DIFFERENTIATION OF PERNICIOUS ANEMIA AND CERTAIN OTHER MACROCYTIC ANEMIAS BY THE DISTRIBUTION OF RED BLOOD CELL DIAMETERS

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It is often difficult to distinguish between Addisonian pernicious anemia and other macrocytic anemias that will not respond to the specific materials potent in pernicious anemia. The purpose of this paper is to demonstrate some of the findings in a study of the distribution of red blood cell diameters that seem to be of help in making such a differentiation. Demonstrable differences of cell diameters in various kinds of macrocytic anemia will suggest fundamental differences of etiology and hence of treatment in such cases.

Mogensen [1] has commented upon differences in the distribution of red blood cell diameters in macrocytic anemias, comparing pernicious anemia with anemias refractory to liver therapy. Such macrocytic anemias have been discussed as cases of refractory anemia by Rhoads and Barker[2] and Bomford and Rhoads.[3] A certain type of refractory macrocytic anemia has been designated "achrestic" anemia by Israels and Wilkinson.[4] Rhoads and Barker divided refractory anemia into primary and secondary groups. In the primary group, the anemia seemed to exist independently of any other pathologic process. In the secondary group, the anemia depended upon a recognizable cause, such as Hodgkin's disease, degenerative disease of the liver, tuberculosis of the bone marrow, or the like. Bomford and Rhoads classified the bone marrows of refractory anemias into four major groups according to distinctive histologic characteristics. It is often difficult clinically to separate these cases of refractory macrocytic anemia from those of pernicious anemia until a proper trial with a liver preparation has been made. Pathologic processes upon which the manifestations of the secondary group depend may remain hidden during life. The clinical features may resemble closely those of pernicious anemia, including glossitis and achlorhydria. The histologic character of the bone marrow is often inconsistent with the blood findings, being aplastic, hypoplastic, hyperplastic, or sclerotic.

One feature that is apparently of value in distinguishing refractory macrocytic anemia from pernicious anemia is the Price-Jones curve. In the former condition there appears to be frequently a smaller degree of anisocytosis of the red blood cells at a given red blood cell level. In order to confirm this impression, the diameters of the red blood cells in a group of cases with macrocytic anemia were measured by the Price-Jones method.[5] The cases studied included 35 of pernicious anemia, 17 of refractory macrocytic anemia, 33 of macrocytic anemia secondary to a variety of causes, and 10 normal individuals (table 1). The cases which were not pernicious anemia were selected particularly with care (1) that the

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TABLE I.—*Summary of Observations on the Blood**

