STUDIES ON CYANOSIS.

II. Secondary Causes of Cyanosis.

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By secondary causes of cyanosis we mean the conditions, physiological or pathological, which can increase the oxygen unsaturation of the venous blood to a degree great enough to give cyanosis. They may be divided into two groups according to the manner in which the oxygen unsaturation of the venous blood is increased: (1) conditions which increase the reduction of the normally saturated arterial blood in the capillaries; (2) conditions which prevent complete oxidation of the venous blood in the lungs.

To decide which of the two factors is responsible in a given case may be somewhat difficult. It could be done by drawing simultaneously samples of arterial and venous blood to find the degree of oxygen saturation in both. This I have not been able to do, because up to the present arterial punctures in patients have not been considered advisable.[1] We must in the present series of cases, therefore, confine ourselves to a judgment of the circumstances under which the cyanosis occurred. Sometimes in a given case it is difficult to decide exactly in which of the two ways cyanosis is produced. In other instances where the circumstances are less complicated, it can be done with certainty. The following is a report of a series of cyanotic patients grouped according to the way in which the cyanosis was produced.

The technique is described in the preceding paper.

[1] This is discussed in a previous publication (1) in which the determinations of the oxygen in the arterial blood by Hürter (Hürter, *Deutsch. Arch. klin. Med.*, 1912, cviii, 1) are quoted. In a recently completed work Dr. W. C. Stadie of the Hospital of The Rockefeller Institute has shown that arterial puncture can be safely performed (Stadie, W. C., *J. Exp. Med.*, 1919, xxx, 215).

Cases in Which the Abnormally High Venous Oxygen Unsaturation Is Probably Due to an Abnormally Great Deoxidation of the Blood in Passing through the Capillaries.

In normal resting individuals the reduction (deoxidation) of the arterial blood, which is supposed to leave the lungs nearly saturated with oxygen, may vary from about 8 to about 2.5 volumes per cent of oxygen, the average being 5.5 volumes per cent (1). The reduction is increased by exercise (2) if the increased oxygen consumption is not compensated by a faster blood flow through the capillaries. It is also increased in some heart diseases on account of slow circulation through the capillaries (1, 3, 4, 5). In some instances the reduction may be increased to such an extent that cyanosis occurs. Cases of both kinds (exercise and heart disease) are reported in Tables I to III. Nos. 1, 3, and 5 are determinations on normal resting individuals. The oxygen unsaturation and the carbon dioxide[2] of the venous blood are normal. Nos. 2, 4, and 6 are similar determinations on the same individuals immediately after exercise. The carbon dioxide is unchanged. The oxygen of the venous blood (reserve oxygen) has fallen to a rather low value, and consequently the oxygen unsaturation has increased considerably (to about 14 volumes per cent). In all instances a just visible cyanosis was discovered at the finger-tips immediately after exercise.

The fourth individual (Determinations 7 and 8) was a patient with a valvular disease compensated at rest. After slight exercise the oxygen unsaturation increased from the normal value to 10.47 volumes per cent. It was impossible to decide whether or not any cyanosis was produced by exercise in this case. Determinations 9 and 11 were done on a resting patient with a slightly decompensated valvular heart disease. The oxygen unsaturation is in both instances a little above the upper normal limit (8 volumes per cent). No cyanosis is present. After heavy exercise (Determinations 10 and 12) a moderate cyanosis was produced. The oxygen unsaturation showed a considerable increase (to about 17 and 20 volumes per cent). The carbon dioxide of the venous blood was a trifle lower after exercise.

[2] Carbon dioxide determination not done on the third patient.

The last individual (Determinations 13 and 14) was suffering from a congenital defect of the interventricular septum and congenital cyanosis. Even at rest he was markedly cyanotic with an oxygen unsaturation of only 10.40 volumes per cent. After heavy exercise the cyanosis had grown very intense and the oxygen unsaturation had increased to 18 volumes per cent. The carbon dioxide, which is low, was slightly decreased after exercise.

There is no doubt that the high oxygen unsaturation in the venous blood of the first three (normal) individuals after exercise (Table I) was due to increased deoxidation in the capillaries, for the reason that the lungs were and had always been perfectly normal. There appears to be no reason why the arterial blood should not be fully saturated. The same is probably the case with the next two patients, whose lungs also were normal at the period of determination. In the last case (Determinations 13 and 14) the matter is more complicated. On account of the communication between the two ventricles of the heart some blood must have been passing over into the arterial system without going through the lungs. This amount may possibly be increased by exercise and take a certain part in raising the unsaturation of the venous blood from 10 volumes per cent to 18 volumes per cent. The greatest part of the increase is, however, probably due to the increased reduction of the capillary blood by exercise. As to the way the deoxidation in the capillaries is increased, there are two possibilities; increased consumption on account of the greater metabolism, or increased deoxidation on account of slower blood flow. The blood samples were drawn from the arm after stair running; it seems unlikely that this form of exercise should be able to increase the metabolism in the arms, which were quiet. It is possible that a reflectory vasoconstriction of the capillaries in the unused areas —the arms—had produced a slower flow here in order to get more blood through the capillaries of the legs. Further investigations on this problem are in progress.

