sensory channel should behave differently from all other sensory channels. The other hypothesis, which is the one toward which the convinced scientists have characteristically gravitated, is that only certain individuals are gifted with DOP. Such individuals are usually identified by their statistically significant performances. On the basis of the follow-up study of high-scoring subjects, I have pointed out (*1*) that, when Youtz (*2*) used the usual statistical test of significance on several hundred trials by a star performer, he reduced the standard error of the mean to the point where the increment of a few percentage points above chance appears to be significant (*3*). While this is technically legitimate, it is possible that during this period of time subjects may adapt to the situation, learn to detect stimulus differences on other dimensions, improve their ability to pattern their guessing behavior, and, as Gardner points out, perhaps learn how to nose peek, all of which might contribute to successively rising scores. Another possibility, evident from the data from my three subjects, is that the highly significant overall performance scores would mask the fact that the daily scores fluctuated widely from significantly above to significantly below chance. These possibilities make an overall test of significance very questionable indeed.

Since the "gifted person" hypothesis is so often used in the fringe areas of science, how are we to regard the many people whose performances on screening tests are significantly *below* chance? Are they to be included among the "ungifted"? It is certainly possible that continued testing with the ungifted might show patterns of above- and below-chance scores such as I found with initially high scorers.

Or is it possible that the convinced DOP researchers are focusing on the positive tail of a normal distribution?

The main problem with the gifted-person hypothesis is that it is so open-ended that it is not subject to refutation. It can always be said of critics of DOP that they have not been lucky enough to find a star subject. And being, unlike the DOP supporters, constrained by rules which require that hypotheses be expressed in such a way as to be both testable and refutable, the critics cannot assert that the null hypothesis is true, that is, that DOP does not exist in man. The final irony is that, despite the focus on the gifted-person hypothesis, in the discussion of the results the DOP supporters very often wander back to the unproven claim that DOP is a new sensory channel.

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Measurement of Anesthetic Potency

In "Temperature dependence of anesthesia in goldfish" (*1*), Cherkin and Catchpool introduce a technique for making quantitative measurements of the anesthetic potency of water-soluble agents. Goldfish are kept swimming by an applied stimulus (an electric shock); anesthetic potency is measured as AD_{50}, the dose at which 50 percent of the experimental animals fail to respond to the stimulus. The technique was developed in order to examine the relation of potency to temperature in the hope of distinguishing among current theories of anesthesia.

Cherkin and Catchpool found that, for each of a number of anesthetic agents, AD_{50} increased as temperature increased. From this they conclude that increasing temperature is antagonistic to the anesthetic process, a conclusion which supports the Pauling (*2*) and Miller (*3*) microhydrate hypothesis of anesthesia. The conclusion would be valid if it were demonstrated that the rise of AD_{50} with temperature is not the result of the effect of temperature on processes other than the unit anesthetic process itself. In other words, a suitable control of the effect of temperature without added anesthetic is required. The Cherkin and Catchpool experiment lacks such a control. At any temperature over a wide range, approximately 100 percent of the goldfish were successful in their response to the test; it was implicitly assumed, therefore, that at all temperatures in this range the goldfish were in a single baseline state, and that AD_{50} at different temperatures could be directly compared. The assumption that organisms are in equivalent states at different temperatures is at variance with a vast body of experimental knowledge. Most of the vital processes of poikilotherms, including those influencing motile responses, speed up as body temperature rises from 0°C to about 45°C. It is widely thought that this speeding up is due to the involvement of rate processes with activation energies. Therefore, it does not seem reasonable that the baseline performance of the goldfish should be independent of temperature. That it appears to be so is a fault in the experimental design, in which the measure used is success or failure in performing at an arbitrary level rather than quantification of a graded response. There is evidence in the report itself of a graded response as a function of temperature. At 1.6°C, even in the absence of anesthetic agent, 50 percent of the fish did not respond. (The authors' broadening of the definition of anesthesia to include this low-temperature effect is unwarranted, in view of the possible involvement of activated processes.)

The temperature coefficients of most of the numerous life processes which have been studied are so large (*4*) that, had they been taken into account, the conclusion drawn might have been qualified or reversed. For example, the temperature coefficient of the rate of opercular movement in goldfish is 16.5 kcal (*5*), while that for AD_{50} is 8.6 to 13.2 kcal. If the significant process in the Cherkin and Catchpool experiment has an intrinsic temperature coefficient similar to that of opercular movement, the fact that the coefficient for AD_{50} is smaller would indicate that anesthesia is more effective at higher temperature. Such a finding has been reported for the influence of anesthetics on the contraction of frog muscle (*6*).

The objection raised here may arise whenever an arbitrary criterion of performance is made the basis of a study. A recent modification of the Cherkin and Catchpool technique, using the brine shrimp *Artemia* (*7*), also employs such a criterion, and would be subject to the same objection if used to study the temperature dependence of anesthesia.

