cess in this endeavor must be tempered by two considerations. First, cholinergic agents might not improve cholinergic function in elderly patients whose cholinergic deficits are due to a structural loss of brain tissue, as would be the case in patients with Alzheimer's disease or multi-infarct dementia. Second, the demonstration of improved memory with a single dose of physostigmine or choline chloride does not necessarily imply that long-term treatment would continue to produce such improvement. The homeostatic process of the brain may act to reverse a temporary increase in acetylcholine availability.

The above considerations may account for the fact that several clinical trials with choline in elderly subjects have failed to demonstrate the expected improvement in memory or other aspects of cognition. Boyd *et al.* (*4*) treated seven patients who were severely impaired with Alzheimer's disease with 5 g of choline chloride per day for 2 weeks and then 10 g per day for 2 weeks. No significant cognitive or clinical changes were produced. In a placebo-controlled study with eight normal elderly subjects, Mohs *et al.* (*5*) found no improvement in memory storage, retrieval, mood, or social functioning after treatment for 7 days with 16 g of choline chloride per day. The memory tests in this study were similar to those used by Davis *et al.* (*1*) in their study of the effects of physostigmine on normal volunteers. A study conducted in our laboratory (*6*) also failed to confirm a memory enhancement with long-term choline chloride treatment. Fourteen elderly outpatients suffering from mild to moderate cognitive impairment received choline chloride treatment for 4 weeks. The dosage was gradually increased during the first 2 weeks, with maximum doses of 12, 16, or 20 g per day, depending on individual patient tolerance; dosage at the highest level of tolerance was maintained during the final 2-week period. Of 26 cognitive test measures, including both memory and performance tasks, none showed statistically significant improvement after treatment. There were also no significant changes in mood or behavior. Finally, Etienne *et al.* (*7*) reported no improvement in three patients with Alzheimer's disease after they were treated for 1 month with up to 8 g of choline bitartrate per day, and in a placebo-controlled crossover study, Smith *et al.* (*8*) found no cognitive changes in ten Alzheimer's patients treated with 9 g of choline bitartrate per day for 2 weeks.

It is thus apparent that preliminary trials of long-term choline treatment in the elderly have failed to demonstrate the improvement in memory reported for younger, cognitively unimpaired adults treated with a single dose of a cholinergic agent. Although several of the cited studies were not placebo-controlled, it is not likely that investigator bias or placebo effects would produce negative rather than positive results. Another possibility is that there is a narrow effective dose-range because of a curvilinear or biphasic dose-response function. However, a wide dose range has been used (5 to 20 g per day), and there is apparently no evidence supporting a presynaptic biphasic effect. It remains possible, however, that a subgroup of individuals may respond to choline; such individuals might have an underlying cholinergic deficiency but retain sufficient functioning presynaptic neurons.

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Ferris *et al.* correctly point out some serious obstacles to the development and use of long-term cholinomimetic treatments for age-related memory deficits. Following our report of enhancement in long-term memory functioning with physostigmine we investigated the effects of choline chloride on memory. Doses of both 8 and 16 g of choline chloride per day, administered in a double-blind crossover design, did not significantly affect memory functioning in the same young normal people who were previously improved by physostigmine (*1*, *2*). Similarly, neither 8 nor 16 g of choline chloride per day, administered under double-blind conditions, significantly enhanced memory functioning in elderly subjects with age-related memory impairments (*3*, *4*). Patients with Alzheimer's disease have also received 2 to 16 g of choline chloride per day in a double-blind crossover study extending 56 days, and also derived no benefit from choline chloride treatment. In contrast, low doses of physostigmine (0.25 to 0.50 mg) administered to elderly demented and nondemented subjects significantly improved their ability to store information into long-term memory (*2*).

These data indicate that if choline chloride, or presumably lecithin, has an effect on memory it is quite subtle, possibly affecting only certain kinds of memory traces (*5*), and may be apparent only in subgroups of people, although choline probably increases striatal cholinergic activity. These results raise the question of whether the use of acetylcholine precursors can increase cholinergic activity in hippocampal and cortical cholinergic synapses.

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Cardiopulmonary Changes in Kittens During Sleep

Baker and McGinty (*1*) asserted in their title that their animal model showed "cardiopulmonary failure" and that this had important implications for the sudden infant death syndrome (SIDS). Whether the heart is primarily involved in SIDS is a matter of intense interest to physicians, scientists, and even lay groups associated with this tragic problem, the foremost cause of death in infants during the first year of life. I submit that Baker and McGinty have based their

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assertion of primary cardiac involvement on a combination of artifact and misconceptions.