The main point is that it is experimentally shown that cyanosis can be produced by increased deoxidation in the capillaries, and that when due to this cause it seems to begin when the venous oxygen unsaturation approaches a value of 13 to 14 volumes per cent.

TABLE I.

Oxygen (Oxygen Unsaturation) and Carbon Dioxide of the Venous Blood in Normal Individuals and Patients with Compensated and Decompensated Heart Diseases at Rest and after Exercise.

Determination No.	Date.	Condition.	Total oxygen capacity (a).	Hemoglobin (calculated).	Oxygen content of venous blood (v).	Oxygen unsaturation (a–v).	Carbon dioxide of venous blood.	Pulse.	Respirations per min.	Remarks on cyanosis.	Conditions at the time of bleeding.	Diagnosis and clinical notes.
	1919		*vol. per cent*	*per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*					
1	Mar. 22	Rest.	20.10	108.5	16.31	3.79	50.5	90	18	No cyanosis.	Blood drawn after 10 min. rest in lying position.	
2		Exercise.	20.40	110	5.72	14.68	50.5	120		Slight cyanosis of fingers.	Blood drawn immediately after running up and down one flight five times in 90 seconds.	Normal individual, age 25 yrs.
3	Apr. 18	Rest.	19.20	104	14.19	5.01	61.7	80	14	No cyanosis.	The same as No. 1.	
4		Exercise.	18.80	102	4.20	14.60	62.1	120	24	Slight cyanosis of fingers.	" " " " 2.	Normal individual.
5	" 1	Rest.	19.20	104	14.00	5.20		62	15	No cyanosis.	" " " " 1.	
6		Exercise.	19.04	103	5.42	13.62		115	24	Slight cyanosis of fingers.	" " " " 2.	Normal individual, age 26 yrs.

7	Apr. 4	Rest.	19.25	104	13.41	5.84		84	20	No cyanosis.	The same as No. 1.	Male, age 26 yrs. Compensated mitral and aortic insufficiency; auricular fibrillation.
8		Exercise.	19.25	104	8.78	10.47		134	?	Doubtful cyanosis of fingers.	Blood drawn after walking up and down one flight twice.	
9	Feb. 20	Rest.	19.82	107	8.88	10.94	58.1			No cyanosis of hands or face.	The same as No. 1.	
10		Exercise.	(19.82)	(107)	2.58	17.24	58.1			Marked cyanosis of hands and face.	Blood drawn after walking up and down one flight five times.	Letter carrier, male, age 56 yrs. Compensated mitral insufficiency and stenosis.
11	" 21	Rest.	19.82	107	8.05	11.77	56.5			No cyanosis of hands or face.	The same as No. 1.	
12		Exercise.	19.82	107	0.00	19.82	55.6			Marked cyanosis of hands and face.	" " " " 10.	
13	Jan. 17	Rest.	28.28	153	17.88	10.40	45.2	82	18	Marked cyanosis of face and hands.	" " " " 1.	Male, painter, age 20 yrs. Congenital cyanosis. Defect of interventricular septum.
14		Exercise.	(28.28)	(153)	9.80	18.48	44.1	108	40	Heavy cyanosis of face and hands.	" " " " 10.	

TABLE II.

Oxygen and Carbon Dioxide of the Venous Blood in a Series of Patients with Decompensated Heart Diseases (All at Rest).

Determination No.	Date.	Total oxygen capacity (a).	Hemoglobin.	Oxygen content of venous blood (v).	Oxygen unsaturation (a-v).	Carbon dioxide of venous blood.	Pulse.	Respirations per min.	Remarks on cyanosis.	Diagnosis and clinical notes.
	1918	*vol. per cent*	*per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*				
15	Apr. 5	(19.20)	104	3.79	15.41		72*/66	34	Moderate cyanosis of hands and face.	Housewife, age 64 yrs. Mitral insufficiency and stenosis; auricular fibrillation; no râles in lungs.
16	" 14	(19.20)	104	8.55	10.65		76/74	24	Moderate cyanosis of hands and face.	
17	" 19	19.20	(104)	5.23	13.97				Moderate cyanosis of hands and face.	
18	" 26	(19.20)	(104)	9.66	9.54				Cyanosis doubtful.	
19	" 26	(16.62)	90	4.29	12.33		72/68	20	Slight cyanosis of hands and lips.	
20	May 2	(16.62)	(90)	3.14	13.48		144/108	22	Cyanosis more marked but still slight.	Housewife, age 42 yrs. Mitral insufficiency; aortic insufficiency; auricular fibrillation; no râles in lungs.
21	" 5	(16.62)	(90)	6.32	10.30		92/90	22	Cyanosis doubtful.	
22	" 10	(16.62)	(90)	4.10	12.52		72/72	22	Slight cyanosis.	

