Light Treatment and Biological Rhythms

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Evolution of Biological Rhythms

In crossing a heath, suppose I pitched my foot against a stone, and were asked how the stone came to be there, I might possibly answer that, for anything I knew to the contrary, it had lain there for ever. Nor would it perhaps be very easy to show the absurdity of this answer. But suppose I had found a **watch** *upon the ground and it should be inquired how the watch happened to be in that place, I should hardly think of the answer which I had before given, that for anything I knew, the watch might have always been there...*

[Rather], the watch must have had a maker: there must have existed, at some time, or at some place or other, an artificer or artificers, who formed it for the purpose which we find it actually to answer, who comprehended its construction, and designed its use...for, in the watch which we are examining, are seen contrivance, design, an end, a purpose, means for the end, adaptation to the purpose...

Every indication of contrivance, every manifestation of design, which existed in the watch, exists in the works of nature; with the difference, on the side of nature, of being greater or more, and that in a degree which exceeds all computation.

William Paley (1802)

Introduction

In the preceding, now famous opening to his polemic *Natural Theology*, Paley conjures his Rolex-in-the-rough to symbolize things of organized complexity and potent functionality. His book goes on to catalogue a far grander list of contrivances, adaptations among living things, and with such a keenness that Darwin (1958) wrote: "The logic of...Paley...gave me as much delight as did Euclid. The careful study of these works...was the only part of the Academical Course which...was the least use to me in the education of my mind. I did not at the time trouble myself about Paley's premises; and taking these on trust, I was charmed and convinced by the long line of argumentation."

Paley's premise, rejected by Darwin first on trust and later on inference, was that the watch implied a watchmaker no less certainly than the marvelous adaptations in living things did a Creator. Darwin's creator, indeed, his creation, was natural selection, The Blind Watchmaker (Dawkins, 1987), an artificer without purpose or forethought but able to generate complex designs suited for environment-specific purposes.

Watches and watchmaking, it seems, have attracted greater consideration as metaphors for adaptation than biological rhythms have as adaptations themselves. Such rhythms, after all, represent the very essence of adaptationist definition: unlikely complexity, exquisite fit with environment, remarkable preservation over taxonomic space. But Darwinian adaptations are defined as units of function and function, in turn, as the way in which a trait provides selective advantage; in short, as problem-solving machinery. For biological rhythms, then, the adaptationist question is not "how do organisms keep time" but rather "how, specifically, and in each evolutionary line inhabiting its own ecologic niche, do rhythmic organisms outpace conspecifics which lack such complex and costly machinery."

Circadian and human seasonal rhythms present immediate, if different, problems for such consideration. Circadian rhythms, despite their very identity as adaptations, nevertheless serve a function which remains obscure. Human seasonality, on the other hand, while analogous to mammalian adaptative traits whose function is clear (ie., surviving and exploiting predictable

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energetic deprivations and opportunities, respectively), is observed in only a minority persons living in living in temperate latitudes and, worse, represents a disorder defined by subjective distress and functional impairment. Circadian rhythms, then, an adaptation in search of a function and seasonal mood rhythms an adaptation in search of a cure.

This issue presents some review and new work on these two questions, namely whether circadian rhythms serve any adaptive function and whether human seasonal rhythms are likely to represent an adaptation.

Adaptationism

Since Darwin, adaptationist research has progressed in fits and starts, at once aided and challenged by conceptual refinements and critiques and by progress in molecular and population biology and comparative phylogeny. Readers are referred to Rose and Lauder (1996a) for a definitive text on current adaptationist thought and methods. Herein, several general points with potential relevance to biological rhythms are worth making.

First, carving or atomizing complex traits into meaningful and testable adaptive units is often difficult. One gene can have multiple simultaneous or sequential phenotypic effects - a concept called pleiotropy. Thus, certain traits may be mere "genetic side-effects" of adaptive genes but functionally useless or indeed costly. Furthermore, selection can select only among what is available in every generation, which in turn is the product of past history and finite random variation. Thus, adaptive traits may be of less than optimal design. For biological rhythms, discerning an "unit of selection" from the myriad interconnected physiologic and behavioral process subject to rhythmic variation seems daunting.

Second, an adaptive trait's current function may differ from the one it served when first evolved, a distinction between the concept of adaptation as Darwinian-historical process and adaptation the current-fitness outcome. The term exaptation (Gould and Vrba, 1982) refers to traits which currently provide benefits for which they sere not originally selected, in other words traits maintained by selective environmental pressures that have changed since affecting ancestral forms with the trait. For biological rhythms, given their long adaptive pedigree, it is likely that specific adaptive functions vary substantially among species or even among populations within a species occupying different environmental niches.

Finally, influential critiques of sloppy adaptationism (e.g., Gould and Lewontin, 1979), while contributing important refinements in theory and method, have at times had an undesirable chilling effect, producing a exaggerated reluctance on the part of biologists to confront questions of adaptation (Rose and Lauder, 1996b). In this issue, Arbisi and Dean suggest that early adaptationist considerations of seasonal mood cycles may have been similarly effected by such types of early critiques (e.g., Mrosovsky, 1989; Zucker, 1989).

Circadian Rhythms

Circadian rhythms present a particular type of problem for adaptationist analysis, a case in which "adaptiveness is assumed

on the indirect evidence of complexity and constancy" (Williams, 1966), even though the exact nature of the function is obscure. Only sleep comes to mind as a comparably common and complex neural process whose function remains unknown.

Ouyang and Johnson, in this issue, review prior consideration of circadian rhythms as adaptations and emphasize the repeated failures of phenotype manipulation experiments to demonstrate physiologic defects among arrythmic organisms when studied in isolation. Conversely, experimental manipulations of environment - e.g., exotic light-dark conditions - have been unsuccessful in identifying selective agents that help maintain circadian function. Ouyang and Johnson also report new findings of directly measured increases in reproductive success (RS) among normally rhythmic compared to mutant arrythmic cyanobacteria, but only when the two are cultured together. Their's is a rare and worthy effort to address the question of circadian adaptiveness, and one which raises two important concepts.

The first is that study of adaptations is essentially comparative in nature, and fitness quantifiable only in relation to alternative available phenotypes. No mere abstraction, this means that adaptations are merely better than their alternatives and not necessarily much better at that. Indeed, traits commonly evolve and are maintained by natural selection while providing advantages so small, but applied over such long periods, that the trait's contribution to fitness may not be apparent when by examining phenotypic variants in isolation or cross-section. Rather, adaptiveness may be detectable only by differential success of competing phenotypes over many generations and within large populations. Even Haldane (1956), to use the textbook example, could not likely have discerned a problem in light-colored moths on soot-covered trees in industrializing Britain, except as reflected by population shifts toward melanic alleles that occurred over a mere twelve generations.

In much the same way that rhythmicity can predominate so completely despite probable small fitness differentials, so too can the specific environmental factors, operating over long periods, constitute sufficient selective pressure to maintain the trait even while remaining "subtle" and difficult to identify. As Ouyang and Johnson's cyanobacteria finding demonstrates, observing selective advantage among rhythmic strains sheds no immediate light on the specific environmental pressures which rhythmicity helps to survive or exploit. Indeed, given the vast array of environmental niches inhabited by circadian organisms, it is certain that specific selective pressures maintaining "circadian advantage" are quite varied and include biotic environmental variables (e.g., predators; DeCoursey and Krulas, 1998) many steps removed from direct variation of light and temperature.

Human mood seasonality

As a potential adaptation, human mood seasonality presents a rather different, if no less difficult, problem for adaptationist analysis. The trait, assuming the accuracy of prior epidemiologic findings, is evident in only a minority of the population, even at high latitudes. Such population heterogeneity of seasonal adaptations is generally uncommon among long lived mammals living at temperate latitudes (Bronson, 1989). Perhaps even more problematic is that SAD and its variants represent a disorder whose morbidity seems at odds with any likelihood of selective advantage. The heterogeneity and morbidity questions will be considered in turn.

An often considered explanation of SAD's low prevalence is that the trait is no longer subject to selective pressures of earlier-and-energetically-harder times, thus no longer adaptive and in the process of downward genetic drift. It seems more likely, however, that such changes in ultimate environmental pressure are too recent to have allowed much negative selection and, instead, recent masking by novel proximate cues - e.g., artificial light and dark - limit the expression of preserved seasonal potential (Wehr, 1998).

