have been used relatively little clinically because of their unpleasantness, complexity and inaccuracies. As outlined in this study, the whole body counter provides a simple method for assessment of suspected iron deficiency, and confirmation of its pathogenesis from excessive menses. A single study involving no menstrual collections and only a few venipunctures defines the degree of iron deficiency present and the nature and extent of blood loss producing this deficiency. It also predicts the efficacy of oral iron therapy by demonstrating the patient's ability to absorb increased amounts of iron as needed. Parenteral iron therapy would then appear to be indicated only in the presence of gastrointestinal intolerance to the various oral iron preparations available.

It must be realized that this method of quantitating menstrual blood loss has not the degree of accuracy associated with some other methods utilizing pad collections. Correlation of whole body counting data with actual menstrual loss in patient RO, determined by pad content of Fe^{59} in an acid-homogenized solution, revealed that an error of 20 to 40 ml per period may not be unusual. Nevertheless, menorrhagia is clearly differentiated from normal menstrual loss, and the added information of degree of iron deficiency and increased iron absorption from this relatively simple clinical procedure more than justify its usefulness.

This technique can also be of value in studying other types of blood loss. In Figure 5, patient SG with hereditary hemorrhagic telangiectasia and hypochromic anemia unresponsive to customary oral iron therapy was discovered to be losing blood steadily from intestinal telangiectasia. The almost exponential rate of blood revealed by whole body counting represents

51 ml of blood of 17 mg of iron to be replaced daily. Oral iron therapy provided insufficient iron to both equal this level of daily iron loss and provide additional iron for restoration of the diminished red cell mass.

Figure 6 shows a radioiron study in patient SA with untreated stress polycythemia and normal radioiron absorption, and two subsequent severe episodes of epistaxis lasting 2 to 3 days each. The unsuspected extensive loss of 51% and 41% of his total blood volume at these times was clearly demonstrated from the whole body counter data. This study suggests a further application of the technique, of tagging the red cell mass of patients before procedures such as major surgery in order to estimate postoperatively the amount of the total blood volume lost.

In conclusion, the whole body counter has proven to be a useful tool for simple studies of menstrual blood loss with Fe^{59}. A single study demonstrates increased iron absorption as an indicator of iron deficiency, and gives a reasonable assessment of intermittent or continuous blood loss such as menorrhagia as the causative mechanism. The presence of increased radioiron absorption augurs well for a good response to oral iron therapy in the absence of gastrointestinal intolerance. Such an investigative procedure would be of great value if available for routine clinical investigation of hypochromic anemias where menorrhagia or some other form of unmeasured blood loss is suspected.

SUMMARY

An established method for determining radioiron absorption by whole body counting[11] has been used to study six parous women with hypochromic anemia and menorrhagia, and a seventh nulliparous woman with normal blood values and normal menses. In addition to demonstrating iron deficiency by

increased radioiron absorption, the method has been found useful in estimating the quantity of blood lost with each menstrual period. As much as 550 ml of menstrual loss was noted in two of the patients studied. Estimates in the patient with normal menses were 59 ml and 33 ml. Two additional patients demonstrated patterns of blood loss found in continuous gastrointestinal hemorrhage due to hereditary hemorrhagic telangiectasia, and in severe epistaxis, as further applications of the technique. Where available, the method is to be recommended for routine investigation of hypochromic anemia when episodic or continuous blood loss such as that of menorrhagia is suspected.

Figure Legends

Figure 1 Whole body Fe^{59} retention in patient CT with polycythemia vera, previously treated by phlebotomies.

Figure 2 Whole body Fe^{59} retention in iron-deficient patient AY, demonstrating the fall in total body activity with each menstrual period.

Figure 3 Whole body Fe^{59} retention in iron-deficient patient BR, demonstrating menstrual loss of Fe^{59} activity.

Figure 4 Whole body Fe^{59} retention in normal patient RO, with little demonstrable loss of activity due to menses.

