# STUDIES ON CYANOSIS.

## I. Primary Causes of Cyanosis.

By CHRISTEN LUNDSGAARD, M.D.

(*From the Medical Clinic of the University of Copenhagen, Copenhagen, Denmark.*)

(Received for publication, May 23, 1919.)

### INTRODUCTION.

In medical terminology cyanosis indicates a blue or bluish color of the skin of the mucous membranes, and of other organs usually not visible (the kidneys, the spleen, etc.). Cyanosis may be general or local. In the latter instances, it is usually found on the lips, nose, ears, fingers, and toes (acrocyanosis). It may be met with in various pathological conditions, and is found especially in patients suffering from diseases of the heart, lungs, and blood. Since it is a striking sign, cyanosis has been known since the early history of medicine, and has attracted much attention.

Various theories have been put forward about its pathogenesis, but none has been generally accepted. Cyanosis is an important symptom in the differential diagnosis of various diseases, and it has always been considered important for the prognosis of the diseases in which it is encountered. Since it is usually considered a harmful condition, special therapeutic procedures (venesection, oxygen inhalations) have often been used against it.

### HISTORICAL.

De Senac (1749) (1) gave the first explanation of the pathogenesis of cyanosis. He considered it the result of an admixture of arterial and venous blood due to an abnormal communication between the two sides of the heart, which he found in autopsy. In 1761 Morgagni (2) showed that cyanosis might be combined with pulmonary stenosis. He explained the cyanosis by stasis caused by the pulmonary stenosis. Grancher (3) found a distention of the capillaries and the smallest arteries in patients suffering from (congenital) cyanosis, and considered this distention as well as the cyanosis as caused by stasis. Later Knapp (4) detected the alterations of the retinal vessels in patients with congenital cyanosis. This, together with experiments on animals by Panum (5), Dareste (6),

Stockard (7), Bardeen (8), Loeb (9), and others, resulted in giving the capillary anatomical changes more prominent and causal relation to cyanosis, which in some instances was considered due to anatomical malformation of the small vessels. Abnormalities in the blood itself have also been held responsible for the production of cyanosis. Since Krehl (10) found polycythemia in patients with congenital cyanosis and Vaquez (11) (1892) described the first case of polycythemia, an abnormally high number of red blood corpuscles has been considered a cause of cyanosis.

Alterations in the blood gases have also been considered the cause of cyanosis, and in spite of lack of experimental confirmation, this idea has never been given up. Some had the opinion that an accumulation of carbon dioxide in the blood, others that too small an amount of oxygen caused the cyanotic skin color. Also the amount of reduced hemoglobin has been considered the cause. Von Bamberger (12) early put this idea forward in his monograph on heart diseases. Since then, several others have used the same explanation, and it is usually considered one of the most important causes of cyanosis. No experimental proof has, however, been established. In a previous paper by the writer (13) it was pointed out that the results of a series of determinations of venous oxygen on decompensated heart patients seemed to show that there existed a close relation between cyanosis and the amount of reduced hemoglobin (called oxygen unsaturation) of the venous blood. Later Langstroth (14) confirmed this in two heart patients suffering from cyanosis. But the problem has never been submitted to a systematic investigation.

### *Present State of the Problem of the Cause of Cyanosis.*

The literature shows that some confusion prevails, primary and secondary causes being intermixed. By primary causes I mean changes of the blood itself; by secondary causes I mean pathological disturbances, which may be more or less localized. Such intermixture of primary and secondary causes results in confusion such as we would have if we defined anemia as a condition caused by different factors; for instance, decreased hemoglobin, bleeding gastric ulcer, toxins, and so forth.

*Primary Causes of Cyanosis.*—Of what we may term primary causes, three are held especially responsible: (1) increased carbon dioxide content of the venous blood; (2) decreased oxygen content of the venous blood; and (3) increased oxygen unsaturation of the venous blood.[1]

[1] The term oxygen unsaturation has previously (15) been defined as "the difference between the venous oxygen and the total oxygen-combining power of the hemoglobin."

