STUDIES ON THE VELOCITY OF BLOOD FLOW

XV. The Velocity of Blood Flow and Other Aspects of the Circulation in Patients with "Primary" and Secondary Anemia and in Two Patients with Polycythemia Vera[1]

By HERRMAN L. BLUMGART, SAMUEL L. GARGILL and DOROTHY ROURKE GILLIGAN

(From the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School, Boston)

(Received for publication September 29, 1930)

Claude Bernard (1) stated that " . . . . the various systems of the body have protective functions to place in reserve the substances essential to life and to maintain uninterruptedly the humidity, warmth and other conditions indispensable to vital activity." The purpose of the present investigation is to study the protective function of the velocity of blood flow in compensating for deficient oxygen carrying capacity of the blood. When the oxygen carrying capacity of the blood is diminished two mechanisms are available to maintain an adequate supply of oxygen to the tissues (22). These mechanisms may act singly or together. The first of these mechanisms consists in relatively more complete abstraction of oxygen from the blood as it passes through the capillaries (16). Normally, 100 cc. of arterial blood contain approximately 18 cc. of oxygen. Under normal basal conditions, only about 5.5 cc. are removed from the blood as it passes through the capillaries. The remaining 12.5 cc. may be regarded as reserve oxygen which can be called upon during exercise or other unusual states to prevent asphyxia of the tissues. The anemic patient in relying on this mechanism of more complete oxygen abstraction, diminishes his reserve oxygen and sacrifices this factor of safety, the degree of sacrifice depending upon the severity of the anemia.

The second mechanism which may compensate for a deficient concentration of hemoglobin consists of an increase in blood flow. If

[1] This investigation was aided by a grant from the DeLamar Mobile Research Fund of Harvard University.

the concentration of hemoglobin is 50 per cent of normal, the blood flow may be doubled. Under such circumstances, the amount of oxygen withdrawn from each cubic centimeter of blood would be one half the normal, but the total amount of oxygen given off to the tissues would be unchanged and the total reserve oxygen would be undiminished. The heart, however, would be required to expend an abnormal amount of energy, and the circulatory reserve would be encroached upon. The extent to which the pulmonary blood flow is accelerated in the presence of anemia has not previously been studied; the following investigation was therefore undertaken in order to gain further knowledge regarding the degree to which increased rate of blood flow compensates for deficient concentration of hemoglobin.

METHODS USED

Preceding studies (2, 3, 4, 5) have shown the feasibility of intravenous injection of radium C for measurement of the velocity of blood flow from the arm to the heart (arm to heart time) and of the velocity of pulmonary blood flow (pulmonary circulation time). The method appeared particularly suited to the study of the circulatory adjustment to anemia because, in contrast to circulatory minute volume estimations, the measurements are more direct and do not involve elaborate estimations of the CO_2 dissociation curves in each patient as is necessary in the carbon dioxide methods. In this research, all measurements were obtained under basal metabolic conditions. The pulse rate was counted several times before and after each test. The venous pressure was estimated according to the direct venipuncture method of Moritz and Tabora. The vital capacity of all patients was measured by means of a Collins spirometer. The hemoglobin concentration of the peripheral blood was measured by the Newcomer method. The blood plasma volume was estimated by the brilliant vital red method used by Thompson (30). In several patients with pernicious anemia observations were made when the hemoglobin concentration of the blood was low and later when, after treatment with liver extract (23), the blood more nearly approached normal.

RESULTS AND DISCUSSION

Thirty-two complete series of measurements were made in twenty-nine subjects with pernicious anemia, with secondary anemia and carcinoma, and with secondary anemia due to causes other than carcinoma (table 1). All patients were free from evidence of congestive heart failure. The patients have been divided into several groups according to the etiology of the anemia in order to learn whether the circulatory adjustment differs according to the underlying pathological condition.