On the other hand, population heterogeneity of a trait does not, in and of itself, rule out an adaptive function. Rather, polymorphisms of phenotype and genotype are common and growing body of evidence suggests that natural selection plays an active role in maintaining such polymorphisms (see Hudson, 1996). Even in classical one-locus, overdominant, random mating genetic models, natural selection leads only to maximization of mean fitness, such that the fitness of any particular individual need not be near that of the maximum of the population (Rose and Lauder, 1996b). For example, heterogeneity in reproductive quiescence induced by short photoperiods have been documented in wild populations of small, temperate-living mammals (e.g., Kerbeshian, 1994), presumably because such heterogeneity allows greater opportunism in short lived populations inhabiting potentially harsh but not fully predictable environments.

In another, perhaps more relevant example, recent findings on the genetics of temperature resistance in the Drosphilia clock gene reveal two major major alleles, (Thr-Gly)17 and (Thr-Gly)20, which are related to the flies' ability to maintain a circadian period at different temperatures (Sawyer, 1997). These two variants are distributed as a highly significant latitudinal cline in Europe and North Africa, meaning that the relative frequencies of the two alleles within each local population shows a gradual transition from preponderance of temperature resistance alleles in the north to relatively more non-resistant alleles in the south. This cline, like others, is thought to represent the averaging by natural selection of different degrees of temperature resistance over a geographic plane defined by the range of migration of individuals over the gradient of temperature variability. (For a lucid theoretical review of adaptive clines, see Kirkpatrick, 1996). The farther the individuals migrate, the broader the genetic cline and the greater the difference in selective pressure (e.g., ambient temperature) across the plane of migration, the greater the difference between phenotypes maintained in the polymorphism.

The relevance of such clines to SAD is that, though the mean population fitness within each locale is kept near an optimum by such selected polymorphism, some individuals within each population are necessarily better suited to conditions further north or south, producing a relative mismatch with local conditions. Given the intensely migratory behavior of humans, it is conceivable that some aspects of SAD's complex epidemiology may be explained by such a model. For example, a higher prevalence of gross mismatch (i.e, clinical SAD) and a broader continuum of symptom severity would be expected within populations constitut-

ed by peoples who migrate more intensively and over steep ecologic gradients (e.g., Kasper et al., 1989) as compared to populations which are more genetically isolated and/or occupy more uniform environments (e.g., Magnusson and Axelsson, 1993; Axelsson and Magnusson, 1993; Partonen et al., 1993).

A different example of selected polymorphism, reflecting a different type of genetic trade-off, is the sex-linked dominant model. In this model, an X-chromosome allele can maintain a stable frequency even while causing selective disadvantage in affected males if, at the same time, the allele confers some benefit, even of relatively lesser magnitude, on females. This is so because the allele frequency is necessarily twice as high in females (XX) as in males (XY) and thus a positive selection in females would insure allelic maintenance if the positive selective effect or equal or greater than half the negative selective effect on males. To cite an unproven and controversial example, this model has been invoked in considering how a putative X-linked contribution to male homosexuality (Hamer et al., 1993) might have arisen despite negative effects on reproductive success (RS) in affected males (Trivers, 1994). According to the model, an allele whose effect was to augment sexual attraction to men would increase in frequency if affected females "enjoyed" reproductive enhancement of greater than half the magnitude of any collateral reduction among affected males.

Of uncertain applicability to SAD, X-chromosome loci for certain affective disorders have nevertheless been proposed (Baron et al, 1987; Pekkarinen, 1995) and the model is at least consistent with the convincing observed preponderance of females among winter depressives.

Probably the most familiar example of adaptive polymorphism, and one which formally embraces the concept of disease as adaptation, is that of the heterozygous advantage. In this model, a mutation which confers net reproductive advantage will increase in frequency even if it causes vulnerability to disease. The classic example is sickle-cell anemia, a single-locus genetic polymorphism in which the recessive allele for hemoglobin S produces enough benefit by protecting heterozygous carriers against malaria in endemic environments that its gene frequency is maintained despite the dire consequences to homozygous individuals (Allison, 1954). The heterozygous advantage argument has been applied to various conditions with known deleterious effects on reproduction but stable gene frequencies within populations (e.g., Huxely, 1964; Srinivasan and Padmavati, 1997). In SAD, the observed population continuum in vulnerability to wintertime symptoms may include some form of heterozygous advantage, with "milder" forms balancing the adverse consequences to more severely affected individuals.

SAD's morbidity, while undeniable, may not then exclude an evolutionary explanation. Indeed, adaptationist perspectives have been previously applied to a broad range of frank mental disorders (e.g., Huxley et al., 1964; Crow, 1991; Klein, 1993; Price et al., 1994; Schlager, 1995; also see McGuire and Troisi, 1998). Recently, Williams and Nesse have provided a more systematic approach to reconciling the seeming incongruity of illness as adaptation based on principles similar to those illustrated in the polymorphism examples above. They state: "the assumption that natural selection maximizes health is...incorrect - selection maximizes reproductive success of genes. Those genes that make bodies having superior reproductive success will become more common, even if, they compromise [some] individuals health in the end" (Nesse and Williams, 1998).

Darwinian medicine (Williams and Nesse, 1991; Nesse and Williams, 1994), offers at least two other relevant perspectives for considering SAD. The first is that of evolved defense. This concept suggests that symptoms or even illnesses can represent evolved defenses which, though painful and even costly to the organism in themselves, are less costly than failing to respond to the threat against which they defend. Examples of such evolved defenses include cough, morning sickness in early pregnancy (to avoid consuming teratogens during morphogensis), and forms of anxiety from simple phobia to panic (Klein, 1993). The concept further suggests that signal detection in certain defenses, like certain types of anxiety, are designed with hair-trigger responses which, though responsible for much normal suffering, are selectively maintained by the dire penalty (e.g., death) incurred by a single missed threat. This concept is illustrated by the common household smoke alarm, whose annoying sensitivity to common "burnt toast" is actively maintained to insure an early alert in the rare case of actual fire.

As applied to SAD, this concept suggests that the adaptivenes of winter depression may have less to do with surviving the predictable component of wintertime energetic stress than the variable component. Temperature and food supply vary not only between summer and winter but also, substantially, from winter to winter. To defend against extreme energetic challenge of an especially harsh winter, sensitivity to a reliable if inexact predictive trigger - photoperiod - could have been maintained by selection even if the energy conserving response was costly and often unnecessary but rarely lifesaving.

Most familiar to chronobiologists is the evolutionary medicine concept of disorders of novel environments, in which current ecologic conditions differ sufficiently from so-called "environment of evolutionary adaptedness" (EEA) to render certain traits mismatched or dysregulated. This broad category includes examples like as jetlag and shift work syndromes, as well as endemic obesity and atherosclerosis, the latter two caused by evolved eating behaviors better adapted to conditions of fat/calorie deprivation and high physical activity but now expressed in environments of dietary abundance and sedentary lifestyle (Eaton and Conner, 1985).

Novel-environment explanations of SAD include those that consider the disorder to represent dysregulated forms of normal rhythms caused by pathogenic shielding from or overexposure to appropriate light-dark zeitgebers. To date however, studies have not found differences between SAD patients and controls in measured exposure to ambient wintertime light (Oren et al., 1994; Guillemette et al., 1998) and both SAD patients and normals have shown significant seasonal differences in exposure to outdoor ambient light (Eastman, 1990; Cole et al., 1995; Hebert et al., 1998). Though still very much subject to controversy, there seems as much evidence that seasonal mood cycles represent rhythms preserved in spite of attenuated signals (Wehr, 1997) as that they represent a dysregulated breakdown product in "vulnerable" individuals.

One final novel-environment consideration suggests that seasonality is a vestige of traits evolved in tropical environments

before modern humans completed their outward migration about 20,000 years ago. Robust annual behavioral rhythms are still in evidence in extant tropical stone-age cultures where, presumably, annual cycles of rainfall and food supply influence human reproduction (for review, see Bronson, 1995).

All of which begs the question of how, exactly, seasonal mood cycles might contribute to human reproductive success. In this issue, Arbisi and Dean present a detailed analysis of evidence suggesting that SAD had served an adaptive function akin to torpor in other large mammals. Readers are also referred to Bronson's (1995) excellent adaptationist review of human reproductive seasonality. Though Bronson finds strong support lacking for an adaptive function of temperate zone reproductive seasonality, the latter trait may well overlap with and have relevance for consideration of the role of seasonal mood cycles in reproductive age women.

