THE BASAL METABOLISM IN ANEMIA WITH ESPECIAL REFERENCE TO THE EFFECT OF BLOOD TRANSFUSION ON THE METABOLISM IN PERNICIOUS ANEMIA *

EDNA H. TOMPKINS, A.B., HAROLD H. BRITTINGHAM, A.B.
AND
CECIL K. DRINKER, M.D.
BOSTON

HISTORICAL

In spite of critical reviews of the investigations on metabolism in anemia published by Strauss,[1] in 1906, and Meyer and DuBois,[2] in 1916, it will be profitable to discuss again the material which has been presented.

1. *Animal Experimentation.* — Work on metabolism in anemic animals has concerned itself almost entirely with posthemorrhagic conditions. Thus Bauer,[3] under the complex disturbances immediately following blood loss, found the metabolism slightly diminished; Delchef[4] found it normal or slightly diminished; Finkler[5] and Pembrey and Gürber[6] found it normal; Fredericq[7] found it transiently diminished and then elevated; Lukjanow[8] and Hári[9] found it elevated. Bauer[3] reported a remarkably diminished metabolism a few days after bleeding. His work has been justly criticized by Pembrey and

* From the Respiration Laboratory and Medical Clinic of the Peter Bent Brigham Hospital and the Laboratory of Physiology of the Harvard Medical School.

1. Straus, H.: Cf. von Noorden's Handbuch der Pathologie des Stoffwechsels, Berlin, **1**:881, 1906.
2. Meyer, A. L., and DuBois, E. F.: The Basal Metabolism in Pernicious Anemia, Arch. Int. Med. Part 2, **17**:965, 1916.
3. Bauer, J.: Ueber die Zersetzungsvorgänge im Thierkörper unter dem Einflusse von Blutentziehungen, Ztschr. f. Biol. **8**:567, 1872.
4. Delchef, J.: Influence de la saignée et de la transfusion sur la valeur des échanges respiratoires, Arch. internat. de physiol. **3**:408, 1905-1906.
5. Finkler, D.: Ueber den Einfluss der Strömungsgeschwindigkeit und Menge des Blutes auf die thierische Verbrennung, Arch. f. d. ges. Physiol. **10**:368, 1875.
6. Pembrey, M. S., and Gürber, A.: On the Influence of Bleeding and Transfusion on the Respiratory Exchange, Jour. Physiol. **15**:449, 1894.
7. Fredericq, L.: De l'action physiologique des soustractions sanguines, Travaux du Laboratoire, **1**:133, 1885-1886.
8. Lukjanow, S.: Ueber die Aufnahme von Sauerstoff bei erhöhtem Procentgehalt desselben in der Luft, Ztschr. f. physiol. Chem. **8**:313, 1884.
9. Hári, P.: Der Einfluss grosser Blutverluste auf die Kohlensäure- und Wasserausscheidung und Wärmeproduktion, Arch. f. d. ges. Physiol. **130**:177, 1909.

Gürber,[6] who found no changes from the time of hemorrhage until recovery, and their findings are apparently verified by Hári,[9] who has reported so slight an elevation during the period of recovery as to fall within normal limits. In the experiments of Pembrey and Gürber[6] the removed blood was at once replaced by saline solution, a procedure which they term "transfusion." Delchef[4] and Hári[10] have reported the only studies on true transfusion. Immediately after the anemic animal received the injected blood Delchef[4] found the oxygen consumption greatly elevated, and attributed this to the agitation and dyspnea attendant on the operation rather than to direct effects from increased blood content. Hári[10] found the metabolism somewhat increased on injection of fresh blood into normal animals. His results may also be attributed to the agitation resulting from the operation or to the actual food received by the animal in the form of the injected plasma.

The diversity of results which all these observations record, while undoubtedly due in part to determinations of the metabolism too soon after the excitement attendant on hemorrhage, is largely due to failure on the part of the observers to take uniform and adequate precautions in regard to food, muscular activity and apparatus.

2. *Clinical Observations.* — The same technical considerations coupled with lack of normal standards have caused a large part of the disagreement found in metabolic studies on clinical anemias. On the basis of Meeh's formula for surface area and the normal of 34.7 calories per square meter per hour, Meyer and DuBois[2] have recalculated the basal metabolism on certain clinical anemias studied prior to their own work. They found that not only the pioneer work of Pettenkofer and Voit,[11] but that of all authors on leukemia shows a considerably elevated metabolism. They also found that the data of Kraus and Chvostek[12] and Bohland[13] on anemias in general give values above or on the upper limits of normal. It should be noted that both of these observers provided experimental conditions which are now known to increase the metabolism. Thiele and Nehring[14] have reported a normal metabolism for secondary anemia, but diminished or on the lower border of normal for chlorosis. For their one case

10. Hári, P.: Ueber den Einfluss der intravenösen Bluttransfusion auf den Stoff- und Energieumsatz, Biochem. Ztschr. **34**:111, 1911; **44**:1, 1912.

11. Pettenkofer, M. v., and Voit, C.: Ueber den Stoffverbrauch bei einem leukämischen Manne, Ztschr. f. Biol. **5**:319, 1869.

12. Kraus, Fr., and Chvostek, Fr.: Ueber den Einfluss von Krankheiten, besonders von anämischen Zuständen, auf den respiratorischen Gaswechsel, Ztschr. f. klin. Med. **22**:449, 1893.

13. Bohland, K.: Ueber den respiratorischen Gaswechsel bei verschiedenen Formen der Anämie, Berl. klin. Wchnschr. **30**:417, 1893.