Figure 5 Whole body Fe^{59} retention in patient SG, with iron deficiency and continuous intestinal blood loss due to intestinal telangiectasia.

Figure 6 Whole body Fe^{59} retention in patient SA, with initially normal radioiron absorption but two subsequent episodes of severe epistaxis.

Chart I Summary of the hematologic and radioiron data on the one normal and six menorrhagic, iron-deficient patients studied.

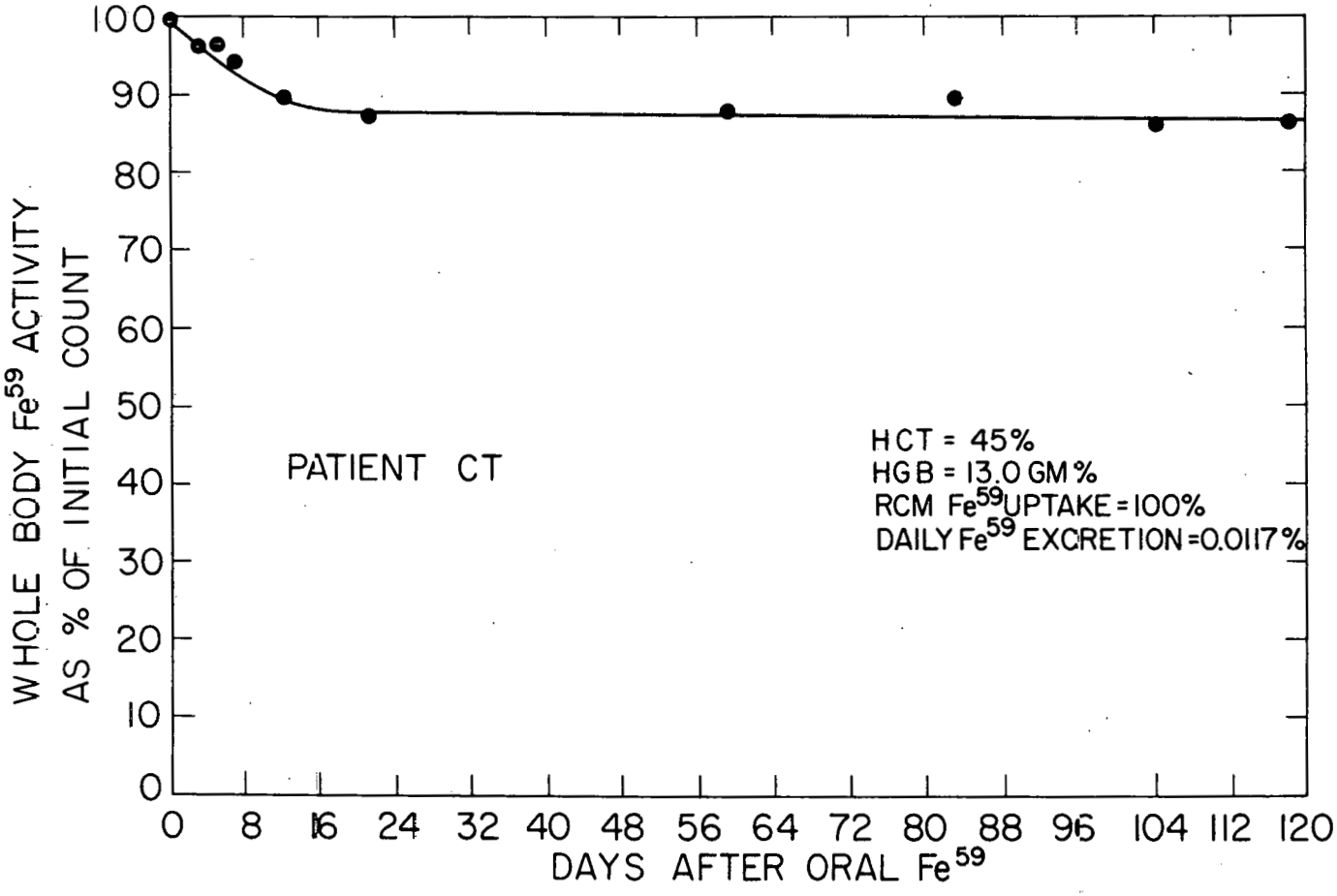
WHOLE BODY Fe59 ACTIVITY
AS % OF INITIAL COUNT
100
90
80
70
60
50
40
30
20
10
0
0
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
DAYS AFTER ORAL Fe59
PATIENT CT
HCT = 45%
HGB = 13.0 GM %
RCM Fe59 UPTAKE = 100%
DAILY Fe59 EXCRETION = 0.0117%