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Are Circadian Clocks Adaptive?

I. A long-pursued question: how are circadian clocks important?

Are circadian clocks important? This question has remained unsolved since the first report of circadian rhythms over 250 years ago. Although attempts have been made to address this issue, none has been able to prove that reproductive fitness is enhanced by circadian programming.

It seems that circadian clocks must be important, given the fact that organisms from almost all kingdoms possess endogenous daily rhythms. However, except for a few obvious cases (e.g., the role of the clock in sun-compass orientation of bees and birds; Hoffmann, 1960), most rhythms have not been demonstrated to have clear adaptive significance. These questionable cases include famous demonstrations of rhythms such as leaf movement and fruitfly eclosion. In addition, a puzzling result from mutation studies shows that clock mutants of different organisms exhibit no detectable physiological defects (Konopka and Benzer, 1971; Vitaterna et al., 1994). These findings suggest two possibilities: one is that the role of the clock is not very important, while the other is that the defects may not be easy to detect against a background of high variation.

One common argument against the laboratory data that clocks are unimportant is that laboratory conditions are too comfortable for clock-mutated organisms to exhibit defects. If this be true, then a harsh condition (e.g., a resource-limited condition) may help to reveal the importance of clocks. In such environments, clock mutants could be handicapped. For example, if circadian programming improves the uptake of nutrients, clock mutants would grow poorly under nutrient deprivation. However, if the primary function of the clock is not for resource exploitation but for a function similar to the reproductive isolation of species, such as might be the case for courtship song cycles in Drosophila (Kyriacou CP, Hall JC, 1986), limiting resources would not reveal a clock function. The inability of early attempts to demonstrate a role for some circadian rhythms may be due to our ignorance of the selective pressures that promoted the evolution of the clock. Therefore, what environment is optimal to discover how clocks make organisms more fit?

II. The effect of "resonance" and non-resonance cycles on individual organisms.

Pittendrigh (1965) proposed that environmental LD cycles were the primary selective agent behind the evolution of the clock. He suggested that the direct cyclic benefits and/or hazards of light and its indirect effects (esp. temperature) provided a selective force for the origin and fine-tuning of the clock. The daily timekeeper was thought to help organisms regulate light-sensitive processes to occur at night to avoid the deleterious effects of light. Concomitantly, other processes that need light (e.g., photosynthesis) were phased to take advantage of sunlight. During further evolution of clock systems, other processes—even those that are not directly affected by light—might come to be regulated by this clock (Pittendrigh, 1976). If Pittendrigh's hypothesis that the LD cycle is indeed the major selective agent, then we may predict:

First, under so called "resonance conditions" (Pittendrigh and Minis, 1972), where the external cycle is 24 hours (natural conditions), circadian clocks confer the highest benefit to organisms. The clock may be unable to entrain to a non-24 hour T-cycle. Alternatively, the clock may entrain to a non-24 hour driving cycle but with an abnormal phase relationship and possibly an altered amplitude of the clock. These altered phase relationships and/or amplitudes could be disadvantageous. Second, in the absence of LD cycles (i.e., constant conditions), the clock may not be as helpful as in LD cycles. (Actually, Pittendrigh [1993] argued that clocks also internally coordinate metabolic processes and therefore would be useful in constant conditions.)

In short, clocks should be most beneficial in 24-hour light-dark cycles. But as we still do not know in what way clocks help, it is unclear which parameter is most appropriate to measure when the organism is in non-24 hour cycles. Despite these uncertainties, pioneer investigations studied parameters such as growth rate, development, and longevity based on the presumption that they are controlled by the clock (see below). In some cases, they were affected, in the others not.

For example, the vegetative growth of some higher plants was inhibited by continuous light or non-24 hour light/dark cycles (Went, 1959, Highkin, 1953). Tomato plants were often studied as they had been found to be the most sensitive to abnormal photoperiodic conditions (Hillman, 1956). It was also reported that under LL conditions, tomato leaves show chlorosis, a symptom of injury (Withrow and Withrow, 1949). Interestingly, another investigation showed that growth rate was a reciprocal function of temperature and the LD cycle (Went, 1960). For example, at 30oC optimal growth was seen in short T-cycles while at 15oC, the optimal growth took place in T-cycles that are longer than 24 hours. Went interpreted these results to be consistent with the hypothesis that altering the temperature also alters the period of the clock and thus the optimal T-cycle for resonance. However, this phenomenon seems to be restricted to only a few species of plants, so further investigation is needed (Went, 1960). An important issue neglected by these investigators is the impact of abnormal T-cycles on reproduction. In the case of plants, reproductive efficacy should be measured by fecundity, not growth rate. This issue is critical in the sense that the reproductive success of organisms is the crucial parameter to be measured when one discusses adaptive significance.

Animals have similar responses to abnormal LD cycles. In the flesh fly Sarcophaga argyrostoma, the number of days for larval development was affected by the duration of the LD cycle (Saunders, 1972). In these experiments, cycle length varied from 24 to 60 hrs with a fixed duration of light of 12, 14 or 16 hrs followed by a variable dark interval. Development was most rapid when the cycle length was 24 h or a multiple of 24 h. Pittendrigh & Minis (1972) and Saint Paul & Aschoff (1978) found that flies of some species tended to have higher survivorship in LD cycles of close to 24 hours than in cycles far from 24 hours (i.e., 21 h, 27 h, and in constant light).

However, the above observations have not been found in other organisms, and some results have not been reproducible (in particular, the Pittendrigh and Minis study could not be repeated, even in Pittendrigh's lab). Moreover, clock mutations, especially null mutations, seem to confer no defects in growth, development, or longevity (except that in Drosophila, it was found that the long period mutant has a significantly slower developmental rate in both LD12:12 and LL than the other strains, but the null mutant was almost identical to wild type; Kyriacou et al., 1990). Taken together, these studies are a muddle; it is not clear whether clocks function to improve growth, development or longevity.

III. Is fitness a measurable parameter ?

As we know, fitness -i.e., reproductive success - is the ultimate parameter in estimating the importance of a trait, and growth, development, longevity etc. may not be direct contributors to fitness (Endler, 1986). Therefore, measuring these factors may underestimate or even neglect the importance of the trait. This is probably why the attempts to determine how clocks enhance fitness have been inconclusive; fitness was not directly measured.

However, measuring fitness requires studying a population for several generations under selective conditions. There are almost no studies that meet this criterion. Two exceptions include, first—H. R. Highkin found that plants grow faster if their parents were grown in a temperature cycle than if their parents grew in a constant temperature environment (Highkin, 1960). This difference was observed even when a 24 h LD cycle was imposed. Longer incubation of plants in normal LD cycles but at constant temperature could even result in degeneration (failure to germinate and abnormal growth). This study suggested that the absence of a temperature zeitgeber to the parents has an impact on the growth of the next generation.

In a preliminary investigation to the second study, SCN and sham lesioned ground squirrels were observed in an outdoor enclosure (DeCoursey et al., 1997). The lesioned animals were more prone to predation due to their irregular activity in the night. This was the first study to show that circadian clocks may be important for survival of mammals in a pseudo-natural environment. These data enouraged an heroic long term study by the same first group. They found that SCN-lesioned chipmunks survived and reproduced in the wild for the first year about as well as control chipmunks (DeCoursey and Krulas, 1998). In the second year of the study, the SCN lesioned chipmunks were preferentially targeted and killed by a predatory weasel. DeCoursey suggested that the absence of an obvious difference between controls and experimentals in the first year might have been due to an exceptionally abundant food supply and lack of heavy predation in that first year, while conditions were more harsh in the second year (Dr. Pat DeCoursey, presentation at 1998 SRBR meeting).

Our observations on cyanobacteria

Theoretically, an adequate fitness test for circadian clocks would compare the reproductive success of populations in the natural environment of wild type organisms with mutant organisms in which the biological clock is disrupted. Such a study should also monitor population changes for multiple generations. There are several species in which clock mutants have been isolated, but performing an adequate test is not feasible for most of these organims. However, cyanobacteria are amenable to this kind of study. Under laboratory conditions, they reproduce asexually and are not known to conjugate. Their small size makes the study of large populations easy. In addition, the cyanobacterium we used can be genetically manipulated; we have a large armory of clock mutants (Kondo et al., 1994), and three of its clock genes have been identified and cloned (Ishiura et al., 1998). Finally, this organism has a short doubling time (can be as short as 6 hrs) that allows a lot of experiments to be done relatively quickly, a feature for which senior graduate students that need to finish their Ph.D. are grateful!

