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12. Int-1 was initially identified physiologically with subsequent verification by intracellular staining with Lucifer yellow (*10*). The "necessity" and "sufficiency" results were repeated in four and five animals respectively.
13. The abdominal DLM's are selectively activated during abdominal steering movements in crickets (*14*). The avoidance steering behavior involves the wings, all the appendages, and major body segments, as well as the abdomen (*5*, *7*). Conventional EMG recordings, using differential a-c amplification, were made from the left and right DLM's of the second abdominal segment. The spike-coded DLM response was electronically integrated after full-wave rectification. Initiation of the behavior was quantified from the integrated EMG response, measured over the duration of the 300-msec ultrasound pulse. The values used in Fig. 1B and Table 1 are expressed in arbitrary units.
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15. Root-mean-square SPL's, expressed in decibels referred to 20 μPa, were measured with a 1/4-inch Bruel & Kjaer 4135 microphone and 2203 meter. The sound field was uniform to ±1 dB within 3 cm of the cricket.
16. In other experiments the critical spike rate in Int-1 ranged from 180 to 250 spikes per second.
17. We were unable to pass sufficient depolarizing current through our electrodes to excite the cell above the threshold spike level required for the behavior. However, we could cause Int-1 to discharge on release of negative current (anode break). The strength and duration of the discharge depended on the amount and duration of current. High discharge rates lasting as long as 3 seconds were typical after several seconds of stimulation. The mechanism of such dramatic anode break excitation is not clear, but it is a characteristic of several cricket auditory interneurons (*7*). To allow comparisons with acoustic stimulation, only the first 300 msec of the integrated EMG response was used in these sufficiency tests (*13*).
18. Because of the short period of current stimulation, the rebound excitation after anode break in Fig. 2B(ii) produced only a small discharge compared with that shown in Fig. 2A (*17*); this modest discharge was insufficient to cause steering.
19. Crickets have one bilaterally symmetrical pair of Int-1's. The dendrites ramify ipsilaterally (with respect to the side of origin of the major auditory innervation) in the auditory neuropile of the prothoracic ganglion. The axon projects through the ipsilateral neck connective, terminating in the ipsilateral subesophageal ganglion and ipsilateral regions of the brain (*6*).
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21. Int-1 was recorded intracellularly with a d-c electrometer (and conventional bridge circuitry) through the use of 100- to 200-megohm Lucifer yellow electrodes. The spike rate in Int-1 was defined as the number of action potentials during the first 100 msec of auditory response divided by 0.10 seconds.
22. Int-1 responds to ultrasound over a wide range of pulse durations between 0.5 msec and >1 second. For convenience in the experiments illustrated in Figs. 1B and 2B and Table 1, we used a 300-msec pulse of ultrasound, which produced responses in Int-1 and the DLM's similar to those produced by a batlike train of short pulses (*6*, *7*).
23. Supported by a research grant from the National Institute of Neurological and Communicative Disorders and Stroke and a research career development award to R.R.H. and an NIH training grant to T.G.N.
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Smooth Curve of Evolutionary Rate:

A Psychological and Mathematical Artifact

Gingerich (*1*) has shown that many of our orthodox comparisons for evolutionary rates between different groups of organisms are wrongly stated as a result of measurement over different temporal scales. Thus, he demonstrates that vertebrates may not evolve more rapidly than invertebrates, while Pleistocene mammals may not exceed their earlier Tertiary forebears in rate of change.

Nevertheless, Gingerich's quantitative apparatus for illustrating this phenomenon is an artifact of human psychology, and his chosen mode of mathematical plotting is not a property of the empirical world. He bases his conclusions on the continuous and straight array of data, with slope of -1.0, for a plot of the natural logarithm of the evolutionary rate (in darwins) as the ordinate and the natural logarithm of the measurement interval (in millions of years) on the abscissa.

