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STUDIES ON RED BLOOD CELL DIAMETER

IV. THE DECREASE IN THE MEAN DIAMETER OF THE RETICULOCYTES AND ADULT RED BLOOD CELLS IN PERNICIOUS ANEMIA FOLLOWING LIVER THERAPY

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Minot and Murphy have shown (1) (2) (3) that in pernicious anemia in relapse one of the first signs of the regular response to adequate liver therapy is a temporary, marked increase of the reticulocytes that develops rapidly. After optimal amounts of liver are given the peak of the reticulocyte increase usually occurs between the sixth and the ninth day, seldom as soon as the fifth or after the tenth day. From the time they have definitely increased until they have returned to a similar level it is rarely less than seven or more than thirteen days, and usually eight to ten days (3).

Persons' studies have shown that in pernicious anemia with a low red blood cell count there is an increase in the mean reticulocyte (immature red blood cell) diameter, as well as in the mean adult red blood cell diameter (4). In view of these findings several sets of measurements have been made of the immature and adult red blood cells from each of nine cases of pernicious anemia over periods ranging from the first twenty-one days to the first six months of remissions induced by the daily ingestion of large amounts of liver. In two of these cases frequent measurements were made during the rise and fall of the reticulocytes.

The measurements on only 5 of the 9 cases are presented in table 1 to conserve space. The data, although obtained at irregular intervals on the other cases, are similar to those presented in graphic form in figure 1. The same method was employed to measure reticulocytes and adult red blood cells as that outlined in a previous paper (5).

TABLE 1
The blood of 5 cases of pernicious anemia treated with liver

Case number	Days	Red blood cells	Hemoglobin	Reticulocytes	Measurements of diameters in microns						Ratio:† reticulocytes adult
					Adult red blood cells				Reticulocytes		
					Spread	Disper- sion	Median diam- eter	Mean diam- eter	Spread	Mean diam- eter	
	millions per cu. mm.	per cent	per cent								
1	0*	1.4	20	0.8	8.7	3.4	8.7	8.2	7.5	10.6	1.29
	10	0.9	22	0.6	8.7	2.7	7.9	7.7	7.5	9.9	1.28
	16	1.7	29	15.5	9.3	3.0	8.2	7.9	5.6	9.1	1.14
	23	2.7	57	2.3	7.5	2.2	9.0	8.7	3.1	8.8	1.02
	32	3.6	72	0.2	8.1	1.9	8.7	8.3	4.3	8.7	1.04
	57	3.8	98	0.6	5.0	1.4	7.8	7.5	3.7	7.8	1.04
	126	5.0	106	0.3	5.0	1.5	8.2	7.9	3.7	9.4	1.18
2	0*	1.2	47	0.3	8.7	2.4	8.2	8.0	8.1	10.0	1.25
	7	1.4	49	2.0	8.1	3.0	8.1	7.7	6.2	10.0	1.30
	24	2.5	68	0.5	7.5	2.5	8.7	8.4	4.3	9.7	1.16
	56	3.5	94	0.3	5.6	1.7	8.0	7.7	4.3	8.8	1.14
	179	5.3	116	0.4	3.7	1.2	7.4	7.0	3.1	7.97	1.13
3	0	1.8	48	1.4	8.1	1.8	8.7	8.4	6.8	10.3	1.23
	12	1.6	35	13.1	6.8	2.7	7.8	7.0	5.0	8.9	1.26
	30	2.9	66	0.6	8.1	2.1	8.7	8.2	3.7	9.0	1.09
	95	4.7	82	0.2	5.0	1.4	8.3	8.0	3.7	8.2	1.02
	177	6.4	94	1.0	3.7	1.1	7.9	7.6	3.1	8.3	1.09
4	0*	2.1	47	0.9	7.5	2.2	8.1	7.8	5.6	9.8	1.25
	14	2.0	65	4.0	8.1	2.6	9.0	8.6	6.8	10.2	1.18
	18	3.0	62	6.4	8.1	2.0	8.5	8.3	4.3	8.7	1.05
	24	3.5	75	0.8	6.8	2.2	8.8	8.6	4.3	8.8	1.03
	50	5.1	110	0.05	6.8	1.6	7.2	6.7	3.7	7.6	1.13
	77	5.5	109	0.3	5.6	1.2	8.1	7.9	3.7	8.5	1.08
	166	5.7	110	0.2	4.3	1.2	7.8	7.6	3.7	8.5	1.12
5	0*	0.7		3.3	10.8	2.5	8.6	8.6	8.4	10.3	1.19
	3	0.8		2.9	9.6	3.1	8.7	8.5	8.4	10.8	1.26
	5	0.9		6.2	9.6	2.7	8.7	8.5	9.0	10.6	1.25
	6	0.9		12.0	9.6	3.3	8.3	8.1	9.0	10.6	1.32
	8			50.9	7.2	3.4	8.4	8.2	8.4	9.3	1.14
	10	1.4		36.4	9.0	2.4	8.7	8.6	6.0	9.2	1.07
	12			16.3	8.4	2.0	8.7	8.7	6.0	9.2	1.05
	19	2.4		4.1	7.8	1.8	8.5	8.6	4.2	8.7	1.01
	21	2.8		0.9	8.4	1.9	8.4	8.3	4.2	8.8	1.06

* Case 1: Liver started on 6th day. Case 2: Liver started on 4th day. Case 4: Liver started on 8th day. Case 5: Liver started on 2nd day.

† The second decimal place is omitted in the table, but was used to determine the ratio $\frac{\text{reticulocytes}}{\text{adult}}$.

Cases 1 to 4 inclusive were among the earliest cases treated by Minot and Murphy. They received only about 150 grams of cooked liver a day and hence their response was definitely slower than occurs in most cases given larger amounts of liver, kidney, or full doses of potent liver extract (3).

