

STUDY OF THE BLOOD IN CHRONIC RESPIRATORY DISEASES, WITH SPECIAL REFERENCE TO THE VOLUME OF THE BLOOD¹

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The character of the changes in the blood in cases of chronic pulmonary diseases has not been settled. Although patients with respiratory disturbances often have the appearance of those with polycythemia, it is questionable whether there is an actual increase in the blood and cell volume. Some investigators believe that the blood in these cases shows a polycythemic picture, which they believe to be due to interference with the proper pulmonary exchange of oxygen, resulting in a low tension of oxygen in the arterial blood which in turn overstimulates the bone marrow. The usual response of the blood to low oxygen tensions obtained for short periods under experimental conditions has been studied extensively. But investigations of the changes occurring in cases of chronic pulmonary diseases with or without anoxemia due to faulty pulmonary exchange are not available except in a few isolated cases. We have attempted to clarify this problem by studying a group of cases with chronic pulmonary diseases; determining not only the characteristics of the erythrocytes and the blood volume but also correlating these findings with various factors such as arterial oxygen saturation, the pulmonary capacity and its sub-divisions and the duration and severity of the disease. We feel that these observations of the volume and morphology of the blood are enhanced by other studies, to be reported later, which we have made on these patients in order better to classify and understand their functional pathology.

Well established standards of the normal morphology of the red blood cells are available in the literature, but the values for the blood volume reported by different observers, using similar technique and experimental conditions, vary markedly. We have collected in Table I the values for

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TABLE I
Values for the plasma and blood volumes collected from the literature
(Normal males)

	Number of cases	Dye	Mixing time	Hemoglobin	Cell volume	Plasma		Blood	
						Total	Per kgm.	Total	Per kgm.
			<i>minutes</i>		<i>per cent</i>	<i>liters</i>	<i>cc.</i>	<i>liters</i>	<i>cc.</i>
Mendershausen	16	Congo red	4		44.1	2.25	39.0	4.13	71.7
Seyderhelm & Lampe	6	Trypan red	3-6	86%	47.9	2.58	44.1	4.93	84.7
Rusznayk	8	Trypan red	3-6	92%		2.84	44.7	5.32	83.3
Rowntree & Brown	49	Congo red	3-6	16.4 grams	42	3.48	51	6.04	88.6
Uhlenbruck	7	Congo red	3-6			2.77	41.4	5.34	79.6
Sparks & Haden	10	Congo red	4			2.63	34.4	4.96	64.9

* Bibliography number.

the plasma and blood volume in normal male subjects reported in the literature, including only those reports dealing with the larger number of cases. All these determinations, in normal male subjects of various age groups were made by injecting a dye into the peripheral blood stream according to the method first introduced by Keith, Rowntree and Geraghty (7). The plasma volume has been variously estimated from 34 cc. to 51 cc., per kilogram and the volume of blood, from 72 cc. to 89 cc. per kilogram of body weight. Fleischer-Hanson (8), who objects to the above procedure because of inadequate mixing of the blood and dye in the time allowed, has the subject perform the so-called "mixing movements" and finds the volume of the blood as low as 49 cc. per kilogram. Because of this wide variation it was felt necessary to determine our own standards for normal individuals in order to have a basis for evaluating our study of pathological cases. A review of the literature also indicates that one must allow generous limits for normal variation.

METHODS

In this investigation the dye method of Keith, Rowntree and Geraghty (7) with the modifications as described by Hooper, Smith, Belt and Whipple (9) was used for determining the plasma volume. All the observations were made with the patient in the recumbent position, following a fast of twelve hours. A needle was inserted into the antecubital vein and 12 to 15 cc. of blood were removed without stasis. About 3 cc. of the blood were placed in an oxalated tube for hemoglobin determination, while the remaining 8 to 10 cc. of blood were placed in a centrifuge tube accurately calibrated to tenths of a cubic centimeter and containing 2 cc. of 1.6 per cent solution of sodium oxalate. The tube was stoppered and inverted several times to prevent clotting. Without removing the needle from the vein, a 1.5 per cent solution of brilliant vital red, freshly prepared and filtered, was injected into the blood stream. In each case four milligrams of the dye per kilogram body weight were introduced. Four minutes after the injection, 8 to 10 cc. of blood were removed from the antecubital vein of the opposite arm. This blood was placed in another graduated centrifuge tube containing 2 cc. of 1.6 per cent solution of sodium oxalate. This was stoppered, inverted and, along with the other tube, was centrifuged at 2700 revolutions per minute for 45 minutes. Then the hematocrit and other readings necessary for the calculation of the plasma volume were made. The standard, made from the filtered solution, and the unknown solution were then prepared for colorimetric comparison. The volumes of the plasma and blood were calculated according to the formulas derived by Hooper, Smith, Belt and Whipple (9). In all cases the hemoglobin concentration was determined on the first sample of blood by measuring the oxygen combining power according to

Van Slyke's method (10). It is possible to calculate the corpuscular volume and hemoglobin per 100 cc. of blood. We have not encountered a single reaction to the injection of the dye in 55 determinations.

The oxygen content and combining power of the arterial blood were determined in the Van Slyke manometric apparatus.

The total pulmonary capacity and its sub-divisions were measured according to the methods used in this clinic (11, 12).

DETERMINATIONS ON NORMAL SUBJECTS

The volumes of the plasma and blood were estimated on 25 normal male subjects, who were students in this University. No selective criteria as to physical characteristics were used save that the subjects were free from any discernible disease. A clinical history was obtained from each individual and a physical examination made.

The physical characteristics and the values for the blood volume and its components of these subjects are summarized in Table II. The weight observed in this group corresponds closely with the average ideal weight calculated from age and height.

TABLE II

The volumes of the plasma and blood in 25 normal males with age and physical characteristics of the subjects
(Dye method—Brilliant vital red)

	Mean	Standard deviation	Coefficient of variation	Range
Age, years.....	26 ± .31‡	2.26 ± .22‡	8.7	22 - 32
Weight, kgm.....	76.2 ± 1.22	9.07 ± .87	11.9	60.6 - 104
Height, cm.....	178.2 ± .55	4.07 ± .39	2.3	170 - 186.5
Surface area, square meters...	1.93 ± .02	.11 ± .01	5.7	1.73- 2.19
Plasma volume, liters.....	3.22 ± .06	.42 ± .04	13.0	2.21- 4.06
Plasma/kgm., cc.....	42.8 ± .59	4.4 ± .42	10.3	34.7 - 50.3
Plasma/square meter, liters...	1.69 ± .02	.17 ± .02	10.1	1.28- 1.88
Blood volume, liters.....	5.93 ± .10	.77 ± .08	12.9	3.95- 7.49
Blood/kgm., cc.....	79.1 ± .97	7.19 ± .69	9.1	62.1 - 91.1
Blood/square meter, liters...	3.10 ± .04	.30 ± .03	9.8	2.28- 3.42
Cell volume, liters.....	2.69 ± .05	.39 ± .04	14.5	1.66- 3.38
Cells/kgm., cc.....	35.8 ± .49	3.62 ± .06	10.1	26.0 - 44.7
Cells/square meter, liters....	1.40 ± .02	.16 ± .02	11.4	.96- 1.68
Total hemoglobin, grams.....	982 ± 20.2	149.9 ± 14.3	15.2	590 - 1216
Hemoglobin/kgm., grams....	12.9 ± .20	1.47 ± .14	11.3	9.3 - 15.3
Hemoglobin/square meter, grams.....	499 ± 8.8	64.9 ± 6.2	13.0	341 - 590
Hemoglobin per 100 cc., grams	16.2 ± .11	.84 ± .08	5.1	14.9 - 17.7
Plasma, per cent.....	54.3 ± .32	2.38 ± .23	4.3	47.9 - 58.4
R.B.C., per cent.....	45.1 ± .31	2.29 ± .22	5.1	40.9 - 51.3

‡ Probable error.

