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Research Article

THE RATE OF REMOVAL OF RADIOACTIVE IRON FROM THE PLASMA—AN INDEX OF ERYTHROPOIESIS[1]

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Transport iron normally exists in the plasma as ferric beta-1-globulinate. Since in most individuals the greater part of the body iron is incorporated in the hemoglobin of the red blood cells, it is probable that changes in the production and destruction of these erythrocytes will be reflected in the turnover of plasma iron. Radioactive iron of high specific activity is particularly useful for a study of iron metabolism since it can be injected intravenously in tracer amounts without changing the steady state of the organism; the turnover of this radioiron will then mirror the metabolism of the iron in the body.

Flexner, Vosburgh, and Cowie (1) demonstrated that shortly after the intravenous injection of radioiron into guinea pigs, all the tagged iron in the plasma was in combination with beta-1-globulin. Following the injection of small quantities of such labelled plasma into other guinea pigs, the circulating plasma radioiron level decreased exponentially for the duration of the experiment. Labelled ferric beta-1-globulinate was also produced *in vitro* by the above investigators by incubating radioactive ferric chloride with a small amount of plasma. However, the intravenous injection of this mixture into guinea pigs was followed by a rapid loss of the plasma radioiron for about 30 minutes, following which the decrease again became exponential. The early rapid loss was presumably due to incomplete combination of the iron with the beta-1-globulin of the plasma and the diffusion of part of the injected iron into the tissues.

Similar results in humans utilizing *in vitro* tagged plasma were reported by Huff, Hennessy and Lawrence (2) and Huff and associates (3). Although in most instances, *in vitro* incubation of radioiron with patients' plasma resulted in a constant rate of disappearance of the radioactivity from the plasma following its injection intravenously, occasionally exponential disappearance rates were not obtained; the latter were thought to be due either to insufficient metal combining protein in the plasma or to the presence of an abnormal protein.

The following investigations of the plasma iron disappearance rate were undertaken to elucidate one phase of iron metabolism in anemic individuals in whom the anemia was due to bone marrow hypofunction; other patients with blood dyscrasias were also studied for comparison. A solution of plasma fraction IV-7 [2] was utilized for incubation with the radioactive iron since it was found that patients' plasma was on the whole unsatisfactory, due to variations in the latent iron binding capacities of such plasmas (4).

METHODS

Five microcuries of Fe^{59},[3] as ferric chloride, were prepared for injection by introducing about 0.05 ml. of the radioactive iron solution (specific activity 1.3 mc./mg.) into a rubber capped test tube, to which enough 4% sodium citrate was added to bring the pH between 6.5 and 7.0 (approximately 5 ml.). The mixture was autoclaved and 1 ml. of plasma fraction IV-7 containing 25 gm. of protein per 100 ml. was added with sterile precautions and incubated with occasional shaking at 37° C. for 30 minutes. During this period all of the iron combined with the protein, as proved by dialysis. Five ml. of this mixture were injected intravenously into suitable subjects in the post-absorptive state and the radioactivity of

[1] Aided by grants from the Anna Ruth Lowenberg and Albert A. List Funds.

[2] Obtained from the Department of Physical Chemistry, Harvard Medical School, through the courtesy of Dr. E. J. Cohn.

[3] The Fe^{59} initially used in this study was obtained through the courtesy of Dr. John H. Lawrence. The high specific activity Fe^{59} subsequently used in the cases of marrow aplasia was obtained on allocation from the Oak Ridge National Laboratories, through the Atomic Energy Commission.

successive samples of plasma measured. There were no untoward reactions to this procedure.

Samples of plasma were prepared by centrifugation of heparinized venous blood obtained at 10 to 30 minute intervals over a two to six hour period following the injection of the radioactive material. Total iron and latent binding capacity of the plasma (5, 6) were determined on at least two of the samples. Aliquots of 1 to 4 ml. were pipetted in duplicate into porcelain crucibles, to each of which were added 5 mg. of carrier iron as ferric chloride. Specimens were dried in an oven at 70° C. and ashed in a muffle furnace at 600° C. for 10 hours. The residue was dissolved in a few ml. of concentrated hydrochloride acid, evaporated almost to dryness and transferred quantitatively with distilled water into electroplating cells. A small amount of ascorbic acid was added to convert the iron to the ferrous form; the solution was then made slightly alkaline with concentrated ammonium hydroxide and buffered with 3 ml. of saturated sodium citrate. The iron was electroplated onto a thin copper disc 2.5 cm. in diameter, using a rotating platinum anode, at 1 ampere and 10 volts until the thiocyanate spot test for iron in the solution was negative (about four to five hours).[4] All the specimens were plated in duplicate.