Case No.	R.B.C. Million per Cu.Mm.	Hb. (%)†	Mean Cell Vol. (Cu. μ)	Mean Cell Diam. (μ)	S.D. of Diam. (μ)	Coeff. of Var. of Diam. (%)	Notes
				PERNICIOUS ANEMIA			
1	0.41	7	105.0	8.51	1.38	16.2	
2	0.77	22	140.3	8.74	1.07	12.2	
3	0.89	26	133.7	7.77	1.13	14.5	
4	1.02	24	109.8	7.90	1.20	15.2	
5	1.16	27	125.0	8.10	1.01	2.5	
6	1.32	32	139.4	8.60	1.10	12.8	
7	1.32	32	129.3	8.21	1.44	17.5	
8	1.38	33	118.8	7.67	1.03	13.4	
9	1.44	37	112.3	8.21	1.12	13.6	
10	1.45	37	124.1	7.80	0.95	12.2	
11	1.50	37	109.9	7.57	0.87	11.4	
12	1.57	43	143.3	8.47	1.32	15.6	
13	1.64	36	112.2	7.67	0.95	12.4	
14	1.74	53	151.7	9.10	1.50	16.5	Splenectomy 11 years before
15	2.25	50	108.0	8.36	1.00	12.0	
16	2.48	50	131.5	8.39	0.76	9.1	
17	2.64	54	114.4	7.84	0.77	9.8	
18	2.73	64	109.3	8.29	0.70	8.4	
19	3.00	65	114.0	8.46	0.76	9.0	
20	3.01	86	124.9	8.06	0.68	7.7	
21	3.07	71	115.0	8.24	0.76	9.2	
22	3.19	78	116.4	8.17	0.61	7.5	
23	3.23	69	86.7	8.10	0.68	8.4	Diagnosed 8 mo. later, when R.B.C. 1,760,000 per cu. mm.
24	3.33	63	108.0	8.35	0.64	7.7	
25	3.36	76	108.2	8.18	0.62	7.5	In partial remission
26	3.36	76	109.9	8.14	0.63	7.7	In partial remission
27	3.57	64	89.1	7.67	0.56	7.3	Iron deficiency also
28	3.70	87	102.3	7.97	0.68	8.5	
29	3.95	86	101.3	8.14	0.64	7.8	Remission for 6 years without treatment
30	4.14	85	104.2	8.45	0.60	7.1	In remission
31	4.19	94	102.7	8.30	0.69	8.3	In remission
32	4.51	87	96.0	7.47	0.57	7.6	
33	4.62	95	96.8	7.99	0.61	7.6	In remission
34	4.76	88	85.3	7.71	0.52	6.7	In remission
35	5.09	101	92.7	7.60	0.49	6.4	In remission
				REFRACTORY MACROCYTIC ANEMIA			
36	0.69	21	133.5	8.35	0.76	9.1	Bone marrow aplastic at autopsy
37	0.71	16	118.3	7.15	0.94	13.2	Bone marrow hyperplastic at autopsy
38	0.92	17	96.9	8.10	0.79	9.7	Bone marrow hyperplastic at autopsy
39	0.93	20	107.0	7.56	0.83	11.0	Bone marrow aplastic at autopsy
40	0.95	26	126.9	8.25	0.89	10.7	
41	1.03	23	104.9	7.29	0.66	9.1	Bone marrow aplastic at autopsy
42	1.08	22	100.0	7.33	0.78	10.6	Benzol poisoning
43	1.40	30	123.6	7.99	0.76	9.5	Bone marrow hyperplastic by sternal biopsy
44	1.48	37	08.6	7.73	0.71	9.2	Bone marrow hyperplastic by sternal biopsy
45	1.53	34	115.7	8.04	0.82	10.2	Benzol poisoning
46	1.99	42	100.0	7.62	0.84	11.0	Bone marrow aplastic at autopsy
47	2.06	42	123.0	8.47	0.81	9.6	Bone marrow hyperplastic by sternal biopsy
48	2.21	48	117.0	7.37	0.73	10.0	Bone marrow aplastic at autopsy
49	2.23	53	100.0	7.57	0.80	10.6	
50	2.36	53	109.7	7.83	0.70	8.9	
51	2.42	50	111.5	8.01	0.61	7.6	Bone marrow hyperplastic by sternal biopsy
52	2.86	71	108.7	7.87	0.62	7.8	Bone marrow hyperplastic by sternal biopsy
				ACUTE BLOOD LOSS			
53	0.94	20	127.7	8.20	0.92	11.2	Laceration of stomach
54	1.42	32	138.7	8.15	0.65	8.0	Cause unknown
55	1.86	45	110.0	7.71	0.62	8.1	Duodenal ulcer
56	1.73	39	101.1	7.67	0.70	9.1	Duodenal ulcer
57	2.16	37	90.2	7.73	0.82	10.6	Duodenal ulcer

