motor responses elicited by a noxious stimulus but also the perceived aversiveness of that stimulus.

Consideration of how brain stimulation exerts its analgesic action is impelled by its obvious importance to our understanding of neural mechanisms of pain perception. For instance, electrical stimulation of these particular brain regions may abolish pain by producing a functional lesion at the stimulation site, which disrupts the normal processing of the afferent pain message. However, this seems unlikely since destruction of an area from which analgesia is produced (the central gray matter, for example) does not clearly lead to a reduction in pain sensitivity (*7*) even though this area has been implicated on electrophysiological grounds in the coding of pain (*8*).

Rather, we propose that brain stimulation attenuates pain by activating a neural substrate that functions normally in the blockage of pain. That such a substrate exists and is capable of being selectively activated is supported by a number of studies concerning the site and mechanism of the analgesic action of morphine. The integrity of certain neurotransmitter systems appears necessary for morphine to exert its analgesic effect (*9*). This suggests that morphine acts, at least in part, by activating a neural pathway in which these transmitters are released. The neurons or chains of neurons in this pathway, then, comprise the substrate of analgesia. The locus of this substrate is suggested by studies that employ intracerebral microinjections of morphine or its antagonist nalorphine. From these studies it appears that morphine acts at certain specific sites in the brain, including the hypothalamus (*10*), the midbrain central gray matter, and the more caudal periventricular regions (*11*). These are areas showing at least partial overlap with those where we find analgesia to result from electrical stimulation. Also, a high transection of the spinal cord abolishes the inhibitory effect of morphine on sensory transmission through the spinal cord (*12*), which suggests the existence of a descending inhibitory influence from those brain regions activated by morphine. Our observation that the spinally mediated flexion or withdrawal reflex was totally suppressed in analgesic animals supports this suggestion.

It seems plausible to us that the analgesia we have observed results from activation of a neural system in the brain which has an ultimate inhibitory action on sensory transmission in the spinal cord. The existence of such a system, a central control mechanism influencing a spinal "gate" for pain perception, has already been proposed (*13*) to account for the powerful modulating effects psychological factors are known to have on nociception. Our results suggest that this system can be effectively activated by focal brain stimulation. These results reinforce continuing attempts to apply this technique to the problem of pain management in man.

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Stage 4 Sleep: Influence of Time Course Variables

Abstract. *Age, length of prior wakefulness, length of time asleep, and a circadian influence all affect stage 4 sleep. The amount of stage 4 sleep decreases as subject's age increases and as time asleep increases. Longer periods of wakefulness before sleep result in greater amounts of stage 4 sleep in the first 3 hours of sleep. Sleep periods that begin at times other than the regular onset time tend to produce less stage 4 sleep; this decrease suggests a circadian effect.*

For many years we have been stalking a segment of sleep that is known as stage 4. We have studied the effects of stage 4 sleep (*1*), and others have studied such variables as drugs (*2*), psychopathology (*3*), exercise (*4*), and growth hormones (*5*). This report is a review and analysis of data from our laboratory on the responsiveness of stage 4 sleep to changes in four commonly variable features of human sleep: age, length of prior wakefulness, length of the sleep period, and time of sleep onset (a circadian effect). The first three variables are a regular part of daily living. With increase in work shifts spread throughout the 24-hour day and in jet travel, the last variable becomes increasingly important for human sleep. We have asked, to what extent can we predict the amount of stage 4 sleep in humans relative to variations in the normal sleep-wakefulness distributions?

Stage 4 is one of five stages of sleep which can be reliably detected by an electroencephalogram (EEG). Stages 1 to 4 are related to depth of sleep, and a fifth stage, 1-REM, is associated with rapid eye movements, an EEG characteristic of stage 1, and visual dreaming in humans. These stages form a complex and changing pattern throughout sleep. For example, there is an average of 32 changes in stage when young adults sleep at night in the laboratory.

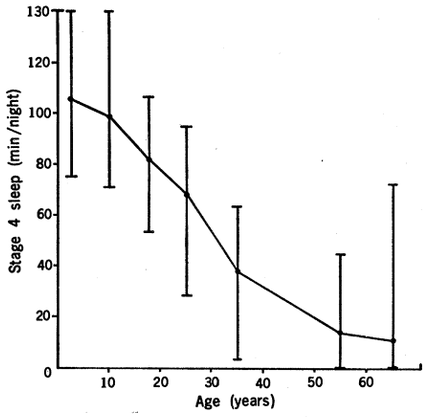

Fig. 1. Stage 4 sleep per night in seven age groups. Subjects slept in the laboratory on four successive nights, and data from nights 2, 3, and 4 were used. Dots represent the mean for each age group. Bars indicate the range of individual means for stage 4 sleep per night.

Stage 4 sleep constitutes between 10 and 25 percent of the sleep of young adults.