The mean value of the *plasma volume* was 3.22 liters with variation between 2.21 and 4.06 liters, while the plasma per kilogram of body weight was 42.8 cc., a value just about midway between the lowest and the highest values reported in the literature.

The *blood volume* was observed to vary markedly both in total volume and volume per kilogram of body weight. The mean value of the former was 5.93 liters varying from 3.95 to 7.49 liters, while that of the latter was 79.1 cc. with variation between 62.1 and 91.1 cc. The mean value for blood volume per kilogram of body weight was again found to be about midway between the extremes in the literature.

The total volume of the cells and total hemoglobin varied markedly from individual to individual. The mean value for the *cell volume* was 2.69 liters while the value for each kilogram of body weight was 35.8 cc. The mean value for the *hemoglobin per kilogram of body weight* was 12.9 grams, a figure almost two grams lower than that reported by Rowntree and Brown (4) in a similar group of cases.

The mean value for the *red blood cell percentage* was 45.1 with variation between 40.9 and 51.3. Determinations of *hemoglobin per 100 cc. of blood* gave a mean value of 16.2 grams. These results correspond very closely with those collected from papers in the literature and reported by Wintrobe (13), who found in 381 cases (all males) that the average value for the hematocrit was 46.3 per cent and in 583 cases the hemoglobin per 100 cc. of blood was 16.0 grams.

The correlation of the blood volume and its components to body weight and body surface area is given in Table III. The most significant correlation exists between the body weight and the volume of the blood and its

TABLE III
Correlation of blood volume with various body measurements

	Correlation coefficient
Total blood volume to body weight.....	.7297 \pm .0631‡
Total blood volume to surface area.....	.6756 \pm .0733
Total plasma volume to body weight.....	.6954 \pm .0697
Total plasma volume to surface area.....	.6387 \pm .0798
Total cell volume to body weight.....	.8014 \pm .0483
Total cell volume to surface area.....	.7840 \pm .0519
Total hemoglobin to body weight.....	.7700 \pm .0549
Total hemoglobin to surface area.....	.7648 \pm .0560

‡ Probable error.

components. This finding indicates that knowing the body weight of an individual in kilograms one can predict the total blood volume with a fair degree of accuracy by means of the regression formula derived from the coefficient of correlation.³ From the predicted blood volume and the nor-

³ The regression formula is:

$$\text{Total volume} = (\text{Kilograms body weight} \times 0.06) + 1.41.$$

mal mean values for hematocrit and hemoglobin per 100 cc. of blood, one can calculate the expected cell and plasma volumes and the total hemoglobin. Rowntree and Brown (4) found the best correlation between surface area of the body and the plasma and blood volume.

The total plasma, blood and cell volume and the total hemoglobin of the 25 normal subjects were calculated from the regression formulas and compared with the observed values for the purpose of establishing the normal range of variability. Of the observed blood volumes 92 per cent fell within the limits plus and minus 15 per cent of the calculated values; while of the observed plasma and cell volumes and total circulating hemoglobin 88 per cent were within this same limit. Individual variations around plus and minus 15 per cent of the calculated may not be significant but when the mean value for a group of pathological cases approaches this limit, the difference becomes of some importance.

DETERMINATIONS ON CASES WITH CHRONIC PULMONARY DISEASES

Literature

Blood volume determinations have been made both by the carbon monoxide and dye methods on patients with chronic respiratory diseases. In five cases with chronic bronchitis, emphysema and asthma, studied by Plesch (14) the average blood volume by the carbon monoxide method was 72 cc. per kilogram of body weight. This was 35 per cent greater than the values which he found in nine normal subjects. These values are of course low when compared with those that one obtains by means of the dye method; a difference found repeatedly by many investigators. Uhlenbruck (5) using the dye method (congo red), confirmed the results of Plesch. He estimated the volume of the blood and plasma in 7 normal males and found mean values of 79.6 cc. and 41.4 cc. per kilogram of body weight respectively. In 8 male patients with emphysema and asthma this investigator found an average blood volume of 101 cc. per kilogram of body weight with extreme variations of 78 and 147 cc. and an average plasma volume of 53 cc. per kilogram, an increase in blood volume of 27 per cent and an increase in the plasma volume of 28 per cent. Lemon (15) reported 12 cases (11 males and 1 female) with pulmonary emphysema, in which he determined not only the volume of the plasma and blood but also the arterial oxygen saturation, the vital capacity and the characteristics of the erythrocytes. He found that the mean value for the blood volume per kilogram of body weight was only slightly higher (4 cc.) than that of the normal group. In several cases there was evidence of increase in the concentration of the blood, i.e. increase in the volume of cells without increase in the blood volume. Along with the concentration of the blood he observed a definite increase in the hemoglobin content of the erythrocytes. Arterial blood was obtained in 7 cases and, in all, the satu-

ration was less than 95 per cent. No correlation was demonstrated between the decrease in the oxygen saturation of the arterial blood and the alterations in the blood volume or between decrease in vital capacity and changes in the blood volume. None of the cases which he studied simulated polycythemia vera. So far as we can find no one has reported determinations of blood volume in a group of cases with pulmonary fibrosis.

Material

Determinations of plasma and blood volume and morphology of the cells were made in 16 cases with chronic pulmonary emphysema and in 14 cases of pulmonary fibrosis. The major purpose of this study was to attempt to correlate these findings with the clinical condition of the patient, the oxygen saturation of the arterial blood and the pulmonary capacity.