TABLE 1—*Continued*

Case No.	R.B.C. Million per Cu.Mm.	Hb. (%)†	Mean Cell Vol. (Cu. μ)	Mean Cell Diam. (μ)	S.D. of Diam. (μ)	Coeff. of Var. of Diam. (%)	Notes
				LIVER CIRRHOSIS			
58	2.90	70	117.9	8.46	0.62	7.3	
59	3.24	62	104.6	7.78	0.73	9.4	
60	3.37	82	121.0	8.02	0.67	8.4	
61	3.50	75	111.9	8.08	0.49	6.1	
62	3.50	74	104.8	7.95	0.65	8.1	
63	3.11	69	103.7	7.68	0.62	8.1	
				HEMOLYTIC ANEMIA			
64	4.41	110	101.7	7.23	0.59	8.2	Chronic hemolytic jaundice
65	4.23	97	103.5	7.45	0.62	8.3	Chronic hemolytic jaundice
66	1.14	30	133.3	7.76	0.83	10.7	Reticulocytes 45 %
67	1.37	30	103.2	7.13	0.70	9.9	Acute hemolytic anemia following use of sulfanilamide
68	3.31	65		7.53	0.63	8.4	Malaria
69	1.74	42	129.3	8.23	0.68	8.3	Nocturnal paroxysmal hemoglobinuria[6]
70	1.87	40	118.0	8.87	0.81	9.2	Nocturnal paroxysmal hemoglobinuria
71	1.90	40	107.4	8.69	0.95	10.9	Nocturnal paroxysmal hemoglobinuria
72	2.25	48	117.8	8.21	0.92	11.2	Nocturnal paroxysmal hemoglobinuria
73	2.78	52	93.2	7.83	0.70	9.0	Nocturnal paroxysmal hemoglobinuria
				LEUKEMIA			
74	0.99	22	109.1	7.42	0.79	10.6	Megakaryocytic leukemia
75	1.18	25	99.5	7.69	0.87	11.3	Aleukemic myelogenous leukemia
76	1.30	28	116.3	7.63	0.72	9.4	Acute monocytic leukemia
77	3.08	68	107.4	7.50	0.61	8.1	Acute myelogenous leukemia
				MISCELLANEOUS CONDITIONS			
78	0.83	16	112.4	7.73	0.85	11.0	Myelosclerosis with myeloid metaplasia[7]
79	2.21	51	105.9	7.73	0.63	8.1	Hemolytic anemia with myeloid metaplasia: reticulocytes 23 %
	0.82	20	138.8	7.81	0.93	11.9	Hemolytic anemia with myeloid metaplasia: reticulocytes 38 %
80	4.03	91	108.9	7.57	0.56	7.5	Scurvy
81	3.51	75	100.4	7.57	0.64	8.5	Scurvy
82	3.02	70	118.4	7.96	0.63	7.9	Echinococcus cyst of liver
83	3.75	83	100.0	7.74	0.74	9.5	Arsenic poisoning; psoriasis
84	5.91	120	101.7	7.50	0.64	8.6	Congenital heart disease
85	3.07	68	109.8	6.77	0.59	8.7	Uremia; pyelonephritis
				NORMAL			
86	4.56	90	91.0	7.35	0.49	6.7	
87	4.48	91	90.8	6.86	0.53	7.7	
88	4.42	86	96.8	7.15	0.50	6.9	
89	4.97	96	95.8	7.03	0.48	6.8	
90	5.00	99	92.8	6.88	0.49	7.2	
91	4.64	90	96.8	7.20	0.51	7.1	
92	5.13	100	90.9	7.14	0.46	6.4	
93	4.63	85	90.0	7.55	0.48	6.3	
94	5.66	113	91.6	7.35	0.53	7.2	
95	4.60	89	94.3	7.47	0.54	7.2	

* All patients were over 21 years of age. The patients with pernicious anemia all responded to liver. Gastric analysis in the cases of pernicious anemia showed no free hydrochloric acid; in the group of refractory anemias, free hydrochloric acid was present in cases 38, 39, 41, 44, 46, 48, 49, 51, and absent in cases 36, 37, 47, 50, 52.

† Hemoglobin instrument is so standardized that 100 per cent = 15.6 Gm.

anemia be macrocytic,* (2) that factors identifying it as quite different from pernicious anemia be clear, e.g., as in hemolytic anemia, (3) that there be an absence of response of the blood to the administration of adequate amounts of liver extract. The cases of pernicious anemia were selected at random and all responded satisfactorily to liver extract. Most of these patients had received no liver or liver extract at the time the measurements of the red cells were first made, but a few, as noted in table 1, were receiving treatment and were in remission. No observations were made during the reticulocyte response to liver extract.