14. Thiele, O., and Nehring, O.: Untersuchungen des respiratorischen Gaswechsels unter dem Einflusse von Thyreoideapräparaten und bei anämischen Zuständen des Menschen, Ztschr. f. klin. Med. **30**:41, 1896.

of pernicious anemia our computations, also based on Meeh's formula and 34.7 calories, show a gradual and unexplained drop in metabolism from the upper to the lower border of normal over a duration of two weeks. The anemias studied by Magnus-Levy[15] show a normal calorific output with the exception of a slight elevation in one case of pernicious anemia and an equally slight diminution in one case of secondary anemia. He also found a small drop in metabolism in two chlorotic, one secondary and one leukemic case under treatment with iron preparations, and under the same conditions a slight rise in one of secondary anemia. Basing their computations on modern standards, Meyer and DuBois[2] found their own cases of pernicious anemia gave a metabolism on the upper limits of normal in mild types, and definitely elevated in severe ones. Their worst case, on observations repeated over an interval of time, showed a drop in metabolism accompanied by a fall in temperature and pulse rate. Grafe[16] and Eberstadt[17] attempted to correlate the blood forming ability of anemic animals with the metabolism. They found that rabbits with exhausted marrow from hemorrhagic anemia or from anemia due to phenylhydrazin injections had diminished metabolism, while those anemic but with normal marrow showed normal metabolism. Rolly[18] contradicts these findings on animals and adds observations on clinical anemias. Our computations of his figures, again based on Meeh's formula and 34.7 calories, show a metabolism considerably elevated for pernicious anemia and for an aplastic type of anemia due to carcinoma, on the upper level of normal for chlorotic and hemorrhagic anemia, on the lower level for secondary anemia due to lead poisoning, and diminished for one due to parasitic infection. Grafe,[19] stimulated by his animal work to belief in the influence of active blood formation in increasing metabolism, carried his observations into the clinic. Contrary to Rolly[18] he suggested that the same relation seemed to hold, since two of the most severe cases of pernicious anemia with signs of marrow insufficiency gave the lowest values in his series, and a third case gave a much higher metabolism during a blood crisis than subsequently when regeneration was less active. According to our computations, the two first cases had a metabolism on the lower border of normal,

15. Magnus-Levy, A.: Der Einfluss von Krankheiten auf den Energiehaushalt im Ruhezustand, Ztschr. f. klin. Med. **60**:177, 1906.

16. Grafe, E.: Beiträge zur Kenntnis der Kompensations- einrichtungen bei chronischen experimentellen Anämien, München. med. Wchnschr. **51**:2840, 1912.

17. Eberstadt, F.: Ueber den Einfluss chronischer experimenteller Anämieen auf den respiratorischen Gaswechsel, Arch. f. exper. Path. u. Pharmakol. **71**:329, 1912-1913.

18. Rolly, Fr.: Ueber den respiratorischen Gaswechsel bei chronisch anämischen Zuständen, Deutsch. Arch. f. klin. Med. **114**:605, 1914.

19. Grafe, E.: Zur Kenntnis des Gesamtstoffwechsels bei schweren chronischen Anämien des Menschen, Deutsch. Arch. f. klin. Med. **118**:148, 1915.

while the third case had an elevated metabolism during the crisis and was normal during the period of moderate regeneration.

It is evident from this review that with the exception of leukemia, no definite conclusions have been obtained concerning the metabolism in anemia. Not only has there been no agreement from case to case, but in one and the same patient with similar experimental conditions, the results have shown wide variations; and unfortunately the time relations of metabolism determination to clinical treatment and blood picture in any such case have not been sufficiently noted to make explicable the changes seen from date to date in the calorific output. On the whole, however, experimental data have given evidence of a tendency toward increased metabolism in anemias of all types.

Many explanations for this increase have been given. They fall into two groups in relation to the experimental solution of the problem:

1. The increased muscular work required by the more rapid respiration and heart rate have been considered in most cases sufficient to cause such increases in metabolism as have been observed, with the exception of leukemia. This explanation depends on simple muscular compensation and demands no consideration of obscure toxic factors, metabolism of young red cells, etc.

2. The increased metabolism of young and nucleated red cells, unusual numbers of white cells, undetermined toxic influences and activity of the blood forming centers have, with other possibilities, been cited as causes of the increased metabolism. None of these causes is definitely compensatory.

If the grade of the metabolism in anemia is due in any degree to the increased muscular work which the disease requires, it should be possible by reducing the heart rate and respiration to normal to gain a true picture of the uncompensated normal metabolism of the case. Blood transfusion, by an almost instantaneous check to the accelerated heart and lung action in these patients, restrains the muscular compensation. We have been able to find no record of work on the gaseous exchange under these conditions, and as transfusion was being employed by two of us[20] in the treatment of anemia, an exceptional opportunity for metabolic study was offered.

EXPERIMENTAL METHODS

1. *Transfusions.*—The technic employed is discussed in a previous article.[20] It is of interest to note that the patients have received transfusions of whole blood and transfusions of washed red cells suspended in physiologic salt solution. The effect of both types of transfusion is the same—a decrease in metabolism. It should be noted that in the transfusions of washed red cells

20. Drinker, C. K., and Brittingham, H. H.: Cause of the Reactions Following Transfusion of Citrated Blood, Arch. Int. Med. To be published.

we have provided the simplest possible conditions—an increase in circulating hemoglobin without introduction of material which can be burned, as is inevitable in introduction of plasma.