23	*1919* Jan. 25	20.40	(110)	8.25	12.15	56.6	$\frac{132}{96}$	28	Moderate cyanosis of face and hands.	
24	" 27	21.43	(116)	4.13	17.30	55.4	$\frac{128}{80}$	30	Moderate cyanosis of face and hands.	Housewife, age 44 yrs. Mitral insufficiency and stenosis; auricular fibrillation; no râles in lungs.
25	" 30	21.48	(116)	7.62	13.86	53.8	$\frac{102}{90}$	32	Moderate cyanosis of face and hands.	
26	Feb. 1	21.02	114	16.20	4.82	48.3	$\frac{100}{94}$		No cyanosis.	
27	" 4	(21.02)	(114)	7.00	14.02	55.9	$\frac{102}{92}$	24	Moderate cyanosis of face and hands.	
28	Apr. 15	20.20	(109)	8.62	11.58	54.7	$\frac{-}{40}$	22	Marked cyanosis of face and hands.	Mitral stenosis; auricular fibrillation; no râles in lungs.

* The upper figure is the apex pulse, the lower the radial pulse.

In Table II a report is made of fourteen determinations on four patients with valvular heart lesions combined with auricular fibrillation. In one of these determinations an oxygen unsaturation of normal value (No. 26) was found. The patient showed no cyanosis and was fully compensated at that time. In all the other instances the oxygen unsaturation was above the upper normal limit and the patients were clinically decompensated. In eleven instances a cyanosis of slight or moderate degree was encountered In two instances (Nos. 18 and 21) it could not be determined whether or not there was cyanosis. In these two instances the oxygen unsaturation was 9.54 and 10.30 volumes per cent. During the cyanotic periods in the case covered by Determinations 15 to 18 the oxygen unsaturation was from 10.65 to 15.41 volumes per cent.

Although it seems to be almost certain that the circulation in the instances of cyanosis shown in Table II was slower than normally and that the deoxidation consequently is due to slower blood flow and not to increased metabolism, it cannot be excluded that a part of the oxygen unsaturation of the venous blood may have been due to incomplete oxidation in the lungs. In spite of the fact that the lungs in all instances were perfectly clear, it might be possible that their function had been impaired from earlier periods of stasis.

It is probably justifiable to say that the cyanosis in these cases was produced mainly, although not exclusively, by increased deoxidation on account of slow circulation. The lowest value of oxygen unsaturation at which cyanosis was found was 10 to 11 volumes per cent, somewhat lower than in the experiments with exercise, a point which will be discussed later.

In Table III three experiments on a normal person (the writer) are reported. No. 29 is a determination of the oxygen and carbon dioxide of the venous blood at rest. The values obtained are normal. Then the blood flow was stopped in the arm by stasis by means of the blood pressure apparatus. For 2 minutes the pressure was kept at 30 mm. of mercury, allowing the arterial stream to get through; then the pressure was raised to 160 mm. (the blood pressure of the individual was $\frac{125}{80}$) for 2 minutes, and a blood sample was drawn. The analysis showed that the oxygen unsaturation had increased from 4.7

TABLE III.

Oxygen and Carbon Dioxide of the Venous Blood after Stopping of the Blood Flow in the Arm of a Normal Individual (the Writer).

Determination No.	Date.	Time.	Total oxygen capacity (a).	Hemoglobin (calculated).	Oxygen content of venous blood (v).	Oxygen unsaturation (a-v).	Carbon dioxide of venous blood.	Remarks on cyanosis of arm.	Pressure in apparatus when blood sample was drawn.	Ordinary blood pressure of the subject.
	1919	*p. m.*	*vol. per cent*	*per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*		*mm.*	*mm.*
29	Mar. 13	3.10	(20.00)	(108)	15.28	4.72	51.9	No cyanosis.	0	$\frac{125}{80}$
30		3.14	19.30	104	9.09	10.21	56.6	Slight cyanosis; veins swollen.	160	
31		3.18	20.70	112	8.17	12.53	58.2	Marked " " "	160	

volumes per cent to 10 volumes per cent, and a slight cyanosis was present in the whole arm. After stasis for 4 minutes more the cyanosis was very marked; the oxygen unsaturation had risen to 12.5 volumes per cent. The stasis had increased the carbon dioxide content from 51.9 volumes per cent to 58.2, both of which values lie within the normal limits.

This experiment shows the production of cyanosis by increased deoxidation of the arterial blood in the capillaries. It is striking that the cyanosis starts at a lower unsaturation (10.2 volumes per cent) than did the cyanosis in the experiments with exercise (13 to 14 volumes per cent). It is especially noteworthy that the cyanosis when caused by retarded circulation became intense at an oxygen unsaturation of 12.5 volumes per cent, which is not much higher than the value at which it was just visible when caused by exercise. This point is discussed later.

Cases in Which Cyanosis Is Exclusively or Chiefly Due to Incomplete Oxidation of the Blood in the Lungs.

