to rapid relearning of a "new" interval at the new temperature. To test these assumptions, a further experiment was performed on two other goldfish; the same basic situation was used as before and the temperature was kept at 25°C. The fish were trained on a 1-minute fixed-interval (FI-1) schedule (36 days), then a 2-minute fixed-interval (FI-2) schedule (36 days), and finally a 1-minute variable-interval (VI-1) schedule (21 days). In the variable-interval schedule, reinforcements within each session were separated by varying time intervals ranging from 3 minutes to a few seconds, averaging 1 minute. Performances during the last 4 days on each schedule were compared, with only the 1-minute intervals on the variable-interval schedule being used. The plot of relative response rate shown in Fig. 3 indicates that there is a slower acceleration in response rate under a longer (2-minute) fixed-interval schedule. Furthermore, on the VI-1 schedule, where reinforcements follow one another more or less randomly in time, there is no increase in relative response rate over the 1-minute interval. Response patterns on the initial days of FI-2 resembled those for the FI-1 schedule, suggesting that in the first experiment the fish could not rapidly relearn a discrimination based on a "new" interval.

This research shows that although absolute response rate is dependent on temperature, relative response rate is not. It appears then that the patterning of responses in a temporal discrimination is independent of temperature. The results suggest that the 1-minute temporal discrimination shown by these fish is not dependent on a mechanism directly tied to metabolic rate.

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Geniculate Unit Responses to Sine-Wave Photic Stimulation during Wakefulness and Sleep

Abstract. *The oscillation in firing rate of units of the lateral geniculate body in response to stimulation with sine-wave light was studied in unanesthetized cats with the brainstem sectioned immediately in front of the fifth nerve (pretrigeminal preparation). During wakefulness, as indicated by behavior and by electroencephalograms, the time course of the oscillation in firing rate followed very closely the change in intensity of sine-wave light. During synchronized sleep there was no such relationship.*

Hughes and Maffei (*1, 2*) studied the transfer properties of the cat's retinal ganglion cells in response to sine-wave light stimuli at different frequencies and found a very close relation between the time courses of stimulation and response. Even for quite low frequencies of light (as low as 0.01 cy/sec), the oscillation in firing rate shown by retinal ganglion cells was an almost perfect replica of the sine-wave photic stimulation.

In the experiments described here our aim was to investigate the response of single units of the lateral geniculate body (LGB) to stimulation with sine-wave light. We show that the behavior of these units is strikingly different during wakefulness and during synchronized sleep.

We used cats in which the brainstem was sectioned immediately rostral to the exit of the fifth nerve [midpontine pretrigeminal preparation (*3*)]. Pupils were dilated with atropine. Extracellular spikes were recorded by microelectrodes inserted in the dorsal nucleus of the LGB. The technique (*2*) can be summarized as follows. The light source was a Sylvania glow modulation tube 1130B, driven by a low-frequency oscillator (Hewlett-Packard). To average the rate of response and reduce random variations of cell firing, a Mnemotron computer of average transients (model 400B), including a modulator by-pass card, was used. The averaging time, the number of intervals per period, and the number of responses averaged were externally controlled and synchronized with the sine-wave generator. The EEG was continuously recorded through screws implanted in the skull.

Cats prepared in this way exhibit spontaneous periods of synchronized sleep and wakefulness, the EEG and behavioral patterns of activity prevailing after midpontine transection (*3*). In good agreement with observations of free-moving cats (*4*) the spontaneous firing of LGB units is strikingly affected by sleep and wakefulness. During wakefulness the spontaneous activity is random; during sleep there are short-lasting, high-frequency bursts of activity (300 to 500) with long intervals of silence between (100 to 600 msec).

During periods of wakefulness (indicated by behavior and by the EEG's), the responses of the LGB units followed the light changes very closely (Fig. 1*A*) at the different frequencies of stimulation (from 0.1 to 1 cy/sec). The response was quite similar to that of retinal units (*1, 2*). The "on" cells were almost in phase with the stimulus, the "off" cells 180° out of phase (see Fig. 1, *A* and *B*), and the "on-off" cells showed a phase relation between the stimulus and response in the region between 0° and 180°. During synchronized sleep every relation between sine-wave stimulus and response was

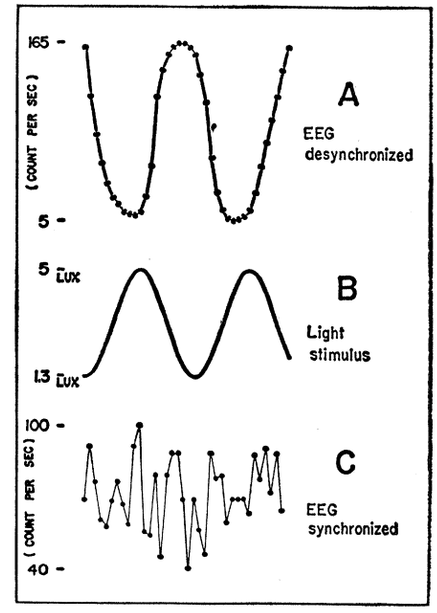

Fig. 1. Time course of firing rate of an "off" LGB unit in response to stimulation by low-frequency sine-wave oscillation of light intensity. Frequency of sine-wave oscillation, 0.1 cy/sec. The position of the dots (20 per cycle) gives the average frequency of firing: each measurement was made every 500 msec and 10 cycles were averaged by the Mnemotron computer. All numbers were converted to cycles per second by dividing the spike count by the duration of the interval. The time relation between stimulus (*B*) and response (*A*, *C*) are carefully preserved. The scales of abscissas and ordinates are linear. Synchronization of the EEG (in *C*) occurred spontaneously.