The amount of radioactive iron electroplated on each disc was determined using an end window (mica, 1.5 mg./cm^2.) Geiger Müller tube; the background was about 1 count per second and the overall sensitivity was approximately 5,000 counts per second per microcurie Fe^{59}. The counts per disc ranged from 3 to 100 counts per second and were determined by observing the time required to accumulate 8,192 counts.

RESULTS

The disappearance of the injected labelled ferric beta-1-globulinate from the circulating plasma was exponential in all cases for the period of time followed. On semilogarithmic paper a straight line plot could be obtained and the rate of decrease in radioactivity determined by the slope of the line. For purposes of this report, this rate is expressed in terms of the half-time of disappearance ($T\frac{1}{2}$), *i.e.*, the time in minutes for the radioactivity of the plasma to be decreased to 50% of its initial value.

Values for absolute plasma iron turnover per unit time may be calculated from the radioiron disappearance data and the total plasma iron (3). Our results agree in general with those of Huff and his coworkers; several factors may influence this absolute iron turnover and form the basis of another report.

Studies on eight normal adult individuals and 32 patients with various blood dyscrasias comprise this report. From the data obtained in the former group, the normal pattern of plasma iron disappearance was derived. No attempt was made to ascertain the influence of various subsidiary factors as age, weight, sex, metabolic rate, and diet in essentially normal persons that could perhaps have some influence upon the plasma clearance data. These factors may require elucidation in the future. However, there is reason to believe that such variables will not have a decisive influence upon the results in the present study.

The results obtained are summarized in Table I and Figures 1, 2, and 3. The half-time of disappearance of the radioiron in the normals ranged from 70 to 140 minutes with an average of 90 minutes.

Three adult patients with chronic aplastic anemia (cases 9, 10, 11), in whom the diagnosis had been made on the basis of the usual clinical and laboratory data, were studied. Each had received 150 or more transfusions over a period of several years, and there was a uniform darkening of the skin and no splenomegaly. Skin biopsies revealed hemosiderosis. The serum iron was elevated and there was complete saturation of the beta-1-globulin. The disappearance of radioiron from the plasma was markedly prolonged with half-time values of 220, 260, and 270 minutes, respectively. A fourth patient (case 12) with a hypoplastic anemia and a superimposed hemolytic component who had received 15 transfusions totalling 7,500 ml. of blood, similarly showed a prolonged half-time of disappearance of 215 minutes. A few weeks following splenectomy, this value remained essentially unchanged at 225 minutes.

In addition, two patients, aged 10 and 22 years (cases 13 and 14) with a syndrome similar to aplastic anemia, namely, chronic aregenerative anemia, who had been transfused approximately bimonthly since birth were studied. They both showed a paucity of red cell precursors in the bone marrow, a severe normochromic anemia with normal white cells and platelets in the peripheral blood and the usual evidence of widespread hemosiderosis. The serum iron was elevated in both and the beta-1-globulin was completely saturated. The half-time of disappearance in both these cases was markedly prolonged to 205 and 245 minutes.

Another group of subjects showing bone mar-

[4] This method was suggested by Dr. Paul Hahn.

row aplasia or hypoplasia but associated with massive splenomegaly and myeloid metaplasia of the spleen was investigated. This series consisted of seven patients (cases 15 through 21) with myelofibrosis in whom the diagnosis was proved by bone marrow biopsy and splenic puncture. In six of these the rate of removal of radioiron from the plasma ranged from a half-time value of 20 minutes to 120 minutes; *i.e.,* 20, 25, 35, 95, 95, and 120 minutes. Two of this group (cases 20 and 21) received localized irradiation to the spleen (250r and 650r, respectively), following which there was a decrease in splenic size; concomitantly, the time of disappearance increased from 30 to 60 and from 20 to 210 minutes, respectively. The two patients with myelofibrosis (cases 18 and 15) who had received large numbers of blood transfusions, 125 and 110 units of blood, respectively, had skin biopsies which were positive for hemosiderin; the serum irons were elevated and the

