glucose above the average value for control animals but cortisone and hydrocortisone were relatively ineffective.

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Plasma Radioactive Iron Turnover in Acute Viral Hepatitis. (20537)

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The literature contains many references to the hypersideremia of acute hepatitis(1), and in the past year additional papers have appeared(2-6). Histochemical studies of liver biopsy sections have revealed an increased deposition of "stainable-iron" in the liver in acute hepatitis(7-9). None of the studies have to date been concerned with an attempt to locate the responsible metabolic defect. Previously proposed theories attempting to explain the disturbance have been either contrary to accepted theories of iron metabolism, or have lacked any strong evidence in their behalf(1). The aberration in iron metabolism may result from a disturbance in the function of: (a) deposition (storage) of iron in the liver, (b) utilization of iron (red cell production), (c) excretion, or (d) absorption of iron.

In this study, the turnover of intravenous radioactive iron^{59} has been made in 8 patients with acute viral hepatitis. Similar studies in 5 normals, one patient with refractory anemia, and one patient with hemolytic anemia have been included for comparison.

Methods. The studies were carried out in a manner similar to the procedure described by Huff(10,11), except that the iron was made up in 2% sodium citrate. Between one to 6 μc and 5 to 30 μg of iron was used. The procedure was carried out in the morning after a 12-hour fast. Serum iron samples were taken at the time of injection and analyzed for non-radioactive iron(12). Samples of plasma and

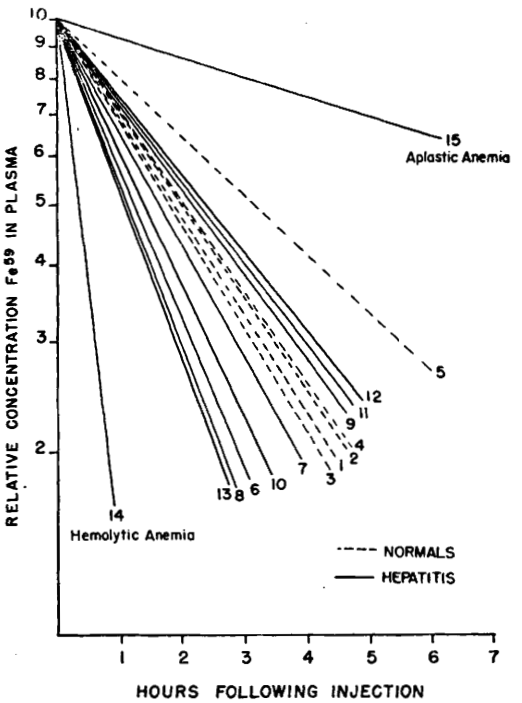

FIG. 1. Disappearance radioactive iron^{59} from plasma following intravenous injection.

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red cells were analyzed for iron^{59} by a procedure described previously(13). Tests of liver function were carried out by methods previously referred to(1). Blood samples were taken ½, 1½, 2½, 3½, and 4½ hours after injection iron^{59} and the radioactivity per ml plasma determined. Plasma volumes were determined by extrapolating the curve of plasma clearance of injected iron^{59} to zero time, and dividing the concentration of iron^{59} at this point into the amount of iron^{59} injected. Blood was taken at 4, 7, 10, and 15 days for determination of the iron^{59} incorporated into the red cells. Counting rates per ml plasma were plotted versus time on semilogarithmic paper (Fig. 1). The rate of removal of iron^{59} from the plasma (plasma iron rate constant) was computed by dividing the natural logarithm of 2 by the half time of disappearance as obtained from Fig. 1. The mg plasma iron turned over per day, per kilo body weight was determined as follows (Fig. 2):

$$\frac{(\text{plasma Fe rate constant}) \times (24\text{ hr}) \times (\mu\text{g Fe/ml plasma}) \times (\text{plasma vol})}{(1000\ \mu\text{g/mg}) \times \text{wt kilos}}$$