Studies from this lab show that this photosynthetic alga clearly benefits from having a clock. Our experiments rely on the simple concept of a competition experiment between two strains. When the growth of a clock-null mutant and wild type cells are measured in pure (i.e., single-strain) cultures, the growth rates are indistinguishble. But, when the two strains are mixed and grown together in batch cultures that are occasionally diluted, wild type performs better in both constant light as well as in 24 hour light/dark cycles. After a number of generations, only wild type cells can be detected in the population. This result clearly demonstrates that the clock is important for fitness. In LD cycles, the loss of mutant cells is very quick (10-20 generations), whereas in constant light, there is a more gradual decrease of the fraction of mutant cells. A possible explanation for this difference is that the LD cycle is an external selective force that rapidly culls the mutant cells, while in constant light this external selective force is absent. Why do the mutant cells lose in constant light? Perhaps temporal coordination of internal processes by a circadian timekeeper also improves efficiency, and this effect is relevant to cells in both constant light and in LD cycles.

The other discovery from our work is that the clock's cycle needs to match that of the environmental cycle to optimize fitness (Ouyang et al., 1998). For example, a short period mutant can do even better than wild type in short T-cycles that match its free running period, while long period mutants can beat wild

type in long T-cycles. Short-period mutants out-compete long-period mutants in short T-cycles, but lose in long T-cycles. And, as predicted, wild type defeats other strains in 24-hour LD conditions. One possible cause for these results, as demonstrated by studying the rhythm of the promoter activity of a photosynthetic gene (psbA1), is that the phase relationship of the clock to the LD cycles is different when the clock's period is dissimilar from that of the environmental cycle. It is likely that cellular activities are turned on/off inefficiently when the clock does not resonate properly with the environment.

Although these data indicate that clocks must be adaptive for cyanobacteria, the physiological mechanism(s) of competitive advantage is unknown. Through which physiological process does the clock improve fitness? In our experiments, conditions (e.g., nutrients, light intensity) were probably much better than in nature for the cyanobacteria, therefore it is not a surprise that selection does not exhibit an immediate effect. So if we know the physiological bases of the clock's benefits, we might design a correspondingly "harsh" condition to amplify the advantage of having a daily timekeeper and thereby better infer the clock's evolution. Nevertheless, our data indicate that even in cyanobacteria growing in relatively good conditions, we can detect a robust fitness advantage conferred by the clock.

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Into the Hibernaculum Again or Is There Seasonal Gold in Them There Gold Mantled Ground Squirrels?

Since the first description of the condition, Seasonal Affective Disorder (SAD) has been thought of as an analog to hibernation, with both conditions being viewed as behavioral strategies directed toward adapting to the environmental challenges of dark, cold, and food scarcity. For example, Galen (129-200 AD) after observing seasonal changes in energy noted the similarity between the winter lethargy he observed in humans and hibernation (Galen, 1976). Indeed, many of the behavioral disturbances observed in SAD appear to bear a striking resemblance to the phenomena of hibernation. Increased sleep duration, overeating, weight gain, lethargy, and social withdrawal that appear gradually during the winter in SAD seem analogous to the behavioral pattern observed in hibernation. The observation that SAD, at least superficially, resembles mammalian hibernation has stimulated investigation into the physiological parameters of sleep, energy expenditure, and thermoregulation, all of which may have relevance for the pathophysiology of SAD.

The context of these investigations rested on an animal model of hibernation and a belief that SAD represents some vestigial remnant of human winter torpor (Rosenthal et al., 1987; Wehr et al, 1987). Early on however, and influenced by critical analyses of Mrosovsky (Seasonal Affective Disorder, Hibernation and Annual Cycles in Animals: Chipmunks in the Sky) and Irving Zucker (Seasonal Affective Disorders: Animal Model Non Fingo) in Rosenthal and Blehar's early book on SAD (1986), investigators became less enthusiastic over the relationship, if any, between hibernation and SAD. Indeed, it became somewhat embarrassing to be called to task by basic animal researchers who were well prepared to disabuse us of any inappropriately held notions regarding the similarity between hibernation and SAD (Mrosovsky, 1989; Zucker, 1989)

Nonetheless, the notion that behaviors associated with SAD have an adaptive function continues to be intriguing, particularly in view of observations of seasonal abnormalities observed among SAD subjects in thermoregulatory parameters (Arbisi et al., 1994; Arbisi et al., 1989; Schwartz et al., 1997b), resting metabolic rate (Gaist et al., 1990), and macronutrient consumption (Krauchi,et al., 1993; Krauchi, et al., 1990). Further, with population estimates of SAD (including subsyndromal SAD) ranging upwards of 25% in the northern tier climes (Booker & Hellekson, 1992; Kasper et al., 1989; Rosen et al., 1990), and considering the dimensional distribution of seasonality (Kasper et al., 1989; Spoont et al., 1991), the sheer percentage of the population experiencing SAD, subsyndromal SAD, or seasonal fluctuation in energy and mood argues for the potential adaptive benefit of seasonality. More importantly, the observed variation in seasonality across the general population combined with findings from twin studies of a genetic contribution to the development of SAD support the assumption that seasonality evolved due to selection pressure since a lack of genetic variation is a constraint on adaptation (Buss et al., 1998; Madden et al., 1996).

Given the above findings, is it time to once again revisit the den of hibernation in hopes that the relevant literature can stimulate and inform clinical researchers? In other words, is there seasonal gold to be mined from gold-mantled ground squirrels, or are we, as N. Mrosovsky would have it, chasing "Chipmunks in the Sky"?

One objection with regard to the similarity between SAD and hibernation is that an isomorphic animal model for SAD does not exist. Further, it may be inappropriate to relate a "normal" periodic phenomena (hibernation) which occurs in widely divergent species to a pathological condition (SAD) occurring in humans. Mrosovsky states, "The similarities between these two states (depression and hibernation) have never been apparent to me. I suspect that they are little more than anthropomorphic projections based on the curled-up posture and inertness of hibernation". (Mrosovsky, 1989)

Although it seems self-evident that the particular mechanisms underlying hibernation and SAD are not the same, the functional aspects of the behavior may be similar. Consider this: as hominids dispersed into higher latitudes, they may have been faced with environmental pressures which in animals led to the development of hibernation, but which in humans led to seasonal torpor, the human equivalent of hibernation. This line of reasoning is not as far fetched as it first appears. For example, even closely related species can differ in terms of the adaptive response to shortened photoperiods (Nelson et al., 1990). After exposure to short (winter) photoperiods, Syrian hamsters gain weight but Siberian hamsters lose weight. Syrian hamsters prepare for winter by increasing energy stored as fat whereas Siberian hamsters decrease their metabolic mass and thus require lower energy intake for energy maintenance (Bartness & Wade, 1985). Here we have the evolution of functional strategies in two closely related species which are quite the opposite, but aimed at meeting the same environmental demands. This illustrates the point that natural selection is concerned "with a particular outcome..... and not with the specific mechanisms by which this end is achieved" (Zucker, 1989; p158).

Humans, like other mammals, have retained the physiological structures and mechanisms to detect changes in daylight and respond accordingly by adjusting the duration of sleep, melato-

nin secretion, and prolactin secretion (Wehr et al., 1993). With respect to consistent seasonal behavioral changes in humans there are reports of seasonal cycling in human behavior (Aschoff, 1981), but there is little direct evidence for the mechanism underlying these periodicities. None the less, the question can still be posed: Are observed annual cycles in humans the result of photoperiodicity or endogenous annual cycles (Nelson et al., 1990)? The fact that primates demonstrate robust circannual rhythms that are entrained by photoperiod and that humans have retained photoperiod-responsive mechanisms lends support to the impression that human seasonal rhythms are circannually generated (Wehr et al., 1993; Zucker, 1989). Granted that no appropriate animal model for SAD exists, could studies of non-human mammals prove heuristically informative in clarifying the mechanisms of SAD and elucidating the source of a clearly established annual pattern of behavior?