The formula for rate in darwins (*2*) is the ratio of final to initial state, or $\ln x_2 - \ln x_1$ (where x is the morphological character being measured at times t_2 and t_1) divided by time in millions of years. (Comparison of rates in darwins is valid regardless of the time interval if the organisms' rate of change is exponential. If rates of change are not exponential, then comparisons are valid only if the same time interval is used for both organisms.) Gingerich then regresses this ratio against time in millions of years. In other words, Gingerich had plotted time (on the abscissa) against its own reciprocal ($1/t$) on the ordinate, and his negative slope arises necessarily from this artificial redundancy. Hallam (*3*) has commented on this problem, while Bonner (*4*) avoided just such an artifact by considering rate in darwins with respect to time as a univariate problem (*5*).

The plotting of a variable against its reciprocal is not devoid of empirical information if the numerator of the ratio is free to vary. The slope must be negative (unless the numerator varies directly with and at least as strongly as its denominator), but it may take a variety of forms with interesting implications. However, in Gingerich's case, as he notes with some puzzlement (*1*, p. 160), the numerator has an average value of 1.2 at all values of the abscissa. In such a situation, the slope must be -1.0 because the plot really does reduce to k/t as a function of t, where k is a constant.

But why should the numerator, a measure of absolute evolutionary change in a lineage, be constant? Surely this invariance cannot be a property of the world. Amounts of evolutionary change smaller than $\ln x_2 - \ln x_1 = 1.2$ must exist unless all changes are *per saltum* to this degree. Likewise, larger amounts of change must occur if mammals have their ultimate ancestors in prokaryotes and all organisms are related by evolutionary descent. The average value of 1.2 at all scales must be a property of human perception, not of the world. That is, we rarely notice smaller degrees of change, while larger amounts are accompanied by so much uncertainty about actual ancestors and descendants that we do not identify lineages with confidence and do not make the evolutionary links. Gingerich says as much when he states: "Organisms differing by a factor of much more (or less) than 1.2 are so different (or so similar) that they are rarely compared in calculating rates" (*1*, p. 160). Nonetheless, whatever the reason for a constant average numerator, the simple fact of its invariance renders the smooth and straight form of Gingerich's plot a mathematical necessity, not a source of empirical information.

Incommensurability of categories represents another problem with Gingerich's analysis. The very fast rates (up to 60,000 darwins) for laboratory selection experiments and the very low rates of longest intervals (less than 1 darwin) are not random samples of their scales and cannot, therefore, be directly compared. As Schindel argues (*6*), the fastest rates are for populations when they change, and do not include the millions of natural populations that are not evolving and would display rates in darwins of flat zero. The slowest rates do represent a potential average for all lineages (since all change to some degree over such long intervals), but they are so low primarily because they average long periods of stasis with shorter intervals of change at higher rates. Even Gingerich, a leading gradualist in the so-called gradualist-punctuationalist debate, says as much: "The longer the interval, the more stasis and evolutionary reversal are likely to be averaged in the result" (*1*, p. 160).

This analysis does not deny the value of Gingerich's main practical point: proper comparison of rates must either

be made over similar intervals or corrected for the differences. To make such a correction, however, one must have enough data for the intermediate points on the curve (between x_1 and x_2) to enable one to determine the values needed to give comparable time intervals for comparing two rates. With only the end points, x_1 and x_2, one cannot do this without assuming the rate of change. If one assumes exponential change, then rates (in darwins) are independent of the time interval. One is free to choose any curve to "correct" the rate based on the longer interval to that of the shorter interval in the absence of intermediate points, and thus can arrive at the rate that best suits his theory. My demonstration of the artificial nature of Gingerich's curve should help us to identify the various reasons for measured differences in rates. Differences measured during intervals of varying lengths may represent the same absolute change of $\ln x_2 - \ln x_1 = 1.2$ occurring over different amounts of time, while differences measured at the same interval must represent real variation of the numerator about its average value of 1.2.

Finally, the artificial character of Gingerich's curve refutes his general conclusion that its smoothly linear character demonstrates that "microevolution and macroevolution are different manifestations of a common underlying process" (*1*, p. 161). The claim is invalid on logical grounds in any case, since continuity in rate does not demonstrate unity of cause. Gingerich's own statements belie his claim since he admits that the high rates (in darwins) over shortest intervals cannot represent the stuff of change over longer times; for he states that "they exceed homeostatic limits and exceed rates to be expected in nature (*1*, p. 161)." Micro- and macroevolution will be united under a common theory encompassing their distinctive causes within a coherent framework.