FIGURE 1

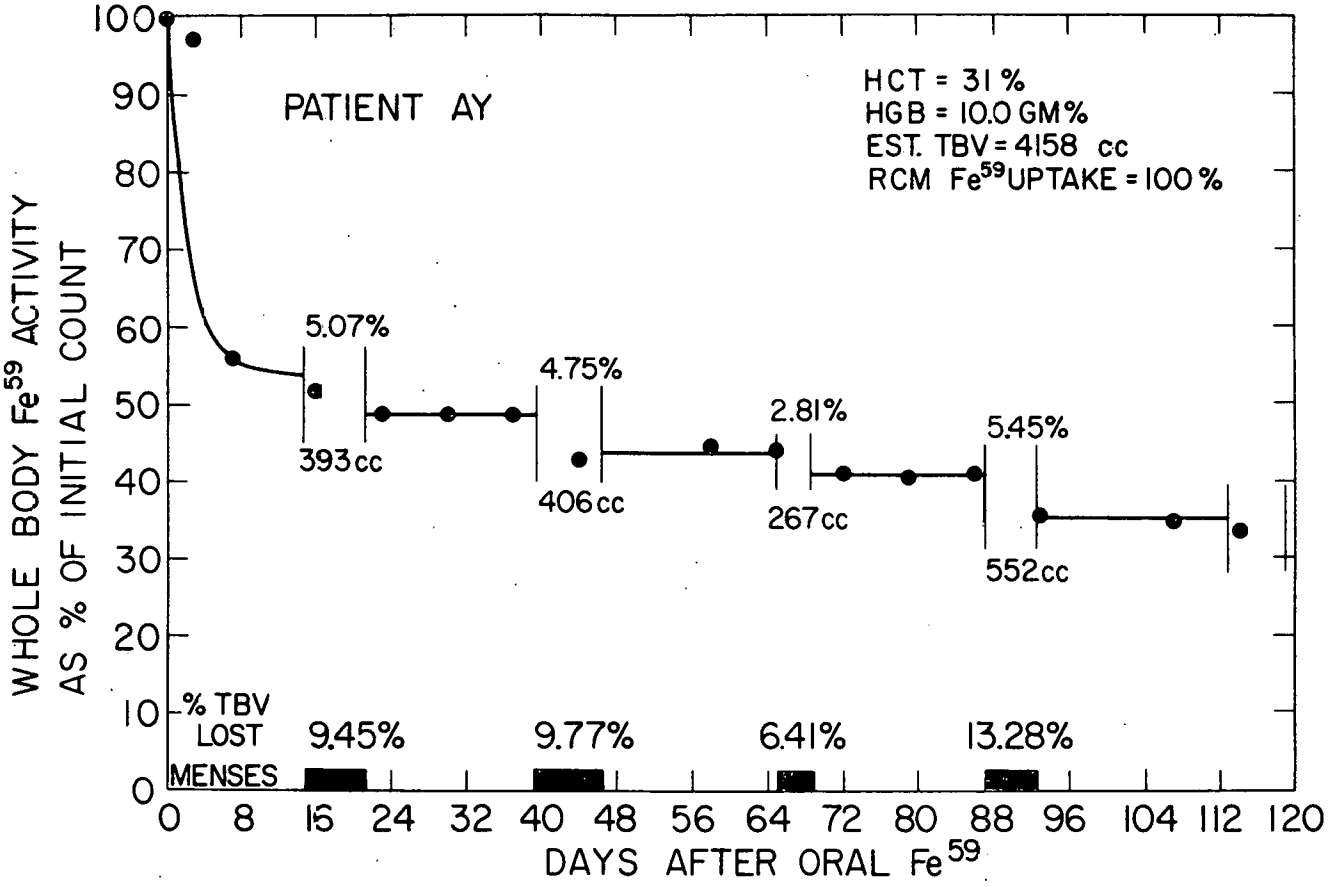
PATIENT AY
HCT = 31 %
HGB = 10.0 GM%
EST. TBV = 4158 cc
RCM Fe59 UPTAKE = 100 %
WHOLE BODY Fe59 ACTIVITY AS % OF INITIAL COUNT
DAYS AFTER ORAL Fe59
5.07%
393cc
4.75%
406cc
2.81%
267cc
5.45%
552cc
% TBV LOST
MENSES
9.45%
9.77%
6.41%
13.28%