Finally, Mrosovsky is far less negative once afforded the point that hibernation is not an animal model for SAD. He acknowledges that the hibernation literature has led to intriguing and potentially productive hypotheses regarding the underlying pathophysiology of SAD (Hallonquist & Mrosovsky, 1987). Mrosovsky indicates that there are specific experimental strategies (guided by what animal researchers have learned regarding hibernation and torpor) that could serve to elucidate seasonal mechanisms in SAD (Mrosovsky, 1989). Specifically, he wonders whether SAD patients demonstrate seasonal reproductive quiescence through gonadostat resetting. Additionally, he suggests the study of body weight regulation with particular emphasis on eating and energy expenditure, and the use of Cabanac's (1971) technique of allesthesia to explore carbohydrate craving (Cabanac 1971; Mrosovsky, 1989).

To our knowledge, several of these recommendations have been followed with varying degrees of success. For example, the findings of attenuated negative allesthesia during the winter in SAD patients (Krauchi et al., 1994), and increased morning BMR (Gaist et al., 1990; Krauchi et al., 1994) provide evidence that reported changes in macronutrient consumption and diurnal variation in energy expenditure have a physiologic basis. By adopting a less restrictive perspective, that is, assuming for the moment that SAD represents a variation of an adaptive seasonal strategy aimed at coping with wide variation in daylight, other fruitful avenues can be explored. However, we must first establish that the behaviors associated with SAD can be construed as adaptive, given certain environmental conditions.

Adaptive Significance of Hibernation and Mammalian Torpor

Animal seasonality comprises a set of phenomena which encompass a wide variety of strategies aimed at responding to environmental demands which challenge the organism's basic fitness. These demands can include nutrient acquisition under circumstances of scarcity, maintenance of thermoregulatory homeostasis under severe temperature extremes, and competition for access to reproductive opportunities. In some instances the fundamental balance of energy may be severely disrupted.

Predictable seasonal cycling of food availability and temperature can lead to adaptive strategies such as hibernation and torpor, whereby the organism decreases its energy needs during the "crunch" portion of the cycle, or increases it's energy stores, or a combination of both. Hibernation and torpor can be modeled on a Cartesian plane defined along one axis by the lowering of energy needs, and along the other by the accumulation of energy stores. Within this domain, adaptive strategies can encompass a broad array of behaviors and physiologic phenomena, with hibernation falling at one extreme and torpor residing closer to the origin.

True hibernators drop their core body temperatures close to the ambient temperature. This is accompanied by lowered metabolism and almost complete behavioral quiescence (Heldmaier et al., 1989). The absolute variation in thermoregulatory displacement in hibernators may reflect the interaction between body mass, surface area, and metabolic rate during the waking state, with the goal of achieving a reduced uniform metabolic rate, rather than a simple thermoregulatory downward shift in set point (Singer & Bretschneider, 1990). During deep hibernation the same uniform specific metabolic rate is achieved for both large and small organisms (Singer & Bretschneider, 1990). Thus, large organisms such as the Black Bear do not require a significant reduction in metabolic rate and body temperature in order to reach this reduced metabolic rate, since they have a relatively low metabolic rate in the waking state. On the other hand, small rodents such as the hazel mouse, reduce their metabolic rates by values of 1/100 of the waking state during deep hibernation (Singer & Bretschneider, 1990). Consequently, defining hibernation or torpor by absolute changes in metabolic rate or core body temperature may be misleading, in that more subtle adaptive changes can be overlooked.

For example, the bear (Ursus americanus) "hibernates" at near normal temperature, but is easily aroused, and can give birth and nurse cubs while denned up (Nelson, 1980). Indeed, other large mammals exhibit a seasonal prolongation in ultradian activity with a decrease in the number of episodes of activity per day during the winter, where as other large mammals simply disappear for periods of time, presumably engaged in energy-conserving bouts of torpor (Ericksson et al., 1981; Nizielski et al., 1985). Clearly, the metabolic needs of true hibernators are much different from the bear, which expends about 4000 kilocalories per day, or the reindeer which, during the winter, decreases episodes of activity from 8 bouts to 4 bouts per day (Ericksson et al., 1981; Nelson, 1980).

Since mammalian adaptation to similar seasonal stressors is quite diverse, it seems reasonable to ask if these same selection pressures have exerted an influence on human evolution, with seasonality representing a behavioral adaptation which falls along a dimension similar to that found in hibernation and mammalian torpor.

Human Ethnological Perspective

Until the later Pleistocene, hominids were essentially a tropical species (Foley, 1993). Thermoregulatory stress caused by exposure to extreme winter seasons is thought to have limited occupation of northern latitudes by hominids until 300,000 and 400,000 years ago, when hominids migrated into the subarctic northern latitudes. This period corresponds with the evolution

from Homo Erectus to H. Sapiens (Foley, 1987, 1993). As hominids dispersed from tropical middle latitudes to northern latitudes, the extreme seasonal change in day length and ambient temperatures presented profound adaptive challenges. For the newly arrived hominid, stress generated by the wide variation in photoperiod can be grouped as follows:

I. Food is more limited, due to the constraints on the growing season by available daylight.

II. The shortened winter day light limits opportunity to forage for scarce resources.

III. Temperature varies with available light.

IV. Large predators were more active at night or at dawn and dusk, limiting hominid activity to day light hours.

Importantly, the environmental factors that vary seasonally at extreme latitudes can have an impact on reproduction and thus fitness. These factors include food availability and quality as well as ambient temperature (Bronson, 1995). Therefore it is conceivable that the ability to adapt to seasonally changing conditions would lend an advantage in reproductive fitness. The concept of "time-stress" has been evoked to describe problems faced by hunter-gathers living in higher latitudes (Torrence, 1983). Time stress refers to the seasonal window which limits the organism's access to resources. It puts a premium on budgeting activities, such that the greatest adaptive advantage is accrued during the window of opportunity. Resource availability is highly seasonal, such that there is an abundance of resources during late summer and early fall, but these become scarce during the winter and early spring. Further, the light available for obtaining scarce resource during the winter is limited. Additionally, thermoregulatory stress interacts with the stress of resources acquisition, since the metabolic demand of euthermia increases during the cold, light-shortened days. Simultaneously, the availability of nutrient resources decreases, resulting in pressure to increase the forage range. Finally, as a corollary, the behavior of nocturnal predators may be relevant, since large carnivores would be operating under the same environmental time stress. Since the usual available prey might be quite limited, non preferred organisms (hominids?) could become prey objects. Indeed, the combined pressures of time-limited resources and increased predator activity in seasonal environments may have led to the formation of social structures (Foley, 1993), as well as the development of technology (Torrence, 1983). As evidence, high-latitude primitive populations have a wider and more complex variety of tools than do primitive populations from the middle latitudes (Torrence, 1983).

Energy Conservation

In any case, adaptive strategies are likely to be diverse and varied, as it would be unreasonable to assume that a single strategy would evolve to cope with the varied stresses presented by a seasonal environment at higher latitudes. Using the adaptive model as a guide, we shall focus heuristically on two inter-related systems that would experience significant evolutionary pressure in an environment characterized by extreme seasonal variations.

Let us first tackle the issue of seasonal fluctuation in resource availability. What would be the adaptive responses to seasonally predicated changes in nutrient availability during the Famine phase of the Feast or Famine cycle? Three basic strategies could evolve in order to cope with the seasonal fluctuation of resources: 1) Decrease energy needs during famine; 2) More actively seek out scarce or spotty resources and; 3) A mixed strategy, wherein the decrease in resources is anticipated by an increase in consumption during the end phase of the feast season, followed by a decrease in consumption and conservation of energy once the energy cost of obtaining resources exceeds the probable benefits. Thus, during the famine season, an initial burst of activity is associated with the acquisition of rapidly diminishing resources, but this is followed by periods of relative inactivity where energy is supplied by accumulated reserves (Foley, 1993).

Generally, adaptation to the depletion of nutritional resources is accomplished by decreasing energy demanding activities which are not associated with resource acquisition. As a general rule, when faced with a period of resource shortage, animals will cut down on non-essential activities, with energy expenditure concentrated on foraging behavior at the expense of other, particularly social, activities. In this way, animals may be able to 'hang on' until conditions improve. At one extreme, this may involve complete hibernation or aestivation, but it is usually less marked" (Foley, 1987; pages 203-204 italics added).