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6. D. Schindel, personal communication and public statement at Geological Society Meeting in Indianapolis, November 1983.

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Evolutionary rates are inversely related to the interval of time over which they are measured. A frequency distribution of observed rates and corresponding intervals forms a hyperbolic trend that is highest near the origin, bounded at zero on both the interval and rate axes, and declines to a limit approaching $Y = 7.4 X^{-1.0}$ (*1*). This smooth curve requires thoughtful interpretation, but it is not an artifact of psychology or mathematics (*2*).

Transforming axes to logarithms makes the original hyperbolic trend linear because the origin vanishes and other values are adjusted on a proportional scale. This linear trend has lower and upper limits. The lower limit is purely operational, arising because small differences cannot be distinguished from zero. The upper limit has an operational component, arising because very different organisms are rarely compared, but it has structural and functional importance as well, reflecting material limits of morphology. Minimum rates are always zero. Maximum rates are of greater interest because they define the upper limit of evolutionary change for any given interval of time.

Given two points and no additional information, a conservative assumption of linearity of intermediate values is axiomatic in all rate calculations. One is not free to manipulate rates to suit particular theories.

Rates are calculated to remove the effect of time in comparing differences produced by evolution. The proportional difference (*D*) between two forms is assumed to be some monotonically increasing function of time (*t*), appropriately modeled in simple cases as a general power function:

$$D = at^b + c \qquad (1)$$

where a is a constant, $b \geq 0$, and c drops out because $D = 0$ when $t = 0$. When $b = 1$, proportional difference is a linear function of time.

Evolutionary rate (*R*) is usually assumed to be independent of time, which is true when $b = 1$. In general:

$$R = D/t = at^b/t = at^{b-1} \qquad (2)$$

R is a hyperbolic function of t whenever $0 \leq b < 1$. Empirically $b = 0$, to a first approximation, and equation 1 reduces to $D = a$. Here the proportional difference between forms is completely independent of time, and comparison of rates measured over different intervals can only be misleading.

The numerator D in Eq. 2 is free to vary within limits ranging from about 1 to 1600, with an average value of about 1.2. A proportional difference less than $D = 1.0025$ cannot ordinarily be distinguished from $D = 1$, corresponding to the logical lower limit of zero absolute difference. Beyond its operational component, the observed upper limit of proportional change, $D = 1600$, is likely to be important for understanding the natural world, differences of greater proportion pose insoluble structural and functional problems in organisms of common body plan. The largest of the great blue whales is about 1600 times larger in most linear dimensions than the least shrew, one of its smallest mammalian relatives. Mammals simply cannot be more different. Time is free to vary by factors exceeding 100,000,000, while morphology is more tightly constrained.

Hallam (*3*) stated that rate and time are not simple reciprocals of each other. Bonner (*4*), like others before him, overlooked the problem. My purpose in presenting data from a diverse range of empirical studies was to show that evolutionary rate and time are inversely related as simple reciprocals, that this inverse relationship is more than an artifact of plotting, that the underlying problem is fundamental and cannot be ignored, and that it renders meaningless any simple comparison of evolutionary rates.

Two modes or classes of rates are distinguished in the theory of evolution by punctuated equilibria (*5*): high "punctuation" rates associated with short intervals of genetical or ecological time, and low "stasis" rates associated with longer intervals of geological time. In view of the above, one might ask whether high rates calculated over short intervals (punctuation rates) are different from low rates calculated over longer intervals (stasis rates) when corrected for differences in measurement interval. Any comparison of rates, including that implicit in portraying "punctuation" as a distinct evolutionary mode, must be made over a common interval or scaled to correct for the difference in intervals. Properly scaled, "punctuation" and "stasis" are not likely to be different.

Continuity of rate does not by itself demonstrate unity of cause, but pragmatism requires that simple and traditional theories prevail as long as they explain observed patterns successfully (*6*). Continuity of rate observed over all scales of time is consistent with a unified interpretation of microevolution and macroevolution.