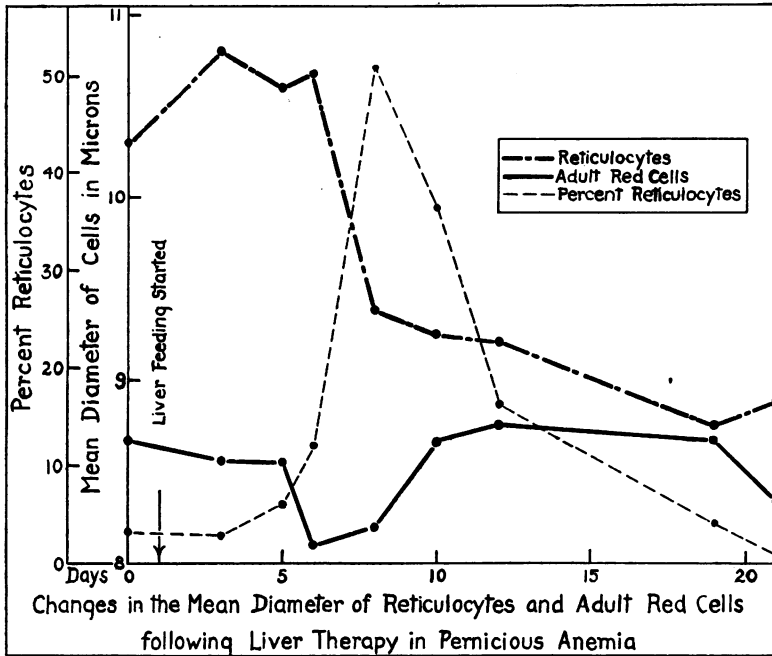


FIG. 1. THE DECREASE OF THE MEAN DIAMETER OF THE RETICULOCYTES AND ADULT RED BLOOD CELLS IN RELATION TO THE TEMPORARY INCREASE OF RETICULOCYTES PRODUCED BY LIVER FEEDING IN PERNICIOUS ANEMIA

The curves in figure 1 which were constructed from the data presented for case 5 (table 1) are comparable to curves plotted for the other cases. The patient received daily 250 grams of raw liver pulp. During the first five days of liver feeding there was a slight rise in the mean diameter of the reticulocytes, but no significant change in the diameter of the adult red blood cells. On the fifth day the rise in the reticulocytes began and reached a peak on the eighth day, gradually

falling to near normal by the nineteenth day. From the fifth to the nineteenth day the most important changes in red blood cell size occurred. They were: (1) A marked drop in mean reticulocyte diameter from the sixth to the eighth day as the reticulocytes rose. (2) A gradual decrease in mean reticulocyte diameter from the eighth day onwards. (3) A distinct rapid drop in mean adult red blood cell diameter from the fifth to the sixth day followed by an increase from the eighth to the twelfth day to within 0.10 micron of the original size. (4) A very gradual decrease in mean adult red blood cell diameter from the twelfth day onwards.

In cases followed for longer periods of time the mean reticulocyte and adult red blood cell diameters decreased gradually so that normal proportions were usually found when the red blood cell count reached normal figures. Not only did the actual diameter measurements become normal but the abnormally high ratio between the diameters of the reticulocytes and adult red blood cells approached normal, as the data in the last column of table 1 shows. Both the spread (difference in diameter between the smallest and largest red blood cell found) and the dispersion (difference between the 16 per cent and 84 per cent grade taken from the curve of red blood cell size plotted on arithmetic probability paper) also approached normal as shown in table 1. Davidson and McCrie (7), using a different method to measure red blood cells, question the findings of Medearis and Minot who state that "The mean diameter of the red blood cells in pernicious anemia may become normal in patients improved by a special diet rich in liver when the red blood cell count increases to between 4,200,000 and 6,300,000 per cubic millimeter." Our findings are in accord with the statement of Medearis and Minot (6). It would appear that one of the signs to indicate that the patient has received and is receiving an adequate amount of anti-pernicious anemia substance is that the red blood cell diameters are normal or essentially normal.

It is not likely that the initial rise in the mean diameter of the reticulocytes which occurred before the rise in the number of these cells is significant. The pronounced drop in mean reticulocyte diameter and the less marked drop in mean adult red blood cell diameter, which occurred as the reticulocytes rose to a peak, are

outstanding rapid changes. The subsequent rise in mean adult red blood cell diameter coincident with the fall in the number of reticulocytes was detected in several cases. It is apparently a change of short duration and lasted only four days in case 5. It was an unexpected finding the cause of which is not evident. The subsequent slow decrease in mean reticulocyte and adult red blood cell diameter, which continued until normal proportions were found, when the red blood cell count approached normal, adds further evidence to that in the literature that continued adequate liver therapy can permit the bone marrow in pernicious anemia to manufacture red blood cells of normal size.

CONCLUSIONS

Measurements of the diameters were made of immature (reticulocytes) and adult red blood cells from 9 cases of pernicious anemia during treatment with liver.

As the reticulocytes increased there occurred an initial drop in the mean adult red blood cell diameter which soon rose again almost to its original level. The size remained approximately the same while the red blood cells increased about 1 million per cubic millimeter and then progressively decreased to about normal as the red blood cell count rose above 4.5 million per cubic millimeter.

The mean reticulocyte diameter decreased markedly as the reticulocytes rapidly rose. It then continued to decrease slowly becoming normal or essentially so when the red blood cells approached 5 million per cubic millimeter.

Decrease to normal values in the mean reticulocyte and adult red blood cell diameters in pernicious anemia can result from continued adequate liver therapy causing changes in the bone marrow.

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