

care and laboratory science not yet represented by either the Editors or Associate Editors, and, as before, we will continue to rely on our Consultant Reviewers for their expertise in these areas.

Finally, this month's masthead reveals the departure of four members of the Editorial Board: Carl Hug, Edward Lowenstein, Ronald Miller, and Harvey Shapiro. They have provided expertise in their respective areas of interest, and their presence as Editors has added prestige to ANESTHESIOLOGY. In addition, Ronald Miller has served in a superb manner as Editor in charge of Clinical Reports for the past 9 years, and it is perhaps fitting that the Clinical Reports category be retired as he retires as Editor. My sincerest and most deeply felt thanks go to the retiring Editors for their efforts on our behalf, and I join the Editorial Board in welcoming three new Editors—

Dennis Mangano, Donald Stanski, and Michael Todd—
as members of the Editorial Board.

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Changing Perspectives in Monitoring Oxygenation

IN THIS ISSUE OF ANESTHESIOLOGY, Tremper and Barker¹ provide a very useful review of pulse oximetry—a tool that has taken the clinical anesthesia world by storm. They describe some of the technical difficulties that had to be overcome in its development, but it is interesting to consider the changes which have occurred in clinicians' perspectives on monitoring oxygenation.

In the late 1800s and early 1900s, two observations were of great importance to future generations of clinicians. A French engineer/physiologist, Paul Bert (1833-1886), was interested in mountain sickness and was the first to demonstrate the relationship between partial pressure of gases and their physiological effects. He noted that animals in a low-pressure chamber died when the oxygen tension fell to a mean of 0.035 atmospheres (approximately 26 mmHg). He subjected himself to a pressure of one-third of an atmosphere and, when his consciousness was dimming, breathed oxygen with recovery. In 1920, Barcroft submitted himself to simulated high altitude for 6 days, with a radial artery surgically exposed for blood sampling. He noted that, at these low inspired oxygen levels, his arterial saturation was always lower than in blood equilibrated *in vitro* with a simultaneously ob-

tained sample of alveolar gas—the first demonstration of an alveolar-arterial oxygen difference.

Perhaps it was the survival that was demonstrable following various types of experimental hypoxia, coupled with very incomplete understanding, which encouraged certain anesthesia practices as recently as the early 1940s. When the author became a House Anaesthetist in London in 1949, it was common to induce nitrous oxide and oxygen anesthesia for brief minor surgery in Emergency Department operating rooms by starting with several breaths of 100% nitrous oxide. FI_{O_2} was then increased, often only to 0.10, for the next several minutes. It is not surprising that the technique was falling out of favor. However, despite the common postoperative vomiting, headache, and confusion, full recovery was the rule and the technique was employed in thousands of patients. At that time, awareness of the importance of maintenance of oxygenation was increasing, but monitoring consisted of watching the patient's color and cardiovascular responses, and perceptions of lower levels of tolerance were inappropriately optimistic. Electronic monitoring was virtually unknown.

Measurements of oxygen saturation of hemoglobin became clinically important in the 1950s in the diagnosis of cardiac disease. The advent of effective cardiac surgery stimulated the growth of cardiac catheterization laboratories. Calculations of cardiac output and right-to-left shunt derived from oxygen content measurements and the Fick equation became common in clinical application. This, together with the advent of "Respiratory Failure

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Units" and the development of the Clarke oxygen electrode, combined to encourage an enormous growth in industry in both fundamental and descriptive research relating to applied pulmonary gas exchange. The late 1950s and the early 1960s saw the spread of insight among clinicians into mechanisms of pulmonary oxygen exchange and oxygen delivery, and anesthesiologists played a prominent part in this research. Among many strong contributors were Bendixen and Laver in Boston, and Nunn in London. In many ways, they wrote the basic scenario for clinical practice in this aspect of anesthesia and critical care that would last for the next two decades. Arterial blood gas sampling, already widely used for acid-base assessment, became even more widely accepted as *the* route to determining the $P(A-a)O_2$ and, therefore, assessing pulmonary oxygen exchange. The insensitivity of SaO_2 to such changes contrasts markedly with the greater sensitivity of the $P(A-a)O_2$, at PaO_2 levels on the horizontal portion of the dissociation curve. Until now, there has been a relative lack of enthusiasm for this variable as a monitoring tool for the anesthetized patient.

Thus, through the 1960s and 1970s, the average anesthesiologist became very well informed on the subject of oxygen exchange between inspired air and cells. Continuous monitoring, however, was limited in availability and patients continued to die unnecessarily from anesthetic "accidents".² In watching the status of the patient's arterial oxygenation, (intermittent) measurements of arterial oxygen tension were only performed in selected patients and, under most circumstances, the anesthesiologist of the 1970s and early 1980s still relied on crude clinical signs, such as the patient's color, the color of the blood in the surgical wound, heart rate, and blood pressure. Occasionally, a catastrophe causing hypoxia would first be noted by observing bradycardia or pupillary dilatation, or even cardiac arrest. The relative sophistication of the information provided by the $P(A-a)O_2$ was usually not available to permit early recognition of such problems. Various options have been introduced to deal with this, and they include indwelling arterial and transcutaneous electrodes. The former have never reached popular clinical application status, partly because of lack of reliability, but also cost and invasiveness. Transcutaneous electrodes have fared better, but also have problems with reliability. Reliable, readily available sensitive measures of cellular oxygenation in target organs have not been developed.