Ordinarily the arterial blood is approximately saturated with oxygen. In some instances, however, the anatomical or physical conditions are changed in such a way that complete saturation does not take place. This is the case (1) when a part of the blood does not pass the lungs on account of an abnormal communication between the arterial and venous part of the vascular system, for instance a patent ductus Botalli, or a deficient septum of the ventricles of the heart; (2) when a part of the lungs is unfitted for the aeration but still allows the blood flow, for instance in pneumonia; (3) when the partial oxygen pressure in the lungs is below a certain point, for instance at high altitudes, mountain sickness; and (4) when a part of the hemoglobin is transformed into such a form that it cannot be converted into oxyhemoglobin and still gives a dark color like reduced hemoglobin, as in methemoglobinemia.[3] In all these instances (the first three of

[3] In methemoglobinemia, which may give an intense cyanosis, it is not quite correct to define the cyanosis as due to increased oxygen unsaturation, for the reason that a certain part of the hemoglobin can neither take up nor give off oxygen.

which are represented by experiments in this publication) the oxygen saturation of the arterial blood is incomplete and there is a non-negligible oxygen unsaturation of the arterial blood. In the capillaries this (arterial) oxygen unsaturation is further increased on account of the (normal or abnormal) deoxidation. The oxygen unsaturation in such cases is therefore a result of two factors, (1) incomplete oxidation in the lungs and (2) reduction in the capillaries.

In a series of twelve patients and one normal individual the clinical and experimental conditions have been such that although we were unable to determine the degree of arterial unsaturation we are certain that arterial unsaturation is the cause of the abnormally high venous oxygen unsaturation causing the cyanosis. The cases fall into three groups and are reported accordingly.

In Table IV a report is given of nine determinations of the blood gases in two patients, both suffering from congenital heart disease (defective ventricular septum). In both cases rather high values for the oxygen of the venous blood were found, from 11 to 19 volumes per cent, in spite of the fact that the oxygen unsaturation of the venous blood showed values which in some instances were higher than those seen in any other case, from 9.9 to 20.89 volumes per cent. The carbon dioxide of the venous blood showed values at the very lowest limit of what can be considered normal.

The cyanosis in the first case in Table IV was fairly moderate, in the last case extremely heavy. No doubt existed that the unusually high oxygen unsaturation was not due to increased deoxidation in the capillaries, because the determinations were done after half an hour's rest, and no clinical reason for slow circulation was to be detected (no stasis, no edema, diuresis normal). The cause of increased venous oxygen unsaturation must therefore lie in incomplete oxidation in the lungs[4] caused either by some lung disease or by a congenital heart lesion. The lungs were absolutely normal, and clinically a defect of the interventricular septum was found.

In Table V a report is given of ten determinations on ten patients suffering from pneumonia (post influenza). In one case (No. 49) the oxygen unsaturation of the venous blood was very low, 2.35 volumes per cent, which is a trifle below the lower normal limit (2.5 volumes

[4] No reason existed for considering methemoglobinemia the cause.

TABLE IV.

Oxygen and Carbon Dioxide of the Venous Blood of Two Patients Suffering from Defect of the Interventricular Septum, Congenital Cyanosis, and Polyglobulism.

Determination No.	Date.	*Total oxygen capacity (a).	Hemoglobin.	Oxygen content of venous blood (v).	Oxygen unsaturation (a-v).	Carbon dioxide of venous blood.	Pulse.	Respirations per min.	Remarks on cyanosis.	Diagnosis and clinical notes.
	1918	*vol. per cent*	*per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*				
32	Oct. 22	(29.10)	156	19.20	9.90		86	20		Male, painter, age 20 yrs. Congenital heart disease (defect of the interventricular septum); congenital cyanosis; pulmonary stenosis (?). Number of red corpuscles varied between 6.2 and 7.2 millions. No stasis or edema. Superficial veins a little more marked than usual. Veins of retina dilated. Slight clubbing of fingers and toes.
33	Nov. 5	29.00	(156)	18.08	10.92		86	20	Moderate cyanosis, especially of face, hands, and feet.	
34	" 16	(28.02)	151	11.40	16.62	51.5	84	24		
	1919									
35	Jan. 16	28.28	(153)	17.45	10.83	41.5	84	22		
13	" 17	(28.28)	(153)	17.88	10.40	45.2	82	18		
	1918									
36	Sept. 19	31.70	(170)	17.44	14.26		100	24	Extremely heavy cyanosis of the skin of the whole body and of the mucous membranes.	Male, age 7 yrs. Congenital heart disease (defect of the interventricular septum); congenital cyanosis. Number of red blood corpuscles varied from 7 to 10 millions. No stasis or edema. Heavy dyspnea, increasing markedly under exercise. Superficial veins marked. Veins of retina dilated. Marked clubbing of fingers and toes.
37	" 23	(31.08)	168	15.40	15.68		90	26		
38	Dec. 15	31.32	(169)	13.87	17.45	46.8	108	36		
	1919									
39	Feb. 2	32.40	(175)	11.51	20.89	42.1	86	34		

TABLE V.

Oxygen and Carbon Dioxide of the Venous Blood in a Series of Patients Suffering from Pneumonia (in Influenza).