TABLE I

Case no.	Diagnosis	Sex	Age (*yrs.*)	Hematocrit (%)	Transfusions (*blood-ml.* $\times 10^3$)	Serum iron (*gamma %*)	Plasma Fe^{59} disappearance ($T\frac{1}{2}$-*min.*)
1	Normal	M	44	48	0	50	100
2	Normal	M	46	40	0	90	70
3	Normal	M	49	50	0	110	80
4	Normal	M	49	42	0	95	70
5	Normal	M	38	41	0	130	140
6	Normal	M	32	43	0	110	100
7	Normal	M	50	46	0	80	95
8	Normal	M	52	40	0	100	75
9	Aplastic anemia	M	16	30	75	153*	220
10	Aplastic anemia	F	60	13	115	205*	260
11	Aplastic anemia	F	52	32	105	288*	270
12	Hypoplastic anemia	M	49	30	7.5	272*	215
12	(post splenectomy)	M	49	38	7.5	212*	225
13	Aregenerative anemia	M	10	31	160	268*	205
14	Aregenerative anemia	M	22	26	140	178*	245
15	Myelofibrosis	M	39	24	110	185*	213
16	Myelofibrosis	F	42	28	0	84	120
17	Myelofibrosis	F	56	21	1.5	137	95
18	Myelofibrosis	F	62	23	125	193*	95
19	Myelofibrosis	F	46	36	0	85	35
20	Myelofibrosis	M	72	32	0	112	25
20	(after splenic irradiation)	M	72	32	0	90	60
21	Myelofibrosis	M	53	31	2.5	125	20
21	(after splenic irradiation)	M	53	27	2.5	143	210
22	Polycythemia vera	M	30	52	0	105	60
23	Polycythemia vera	M	50	80	0	113	20
24	Polycythemia vera	M	37	63	0	55	11
25	Polycythemia vera	M	47	53	0	120	45
26	Polycythemia vera	F	51	51	0	120	30
26	(after 5 mc. P^{32})	F	51	48	0	130	145
27	Pernicious anemia	F	76	31	1	235*	40
27	(after vit. B_{12})	F	76	37	1	118	90
28	Pernicious anemia	F	74	26	0	265*	30
28	(after vit. B_{12})	F	74	38	0	78	55
29	Acquired hemolytic anemia	F	51	22	5	150	25
30	Sickle cell anemia	F	48	22	5.5	188	35
31	Chronic lymphatic leukemia	F	46	26	1.5	108	120
32	Reticulum cell leukemia	F	44	21	35	118	265
33	Chronic lymphatic leukemia	F	60	35	7.5	102	68
33	(after cortisone)	F	60	37	8.0	112	36
34	Hypochromic anemia	F	30	27	0	26	30
35	Hypochromic anemia	F	55	35	0	25	60
36	Myxedema	M	49	40	0	148	85
37	Uremia	F	59	24	0	195	185
38	Lymphosarcoma (post HN_2)	F	60	27	2	115	290
39	Disseminated lupus erythematosus	F	40	22	0	77	88
40	Lymphosarcoma	M	53	21	2.5	133	85

* Beta-l-globulin 100% saturated.

