Ever since the discovery that incomplete oxygenation of arterial blood is the cause of central cyanosis, the question has been asked: How much reduced (deoxygenated or unsaturated) hemoglobin (RHB) is needed to generate central cyanosis? The amount commonly quoted, 5 g of RHB/dl of blood, comes from the classic 1923 monograph by Lundsgaard and Van Slyke (emphasis added).\textsuperscript{2,4}

About 5 grams of reduced hemoglobin per 100 c.c. of capillary blood appear necessary to cause cyanosis, the amount of oxygenated hemoglobin also present having relatively little effect. An anemic with less than 5 grams of hemoglobin per 100 c.c. of blood cannot usually become cyanotic. It is the blood in the capillaries, and possibly in the arterioles and venules of the subpapillary plexus as well, which produces the cyanotic skin color. The arteries and most of the veins are so far away from the skin that their content cannot influence the skin color.

Unfortunately, the location of the 5 g/dl RHB, so clearly stated by Lundsgaard and Van Slyke, is often overlooked by modern authors. As a result, the medical literature reflects confusion over the difference between what is measured (arterial levels of oxygenated and reduced hemoglobin) and what actually generates cyanosis (quantity of reduced hemoglobin in the capillaries). Several authors have mistakenly compared arterial levels of RHB with the capillary value of Lundsgaard and Van Slyke and as a result found the Lundsgaard and Van Slyke value too high.\textsuperscript{3,6}

To clarify this confused state of affairs we searched for all original articles that provide data on the oxygen levels at which cyanosis is detectable (Table 1).\textsuperscript{3,4,7-15} We also examined all review papers and letters on the subject that are either indexed in Medline (1966 to present) or referenced in other articles.\textsuperscript{5,16-24} as well as 24 textbooks (12 pulmonary medicine,\textsuperscript{25-36} seven internal medicine,\textsuperscript{5,37-42} and five emergency medicine\textsuperscript{43-47}) for their discussions of cyanosis.

**LITERATURE SURVEY (Table)**

Of the ten original articles published after 1923,\textsuperscript{3,4,8-15} all but two\textsuperscript{13,14} reference the Lundsgaard and Van Slyke paper by footnote. Two of the ten articles\textsuperscript{3,4} erroneously compare an arterial value of RHB to the capillary value of Lundsgaard and Van Slyke.

One review article also makes this erroneous comparison\textsuperscript{9} and as a result states that the value of 5 g/dl is "incorrect." Two other review articles\textsuperscript{23,24} err by placing the value of 5 g/dl RHB in the arterial circulation. None of the three errant review articles references the 1923 Lundsgaard and Van Slyke article.

A fourth review article\textsuperscript{30} notes that the capillary RHB value of Lundsgaard and Van Slyke and the arterial value quoted in "medical textbooks" are the same, but does not discuss or try to resolve the discrepancy. Four of eight review articles seem to provide a satisfactory discussion of RHB in cyanosis.