Determination No.	Date.	Total oxygen capacity (a).	Hemoglobin.	Oxygen content of venous blood (v).	Oxygen unsaturation (a-v).	Carbon dioxide of venous blood.	Pulse.	Respirations per min.	Temperature.	Degree of cyanosis.	Diagnosis and clinical notes.
	1918	*vol. per cent*	*per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*			*°C.*		
40	Oct. 15	(17.20)	93	8.52	8.68		92	38		+++	Male, student, age 16 yrs. Double pneumonia.
41	" 22	(19.33)	104	11.40	7.93		96	50		++	Female, age 38 yrs. Double pneumonia.
42	" 23	(15.72)	85	3.56	12.16		132	48	40.8	+++	" " 23 " " "
43	" 23	(17.56)	95	6.75	10.81		120	36	40.6	+++	" " 23 " " "
44	" 29	(14.79)	80	6.76	8.03		86	48	39.7	++	" " 39 " " " mitral and aortic stenosis.
45	" 30	(17.56)	95	4.95	12.61		120	40		+++	Female.
46	" 31	(16.62)	90	7.76	8.86		100	50	40.3	+++	" age 29 yrs. Double pneumonia.
47	Nov. 9	(12.92)	70	6.73	6.19	67.7	124	36	40.0	−	Age 16 yrs. Double pneumonia.
48	Dec. 1	25.00*	(135)	16.22	8.78	61.5	84	24	39.0	+++	Male, porter, age 43 yrs. Double pneumonia.
49	" 4	(14.61)	80†	12.26	2.35	50.8	84	28	38.8	−	Female, housemaid, age 19 yrs. Pneumonia involving left lower lobe.

* Total oxygen capacity directly determined (Van Slyke's method).

† Total oxygen capacity calculated from hemoglobin determination (Sahli).

In the rest the total oxygen capacity was calculated from the hemoglobin percentage determined by Haldane's method. Nos. 41 and 49 recovered; the rest died from pneumonia.

per cent). This patient was not cyanotic. In another (No. 47) the unsaturation value was within normal limits, and just above the normal average. No cyanosis was present in this patient either.

The other eight patients were cyanotic, most of them markedly so. In these cases the oxygen unsaturation of the venous blood had values from 7.93, a trifle below the upper normal limit, to 12.61 volumes per cent. As a whole, the oxygen unsaturation is abnormally high in the venous blood from the cyanotic individuals, but by far not to the same degree as was found in normal individuals after exercise, although the cyanosis in pneumonia was much more intense and generalized. In three patients, two non-cyanotic and one cyanotic, the carbon dioxide was determined. In one of these (No. 47, non-cyanotic), it was just above the upper normal limit. In the other two it was normal. The total oxygen-combining power of the blood was in one case (No. 48) very high, corresponding to a hemoglobin percentage of 135 (verified twice). In another case (No. 41) it was a little above normal. In the rest of the cases it was decreased (hemoglobin from 95 to 70 per cent).

The decision of the pathogenesis of cyanosis in these cases is somewhat difficult for several reasons. In the first place, it is possible that it might in part be due to formation of methemoglobin. From the investigations of Butterfield and Peabody (6) it is known that a discrepancy between the amount of iron in blood and its oxygen-combining power may be produced by pneumococci on account of formation of methemoglobin. No determinations of the bacteria in the blood of the present pneumonia patients were done.

If a part of the hemoglobin is transformed into methemoglobin it may or may not be included in the oxygen unsaturation values. That depends on the method used in determining the total oxygen-combining power. If this is done directly by the Van Slyke method (7) only that part of the hemoglobin which can take up and give off oxygen is included.

By the Haldane or Palmer method a mixture of carbon monoxide hemoglobin and methemoglobin is obtained which cannot be accurately matched against the standard of pure carbon monoxide hemoglobin. Neither is it possible by the Sahli method to determine accurately the total hemoglobin if a part of it is transformed into

methemoglobin.[5] In the determinations in Table V Haldane's method was used in eight cases, seven of which had cyanosis, Van Slyke's method in one (No. 48), and Sahli's in one (No. 49) in which no cyanosis was present. In one case (No. 41) blood and urine were examined spectroscopically. No methemoglobin was detected. This means that there is a possibility that methemoglobin may have been partly responsible for the cyanosis, although it cannot be seen from the oxygen saturation values. The rather low values for the total oxygen-combining power in some of these cases might also be interpreted as caused by transformation of some part of the hemoglobin into methemoglobin, although this is entirely conjecture.