The circulatory adjustment in patients with "primary" anemia and anemia secondary to diseases other than carcinoma

To clarify the relation between certain important findings, the relation between the hemoglobin and the pulse rate (fig. 1), between the pulse rate and the velocity of pulmonary blood flow (fig. 2), and the relation between the velocity of pulmonary blood flow and the hemoglobin concentration of the blood (fig. 3) were plotted in patients with primary anemia and in patients with secondary anemia not due to carcinoma. The results show that, while there are considerable variations, the velocity of blood flow through the lungs in these patients generally tends to increase in proportion to the degree of anemia. The variations may well be due to small differences in the basal metabolic rate, some investigators having found normal values, others an increase (15). Previous studies have indeed shown that the pulmonary circulation time may be affected by the metabolic rate (6, 7). The variations may also be due in part to the fact that different individuals with anemia probably rely in varying degree on the abstraction of a greater percentage of oxygen from the capillary blood.

These alterations in the velocity of blood flow are in accord with observations on the minute volume output of the heart in anemia. Plesch (26), by an indirect method, found that the total volume output was always increased roughly in proportion to the severity of the anemia. Liljestrand and Stenström (20) likewise observed a rise in the minute volume output of the heart but believed that the oxygen unsaturation of the venous blood in anemia was greater and that the increase in the minute volume output was less than that found by

TABLE 1

Measurements of the pulmonary circulation time and related functions of the circulation in patients with anemia and with polycythemia vera

Subject	Age	Vital capacity per square meter	Pulse rate	Hemoglobin	Red blood cells	Plasma volume per kilogram	Blood volume per kilogram	Arterial pressure			Circulation time			Diagnosis
								Systolic	Diastolic	Mean	Arm to heart	Pulmonary		
Group A. Patients with secondary anemia														
		cc.		*per cent*	*millions per cu. mm.*	*cc.*	*cc.*	*mm. Hg*	*mm. Hg*	*mm. Hg*	*seconds*	*seconds*	*velocity per cent of normal*	
C. H.	27	1,320	122	33	1.85			90	65	77	3.0	6.5	166	Miscarriage
H. B.	21	1,940	96	30	1.42	58.7	68.0	100	60	80	6.0	6.5	166	Miscarriage
C. M.	30	1,480	108	48	3.10			100	60	80	3.5	7.0	154	Miscarriage
J. S.	50	2,260	74		2.47	53.7	69.6	148	80	114	6.5	7.0	154	Duodenal ulcer
P. L.	27	2,200	102	54	3.58	49.5	70.0	110	80	95	5.0	8.0	135	Duodenal ulcer
H. W.	26	2,180	102	37	1.80	52.0	64.5	100	60	80	4.0	8.0	135	Miscarriage
C. M.	34	2,140	57	38	2.12	51.8	66.0	90	50	70	6.5	9.0	120	Peptic ulcer
J. C.	42	2,320	60	46	2.45	52.3	65.9	100	65	82	12.0	10.0	108	Duodenal ulcer
O. C.	58	2,290	84	62	2.85			120	80	100	12.0	10.0	108	Peptic ulcer
F. T.	65	1,170	75	37	1.67	61.7	74.6	155	85	120	8.0	10.5	103	Chronic nephritis
C. D.	72	1,830	72	60	2.78	42.5	59.6	130	80	105	3.0	14.0	77	Scurvy; arteriosclerosis
T. K.	53	1,900	62	70	3.75	53.0	83.7	110	70	90	24.5	14.5	74.5	Duodenal ulcer
Group B. Patients with pernicious anemia														
M. A.	54	1,150	82	30	1.86	58.2	75.0	110	80	95	2.5	7.0	154	
M. A.	54	1,620	66	64	3.54	37.3	56.2	100	60	80	8.0	8.0	135	
D. T.	55		70	36	2.02	75.3	90.3	110	80	95	6.5	8.5	127	
F. D.	43	1,890	76	60	2.62	61.9	89.9	116	80	98	12.0	9.0	120	
S. B.	53	1,160	68	69	2.74	48.7	70.5	120	76	98	8.0	9.0	120	
F. H.	67	1,010	87	27	0.86			118	52	85	7.0	9.0	120	
A. H.	56	1,800	86	39	1.52	54.3	65.7	100	55	77	8.0	10.0	108	
D. T.	55	1,370	66	64	2.86	49.1	65.5	130	70	100	9.0	10.0	103	
W. M.	54	2,230	63	55	2.0	59.5	80.0	110	60	85	11.0	13.0	83	Combined system disease
A. H.	56	2,030	72	70	3.2			100	60	80	17.0	17.0	64	