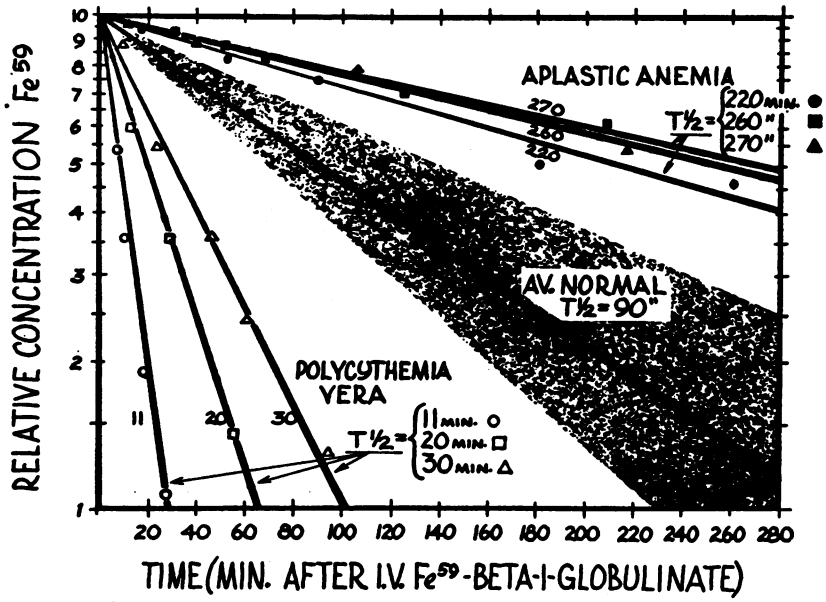

FIG. 1. COMPARISON OF THE PLASMA RADIOIRON DISAPPEARANCE IN THREE PATIENTS WITH APLASTIC ANEMIA (CASES 9, 10, 11), T½ = 220, 260, AND 270 MIN., WITH THREE PATIENTS WITH POLYCYTHEMIA VERA (CASES 24, 23, 26), T½ = 11, 20, AND 30 MIN.

Shaded area is normal range with average T½ = 90 min. Note the very rapid half-times of disappearance in the presence of hyperactive erythropoiesis, and the markedly prolonged T½ when red cell production is diminished or absent.

latent binding capacities of the sera were zero. In the former case, the half-time of disappearance was 95 minutes while in the latter it was markedly prolonged to 210 minutes. This patient was the only member of the myelofibrosis group to have an abnormally prolonged T½. Subsequent postmortem examination revealed marked myeloid metaplasia of the spleen and widespread generalized hemosiderosis.

In two cases of chronic lymphatic leukemia the half-times of disappearance were 120 and 68 minutes. Following one month of cortisone therapy the value in the latter subject (case 33) had decreased to 36 minutes. During this time there was a reticulocytosis of 9%, a slight increase in the packed cell volume and in normoblasts in the bone marrow. Another patient with reticulum cell leukemia who had been splenectomized and had received 70 transfusions, had a T½ increased to 265 minutes; a sternal marrow examination done at that time revealed only 3% of erythroid elements.

The clearance of the tagged iron from the plasma was increased in polycythemia vera. Five patients with the typical clinical and laboratory findings of idiopathic polycythemia had half-time values of 11, 20, 30, 45, and 60 minutes. One of these patients (case 26) was treated with 5 millicuries of radioactive phosphorus and one month after the injection, the T½ became increased from 30 to 145 minutes.

A patient with acquired hemolytic anemia (case 29) who had a severe anemia, splenomegaly, reticulocytosis, increased urinary and fecal urobilinogen, a positive Coombs' test and a markedly erythro-normoblastic marrow, had a T½ of 25 minutes. In another patient with the hemolytic syndrome of sickle cell anemia, the T½ was 35 minutes.

Two women with severe hypochromic microcytic anemia (cases 34 and 35) and low serum iron concentrations had rapid half-times of disappearance of 30 and 60 minutes.

Two patients over 70 years of age with pernicious anemia in relapse who had severe macrocytic anemia and combined system disease, showed increased half-time rates of 30 and 40 minutes. Six weeks following continuous therapy with vitamin