Each 1-minute epoch in the EEG records was scored visually for stage of sleep. An epoch was classified as stage 4 if, for more than 30 seconds, the EEG showed a frequency of 0.5 to 3.5 hz and peak voltage of 40 μv or more. Procedures for recording the EEG are described (*6*). The age groups and numbers of subjects in each were as follows: 21 to 31 months, 15; 8 to 10 years, 18; 16 to 19 years, 25; 20 to 29 years, 29; 30 to 39 years, 15; 50 to 59 years, 16; and 60 to 69 years, 15. Of these subjects, 14 young adults and 4 in the oldest group were females. Each subject slept in the laboratory for four nights. Data for nights 2, 3, and 4 were used. Most of the data have been published in studies of single age groups (*7–9*).

One of the most certain characteristics of stage 4 sleep became apparent in an early study of subjects aged 50 to 59 (*8*). The amount of stage 4 sleep in these subjects was markedly less than that of younger subjects. Figure 1 shows the relation between age and the amount of stage 4 sleep per night during three nights of uninterrupted sleep. Similar results have been reported by others (*10*).

Stage 4 sleep occurs predictably with respect to time in the sleep period. In one study (*9*), three-fourths of the stage 4 sleep occurred during the first third of the sleep period. Figure 2 shows an hour-by-hour analysis of stage 4 sleep of subjects 20 to 29 years old, and reflects several interacting and complex characteristics of stage 4 sleep. This type of sleep is quite episodic (*11*), and varies in the number of episodes per night, the length of episodes, and the interval between episodes. In nightly records from 87 nights of sleep of young adults, three records each showed only one episode of stage 4 sleep, four records each showed five episodes, and 69 percent of the records showed two or three episodes.

In general, the length of episodes of stage 4 sleep decreases as the number of episodes increases. When there was only one stage 4 episode, the mean duration was 55 minutes; when five episodes occurred, the mean duration was 25 minutes for the first episode and only 15 minutes for the fifth episode. The interval between median times of onset also tends to decrease as the number of episodes increases. This interval was 102 minutes for nights with two episodes but was 80 minutes for nights with five episodes. The median time of onset of the first interval was between 21 and 31 minutes regardless of the number of subsequent episodes.

In summary, more than two-thirds of the records showed two or three episodes of stage 4 sleep, but less than 10 percent showed one or five episodes. As the number of episodes per night increased, decreases occurred both in the length of interval between episodes and in the length of episodes. These factors interact to result in the smooth curve in Fig. 2.

A common variation in the normal sleep-wakefulness cycle is a change in the length of time awake. There were increasing hints of the sensitivity of the amount of stage 4 sleep to the length of prior wakefulness. In one study, subjects were permitted only 3 hours of sleep per 24 hours (*12*), and thus were awake 21 hours before the sleep period instead of the usual 16. The result was an increase in stage 4 sleep during the restricted sleep period. In addition, several studies of total sleep deprivation showed marked increases in the amount of stage 4 sleep on recovery nights. Berger and Oswald reported a 92 percent increase in the Loomis stages D and E (stage 4) sleep on the night after total deprivation (*13*). Williams and Hammock reported a 69 percent increase in stage 4 sleep for the first uninterrupted night of sleep after 4 days of total deprivation (*14*).

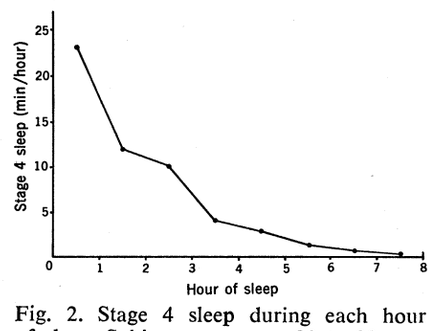

Fig. 2. Stage 4 sleep during each hour of sleep. Subjects were ages 20 to 29.

We abstracted from our data pool (*12, 15*) those sleep records in which the sleep periods began at 11 p.m. but were preceded by varying lengths of time awake. Figure 3 shows the amount of stage 4 sleep in the first 3 hours of sleep as a function of length of time awake. The first 3 hours of sleep were selected because some of these experiments limited sleep to 3 or 4 hours. The increase in amount of stage 4 sleep is quite limited when time awake is increased beyond 21 hours.