Group C. Patients with carcinoma														
M. E.	67	1,550	96	24	1.78	45.6	52.9	112	70	91	4.5	7.0	154	Carcinoma of pylorus
A. W.	54	1,830	70	67	4.06	55.6	90.6	116	84	100	5.0	8.0	135	Carcinoma of stomach
B. G.	70	1,050	100	59	3.60	49.8	72.1	110	60	85	5.0	11.0	98	Carcinoma of stomach
J. M.	53	1,730	84	28	1.74	54.5	63.9	140	80	110	12.5	12.0	90	Carcinoma of stomach
J. S.	65	1,680	72	55	3.70			96	58	77	7.0	12.0	90	Carcinoma of pylorus
J. H.	62	1,174	105	80	3.97			110	68	89	5.5	12.0	77	Carcinoma of stomach
P. M.	46	1,970	108	58	3.59	61.9	89.8	90	50	70	10.5	15.0	72	Carcinoma of colon
M. M.	65	1,270	84	60		51.6	74.2	100	60	80	8.5	16.0	67.5	Carcinoma of sigmoid
M. C.	76	1,150	82	31	2.70	64.1	80.0	90	45	67	4.0	16.5	65	Carcinoma of colon
P. H.	40	1,080	84	57	3.30	64.7	96.0	95	50	72	13.0	24.0	45	Carcinoma of esophagus
Group D. Patients with polycythemia vera														
E. M.	42	2,780	86	147	10.56	45.8	175.0	120	90	105	17.0	17.0		
E. M.	42	2,850	78	147	10.56	45.8	175.0	130	92	111	10.0	17.0		
P. S.	54	1,160	80	156	8.99	45.6	149.0	106	78	92	21.0	26.0		Auricular fibrillation; pericarditis

Plesch. The observations of Richards and Strauss (27) were in entire agreement with the findings of Liljestrand and Stenström (20).

Certain investigators have inferred the general state of the circulation in anemia by studying the difference in oxygen content of the arterial and venous bloods of the arm. Morawitz and Röhmer (24) observed a relatively greater loss of oxygen during anemia than nor-

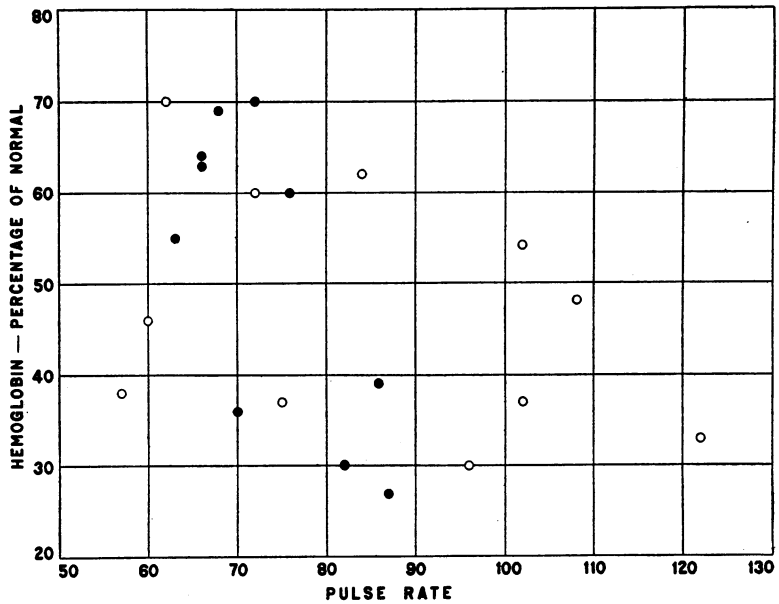

FIG. 1. RELATION BETWEEN HEMOGLOBIN CONCENTRATION (PERCENTAGE OF NORMAL) AND PULSE RATE IN PATIENTS WITH "PRIMARY" ANEMIA AND ANEMIA SECONDARY TO DISEASES OTHER THAN CARCINOMA

The solid dots refer to measurements in patients with "primary" anemia, the circles, to measurements in patients with anemia secondary to diseases other than carcinoma.

mal indicating that a certain degree of compensation in anemia is attained by increased oxygen unsaturation. They considered, that an increase in blood flow was, however, of still greater importance. Lundsgaard (21), as a result of his studies of the peripheral blood, concluded, "The results seem to show that the resting organism does not increase its circulation until all the reserve oxygen is used. This

means that the resting anemic organism does not need or use any compensation for its anemia until the hemoglobin has sunk below 30 per cent. Below that value the organism increases the blood flow in order to secure to the tissues the normal amount of oxygen."