2. *Metabolism Determinations.*—For the metabolic study a combination of the Douglas and Tissot[21] methods was employed. The half mask and modified valves as supplied by Siebe Gorman & Co. were used in connection with a modified Tissot spirometer. The latter is made of aluminum, has a syphon counterpoise, but a constant volume water bath so that corrections must be made for the displacement.

Two portable Haldane gas analyzers[22] were used for the analyses of the expired air. Duplicate analyses were made on every period of a determination. After each day's analyses, air was drawn through the outdoor tube and analyzed. This checked at once the patient's inspired air and the accuracy of the analyses on his expired air.

Without leaving his bed, the patient was wheeled to the laboratory from fourteen to sixteen hours after his last nourishment—a light supper—and eight or more hours after his last drink of water. There the metabolism nurse took charge of his comfort. He lay on his back with never more than two soft pillows under his head, and with perhaps one under back or knees. Pulse and respirations were taken every three minutes until such time as the chart showed constancy—an interval never less than twenty minutes, usually thirty. The mask was then tied in position and five minutes elapsed before the first period was begun. This was found to be time enough to overcome any effects due to the excitement of the adjustment of the mask. The period was run nine to ten minutes. A kymographic record of the respiration was made throughout and all movements possible of detection were recorded. At the end of the period the mask was removed, the buccal temperature was taken and the patient was permitted to make slight movements. In about ten minutes the mask was again placed in position; this time the patient exhaled into the room for but one minute and a second period was carried through exactly as the first. We prefer this double placement of the mask as it enables us to detect readily any possible leak. When muscular and nervous activity are ruled out and the two periods agree satisfactorily we are sure that the mask was air tight. At the end of the second period the patient's height and weight were taken and he was returned to the ward.

The respiration rate and volume per respiration were established from the pneumographic records. The percentage normality of the metabolism was based on the DuBois linear formula[23] and the corresponding standards of normal calorific output.[24] Use of these standards was governed not by our conviction of their finality, but by our belief that at present they form the best basis for presentation of the material we have to offer. The nitrogen metabolism was not studied. The nonprotein respiratory quotient,[25] however, was used to compute the total heat production. Benedict[26] has shown that

21. Carpenter, T. M.: A Comparison of Methods for Determining the Respiratory Exchange of Man, Carnegie Institution of Washington, Publication 216, 1915, p. 61.

22. Haldane, J. S.: Methods of Air Analysis, London, 1912.

23. DuBois, D., and DuBois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be known, Arch. Int. Med., Part 2, **17**:863, 1916.

24. Aub. J. C., and Dubois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. Part 2, **19**:823, 1917 (page 831 only).

25. Lusk, G.: The Science of Nutrition, Ed. 3, Philadelphia, W. B. Saunders Co. 1917, p. 61.

26. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations with Special Reference to the Stimulating Effect of Nutrients, Carnegie Institution of Washington, Publication 261, 1918, p. 203.

such a method of computation ordinarily causes an error in percentage normality of from 1 to 2 per cent. While this could in no way affect agreement between closely following periods, it might easily do so between the results of different days. We, therefore, consider that in order to be significant, a change in the metabolism on different days must show a variation of the averages of at least 5 per cent., while in any one determination the two periods, to be satisfactory, must vary by not more than 3 per cent.

TABLE 1.—METABOLISM STUDIES ON—

Case No. and Name	Med. No.	Diagnosis	Sex	Age	Metabolism		
					Date	Height, Cm.	Weight, Kg.
1 M. C.	7552	Pernicious anemia; chronic type; duration July, 1915 to November, 1917; no remissions	♂	53	11/15/17	164.1	59.9
2 L. A. T.	7793	Pernicious anemia; chronic type; duration August, 1916 to January, 1918; remission September, 1917, to November, 1917	♂	46	1/ 4/18	173.2	70.7
3 M. A. O.	8448	Pernicious anemia; chronic type; duration April, 1917 to April, 1918; yellow pallor of skin noticed first April, 1918; no remissions	♀	62	4/15/18	158.6	49.1
4 A. J. N.	5811	Necropsy diagnoses: Emaciation; hyperplasia of lymphatics of small intestine and mesenteric glands; atrophy of liver and spleen; congestion of kidney; Meckel's diverticulum. Chronic anemia; duration June, 1915 to January 1917; progressing slowly and without remission	♂	42	1/16/17	175.0	58.4
5 J. F. G.	8473	Secondary anemia; carcinoma of stomach; hypertension; duration of anemia, April, 1917 to April, 1918; progressing slowly and without remission	♂	59	4/12/18	169.1	57.0
6 F. K.	8191	? Pernicious anemia; neuritis; dilation aortic arch; syphilis; fever (cause unknown); duration of anemia, November, 1917 to March, 1918; progressing slowly and without remission	♀	58	3/23/18	158.4	53.3
7 L. K.	6951	Pernicious anemia; chronic type; furunculosis; duration July, 1916 to August, 1917; no remissions	♂	73	8/13/17	165.8	50.4
8 A. H. P.	8220	Pernicious anemia; acute type; duration, February, 1918 to March, 1918	♂	58	3/ 6/18	177.4	67.3
9 F. D.	8624	Pernicious anemia; chronic type; duration January, 1917 to May, 1918; one remission March, 1917 to January, 1918	♀	42	5/10/18	162.0	64.3
10 A. S.	7470	Splenic anemia; splenomegaly; duration of anemia, October, 1916 to October, 1917; progressing slowly and without remission	♀	18	11/10/17	160.2	48.3
11 J. J. M.	8140	Banti's disease; bronchitis; duration of anemia, December, 1917 to February, 1918; no remissions	♂	33	2/28/18	178.0	77.6
12 G. A. C.	7739	Pernicious anemia; chronic type; arteriosclerosis; ventral hernia; duration February, 1916 to March, 1918; remission September, 1917 to November, 1917	♀	59	12/26/17	155.9	41.8
13 W. E. M.	8192	Pernicious anemia; chronic type; laryngitis; duration January, 1915 to February, 1918; diagnosed pernicious anemia January, 1915; had long and rather complete remission during years of 1916–1917	♂	53	3/ 2/18	175.5	59.7
14 T. G. H.	8204	Secondary anemia (brief duration); menorrhagia; duration of anemia, September, 1917 to March, 1918	♀	35	3/ 7/18	164.7	39.5
15 E. F. M.	8217	Pernicious anemia; acute type; duration of anemia, February, 1918 to March, 1918; no remissions	♀	56	3/ 8/18	170.6	59.7
16 A. J. C.	7400	Splenic anemia; splenomegaly; duration of anemia, September, 1917 to October, 1917	♀	60	10/23/17	157.0	56.6
17 E. M.	7586	Secondary anemia; carcinoma of stomach; abdominal metastases; duration of anemia, June, 1917 to November, 1917	♂	41	11/23/17	175.3	55.5
18 E. M. C.	8040	Pernicious anemia; chronic type; febrile and dangerously ill at present; anemia first noted June, 1916; complete remission January, 1917 to August, 1917; gradual decline August, 1917 to February, 1918; death May, 1918	♀	29	2/10/18	150.1	40.7