The chief aim of the present work has been to investigate whether or not any of these alterations of the blood really accounts for the cyanosis; *i.e.*, is the primary cause. For that purpose the cyanosis and the blood findings on a series of cyanotic and non-cyanotic individuals have been compared.

### *Technique.*

The cyanosis is simply estimated (always in full daylight) and its degree indicated by plus signs. Three plus signs mean a very dark blue color. It has always been general (skin and mucous membranes) but never quite equally distributed. One plus indicates a just visible bluish color, usually but not always localized to the peripheral parts (acrocyanosis). Two pluses indicate an intermediate stage, in which the cyanosis is usually general but is pronounced only at certain places, such as the ears, lips, and finger-tips.

The blood samples have all been drawn and kept after the procedure given in previous publications (15, 16).

The total oxygen capacity is determined either directly by the Van Slyke method (17) or (in a minority of the cases) indirectly by calculation from the color index (Haldane's method). The venous oxygen and carbon dioxide are measured by the Van Slyke method (18). The carbon dioxide is determined on whole blood kept under oil for a very short time (19).

### *Determinations.*

The results of the estimation of the cyanosis and the determination on the blood are given in Tables I to III. The figures of the first column indicate the serial number of the determination. In the second column are given in volumes per cent the values of the carbon dioxide (in Table I), the oxygen (Table II), and the oxygen unsaturation (Table III) of the venous blood. In Column 3 are the remarks on cyanosis, which are to be compared with the blood findings in Column 2. The figures in the fourth column indicate the serial numbers of corresponding determinations in Tables I to VI of Paper II (20), in which details about the patients and the blood determinations are given. In the last column are remarks about the condition of the individual from whom the blood has been drawn.

TABLE I.

*Carbon Dioxide Content of the Venous Blood (Whole Blood Kept under Oil) in a Series of Cyanotic and Non-Cyanotic Individuals.*

| Determination No. | Carbon dioxide of venous blood kept under oil. | Cyanosis. | Serial No. of determination in Tables I to VI (Paper II). | Remarks (diagnosis, etc.). |
|---|---|---|---|---|
| | *vol. per cent* | | | |
| 1 | 69.8 | − | Not published. | Anemia (hemoglobin 44 per cent by Haldane's method). |
| 2 | 67.7 | − | 47 | Pneumonia. |
| 3 | 62.1 | + | 4 | Normal individual after exercise. |
| 4 | 61.7 | − | 3 | " " resting. |
| 5 | 61.5 | +++ | 48 | Pneumonia. |
| 6 | 58.2 | +++ | 31 | Normal individual; artificial stasis on arm. |
| 7 | 58.1 | − | 9 | Slightly decompensated heart failure; rest. |
| 8 | 58.1 | ++ | 10 | " " " " exercise. |
| 9 | 57.0 | − | Not published. | Normal individual; rest. |
| 10 | 56.6 | + | 23 | Decompensated heart failure. |
| 11 | 56.6 | + | 30 | Normal individual; artificial stasis on arm. |
| 12 | 56.5 | − | 11 | Decompensated heart failure; rest. |
| 13 | 55.9 | + | 27 | " " " " |
| 14 | 55.6 | ++ | 12 | " " " exercise. |
| 15 | 55.4 | + | 24 | " " " rest. |
| 16 | 55.1 | − | Not published. | Normal individual; rest. |
| 17 | 54.7 | ++ | 28 | Decompensated heart failure; rest. |
| 18 | 54.1 | − | Not published. | Normal individual; rest. |
| 19 | 53.8 | + | 30 | Decompensated heart failure; rest. |
| 20 | 53.0 | + | 51 | Normal individual inhaling air with low oxygen percentage. |
| 21 | 52.1 | − | 50 | Normal individual; rest. |
| 22 | 51.9 | − | 29 | " " " |
| 23 | 51.5 | + | 34 | Congenital heart failure; cyanosis. |
| 24 | 51.3 | +++ | 52 | Normal individual inhaling air with low oxygen percentage. |
| 25 | 50.8 | − | 49 | Pneumonia. |
| 26 | 50.5 | − | 1 | Normal individual; rest. |
| 27 | 50.5 | + | 2 | " " exercise. |
| 28 | 49.4 | − | Not published. | Cardiac neurosis; tachycardia. |
| 29 | 48.3 | − | 26 | Compensated heart failure. |
| 30 | 46.8 | +++ | 38 | Congenital " " cyanosis. |
| 31 | 45.2 | ++ | 13 | " " " " |
| 32 | 44.6 | − | Not published. | Normal individual; exercise. |
| 33 | 44.1 | +++ | 14 | Congenital heart failure; cyanosis; exercise. |
| 34 | 42.1 | +++ | 39 | " " " " " |
| 35 | 41.5 | ++ | 35 | " " " " rest. |