FIGURE 2

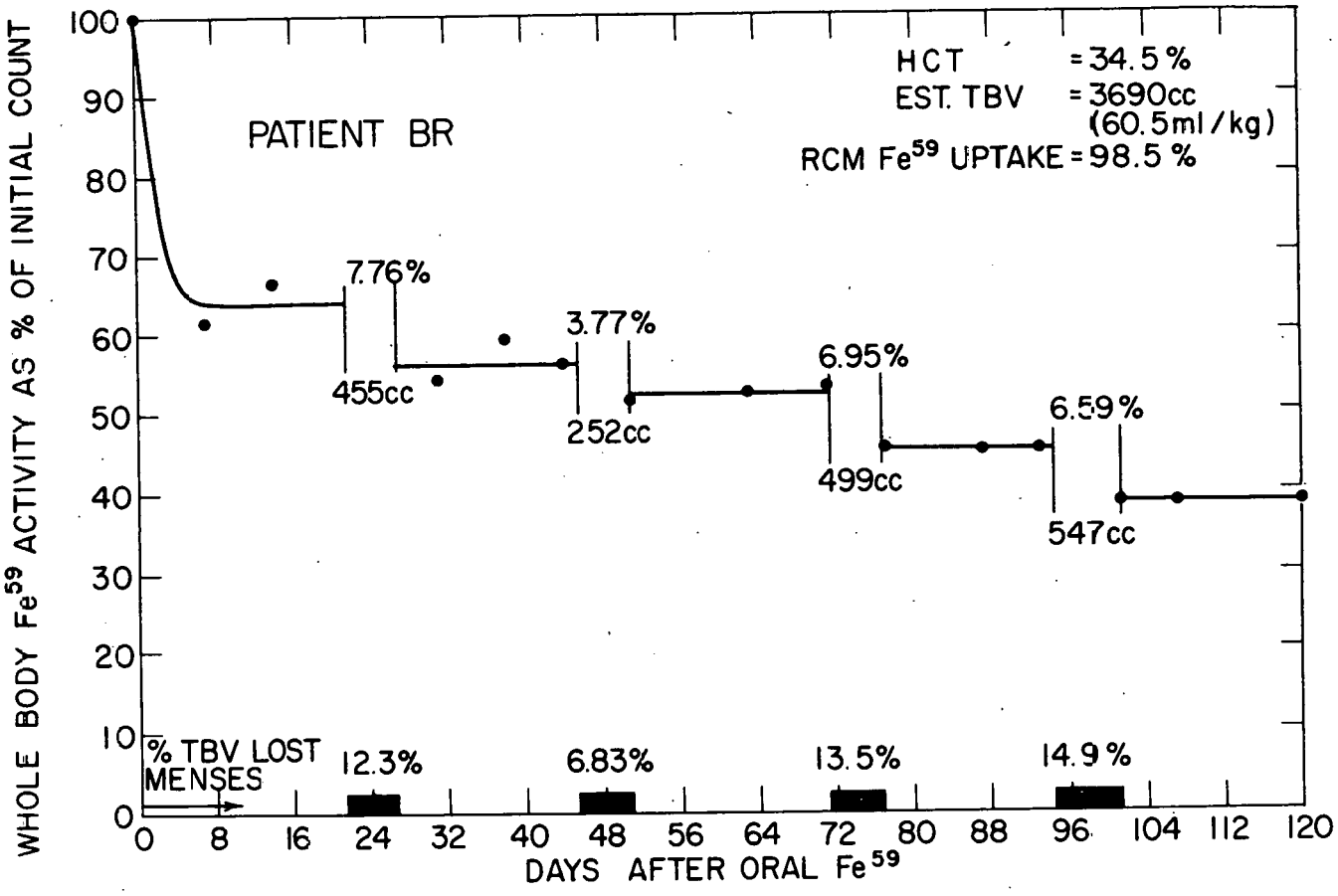
PATIENT BR
HCT = 34.5 %
EST. TBV = 3690cc
(60.5ml/kg)
RCM Fe59 UPTAKE = 98.5 %
WHOLE BODY Fe59 ACTIVITY AS % OF INITIAL COUNT
DAYS AFTER ORAL Fe59
7.76%
455cc
3.77%
252cc
6.95%
499cc
6.59%
547cc
% TBV LOST
MENSES
12.3%
6.83%
13.5%
14.9%