The standard deviation† of the red blood cell diameters is a convenient measure of the degree of anisocytosis. A certain variability in the diameters of red blood cells from normal persons is always present, but the standard deviation in the normal is usually not more than 0.55 micron. In severe anemia, the standard deviation of the red blood cell diameters may be as high as 1.5 microns when the red blood cells are less than 1,000,000 per cubic millimeter. The coefficient of variation‡ is also a measure of anisocytosis and shows values of from 6 to 8 per cent in normal persons to about 18 per cent in pernicious anemia. The figures for standard deviation and the coefficient of variation are given for the individual cases in table 1.

The Price-Jones technic of measuring the diameter of red blood cells by projection was used, with the exception that smears of capillary blood stained with Wright's stain were employed instead of venous blood and Jenner stain. Two diameters, maximum and minimum, of each of 500 cells were measured in every case. The red blood cell counts and hemoglobin values were obtained on venous blood. The hemoglobin was determined by the Sahli method, with apparatus calibrated so that 15.6 grams of hemoglobin or 100 per cent was equivalent to an oxygen capacity of 20.9 volumes per cent. The mean corpuscular volume was determined by the Wintrobe method.[8]

In figure 1, the standard deviation of the red blood cell diameters has been plotted as abscissa against the red cell count as ordinate for each case. The figure shows a reverse relationship between the standard deviation and the red cell count for the whole group of cases. When the red blood cell count was less than 2,500,000 per cubic millimeter, the standard deviation served to separate with fair distinctness cases of pernicious anemia from the other cases. At these levels all but 2 cases of pernicious anemia had standard deviations of more than 0.9 micron. The other cases of macrocytic anemia showed standard deviations of less than 0.9 micron except in five instances; in none of these was it more than 0.95 micron. In one of the cases of refractory anemia (case 37) the standard deviation was 0.94 micron at a red cell level of 710,000 per cubic millimeter. In one case of acute blood

* No case having a mean corpuscular volume of less than 100 cu. micra was included, with the exception of only a few cases in which the mean corpuscular diameter was definitely increased. This excluded quite a large group of refractory normocytic or microcytic anemias in which the etiology was unknown. In 5 of the cases of pernicious anemia at high red cell levels, the mean volumes were less than 100 cu. micra but the mean diameters were increased.

† The standard deviation is the measure in microns of the dispersion of the diameters, their range in size, and the way in which the numerical frequencies of the different diameters are arranged.

‡ The coefficient of variation is the standard deviation expressed as a percentage of the mean, and forms a measure of the variability that is independent of the unit in which the measurements have been made.

loss the standard deviation was 0.92 micron at a red cell level of 940,000 per cubic millimeter. Two cases of nocturnal paroxysmal hemoglobinuria[6] showed standard deviations of 0.95 and 0.92 micron at red cell levels of 1,900,000 and 2,250,000 per cubic millimeter respectively. In one case of "agnogenic" myeloid metaplasia the standard deviation was 0.93 micron.[7] The standard deviation of the red cell diameters in the miscellaneous group of patients was not significantly different from that for refractory anemia, but was considerably lower than that for pernicious anemia.

In cases with red blood cell counts that were greater than 2,500,000 per cubic millimeter, the standard deviation did not reliably distinguish pernicious anemia from the other types of macrocytic anemia.

In figure 1, it may be observed that the degree of anisocytosis varied with the degree of anemia. Average values for some of the observations in table 1 are given

TABLE 2.—*Different Types of Macrocytic Anemia: Average Values of Mean Cell Diameter and Standard Deviation at Varying Red Cell Levels*