**Table 1—Value of \(PaO_2\), \(SaO_2\), or Reduced Hemoglobin at Which Central Cyanosis Is Detectable**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Arterial Blood</th>
<th>Capillary Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lundsgaard (1923)\textsuperscript{4}</td>
<td>NS</td>
<td>RHB 5</td>
</tr>
<tr>
<td>Campbell (1923)\textsuperscript{3}</td>
<td>(SaO_2&lt;90)%</td>
<td>NS</td>
</tr>
<tr>
<td>Brinkman (1938)\textsuperscript{4}</td>
<td>(SaO_2&lt;94)%</td>
<td>NS</td>
</tr>
<tr>
<td>Bluhm (1942)\textsuperscript{4}</td>
<td>(SaO_2&lt;95)%</td>
<td>NS</td>
</tr>
<tr>
<td>Comroe (1947)\textsuperscript{30}</td>
<td>Most observers could not detect cyanosis until (SaO_2 80)% or less</td>
<td>†</td>
</tr>
<tr>
<td>Geraci (1951)\textsuperscript{11}</td>
<td>Definite: &quot;(SaO_2) about 75%&quot;</td>
<td>†</td>
</tr>
<tr>
<td>Medd (1959)\textsuperscript{11}</td>
<td>Variable detection until (SaO_2 75% or less</td>
<td>NS</td>
</tr>
<tr>
<td>Kelman (1966)\textsuperscript{13}</td>
<td>(SaO_2&lt;90)%</td>
<td>NS</td>
</tr>
<tr>
<td>Morgan-Hughes (1968)\textsuperscript{14}</td>
<td>(SaO_2 85-89)%</td>
<td>NS</td>
</tr>
<tr>
<td>Barnett (1982)\textsuperscript{3}</td>
<td>RHB 3.48 (mean)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>RHB 2.38 (threshold)</td>
<td></td>
</tr>
<tr>
<td>Goss (1988)\textsuperscript{a}</td>
<td>RHB = 1.50</td>
<td>NS</td>
</tr>
<tr>
<td>Coté (1988)\textsuperscript{15}</td>
<td>(SaO_2&lt;72)%</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Articles are listed by senior author. Unless otherwise noted, values quoted are those at which cyanosis was easily detectable in a majority of patients. Data from each article show a wide range of--arterial oxygen values at which the sign is first apparent. RHB = reduced (deoxygenated) hemoglobin, g/dl blood; NS = specific value not stated.
†Authors quote 5 g/dl RHB value published by Lundsgaard and Van Slyke.
One recent letter, attempting to clarify the importance of capillary RHB, confused the arterial and capillary SaO₂ values in cyanosis; the reply to this letter did not clear up the confusion.

Of the 24 standard textbooks we examined, only one references the 1923 Lundsgaard and Van Slyke article, but it does not specify that the 5/dl RHB is in the capillaries. In fact, only eight of the 24 textbooks, state a specific value for RHB and place it in the capillaries.

**DISCUSSION**

Central cyanosis (blueness of skin, lips, mucous membranes), as opposed to peripheral cyanosis, is always a manifestation of hypoxemia. Except for the relatively uncommon causes of methemoglobinemia, sulfaemoglobinemia, and some hemoglobinopathies, central cyanosis is always accompanied by a low arterial Po₂. As a result of hypoxemia an excess amount of hemoglobin is not saturated with oxygen; in currently accepted terminology this unsaturated hemoglobin is said to be reduced. It is the quantity of reduced hemoglobin (RHB) per deciliter of capillary blood, not the relative lack of oxygenated hemoglobin, that accounts for the bluish color of cyanosis.

In their monograph Lundsgaard and Van Slyke noted that:

since it is impossible to know what condition prevails [in the capillaries], we have, in relating cyanotic color to the content of reduced hemoglobin in the capillary blood, assumed . . . the average unsaturation of capillary blood is midway between that of the arterial and venous bloods respectively . . .

and

The effect of . . . modifying factors is to cause the mean capillary concentration of reduced hemoglobin at which cyanosis becomes perceptible to vary from 4 to 6 grams of reduced hemoglobin per 100 c.c. of blood, and perhaps sometimes even more widely, although it appears usually to lie near 5.

Since, to our knowledge, no other investigators independently arrived at 5 g/dl RHB as the value necessary for central cyanosis, it is safe to assume that this widely quoted number originated with the 1923 Lundsgaard and Van Slyke article.

We began this review after reading a study that compared its arterial RHB with Lundsgaard and Van Slyke's higher capillary RHB value yet failed to acknowledge the different locations of the two RHB values. After reviewing that paper's references, plus additional articles and textbooks, we discovered other instances of such miscomparison, including assertions that the Lundsgaard and Van Slyke value of 5 g/dl value is too high, "incorrect," or "false."

The "false" label is an unreferenced assertion based on apparent ignorance of the Lundsgaard and Van Slyke paper. The author justifies his claim by stating that an SaO₂ of 87%-2.6 g of reduced Hb is readily detectable. Calculations show that 2.6 g/dl of RHB in arterial blood represents a capillary RHB of about 4.4 g/dl (Fig 1). Had the author appreciated this fact it seems highly unlikely he would have labeled the 5 g/dl value "false."