Unlike hibernation, which in its extreme represents an almost complete cessation of energy expenditure, SAD might represent a mixed strategy, wherein a seasonally synchronized shift to a high energy diet is accompanied by bursts of activity associated with the acquisition of food, and then prolonged periods of torpor. During the winter, SAD subjects report late-afternoon "craving" for sweet, high carbohydrate (high-fat?) foods (Krauchi, et al., 1990). Further, activity and mood follow an exaggerated diurnal pattern with a relative increase in energy expenditure during the first half of the day, decreasing energy across the late afternoon, and a slight recovery in the evening followed by early sleep onset (Krauss et al., 1992). Combined with the widely documented winter weight gain, changes in appetite, loss of energy, and sleep disturbance presage the development of depression in SAD (Young et al., 1991); which in turn may further serve to store energy and accumulate resources. Hence the "core" symptoms of SAD (decreased energy and fatigue, increased sleep, increased appetite, and weight gain) can be viewed as the result of a mixed strategy aimed at coping with the challenges of winter. In support, we note that the symptoms of increased sleep, increased appetite, sweet craving, and weight gain best predict response to light therapy (Krauchi, et al., 1993; Terman et al., 1996). This lends further credence to the hypothesis that the "core" symptoms of SAD are fundamentally tied to environmental cues associated with light, and thus may serve an adaptive function during the winter.

Another line of evidence which argues for the adaptive advantage of the "core" symptoms of SAD derives from population studies of seasonal variation in mental illness. SAD has been repeatedly shown to vary with latitude across industrial populations (Booker & Hellekson, 1992; Lingjaerde & Reichborn-Kjennerud, 1993; Rosen et al., 1990). However, estimates

of winter depression in indigenous populations from extreme northern latitudes (>70° N) have resulted in lower than expected rates of SAD (Nayha et al., 1994; Partonen et al., 1993). Indeed, in data derived from health surveys of Finish reindeer herders, the rate of depressive symptoms was lower during the winter than in the summer (Nayha et al., 1994). This raises an intriguing possibility: Populations which migrated to the far north, and whose livelihood is tied more closely to the natural cycle, report less depression because they are not forced to conform to the arbitrary 12:12 light dark cycle imposed by industrialized society. In explaining the relatively low rates of depression during the winter in Finland, the authors state, "The general experience that mild depression is a rather accepted phenomenon during the autumn months, however, might also have influenced the low frequency of depressive symptoms reported by the subjects living in the northern regions. Adaptive mechanisms to a northern environment will be an essential focus of future studies" (Partonen et al., 1993; pp. 191, italics added).

The ability to adapt to the extremely short winter days by contracting the activity portion of the rest-activity cycle without social or occupational consequence might eliminate the cognitive and affective response to such a behavioral strategy. Supporting this explanation is the observation that the onset of depressed mood in SAD lags behind the onset of energy, sleep, and appetite changes (Young et al., 1991), presumably because the social and vocational consequences of tardiness, decreased productivity, and disrupted interpersonal relationships extracts an ever increasing emotional toll across the winter before they culminate in an episode of major depression. Consequently, depressed mood may represent an epiphenomenon which results from a consequence of failure to conform to a 12:12 light dark cycle rather than being an intrinsic feature of seasonality or SAD.

Resource Acquisition and Energy Conservation

Several hypotheses follow which relate to the adaptive benefit of SAD. Does the shift in appetite represent a behavioral response to a physiological need or is it secondary to depressed mood? SAD patients, after an oral glucose load, perceived high sucrose concentrations as more pleasant during the winter (Krauchi, et al., 1994). Further, insulin sensitivity was found to be modestly impaired during the winter in the same group, suggesting that a real metabolic demand for glucose underlies the report of CHO-craving during the winter (Krauchi, et al., 1994). Our group found changes in taste detection and recognition threshold in SAD subjects for sweet, sour, and bitter tastes during the winter. These changes lagged behind mood, in that successful light treatment failed to alter the taste detection and recognition thresholds in the SAD group, yet during the summer sweet taste normalized (Arbisi et al., 1996a). These findings suggest a physiological response to light that may be independent of mood. Hence mood changes might represent an epiphenomenon related to a formerly adaptive physiological change.

Another, more speculative, yet intriguing, hypothesis it that CHO craving associated with SAD represents a vestigial adaptation for women that prevented reproductively costly excess protein consumption. Speth (1991) argues that there is a critical upper limit of protein that can be consumed on a regular basis as a proportion of other macronutrients. Fifty percent of daily energy must be derived from non-protein sources including fats and carbohydrates. This limit may change under conditions of high energy demands and resource scarcity as well as during pregnancy. During seasonal low points in food availability, winter or late spring, edible plants became scarce to ancestral hunter gathers living at higher latitudes. Given the increased demands of thermoregulatory homeostasis and the need to procure adequate non-protein energy sources, the winter would represent a particularly challenging adaptive bottle neck for females (Speth, 1991). It is possible that winter CHO craving, which is more commonly observed in females, served an adaptive purpose by maintaining the critical protein balance through preferential consumption of fats and carbohydrates. In support, craving for chocolate, a mixture of simple carbohydrates and fat, is consistently reported by woman randomly selected from the general population and more frequently reported consumed during the fall and winter (Rodin et al., 1991; Weingarten & Elston, 1991). Further, food cravings associated with pregnancy and morning sickness during the first trimester have been viewed both as an adaptive impediment against the ingestion of teratogens and a safe guard against excessive protein consumption (Profit, 1992; Speth, 1991). Consequently, this approach predicts that women will be more prone to report craving for sweet high fat foods during the winter and particularly during winter pregnancies.

Another hypothesis relates to actual energy conservation. Should SAD patients demonstrate lower basal metabolic rate (BMR) during the winter when they are hypothetically conserving energy? There are several studies which speak directly to this question, but there is a corollary issue. During the winter, SAD must represent a physiologically sound strategy for conserving energy in toto. Recall here that SAD may represent a mixed strategy where there are shifts in both diet and activity patterns across the day. While two studies have provided evidence of disturbed metabolic rate in SAD, the direction of deviation was in the opposite direction from that predicted. Resting metabolic rate (RMR) was found to be higher in a mixed gender group of SAD patients, but unfortunately the menstrual cycle was uncontrolled. Light treatment resulted in a 9% decrease in RMR, an observation that runs counter to the hypothesis that SAD is associated with a strategy of energy conservation (Gaist, et al., 1990). Additionally, Krauchi et al., (1994) found a moderately increased resting metabolic rate in a group of mixed gender SAD subjects.

Both studies, however, measured RMR in the morning, when SAD patients report increased activity. From an evolutionary perspective, it is possible that mornings represent a period (associated with bright day light during the winter) when hominids were more actively engaged in foraging activities. Consequently, measurement of BMR across the day with special attention to the late afternoon, when SAD patients have reported a fall in activity and mood, might yield data indicative of a fall in BMR relative to controls (Krauss, et al., 1992).

Further, higher BMR is associated with greater daily sleep quota across species (Berger & Phillips, 1995; Walker & Berger,

1980; Zepelin, 1994). This association may represent an adaptive synergy in that during sleep a decrease in energy expenditure occurs. By increasing sleep duration total energy expenditure can be budgeted across the day. Hence reported hypersomnia and observed increase in BMR in SAD may be related and subsume an adaptive limiting of winter energy expenditure.

Rest Activity Cycle:

An additional strategy to conserve energy during "crunch" periods could be to alter the frequency or duration of periods of activity akin to the strategies adopted by reindeer and bears during winter periods marked by limited forage (Ericksson, et al., 1981; Nelson, 1980). Recently, a reduction in activity throughout the day accompanied by significant phase delay and poor entrainment of the rest-activity cycle were found in SAD patients (Teicher et al., 1997). SAD patients, assessed via wrist-worn actigraphs, displayed an 11% decrease in activity level across the day that was more pronounced in the first two hour after arising when compared with healthy adult controls. The reduction in day-time motor activity is common across affectively ill patients (Wolff et al., 1985), but it appears that only SAD patients report a seasonally tied decrease in energy accompanied by an increase in sleep (Albert et al., 1991). On self-report, SAD patients indicated they were less energetic and engaged across the day during the winter than normal controls with a trough in energy and interest occurring in the late afternoon (Krauss, et al., 1992). Further, the exaggerated diurnal rhythm in activity, energy, appetite, and mood associated with the report of late afternoon worsening could represent the onset of an energy conserving bout of torpor.