However, the main part and probably the whole of the cyanosis must be due either to increased reduction or incomplete oxidation of the blood. As to the first possibility, nothing could be detected in the circulation signs which could indicate slow circulation (no stasis, pulse powerful, the mitral stenosis found in one patient was compensated), and the patients were all resting. But the temperature was increased, which undoubtedly caused an increase in the metabolism and this means again an increased oxygen consumption in the tissues. That fever does not necessarily cause an increased oxygen unsaturation of the venous blood is seen in No. 49, where it was even subnormal in spite of a temperature of 38.8°C. This probably means that the increased activity of the heart, which was clinically very marked, had overcompensated the increased oxygen consumption, so that the venous blood was even more arterialized than normally. It is probably justifiable to ascribe the cyanosis in these cases to incomplete oxidation of the venous blood in the lungs on account of the pneumonic infiltration, which allowed the blood to pass but did not permit the air to come in contact with it. As in the patients with congenital cyanosis, the blue color is more general and begins at a lower oxygen unsaturation value than is the case in individuals when cyanosis is caused by increased reduction of hemoglobin in the capillaries.

This is also seen in an experiment in Table VI in which the influence of low oxygen pressure on the oxygen unsaturation of the venous blood is investigated. The experiment was arranged as follows: The subject

[5] Stadie, W. C., personal communication.

TABLE VI.

Effect of Inspiration of Decreasing Amounts of Oxygen on the Skin Color and on the Oxygen and Carbon Dioxide of the Venous Blood of a Normal Individual (the Writer).

Determination No.	Date.	Time.	Total oxygen capacity (a).	Hemoglobin (calculated.)	Oxygen content of venous blood (v).	Oxygen unsaturation (a–v).	Carbon dioxide of venous blood.	Pulse.	Respirations per min.	Oxygen content of expiratory air.	Carbon dioxide content of expiratory air.	Remarks on cyanosis.
	1919	*p. m.*	*vol. per cent*	*per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*			*per cent*	*per cent*	
50	Mar. 18	3.28	20.80	(112)	17.03	3.77	52.1	88	17			No cyanosis.
51		3.45	(20.80)	(112)	12.62	8.18	53.0	90	24	5.68	3.69	Cyanosis starting (hands, arms, and face).
52		3.48	(20.80)	(112)	7.37	13.43	51.3	90	28	5.53	2.77	Cyanosis of skin and mucous membranes very marked.

(the writer) was lying on a bed. Through a mask respiration took place from a spirometer with a capacity of about 30 liters. By means of a double valve arrangement the exposed air on its way to the spirometer passed a tower filled with soda lime, which absorbed the carbon dioxide. By thus rebreathing into the spirometer the oxygen percentage of the air decreased regularly and no increase in the carbon dioxide took place. A propeller mixed the air in the spirometer.

In several preliminary experiments the same results were obtained as in Haldane's (8). After a certain period of rebreathing the individual became cyanotic. An analysis of the air in the spirometer would then show between 8 and 5.5 per cent oxygen; the carbon dioxide about 0.5 volume per cent. The cyanosis usually started after rebreathing for about 20 minutes, and a few minutes later it would be impossible for the individual to continue on account of dizziness, throbbing in the head and extremities, palpitation, and a choking feeling.

In the experiment reported in Table VI a sample of blood was drawn from an arm vein before the spirometer breathing started. Then the respiration from the spirometer began without any change in the position of the individual on whom the experiment was performed. After 20 minutes a slight but distinct cyanosis was to be seen on the arms and cheeks. A sample of air from the mask just outside the mouth was drawn and at the same time a blood sample was taken.

The experiment was now pushed on as far as possible and three minutes after the drawing of the second sample of blood a third sample was taken together with an air sample. At that time the cyanosis was very marked and could be seen in the skin and the mucous membranes. Although it was generalized it was most conspicuous on the hands, cheeks, nose, and ears. At this time the individual was nearly fainting and felt very uneasy. The pulse rate had increased a little and the respiration had gone up from 17 to 28.

The analyses show that the cyanosis started at a venous oxygen unsaturation of 8.18 volumes per cent and was very heavy at 13.43 volumes per cent. The oxygen of the venous blood had decreased from 17.03 volumes per cent to 7.37 volumes per cent. The carbon dioxide was practically uninfluenced and showed a normal value.

The pathogenesis of the low venous oxygen unsaturation is clear. Nothing occurred which could give an increased deoxidation in the capillaries. But oxidation in the lungs must have been incomplete on account of the low oxygen percentage found in the lung air.

It is impossible to give the exact figure of the alveolar oxygen pressure because it was impossible to get a deep expiration on account of the dyspnea. The air sample, which was taken from just outside the mouth of the individual simultaneously with the drawing of the second and third blood samples, therefore shows oxygen values a little higher than the alveolar air. The oxygen percentage was, in the first sample, 5.68, in the second 5.53; the corresponding pressure was 39.7 and 38 mm. of mercury. From this we can calculate the approximate saturation of the arterial blood, using the normal average curve for the dissociation of the oxyhemoglobin. The degree of saturation could not be far from 70 per cent. Since the total oxygen-combining power is 20.80, this gives an oxygen content of the arterial blood of 15.25 volumes per cent. The difference is the oxygen unsaturation of the arterial blood, 5.55 volumes per cent. The oxygen unsaturation of the venous blood was 8.18 volumes per cent; of this 5.55 are consequently due to arterial unsaturation, whereas 2.63 volumes per cent are the result of the reduction in the capillaries on account of the oxygen consumption.