Emphysema. The 16 patients in this group had varying degrees of emphysema associated with chronic bronchitis, bronchiectasis or asthma. The physical characteristics, symptoms and signs, with interpretations of the roentgenograms of the chest are given in Table IV. The age of the individuals varied from 31 to 59 years. None of the patients was particularly obese; many of the subjects weighed less than their "ideal" weight calculated according to the height and age. The average weight of the group was 6 kilograms below that of their "ideal" weight. All of the patients except one complained of cough. Dyspnea was a symptom of all the subjects, and in two it was present during rest. All but three had asthmatic attacks. The duration of the symptoms varied from 1 to 25 years. None of the patients complained of nervous or psychic symptoms. Cyanosis was observed in half the cases; clubbing of the fingers was found in 6 of the 16 subjects. The spleen was not palpable in any of these individuals. The degree of emphysema was estimated from the relative values of the residual air and the total pulmonary capacity. The blood pressure was within normal limits in all subjects. The electrocardiogram was normal in all except Case 1, in which there was evidence of myocardial damage, and in Cases 13, 14 and 15, in which left ventricular preponderance was indicated.

Fibrosis. In 10 of the 14 cases, the fibrosis was suspected to be due to inhalation of silica. The etiology of the fibrosis in the remaining cases is not known. One patient had arteriosclerotic heart disease which was well compensated at the time of the examination; another, Case 22, had a secondary anemia. The clinical observations in this group of patients are summarized in Table V. The age of the subjects varied from 32 to 65 years. The average "ideal" weight of the group was 68.6 kilograms as compared with that of the observed which was 67.7 kilograms. A high percentage of the patients complained of cough and dyspnea, while only two of them (Cases 19 and 24) gave a history of asthma. The duration

TABLE IV
Clinical observations made on 16 cases of pulmonary emphysema

Case	Age years	Wt. kgm.	Height cm.	Cough	Dyspnea	Asthma	Cyanosis	Duration of symptoms	Club- bing of fingers	Degree of em- physema*	Diagnosis	X-ray findings
1	51	52.0	157	++	++	0	0	1 year	++	+++	Bronchitis Emphysema	Increased linear markings in both lung fields.
2	54	60.8	174.5	+	++	++	+	Asthma 20 years	0	+++	Asthma Emphysema	Slight increase in linear markings of both lung fields.
3	41	58.4	179.5	++	+++	++	+	2 years	0	+++	Bronchiectasis Asthma Emphysema	Increased linear markings. After lipiodal definite evidences of bronchiectasis.
4	44	54.0	157.5	++	++	+++	+	2 years	-	++	Asthma Emphysema	Increased lung markings; local areas of increased radiability; slight amount of rib flaring.
5	40	49.7	160.5	+++	++	++	0	2 years	+	+	Bronchitis Asthma Emphysema	Pulmonary markings were greatly exaggerated.
6	38	81.2	159.5	++	++	++	0	?2 years	++	++	Bronchitis Asthma Emphysema	Some increase in linear markings.
7	41	54.4	152.5	+	+	++	0	Every winter 10 years	+	++	Bronchitis Asthma Emphysema	Linear markings increased. Increased radiability of both lung fields.
8	31	46.0	159.0	++	++	++	+	3 years	+	++	Emphysema Asthma	Exaggeration of lung markings, particularly in the right lung.

* Established according to alterations in the pulmonary capacity and its sub-divisions.

TABLE IV (continued)

Case	Age	Wt.	Height	Cough	Dyspnea	Asthma	Cyanosis	Duration of symptoms	Clubbing of fingers	Degree of emphysema*	Diagnosis	X-ray findings
9	32 years	42.6 kgm.	150.0 cm.	0	+	++	0	12 years	0	++	Asthma (Allergic) Emphysema	Increased radiability at the lung bases; flaring of rib cage.
10	44	79.4	177.2	++	++	++	+	13 years	-	+++	Emphysema Asthma	General increase in linear markings. Diaphragms low; slight amount of rib bulging.
11	59	83.2	169.5	+	+++	++	++	25 years	0	+++	Asthma Emphysema	Large lung fields; increased lung markings; increased radiability at the lung bases.
12	52	67.4	176.0	+++	++	++	0	5 years	0	++	Bronchitis Asthma Emphysema	Increased radiability of lung fields; moderate amount of rib flaring; low diaphragms.
13	49	76.6	171.5	++	++	++	+	2 years	0	++	Bronchitis Asthma Emphysema	Increased linear markings. Hilus shadows enlarged.
14	36	78.0	165.0	++	+	+	+	14 years	+	+	Bronchiectasis Emphysema Asthma	Increased linear markings; increased radiability of lung bases. Definite saccular bronchiectasis at both bases after lipiodal.
15	48	69.4	163.4	+	++	0	0	3 years	0	+	Bronchitis Emphysema	Slight increase in linear markings; Slight flaring of rib cage.
16	45	57.0	172.5	++	+	0	0	Several years	0	+	Bronchitis Emphysema	Exaggerated lung markings, more pronounced on the right associated with pleural thickening.

TABLE V
Clinical observations made on 14 cases of pulmonary fibrosis

Case	Age years	Wt. kgm.	Height cm.	Cough	Dyspnea	Dust exposure	Cyanosis	Club- bing of fingers	Duration of symptom	Examination of chest	Diagnosis	X-ray findings
17	45	70.0	166.0	+	++	Coal miner 5 years	0	0	2 years	Musical râles at bases	Fibrosis of lungs	Increased linear mark- ings.
18	41	70.8	177.0	++	0	0	0	0	?	0	Fibrosis (no etiological factor)	Pronounced exaggera- tion of lung markings and feathering.
19	48	48.8	154.0	++	+++	Sand blasting 6 years	+	+	5 years	Coarse bub- bling râles	Fibrosis Bronchitis	Marked increase in lin- ear markings. Hilus shadows enlarged.
20	47	66.8	165.4	0	+	Sand blasting 2 years	0	0	2 years	Negative	Fibrosis Emphysema (?)	Both lung fields show diffuse mottling and feathering. Hilus shad- ows increased. Bases show increased radia- bility.
21	47	56.2	152.6	+	++	Coal miner 26 years Some drilling or rock	0	0	3 years	Percussion note impaired with fine râles over right lung posteriorly	Fibrosis	Upper lung fields show massive nodular shad- ows. Increased radia- bility of bases.
22	42	73.2	174.0	+++	++	Salesman Spraying of paints & lacquer	0	0	3 years	Fine râles at both bases	Fibrosis Secondary anemia	Increased linear mark- ings. Slight mottling in both lungs.
23	36	55.0	163.0	+	++	Sand blasting 5 years	+	0	3 years	Scattered tran- sient râles	Fibrosis	Mottling throughout both lungs.