† The two periods disagreed by 4 per cent.
‡ The two periods disagreed by 6 per cent.

PRESENTATION OF DATA

In the accompanying tables we have given the average data of the two periods of a day's determination and have pointed out cases in which the parallel periods did not fall within the 3 per cent. limit. In most cases a determination of metabolism was made before any type

of treatment was undertaken. Exceptions are noted in Table 3. The metabolism was then followed from time to time during spontaneous improvement or in connection with the transfusions. Of necessity a number of patients received an original determination before treatment, but could be studied no further. Such cases we have placed in

—Untreated Cases of Anemia

Metabolism								Blood Picture						
Buccal Temperature, F.	Pulse	Respiration	Volume per Minute, L.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Linear	Date	Hemoglobin, per Cent.	R. B. C., Million	W. B. C.	Nucleated R. C.	Anisocytosis	Poikilocytosis	Remarks
98.6	70	9.8	4.02	186	0.75	52.7	—15	11/16/17	98	4.3	6,700	0	++	+	Many macrocytes seen
98.6	67	9.3	4.31	215	0.78	61.5	—13	1/ 3/18	69	2.3	6,000	0	++	++	
98.8	80	14.9	4.56	159	0.75	45.1	—11	4/15/18	30	1.0	5.000	0	++	0	
98.2	69	11.0	4.93	219	0.80	63.1	— 4	1/17/18	73	2.9	6.600	2	+	+	
97.0	69	14.3	6.33	210	0.76	59.8	— 4	4/11/18	50	3.0	18,800	0	+	+	
98.6	72	20.2	4.55	187	0.74	53.1	— 2	3/20/18	60	3.1	4,600	0	+	0	Plate counts: March 23, 146,000 March 26. 184,000
96.8	66	16.7	5.70	193	0.73	54.6	— 1	8/12/17	35	1.5	3,800	16	++	++	10 megaloblasts in the 16 blasts seen in counting 100 leukocytes
99.2	95	16.3	6.00	247	0.77	70.4	+ 2	3/ 7/18	39	0.9	5,000	0	++	0	
99.0	84	16.0	5.84	221	0.77	63.2	+ 5	5/ 9/18	40	2.5	6,100	0	+	+	
98.6	61	19.1	5.22	209	0.73	59.1	+ 5	11/ 8/17	68	3.0	4,800	0	0	0	Splenectomy showed large splenitis
98.6	90	13.5	7.11	293	0.75	83.3	+ 8	2/25/18	75	2.8	3,000	0	0	0	Plate count 66,000; patient died May, 1918; no necropsy
99.4	72	13.7	4.50	182	0.76	51.8	+ 9†	12/23/17	40	1.5	6,700	0	0	0	Plates decreased; patient rarely showed blasts
98.4	71	17.5	6.51	253	0.76	72.1	+11	3/ 2/18	41	1.4	7,000	0	+	+	
99.2	102	18.4	5.11	198	0.74	56.2	+11	3/ 6/18	30	2.2	3,800	0	+	+	Patient recovered with 1 transfusion and iron medication
100.0	101	22.1	6.55	241	0.73	68.0	+15	3/ 7/18	25	0.8	2,500	1	++	++	One megaloblast seen
98.8	97	14.6	5.42	217	0.75	61.5	+15†	10/22/17	68	3.6	7,000	0	+	+	Patient developed large splenic tumor; death April. 1918; no necropsy
98.8	87	11.9	5.31	265	0.71	74.5	+16	11/20/17	36	3.7	11,400	2	++	++	
102.8	118	17.8	5.50	205	0.75	58.1	+20	2/ 8/18	55	2.1	3,200	0	+	++	

Table 1, together with the original determination of all cases studied during treatment. Table 1 thus tabulates the data of the metabolism studies on our untreated anemias, together with that necessary for an estimation of the clinical picture and for the basis of computations.

Table 2 is so arranged as to show in detail the data and time relations of metabolism to treatment and blood picture in a complete course of study on six characteristic patients.

Table 3 gives the admission and the end data on the remainder of our cases studied during a course of treatment.