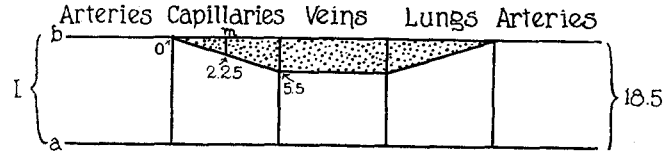
DISCUSSION.

It has been shown in this and the preceding paper (1) that an abnormally high oxygen unsaturation of the blood results in the clinical condition known as cyanosis;[6] (2) that this increased oxygen unsaturation may be produced in two ways, (*a*) by an increased reduction of oxyhemoglobin to reduced hemoglobin in the peripheral capillaries, and (*b*) by an incomplete oxidation of the venous blood in the lungs.

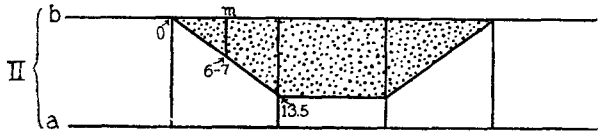
It was pointed out that no quantitative parallelism exists between the degree of cyanosis and the amount of oxygen unsaturation of the venous blood. This lack of parallelism was first thought to be

[6] The possible production of cyanosis by methemoglobinemia has been mentioned but not discussed in detail as no data are available.

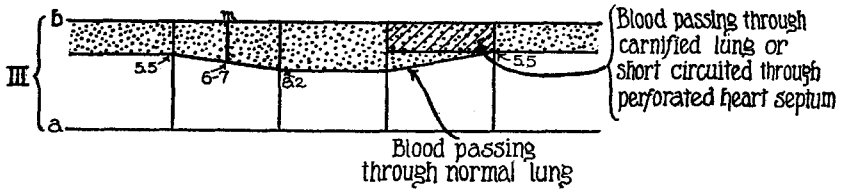
due to individual differences; for instance, of the skin and the subcutaneous tissue. However, the separation of the cyanotic patients into two groups according to the way the cyanosis was produced (the secondary causes) seemed to offer an opportunity for a better understanding of the problem. The results on the two groups of cyanotic patients seemed, as previously mentioned, to indicate that



Oxygen unsaturation for normal individuals.



Oxygen unsaturation when the reduction of hemoglobin in the peripheral capillaries is abnormally increased.



Oxygen unsaturation when the oxidation of hemoglobin in the lungs is incomplete.

TEXT-FIG. 1. Oxygen unsaturation of the blood in the different parts of the vascular system under various conditions. Total areas between lines *a* and *b* represent oxygen capacity, shaded areas oxygen unsaturation.

there was an important difference between them. In the first group the cyanosis was as a whole local and not very intense, beginning at a rather high degree of oxygen unsaturation of the venous blood, whereas in the second group it was usually generalized, often very intense, and it seemed to start at a low degree of oxygen unsaturation.

Text-fig. 1 represents the conditions in the different parts of the circulatory system. The distance from *a* to *b* represents the total

oxygen-combining power of the blood. The arterial system, the peripheral capillaries, the venous system, and the lungs are represented as indicated on the figure. Diagram I gives the condition in normal resting individuals. In the arteries the hemoglobin is approximately saturated with oxygen. The proportion of hemoglobin which is saturated with oxygen is represented by the white areas. In the capillaries a certain amount of oxygen is taken away by the tissues, and the highest degree of unsaturation is found at the end of the capillaries (on the average 5.5 volumes per cent). This unsaturation is unchanged until the venous blood reaches the lungs and is again oxidized.

Diagram II represents conditions in individuals, in whom the oxygen unsaturation of venous blood for some reason is increased on account of increased deoxidation in the capillaries (after exercise, slow circulation).

Diagram III gives a picture of the condition in which only part of the reduced hemoglobin of the venous blood is changed to oxyhemoglobin in the lungs. There is consequently a certain proportion of reduced hemoglobin in the arterial blood when it enters the tissue capillaries. This is further increased by the deoxidation normally occurring in the capillaries. The sum of arterial unsaturation plus reduction in the capillaries is the venous oxygen unsaturation. This condition may be found in pneumonia, some congenital heart diseases, and after respiration of air with low oxygen percentage.

All the blood samples were drawn from the veins, and the results of the analyses of these samples are compared with the cyanotic color. It is clear, however, that it is not the blood in the venous, or in the arterial system which causes the cyanosis; it is the color of the blood in the capillaries. But any part of the capillaries lying sufficiently superficially must take the same part in producing the skin color, which is to be looked upon as the result of a mixture of the condition in any small sector of the capillaries. In other words, it must be the sum of these sectors, which is responsible for the cyanosis. As to cyanosis, the sum is approximately represented by the average between the value at the beginning and the end of the capillaries. If we can calculate this average, indicated by the line *m* on the diagram, we may find the real oxygen unsaturation which is responsible

for the cyanosis. In normal individuals the values for the oxygen unsaturation at the beginning and end of passage through the capillaries are approximately 0 and 5.5 volumes per cent respectively. This indicates an average capillary oxygen unsaturation of 2.25 volumes per cent.