TABLE V (continued)

Case	Age years	Wt. kgm.	Height cm.	Cough	Dyspnea	Dust exposure	Cyanosis	Club- bing of fingers	Duration of symptoms	Examination of chest	Diagnosis	X-ray findings
24	43	55.0	158.0	+++	+++	Silica for 13 years	0	0	2 years	Bronchial breath sounds at left apex and right base. Râles both bases	Fibrosis	Coarse mottling through- out both lungs.
25	33	76.0	178.5	+	++	Sand blasting 5½ years	+	0	1 year	Few scattered râles	Fibrosis	Diffuse coarse mottling throughout both lungs. Confluent lesions in up- per lung fields
26	38	61.0	168.0	+	+	0	+	0	1 year	Negative	Fibrosis Emphysema	Increased linear mark- ings. Increased radia- bility right upper.
27	56	72.2	158.0	+	+++	Iron moulder 7 years	+++	++	1 year	Breath sounds harsh. No râles	Fibrosis	Mottling and feathering throughout both lungs.
28	57	86.2	174.0	0	++ 6 months	Moulder (1896-1917)	+++	+	12 years "tired feeling"	Negative	Fibrosis	Fine feathering through- out both lungs.
29	65	68.8	171.5	+	+	Sand, Stone cutter for 10 years	+	0	2 years	Negative	Fibrosis	Infiltration of right lung. Fine mottling through- out.
30	32	90.2	165.0	+	+	Sand blasting 7 months	0	0	3 months	Scattered râles	Fibrosis	Diffusely accentuated lung markings.

of symptoms varied from 3 months to 12 years. The duration of exposure to silica in the patients suspected of having pneumokoniosis varied from 7 months to 25 years. One patient (Case 28) complained of muscular pains and dizziness. Cyanosis was observed in half and clubbing of the fingers in 3 of the 14 cases. The blood pressure was within normal limits except in Cases 19 and 30 where it was 140/100 and 160/105 respectively. Electrocardiograms showed left ventricular preponderance in Cases 17, 18 and 26 while a preponderance of the right ventricle was found in only one (Case 17). The spleen was not felt in any of the subjects.

Results

Emphysema. In Table VI are presented the individual and the mean values for the total volume and the volume per kilogram of body weight for the blood, plasma, cells and circulating hemoglobin. The total *blood volume* varied between 3.18 and 7.27 liters with a mean value of 4.87 liters. The mean value of the blood volume per kilogram of body weight was 76.7 cc., a figure somewhat below that of the normal subjects. The extremes were 68.4 and 91.6 cc. All the observations fell within normal limits as shown in Figure 1. The mean value of the *plasma volume* per kilogram was slightly below that of the normal, 40.7 cc. as compared with 42.8 cc. On the other hand the mean value of *cell volume* per kilogram in the pathological cases was 35.5 cc., which was approximately the same as that of the normal group. Only two observations were slightly outside the normal limits as shown in Figure 1. The mean value for the *hemoglobin per kilogram of body weight* was 12.5, slightly below the normal; with 2 cases beyond the lower limits of normal. (Figure 2.) The *hemoglobin per 100 cc. of blood* varied between 11.6 and 18.7 grams with a mean of 16.2 grams, which is identical with that of the normal. The *hematocrit* readings of cell volume also varied markedly between 38.5 to 52.6 per cent with a mean value of 46.3 per cent. We find then, in this group of cases with emphysema, a slight though not significant decrease in the blood and plasma volume and the hemoglobin per kilogram of body weight, while the cell volume remains the same.

Fibrosis. The results in a study of 14 cases of chronic pulmonary fibrosis are tabulated in Table V. In this group we find a definite increase in the mean values of *blood* and *cell volume* per kilogram of body weight, the former mean value being 88 cc. as compared with 79.1 cc. of the normal group; while the latter value was 45.2 cc. compared with the normal value of 35.8 cc. It is evident from Table VI and Figure 1 that the mean values of the whole group are high due to marked increase in the volume of the blood and cells in three (Cases 19, 27 and 28) of the fourteen cases while in the remaining ones the values obtained were within normal limits. The mean value for the *plasma volume* was 42.4 cc., approximately that of the

TABLE VI
Results of the determination of blood volume in 30 cases of chronic pulmonary diseases

Case	Total blood volume liters	Blood/kgm. cc.	Total plasma volume liters	Plasma/kgm. cc.	Total cell volume liters	Cell volume/ kgm. cc.	Total hemoglobin grams	Hemoglobin/ kgm. grams	Hemoglobin/ 100 cc. grams	Hematocrit per cent
	Mean and standard deviation of 25 normal subjects									
	5.93 ± .77*	79.1 ± 7.19	3.22 ± .42	42.8 ± 4.4	2.69 ± .39	35.8 ± 3.62	982 ± 149.9	12.94 ± 1.47	16.2 ± .84	45.1 ± 2.29
Pulmonary emphysema										
1	3.90	73.5	2.20	41.4	1.76	33.2	640	12.1	16.4	45.2
2	5.30	86.2	2.90	47.1	2.37	38.5	949	15.5	17.9	44.7
3	4.99	85.4	2.78	47.6	2.16	36.9	886	15.2	17.8	43.2
4	3.76	69.6	1.79	33.1	1.95	36.1	648	12.0	17.2	51.7
5	3.80	76.5	1.76	35.4	2.00	40.2	709	14.3	18.7	52.6
6	6.42	79.1	3.21	39.5	3.17	39.0	1029	12.7	15.9	49.4
7	3.86	71.0	1.93	35.9	1.91	35.1	685	12.6	17.8	49.4
8	3.18	69.2	1.92	41.8	1.23	26.8	370	8.0	11.6	38.7
9	3.55	83.3	1.96	46.0	1.57	36.9	546	12.8	15.4	44.1
10	7.27	91.6	3.68	46.3	3.54	44.6	1181	14.9	16.2	48.7
11	6.03	72.5	3.55	42.7	2.44	29.3	865	10.4	14.4	40.5
12	4.65	69.1	2.69	39.9	1.94	28.8	621	9.2	13.4	41.7
13	5.24	68.4	2.86	37.3	2.34	30.6	876	11.4	16.7	44.7
14	6.85	87.8	3.71	47.6	3.10	39.7	1089	14.0	15.9	45.2
15	4.84	69.7	2.31	33.3	2.49	35.9	833	12.0	17.2	51.5
16	4.27	74.9	2.15	37.7	2.09	36.7	726	12.7	16.9	48.9
Mean standard deviation	4.87±1.20*	76.7±7.9	2.59±.65	40.7±5.60	2.25±.36	35.5±4.70	789±213	12.5±1.94	16.2±1.87	46.3±3.59

* Standard deviation.