Thermoregulation:

The maintenance of thermoregulatory homeostasis is another significant adaptive challenge faced by hominids migrating into higher latitudes. Thermoregulatory stress caused by exposure to extreme temperatures during the winter is thought to have been a significant barrier to hominid expansion (Foley, 1993). Consequently, the adaptive response to changing thermal conditions would have been critical as hominids expanded their range, " The fact that during their evolution hominids have modified their thermoregulatory system so drastically, and achieved such high levels of efficiency, suggest that selection as a result of thermal stress was considerable." (Foley, 1987; p. 101). Later Pleistocene hominids were essentially a tropical species, adapting to the thermoregulatory demands of a hot climate through a combination of several strategies, including a relative increase of surface area to volume through the extension of distal limb proportions, a decrease in surface area exposed to solar radiation (bipedalism), and the development of perspiration and concomitant water dependence (Foley, 1987).

Adaptation to cold climates requires a strategically different approach. For example, in order to conserve heat, body proportion alters with a relative decrease in distal limb proportions relative to volume. This appears to hold true in modern human populations. Mean annual temperature and crural index (tibial length/femur length x 100) are highly correlated (r=.81). Lapp and Eskimo populations have the lowest crural index, approximating that of Neanderthals (data: Trinkaus 1981, in Foley, 1987, p. 268). That being said, the thermoregulatory strategy adopted by successful migrants to higher latitudes was likely a compromise between the demands of both a hot and cold environment, since thermal stress varies across wide temperature ranges during the year. The evolutionarily successful hominid would have to adapt to both cold winters and hot summers. Thus, a mixed physiological and technological strategy evolved which allowed for survival and reproduction in a climate marked by extreme variation in temperature. Accepting for the moment that SAD represents a complex adaptation to extreme seasonal conditions, thermoregulatory homeostasis in SAD would also seem a fertile area of exploration.

Several groups have found abnormal thermoregulation in SAD patients. Specifically, premenopausal female SAD subjects in the late afternoon failed to dissipate an exercise induced increase in core body temperature as rapidly as controls. This abnormality normalized after successful light treatment and during the summer (Arbisi, et al., 1994; Arbisi, et al., 1989). The NIMH group found normal nighttime temperature amplitude during the winter, but after light treatment the SAD group demonstrated an enhanced night time amplitude due to decreased night time minima (Rosenthal et al., 1990). Moreover, during the summer the entire temperature profile was lowered in both SAD and controls rather than just the nocturnal temperature (Levendosky et al., 1991). More recently, nocturnal core temperature minima were found to be higher in the winter in twenty-two SAD patients relative to the summer, but not in controls (Schwartz, et al., 1997b). Further, the improvement in mood following light treatment was associated with a decrease in nocturnal core temperature during the winter in depressed SAD subjects (Schwartz et al., 1997a). Moreover, since SAD patients have lower nocturnal facial temperature while depressed then do controls, nocturnal brain cooling may be abnormally regulated during the winter in SAD patients (Schwartz, et al., 1997b).

Taken together, findings from the above studies point to dysregulation in the thermoregulatory system in SAD which may lead to ineffective dissipation of accumulated heat loads during the winter (Arbisi, et al., 1994; Arbisi, et al., 1989; Schwartz, et al., 1997b). At this juncture, however, it is difficult to firmly place the thermoregulatory findings within our adaptive model of SAD. Without further study and consideration, the adaptive significance of these findings in SAD subjects is enigmatic at best, particularly since there are other explanations which are equally viable, especially those relating to circadian disturbances (Avery, Dahl et al., 1997; Lewyet al., 1989; Teicher, et al., 1997). Nonetheless, disturbances in thermoregulatory function are intriguing and warrant further investigation.

Neurobiology of Hibernation: HIT and Endogenous Opioids

As argued above, hibernation and mammalian torpor are a result of convergent evolution where similar adaptive strategies evolved in distinct species to meet the same environmental challenge (Lyman, 1963). Given the similarities between strategies across species, the analogy is tempting: could similar mechanisms have developed independently to regulate hibernation across species? At first glance, this seems unlikely, given

the range of variation in thermoregulation and metabolism in hibernating species. Nonetheless, a single ubiquitous class of neuroactive peptides, the endogenous opioids, appears to be involved in regulating hibernation in a broad range of species (Nurnberger et al., 1991). The similarity between high-dose opioid depression of physiological systems and the hibernation-induced depression in these same systems, led to the investigation of the endogenous opioids as candidate hibernation regulators (Nurnberger, et al., 1991). Indeed, the observation that opioid antagonists disrupted the hibernation cycle supported this line of inquiry (Beckman & Llados-Eckman, 1985). Thermoregulatory response to exogenous opioids varied across seasons in ground squirrels. During the hibernation phase a low dose of exogenous opioid produces a blunted hyperthermic response, while high dose morphine yields hyperthermia. These findings suggest a reduction of thermoregulatory responsiveness to morphine during the hibernation phase (Wang et al., 1987). An increase in methionine-enkephalin immunoreactive fibers was found in the lateral spetal region during hibernation, lending further support for the existence of an endogenous opioid substance that "triggers" hibernation through an initial increase in endogenous opioid activity especially in the lateral septal region, an area closely linked to thermoregulation (Nurnberger, et al., 1991).

An endogenous opioid peptide first isolated from the plasma of hibernating woodchucks and 13-lined ground squirrels demonstrated a remarkable ability to induce summer hibernation in a number of species (Oeltgen et al., 1987). This substance, Hibernation Induction Trigger (HIT), has been isolated from plasma, brain, and urine of a wide variety of hibernating animals (Oeltgen, et al., 1987). Moreover, HIT was isolated from the polar bear (Ursus maritimus), a non-hibernating species that is closely related to a true hibernator, the brown bear, Ursus arctos, (Bruce et al., 1990). Indeed, injection of HIT derived from hibernating woodchuck into the cerebral ventricle of the conscious rhesus monkey induced hypothermia, behavioral depression, bradycardia, and aphagia, suggesting that non-hibernating primates possess receptor sites that are capable of responding to HIT (Oeltgen et al., 1982).

Given the ubiquitous nature and functional diversity of the endogenous opioids and their well established role in feeding (Cooper et al., 1988) and thermoregulation (Clark & Lipton, 1983), is there any evidence that endogenous opioids play a role in the pathophysiology of depression or SAD?

Recently, the endogenous opioids have been implicated in the maintenance of carbohydrate craving in depressed SAD patients. Blunted sweet taste detection threshold was observed in depressed SAD patients who reported craving sweet high-carbohydrate foods during the winter (Arbisi et al., 1996b). When euthymic during the summer, taste detection thresholds normalized in these patients. Adam Drewnowski, among others, has proposed that the most relevant neurobiological system involved in the development of food craving and consumption of highly palatable foods is the endogenous opioid system (Cooper, et al., 1988; Drewnowski et al., 1992). With that in mind, sweet taste detection threshold was determined during the winter in 5 depressed female SAD patients who reported carbohydrate craving. Subjects were then retested in a double blind placebo control study after a single 50 mg challenge dose of Naltrexone, an opioid peptide antagonist. Relative to controls, sweet taste detection threshold normalized in the SAD subjects (Arbisi, et al., 1996b). These findings, although tentative, provide support for an endogenous opioid link to carbohydrate craving in SAD, and should serve to stimulate further investigation into a possible link between the endogenous opioid system and the pathophysiology of SAD.

Conclusion

Admittedly, the above discussion is highly speculative, and represents the early stages of a second look at SAD through the lens of comparative evolutionary psychology. Hibernation and mammalian torpor have been discussed not in terms of an animal model for SAD, but as examples of species-adaptive strategies aimed at solving similar environmental challenges (Mrosovsky, 1989). This perspective can serve as a context for further inquiry into the pathogenesis of SAD. For example, blunted negative allesthesia and blunted sweet taste detection threshold in SAD suggest underlying physiological changes associated with carbohydrate craving. Further, the interest in thermoregulation prompted by the hibernation literature has yielded consistent findings of blunted thermoregulatory heat loss during the winter (Arbisi, et al., 1994; Arbisi, et al., 1989; Schwartz, et al., 1997b).

