Retrospect

CYANOSIS

Lundsgaard, C., and Van Slyke, D.
Medicine, 1923, II, 1-76.

MAUDE E. ABBOTT, M.D.

Montreal

THIS important monograph presents what may be termed the last word to date from a series of studies on the oxygen content of the venous blood and the causation of cyanosis in various normal and disordered conditions of the circulation that have been carried out by Lundsgaard and his associates during the last five years by means of the method and apparatus devised by Van Slyke, for the estimation of its oxygen content and oxygen combining capacity (reduced haemoglobin). The conclusions formulated and applied here are based upon large series of experments reported in these earlier publications,* which may be re-read with much interest in this connection. Certain values for oxygen consumption under similar conditions of the circulation, obtained by Lundsgaard in earlier researches† upon the gaseous content of the alveolar air by the nitrous oxide method of Krogh and Lindhard are also quoted for purposes of control and comparison. The result is a mass of authoritative and exact quantitative information upon the nature and interrelationship of the various etiological factors taking part in the phenomena of cyanosis, which dispels much of the confusion surrounding our ideas of this condition and also throws a searchlight across many obscure questions in cardiac decompensation. The problems that have been attacked and disentangled are so complex and their solution here is of such great practical importance in clinical medicine that a somewhat detailed review is desirable.

The authors begin with a brief introductory statement defining the term cyanosis as "a diffuse bluish discolouration of the skin and mucous membrane, more marked in certain regions of the body than in others, (lips, fingers, etc.,), but generalized in its distribution and varying both in shade of colour from heliotrope to leaden, and in degree of intensity, in different cases, according to the variations in the conditions inducing the essential cause, which is defined as a change in the character of the blood, due either to an increase of the reduced haemoglobin physiologically present, or to the formation of the abnormal components, methaemoglobin and sulphaemoglobin." The present enquiry is confined to that form of cyanosis produced by an increased amount of reduced haemoglobin in the blood. To express the volume of concentration of this body the term "oxygen unsaturation," now in general use, has been introduced by Lundsgaard, for the reason that oxygen values are thus experimentally determined and are, therefore, most convenient both for notation and expression. This term is employed throughout in this article, and the calculation is made that, since 1 cc. of oxygen combines with 0.75 grams of haemoglobin, 5 grams of haemoglobin may be expressed as $\frac{5}{0.75}$ or 6.7 volumes per cent. of oxygen unsaturation, which has been experimentally determined by the authors to be the "threshold value" at which cyanosis may be expected to appear. This figure is in volumes per cent. of 100 cc. of haemoglobin, and it has been arrived at by taking the average or mean of the oxygen unsaturation of the arterial and venous bloods (at the entrance and exit of the capillary) obtained by the Van Slyke method as follows: $C = \frac{A+V}{2}$; for we understand by cyanosis the altered colour of the blood as it is seen through the *capillary* walls.

The essential or primary cause of cyanosis having thus been established as an increased "mean capillary oxygen unsaturation" of known "threshold value," the various elements entering into its production and modifying the character and intensity of the cyanosis to which it leads are discussed. They are divided by the authors into two groups, (*a*) modifying factors, and (*b*) factors directly *influencing the concentration of reduced haemoglobin (oxygen unsaturation) in the blood stream.* As modifying factors

*Gasometric Determination of Oxygen and Haemoglobin of the Blood: D. D. Van Slyke, *Jour. Biol. Chem.*, 1918, XXX, 127-132. Studies of Oxygen in the Venous Blood in Normal Individuals: C. Lundsgaard, *Ibid*, 1918, XXXIII, 119-144. Studies on Oxygen Unsaturation in the Venous Blood in a Group of Patients with Circulatory Disturbances: C. Lundsgaard, *Jour. Exp. Med.*, XXVII, 179-247. Studies on Cyanosis, its Primary and Secondary Causes—Erythrosis or False Cyanosis: C. Lundsgaard, *Jour. Exper. Med.*, XXX, 259-269, 271-293.