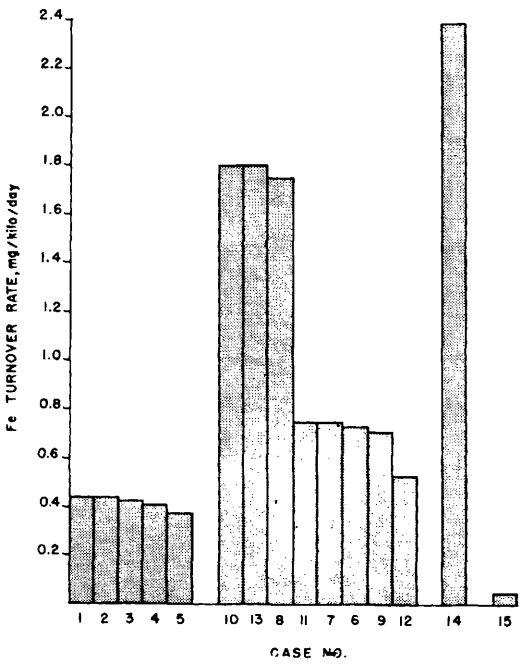

FIG. 2. Plasma iron turnover rate, mg/kilo/day.

The iron turnover in the red cells (mg/kilo/day) was computed as follows (Table I):

$$\frac{\text{Fe}^{59}\text{ red cells}}{\text{Fe}^{59}\text{ injected}} \times \text{plasma Fe turnover.}$$

The fraction of the red cell iron turned over per day (% red cell mass turned over per day, Table I) was determined by first multiplying the red cell volume by the amount of iron contained in one ml red cells (1 mg Fe/ml packed red cells).

Results and discussion. In 4 of the 8 cases (Nos. 8-11) the turnover studies were done at the time of maximal sideremia (usually at a point when the serum bilirubin begins to fall(1)). In Case No. 7 the study was done at the time of maximal bilirubinemia and at a time when the patient had a normal serum iron, but subsequently developed a mild hypersideremia. Patient No. 6 was studied prior to the time of maximal bilirubinemia and sideremia, but also subsequently developed a mild hypersideremia. Case No. 12 was studied on the 25th day after the onset of icterus, and 19 days following maximal bilirubinemia, at a time when the serum iron and bilirubin were only slightly elevated. Case No. 13 had a long-standing recurrent "cholangiolitic" hepatitis with a serum bilirubin maintained around 9 mg %, and on occasion was found to have a hematocrit as low as 38%.

Plasma iron rate constant. In the patients with hepatitis there was considerable variation in the rate constant and in the half-time of disappearance of the iron (Fig. 1); however, in 4 of the 8 cases these values were greater than the normals. In the 5 normals the plasma iron turnover rate constant was around 0.35, except in No. 5 with a value of 0.22. This was associated, however, with a high normal serum iron level.

Plasma iron turnover rate. The plasma iron turnover rate in terms of mg per kilo per day averaged 0.42 mg in the normals (26 to 37 mg per day). In the patients with hepatitis the turnover in mg per kilo per day was in all cases higher (40 to 115 mg per day) than the normal range (Fig. 2). The much higher rates of iron turnover in these patients in the absence of greatly increased turnover

TABLE I. Radioactive Iron Turnover Studies.

Case No.	Plasma Fe, μg/ml	Plasma vol, L	Red cell vol, L	Red cell Fe turnover, mg/kg/day	% red cells turned over/day	Day icterus	Max. serum bilirubin
				Normals			
1	1.4	3.0	2.8	.37	1.11		Normal
2	1.5	2.5	2.2	.40	1.22		"
3	1.3	3.0	2.9	.30	.86		"
4	1.2	2.6	2.3	.33	.92		"
5	1.9	3.0	2.6	.34	1.04		"
				Acute hepatitis			
6	1.5	2.5	2.6	.51	1.34	5	
7	1.7	3.0	2.8	.63	1.54	8	12.0
8	3.2	2.5	2.2	1.67	5.00	10	7.1
9	2.4	2.3	1.8	.57	1.83	11	6.5
10	3.3	2.6	3.2	1.35	2.40	12	32.0
11	3.1	2.7	2.4	.60	2.04	13	11.0
12	2.2	2.6	2.5	.49	1.44	25	29.0
13	2.8	2.5	2.0	1.70	5.00		9.6
				Acquired hemolytic anemia			
14	1.2	2.8	1.2				
				Refractory anemia			
15	2.6	2.9	1.5	.04	.17		