TABLE II.

*Oxygen Content of the Venous Blood in a Series of Cyanotic and Non-Cyanotic Individuals.*

| Determination No. | Oxygen content of venous blood. | Cyanosis. | No. of determinations in Tables I to VI (Paper II). | Remarks (diagnosis, etc.). |
|---|---|---|---|---|
| | *vol. per cent* | | | |
| 1 | 0.00 | ++ | 12 | Decompensated heart failure; exercise. |
| 2 | 1.16 | − | Not published. | Anemia (34 per cent hemoglobin by Haldane's method). |
| 3 | 1.19 | − | " " | Anemia (32 per cent hemoglobin by Haldane's method). |
| 4 | 1.48 | − | " " | Anemia (44 per cent hemoglobin by Haldane's method). |
| 5 | 1.98 | − | " " | Anemia (44 per cent hemoglobin by Haldane's method). |
| 6 | 2.20 | − | " " | Anemia (43 per cent hemoglobin by Haldane's method). |
| 7 | 2.58 | + | 10 | Decompensated heart failure. |
| 8 | 3.14 | + | 20 | " " " |
| 9 | 3.79 | + | 15 | " " " |
| 10 | 3.95 | − | Not published. | Anemia (60 per cent hemoglobin by Haldane's method). |
| 11 | 4.10 | + | 22 | Decompensated heart failure. |
| 12 | 4.13 | + | 24 | " " " |
| 13 | 4.20 | + | 4 | Normal individual; exercise. |
| 14 | 4.29 | + | 19 | Decompensated heart failure. |
| 15 | 4.87 | − | Not published. | Anemia (55 per cent hemoglobin by Haldane's method). |
| 16 | 4.95 | +++ | 45 | Pneumonia. |
| 17 | 5.09 | − | Not published. | Anemia (55 per cent hemoglobin by Haldane's method). |
| 18 | 5.23 | + | 17 | Decompensated heart failure. |
| 19 | 5.42 | + | 6 | Normal individual; exercise. |
| 20 | 5.72 | + | 2 | " " " |
| 21 | 6.32 | ? | 21 | Decompensated heart failure. |
| 22 | 6.73 | − | 47 | Pneumonia. |
| 23 | 6.75 | +++ | 43 | " |
| 24 | 7.00 | + | 27 | Decompensated heart failure. |
| 25 | 7.32 | − | Not published. | Anemia (68 per cent hemoglobin by Haldane's method). |
| 26 | 7.37 | +++ | 52 | Normal individual inhaling air with low oxygen percentage. |
| 27 | 7.62 | + | 25 | Decompensated heart failure. |
| 28 | 7.76 | +++ | 46 | Pneumonia. |