†*Untersuchungen ueber das Minutenvolumen des Herzens*: C. Lundsgaard, *Deutsch. Arch. f. klin. Med. Leipz.*, 1916-16, cxviii, 481; 1916, cxx, 481.

are enumerated, (1) the thickness of the epidermis, (2) the normal pathological pigmentation of the skin, (3) the colour of the blood plasma, (4) the concentration of oxyhaemoglobin in the blood, (5) the number, width and extent of the blood-filled capillaries of a given surface area, (6) the extent to which the oxygen unsaturation in the capillary approximates more closely to that of the artery or the vein with which it communicates (oxyhaemoglobin-dissociation curve). The fifth factor, the increase in size and thickness of the wall of the surface capillaries, which has long been recognized as a constant and prominent feature in all cyanosis of long standing, has been much elucidated by recent advances in methods of investigation, such as the invention by Lombard and Weiss of capillary microscopy, and the discovery by Krogh of a "capillary motor function." The results obtained by these authors in proving by actual measurement the increase in size and number of the capillaries are fully described and figured, as also the alterations in the capillaries in polycythaemia, acro-cyanosis, stasis of cardiac origin, or produced by thermic stimuli, etc. The sixth factor, changes in the oxygen content of the capillary blood as it passes from its arterial to its venous end, is represented graphically as a curve which may be greater at either arterial or venous end according to the conditions; for practical purposes of calculation these variations are ignored and the "mean capillary unsaturation" is considered to be the average, that is the exact half of the volumes per cent. of the oxygen unsaturation in the arterial and venous ends, which gives, for purposes of calculation the simple formula C (mean capillary oxygen unsaturation) $= \frac{A+V}{2}$, A representing the arterial, and V the venous, unsaturation at either end of the capillary.

The second group of factors, those influencing the concentration of oxygen unsaturation in the blood, is by far the most important part of this communication, and is that which gives to it its epoch-making character. Four possible factors are recognized, the decreased pulmonary oxygenation, increased haemoglobin total, stasis in the systemic capillaries, and entrance of arterial blood into the arterial stream. Each of these factors can be stated quantitatively and the "normal values" in terms of mean capillary oxygen unsaturation, have been numerically established. By a brilliant process of reasoning, the effect of the relative magnitude of each upon the "threshold value" of each of the others has also been calculated. The following brief outline of the figures and symbols used is necessary for their clear exposition:

The oxygen capacity of the blood is normally about twenty volumes per cent., and in normal individuals the blood emerges from the lungs ninety-five per cent. saturated; that is, the arterial blood normally contains nineteen volumes of oxyhaemoglobin and one volume per cent. of oxygen unsaturation; this portion which passes through the lungs unsaturated under physiological conditions is called *l*; and an increase of it in the arterial blood coming from the aerated parts of the lungs beyond the one volume per cent. physiologically present is our first "influencing factor" in the production of cyanosis.

In passing through the tissues, the blood loses five volumes per cent. of oxygen and it, therefore, emerges in the veins with fourteen volumes per cent. of oxyhaemoglobin and six volumes per cent. of oxygen unsaturation, making the normal "mean capillary unsaturation" $\frac{1+6}{2} = 3.5$ volumes per cent. The amount of oxygen thus lost in passing through the tissues (five volumes) is called D. It is readily understood that if through slowing of stream in the capillaries or other cause, oxygen consumption in the tissues be raised beyond five volumes per cent., the "threshold value" of cyanosis will be passed. D is thus a second possible factor in the production of cyanosis.

The third factor is pointed out to be an increase of the total haemoglobin in the blood. This is called T. An increased T tends to influence the degree of oxygen unsaturation produced by decreased pulmonary oxygenation (increased *l*) and acts in conjunction with this factor to deepen the cyanosis, but is of relatively little effect alone.

Finally, a fourth factor arises in certain pathological states of the circulation, when, either by passage through a cardiac septal defect in certain congenital lesions, or by passage through a part of the lung which is entirely cut off from its air supply, as in pulmonary emphysema, a portion of unaerated (venous) blood is projected directly into the arterial stream. To this "right to left shunt" of the circulation the symbol a has been given. It is regarded as a very powerful factor in producing cyanosis, and when it is combined with an increased D (stasis in the systemic capillaries) as is very commonly the case, its effect is very marked.