It is questionable, however, whether results gained by the study of the blood flow through the arm can rightly be used as an index of the

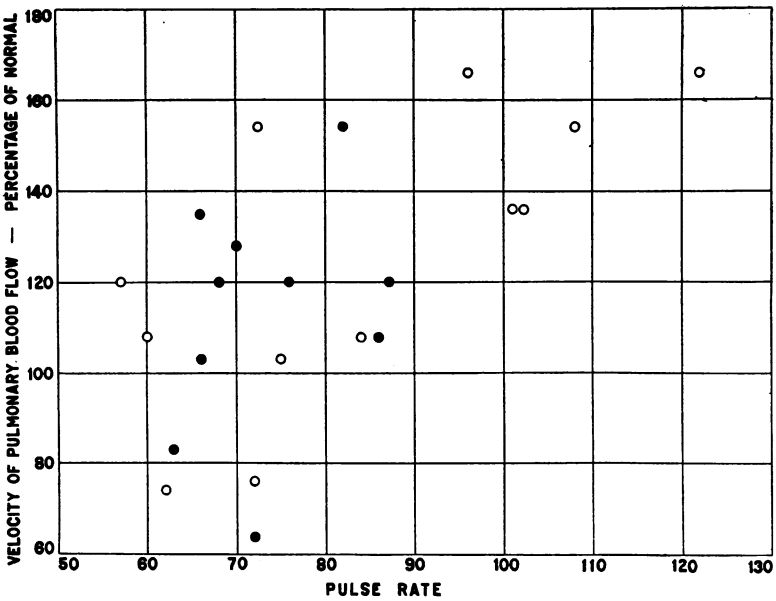

FIG. 2. RELATION BETWEEN THE PULSE RATE AND THE VELOCITY OF PULMONARY BLOOD FLOW IN PATIENTS WITH "PRIMARY" ANEMIA AND ANEMIA SECONDARY TO DISEASES OTHER THAN CARCINOMA

The solid dots refer to measurements in patients with "primary" anemia, the circles, to measurements in patients with anemia secondary to diseases other than carcinoma.

general circulatory adjustment of the body. G. N. Stewart (29) was evidently of similar opinion. He found that the volume of blood flow in the arms was diminished in anemic patients but stated that this might be due to peripheral vasoconstriction allowing the volume flowing through other parts of the body to be markedly increased.

It should be noted that the vital capacity of the lungs in our patients was moderately reduced in the absence of any signs of congestive

heart failure. Some patients complained of weakness and fatigue but these factors, according to Peabody and Sturgis (25), are not important in causing a reduction of the vital capacity of the lungs. We are unable to explain this lowering in the vital capacity, though it may well be related to the presence of an increased amount of blood in the lungs (14, 6), coincident with an increased rate of blood flow.