TABLE VI (continued)

Case	Mean and standard deviation of 25 normal subjects									
	Total blood volume liters	Blood/kgm. cc.	Total plasma volume liters	Plasma/kgm. cc.	Total cell volume liters	Cell volume/ kgm. cc.	Total hemoglobin grams	Hemoglobin/ kgm. grams	Hemoglobin/ 100 cc. grams	Hematocrit per cent
	5.93 ± .77*	79.1 ± 7.19	3.22 ± .42	42.8 ± 4.4	2.69 ± .39	35.8 ± 3.62	982 ± 149.9	12.94 ± 1.47	16.2 ± .84	45.1 ± 2.29
Pulmonary fibrosis										
17	6.15	91.4	3.47	51.6	2.64	39.2	934	13.9	15.2	42.9
18	5.98	84.4	2.96	41.7	2.99	42.2	1017	14.3	17.0	50.0
19	4.70	96.4	1.92	39.4	2.75	56.8	862	17.6	18.3	58.5
20	5.41	81.0	2.80	41.9	2.57	38.5	861	12.90	15.9	47.4
21	3.99	71.0	2.05	36.5	1.91	34.0	627	11.16	15.7	47.8
22	4.56	62.3	2.39	32.6	2.30	31.4	712	9.73	15.6	41.0
23	4.54	82.5	2.52	45.8	1.99	36.2	676	12.3	14.9	43.8
24	4.57	83.1	2.47	45.0	2.08	37.8	684	12.4	15.0	45.4
25	6.54	86.1	3.20	42.1	3.29	43.3	1102	14.50	16.8	50.3
26	5.64	92.5	3.00	49.2	2.59	42.5	809	13.26	14.3	45.8
27	7.94	108.5	3.29	45.5	4.56	63.1	1580	21.8	19.9	57.4
28	11.72	135.9	3.59	41.6	8.06	93.5	2494	28.9	21.3	68.8
29	5.86	85.1	3.27	47.5	2.59	37.6	921	13.4	15.7	44.2
30	6.42	71.1	3.04	33.7	3.35	37.1	1090	12.1	17.0	52.1
Mean standard deviation	6.00±1.87*	88.0±17.80	2.85±.52	42.4±5.63	3.12±1.51	45.2±15.8	1026±469	14.9 ±4.82	16.6±2.05	49.7±7.06
Both groups mean standard deviation	5.3 ±1.65*	82.0±14.12	2.70±.65	4.18±5.4	2.67±1.28	39.3±12.8	916±375	13.33±3.60	16.4±1.87	47.8±5.85

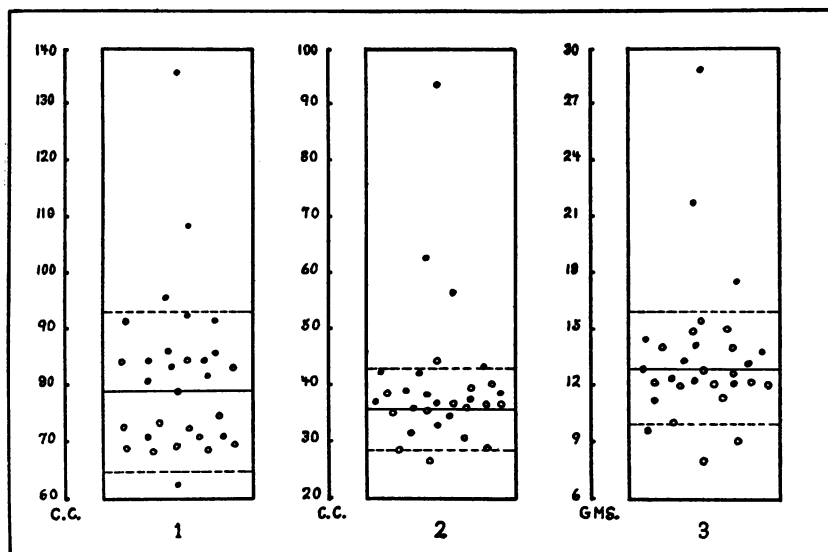


FIG. 1. DETERMINATIONS OF BLOOD AND CELL VOLUME AND HEMOGLOBIN PER KILOGRAM OF BODY WEIGHT IN 30 CASES OF CHRONIC RESPIRATORY DISEASES.

The mean values for the normal subjects are represented by the unbroken lines, while the broken ones show the deviations from the mean. Circles indicate cases with emphysema. Dots, those with fibrosis.

1. Blood volume. 2. Cell volume. 3. Hemoglobin.

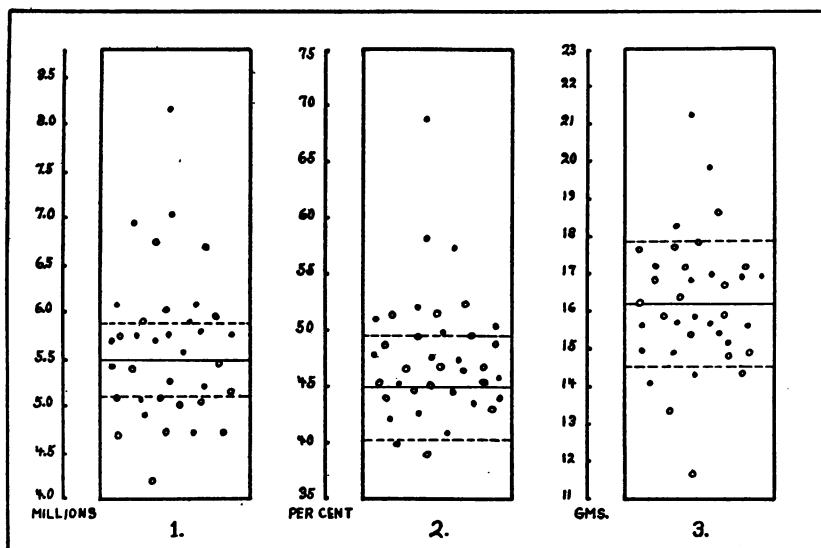


FIG. 2. ERYTHROCYTE COUNT, HEMATOCRIT, AND HEMOGLOBIN PER 100 CC. OF BLOOD IN 30 CASES OF PULMONARY EMPHYSEMA AND FIBROSIS

1. Red blood cell count per cubic millimeter.

2. Hematocrit.

3. Hemoglobin per 100 cc. of blood.

normal group. Although the values for the *hemoglobin per kilogram of body weight* varied widely, the mean value was 2 grams higher than that of the normal subjects. Here again Cases 19, 27 and 28 were definitely above the normal limits while Case 22 was slightly below, as illustrated in Figure 1. Likewise the mean value of the *hemoglobin per 100 cc. of blood* was somewhat above that of the normal group, while in the same three cases mentioned above the hemoglobin was elevated. Along with the above findings we found the mean for the *hematocrit* somewhat increased, 49.7 per cent as compared with the normal of 45.1 per cent, while 6 of the cases showed an abnormally high value (Figure 2.)