FIGURE 3

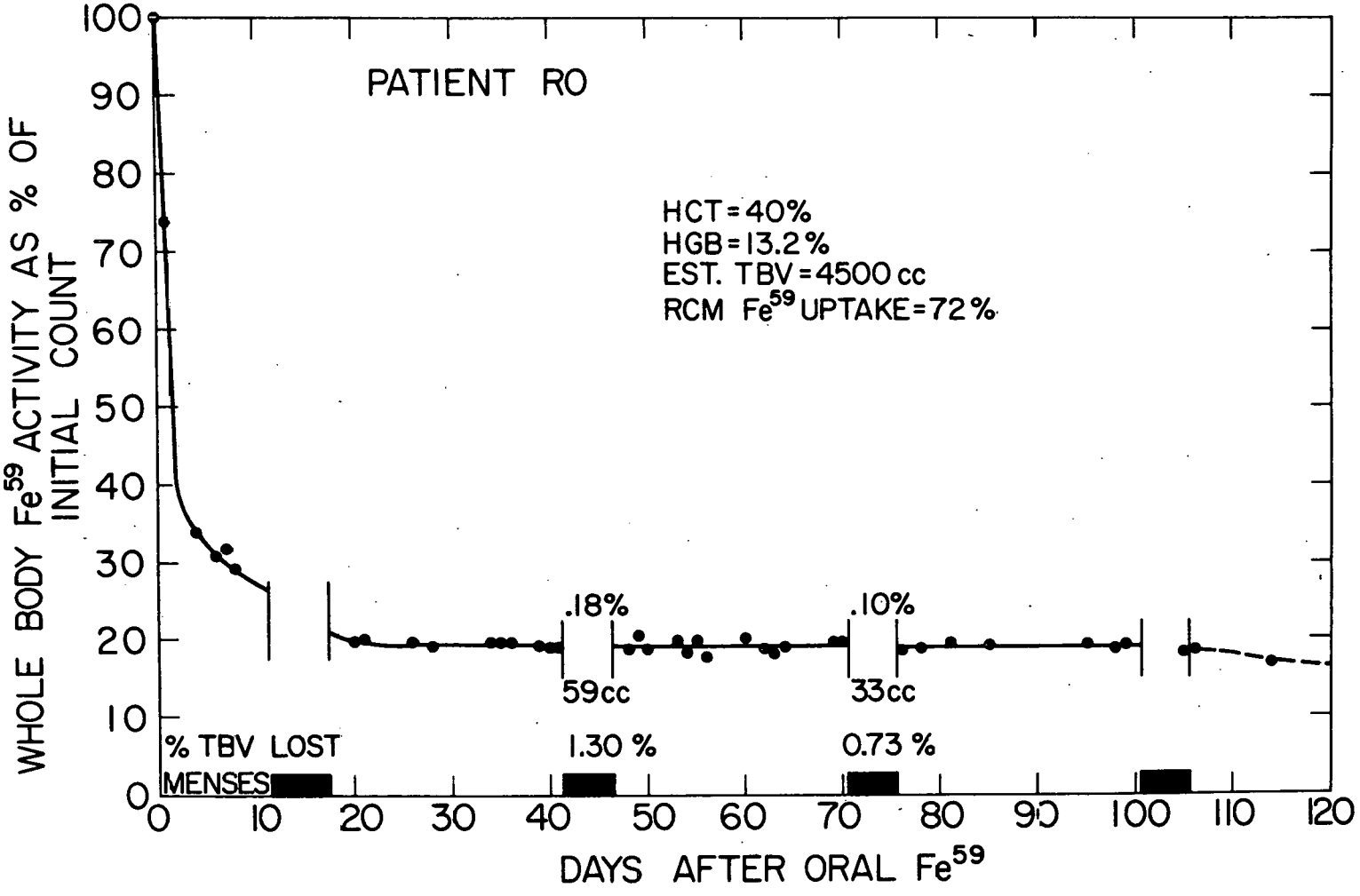
PATIENT RO
HCT=40%
HGB=13.2%
EST. TBV=4500 cc
RCM Fe59 UPTAKE=72%
WHOLE BODY Fe59 ACTIVITY AS % OF INITIAL COUNT
100
90
80
70
60
50
40
30
20
10
0
.18%
59cc
.10%
33cc
% TBV LOST
MENSES
1.30 %
0.73 %
0
10
20
30
40
50
60
70
80
90
100
110
120
DAYS AFTER ORAL Fe59