The blocked-in figures are calculated on the assumption that iron[59] cleared from the plasma goes directly to erythrogenic sites.

rate constants and disappearance times is the consequence of the higher serum iron levels.

Red cell uptake. In the normals and the patients with hepatitis there was no significant difference in the % of the administered iron that was taken up by the red cells at 10 to 15 days, and no measurable difference in the speed of uptake. In both groups between 70 to 95% was utilized for the production of hemoglobin after 2 weeks.

This study indicates that the iron is cleared from the plasma of patients with acute hepatitis faster than normally, and that more than 70% of the iron cleared appears in the red cells in 10 to 15 days. Three possible explanations for this rapid turnover appear likely:

1) *Increased red cell (hemoglobin) production.* Following intravenous administration of iron[59] there is a maximum concentration in the marrow after one day(14). Presumably all of this iron will be released from the marrow and appear in the peripheral blood by about 2 weeks—70 to 95% of the intravenously administered dose in normals(15,16). Therefore, the rate of clearance of iron from the plasma is presumed to be an index of the rate of red cell production(10,11,17-19), *viz.*: (a) conditions that inhibit erythropoiesis slow iron turnover—irradiation, nitrogen mustard, increased alveolar oxygen tension, aplastic anemia, (b) conditions associated with increased red cell production increase iron turnover—altitude and primary polycythemia, and hemolytic syndromes. In the patients with hepatitis more than 70% of the plasma iron cleared was used for hemoglobin production—0.49 to 1.7 mg per kilo per day (Table I). If this rapid turnover rate of plasma iron is the result of an increased utilization of iron for hemoglobin production, then a greater than normal % of the red cell mass is renewed per day—1.34 to 5% (Table I). In the presence of a constant hematocrit (red cell mass) this would indicate an increased rate of red cell destruction, and thus a shortened red cell survival time.

2) *Increased clearance by the liver, or some other tissue or iron "pool".* These data do not conclusively establish that all of the iron cleared from the plasma in the first day and eventually used for hemoglobin production (70-95%) went directly to the bone marrow. It might be postulated that there is a greater than normal clearance by the liver (non-erythrogenic), and a slower release to the

marrow, but not slow enough to depress the rate of uptake in the red cells, or the final concentration in the red cells(20).

3) *Increased excretion.* Analyses of the stools (3 to 4 days) and urine (24-48 hours) were made following the injection of the iron(21). In the normals and hepatitis cases the excretion of the iron^{59} in the gut was infinitesimal (0.15-0.35% of the injected dose). In most of the hepatitis cases the urinary excretion was 2 to 10 times normal (normal—0.01 to 0.05% of the injected dose). However, this represented only a trace of the amount administered and could not have accounted for the increased rate of disappearance of iron^{59} from the plasma.

Iron-binding capacities of the sera as done by a modification of the procedure of Rath and Finch(22) have failed to show greatly increased saturation of the iron-binding protein in these patients with hepatitis, and thus there should have been no failure of the injected iron^{59} binding to the iron binding globulin.

Summary. Radioactive iron^{59} injected intravenously disappears from the plasma of patients with hepatitis faster than normally. Seventy to 95% of this administered iron appears in the circulating red cells in 2 weeks. This increased plasma clearance of iron is not the result of increased excretion of the radioactive iron by the kidneys or gastrointestinal tract. It is suggested that this increased plasma iron turnover may be related to increased red cell production.

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