TABLE 2.—Relation of Metabolism to—

Case No. and Name	Med. No.	Diagnosis	Sex	Age	Treatment: Description	Dates Metabolism and Treatment	Metabolism: Height, Cm.	Weight, Kg.	Buccal Temperature, F.	Pulse	Respiration
1 M. C.	7552	Pernicious anemia; chronic type; duration, July, 1915 to November, 1917; no remissions	♂	53	.....	11/15/17	164.1	59.9	98.6	70	9.8
					700 c.c. washed R.B.C. in physiol. saline	11/16/17					
					600 c.c. washed R.B.C. in physiol. saline	11/18/17					
						11/19/17	.....	60.3	98.4	66	12.1
					550 c.c. washed R.B.C. in physiol. saline	11/21/17					
						11/26/17	.....	59.7	97.8	60	10.6
						12/ 5/17	.....	59.7	98.4	65	9.3
3 M. A. O.	8448	Pernicious anemia; chronic type; duration, April, 1917 to April, 1918; yellow pallor of skin noticed first April, 1918; no remissions	♀	62	.....	4/15/18	158.6	49.1	98.8	80	14.9
					900 c.c. washed R.B.C. in physiol. saline	4/16/18					
						4/17/18	.....	48.5	98.0	73	18.5
					900 c.c. washed R.B.C. in physiol. saline	4/18/18					
						4/20/18	.....	48.6	98.0	68	15.9
					800 c.c. washed R.B.C. in physiol. saline	4/29/18	.....	50.8	98.2	72	13.8
						4/30/18	.....	49.3	99.2	70	13.0
12 G. A. C.	7739	Pernicious anemia; chronic type; arteriosclerosis; ventral hernia; duration, February, 1916 to March, 1918; remission September, 1917 to November, 1917	♀	59	.....	12/26/17	155.9	41.8	99.4	72	13.7
					600 c.c. washed R.B.C. in physiol. saline	1/ 6/18					
						1/ 9/18	.....	40.8	99.0	85	13.2
						1/16/18	.....	39.3	99.2	80	14.0
						2/ 7/18	.....	41.3	99.0	79	13.3
					150 c.c. plasma and platelets.....	2/24/18					
					700 c.c. washed R.B.C. in physiol. saline	2/25/18	.....	39.9	99.6	87	13.8
						2/26/18	.....	40.2	98.4	72	12.4
					700 c.c. washed R.B.C. in physiol. saline	2/28/18	.....	40.1	98.6	74	12.9
					135 c.c. plasma and platelets.....	3/ 1/18					
						3/ 5/18	.....	40.6	98.6	66	13.6
14 T. G. H.	8204	Secondary anemia (brief duration); menorrhagia; duration of anemia, September, 1917 to March, 1918	♀	35	.....	3/ 7/18	164.7	39.5	99.2	102	18.4
					750 c.c. washed R.B.C. in physiol. saline	3/21/18	.....	39.0	99.4	84	16.3
						3/25/18	.....	39.1	98.4	67	16.1
15 E. F. M.	8217	Pernicious anemia; acute type; duration of anemia, February, 1918 to March, 1918; no remissions	♀	56	.....	3/ 8/18	170.6	59.7	100.0	101	22.1
					950 c.c. washed R.B.C. in physiol. saline	3/10/18					
					900 c.c. washed R.B.C. in physiol. saline	3/12/18					
					500 c.c. washed R.B.C. in physiol. saline	3/14/18					
						3/15/18	.....	61.8	98.6	77	24.6
					900 c.c. washed R.B.C. in physiol. saline	3/19/18					
						3/20/18	.....	61.7	98.6	77	23.7
						3/25/18	.....	60.9	98.6	83	21.7
					450 c.c. washed R.B.C. in physiol. saline	4/ 2/18	.....	59.4	98.8	80	20.6
					450 c.c. washed R.B.C. in physiol. saline	4/ 4/18					
						4/ 5/18	.....	59.5	97.6	74	20.1
						4/ 9/18	.....	59.9	98.6	78	20.1
18 E. M. C.	8040 8337	Pernicious anemia; chronic type; febrile and dangerously ill at present; anemia first noted June, 1916; complete remission January, 1917 to August, 1917; gradual decline August, 1917 to February, 1918; death, May, 1918	♀	29	800 c.c. washed R.B.C. in physiol. saline	2/10/18	150.1	40.7	102.8	118	17.8
					825 c.c. washed R.B.C. in physiol. saline	2/13/18					
					675 c.c. citrated whole blood.....	2/15/18					
						2/16/18	.....	40.0	97.8	55	13.6
						3/26/18	.....	39.4	100.6	102	14.2
					800 c.c. washed R.B.C. in physiol. saline	3/29/18					
						3/30/18	.....	39.6	98.8	79	14.0

* The two periods disagreed by 6 per cent.
† The two periods disagreed by 4 per cent.
‡ The two periods disagreed by 5 per cent.
§ The two periods disagreed by 4 per cent.