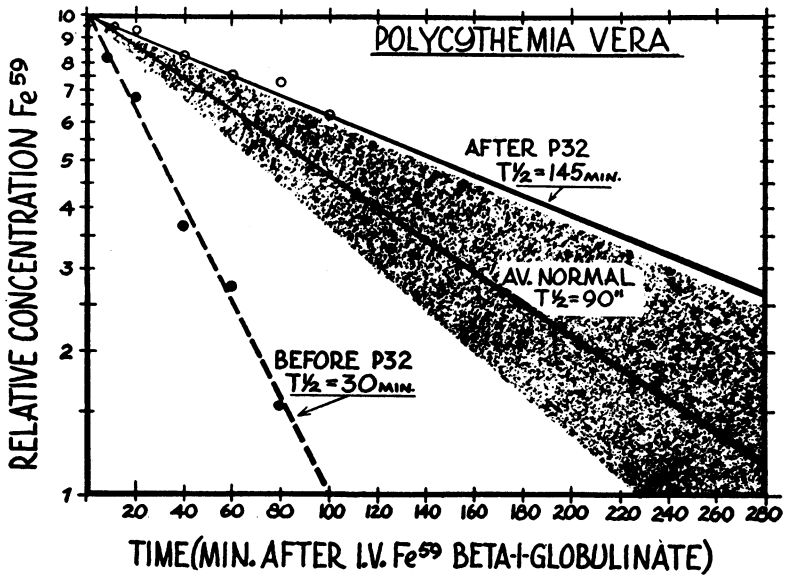

FIG. 2. PATIENT WITH POLYCYTHEMIA VERA (CASE 26) WHO RECEIVED 5 MILLICURIES P^{32} INTRAVENOUSLY

Note the increase in the T½ from a pretreatment value of 30 min. to 145 min. one month later. This illustrates the known effect of P^{32} in depressing erythropoiesis.

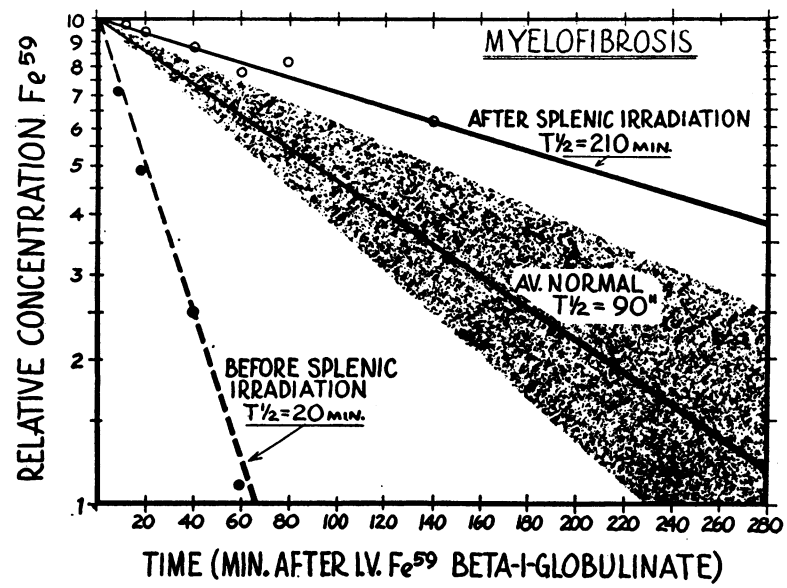

FIG. 3. COMPARISON OF THE HALF-TIME OF DISAPPEARANCE OF PLASMA RADIOIRON BEFORE AND AFTER SPLENIC IRRADIATION IN A PATIENT WITH MYELOFIBROSIS AND MARKED SPLENOMEGALY

From a pretreatment half-time value of 20 min. following 650r to the spleen, the disappearance rate became prolonged to 210 min. The importance of the spleen as a site for extra-medullary erythropoiesis in this syndrome is thus indicated and the influence of the degree of red cell production on the plasma radioiron clearance is demonstrated.

B_{12}, the anemia improved, the marrow became normal and the T½ became prolonged to 55 and 90 minutes respectively.

A miscellaneous group of patients was also examined. The half-time of disappearance in the various cases was as follows: severe myxedema, 85 minutes; uremia, 185 minutes; disseminated lupus erythematosus, 88 minutes; lymphosarcoma, 85 minutes. Another patient with lymphosarcoma who had received 2,000 ml. of blood, was given nitrogen mustard therapy; two weeks later the T½ was greatly prolonged to 290 minutes. A sternal marrow examination done before treatment was normally cellular with 20% erythroid elements. Following HN_2 therapy at the time of the studies with radioiron, the marrow was markedly hypoplastic with only 3% of red cell precursors.

DISCUSSION

In early experiments, the radioiron was incubated *in vitro* with the patient's own plasma prior to its intravenous injection. Although this technique gave reliable results in many individuals, it was observed that in subjects with hemosiderosis, the radioactive iron was lost from the plasma at a very rapid rate. This was found to be due to the fact that the beta-1-globulin of the plasma of these patients was already saturated with iron, hence combination between the radioiron and the plasma globulin did not occur. The iron injected thus remained in the ionic form and its rate of disappearance from the blood stream was markedly different from that of iron bound to globulin (4). The initial rapid loss of the tagged iron is probably due to diffusion into the intercellular space whereas the subsequent exponential disappearance of globulin bound iron results in part from the incorporation of the metal into hematopoietic foci, preparatory to hemoglobin synthesis, and deposition into the miscible iron pool.

