

## Hereditary Methemoglobinemia as a Cause of Cyanosis during Anesthesia

RONALD A. GABEL, M.D.,\* AND H. FRANKLIN BUNN, M.D.†

The clinician should look upon cyanosis as primarily a sign of reduction in the proportion of hemoglobin saturated with oxygen. It is generally accepted that mucous membranes and skin begin to turn from pink to blue when the concentration of deoxyhemoglobin in capillary blood exceeds 5 g/100 ml.<sup>1</sup> Only after exhaustive investigation has failed to turn up a reason for hypoxemia can the anesthesiologist safely devote attention to less common causes of cyanosis. This process of diagnosis by exclusion is exemplified by the following case report.

### REPORT OF A CASE

A 47-year-old American-born Chinese woman was anesthetized with thiopental, nitrous oxide, and *d*-tubocurarine for cholecystectomy. The inspired fraction of oxygen ( $F_{iO_2}$ ) was 0.25 until the blood appeared desaturated as the skin was incised.  $F_{iO_2}$  was increased first to 0.50, then to 0.99, and halothane, 0.25–0.5 per cent, was substituted for nitrous oxide.

The flowmeters were visually double-checked, the chest auscultated, the source of oxygen changed from wall to cylinder, the patient's body temperature taken, and a sample of inspired gas analyzed for oxygen. None of these measures suggested an origin of the cyanosis. A sample of arterial blood was then drawn and analyzed with conventional electrodes, giving values of  $P_{aO_2}$  449 torr,  $P_{aCO_2}$  17 torr, pH 7.68, and base excess (calculated) +1.8 mEq/l. On an IL 182 CO-Oximeter, oxygen saturation read 95.3 per cent, hemoglobin 10.1 g/100 ml. Hematocrit was 39

per cent. Two further samples drawn at 30-min intervals, with  $F_{iO_2}$  0.99, each showed a  $P_{aO_2}$  greater than 500 torr and oxygen saturation 95.2 per cent.

Blood taken from an external jugular vein could not be visually distinguished from the arterial samples. This, combined with the discrepancies between values for  $P_{aO_2}$  and saturation, and between hemoglobin concentration and hematocrit, led us to consider an abnormal hemoglobin as a possible explanation for the cyanosis. Meanwhile, cholecystectomy was uneventfully completed.

A venous blood sample drawn intraoperatively for methemoglobin analysis was inadvertently discarded, but samples drawn 6 and 13 days post-operatively showed 9 and 14 per cent methemoglobin, respectively, by the method of Evelyn and Malloy.<sup>2</sup> NADH-methemoglobin reductase, assayed according to Hegesh, was totally absent from the patient's blood.<sup>3</sup> Deficiency of this enzyme was confirmed by treating the patient's erythrocytes with nitrite to oxidize hemoglobin, then incubating the erythrocytes in the presence of glucose and lactate.<sup>4</sup> In contrast to normal, methemoglobin in the patient's blood was reduced very slowly. There was no M-hemoglobin by spectral and electrophoretic analyses.

Questioning of the patient disclosed pertinent medical history not given during surgical or pre-anesthetic evaluation. Since childhood, she had had "spells" during which her skin turned quite blue, sometimes for as long as a day or two. These episodes occasionally were accompanied by dyspnea and once led to syncope. An attack at 25 years of age might have been precipitated by a dose of aspirin. Current medication included Percodan, Stelazine, pentobarbital (Nembutal), Metamucil, and multivitamins. There was no known family history of cyanosis.

Despite this history, the patient had been an acrobat until 18 years of age when she had been injured falling from a trapeze and required a cup arthroplasty of the right hip. Over the subsequent 29 years, she had had several further surgical procedures on the hip, and at the time of the cholecystectomy chronic pain necessitated the use of crutches for ambulation. (Total hip replacement is scheduled within the year.)

The patient was started on methylene blue, 200 mg by mouth daily. Because ingestion of this drug was associated with the development of generalized urticaria, the patient is currently being treated with ascorbic acid, 1 g/day.

\* Assistant Professor, Departments of Anaesthesia, Peter Bent Brigham Hospital and Harvard Medical School.

† Associate Professor, Departments of Medicine, Peter Bent Brigham Hospital, Children's Hospital Medical Center, and Harvard Medical School, Boston, Massachusetts 02115.

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Address reprint requests to Ronald A. Gabel, M.D., Department of Anaesthesia, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.

### DISCUSSION

Within the human erythrocyte, about 1 per cent of the hemoglobin has its iron moiety in the ferric rather than the ferrous state. This oxidized variant, called methemoglobin, exists in equilibrium with "normal" hemoglobin. The erythrocyte has the enzymatic capability of reducing ferric to ferrous heme. Most important is NADH-methemoglobin reductase, deficiency of which leads to hereditary methemoglobinemia, the condition present in our patient. This genetic disorder is autosomal recessive, the disease manifested in homozygotes.