DISCUSSION OF RESULTS

A survey of Table 1 — the data on the untreated cases — reveals the same irregularities found throughout the literature. The metabolism falls in part within normal limits, in part above and below

normal. It is parallel neither with the marrow activity as represented by the blood picture, history and general condition of the patient, nor

—Treatment in Six Cases of Anemia

Metabolism						Blood Picture							
Volume per Minute, L.	Volume per Respiration, C.c.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Linear	Date	Hemoglobin, per Cent.	R. B. C., Million	W. B. C.	Nucleated R. C.	Anisocytosis	Poikilocytosis	Remarks
4.02	410	186	0.75	52.7	—15	11/13/17	87	3.2	8,400	0	++	+	Plates decreased. Many macrocytes
						11/18/17	96	4.0	8,500	0	++	+	Many macrocytes
						11/26/17	104	4.5	5,400	0	+	0	
3.93	327	179	0.81	51.6	—17	12/ 5/17	83	5.4	6,200	8	+	0	Eight normoblasts
3.62	344	161	0.80	46.2	—26								
3.60	388	161	0.78	45.9	—26								
4.56	307	159	0.75	45.1	—11	4/15/18	30	1.0	5,000	0	++	+	
						4/17/18	55	1.9	2,400	0	0	0	One myelocyte seen on this date
5.12	277	163	0.72	45.8	— 8	4/20/18	90	3.4	3,800	2	0	0	One normoblast, one megaloblast seen
						4/29/18	75	3.2	3,200	0	0	0	Rare stippled cells present
4.48	283	152	0.75	43.3	—14	4/30/18	75	3.3	3,300	1	0	0	Four myelocytes seen
4.38	319	153	0.85	44.6	—13								
4.13	318	148	0.84	43.1	—14*								
4.50	329	182	0.76	51.8	+ 9†	12/29/17	40	1.2	6,600	1	+	++	One myelocyte, one normoblast
						1/ 7/18	44	2.1	4,000	0	+	+	Marked stippling
3.93	298	170	0.76	48.4	+ 3‡	1/14/18	45	2.2	5,300	0	+	+	
3.60	258	155	0.72	43.6	— 7	2/ 6/18	60	2.4	8,200	0	+	0	
3.99	301	166	0.76	47.1	— 2	2/26/18	58	2.2	3,400	0	0	+	Polychromatophilia constant in this patient
4.16	302	168	0.75	47.8	+ 2								
4.25	344	169	0.77	48.3	+ 3§								
4.20	325	156	0.78	44.5	— 5								
3.95	290	149	0.81	42.9	— 9								
5.11	278	198	0.74	56.2	+11	3/ 6/18	30	2.2	3,800	0	+	+	Plate count, March 3, 254,000
4.88	300	183	0.79	52.4	+ 4	3/20/18	46	4.2	7,800	0	0	+	Many macrocytes
4.19	260	160	0.78	45.7	—10	3/25/18	74	4.9	5,600	0	+	+	Few polychromatophilic, stippled cells present
6.55	297	241	0.73	68.0	+15	3/ 7/18	25	0.8	2,500	1	++	++	One megaloblast. Polychromatophilia slight
						3/15/18	64	2.4	1,800	0	+	+	
						3/22/18	70	2.8	3,100	1	+	+	Macrocytes numerous
						3/25/18	70	3.2	2,400	0	+	+	Macrocytes numerous
6.52	266	216	0.79	62.0	+ 3	4/ 1/18	64	3.1	2,900	0	+	+	Macrocytes numerous
						4/ 5/18	75	3.5	4,800	0	+	+	No polychromatophilia nor stippling
6.12	258	213	0.77	60.7	+ 1	4/ 9/18	95	4.0	4,200	0	+	+	No polychromatophilia nor stippling
5.72	264	212	0.80	61.0	+ 2								
5.89	286	225	0.79	64.6	+10								
5.77	287	217	0.81	62.8	+ 6								
5.51	275	213	0.80	61.3	+ 3¶								
5.50	309	205	0.75	58.1	+20	2/ 8/18	55	2.1	3,200	0	+	+	Achromia marked
						2/16/18	..	4.5	2,400	0	+	+	
						3/25/18	55	...	2,500	1	0	+	One megaloblast seen
3.67	271	153	0.74	43.2	—10#	3/30/18	65	...	1,800	0	0	+	Polychromatophilia not pronounced in this case
4.18	294	181	0.78	51.9	+ 9								
4.05	290	167	0.76	47.6	— 1‖								

¶ The two periods disagreed by 4 per cent.
# The two periods disagreed by 4 per cent.
‖ The two periods disagreed by 7 per cent.

with the immediate gravity of the case. Indeed, with the exception of Numbers 4, 9 and 12, the most severe cases were those who showed a metabolism beyond normal limits in either direction. In general, these severe types followed the order that the long standing, chronic cases gave a diminished, and the recent more acute ones, an elevated metab-

olism. It should be noted, however, that of those with a calorific output above normal, two patients (Numbers 15 and 18) had distinctly elevated temperatures, which would suggest that the increased metabolism was attributable, in part at least, to some influence other than the anemia. Two others (Numbers 16 and 17) of those with an increased energy output showed complications in the larger organs. Besides this coincidence between the intensity of metabolism and the duration of the disease, there is a certain parallelism to be seen between