Diagnosis	Red Blood Cells per Cubic Millimeter: up to 1,500,000 No. Cases	up to 1,500,000 Average Value M.C.D.* (μ)	up to 1,500,000 Average Value S.D.* (μ)	1,510,000–2,500,000 No. Cases	1,510,000–2,500,000 Average Value M.C.D. (μ)	1,510,000–2,500,000 Average Value S.D. (μ)	2,510,000–3,500,000 No. Cases	2,510,000–3,500,000 Average Value M.C.D. (μ)	2,510,000–3,500,000 Average Value S.D. (μ)	3,510,000–4,500,000 No. Cases	3,510,000–4,500,000 Average Value M.C.D. (μ)	3,510,000–4,500,000 Average Value S.D. (μ)	4,510,000–5,500,000 No. Cases	4,510,000–5,500,000 Average Value M.C.D. (μ)	4,510,000–5,500,000 Average Value S.D. (μ)
Pernicious anemia	11	8.09	1.11	5	8.35	1.11	10	8.20	0.68	5	8.11	0.63	4	7.69	0.55
Refractory anemia	9	7.75	0.81	7	7.84	0.76	1	7.87	0.62						
Acute blood loss	2	8.17	0.78	3	7.70	0.71									
Liver cirrhosis							6	7.99	0.63						
Hemolytic anemia	2	7.44	0.77	4	8.49	0.84	2	7.68	0.66	2	7.34	0.60			
Normal condition													10	7.22	0.50

* M.C.D. = mean cell diameter. S.D. = standard deviation of diameter from the mean.

in table 2, with consideration of the different red cell levels. These showed distinctly higher values for the standard deviation in cases of pernicious anemia at red cell levels of 2,500,000 or less.

Figure 2 shows drawings of red blood cells, traced by projection as in the Price-Jones technic, in two severely anemic patients, one having pernicious anemia, the other "refractory" anemia. Although the mean corpuscular volume and the mean corpuscular diameter in the 2 cases are approximately the same, the standard deviation in the case of pernicious anemia is much larger than in the case of refractory anemia. From the drawings of the red blood cells, this difference in degree of anisocytosis can readily be seen. The characteristic shapes of such curves have been commented upon by Price-Jones and by Mogensen. The curve for pernicious anemia at low red blood cell levels has a very broad base and shows skewness with the longer slope to the left. Such skewness signifies a relative predominance of

