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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3 May 1971; revised 2 September 1971

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

examination to have hyperkinesis and decreased attention span without psychomotor retardation were chosen for the study. Subjective scoring by parents and school teachers and objective measurements of activity level, impulsivity, performance, and coordination were obtained for each child. One of the CNS stimulant drugs (dextroamphetamine in a dose of 10 mg per square meter of body surface or methylphenidate in a dose of 20 mg per square meter of body surface) or saline in equivalent volume was injected intravenously into each child during an electroencephalographic examination. (The experiment was conducted by "double blind" methods.) Silver disk electrodes were applied, with the use of the international 10–20 system (*2*) with measurement of interelectrode distances and resistances. The EEG's were recorded on Grass model III-D electroencephalographs, and Grass model PS-3 photostimulators were used. The time constant used was 0.3 second and amplification 10 μv/mm. Photic stimulation was conducted 10 minutes before and 10 minutes after the intravenous injection. Eyes of the subjects were kept closed during the photic stimulation. The intensity of the stimulus used was constant at 750,000 candle power; the frequencies used were 4, 6, 8, 10, 12, 14, 16, 18, 20, and 21 per second; and each frequency was used for a duration of 2 seconds in the pre- and postinjection periods. Six healthy adults, between the ages of 19 and 23 years, employed in the EEG laboratory as technician trainees and known to have driving responses to photic stimulation, were injected with one of the stimulant drugs (four had dextroamphetamine and two had methylphenidate) in equivalent doses during a similar EEG recording. These normal young adult volunteers formed the control group because of the ethical problem involved in using children as volunteer control subjects.

Only the effects on the photic responses are described in this report (*3*). The montage used during the photic stimulation recorded potentials between right frontal pole-central (FP_2-C_4), right central-occipital (C_4-O_2), left frontal pole-central (FP_1-C_3), left central-occipital (C_3-O_1), right temporal-parietal (T_4-P_4), right parietal-left parietal (P_4-P_3), and left parietal-temporal (P_3-T_3) leads respectively in the first seven channels. The strobe stimulus was recorded in the eighth channel. Driving response was defined as evocation of EEG waves at fundamental or harmonic frequencies of photic stimulation for two consecutive seconds with no other EEG waves visually detectable during that time between leads C_3-O_1 and C_4-O_2. Driving responses were scored as present or absent. Questionable or minimal amounts of driving were scored as absent.

Of the 36 hyperkinetic children, 11 showed driving responses to photic stimulation in the period before injection and two others showed a photomyoclonic response. The mean age of these 13 children was 7.7 years (S.D. of 1.7 years). All six control subjects (mean age 20.3 $\pm$ 1.5 years) had driving responses that did not alter in the period after injection. When the "double blind" code was broken, it was found that those hyperkinetic children who had received saline injection (4 of the 11) showed no alteration in their driving responses after the injection. Six of the seven hyperkinetic children who had received one of the CNS stimulant drugs (four had dextroamphetamine and three had methylphenidate) showed absence of driving responses to all frequencies used in the postinjection period. The other 23 children, who did not have a driving response in the preinjection period, did not have any altered response to photic stimulation in the postinjection period. One-sided Fisher's exact test was used in the statistical analysis of these results and showed significant differences in the alteration of photic driving responses between the hyperkinetic children with driving who received one of the drugs and those who received saline ($P = .015$); also the difference was significant in the alteration of photic responses between the hyperkinetic children with driving who received one of the drugs and the normal control group ($P = .0041$). The two children who had shown the photomyoclonic response in the preinjection phase showed the total absence of such response after injection of the drug (methylphenidate in each case).

The results of the stimulant drug injection on the photomyoclonic response supports the results of Laufer *et al.* (*1*) and suggests a neurophysiological difference in hyperkinetic children from normal individuals. Psychopharmacological drugs like imipramine, prothiadine, and thioradazine have been shown to lower photometrazol threshold (*4*), and estrogens have been shown to lessen driving responses (*5*). The EEG driving has been shown to be decreased by substances producing adrenergic state by either impairing central cholinergic mechanisms (intravenous atropine) (*6*) or by enhancing central adrenergic mechanisms (intravenous noradrenaline) (*7*). Suppression of occipital driving has also been produced by experimental stress (*8*), sensory stimuli and mental work (*9*), and effort in athletes (*10*)—all of which might be characterized by enhancement of central adrenergic mechanisms. A lesser response to photic stimulation has also been shown to correlate well with greater ability to perform simple repetitive tasks (*11*).

The greater suppression of photic driving responses by stimulant drugs in hyperkinetic children suggests that these drugs are able to enhance central adrenergic mechanisms in these children to a greater extent as compared to normal young adults. Amphetamine inhibits neuronal uptake of norepinephrine in brain (*12, 13*) and also releases norepinephrine and dopamine from neurons (*13*). Because of these and similar results it has been suggested that amphetamine exerts its central effects by releasing catecholamines and preventing inactivation of these monoamines at central adrenergic synapses in brain (*14*). It seems possible that CNS stimulant drugs are able to induce one of these mechanisms with greater facility in hyperkinetic children.

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12 July 1971; revised 9 August 1971