The calculated values based on body weight, and the observed values for the total blood, plasma and cell volume and hemoglobin in the 30 pathological cases are represented in Figure 3. This shows graphically

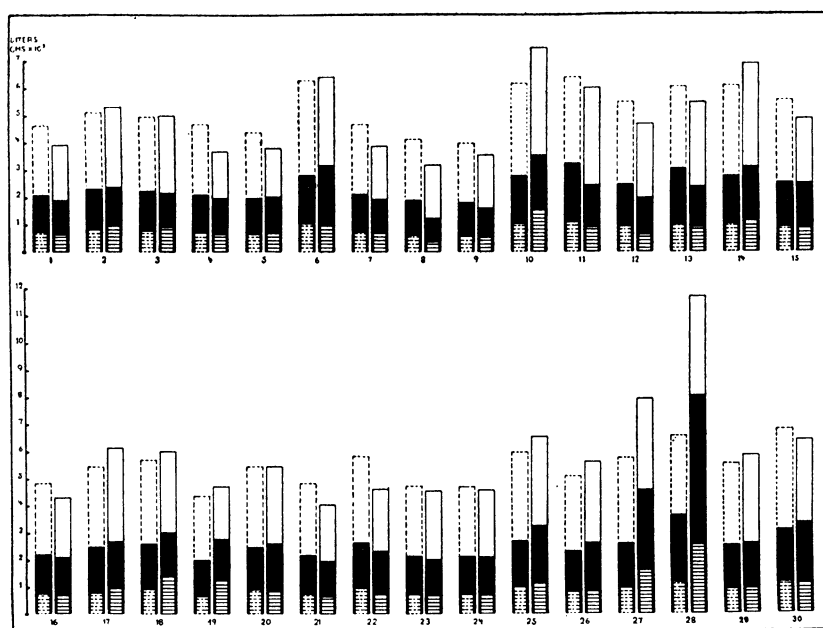


FIG. 3. CALCULATED AND OBSERVED BLOOD VOLUME IN CASES OF PULMONARY EMPHYSEMA AND FIBROSIS

Cases 1 to 16 inclusive are those with emphysema; from 17 to 30 inclusive, cases of fibrosis. Each case is represented by two columns. The one on the left, with broken lines is the predicted while the right hand column is the observed volume. The white area is plasma; the black, cell volume while the transverse lines represent the total hemoglobin.

that there are no significant variations in cases of pulmonary emphysema (Cases 1 to 17) while in the group with pulmonary fibrosis Cases 27 and

28 show evidence of hydremic plethora ⁴ and Case 19 shows an increase in the blood and cell volume and hemoglobin while the plasma is slightly reduced.

When the two groups are taken together we find that the mean values for the blood and cell volume, the total hemoglobin and the hematocrit are slightly above those observed in the normal subjects, while the plasma volume is slightly decreased; thus showing slight concentration of the blood.

The mean values for the blood, plasma and cell volume and circulating hemoglobin expressed in terms of cubic centimeters per kilogram of body weight for the three groups (normal, emphysema, and fibrosis) are compared graphically in Figure 4. A slight decrease in the blood and plasma

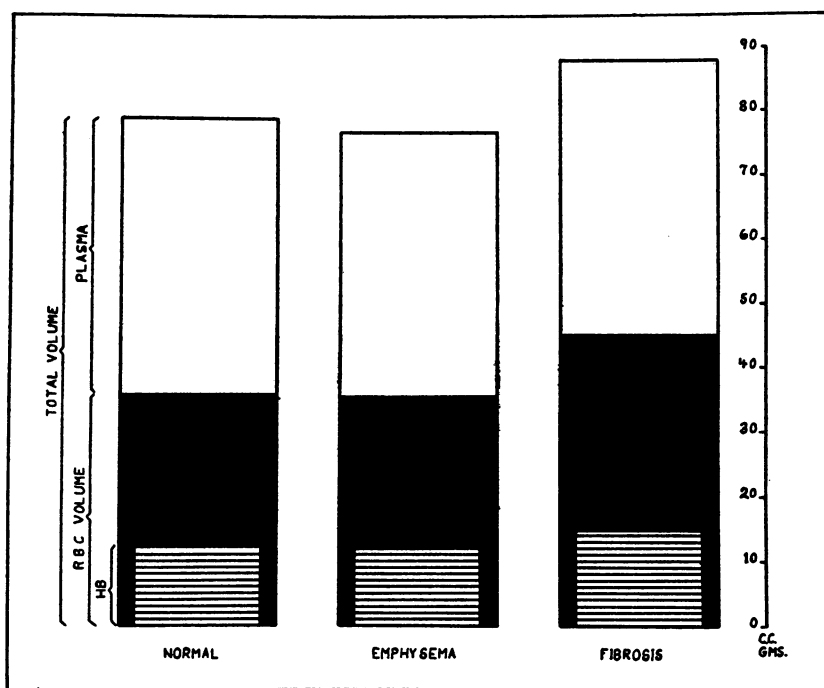


FIG. 4. MEAN VALUES FOR THE BLOOD VOLUME AND ITS COMPONENTS PER KILOGRAM OF BODY WEIGHT

volume is evident in the cases of emphysema while the cell volume and hemoglobin are practically identical with the normal group. On the other hand, the cases with pulmonary fibrosis show an increase in mean values of 11 per cent in the blood volume, of 26 per cent in the cell volume and of 15.5 per cent in hemoglobin as compared with the normal, while no abnormality in the mean plasma volume was observed.

⁴ Same as polycythemic hypervolemia used by Rowntree, designating increase of the volume of blood and cells above the limits for normal individuals.

RELATIONSHIP OF BLOOD VOLUME TO VARIOUS FACTORS

Duration and severity of symptoms. Those cases which showed an increased blood and cell volume had moderate or severe respiratory disability, but not all the patients complaining of marked dyspnea and severe asthmatic attacks showed abnormality in the volume of the blood. No definite relationship could be demonstrated between alteration in the blood volume and duration of symptoms. For instance, in Case 27 who had had symptoms for only one year, a blood volume of 108.5 cc. per kilogram of body weight was found.

Arterial oxygen saturation. The carbon dioxide and oxygen content and oxygen combining power of the arterial blood was determined in 22 of these cases. All except 6 were found to have an oxygen saturation less than 93 per cent, with extremes of 67 and 98 per cent. The oxygen saturation in Cases 19, 27 and 28 which showed an increase in blood volume was found to be very low, 80.6, 67.2 and 81.1 per cent respectively, while in Cases 1, 2, 3 and 11 in which the arterial oxygen saturation ranged between 74 and 84 per cent there was no increase in blood volume. In the group of cases in which the arterial oxygen saturation was below 90 per cent, the blood volume per kilogram body weight was increased as shown in Table VII.

Pulmonary capacity. That no relationship exists between decrease in vital capacity and changes in the blood volume, hematocrit and hemoglobin is shown in Table VII. The decrease in vital capacity varied between 16.5 and 71.8 per cent, all values being beyond the limit of normal variation which is considered to be 15 per cent. No correlation was found between the ratio of residual air to total pulmonary capacity and alterations in the blood volume or any of its components. The ratio varied between 23.6 and 73.4 per cent with only 8 cases or 35 per cent within normal limits.

CHARACTERISTICS OF THE ERYTHROCYTES

Very few studies have been made on the characteristics of the red blood cells of patients suffering from pulmonary emphysema and fibrosis. In 22 cases of pulmonary emphysema Price-Jones (16) found the size of the red cell larger than in a corresponding group of normal subjects used as controls. The mean diameter of the erythrocytes in the former group was $7.69\ \mu$ while in the latter it was $7.24\ \mu$, an increase which the author believed significant. Lemon (15) found an increase of 20 per cent in the corpuscular hemoglobin in 12 cases of chronic pulmonary emphysema, while the volume of the individual cells was not significantly increased. The average number of red blood cells in each cubic millimeter was 5.02 millions with a range between 4.05 and 6.86 millions.