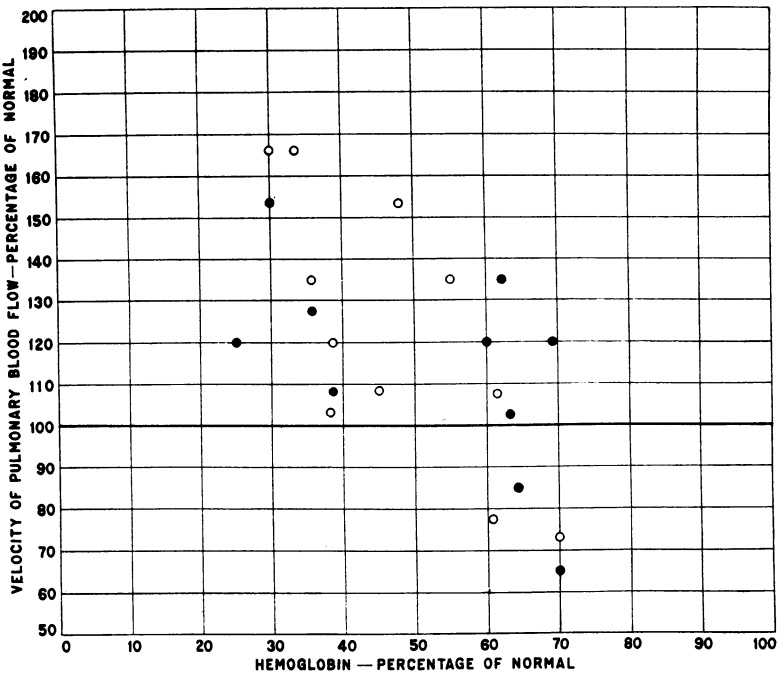

FIG. 3. RELATION BETWEEN THE VELOCITY OF PULMONARY BLOOD FLOW AND THE HEMOGLOBIN CONCENTRATION OF THE BLOOD

The solid dots refer to measurements in patients with "primary" anemia, the circles, to measurements in patients with anemia secondary to diseases other than carcinoma.

The mean plasma volume per kilogram of body weight was within the range of normal, again indicating the constancy of this characteristic of the circulation (8). The mean blood volume per kilogram was moderately decreased.

In previous communications the response of the circulation to wide

variations in basal metabolic rate in myxedema and thyrotoxicosis was studied (6, 7). The pulse rate was related more closely to changes in pulmonary blood velocity than to changes in the basal metabolic rate. Similarly, in the present study the pulse rate is more closely related to changes in velocity of the pulmonary circulation than to variations in the degree of anemia. This result is in accord with expectation for the pulse rate and velocity of blood flow are both characteristics of the general circulatory adjustment and as such are more closely related physiologically to each other than to change in the oxygen carrying capacity of the blood.

During muscular exercise in normal individuals the minute volume output of the heart rises as a linear function of the oxygen absorption, but at the same time the oxygen abstraction is on the whole more complete, though the type of work may to some extent affect the relative degrees to which these two mechanisms are employed (11, 12). In thyrotoxicosis, on the other hand, the compensation is almost entirely circulatory for the increased oxygen demands of the body are usually supplied without diminishing the oxygen tension of the mixed venous blood (19, 28). In anemia the greater the diminution in hemoglobin, the greater the extent, even at rest, to which the blood supply must be increased to supply adequate amounts of oxygen to the tissues. Under such circumstances, any muscular exercise places a relatively great burden on the cardiovascular system. This doubtless is an important factor in the frequent presence of dyspnea in patients with severe anemia, such as pernicious anemia. The clinical observations of Herrick (17), Bullrich (9), and Coombs (13) that anemic patients with angina pectoris may be relieved of the attacks of pain by improving the condition of the blood is readily understood on the basis of these considerations. The heart in such patients may be damaged to so slight an extent that it is able to maintain an adequate blood flow provided that the oxygen carrying capacity of the blood is normal. In the presence of anemia, however, the increased amount of work necessary to compensate for this condition cannot readily be accomplished, particularly since the blood supply to the heart is affected in common with that of the rest of the body.

The circulatory adjustment to secondary anemia in patients with carcinoma

Patients with anemia secondary to carcinoma were studied as a separate group because clinical experience suggests that the circulation is frequently affected adversely in this condition. Symptoms such as dyspnea, signs of congestive failure, peripheral edema, weakness and cyanosis are frequently more pronounced than one would expect on the basis of the degree of the anemia, malnutrition or toxicity (10). The findings in the group of patients studied are in accord with clinical experience. The average concentration of hemoglobin was practically the same in patients with carcinoma and with pernicious anemia, but the average velocity of pulmonary blood flow was reduced to 89 per cent of normal when carcinoma was present but was raised to 113 per cent in patients with pernicious anemia.