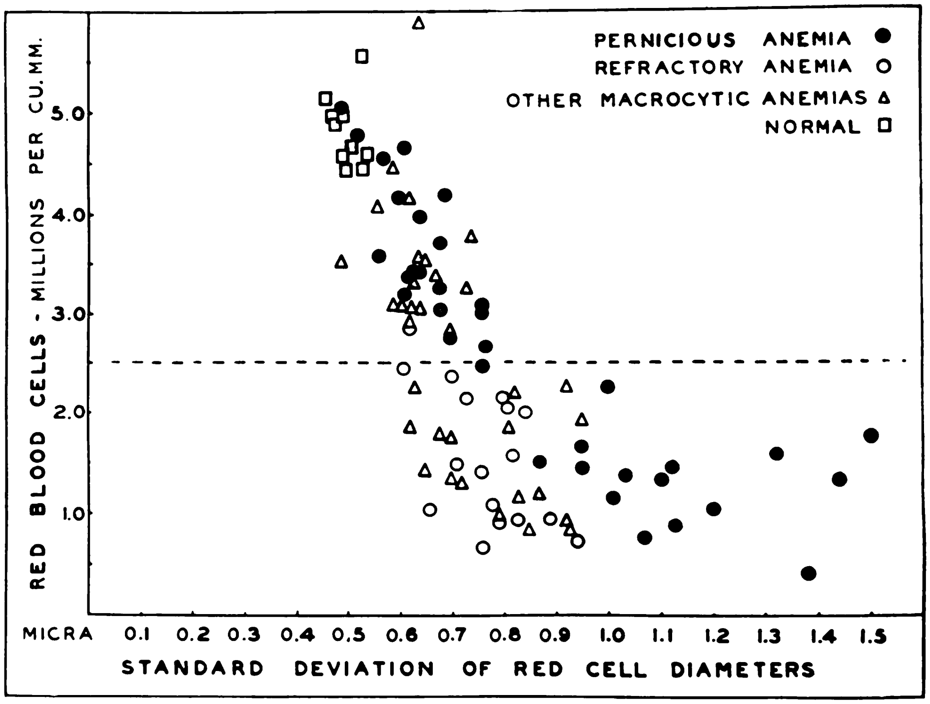

FIG. 1. RED BLOOD CELL COUNT AND STANDARD DEVIATION OF RED CELL DIAMETERS IN DIFFERENT TYPES OF MACROCYTIC ANEMIA

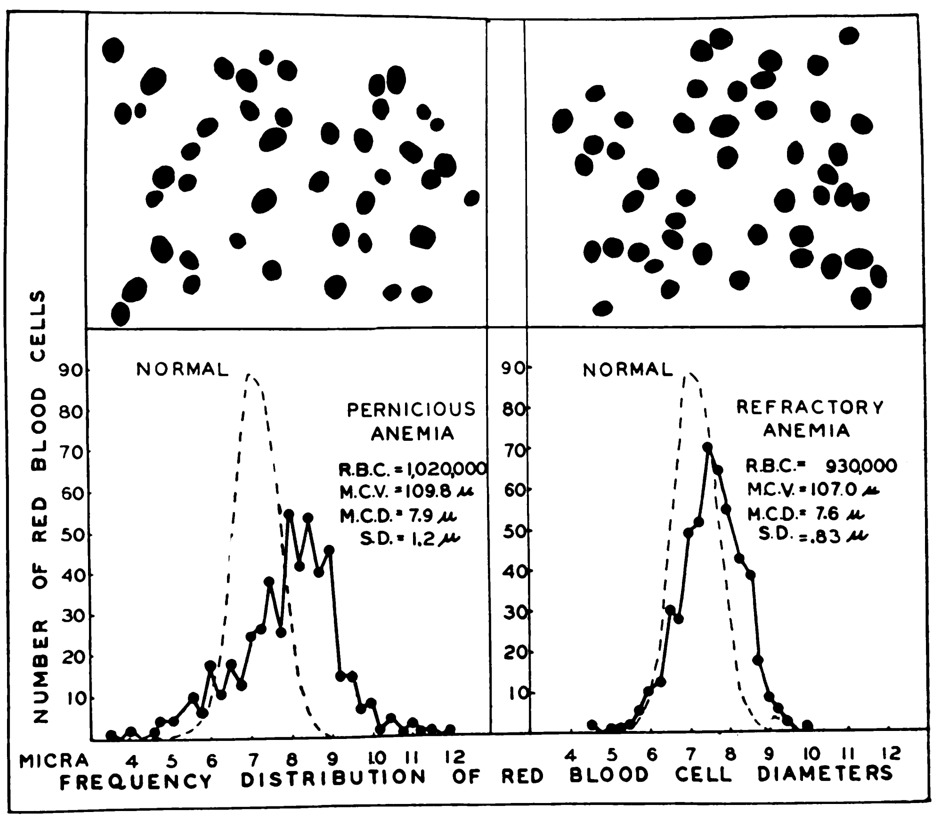

FIG. 2. COMPARISON OF PRICE-JONES CURVES AND SIZE AND SHAPE OF RED CELLS IN PERNICIOUS ANEMIA AND REFRACTORY ANEMIA

microcytes over macrocytes. At the higher levels, the Price-Jones curve tends to be symmetric, but occasionally there is slight skewness to the right. In a well treated patient the Price-Jones curve becomes normal.

Table 3 shows the frequency with which skewness to the left in the Price-Jones curve occurred at red blood cell levels of less than 3,000,000 per cubic millimeter in Addisonian pernicious anemia and the other cases of macrocytic anemia. Several methods of quantitating the degree of skewness may be employed—for example, determination of the mean-mode* difference, which will be zero in normal curves, negative in skewed curves with longer slope to the left, and positive in skewed curves with longer slope to the right. The mathematical analysis of skewness does not seem to be more advantageous than the results of simple inspection, which is sufficiently accurate for clinical purposes.