To a great extent, these research strategies were stimulated by research first conducted in non-human species on processes that had adaptive significance (Arbisi, et al., 1996a; Krauchi, et al., 1994). The question remains as to whether these findings have adaptive significance and whether, for example, under a cold thermal stressor, SAD patients would exhibit adaptive thermoregulatory abnormalities. Finally, the adaptive lens allows us not only to focus on potentially important processes such as weight gain, carbohydrate craving, metabolism, and thermoregulation, but also warns us that the timing of experiments is critical. If we consider SAD to be adaptive, in that it represents a complex seasonal strategy that includes a shift in the number or length of bouts of activity across the day, then potentially interesting control-SAD differences might be observed only during those times marked by bouts of decreased activity. Certainly a prime candidate would be the late-afternoon, which in SAD patients is marked by increased fatigue, lack of energy, and craving for carbohydrates. In fact, consistent SAD-control differences in sweet taste detection threshold, basal prolactin level, spontaneous eye-blink rate, and thermoregulation have been observed at that time (Arbisi, et al., 1994; Arbisi, et al., 1996a; Depue et al., 1990). These findings demonstrate a need for a more careful look at SAD control differences in the late afternoon while simultaneously controlling for the effects of potentially relevant circadian phase desynchronization between the two groups (Lewy, et al., 1989; Teicher, et al., 1997).

In sum, SAD may represent a "harmful dysfunction" whereby harm is a societal judgment related to the undesirability of the condition and dysfunction refers to the failure of the mechanism to perform the adaptive function that evolved through natural selection(Wakefield, 1992). Currently, under modern artificial lighting conditions, the capacity to respond to seasonal changes in photoperiod becomes adaptively inert. Nonetheless, individu-

als who are sensitive to the greatly weakened photo signals of seasonal change manifest behavioral responses (increased sleep duration, increased appetite and weight gain, exaggerated diurnal fluctuation in energy) that result in "dysfunction" with respect to the demands of contemporary industrial society. By viewing SAD as a by product of a theoretically adaptive trait of seasonality which evolved to meet challenges presented by extreme fluctuations in photoperiod at higher latitudes, potentially fruitful lines of research can be pursued into aspects of SAD (thermoregulation, carbohydrate craving, diurnal variation in mood and energy) which may have led to enhanced fitness in the environment of evolutionary adaptiveness.

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A NEW STRUCTURED INTERVIEW FOR ATYPICAL DEPRESSION

In 1974, Klein first identified mood reactivity as a primary symptom of atypical depression. Ten years later, Rosenthal et al. (1984) observed reverse neurovegetative symptoms (hypersomnia, hyperphagia, and carbohydrate craving) in people who suffered from seasonal affective disorder; these, too, fall in the atypical spectrum and were included in the Structured Interview Guide for the Hamilton Depression Rating Scale - Seasonal Affective Disorder Version (SIGH - SAD) (Williams et al., 1994). The current "Columbia" definition of atypical depression (Stewart 1990a,b) includes mood reactivity, coupled with two or more of the following: hypersomnia, hyperphagia, leaden paralysis, and rejection sensitivity that leads to functional impairment. Although Rosenthal and colleagues did not include mood reactivity and rejection sensitivity in their portrait of seasonal affective disorder, two recent studies have found these features in patients with SAD (Terman and Stewart, 1993; Tam et al., 1997). An ongoing question is whether seasonal and nonseasonal atypical depressions are distinct disorders.

Researchers and clinicians need a reliable tool to detect and scale the presence and severity of atypical symptoms. Stewart (1990a) developed a semi-structured interview, the Atypical Depression Diagnostic Scale (ADDS). The criteria for atypical features on the ADDS differ from those of DSM-IV (1994, pp. 384-386). Although the DSM-IV criteria were derived from the original Columbia criteria (Rabkin et al., 1996), those criteria were subsequently amended, as reflected on the ADDS. Specifically, the criteria for hypersomnia, weight gain, and relationship avoidance (due to rejection sensitivity) differ between the two instruments. Given these discrepancies, we felt that creating a tool that could give both an ADDS and a DSM-IV diagnosis would be useful to researchers and clinicians alike.

For the purposes of research, we feel that a structured interview is essential when diagnosing patients, in order to maximize reliability. Neither the Structured Clinical Interview for Axis I Disorders (First et al., 1995) nor the ADDS is a sufficient tool. The questioning on the SCID is so brief and superficial that the interviewer cannot confidently rate the items. This problem is especially apparent on the questions dealing with rejection sensitivity. And even though the ADDS provides more detailed questions with follow-up probes, it, too, needs improvement. Not only are some of the questions presented in a biased manner ("Did you ever react as much as 50%?"), other questions are simply intimidating, implying social norms, and potentially leading to inaccurate responses ("Do you have an ongoing romantic relationship? . . . Why not?") (Stewart 1990a). We find such questions awkward for both the interviewer and the patient. Additionally, despite Stewart's (1990b) original intentions , the questions are likely to elicit responses based on hypothetical situations, rather than on actual life events, which could lead to lower reliability and validity of the diagnosis.

Our goal was to create a structured interview that detects and scales the severity of atypical symptoms, as defined by both the ADDS and DSM-IV. The Diagnostic Interview for Atypical Depression (DIAD) (Terman et al., 1998) is more thorough than the SCID and is also more friendly than the ADDS. To make the questions easier to ask and answer, we shifted the focus from hypothetical scenarios to actual life events. If patients cannot provide examples from their own lives, even after probing by the interviewer, only then do we defer to hypothetical situations. And, as stated above, we strived to avoid implicit value judgments by creating a narrative that lists a range of possible responses, emphasizing that people react in a variety of ways when they are rejected or criticized.

In addition to the changes in the tone of questioning, we also wanted to expand the instrument so that it can assess a current or past depressive episode, or seasonal depression. The various time frames are presented in each question, as appropriate.

Because some atypical items on the SIGH-SAD are not part of the DSM-IV or ADDS criteria for atypical depression, we added two new measures to the DIAD. These scores reflect the number and severity of the atypical neurovegetative (ANV) symptoms that do contribute to a DSM-IV and ADDS diagnosis of atypical depression. The ANV scores may prove useful in predicting response to treatment, as was suggested in a recent analysis of atypical symptoms assessed by the SIGH-SAD (Terman et al., 1996).

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Benefits of Phototherapy in SAD Illuminated

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Morning bright-light therapy reduces the symptoms of seasonal affective disorder (SAD), report three US research teams (Arch Gen Psychiatry 1998; 55: 875-82, 883-89, 890-96). The findings "signal the entrÈe of light therapy into the psychiatric mainstream", says Michael Terman of Columbia University (New York, NY, USA), lead author of one of the studies. Critics have stated that light therapy's effects are no different from placebo, he adds, but "these studies take care of that objection for the first time".

Charmane Eastman and co-workers at Rush-Presbyterian-St Luke's Medical Center (Chicago, IL, USA) gave 96 patients with SAD morning light, evening light, or placebo for 4 weeks. The placebo was a sham negative ion generator, a device accepted by most patients as a mood enhancer. 61% of patients improved with morning light; 50% with evening light; and 32% with placebo.

Terman and co-workers compared the effects of morning light, evening light, and low and high-density negative ions in 158 patients. Morning light produced most remissions, but evening light was superior to placebo (low-density ions). High-density ions also reduced depression more than placebo—a "surprise" finding that Terman is now pursuing. Morning light was also superior to evening light in a study done by Al Lewy's team at Oregon Health Sciences University (Portland, OR, USA).

These findings support the use of morning light for treatment of SAD, and are in keeping with the "phase-shift hypothesis", says Lewy. "People get depressed in winter at least in part because of a delay in their body clocks", he proposes. In summer, exposure to bright light occurs on waking. In winter, dawn is later, "and since we cue mainly to dawn, our other circadian rhythms drift later, and get out of phase with sleep". Morning light pushes the rhythms back into phase with sleep, reducing SAD by "removing the internal dysynchrony". Alternatively, people could simply be more sensitive to light in the morning, he notes.

Regardless of why it works, "the results are positive, and practitioners can now recommend and supervise this therapy", says Terman. But documentation of safety and effectiveness should be requested from the maker of any light-therapy apparatus because there are no agreed standards. Some systems may produce excessive glare or ultraviolet radiation, he warns. For more information, see www.websciences.org/sltbr.

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