As an example of the condition represented in Diagram II, we shall take the results on the normal exercising individuals. The oxygen unsaturation of the arterial blood is about 0 volume per cent, that of the venous blood about 13 to 14 volumes per cent. This gives a mean capillary oxygen unsaturation of about 6.5 to 7 volumes per cent.

Diagram III may be applied to the experiment with the inspiration of air with low oxygen percentage. The arterial oxygen unsaturation was calculated to be not far from 5.55 volumes per cent. The venous oxygen unsaturation at the beginning of the cyanosis was 8.18 volumes per cent. The average is between 6 and 7 volumes per cent. In other words, the average capillary oxygen unsaturation that initiated barely visible cyanosis in selected examples from both groups, was between 6 and 7 volumes per cent, which consequently is to be looked upon as the threshold value for the cyanosis.

This view-point gives us means to a better judgment of the two factors which usually are alone available, the cyanosis and the venous oxygen unsaturation. If a cyanosis starts at a venous oxygen unsaturation lower than 13 volumes per cent, some arterial oxygen unsaturation must be present, and the more the lower the venous unsaturation is. This is often seen in heart patients, particularly in patients suffering from mitral disease, rarely in patients with aortic involvement. It is seen even if no râles are heard and no dullness is present. Almost all the results in Table II show this condition. This means that the incomplete oxidation causing arterial oxygen unsaturation plays a very important part and may be present even if no physical signs of lung involvement can be detected.

This also explains why the cyanosis in pneumonia patients starts at a very low degree of venous oxygen unsaturation and indicates that it is the lung ventilation and not the circulation which is impaired in these cases. In one patient (No. 41) the cyanosis was well developed at the venous oxygen unsaturation of 7.93 volumes per cent. This means that the arterial oxygen unsaturation was at

least between 5 and 6 volumes per cent, and from this it can be calculated that about one-third of the blood passed through lung tissue which was not ventilated.

In the experiments with artificial stasis of the arm the cyanosis begins at a venous oxygen unsaturation of 10.21 volumes per cent. This, on the basis of the above theory, would indicate the presence of some arterial unsaturation. However, it is unlikely that the arterial blood was not practically saturated with oxygen in the subject. The determination (No. 29) 4 minutes before showed that the arterial blood in this individual must have been saturated. The explanation is that back pressure from the veins caused stasis in the capillaries and reduction of an unusual proportion of the oxyhemoglobin on entering the first parts of the capillaries. Consequently the condition simulates that observed when incomplete oxygenation of the arterial blood is the cause of the presence of reduced hemoglobin at the entrance to the capillaries.

Still another phenomenon finds its explanation from the fact that it is the average capillary oxygen unsaturation which parallels the degree of cyanosis. It has been pointed out before that there must necessarily be a certain amount of hemoglobin in the blood to cause cyanosis; in other words, that patients suffering from anemia above a certain degree could not turn cyanotic. This limit can be determined by applying artificial stasis to such patients. In a series of such patients it was found that the threshold value was about 35 per cent hemoglobin, or a total oxygen-combining power of about 6.5 volumes per cent.

SUMMARY.

1. The primary cause of cyanosis is an increase in the reduced hemoglobin, or oxygen unsaturation, of the blood in the peripheral capillaries.

2. When the mean capillary oxygen unsaturation, which is calculated as the mean between venous and arterial unsaturation, and is normally about 2 to 3 volumes per cent, is increased to about 6 to 7 volumes per cent, cyanosis appears. For this reason 6 to 7 volumes per cent may be called the threshold value of mean capillary oxygen unsaturation for the incidence of cyanosis.

3. The increased mean capillary oxygen unsaturation is produced in two ways (secondary causes of cyanosis), either by an abnormally great reduction during passage through the capillaries (Text-fig. 1, Diagram II) or by a state of partial reduction in the arterial blood entering the capillaries (Text-fig. 1, Diagram III). The first condition (abnormally great reduction) occurs during exercise, or when the blood flow is retarded, as in decompensated heart condition. The second condition (partial arterial unsaturation) occurs in certain lung and heart diseases, and when the alveolar oxygen tension is greatly decreased, as at high altitudes.

4. If the blood is completely saturated with oxygen in the lungs, the oxygen unsaturation of the venous blood may increase to 13 to 14 volumes per cent before cyanosis appears.

5. If cyanosis appears at a venous oxygen unsaturation less than 13 to 14 volumes per cent, some arterial oxygen unsaturation may be assumed, and the more the lower the venous oxygen unsaturation is.

6. Even if neither râles nor dullness can be detected in the lungs, conditions may exist which prevent complete oxidation of the arterial hemoglobin. This is especially frequent in patients with mitral lesions.

7. Cyanosis cannot be produced in patients whose hemoglobin percentage is below 35 per cent on the Haldane scale (oxygen capacity of 6.5 volumes per cent).

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