FIGURE 4

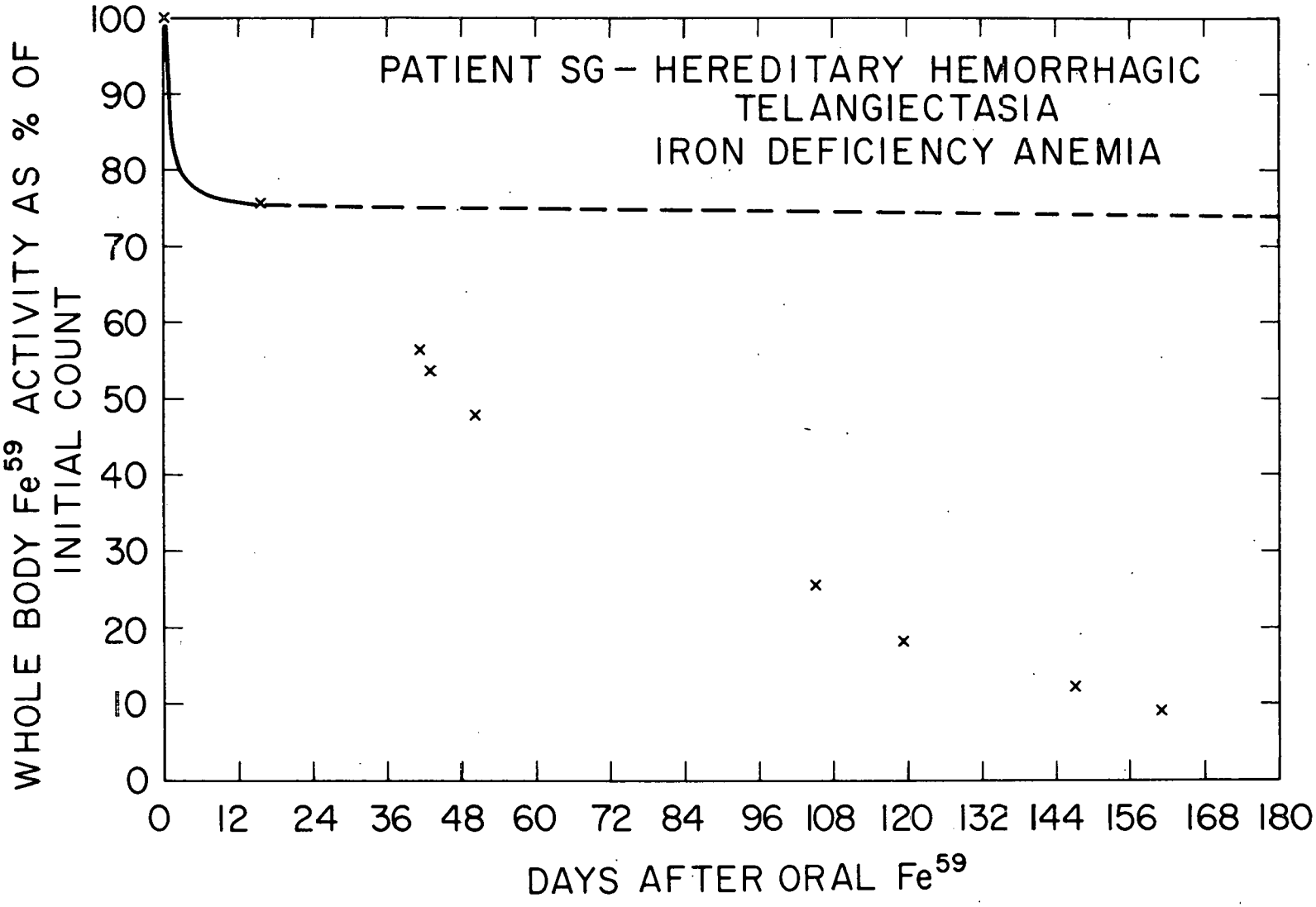
PATIENT SG – HEREDITARY HEMORRHAGIC
TELANGIECTASIA
IRON DEFICIENCY ANEMIA
WHOLE BODY Fe59 ACTIVITY AS % OF
INITIAL COUNT
100
90
80
70
60
50
40
30
20
10
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180
DAYS AFTER ORAL Fe59