TABLE 3.—ADMISSION AND END DATA ON—

Case No. and Name	Med. No.	Diagnosis	Sex	Age	Treatment: Description	Dates Metabolism and Treatment	Metabolism: Height, Cm.	Weight, Kg.	Buccal Temperature, F.	Pulse	Respiration
2 L. A. T.	7793 8298	Pernicious anemia; chronic type; duration, August, 1916 to January, 1918; remission, September, 1917 to November, 1917	♂	46	700 c.c. washed R.B.C. in physiol. saline 700 c.c. washed R.B.C. in physiol. saline 700 c.c. washed R.B.C. in physiol. saline 700 c.c. washed R.B.C. in physiol. saline	1/ 4/18 1/ 8/18 3/16/18 3/17/18 3/18/18	173.2	70.7 68.5	98.6 98.0	67 71	9.3 10.7
10 A. S.	7470 7669*	Splenic anemia; splenomegaly; duration of anemia, October, 1916 to October, 1917; progressing slowly and without remission	♀	18	..... Splenectomy.....	11/10/17 11/13/17 12/11/17	160.2	48.3 44.8	98.6 98.4	61 60	19.1 20.6
19 L. T. S.	7434	Pernicious anemia; lateral sclerosis; chronic type; duration of anemia, July, 1916 to October, 1917; no remissions	♀	40	250 c.c. citrated whole blood.....	10/26/17 10/31/17	..... 157.5	..... 56.6	..... 98.2	.. 69	..... 13.6
20 H. A. C.	7951	Secondary anemia; hemophilia; had had many attacks of bleeding but was well and at heavy work before the present hemorrhage	♂	52	650 c.c. citrated whole blood.....	1/15/18 2/ 6/18	..... 178.8	..... 66.7	..... 98.2	.. 68	..... 11.0
21 C. F. W.	8562	Pernicious anemia; chronic type; duration, January, 1917 to April, 1918; no remissions	♂	58	900 c.c. washed R.B.C. in physiol. saline	4/25/18 4/26/18	..... 184.4	..... 63.5	..... 98.0	.. 65	..... 14.1
22 G. A. C.	7527	Secondary anemia; pericarditis; pleurisy; peritonsillar abscess; duration of anemia about eight months	♂	39	550 c.c. washed R.B.C. in physiol. saline	1/ 5/18 1/ 8/18	..... 172.2	..... 53.1	..... 99.2	.. 78	..... 13.5
16 A. J .C.	7400	Splenic anemia; splenomegaly; duration of anemia, September, 1917 to October, 1917	♀	60	..... 117 millicuries radium applied to spleen 24 hours	10/23/17 10/28/17 10/30/17	157.0	56.6 55.8	98.8 99.2	97 90	14.6 14.5

* Surgical number.

pulse and metabolism. The abnormality of the metabolism, however, is far more marked than that of the pulse.

Tables 2 and 3, in contrast to Table 1, present a decidedly consistent picture. Most striking is the effect found as the result of treatment in all except three cases (Numbers 2, 3 and 16). Not only did the metabolism invariably fall, but, with the exception of Case 15, it reached a level either on the lower limit of or below normal. And this new level tended to hold despite further transfusions, and to repeat itself when a similar course of treatment was instituted in any later relapse. Parallel with this diminution in metabolism was a drop

in the pulse, in the respiratory activity as represented by the minute volume, and in the temperature if it had previously been elevated. The respiratory quotient was higher and, as was natural after transfusion, the simple cell count and the percentage hemoglobin were increased.

Of these changes following on treatment, the metabolism alone was of slow response. While the pulse and respiratory activity, the temperature and the blood picture reacted at once, or at least within

—CASES STUDIED DURING TREATMENT

Metabolism						Blood Picture							
Volume per Minute, L.	Volume per Respiration, C.c.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Linear	Date	Hemoglobin, per Cent.	R. B. C., Million	W. B. C.	Nucleated R.C.	Anisocytosis	Poikilocytosis	Remarks
4.31	463	215	0.78	61.5	—13	1/ 3/18	69	2.3	6,000	0	++	++	Few polychromatophilic and stippled cells seen
						3/18/18	55	2.3	4,800	0	++	0	Many macrocytes. No stippling
4.94	460	208	0.80	60.0	—15								
5.22	281	209	0.73	59.1	+ 5	11/ 8/17	68	3.0	4,800	0	0	0	Slight achromia
						12/ 8/17	75	4.4	12.000	0	0	0	
4.55	222	159	0.88	46.5	—15†								
....	....	....	....	....	....	10/29/17	68	2.2	4,200	0	+	+	Moderate polychromatophilia on Oct. 24, 1917
4.15	307	172	0.75	48.7	—14								
....	....	....	....	....	....	2/ 7/18	55	2.8	5,400	0	+	+	Marked achromia
5.52	501	210	0.84	61.1	—12								
....	....	....	....	....	....	4/26/18	90	3.0	2,300	0	+	+	
5.59	397	228	0.76	65.1	— 6								
....	....	....	....	....	....	1/ 5/18	53	1.9	10,000	0	+	+	A case of chronic sepsis with constant slight evening rise in temperature
4.92	364	225	0.71	63.2	— 2								
5.42	376	217	0.75	61.5	+15‡	10/22/17	68	3.6	7,000	0	+	+	Moderate polychromatophilia
5.38	372	212	0.76	60.4	+15								

† The two periods disagreed by 4 per cent.
‡ The two periods disagreed by 6 per cent.

twelve hours, the maximum effect on the metabolism seemed to take place only after a few days.

A discussion of the six cases reported in Table 2 will best show the facts as summarized in the foregoing.

Case 1 is of peculiar interest as representing chronic pernicious anemia of long duration. A hospital report shows this patient to have had a metabolism of minus 7 per cent. in 1916 (a year prior to the determination we have recorded). While his pulse and minute volume diminished soon after transfusion, it was not until some days later

that his heat output showed any change. It then seemed to have reached the true and remarkably low level at which it held.

Case 3 was likewise one of chronic anemia. This patient, however, as noted before, showed no metabolic response to transfusion. Her pulse, respiratory activity and respiratory quotient reacted in the general way, as did also her subjective symptoms. Of the last, the increased power to take food is especially worthy of mention. It may possibly be that this improved absorption of nutriment on the part of a person who had been using a decidedly subnormal amount of food masked what would otherwise have shown as a decreased metabolism.