The pulmonary circulation time and related functions of the circulation in two patients with polycythemia vera

Since the velocity of blood flow is increased in patients with a diminished concentration of hemoglobin, it was thought to be of interest to learn whether the circulation is slow in patients with abnormally great concentrations of hemoglobin. In contrast to the unusually rapid blood flow found in the former group, two patients with polycythemia vera showed definite retardation of the blood flow below the average of normal. In one patient the extent to which slowing was related to the increased amount of hemoglobin cannot be accurately stated, for, although the patient showed no signs of congestive failure at the time of the test, fibrillation of the auricles was present. We have observed, however, that in the absence of signs of circulatory failure the blood velocity (4) may be normal, even in the presence of this abnormal mechanism. This slowing of the blood flow in polycythemia vera corresponds in degree to the diminished minute volume output of the heart observed by Liljestrand and Stenström (20). The increase in blood volume is due to the increased number of red blood cells, the plasma volume per kilogram of body weight being greatly diminished below the average of normal (18). The characteristics of the blood are the reverse of those present in anemia and the circulatory adjustment is correspondingly altered.

These findings illustrate anew the close interrelationships among apparently diverse functions of the body; in this case, among the respiratory, circulatory and metabolic systems. In a former study of the velocity of blood flow and related functions of the circulation in pulmonary emphysema evidence was presented which suggested that the circulation was accelerated to compensate for the defect in "external respiration" (31). In this communication evidence is presented which indicates that, similarly, in patients with anemia, the circulation is accelerated to compensate for failure of the "internal respiration."

SUMMARY AND CONCLUSIONS

1. The degree to which increased blood flow compensates for a deficient concentration of hemoglobin was studied in patients with pernicious anemia, with secondary anemia and carcinoma, and with secondary anemia due to causes other than carcinoma.

2. Thirty-two complete series of measurements of the vital capacity of the lungs, the blood plasma volume, the pulse rate, the arterial and venous blood pressures, and the velocity of blood flow through the lungs and from the arm to the heart were made in twenty-nine subjects.

3. In patients with "primary" anemia or with secondary anemia not due to carcinoma, the velocity of blood flow through the lungs tended to increase in proportion to the degree of anemia.

4. The increased burden on the cardiovascular system is accentuated by exertion and serves to explain the frequent presence of dyspnea in severely anemic patients and also the alleviation of angina pectoris in such patients after improvement in the condition of the blood.

5. The average concentration of hemoglobin was practically the same in patients with anemia due to carcinoma as in patients with pernicious anemia but the velocity of pulmonary blood flow in the former group was relatively slower. This serves to explain why symptoms such as dyspnea, signs of congestive failure, peripheral edema, weakness and cyanosis are frequently more pronounced in patients with carcinoma than one would expect on the basis simply of anemia, malnutrition or toxicity.

6. In contrast to the unusually rapid blood flow in patients with anemia, two subjects with polycythemia vera showed definite retarda-

tion of the blood flow below the average normal; the characteristics of the blood in this condition are the reverse of those present in anemia and the circulatory adjustment is correspondingly altered.

7. In a previous study of the velocity of blood flow and related functions of the circulation in pulmonary emphysema evidence was presented which suggested that the circulation was accelerated to compensate for the defect in "external respiration." In this communication evidence is presented which indicates that, similarly, in patients with anemia, the circulation is accelerated to compensate for failure of the "internal respiration."

BIBLIOGRAPHY

1. Bernard, Claude, Introduction a l'étude de la Médecine Expérimentale. J. B. Bailliere et Fils, Paris, 1865.
2. Blumgart, H. L., and Weiss, S., J. Clin. Invest., 1927, iv, 15. Studies on the Velocity of Blood Flow. II. The Velocity of Blood Flow in Normal Resting Individuals and a Critique of the Method Used.
3. Blumgart, H. L., and Weiss, S., J. Clin. Invest., 1927, iv, 399. Studies on the Velocity of Blood Flow. VII. The Pulmonary Circulation Time In Normal Resting Individuals.
4. Blumgart, H. L., and Weiss, S., J. Clin. Invest., 1928, v, 343. Clinical Studies on the Velocity of Blood Flow. IX. The Pulmonary Circulation Time, The Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation In Patients with Cardiovascular Disease.
5. Blumgart, H. L., and Weiss, S., J. Clin. Invest., 1928, v, 379. Clinical Studies on the Velocity of Blood Flow. X. The Relation between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons.
6. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R., J. Clin. Invest., 1930, ix, 69. Studies on the Velocity of Blood Flow. XIII. The Circulatory Response to Thyrotoxicosis.
7. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R., J. Clin. Invest., 1930, ix, 91. Studies on the Velocity of Blood Flow. XIV. The Circulation in Myxedema with a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis.
8. Bock, A. V., Arch. Int. Med., 1921, xxvii, 83. The Constancy of the Volume of the Blood Plasma.
9. Bullrich, R. A., Semana Med., 1925, ii, 1137. Influencia patogénica de los estados anémicos sobre la angina de pecho. Quoted by Herrick (17).