The data on the effect of displacement of sleep period on the amount of stage 4 sleep are quite limited. Although individuals do, of course, go to sleep at various times other than normal, few experiments have introduced such varied times of sleep onset. The data are almost inevitably confounded with changes in length of time awake and often in length of time slept. In a study of split periods of sleep (*16*), two controlled periods of prior wakefulness were used, and the sleep period began at the normal time or was displaced to 3 p.m. and 7 a.m. (Table

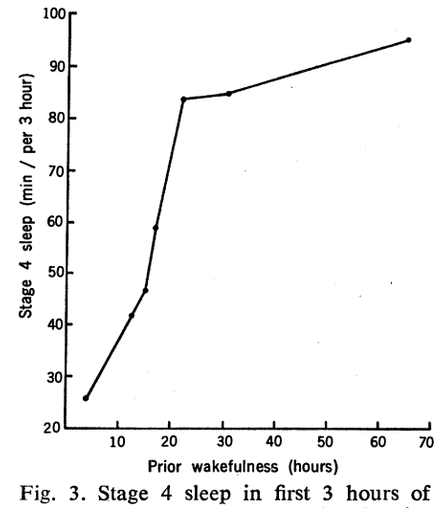

Fig. 3. Stage 4 sleep in first 3 hours of sleep as a function of length of prior wakefulness.

1). Table 1 suggests a circadian influence: there was less stage 4 sleep when sleep began at times other than the regular 11 p.m., even when prior wakefulness was held constant at 12 hours or at 4 hours. A circadian influence on stage 4 sleep is suggested but not proved, since analyses of variance (with respect to hours awake and to sleep onset time) yield a significant value for F only for the length of time awake.

This result reflects our sense of the considerable data we have reviewed relative to effects of displaced sleep periods on stage 4 sleep. Despite the problem of separating length of time awake from other variables, the data indicate that displacement of sleep period has a slight dampening effect on amount of stage 4 sleep. But the effect does not seem to be a major one.

To this point we have reported the effects of certain time course variables on stage 4 sleep. As with almost all biological systems, stage 4 sleep displays a range of individual differences. In the experiments shown in Fig. 1, prior wakefulness, length of sleep, and time of sleep onset were all held constant, yet there is a wide range of individual amounts of stage 4 sleep at each age level. A significant proportion of this variance is attributable to consistent individual differences between subjects from night to night. The intraclass correlation coefficient between nights 2 and 3 and nights 3 and 4 for individual amounts of stage 4 sleep is 0.70 for young adult subjects.

Our data indicate a strong determinative effect of three variables on stage 4 sleep in humans: age, length of time awake, and length of time asleep. If these variables are specified, we believe that statements of considerable confidence can be made about the amount of stage 4 sleep that normal subjects will display at particular periods of time under normal conditions. We recognize that our statements about these variables are incomplete, and a weighted prediction formula cannot be achieved at this time. Our data on the relations between stage 4 sleep and length of time asleep and between stage 4 sleep and prior wakefulness have been drawn from a young adult population. We do not have data on the interaction of these variables and age. Our data on prior wakefulness and stage 4 sleep is confined to the first 3 hours of sleep. A more complete prediction formula will certainly be possible when further data are collected.

We are aware, of course, that the time indices with which we have been concerned are, in fact, indices of highly complex processes within these time periods, and that these processes are the ultimate determinants of stage 4 sleep. The same may be said for individual differences indexed by simply identifying individuals from night to night.

We are further aware that the large variances about the group means represent yet undefined determinants that vary both with time and among individuals. Despite these limitations, we remain impressed that strong predictive statements can be made about stage 4 sleep from consideration of three variables that are a common part of human existence: time awake, time asleep, and age (*17*).

Table 1. Stage 3 and 4 sleep. Sleep periods began at different times of the day and were preceded by different lengths of time awake.

Time of sleep onset	Stage 3 and 4 sleep (minutes) after wakefulness for	
	12 hours	4 hours
11 p.m.	62.2	39.2
3 p.m. or 7 a.m.	51.0	28.4

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Photic Responses in Hyperkinesis of Childhood

Abstract. *Intravenous injections of drugs that stimulate the central nervous system decreased photic driving responses and photomyoclonic responses in hyperkinetic children. Neither injections of saline in these children nor injections of stimulant drugs in normal subjects produced such diminution. The neurophysiological implications are discussed.*

Excessive motor activity, a short attention span, low frustration tolerance, and hyperexcitability are common accompaniments of known structural disease of the brain in childhood. However, the same syndrome may be seen in the presence of normal intelligence and in the absence of any other signs of involvement of the central nervous systems (CNS). The neurophysiologic substrate of this disorder remains undefined. Some children with this disorder improve when given CNS stimulant drugs. The mechanism of this paradoxical effect is unclear.

An unreplicated neurophysiologic study by Laufer *et al.* (*1*) showed that hyperkinetic children had a lower photometrazol threshold as compared to nonhyperkinetic children, and that this threshold can be raised by amphetamine administration. Laufer *et al.* (*1*) suggested that amphetamines can raise the threshold for disorganization in the higher CNS, perhaps by acting on the inhibitory portion of reticular activating system. I have studied the effects of intravenous CNS stimulant drugs on the electroencephalogram (EEG) responses to photic stimulation (a conventional index of CNS threshold for disorganization) in hyperkinetic children.

Children (36) between the ages of 5 and 12 years recognized by history and