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Gut Flora and Urinary Phenylacetic Acid

Sabelli *et al.* (*1*) suggested that urinary phenylacetic acid (PAA), a metabolic product of phenylethylamine, may be a marker for the diagnosis of some major depressive disorders. These researchers strengthened their argument that urinary PAA reflects metabolism in the body rather than in the gastrointestinal tract by including a number of references, one of which (*2*) reports a personal communication that ingestion of neomycin, which kills intestinal flora, did not reduce significantly the total urinary PAA excretion. Seakins (*3*) reported that less than 0.4 percent of an ingested 7-g sample of L-phenylalanine was recovered as urinary PAA. However, when 600 mg of phenylalanine was taken in an enteric-coated capsule, the increase in PAA output corresponded to 22 percent of the ingested dose. Noting the wide range in results on normal subjects, Seakins concluded (*3*, p. 129) that PAA excretion was affected by "variations in feacal flora, transit time, efficiency of digestion as well as variations in the intake of dietary protein and its digestibility."

We obtained 46 24-hour urine samples from 12 healthy volunteers. The samples were analyzed by the method of Sabelli *et al.* (*1*) with the exception that 2-phenylbutyric acid was used as an internal standard instead of phenylpropionic acid. The PAA outputs of these individuals were consistent with those reported in (*1*).

In addition to the volunteers, we obtained urine samples from an individual who was under medical care and was ingesting cloxacillin (8 g per day). Twenty-four–hour urine samples collected on days 25, 26, 27, and 30 of treatment contained 38.4, 24.5, 25.7, and 29.0 mg of PAA, respectively. On days 25, 39, and 46 after the cessation of treatment, the respective PAA values were 121.9, 161.6, and 217.4 mg.

Two of the 12 volunteers were also subsequently placed on antibacterial medication after which their PAA outputs dropped significantly. Prior to receiving medication, one of these indi-vidual's four consecutive 24-hour urine samples contained 175.6, 134.2, 106.0, and 76.7 mg of PAA. For 4 days this individual ingested penicillin V (1.5 g per day) and then for 5 days cephalexin (Keflex) (1 g per day); urine collected on days 8 and 9 of treatment contained, respectively, 24.0 and 36.2 mg of PAA. The other subject excreted 134.1, 138.8, 188.0, and 160.1 mg of PAA in four sequential 24-hour urine samples; on days 5, 6, 7, and 8 of treatment with ampicillin (1 g per day), the PAA values were 127.0, 83.4, 113.0, and 44.3 mg, respectively.

These results lead us to conclude that urinary PAA values seem to be influenced by the condition of the gut flora. The involvement of the gastrointestinal tract would indicate that the PAA output may also be affected by diet. These findings would limit the use of PAA as a marker for major depressive disorders.

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In our studies we have proposed that a deficit in brain phenylethylamine (PEA), an amphetamine-like substance that was first identified in the brain (*1*), causes depressive illness. More recently, we reported a reduction in the PEA metabolite phenylacetic acid (PAA) in the urine (*2, 3*) and blood (*4*) of depressed subjects. These individuals were otherwise healthy and untreated. In these reports we made no claims that PAA excretion could not also be altered in other illness-es or with drug treatment. Many factors affect any biochemical variable, and the most important of these should be known before a biochemical measurement is used as a diagnostic test. Thus, the contribution of Hryhorczuk *et al.* is of value to researchers. Some cautionary remarks are, however, in order.

1) Hryhorczuk *et al.* report no measures of mood or any other clinical variable in the patients. Was there diarrhea? What was the protein intake? Many patients with viral illnesses show depressive-like symptoms.

2) There is no evidence presented by Hryhorczuk *et al.* indicating that antibiotics reduce urinary PAA by reducing its dietary absorption. Many antibiotics affect protein metabolism systemically (*5*). Earlier reports demonstrated that drugs that do not affect the gut flora, such as amphetamines and antidepressants, rapidly modify PAA excretion (*6*). Changes brought about by antidepressants appear to correlate with therapeutic response.

3) The considerations about diet are highly speculative. Karoum *et al.* (*7*) have shown that marked dietary manipulations fail to affect PAA excretion. On the other hand, we have found that loading with L-phenylalanine, the amino acid precursor of PEA and PAA, ameliorates depression and can even terminate an episode in bipolar subjects (*8*). These therapeutic studies strengthen, in our view, the importance of pursuing the study of PEA and PAA in affective disorders.

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