lost (Fig. 1*C*). If the cell response was averaged many times (up to 100 times) a peak of activity could sometimes be observed to correspond with the minimum or the maximum intensity of light, according to the cell type ("off cells" or "on cells," respectively). The shape of the response, however, remained completely chaotic. An example of these results is shown in Fig. 1. Control experiments showed that the response of the retinal ganglion cell to sine-wave stimulation is not affected by either the waking or the sleeping state. This observation shows that the striking difference observed with LGB units is probably due to extraretinal influences acting upon the LGB neurons during sleep.

The inability of LGB units to follow sine-wave photic stimulation during synchronized sleep might be explained in two different, but not mutually exclusive, ways. (i) During spontaneous sleep, unit firing is clustered in irregular bursts. The "noise" of the carrier (spontaneous activity) could be so high as to mask modulation from the retina. Experiments in which the cell response was averaged up to 100 times suggest that noise is not the only factor. (ii) The response of LGB units to retinal volleys is markedly decreased during synchronized sleep, as shown by observations made in the same experimental situation with single flashes of light (*5*). Even with a threefold increase in the amplitude of the intensity oscillation of the photic stimulus, we were unable to obtain, during synchronized sleep, the close correspondence between stimulus and rate of firing which can be observed constantly during wakefulness.

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Melphalan and Antigenic Type of Bence Jones Proteins in Myeloma

Bergsagel, Migliore, and Griffith report [*Science* **148**, 376, 1965] that none of nine myeloma patients with λ-type (type II) Bence-Jones (BJ) proteinuria responded to melphalan (L-phenylalanine mustard), whereas all 11 patients with κ-type (type I) BJ protein showed objective improvement. They conclude that the biochemical differences between these two types of myeloma cells may be related to their respective chemotherapeutic responsiveness. Results in our clinic, however, are at complete variance with those of Bergsagel *et al.* Using the same criteria for evaluating drug efficacy, we have discerned no difference in the responsiveness to melphalan of κ-BJ and λ-BJ producers. Objective remissions as evidenced by diminished BJ-proteinuria, improved hematologic status, and performance status have been observed in 38 of 45 myeloma patients treated with melphalan for 6 months or longer; three of the 38 had λ-BJ as their only protein abnormality. One case with κ-BJ was considered a treatment failure. Of the three patients with λ-BJ proteinuria who responded to melphalan, all showed reduction in BJ proteinuria of over 10 g/24 hr, increase in hemoglobin of over 2 g percent, and major pain relief and functional improvement, and one showed partial skeletal recalcification. Comparable results were obtained in our patients with κ-BJ, three of four of whom responded to melphalan. Similarly, we have found no differences in the responsiveness of patients with γG or γA globulin abnormalities with κ or λ L-chain determinants, with or without associated BJ proteinuria.

The reason for the failure of the Southwest Cancer Chemotherapy Study Group to observe remissions in any of their nine λ-BJ cases is obscure but may be related to the therapeutic protocols employed. The authors state that two different dosage schedules—A and B—were used, but do not report how many cases in each group were on schedule A and how many on schedule B. Since schedule A was apparently found to be excessive and associated with considerable toxicity, it may have contributed to poor results in certain cases. In our series, all patients received an initial course of 10 mg/day for 7 to 10 days; therapy was then interrupted for 3 to 8 weeks, until the maximum leukopenia had passed, at which time continuous maintenance therapy with 2 mg/day was instituted. On this dosage schedule, serious toxicity has not been encountered.

Two additional aspects of management are also deserving of emphasis: first, the importance of maintaining adequate hydration, particularly in cases with hypercalcemia and BJ proteinuria, and, second, the value of encouraging ambulation and exercise in the long-term management program. In this latter regard, two of our λ-BJ patients responding to melphalan have progressed from initially serious incapacitation, hypercalcemia, anemia, and bed-chair status, to regular golfing (18 to 27 holes, "in the 90's") in one case, and, in the other, to a program of daily pool-swimming (100 to 150 yards). Obviously, these ancillary aspects of management must be individualized to the capacities of individual patients, and, unfortunately, this tailoring is virtually impossible in a cooperative group study with a rigid protocol.

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We are unable to confirm the observations of Bergsagel, Migliore, and Griffith that patients producing only Bence-Jones κ proteins consistently do well on melphalan therapy, and that patients producing only Bence-Jones λ proteins do not respond to the drug. At Memorial and James Ewing Hospitals over the past 2 years we have treated 40 patients with Alkeran. To date 6 of our 27 adequately treated patients have had excellent subjective and objective responses to the drug, according to criteria of evaluation similar to those of Bergsagel *et al.* Under our terminology these six patients have had "IA" responses, comparable to Bergsagel's "significant" response. Of these six, two excreted Bence-Jones protein only. Both were of the λ type. Twelve of our adequately treated patients have had no response whatsoever to Alkeran. All have been observed on therapy for a minimum of 3 months. Six excrete Bence-Jones only. Four of these have λ L-chains and two have κ L-chains.

Thus, our data are strikingly different from those of Bergsagel *et al.* with re-