Baker and McGinty did not define "failure," but from the text, the cardiac component of cardiopulmonary failure was derived from (i) "depressed heart rate," and (ii) "cardiac arrhythmia with ectopic beats." In support of the latter, they referred to their figure 1D. This figure consisted of two electrocardiographic records, one during active sleep and one during quiet sleep. In quiet sleep they described an arrhythmia with ectopic beats, but in fact, the rhythm is quite stable and is almost precisely the same as that recorded in active sleep. An artifact that resembles a T wave occurs at irregular intervals during the record, but the total lack of interference with the regular ventricular (QRS) complexes rules out a cardiac origin of this electrical event. One of these extra complexes is actually superimposed on a QRS complex, thereby occurring during the absolute refractory period. It is equally clear that the extra complexes are not p waves, since they do not disturb the rhythm of the regular sinus pacemaker, nor are they repolarization (T waves), since they do not follow a QRS. The magnitude of these artifacts is sufficiently great that they were undoubtedly treated by the computer as though they were QRS complexes, which would appear in their output as increased "heart rate variability."

Even had the authors demonstrated an arrhythmia, "failure" is not an appropriate term, since that term is applied by physiologists and clinicians as inadequate cardiac output associated with increased filling pressure, referred to a normal Frank-Starling relationship.

A more serious conceptual error is involved in the designation of bradycardia ("depressed heart rate") as "failure." Sinus bradycardia with hypoxia is a vagally mediated reflex which is accompanied by vasoconstriction, referred to as the dive reflex (*2*) or the oxygen-conserving reflex. This reflex is present in man (*3*) and in infant monkeys (*4*); it preserves cerebral and coronary perfusion during transient hypoxia and should not be regarded as failure or even depression.

Although Baker and McGinty have not established a primary role for the cardiovascular system in their hypoxic kittens, let alone in the SIDS, I respect the very substantial contributions of their research in the areas of sleep, respiration, and hypoxia.

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We agree that the electrocardiographic pattern shown in figure 1D of (*1*) does not fulfill the criteria for cardiac arrhythmia, and we apologize for any confusion that may have resulted from our assertion. However, this "pseudoarrhythmia" was reported for only one kitten and did not contribute significantly to the data indicating increased heart rate variability in the subgroup of kittens designated noncompensators. Noncompensators were hypoxic kittens exhibiting sustained episodes of extremely slow respiration primarily during quiet sleep (QS) [less than 60 percent and as low as 15 percent of active sleep (AS) rates], usually accompanied by irregular and decelerated heart rates, and in some cases leading directly to terminal gasping and death.

Our decision to term these episodes "cardiopulmonary failure" was not intended to establish a primary role for the heart in either hypoxic death in kittens or in the sudden infant death syndrome (SIDS). On the contrary, our data indicate that these heart rate changes were secondary to the respiratory depression that resulted from chronic hypoxemia. For example, the combination of bradycardia with increased heart rate variability never occurred without slow, labored breathing, and it did not invariably accompany the depressed respiratory patterns (seven of ten cases). Normalization of the heart rate was always preceded by augmented respiration. Finally, the heart continued to beat vigorously long after respiratory movements had stopped in the terminal hypoxic sequences we recorded.

The central theme of our report was that these noncompensatory cardiopulmonary patterns occurred during QS and at state transitions, whereas the onset of AS was associated with an immediate return to the rapid breathing and stable heart rate patterns shown by adequately compensating hypoxic kittens. Kittens that died had the lowest AS percentages in their age groups. Thus, AS appeared to protect hypoxic kittens from developing terminal gasping.

Several observations are difficult to reconcile with the suggestion of Guntheroth that these cardiopulmonary patterns related to QS reflect an oxygen-conserving reflex rather than hypoxic "failure or even depression." (i) Most hypoxic kittens that exhibited these cardiopulmonary patterns subsequently died. (ii) Cardiorespiratory depression related to QS and reversed by AS was also observed in a normal oxygen atmosphere after termination of hypoxic conditioning [reference 7 in (*1*)]. (iii) Hypoxic kittens showed flattening of the electroencephalogram that was most pronounced during the noncompensatory episodes leading to terminal gasping. This flattening indicates cortical ischemia and circulatory failure rather than maintenance of cerebral perfusion. Further evidence is necessary to relate SIDS to respiratory and heart rate changes in chronically hypoxic kittens, but the patterns we observed must be regarded as pathological.

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