TABLE II—*Concluded.*

| Determination No. | Oxygen content of venous blood. | Cyanosis. | No. of determinations in Tables I to VI (Paper II). | Remarks (diagnosis, etc.). |
|---|---|---|---|---|
| | *vol. per cent* | | | |
| 29 | 8.05 | − | 11 | Decompensated heart failure. |
| 30 | 8.17 | +++ | 31 | Normal individual; artificial stasis on arm. |
| 31 | 8.25 | + | 23 | Decompensated heart failure. |
| 32 | 8.52 | +++ | 40 | Pneumonia. |
| 33 | 8.54 | − | Not published. | Normal individual; slight exercise. |
| 34 | 8.55 | + | 16 | Decompensated heart failure. |
| 35 | 8.62 | + | 28 | " " " |
| 36 | 8.78 | ? | 8 | Compensated " " exercise. |
| 37 | 8.88 | − | 9 | Decompensated " " rest. |
| 38 | 9.09 | + | 30 | Normal individual; artificial stasis on arm. |
| 39 | 9.66 | ? | 26 | Decompensated heart failure. |
| 40 | 9.80 | +++ | 14 | Congenital " " exercise. |
| 41 | 10.13 | − | Not published. | Anemia (93 per cent hemoglobin by Haldane's method). |
| 42 | 11.40 | ++ | 34 | Congenital heart failure. |
| 43 | 11.40 | +++ | 41 | Pneumonia. |
| 44 | 11.51 | +++ | 39 | Congenital heart failure. |
| 45 | 12.26 | − | 49 | Pneumonia. |
| 46 | 12.62 | + | 51 | Normal individual inhaling air with low oxygen percentage. |
| 47 | 13.41 | − | 7 | Compensated heart failure. |
| 48 | 13.87 | +++ | 38 | Congenital " " |
| 49 | 14.00 | − | 5 | Normal individual; rest. |
| 50 | 14.19 | − | 3 | " " " |
| 51 | 15.28 | − | 29 | " " " |
| 52 | 15.40 | +++ | 37 | Congenital heart failure. |
| 53 | 16.20 | − | 26 | Compensated " " |
| 54 | 16.22 | +++ | 48 | Pneumonia. |
| 55 | 16.31 | − | 1 | Normal individual; rest. |
| 56 | 17.03 | − | 50 | " " " |
| 57 | 17.44 | +++ | 36 | Congenital heart failure. |
| 58 | 17.45 | ++ | 35 | " " " |
| 59 | 17.88 | ++ | 13 | " " " |
| 60 | 18.08 | ++ | 33 | " " " |
| 61 | 19.20 | ++ | 32 | " " " |
| 62 | 28.00 | − | Not published. | Polycythemia (Vaquez' disease). |

TABLE III.

*Oxygen Unsaturation of the Venous Blood in a Series of Cyanotic and Non-Cyanotic Individuals.*

| Determination No. | Oxygen unsaturation of venous blood | Cyanosis. | No. of determinations in Tables I to VI (Paper II). | Remarks (diagnosis, etc.). |
|---|---|---|---|---|
| | vol per cent | | | |
| 1 | 20.89 | +++ | 39 | Congenital heart failure. |
| 2 | 19.82 | ++ | 12 | Decompensated " " exercise. |
| 3 | 18.48 | +++ | 14 | Congenital " " " |
| 4 | 17.45 | +++ | 38 | " " " rest. |
| 5 | 17.30 | + | 24 | Decompensated " " " |
| 6 | 17.24 | + | 10 | " " " exercise. |
| 7 | 16.62 | ++ | 34 | Congenital " " |
| 8 | 15.88 | +++ | 37 | " " " |
| 9 | 15.41 | + | 15 | Decompensated " " |
| 10 | 14.68 | + | 2 | Normal individual; exercise. |
| 11 | 14.60 | + | 4 | " " " |
| 12 | 14.26 | +++ | 36 | Congenital heart failure. |
| 13 | 14.02 | + | 27 | Decompensated " " |
| 14 | 13.97 | + | 19 | " " " |
| 15 | 13.86 | + | 30 | " " " |
| 16 | 13.62 | + | 6 | Normal individual; exercise. |
| 17 | 13.48 | + | 20 | Decompensated heart failure. |
| 18 | 13.43 | +++ | 52 | Normal resting individual inspiring air with low percentage of oxygen. |
| 19 | 12.88 | − | Not published. | Normal individual; exercise. |
| 20 | 12.62 | ++ | 34 | Congenital heart failure. |
| 21 | 12.61 | +++ | 45 | Pneumonia. |
| 22 | 12.53 | +++ | 31 | Normal individual; artificial stasis on arm. |
| 23 | 12.52 | + | 22 | Decompensated heart failure. |
| 24 | 12.33 | + | 19 | " " " |
| 25 | 12.16 | +++ | 42 | Pneumonia. |
| 26 | 12.15 | + | 23 | Decompensated heart failure. |
| 27 | 11.58 | ++ | 28 | " " " |
| 28 | 10.94 | − | 9 | " " " |
| 29 | 10.92 | ++ | 33 | Congenital heart failure. |
| 30 | 10.83 | ++ | 35 | |
| 31 | 10.81 | +++ | 43 | Pneumonia. |
| 32 | 10.68 | − | Not published. | Cardiac neurosis; exercise. |
| 33 | 10.65 | + | 16 | Decompensated heart failure. |
| 34 | 10.47 | ? | 8 | " " " exercise. |
| 35 | 10.40 | ++ | 13 | Congenital " " |