Case 12, also one of long standing anemia, was carried through two periods of transfusion and moderate improvement, with an intervening relapse. Here the pulse rose after the first transfusion, but later pulse, metabolism, and respiration showed the usual diminution. At the end of each course of treatment the basal heat output showed the same level. Here, as in Case 1, this metabolic response to transfusion occurred only after a few days (compare the determinations of January 9 and 16, and of February 26 and 28), while the pulse and respiration dropped within twelve hours.

Case 14, under spontaneous improvement in a secondary anemia, showed the same type of changes, even to the blood picture, as occurred in all the cases after transfusion. Transfusion in this instance merely hastened the normal process of regeneration. In other words, natural improvement of the blood composition in anemia, as well as artificial improvement by transfusion, at first suppresses the stimulus acting on the body cells. This seems true no matter what the initial metabolism.

Case 15 represents a type diametrically opposite to Case 1. The onset of the disease was recent, the temperature before treatment was high, the metabolism and pulse elevated, the subjective symptoms grave. The response to transfusion, both metabolically and symptomatically, was marked, but of comparatively short duration. The cause of the disease was active, and the original symptoms soon reappeared, to subside once again to the same level as after the first series of transfusions. Even here, in an acute febrile case, responding to transfusion almost instantaneously in all other ways, the pronounced effect on the metabolism occurred only after an interval of a few days. (Compare date of April 5 and 9.) Likewise transfusion beyond a certain point had no effect on the energy requirement. (Compare the date of March 15, 20 and 25.)

What was stated for Case 15 may be practically repeated for Case 18. The patient here was dangerously ill and in the terminal stage of the disease. The metabolic level of the former was slightly lower, but otherwise the two patients presented very similar symptoms and reactions.

From the fact that the metabolism always falls after transfusion, no matter what its initial relation to normality, that this drop is preceded over a considerable interval of time by a fall in the pulse and respiratory activity, that the energy output seems to find a constant level beyond which it shows no further diminution, and that this level is either below or on the lower limit of normal — from these facts we feel that *two opposing factors, outside of any muscular activity, exert an influence on the metabolism of the anemic individual.*

First, there is a stimulus to the cells — perhaps only to certain ones such as those of the blood producing organs. The extent of this stimulus is expressed in the diminution of the metabolism which follows on transfusion. It is lost slowly as the cells readjust themselves to blood of more normal composition. Hence, the time interval between the introduction of blood into the body and the energy response of the organism.

Secondly, there is the opposing factor to the increased metabolism — namely, the tissue alterations attendant on the disease. The pathologic result of any anemia, and particularly of pernicious anemia, is replacement of normally active tissue by fat and water. In chronic pernicious anemia this replacement may reach an extreme degree, and expresses itself by the diminished heat output found in typical chronic cases and by the apparent tendency of all the cases to show a low metabolic level after transfusion when the stimulating factor has subsided.

The amount by which the metabolism falls after transfusion shows the strength of the stimulus exerted on the body cells, possibly for the purpose of blood production. And the level to which the metabolism falls shows the true bodily condition of the patient. A chronic case may thus be expected to reveal a decidedly lowered energy output, while from a recent case, where tissue compensation had not yet become an active factor, one may look for a practically normal calorific requirement. In our opinion, transfusion is a measure by which early cases of pernicious anemia may be assisted toward a remission and may be saved some degree of the fatty replacement of active tissue which in the end reduces them to a condition of sluggishness somewhat comparable to that seen in myxedema. If the case simply has a long history, the whole story is not told, since what is of importance is the length of the anemic periods and the possibility for bodily change which they present.

As a result of the work we have reported our course of action is now as follows: A typical case of pernicious anemia is admitted to the ward. After several days rest in bed, if food is being taken well

and if the temperature has become normal, a metabolism determination is carried out. Let us suppose the result is minus 10. In such an instance transfusion may result in a certain amount of immediate comfort, but there is little probability it will do more. The case is a chronic one in terms of the patient's actual physiologic condition. If the result is plus 10, transfusion is worth while. Such a result, a plus determination, will be given in persistently febrile cases on the first trial, and if as a consequence of transfusion the fever disappears and subsequent determinations give a pronounced minus value, again we can feel that further transfusion holds little in store. On the other hand, if the reduction in metabolism does not fall below normal either as a result of rest in bed or the first transfusion, the individual is one who has not progressed far in the disease, and transfusions should be pushed. While a course of transfusions does not prevent the development and progress of neurologic lesions, it does postpone the muscular sluggishness, which eventually reduces the chronic case of pernicious anemia to the state of a helpless burden.

CONCLUSIONS

1. Transfusion in cases of anemia produced the following results:
   a. a diminution of metabolism;
   b. a diminution of pulse and respiratory activity;
   c. a drop in temperature if it had previously been elevated;
   d. a rise in percentage hemoglobin and in the simple blood count.

2. The response of the metabolism to transfusion lags behind that of all the other factors by an interval of several days.

3. The lowering of metabolism is, therefore, not due simply to a cessation of the compensatory muscular activity of the anemic individual.

4. Before treatment the metabolism may be within normal limits or it may be above or below normal.

5. After transfusion the metabolism always reaches a normal or diminished level.

These facts suggest that the metabolism of the anemic individual is dependent on two contending factors, outside of any effects from compensatory muscular activity.

1. In untreated acute cases there is evidently some type of stimulation to the body cells in general and the amount of this stimulation is represented by the fall in metabolism after transfusion.

2. There are coincident progressive tissue alterations which tend to reduce metabolism. These alterations are represented by the diminished metabolism of the chronic cases, and by the low level to which the metabolism falls in practically all cases as a result of transfusion.