These factors thus act in pairs, T increasing the importance of *l*, and D the seriousness of *a*. From formulae based upon the simple initial one that $C = \frac{A+V}{2}$, together with the actual values of T (obtained by direct estimation of the haemoglobin content), and of l and D (by determination of the reduced haemoglobin in the arterial* and the venous blood respectively), the value of *l*, that is, the amount of oxygen unsaturation transmitted by the right to left shunt, may be numerically determined in any given case where the diagnosis is made.

The relative magnitudes of these factors are shown graphically in terms of mean capillary oxygen unsaturation, by curves calculated numerically on the basis of experimental determinations, in the form of three charts, which present this remarkable series of inductions in a highly ingenious manner. In the first of these, the relation of all four curves to each other and to the normal threshold values of capillary oxygen unsaturation appears. From it, it is evident that of the four factors *l* and *a*, the unsaturation of the blood coming from the aerated parts of the lungs and the shunt of venous into arterial blood), are the most severe in their influence, in that they approach most quickly the threshold value, rise higher, and produce cyanosis at a smaller deviation from their physiological values, other factors remaining normal, than any other; and that T has the lowest range of all in its influence on unsaturation and cannot of itself reach the cyanosis threshold. The two other charts show by means of the same curves the interaction of these four factors in pairs, *l* with T (decreased pulmonary oxygenation and increased haemoglobin content—witness the mountain sickness of the polycythaemia of high altitude); and *a* with D (shunting of venous into arterial blood with stasis in the systemic capillaries, as in pulmonary stenosis with septal defect and in pulmonary emphysema).

The clinical conditions associated with cyanosis are next briefly reviewed and the factors at work analyzed. In tracheal and bronchial stenosis, where the obstruction is only partial, in bronchitis, bronchial asthma, emphysema, influenzal pneumonia (especially that of the "heliotrope" type) and oedema of the lungs, an increased *l*, due to lowered diffusion of oxygen from fluid in the alveoli and other causes, is the chief factor at work. Hence the value here of oxygen therapy. In complete obstruction of the bronchus or in certain cardiac septal defects, or again, in certain types of pneumonia the *a* factor is present, in that a stream of entirely unaerated blood is deflected into the arterial stream. Under these conditions the author has demonstrated that, other factors being equal, cyanosis does not appear until one-third of the pulmonary circulation is so deflected, or until the venous blood passing through a septal defect assumes this proportion to the arterial current into which it flows. Oxygen therapy is here, of course, of no value. Again, in cardiac decompensation of myocardial origin, as in aortic and pulmonary stenosis, an increased D from stasis of the stream produces the chief effect, while in mitral lesions we have both an increased *l* and D at fault.

The subject of a "left to right shunt" of arterial into venous blood, such as occurs in so-called compensated cardiac septal defects, is discussed at some length. It has, of course, no bearing on the causation of cyanosis.

The monograph closes with a complete bibliography following upon an historical survey of our knowledge of this subject. In the latter connection it is of interest to note that Senac, in 1749, in reporting the first fully studied case of congenital cyanosis with autopsy, pointed out, with truth, that a right to left shunt (*a*) through a deficient septum was here the factor producing the cyanosis; and that Morgagni, in 1761, in making the then apparently conflicting statement that the cyanosis in pulmonary stenosis was due to stasis of the stream (Lundsgaard's D factor) was equally in the right!

In conclusion, this review cannot fairly end without a word of comment on the epoch-making character of the communication here presented. From a careful study of it and of the various charts and diagrams with which this article is enriched, numerous inevitable and highly suggestive inferences present themselves to the reader, which are borne out at all points by the clinical and pathological facts of congenital cardiac disease. In the revelation here presented of the scope and value of the knowledge both of the circulation and the respiration that has become available to us through the Van Slyke technique, we stand as it were before an open door through which a stream of light radiates into the very heart of cardiac pathology. Moreover, the brilliant series of inductions by which the facts so obtained have been applied to the

*The capillary blood obtained by cutting the finger without pressure is found to be sufficiently close to the arterial blood in oxygen content for use.

elucidation of this obscure subject, seem to us to have their only parallel in this field in the great work of Rokitansky on cardiac defects, which formulated, on the basis of physiological law, hypotheses of far-reaching significance that have since found their verification in the previously uncorrelated morphological details.