To obviate this variation in combining capacity of different plasmas, a fairly pure source of beta-1-globulin was utilized to prepare the iron proteinate. The plasma fraction IV-7 (Cohn) as supplied is concentrated approximately 70-fold over normal plasma with respect to the metal combining globulin. When the radioiron is incubated with fraction IV-7 all radioiron disappearance rates are exponential irrespective of plasma iron concentration and the concentration and saturation of the circulating beta-1-globulin.

The nature of the radioiron disappearance curve deserves comment. Although no data for any period greater than six hours are available due to experimental limitations, it seems unlikely that any deviation from the exponential removal would occur. If this should happen, one would have to assume either an interruption of the steady state of the iron cycle or a feed-back of injected iron which has left the plasma. In the former instance, a new equilibrium would probably be reached and the function would again become exponential although possibly with a different rate constant. If feed-back is considered a possibility, this would imply a completion of the marrow or tissue store cycle which is highly improbable for the first few weeks, at least.

The rate of disappearance may be an average of several similar rates which are in turn dependent upon the uptake of iron by separate end organs, *i.e.*, the erythropoietic tissue, the fixed iron stores and the available iron pool; or perhaps in a particular metabolic state, one rate, exponential in nature, so dominates the plasma iron turnover that other rates become insignificant. Thus, in marrow aplasia where only a few percent of an injected dose of radioactive iron ultimately appears in the red cells, the disappearance rate is influenced largely by the uptake of iron by the tissues; iron leaves the plasma at a very slow rate in the blood dyscrasias in which the production of red cells is grossly impaired, as in aplastic and aregenerative anemia (7–9). On the other hand, in marrow hyperplasia, most of the radioiron becomes incorporated into the circulating erythrocytes (7–9); the rate of disappearance in this case is dependent in the main upon erythropoiesis, so that the presence of greater than normal numbers of red cell precursors, such as are known to exist in the bone marrow of polycythemia vera, hemolytic anemia and iron deficiency anemia, is accompanied by a rapid clearance of iron. These findings suggest that the turnover of the plasma iron as measured by the radioactive technique is an index of the degree of erythropoiesis in the body.

In pernicious anemia in relapse, in view of the megaloblastic arrest of the marrow a decreased rate of plasma iron disappearance might be antici-

pated. However, the values in two patients (cases 27 and 28) were quite rapid, 40 and 30 minutes, respectively. Six weeks following vitamin B_{12} therapy when the bone marrows were normal and the peripheral blood had returned nearly to normal, the study was repeated and respective rates of 90 and 55 minutes were obtained. In view of the high serum iron, complete saturation of the metal combining globulin and tissue hemosiderosis that exists in this disease, abnormal and rapid iron storage may play a role in the increased rate of plasma iron disappearance. Another possible explanation is the avidity of the marrow for iron in these cases because of actual increased erythropoiesis. The gross morphologic picture of red marrow replacing the normally yellow marrow areas coincides with this idea. It is possible that the erythrocytes and red cell precursors which are formed in pernicious anemia are broken down *in situ*. This is suggested by an excretion of urobilinogen far above that which would be derived from ordinary hemolysis in this disease. In this regard, London and West (10) have shown, using N^{15} labelled glycine in a case of pernicious anemia in relapse, that 40% of the urobilinogen appearing in the stool was not derived from circulating erythrocytes.

The bone marrow in myelofibrosis is hypocellular and a large portion of the marrow cavity is replaced by fibrous tissue or bone. There is usually a progressive splenomegaly with the spleen gradually assuming the erythropoietic function. Because of this compensatory metaplasia in the spleen, relatively good hemoglobin levels may be maintained for long periods of time. In view of the hypoplastic, fibrotic bone marrow, a slow rate of clearance of iron could be expected; however, most of the rates were rapid or within the normal range in the cases studied. This may be due to active red cell production in the spleen with, in some cases, a concomitant increased destruction of erythrocytes to account for the anemia. An elevation in the fecal and urinary urobilinogen was present in these latter cases and is suggestive confirmatory evidence of such a process. One of these patients (case 21) who had received a total of 650r to the spleen in a three week period, died subsequently. At autopsy the spleen showed very slight erythropoiesis contrary to that usually observed in myelofibrosis of advanced degree with myeloid metaplasia in the spleen. The prolongation of the half-time of disappearance of the plasma radioiron by splenic irradiation in the two patients mentioned above, demonstrates the effect of erythropoietic activity on plasma radioiron clearance. Furthermore, it emphasizes the importance of the spleen as a blood forming organ in this syndrome. The only patient of this group with a prolonged rate of disappearance was case 15, in whom there was a marked degree of exogenous hemochromatosis, secondary to multiple blood transfusions.