The important diagnostic information to be gained in studying the distribution curves of the red blood cell diameters in pernicious anemia appears to be derived from the following factors: (1) the degree of anisocytosis as revealed by the standard deviation or coefficient of variation, (2) the presence or absence of skewness of the curve with the longer slope to the left, and (3) the relation of these factors

TABLE 3.—*Presence or Absence of Skew Distribution Curves of Red Blood Cell Diameters in Different Types of Macrocytic Anemia with Red Blood Count of Less than 3,000,000 per Cubic Millimeter*

Type of Anemia	No. Cases	Skewness					
		Slope to Left		None		Slope to Right	
		No. Cases	%	No. Cases	%	No. Cases	%
Refractory macrocytic	16	0	0	12	75	4	25
Pernicious	18	10	56	7	30	1	6
Miscellaneous macrocytic	20	2	10	12	60	6	30

to the level of the red blood cell count. Other relationships have been studied, but require only brief mention. The standard deviation varies with the hemoglobin in the same manner as it does for the red blood cell count. In cases with less than about 40 per cent hemoglobin, the standard deviation serves as an aid in differentiating between pernicious anemia and the other macrocytic anemias. Mean diameter and mean volume of the red blood corpuscles at given levels do not distinguish pernicious anemia from the other macrocytic anemias. There is, moreover, only little relation between the mean diameter and the standard deviation of the red blood cell diameters in all the cases under consideration. The comparison of these two factors did not serve in any way to distinguish pernicious anemia from the other cases of macrocytic anemia. The same may be said in regard to comparison between the mean corpuscular volume and the standard deviation. The relative numbers of macrocytes and microcytes in a given preparation of blood, or the degree of anisocytosis, have been ascertained by various methods. These values provided no information of diagnostic help additional to that obtained through the use of the standard deviation.

* The arithmetic mean of the cell diameters is the average of the diameters as determined on 500 cells, expressed in micra.

Certain unusual types of macrocytic anemia responding to liver may be exceptions to the findings above. Those most commonly encountered in this country are the macrocytic anemia of pregnancy, sprue, and nutritional anemias, such as those associated with pellagra. On the other hand, such cases do not usually present the difficulties in diagnosis encountered between Addisonian pernicious anemia and certain macrocytic anemias refractory to specific therapy.

Three cases of macrocytic anemia accompanying pregnancy and responding to liver therapy have been studied by the present methods. The red blood cell levels and standard deviations of the red blood cell diameters in these cases were, respectively: case 1, R.B.C. 860,000, standard deviation 0.77; case 2,* R.B.C. 1,260,000, standard deviation 0.86; case 3, R.B.C. 895,000, standard deviation 0.86. Here, it will be recognized, the anemia was severe, yet the degrees of anisocytosis as shown by standard deviations were relatively small. The Price-Jones curves in the first 2 cases were symmetric; in the third case, the curve was slightly skewed, with the long slope to the right.

Although macrocytic anemia is common in sprue, the literature suggests that the Price-Jones curves in this condition are often dissimilar in many respects to those in Addisonian pernicious anemia. Thus Fairley, Mackie, and Billimoria,[10] who analyzed 67 cases of sprue, state: "Anisocytosis was the one outstanding feature especially as regarding increase in size. Microcytes were much less in evidence than the larger forms. Poikilocytosis and polychromasia occur, but to nothing like the degree observed in pernicious anemia." Examination of the Price-Jones curves of the cases reported by these authors reveals relatively symmetric curves with little tendency to skewness. The standard deviation was 0.95 micron or more in 5 of 7 cases in which the red cell count was 2,500,000 per cubic millimeter or less. Newham, Morris, and Manson-Bahr[11] report similar findings.

Little is known of the distribution of red blood cell diameters in other macrocytic anemias associated with nutritional deficiency. The anemia of nontropical sprue or of idiopathic steatorrhea is variable and often associated with iron deficiency. Rather marked increase of anisocytosis may be present, but the Price-Jones curves in the few cases reported[1] suggest certain differences from pernicious anemia, notably lack of the skewness with large left component.

CONCLUSIONS

1. Below the level of about 2,500,000 red blood cells per cubic millimeter, the degree of anisocytosis as revealed by the standard deviation and the coefficient of variation of the red cell diameters serves as a fairly accurate criterion for distinguishing Addisonian pernicious anemia from many other types of macrocytic anemia.

2. Below the level of 3,000,000 red blood cells per cubic millimeter, the asymmetric skewness of the distribution curve of the red cell diameters in pernicious anemia is an aid in distinguishing these cases from certain other types of macrocytic anemia.

* This case has been reported by Watson and Castle.[9]

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