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Fenichel and Horowitz interpret our temperature-dependence data as reflecting changes in the baseline response of goldfish rather than changes in anesthetic potency. We question this interpretation. Reduced temperature without added anesthetic agent caused no anesthetic effect in the range of 10° to 30°C, to which our temperature coefficients were limited. The "graded response as a function of temperature" did not appear until the temperature fell below 2°C. Spontaneous inactivity, or unresponsiveness to mild stimuli, was never observed in 2600 goldfish stored at 5° to 10°C for days.

We fixed the test stimulus at a 9-volt shock because behaviorally it seemed to approximate the effect of a surgical incision and because the response it elicited was relatively insensitive to voltage level. For example, an increase from 6 volts to 9 volts caused an increase of only 3.6 percent in the AD_{50} values of chloroform and halothane at 20°C (*1*). In contrast, a stimulus increase from 0.30 volt to 0.45 volt, applied at 24.6°C to the frog sartorius preparation used by Horowitz and Fenichel (*2*), correlated with a 250-percent increase of the anesthetic concentration. With goldfish at a given test stimulus, doubling the AD_{50} partial pressure of anesthetic agent increased the percentage anesthetized from 50 to over 99 (*1*). Doubling the 1-pentanol concentration in the sartorius muscle, from 4 m*M* to 8 m*M*, correlated with a stimulus increase from 0.3 volt to 0.4 volt only. Clearly, the goldfish is relatively insensitive to changes in stimulus voltage but highly sensitive to changes in anesthetic partial pressure, whereas the sartorius muscle is highly sensitive to voltage but relatively insensitive to anesthetic concentration. These differences render irrelevant the changes in methodology suggested by Fenichel and Horowitz and may partly explain our divergent views of anesthetic action.

The critique proposes correcting our temperature coefficients for the temperature coefficient of opercular rate. This control would be worth considering for experiments on the rate of induction of anesthesia, because respiratory rate affects uptake, but we question its relevance to experiments on the unknown anesthetic process under steady-state conditions. Although most vital functions are depressed at lowered temperatures, a number of neural functions are not affected or are even enhanced (*3*). We consider it premature to apply a large arbitrary correction before knowing what neural functions are critical to the anesthetic process.

Eger, Saidman, and Brandstater (*4*) recently published ΔH values for halothane (14.8 ± 4.6 kcal) and for cyclopropane (5.5 ± 2.9 kcal) in the dog. The value for halothane in this homeothermic animal agrees with our value in the goldfish (12.5 kcal). Eger *et al.* (*4*) discussed the evidence for and against interpreting the goldfish and dog results as a direct effect of cold alone and decided that their data reflected an increased potency of their anesthetic agents at lower temperatures.

On the other hand, Fenichel and Horowitz consider that "anesthesia is more effective at higher temperature." The evidence that they cite is their experiment on the frog sartorius (*2*), in which they measured the minimum voltage to stimulate contraction, as a function of the intracellular concentration of an anesthetic compound, 1-pentanol, at 5.8° and 24.6°C. At all concentrations, a higher voltage was required at 24.6°C. They concluded that "the temperature coefficient suggests a process having a $\Delta H \approx +10$ kcal." The level of 1-pentanol was, however, expressed in terms of *concentration* (m*M*), a basis that is undesirable for comparing anesthetic potency because concentration has a different value in each phase of a biological system at equilibrium (*5*). Comparisons of volatile compounds at different temperatures are more logically made on the basis of equilibrium partial pressure (more strictly, fugacity) that has the same value in every phase, including the unknown site of anesthetic action. The anesthetizing partial pressure of 1-pentanol in the sartorius experiment, at a stimulus of 0.25 volt, can be calculated in the manner described in the report under discussion. At a stimulus of 0.25 volt, it was 0.008 mm-Hg at 5.8°C and 0.013 mm-Hg at 24.6°C. On this basis, 1-pentanol was more potent at the lower temperature, a finding that is inconsistent with the Horowitz and Fenichel hypothesis on anesthesia (*2*). As mentioned in our goldfish report, diethyl ether showed the same reversal of temperature dependence when calculated on the basis of partial pressure instead of concentration.

The critique raises questions of terminology. It may mislead in calling our compounds "water-soluble," because chloroform, halothane, and methoxyflurane have solubilities of only 0.2 to 0.9 percent in water at 20°C. It errs when it charges an unwarranted "broadening of the definition of anesthesia" to include low-temperature effects; such usage is well accepted (*4*; (*6*, pp. 189, 501–2), and the *Index Medicus* uses "Refrigeration Anesthesia" as a standard heading. The temperature-dependence technique has long been the subject of controversy; it has both limitations (*7*) and useful applications (*3*, *4*; *6*, pp. 187–285). The general objections voiced by Fenichel and Horowitz apply to all studies of the temperature dependence of drug action. Their specific evidence does not contradict our original conclusion that "the observed fall in potency with rise in temperature is qualitatively in accord with the hydrate microcrystal theory and other theories of anesthesia but contrary to the Meyer-Overton theory."

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