Flenley, the author of the "incorrect" label, states:

The commonly quoted figure of 5 g/dl of reduced haemoglobin for the detection of arterial cyanosis is incorrect, as with a normal haemoglobin concentration this would mean that central cyanosis can only be detected when the arterial Po₂ is below 35 mm Hg—by which time the patient may well be nearly dead from hypoxaemia!

Assuming a hemoglobin content of 15 g/dl, this statement would be true only if the 5 g/dl RHB is in arterial blood. Figure 1 shows that a capillary RHB of 5 g/dl is reached when SaO₂ is between 78 percent (hemoglobin content [HC] 15 g/dl; PaO₂, 44 mm Hg) and 73 percent (HC, 12 g/dl; PaO₂, 39 mm Hg). A threshold PaO₂ of 35 mm Hg for detecting cyanosis occurs only when the HC is about 10 g/dl (ie, anemia).

Two recent original articles also manifest the error made by Flenley. Barnett et al found, in 20 patients with central cyanosis, a mean arterial deoxyhemoglobin concentration of 3.48 g/dl . . . [this concentration] rather than 5 g/dl, as suggested by others, is necessary before central cyanosis can be detected.

However, note that the Barnett et al arterial RHB represents a capillary RHB of about 5.3 g/dl (Fig 1). Barnett et al found an arterial RHB "threshold value" for detecting cyanosis of 2.36 g/dl; this value represents a capillary RHB of about 4.3 g/dl.

**Reduced Hemoglobin Content in Arterial and Capillary Blood**

**Figure 1.** Values for capillary and arterial reduced hemoglobin (RHB, g/dl) are shown on the vertical axis and percent saturation of hemoglobin in arterial blood (SaO₂) on the horizontal axis, with corresponding PaO₂ (mm Hg). Each diagonal line represents a different hemoglobin content (g/dl). Based on the study by Lundsgaard and Van Slyke, patients with capillary RHB around 5 g/dl (horizontal line) should manifest cyanosis. Calculations used to draw the graph are based on the following assumptions: Cardiac output = 5 L/min; PaCO₂ = 40 mm Hg; arterial pH = 7.40; carboxyhemoglobin, methemoglobin = 0; oxygen uptake = 550 O₂ / min; C (Ar+v) O₂ = 5 ml O₂/dl blood.
Goss et al4 state: The important new finding in our study was that central cyanosis can be detected reliably at deoxyhaemoglobin concentrations of 1.5 g/dl or more, thus confirming Flenley’s conclusions.

No other original article has reported such a low arterial RHB threshold for cyanosis, yet even this arterial RHB value represents a capillary RHB content of about 3.30 g/dl (Fig 1).

Our review of original articles (Table 1) shows a wide range of SaO2 values at which cyanosis was detectable. Such variability in detection is explained by the numerous factors involved, including hemoglobin content, skin color and perfusion, lighting, and interobserver variation. Nonetheless, all other factors being equal, the greater the hemoglobin content the more readily cyanosis appear as SaO2 falls; conversely, the lower the hemoglobin content the more SaO2 has to fall before cyanosis becomes manifest (Fig 1).

It is best to view the value 5 g/dl RHB in the capillaries the way Lundsgaard and Van Slyke intended—as the quantity, plus or minus 1 g/dl, at which cyanosis should be detectable in the majority of patients. Our review of the literature does not support the contention that this value is too high, “false,” or “incorrect.” At this level of capillary RHB, cyanosis should be detectable when SaO2 is between 73 percent (hemoglobin, 12 g/dl) and 78 percent (hemoglobin, 15 g/dl, Fig 1). In some patients cyanosis may be detectable at higher levels of oxygenation.

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How Much Reduced Hemoglobin Generates Central Cyanosis? (Martin, Khalil)