FIGURE 5

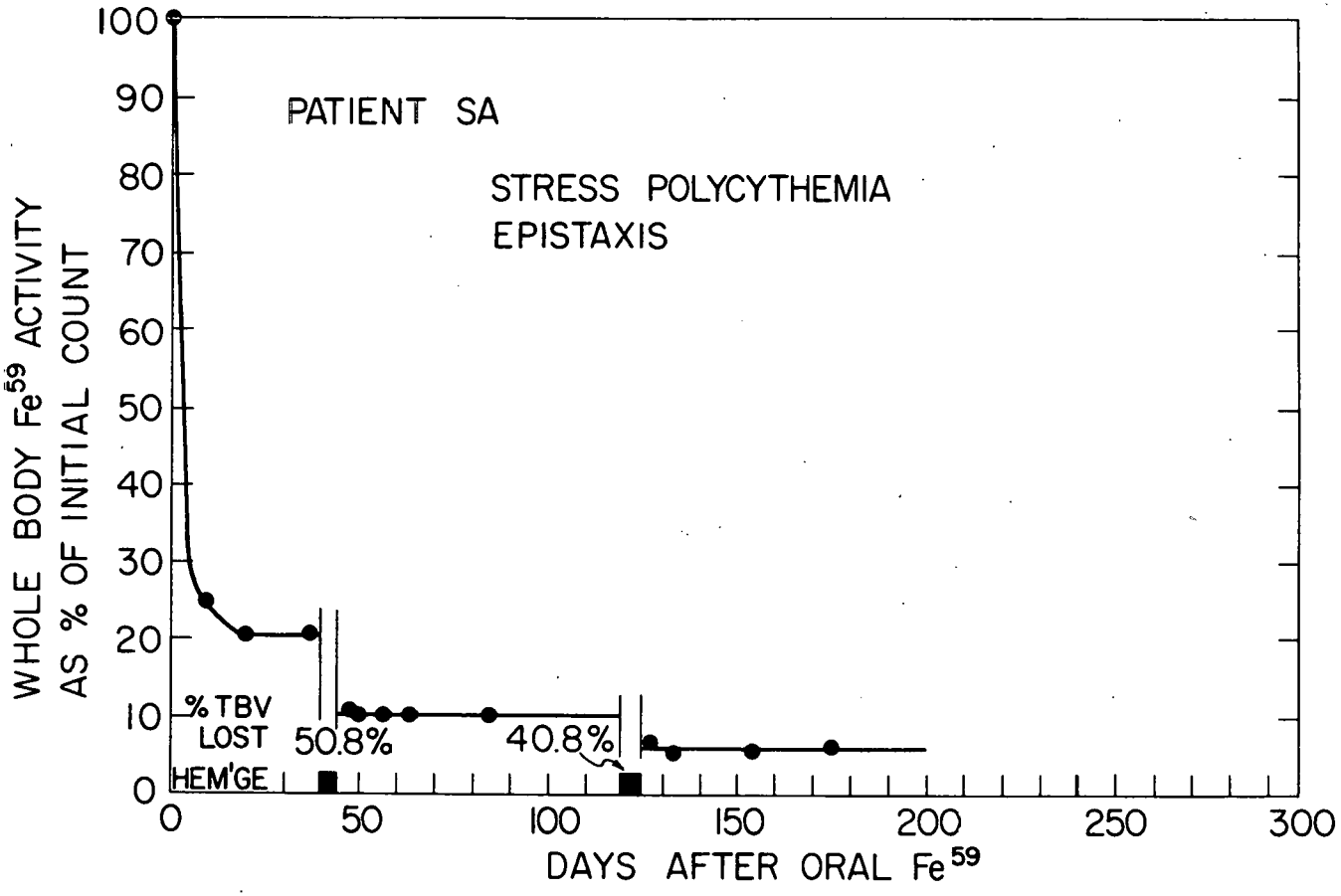
PATIENT SA
STRESS POLYCYTHEMIA
EPISTAXIS
WHOLE BODY Fe59 ACTIVITY
AS % OF INITIAL COUNT
100
90
80
70
60
50
40
30
20
10
0
% TBV
LOST
HEM'GE
50.8%
40.8%
0
50
100
150
200
250
300
DAYS AFTER ORAL Fe59

FIGURE 6

CHART I

Patient	Age (yr)	Preg.	Hgb (Gm%)	Hct (%)	MCV (μ^3)	MCH ($\gamma\gamma$)	MCHC (%)	Pl. Fe (γ%)	UIBC (γ%)	Fe^{59} Absorp. (%)	Fe^{59} RCM (%)	Menses (c.c.)
RO	33	0	13.2	40.0	94.3	31.1	33.0	65	159	19.6	72	33-59 (2)
AY	46	7	10.0	30.5	77.4	25.3	32.7	65	363	53.7	100	267-552 (4)
SC	24	1	11.3	36.0	79.5	24.9	31.8	70	212	61.5	96	111-255 (3)
BR	39	3	8.9	34.5	72.7	18.8	25.8	60	295	66.4	99	252-547 (4)
TD	41	2	8.8	30.0	74.8	21.9	29.3			72.1	96	
AU	35	2	11.8	36.0	71.4	23.4	32.8	55	397	75.0	100	184-304 (4)
SR	41	5	11.3	38.0	82.6	24.5	29.7	35	147	97.5	96	208-368 (2)

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