It was not until effective pulse oximetry became commercially available, for the first time, that large numbers of anesthesiologists could continuously monitor their patients' arterial oxygen levels. It is very important to recognize the nature of this monitoring. Since virtually every anesthetized patient breathes an oxygen enriched mixture, desaturation only occurs when there is a substantial increase in the difference between the (perceived) inspired

oxygen tension and that in the arterial blood. Metaphorically, as the blindfolded anesthetist walks unknowingly towards the cliff of hypoxia—whether due to problems of inspired gas, equipment failure, underventilation, or abnormal pulmonary shunting—the protective hand of the pulse oximeter sentry stops him from falling over the edge. The oximeter will not tell him why he has been proceeding in that direction, or the direction back! On the other hand, should he start falling, the sentry functions on the vertical part of the dissociation curve and becomes an extremely sensitive (if not always accurate) indicator of progress during the drop. Interestingly, it is highly probable that many fewer blood gas samples are being drawn during anesthesia now that pulse oximeters are so universally available. Our detailed insight into our patients' pulmonary oxygen exchange is less than with PaO_2 measurements but, because of the continuously available sentry, we believe our patients are safer. A prospective study to prove that important point with certainty may never be performed but, already, opinion seems overwhelmingly in favor of that belief.

With the introduction of any new measurement device relevant to clinical practice, descriptive research is quickly performed. It is not surprising, therefore, to note reports of episodes of desaturation that occur during apparently routine anesthesia, particularly during induction and surrounding extubation. Nor is it surprising to note the episodes of desaturation found on arrival of patients in our Post-Anesthesia Care Units and, indeed, when they seem ready to depart for the ward. Undoubtedly, we will see reports of desaturation levels during the postoperative days and, were we to take oximeters home, perhaps during various parts of some individuals 24-h day. We already have randomly acquired data in that regard. What we lack is perspective. What level of desaturation is unacceptable? Under what circumstances? For how long? In whom? I note the old pros varying between evangelism in some, and denigration of the importance of some episodes of desaturation by others ("I have often seen situations like this and have never been concerned about them before we started using pulse oximeters"). Perhaps some of the latter were comfortable with their patients breathing 100% nitrous oxide for a while, some 40 yr ago. After all, most patients survived! On the other hand, there may sometimes be a grain of truth in the implication that we do not know the threshold values at which physiology gives way to pathology. Clearly, the wheel has turned in its always-interesting way, and we need to do that at which we have not always excelled in the past—relate numbers to outcome.

In the meantime, I await with interest the arrival of the next measurement device to cause a revolution and revelation in our everyday practice. Continuously available arterial or cellular P_{O_2} ? I would hope so, but perhaps

not. After all, without surprise as well as innovation, our field would not hold quite the same excitement.

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Studies in Animals Should Precede Human Use of Spinally Administered Drugs

SPINAL (INTRATHECAL AND/OR EPIDURAL) clonidine has been shown to have no effect on spinal histomorphology in rats,¹ cats,² dogs,³ sheep,⁴ and in terminal cancer patients at autopsy.⁵ In pigs, clonidine has been shown to have no effect on spinal cord blood flow.^{6,7} Behaviorally in rats,⁸ cats,⁹ and primates² over extremes of concentration, neither clonidine nor its structural analogues produce any neurological sequelae. In rats, cats,⁹ pigs,⁶ and sheep,⁴ spinal clonidine has no untoward effects on blood pressure that cannot be accounted for by a systemic effect. These studies suggesting the safety margin in well characterized animal models thus provide a firm basis for spinal administration of clonidine in humans. In fact, the lack of neurological sequelae or toxicity have been similarly observed in patients with terminal cancer or postoperative pain receiving spinal clonidine (see ref. 10 for references).

This orderly development of an extensive knowledge base with clonidine given spinally and its apparent lack of physiologic or tissue toxicity leads to the current consideration by Eisenach *et al.* in this issue of ANESTHESIOLOGY of its use in the female with fetus.¹⁰ Clonidine administered epidurally in concentrations that are anticipated to be effective in humans had little effect on maternal or fetal physiologic and biochemical indices. After the fact, these data might be presumed to be not surprising and the experiments in fact trivial, in view of the extensive animal studies which have shown no neurotoxicity, no change in spinal cord blood flow, and no dramatic effects on sympathetic outflow in concentrations that produce a powerful analgesia and ultimately no difficulty when given to humans.

We wish to take this opportunity to pose the rhetorical question: Were these studies necessary, given the exten-

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sive toxicology extant with this drug? As pharmacologists closely involved with investigations on mechanisms, we consider the answer, from a scientific standpoint, to be unequivocally yes. As individuals concerned about the continued use of the perispinal route of drug administration, the answer is even more emphatically affirmative. The animal studies have been exceedingly predictive of the efficacy, physiological effects, and toxicity for humans of spinally administered drugs. Yet, the studies noted above reveal mechanisms relevant to the models that are investigated. It may appear simplistic and obvious, but the mother with fetus possesses physiological systems not present in the animals and humans thus far discussed. Regulation of placental transfer, placental blood flow, and the role of circulating hormones in fetal physiology are issues that are not examined in animal or human studies in which the female-fetus is not considered. It might be argued that clonidine taken systemically by hypertensive human mothers has not been shown to possess deleterious side effects.¹¹ Thus, if experience suggests that the systemic effects are not detrimental, and if clonidine has no central toxicity, then its spinal physiology must be benign. That observation overlooks the fundamental fact that spinally administered drugs may exert physiological actions that are not observed at concentrations reached by systemic doses. Two examples with morphine, the drug most commonly administered via the spinal route, will suffice to make the point.

First, systemic morphine does not routinely inhibit the micturition reflex, but it is quite clear that opioids, with an action limited to the spinal cord, will produce a dose-dependent, naloxone reversible inhibition of the volume evoked micturition reflex in humans and animals.^{12,13} Second, systemic morphine at analgesic doses has relatively little effect on peripheral vascular perfusion other than some idiosyncratic reactions or vasodilation due to histamine release. Following spinal administration, morphine has little effect on measures of sympathetic function,

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