Another type of hereditary methemoglobinemia is caused by the presence of hemoglobin M, codominant with hemoglobin A in affected individuals. The M hemoglobins have an amino-acid substitution on either the alpha or beta chain at or near the attachment of the heme group. Methemoglobin M, formed by normal oxidative activities within the erythrocyte, is not a suitable substrate for enzymatic reduction. Therefore, most of this abnormal hemoglobin remains oxidized. The proportion of methemoglobin is related primarily to the relative amounts of hemoglobin M and hemoglobin A.

In addition to having a genetic cause, methemoglobinemia can be an expression of chemical or drug toxicity. Nitrites, nitrates, nitrosobenzene, nitrobenzene, acetanilide, and aniline dyes are a few of the more common causative agents. The local anesthetic agent, prilocaine, can induce formation of methemoglobin.

Primary treatment for methemoglobinemia is administration of methylene blue, which activates a reserve NADPH-methemoglobin reductase system in the presence of glucose. In toxic methemoglobinemia, the initial intravenous dose is 1-2 mg/kg body weight, which may be repeated. Hemodialysis to remove the toxic agent or metabolite may be useful. Hereditary methemoglobinemia is usually treated only for cosmetic or psychological purposes. A daily oral dose of methylene blue, 200 mg, or ascorbic acid, 500-1,000 mg, will slowly reduce methemoglobin levels.

There is no known effective therapy for M methemoglobinemia.<sup>4</sup>

The presence of methemoglobin in this case was suggested by gross appearance of the patient's blood and by incompatibility between values for  $P_{ao_2}$  and oxyhemoglobin saturation and between the hematocrit and hemoglobin. Deoxygenated hemoglobin, oxyhemoglobin, and carboxyhemoglobin each have a unique absorption spectrum, allowing simultaneous determination of the amounts of all three in a sample. The absorbance of visible light by hemolyzed blood is measured in the CO-Oximeter at three wavelengths, and a set of simultaneous equations is solved by a calculating matrix to give: 1) the concentration of total hemoglobin; 2) the percentage of this which is oxygenated (oxygen saturation); 3) the percentage which is carboxyhemoglobin. Accuracy of this procedure assumes the absence of other pigments with substantial absorbance within the hemoglobin spectrum. Because methemoglobin absorbs light at all three wavelengths evaluated in the CO-Oximeter, methemoglobin interferes with accurate measurement of both oxygen saturation and hemoglobin concentration.

At 548 nm, the wavelength at which total hemoglobin is measured, absorbance by methemoglobin is lower than absorbance by carboxy-, oxy-, or deoxygenated hemoglobin. The result is an erroneously low reading for concentration of total hemoglobin (including methemoglobin). A correct reading could be obtained by reducing the methemoglobin with dithionite solution, rerunning the sample in the CO-Oximeter, and correcting for dilution by the reducing agent.<sup>5</sup>

Similarly, the presence of methemoglobin interferes with spectrophotometric measurement of oxyhemoglobin concentration. Because this measurement is attenuated proportionally more than that of total hemoglobin, the quotient (oxyhemoglobin concentration/total hemoglobin concentration) calculated by the CO-Oximeter to given oxygen saturation is also erroneously low. Methemoglobinemia of 10 per cent will lower the

measured oxygen saturation to about 95.5 per cent of that without methemoglobin present.†

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† de la Huerga, J.: Personal communication.

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## Correspondence

## Potencies of Fentanyl and Morphine

*To the Editor:*—Dr. Romagnoli's observations about the relative potencies of morphine and fentanyl during open-heart surgery (*ANESTHESIOLOGY* 39:568, 1973) were read with interest because similar data have been compiled here, too. We have established morphine or fentanyl requirements in 70 patients of either sex subjected to major noncardiac surgery.

Our subjects were unpremedicated or received the narcotic with scopolamine for premedication. During operation they were exposed only to the narcotic, 70 per cent nitrous oxide, and essentially the same amount of *d*-tubocurarine as the Houston series. All were mechanically ventilated during operation, but postoperatively they breathed—with very few exceptions—spontaneously. Arterial  $P_{CO_2}$ 's following morphine averaged 45 torr 60 minutes after arrival in the recovery room. The corresponding values after fentanyl have not been recorded.

The speed of recovery in these patients was measured as the interval (T) between the last narcotic increment during operation (1 mg morphine or .025 mg fentanyl) and the first postoperative request for pain relief. This level of arousal should roughly correspond to the level where the Houston patients would not tolerate their endotracheal tubes any longer.

In our patients we have established mean loading ( $C_0$ ) and maintenance requirements separately. The maintenance rate-to-loading dose ratio (k) is the drug's apparent first-order elimination rate constant. With its aid, using the law of first-order kinetics, one can calculate the amount of active drug retained in the body at T time ( $C_T$ ). Expressing our data in units used in Dr. Romagnoli's report (75 kg weight, 120 minutes administration time), our findings are shown below:

	$C_0$ (mg × 75 kg <sup>-1</sup> )	120 Min Total (mg × 75 kg <sup>-1</sup> )	K (hr <sup>-1</sup> )	T (hr)	$C_T$ (mg × 75 kg <sup>-1</sup> )
Fentanyl	.228	.350	.266	1.97	.164
Morphine	24.75	30.3	.122	4.53	15.5
Morphine fentanyl	108.5	86.6	2.38	2.30	94.5