The results of a study of the characteristics of the erythrocytes in 36 cases of pulmonary emphysema and fibrosis are summarized in Table VIII.

TABLE VII
Relationship of changes in blood volume to various factors

Arterial saturation	Number of cases	Blood per kgm.	Cell volume	Hemoglobin per 100 cc.	Decrease in vital capacity	Number of cases	Blood per kgm.	Cell volume	Hemoglobin per 100 cc.	Residual air to total capacity	Number of cases	Blood per kgm.	Cell volume	Hemoglobin per 100 cc.
<i>per cent</i>		<i>cc.</i>	<i>per cent</i>	<i>grams</i>	<i>per cent</i>		<i>cc.</i>	<i>per cent</i>	<i>grams</i>	<i>per cent</i>		<i>cc.</i>	<i>per cent</i>	<i>grams</i>
95-100	4	77.5	49.2	17.03	10-20	5	86.1	47.6	16.37	20-30	6	89.6	48.7	16.36
90-95	10	75.0	45.7	15.69	20-30	5	92.6	51.4	17.46	30-40	9	78.8	49.0	16.70
85-90	1	83.1	46.2	15.34	30-40	6	79.6	46.8	16.19	40-50	7	81.2	46.7	15.91
80-85	5	92.9	51.5	17.65	40-50	9	77.2	45.2	15.56	50-60	3	91.1	49.3	16.79
75-80	1	85.4	43.2	17.76	50-60	7	79.0	44.2	15.35	60-70	3	75.0	45.0	15.58
70-75	1	108.5	57.4	19.9	60-70	5	87.7	49.3	16.73	70-80	2	73.0	42.9	15.39

TABLE VIII
Characteristics of the erythrocytes in 36 cases of pulmonary emphysema and fibrosis

	Normal mean*	Emphysema (18 cases)		Fibrosis (18 cases)		Both groups (36 cases)	
		Mean \pm standard deviation	Coefficient of variation	Mean \pm standard deviation	Coefficient of variation	Mean \pm standard deviation	Coefficient of variation
Red blood cells, millions.....	5.50	5.39 \pm 0.68†	per cent 12.6	5.87 \pm 0.80†	per cent 13.6	5.70 \pm 0.80†	per cent 14.0
Corpuscular volume, cubic microns...	82.2	86.8 \pm 9.95	11.4	83.5 \pm 6.56	7.8	84.5 \pm 8.46	10.0
Corpuscular hemoglobin, grams X 10 ⁻¹²	28.8	30.1 \pm 3.16	10.5	27.9 \pm 2.45	8.7	28.9 \pm 2.87	9.9
Corpuscular hemoglobin Concentration, per cent	34.2	34.7 \pm 2.64	7.6	33.4 \pm 2.65	12.6	34.2 \pm 2.65	7.7

* Mean of normal values in 352 males (18 to 30 years) calculated from Osgood, Wintrobe and Foster.

† Standard deviation.

The blood volumes of 30 of these cases are reported above. The mean value for the number of red cells per c.mm. in both groups was 5.70 millions, a slight increase over that of the normal (5.50 millions) calculated in 352 males reported by Osgood (17), Wintrobe (18), and Foster and Johnson (19). The mean value for the group with emphysema was 5.39 millions a figure slightly below the normal value while that for the group with fibrosis was 5.87 millions, which is definitely above the normal. The extremes in the two groups were 4.2 and 8.17 millions. As illustrated in Figure 2, an equal number of cases fell below as above the limits of normal.

The corpuscular volume for both groups was increased, the mean value being $86.8 \mu^3$ for the cases showing emphysema and $83.5 \mu^3$ for the group exhibiting fibrosis, while for the whole group it was $84.5 \mu^3$ (normal value 82.2 cubic microns).

Correspondingly, the corpuscular hemoglobin for the cases with fibrosis was slightly lower than for those with emphysema, having mean values of 27.9 and 30.1 micromicrograms ($\text{gm.} \times 10^{-12}$) respectively. (Normal value $28.8 \text{ gm.} \times 10^{-12}$.)

As shown in Table VIII the mean for the corpuscular hemoglobin concentration in both groups was identical with that of the normal. The mean value in cases with emphysema was slightly above, while in the group with fibrosis it was just below the normal value.

TABLE IX

Relation of the number of erythrocytes to their size and hemoglobin concentration

Number of erythrocytes	Cases	Hemoglobin per 100 cc.	Corpuscular volume	Corpuscular hemoglobin	Corpuscular hemoglobin concentration	Percentage of red blood cells hematocrit
<i>million</i>		<i>grams</i>	<i>cubic microns</i>	<i>grams $\times 10^{-12}$</i>	<i>per cent</i>	<i>per cent</i>
4.5	5	15.1	93.3	30.4	32.4	44.5
5.0	11	16.2	88.8	31.0	34.9	46.3
5.5	11	15.7	81.2	27.3	33.6	46.8
6.0	3	16.8	81.4	28.0	34.5	49.1
6.5	3	18.3	74.3	26.8	36.4	50.7

Table IX shows the variation of the cellular characteristics, hemoglobin per 100 cc. of blood, and the hematocrit in these cases according to the red cell count. Here was found the inverse correlation of the corpuscular hemoglobin and volume to the red cell count, such as occurs in normal subjects; in other words as the red cell count increased the cells became smaller and contained less hemoglobin; both of these changes being proportional, the corpuscular hemoglobin concentration remained the same.

DISCUSSION

Investigations of the blood volume in cases of chronic pulmonary disease are important from the standpoint of the various theories advanced to explain the production of polycythemia and its relation to a low oxygen tension. The development of these ideas is closely correlated with and based upon observations made at high altitudes, or in chambers where the barometric pressure is lowered to simulate the effects of higher levels. A brief review of the results obtained by such investigations will be useful in understanding the present status of the pathogenesis of polycythemia.