TABLE III—*Concluded.*

| Determination No. | Oxygen unsaturation of venous blood. | Cyanosis. | No. of determinations in Tables I to VI (Paper II). | Remarks (diagnosis, etc.). |
|---|---|---|---|---|
| | *vol. per cent* | | | |
| 36 | 10.30 | ? | 21 | Decompensated heart failure. |
| 37 | 10.21 | + | 30 | Normal individual; artificial stasis on arm. |
| 38 | 9.90 | ++ | 32 | Congenital heart failure. |
| 39 | 9.54 | ? | 18 | Decompensated " " |
| 40 | 9.40 | − | Not published. | Normal individual; exercise. |
| 41 | 8.86 | +++ | 46 | Pneumonia. |
| 42 | 8.78 | +++ | 48 | " |
| 43 | 8.68 | +++ | 40 | " |
| 44 | 8.58 | − | Not published. | Normal individual; exercise. |
| 45 | 8.18 | + | 51 | " " inhaling air with low oxygen percentage. |
| 46 | 8.03 | ++ | 44 | Pneumonia. |
| 47 | 7.98 | − | Not published. | Cardiac neurosis; rest. |
| 48 | 7.93 | ++ | 41 | Pneumonia. |
| 49 | 7.12 | − | Not published. | Normal individual; rest. |
| 50 | 6.19 | − | 47 | Pneumonia. |
| 51 | 5.84 | − | 7 | Compensated heart failure; rest. |
| 52 | 5.20 | − | 5 | Normal individual; rest. |
| 53 | 5.01 | − | 3 | " " " |
| 54 | 4.82 | − | 26 | " " " |
| 55 | 4.72 | − | 29 | " " " |
| 56 | 3.79 | − | 1 | " " " |
| 57 | 3.77 | − | 50 | " " " |
| 58 | 2.35 | − | 49 | " " " |

In Table I are given the values in volumes per cent of the carbon dioxide of the whole (unchanged) venous blood. In twenty-three instances cyanosis of different degrees was encountered; in twelve instances no cyanosis was found. The table is arranged according to decreasing values of carbon dioxide. It is easily seen that no relation exists between the carbon dioxide content of the (venous) blood and cyanosis. A cyanotic color may be associated with low as well as with high values of carbon dioxide.[2]

[2] The upper normal limit of the carbon dioxide of the venous blood (whole blood drawn and kept under oil) is approximately 65 volumes per cent, the lower limit about 40 volumes per cent. Determinations of the carbon dioxide of whole blood in a series of individuals will be published later.

In Table II are given the values of the oxygen of the venous blood in volumes per cent. The table is arranged according to increasing values of oxygen content. A glance at the table shows that the amount of oxygen left in the venous blood[3] has no simple relation to the production of cyanosis. One may find cyanotic patients with very low values for the venous oxygen and others with very high values. As in Table I, the non-cyanotic are distributed over the same range.

The table shows that one may find very high (28.00 volumes per cent), as well as extremely low values for the venous oxygen. In one case (Determination 1) the venous blood contained no oxygen. The importance of this fact is discussed in a previous paper (21).

Table III presents the values of the oxygen unsaturation[4] arranged according to decreasing values. There is no doubt that some intimate relation exists between the oxygen unsaturation and the cyanosis. The most striking feature is undoubtedly that cyanosis is not associated with values of the oxygen unsaturation below about 8 volumes per cent (7.93 volumes per cent for No. 48).[5] This is of considerable importance because the upper limit of oxygen unsaturation in resting normal individuals has previously (16) been found to be about 8 volumes per cent.