THE BLOOD SEDIMENTATION TEST:—ITS HISTORY, TECHNIQUE, NATURE AND CLINICAL APPLICATION*

THEO. R. WAUGH, M.D.

James Douglas Fellow in Pathology, McGill University

Many years ago when blood letting was the almost universal treatment of disease the observation was made by Galen, Hunter, Virchow, Wunderlich, and others that in some affections, particularly the acute inflammatory processes, there occurred a marked acceleration of sedimentation of the blood cells in the drawn blood. This was at times so rapid that, even in the absence of a substance to prevent coagulation, there occurred before coagulation set in a partial sinking of the cells away from the surface, leaving a clear, yellowish serum. This was given the name *crusta phlogistica* or *crusta inflammatoria* and was looked upon as an extremely grave sign. With the gradual exit of "bleeding" as a therapeutic measure in such conditions, the phenomenon was forgotten or at least disregarded. Recently in 1917, Robin Fahraeus of Stockholm, working in the Physiological Institute of the University of Kiel, rediscovered the fact, and in articles published in *Hygiea*, in 1918, and in the *Biochemische Zeitschrift* of the same year, stated that the phenomenon might be employed in the form of a test for pregnancy, as there was considerable acceleration of sedimentation velocity in that condition. He noted that it occurred also in infectious diseases and malignant tumours. Linzenmeier, of Kiel, also took up the question, developed a precise technique, and applied the test to a large gynaecological service. Many others followed and soon continental literature was flooded with a wealth of articles dealing with the various phases of the phenomenon; some interesting themselves with its explanation while others applied the test to the difficulties of clinical diagnosis.

THE TECHNIQUE

True to the spirit of modern scientific medicine, the workers on this subject immediately fell to the task of establishing a definite technique whereby the change in velocity of sedimentation of the red cells could be expressed numerically. Various methods have been advocated, all more or less alike, but differing in the size of tube and amount of material employed and the so-called "end-point" or time of reading. More recently the method brought out by Linzenmeier has been quite generally accepted and adopted. His own description of his technique is as follows:

Necessary utensils: (a) A 1 ccm. glass syringe tested to 1 ccm. and with divisions into tenths. (b) Small settling-tubes about 6.5 cm. high and 5 mm. clear breadth, which will contain somewhat more than 1 ccm. and bear the following marks: An upper mark which corresponds to the bottom of the meniscus formed when 1 ccm. of water is placed in the tube and below this four other marks at distances of 6, 12, 18, and 24 mm., respectively, from the 1 ccm. line. (c) A 5% sodium citrate solution in a wide-necked flask. (This becomes turbid after long use and must be replaced).

Technique: (1) The syringe to be used must be completely dry or rinsed with the sodium-citrate solution. (2) 0.2 ccm. of the sodium-citrate solution is drawn into the syringe. (3) The sedimentation tube must be absolutely clean and dry. (4) The cubital vein is punctured after short stagnation of the blood. (Long stagnation tends to increase the red corpuscle content and to allow carbonic acid increase in the blood which alters the result). (5) Withdrawal of 0.8 ccm. of blood into the syringe, making with the 0.2 ccm. of sodium-citrate which it already contains, 1ccm. (6) The syringe is immediately emptied into the sedimentation-tube, which should be filled exactly to the 1 ccm. mark. (7) Mixing of the solution and blood to prevent clotting by slowly inverting the tube twice. (8) Note the time required for the line of separation between blood corpuscles and plasma to reach the various lines,—that is 6, 12, 18, and 24 mm. below the 1 ccm. mark. This is the sedimentation time. (9) The tube should be placed in perfectly perpendicular position at room temperature. (10) Should the

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