Since the discovery by Paul Bert (20) in 1882 (confirmed a few years later by Viault (21)), that the blood of animals living in the Peruvian Andes has an increased number of red blood cells and an increased capacity for combining with oxygen, practically all investigators agree that such a change occurs both in animals and man at low barometric pressure, although its intensity varies markedly in different individuals. Miescher (22) in 1893 formulated the theory that oxygen deficiency in the bone marrow was the stimulus for the formation of new red cells. His idea has had general acceptance and was substantiated indirectly both by the studies of Bence (23) who claimed that inhalation of oxygen decreases the erythrocytosis which one encounters at high altitudes, and by the observations of Dersca and Valter (24) who succeeded in decreasing the number of red cells in the peripheral blood of patients with anoxemia by the intravenous injection of oxygen. The work of Barcroft and his co-workers (25) demonstrating that the spleen is a storehouse for red cells which are liberated and thrown into the circulation in conditions of oxygen want, has thrown new light on the explanation of erythrocytosis at high altitudes. At the present time most observers agree that this increase in red cells and hemoglobin is primarily produced by the contraction of the spleen, liberating the red cells stored in its pulp, and possibly also by releasing the supply of red cells stored in the bone marrow (McNee (26)). Secondly, if the condition of oxygen want persists, signs of bone marrow activity appear and the increase in the number of red cells may then be correlated with the signs of overactivity of the hematopoietic system. However, because so few estimations of blood volume have been made, it is still a debated point whether this erythrocytosis in new comers and residents at a high altitude is associated with a real increase in the total volume of blood cells or with changes in their concentration in the blood. In 1910 Douglas (27) made observations by means of the carbon monoxide method on Teneriffe (altitude 7,000 feet) and was unable to detect any changes. The Pike's Peak Expedition (by Haldane and others (28)) found evidence of a temporary concentration of red blood cells during the first few days and later a true increase in the total volume of cells. Smith, Belt, Arnold and Carrier (29) found minimal changes in the blood volume

after a brief stay at Long Lake in the Sierra Nevada Mountains (altitude 11,000 feet), and Lippmann (30) and Laquer (31) found very slight alterations at Davos (5,100 feet). Monge (32) has described the existence of a primary polycythemia in the residents of the Peruvian Andes, but studies of the blood volume have not been made in such cases. It is evident from this review that our knowledge concerning the true nature of the erythrocytosis that man develops at high altitude is insufficient. Whether or not there is an increase in the blood volume similar to that found in cases of polycythemia vera at sea level is not known. Further studies in this connection will undoubtedly help solve this interesting problem.

Harrop and Heath (33), who called attention to the marked resemblance of the symptoms of "mountain sickness" to those found in cases of polycythemia vera, advanced the opinion that polycythemia vera may be due to lowered oxygen tension of the arterial blood caused by a change in the alveolar wall, resulting in decreased oxygen diffusion. In three cases of polycythemia they observed a lowering of the arterial oxygen saturation after exercise. The results of these observations would naturally suggest that polycythemia should be found more frequently in cases of chronic pulmonary diseases, in which pathological alterations in the lung parenchyma exist producing a decrease in the oxygen saturation of the arterial blood. That such is not commonly the case is a well known clinical fact; however, actual studies of the blood volume have been reported in only a few cases. Plesch (14) and Uhlenbruck (5) found an increase of the blood volume in a small number of cases with chronic bronchitis and emphysema, but the degree of anoxemia was not determined. Lemon (15), who studied 12 cases of chronic pulmonary emphysema, did not find any significant increase in the blood and cell volume, in spite of a low value (average 88 per cent) of the arterial oxygen saturation in seven of his cases. From these studies Lemon concluded that there is no relationship between the development of polycythemia and pathological alterations in the alveolar wall. It is clear that the evidence against the relationship between development of polycythemia and pulmonary changes resulting in a decreased oxygen tension is rather negative in character and inconclusive in view of the limited number of cases studied.

A point frequently lost sight of is that the response of the bone marrow to any stimulus calling for the formation of new red cells is extremely variable from individual to individual. This fact is easily demonstrated by the response of the blood to low barometric pressures. Although subjects are exposed to exactly the same stimulus, some will exhibit a great increase in the circulating hemoglobin and red cells, while others will show only a slight increase. This difference is also found among the residents at high altitude (Hurtado (34)). One can not dismiss the hypothesis that

a case of polycythemia vera represents a pathological response of a very sensitive bone marrow to a slight or moderate decrease in the oxygen tension of the arterial blood, and that the background of such an occurrence is the existence of anatomical alterations in the lung parenchyma. In a large majority of cases such alterations may not be sufficient to cause such an abnormal response on the part of the hematopoietic system. It is significant in this connection that in most cases of polycythemia vera in which the arterial blood has been studied, the oxygen saturation was found to be lower than normal.

That we found a hydremic plethora in three cases of pulmonary fibrosis is quite significant and indicates that perhaps these two conditions will be found to be more frequently associated if a greater number of cases are studied. It is also significant that in these three cases the arterial oxygen saturation was markedly decreased. It is fair to assume from the history that in these cases the fibrosis of the lung resulting from inhalation of silica probably preceded the development of the polycythemia. In two of these cases the signs and symptoms with the exception of an enlarged spleen were identical with those of so-called "primary" polycythemia or polycythemia vera. These results indicate that, whereas in most cases of chronic pulmonary diseases there is no significant change in the volume of the blood except possibly slight concentration even though anoxemia exists, there are, however, occasional cases in which a hydremic plethora develops closely simulating polycythemia vera. It is interesting that this change was found only in cases with pulmonary fibrosis. Our cases with emphysema, as well as those reported by Lemon (15), in spite of the existence of anoxemia showed normal blood findings. This cannot be explained in the light of our present knowledge. Whether or not the nature of the pathological changes in the lungs has some relation to the development of polycythemia is unknown.

SUMMARY AND CONCLUSIONS

Determinations of blood and plasma volumes were made on 25 normal male subjects whose average age was 26 years. Intravenous injection of brilliant vital red was used in the estimation of the plasma volume. Studies were made also in 16 cases of pulmonary emphysema and in 14 cases of pulmonary fibrosis. The determinations were made in conjunction with clinical observations and measurements of the pulmonary capacity and of the gas content of the arterial blood. From the results of this investigation the following conclusions are drawn:

1. In a group of normal males there were marked variations in the values for the total blood volume and its components. There was a high and significant correlation between the volume of the blood and body weight and on this basis the expected values for the blood volume in the pathological cases were calculated.

2. In a group of cases with varying degrees of pulmonary emphysema, no significant alterations from the normal were found in the plasma, blood and cell volume or in the total circulating hemoglobin per kilogram of body weight.

3. The mean values for the cell volume and total hemoglobin were definitely increased in the group of cases with pulmonary fibrosis. This was due to marked alterations found in three cases, and not to a consistent increase in all the subjects. The volume of the plasma was normal.

4. No definite correlation was found between the severity and duration of symptoms and the increase in the blood volume.

5. A decreased arterial oxygen saturation was found in the three cases which showed marked alterations in the blood volume, but in the remaining cases no correlation was demonstrated between the degree of anoxemia and the blood findings.

6. Likewise no definite relationship was found between alterations in the blood volume and changes in the pulmonary capacity.

7. The mean values for the grams of hemoglobin and the red cell volume per 100 cc. of blood were within normal limits in the group of cases with pulmonary emphysema, but there was a moderate increase in those with pulmonary fibrosis. Marked individual variations were observed.

8. The mean value for the red cell count was found to be within normal limits in both groups of cases, those with pulmonary emphysema and those with fibrosis. No significant changes were demonstrated in the volume or hemoglobin content of the red blood cells.

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