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## *Fashion, Darwin, and Anesthetics as Poisons*

IN THIS ISSUE OF ANESTHESIOLOGY, Segal *et al.* report further studies on a remarkable reduction of anesthetic requirement (MAC) by the use of the d isomer of medetomidine, an  $\alpha_2$  adrenergic agonist.<sup>1</sup> At the highest dose tested, the effect of this compound appears to have completely replaced that of the inhaled agent in abolishing the tailflick response of the rat. They have demonstrated that this is an action beyond that occurring as a result of decrease in central nervous system catecholamines. This current report adds yet further promise to a report from the same laboratory reporting an 85% decrement in MAC with the  $\alpha_2$  agonist azapexole.<sup>2</sup>

These studies provide material for enthusiastic speculation in two basic and overlapping areas of interest to anesthesia. The determination that these agents work at post-synaptic receptor sites and the dramatic reduction in MAC should rekindle interest in mechanisms of anesthetic action. This may be a giant step forward opening new doors through which pursuit of this elusive target may proceed. The second speculation relates to the possibility of future anesthesia being conducted without conventional anesthetic agents but with a series of specific "magic bullets" aimed with new accuracy at a group of specific targets, the collection of which will comprise the anesthetic state. Unlimited visions and dreams may result.

As we seem to regard inhaled anesthetics as toxins, the potential for eliminating them may be met with unbounded joy and enthusiasm. However, after a period of

imagining a world greatly improved by the absence of anesthetics (and anesthesiologists?), my thoughts return rather abruptly from that dreamstate to one that is probably more realistic. These latter thoughts in no way discredit the observations reported, but do suggest some damping of their call for "early clinical studies" and propose that this newest fashion in anesthetic adjuvants or agents might await more complete investigation without serious deprivation for society.

Let's first look at what "safety" we might expect by either reducing or eliminating currently used inhalation agents. The real toxicity of these current drugs is *extremely* low. We see many complications of anesthesia in our practice, but these complications are only rarely due to the anesthetic agents *per se*. Complications do occur due to the unconscious state, postoperative depression, and the complete neuromuscular blockade commonly used to create the very best conditions for our surgical colleagues. It would seem most likely that unconsciousness and muscle relaxation will still be necessary components of anesthesia. Therefore, a marked reduction in complications, or a marked reduction in morbidity or mortality, must be demonstrated—not assumed. Reports so far do not tell us of effects of the  $\alpha_2$  agonists on respiration or muscle tone.

Almost since the first use of inhalation anesthetics agents, there has been a procession of adjuvant drugs introduced to reduce the amount of inhalation anesthetic agent required. The additions represent several classes of drugs changing in fashion from time to time. Hypnotics were stylish in the 1930s, relaxants gained favor in the 1940s, and opiates have had several periods of being the "in" drug. Those familiar only with the mixture of many drugs commonly used today would register surprise at earlier arguments against polypharmacy and for the utilization of a single drug (ether-cyclopropane-chloroform) which could do it all.<sup>3</sup> The mindset seems to be that if

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Key words: Anesthetics, volatile: halothane. Potency: MAC. Sympathetic nervous system, receptors,  $\alpha_2$  agonist: 4(5)-[1-(2,3-dimethylphenyl)ethyl]imidazole; dexmedetomidine; levomedetomidine. Sympathetic nervous system, receptors: postsynaptic; presynaptic.

you breathe it, it's toxic, and if you inject it, it's safe. I don't recall a recent investigation that has looked at whether, in fact, the addition of an injectable component did create an inherently safer approach to anesthesia. In fact, the famous Beecher-Todd Report suggested an inherent toxicity of the injectable addition.<sup>4</sup> At any rate, as of today, it is difficult to support the addition of new or different drugs simply because they reduce anesthetic requirement.

Additionally, the Darwinians among us intuitively assume a purposeful role for the adrenergic nervous system. Having finally accomplished the difficult mental gymnastics to realize that any adrenergic agonist will be sympatholytic, I'm left with questions that I believe should be investigated before trials on human subjects are instituted. These include describing the distribution of cardiac output among and within organs and the adequacy of perfusion of the entire organism and its component parts. We should look at the organism's ability to respond to the inevitable challenges of blood loss, carbon dioxide excess, oxygen want, and biochemical alterations such as severe acidosis.

The previous report from this laboratory suggests that with the 1 MAC combination of that  $\alpha_2$  agonist<sup>2</sup> and isoflurane is associated with a 50% reduction of cardiac output and heart rate. Shouldn't we have some idea as to whether there is an equivalent reduction in metabolism? Are all vascular beds adequately perfused if surgery lasts for several hours? Are the brain, heart, or other vital structures deprived of a rightful share? What is the time dimension of the effect of these drugs? Can these effects

be reversed or withdrawn at the completion of surgery? How do they relate to postoperative pain control? Is the bradycardia resulting from the  $\alpha_2$  agonists a stable rhythm? Increases in pulse rate may be beneficial on occasion—is this prohibited by the sympatholysis?

The potential for a most interesting era in the development of anesthesia is raised by these studies and we will anxiously await and or seek additional information. The specialty is mature enough now to investigate this thoroughly and wisely. We must ask and try to answer all the questions along the way.

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## *Understanding Images: Correlation Between Computerized Tomographic Scans of Lung Structure with Impaired Function in ARDS*

CONVENTIONAL WISDOM REGARDS the adult respiratory distress syndrome as an acute, homogeneous, bilateral inflammatory lung disease in which widespread damage to pulmonary microvasculature causes diffuse pulmonary

edema and produces symmetrical bilateral pulmonary infiltrates on the chest radiograph. Research over the past several years substantiates this as an accurate portrayal of ARDS in its milder and earlier stages.

In this issue of *ANESTHESIOLOGY*, Dr. Luciano Gattinoni and his colleagues<sup>1</sup> in Milan have further enhanced our understanding of this early form of ARDS by correlating physiological measurements with images of the lung obtained by computerized tomography. The most important relationships they demonstrate are: 1) pulmonary artery pressure increases in concert with lung weight;

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Key words: Lung: acute respiratory failure; gas exchange. Measurement techniques: computer-assisted tomography. Ventilation: positive end-expiratory pressure.