This does not at all mean that we find a cyanotic color in all instances in which the oxygen unsaturation is above that limit. It is seen that values of the oxygen unsaturation from 8 to about 13.0 volumes per cent (12.88 volumes per cent for No. 19) may be encountered in cyanotic as well as in non-cyanotic individuals. Values above 13.0 volumes per cent have in all instances been associated with cyanosis. The highest observed value for the oxygen unsaturation is about 21 volumes per cent (20.89).

[3] In a previous publication (21) this is termed rest oxygen or reserve oxygen of the blood, analogous to the reserve force of the heart muscles.

[4] That is, the difference between the total oxygen capacity of the blood and the venous oxygen.

[5] In several other unpublished determinations of oxygen unsaturation the same holds true.

## SUMMARY.

These data prove that abnormally high oxygen unsaturation of the blood is a cause of cyanosis.

The fact that the lowest value of oxygen unsaturation (in the venous blood) associated with cyanosis is about 8 volumes per cent seems to indicate that this amount of reduced hemoglobin is the lowest capable of producing a cyanotic color. We shall later discuss this point more in detail.

Table III shows furthermore that in spite of the fact that cyanosis is due to abnormally high oxygen unsaturation, no proportionality exists between the intensity of the blue color and the amount of reduced hemoglobin. This may in small part be due to individual peculiarities of the skin and subcutaneous tissue, which are known to influence in anemia the relation between paleness of the skin and the decrease in hemoglobin.

We shall, however, in the succeeding paper show that the main cause of the disproportionality between cyanosis and venous oxygen unsaturation is found in another factor, the recognition of which throws a clearer light on the pathogenesis of cyanosis, and explains why we may find values of oxygen unsaturation as high as 13 volumes per cent in non-cyanotic individuals.

## BIBLIOGRAPHY.

1. de Senac, J. B., Traité de la structure du cœur, de son action et de ses maladies, Paris, 1749.
2. Morgagni, J. B., De sedibus et causis morborum per anatomen indagatis libri quinque, Venice, 1761.
3. Grancher, J., quoted from Hirschfelder, Diseases of the heart and aorta, Philadelphia and London, 2nd edition, 1913, 552.
4. Knapp, quoted from Posey, *Am. J. Med. Sc.*, 1905, cxxx, 415.
5. Panum, P. L., Untersuchungen über die Entstehung der Missbildungen zunächst in den Eiern der Vögel, Berlin, 1860.
6. Dareste, C., Recherches sur la production artificielle des monstruositiés, ou essais de téra togénie expérimentale, Paris, 2nd edition, 1891.
7. Stockard, C. R., *J. Exp. Zool.*, 1906, iii, 99.
8. Bardeen, C. R., *J. Exp. Zool.*, 1907, iv, 1.
9. Loeb, J., *Arch. ges. Physiol.*, 1893, liv, 528.
10. Krehl, L., *Deutsch. Arch. klin. Med.*, 1889, xliv, 426.

11. Vaquez, H., *Compt. rend. Soc. biol.*, 1892, iv, series 9, 384.
12. von Bamberger, H., Lehrbuch der Krankheiten des Herzens, Vienna, 1857.
13. Lundsgaard, C., *J. Exp. Med.*, 1918, xxvii, 219.
14. Langstroth, L., *Arch. Int. Med.*, 1919, xxiii, 56.
15. Lundsgaard, C., *J. Biol. Chem.*, 1918, xxxiii, 133.
16. Lundsgaard, C., *J. Exp. Med.*, 1918, xxvii, 179.
17. Van Slyke, D. D., *J. Biol. Chem.*, 1918, xxxiii, 127.
18. Van Slyke, D. D., *J. Biol. Chem.*, 1917, xxx, 347.
19. Van Slyke, D. D., and Cullen, G. E., *J. Biol. Chem.*, 1917, xxx, 307.
20. Lundsgaard, C., *J. Exp. Med.*, 1919, xxx, 271.
21. Lundsgaard, C., *J. Exp. Med.*, 1919, xxx, 147.