10. Cohn, A. E., Nelson Loose-Leaf Living Medicine, 1927, iv, 267. Thomas Nelson and Sons, New York. Etiology of Chronic Diseases of the Heart.
11. Collett, M. E., and Liljestrand, G., Skandinav. Arch. f. Physiol., 1924, xlv, 17. Variations in the Resting Minute Volume of the Heart in Man.
12. Collett, M. E., and Liljestrand, G., Skandinav. Arch. f. Physiol., 1924, xlv, 29. The Minute Volume of the Heart in Man during some Different Types of Exercise.
13. Coombs, C. F., Brit. Med. J., 1926, ii, 185. A Note on the Cardiac Symptoms of Pernicious Anemia.
14. Drinker, C. K., Peabody, F. W., and Blumgart, H. L., J. Exp. Med., 1922, xxxv, 77. The Effect of Pulmonary Congestion on the Ventilation of the Lungs.
15. DuBois, E. F., Basal Metabolism in Health and Disease. Lea and Febiger, Philadelphia, 1924.
16. Harrop, G. A., Jr., J. Exp. Med., 1919, xxx, 241. The Oxygen and Carbon Dioxide Content of Arterial and of Venous Blood in Normal Individuals and in Patients with Anemia and Heart Disease.
17. Herrick, J. B., Trans. Assoc. Am. Phys., 1927, xlii, 23. On the Combination of Angina Pectoris and Severe Anemia.
18. Keith, N. M., Rowntree, L. G., and Geraghty, J. T., Arch. Int. Med., 1915, xvi, 547. A Method for the Determination of Plasma and Blood Volume.
19. Liljestrand, G. and Stenström, N., Acta Med. Skandin., 1926, lxiii, 99. Clinical Studies on the Work of the Heart during Rest. I. Blood Flow and Blood Pressure in Exophthalmic Goiter.
20. Liljestrand, G., and Stenström, N., Acta. Med. Skandin., 1926, lxiii, 130. Clinical Studies on the Work of the Heart during Rest. II. The Influence of Variations in the Hemoglobin Content on the Blood Flow.
21. Lundsgaard, C., J. Exp. Med., 1919, xxx, 147. Studies of Oxygen in the Venous Blood. V. Determinations on Patients with Anemia.
22. Means, J. H., Medicine, 1924, iii, 309. Dyspnoea.
23. Minot, G. R., and Murphy, W. P., J. Am. Med. Assoc., 1926, lxxxvii, 470. Treatment of Pernicious Anemia by a Special Diet.
24. Morawitz, P., and Röhmer, W., Deutsch. Arch. f. klin. Med., 1908, xciv, 529. Über die Sauerstoffversorgung bei Anämien.
25. Peabody, F. W., and Sturgis, C. C., Arch. Int. Med., 1921, xxviii, 501. Clinical Studies of the Respiration. VII. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs.
26. Plesch, J., Ztschr. f. exp. Path. u. Therap., 1909, vi, 380. Hämodynamische Studien.
27. Richards, D. W., Jr., and Strauss, M. L., J. Clin. Invest., 1928, v, 161. Circulatory Adjustment in Anemia.
28. Robinson, G. C., J. Am. Med. Assoc., 1926, lxxxvii, 314. The Measurement of the Cardiac Output in Man and its Variations.

29. Stewart, G. N., Harvey Lectures 1912–13, viii, 86. J. B. Lippincott Co., Phila. Studies on the Circulation in Man.
30. Thompson, W. O., J. Clin. Invest., 1926, ii, 477. Studies in Blood Volume. I. The Blood Volume in Myxedema with a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema.
31. Weiss, S., and Blumgart, H. L., J. Clin. Invest., 1927, iv, 555. Studies on the Velocity of Blood Flow. VIII. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Pulmonary Emphysema.