The influence of increased iron stores upon the rate of radioiron disappearance from the plasma is important. Data bearing on a closely allied problem have been reported by Finch and associates (7, 11). They found that in patients with endogenous hemochromatosis, radioiron utilization is profoundly depressed while erythrocyte production proceeds normally. Similarly, in normal subjects fed large quantities of iron for fairly long periods, the utilization of iron is reduced. Again, in iron loading experiments in dogs, comparison of pre- and post-loading utilization curves showed a markedly decreased uptake in the latter. It appears fairly definite therefore that increased iron stores depress the utilization of radioiron for hemoglobin production. Increased iron stores may similarly affect the rate of disappearance of radioactive iron from the plasma. Our data are as yet too meager to resolve this question. As has been noted above, case 15 with myelofibrosis and hemosiderosis exhibited a markedly prolonged $T\frac{1}{2}$; however, another subject (case 18) with the same combined syndrome, who had received an even larger number of blood transfusions, had a normal iron disappearance rate. All the patients with aregenerative and aplastic anemia had hemosiderosis, but it appears more likely that the marrow aplasia rather than the enlarged iron depots is the primary factor in prolonging the disappearance rate in these cases.

Although it is possible that iron stores may affect the radioiron disappearance rate, it has been demonstrated that marked variations in plasma iron clearance may occur in the same patient with no change in iron stores. Thus, the patient with polycythemia vera (case 26) who received 5 millicuries of P^{32} exhibited a pretreatment of $T\frac{1}{2}$ of 30 minutes which then became prolonged to 145 minutes one month later. At the same time, the

packed cell volume decreased from 51% to 48% and the per cent of erythroid elements in the sternal marrow similarly showed a reduction from 60% to 25%. The decrease in the half-time of disappearance was then a gauge of the effectiveness of bone marrow irradiation in depressing erythropoiesis. In view of the very slight decrease in hematocrit and no essential change in serum iron concentration (see Table I), it is clear that no alteration in iron stores was likely.

As has been previously noted, two patients with myelofibrosis had received localized irradiation to the spleen immediately following which the radioiron disappearance rates decreased. No bleeding was observed nor were any transfusions administered in the interim. During this period, the packed cell volumes decreased moderately while the serum iron remained essentially unchanged. Here again in the presence of constant iron stores a marked decrease occurred in the turnover of radioactive iron from the plasma.

It is apparent that the removal of radioiron from the plasma is an index of red cell production in the body in patients with normal iron stores. A change in the steady state of the turnover of iron will produce an effect on the iron clearance from the plasma. Following the establishment of a new equilibrium, a new iron disappearance rate constant will be obtained. The rate of iron disappearance may be of value as a diagnostic test, particularly when combined with a study of the utilization of iron by the red cells. However, where large numbers of transfusions have been given, the rate of disappearance may be influenced by the increased fixed iron stores. The latter problem is currently being investigated in this laboratory.

SUMMARY

1. A method for the determination of the rate of disappearance of iron from the plasma using radioactive iron and a solution of beta-1-globulin has been described.

2. A correlation between erythropoiesis and the rate of disappearance of radioiron from the plasma has been established.

3. In aplasia of the bone marrow, the rate of removal of radioiron from the plasma is markedly prolonged. Increased marrow erythropoiesis as occurs in polycythemia vera, hemolytic anemia and severe hypochromic anemia results in an increased rate of removal of radioiron from the plasma.

4. Greater than normal iron stores, as occurs in hemosiderosis, may prolong the plasma radioiron turnover.

5. It is suggested that with normal body iron stores the half-time of plasma radioiron disappearance is a sensitive measure of the integrity of the erythropoietic tissue of the body.

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