

## CRITICAL FLICKER FREQUENCY AND CENTRALLY-ACTING DRUGS\*†

BY

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THE critical flicker frequency (cff) may be defined as the fastest rate at which a flickering source of light appears to be flickering as opposed to being steady. It has a number of determinants including the luminance, wave-length, wave-form, and light-dark ratio of the stimulating light, the area, position, and light-adapted state of the retina illuminated, the duration of exposure, and the size of the pupil. Age and constitutional factors may also influence the threshold, and recently the importance of intersensory effects and previous adaptation to intermittent light have been emphasized (Turner 1965a, b).

Cff has been used as a test of central nervous activity in response to drugs for many years.

**Central Depressant Drugs.**—Alcohol produces a marked depression of cff which is proportional to the alcohol concentration in blood and urine (Bernhard and Skoglund, 1941; Goldberg, 1943; Enzer, Simonson, and Ballard, 1944). Bjerver and Goldberg (1950) found that driving performance and cff were both impaired at similar concentrations of blood alcohol, and Rokseth and Lorentzen (1954) showed that hypoxia increased the depressant action of alcohol on cff.

Barbiturate drugs produce depression of cff (Roback, Krasno, and Ivy, 1952; Ideström, 1954) and Ideström and Cadenius (1963) obtained dose response effects with 150, 300, and 450 mg. amylobarbitone. Meprobamate in doses of 400 mg. and above, and chlordiazepoxide 40 mg. and above have been shown to impair cff (Aiba, 1959; Holland, 1960; Ideström, 1962; Ideström and Cadenius, 1963). Pollack, Karp, Krauthamer, Klein, and Fink (1961) showed that chlorpromazine depressed cff but in doses of 300–1,200 mg. daily.

Holland and Gooch (1962) found that cff fell in direct relation to the proportion of N<sub>2</sub>O in a nitrous oxide/oxygen mixture administered to five subjects.

**Central Stimulant Drugs.**—Although central depressant drugs readily impair cff, stimulant drugs are less predictable in their effects. While Simonson and Brožek (1952) claimed that amphetamine 10–15 mg. produced a rise, Ikeda (1960) found only a slight and insignificant increase with 10 mg. and Aiba (1963) did not obtain a significant effect on mean threshold. Roback and others (1952) found that dexamphetamine 5 mg. prevented the depression of cff produced by antihistamine drugs. Results with caffeine have been variable (Simonson and Brožek, 1952; Roback and others, 1952). Keeler (1963) claimed that psilocybin produced consistent increases in cff, and Larson, Finnegan, and Haag (1950) and Warwick and Eysenck (1963) showed that nicotine taken orally or in cigarettes produced a rise in threshold.

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### Adaptation to Intermittent Light

In an attempt to increase the sensitivity of the method of measuring cff in order to obtain changes with modest therapeutic doses of centrally-acting drugs, the influence of adaptation to intermittent light was studied. Simonson (1959) noted that exposure to a flickering light below cff produced a fall in cff, and Alpern and Sugiyama (1961) found that cff was elevated by first exposing the eye to a light source with an intermittency greater than the cff and lowered by pre-exposure to a light of lower frequency. In a further series of experiments (Turner, 1964; 1965a, b) it was shown that there was a linear relationship between cff and adapting frequencies between values of 24 and 54 c/s of the latter. As exposure of one eye to the adapting light altered the cff of the contralateral unexposed eye, the changes in cff appeared to be central and not peripheral in origin. This adaptation phenomenon appeared to be very stable and not influenced by hyperventilation or rebreathing (Turner, 1965a), by changes in the light-dark ratio or wave-length of the light source, or by the state of luminance of the opposite eye, factors which influence cff itself (Turner, Patterson, and Smart, 1966). It was also noted (Turner and Smart, 1964) that intermittent auditory stimuli of varying frequency modified visual cff. A technique of measuring cff was developed, in which ascending and descending thresholds of cff were determined after exposure for 1 minute to intermittent light of 25 or 50 c/s, thus giving four readings at any one time. The effects of drugs on mean threshold and on adaptation could thus be statistically assessed. The light source was a neon lamp of luminance 350 lumens/m.<sup>2</sup> exposing an area of 0.64 cm.<sup>2</sup>, driven by a rectangular pulse generator (Solartron Pulse Generator Type GO 1101.2) with a mark-space ratio of 1:1, and the experiments were carried out in the light-adapted state under constant conditions of illumination. In a series of experiments, single therapeutic doses of centrally-acting drugs were given to normal volunteer subjects of both sexes between the ages of 20 and 30 years. The effects of these agents on cff were compared in the same subjects with those of identical placebo tablets under double-blind conditions, and the results submitted to analysis of variance. They were considered statistically significant if their P values were equal to or less than 0.05.

### Results

The results of several experiments are given in a composite form in Fig. 1 (opposite). Each compares the maximum response to a drug with that to a placebo, but as they have been obtained in different experiments on different groups of subjects, the drugs cannot be strictly compared with each other in this figure.

### Effects on Central Function

The method described has permitted significant effects on mean cff to be detected following administration of therapeutic doses of several centrally-acting drugs. Dose response effects were obtained with chlorpromazine 10 and 25 mg. and amylobarbitone 50 and 100 mg., and the latter are shown in Fig. 2 (opposite).

In a comparison of appetite suppressant agents, amphetamine 15 mg., phenmetrazine hydrochloride 25 mg., phenmetrazine theoclate 30 mg. and phenbutrazate hydrochloride 20 mg., and diethylpropion 25 mg. produced a significant elevation of cff, while dexamphetamine 10 mg. and chlorphenteramine 25 mg. did not (Turner, 1965b; Smart, Sneddon, and Turner, 1967).

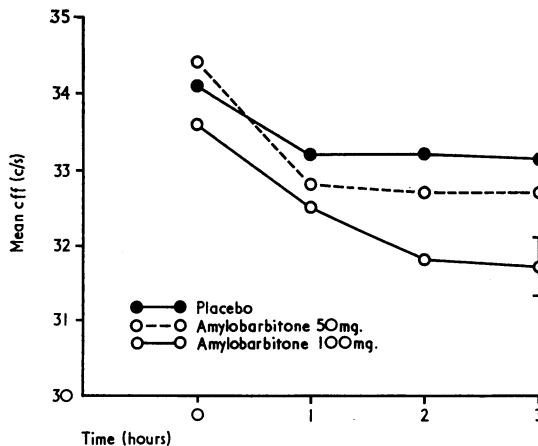
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Five antihistamine preparations were compared in ten subjects. Promethazine 25 mg. and chlorcyclizine 50 mg. produced significant depression of cff while phenindamine 25 mg., chlorpheniramine 4 mg. and diphenhydramine 25 mg. produced no significant effect.

Treatment	Dose (mg.)	Percentage										Significance	
		-5	-4	-3	-2	-1	0	+1	+2	+3	+4		
Phenmetrazine (Theoclate)	30												*
Phenmetrazine (HCl)	25												*
Amphetamine	15												*
Diethylpropion	25												*
Chlorphenteramine	25												NS
Dexamphetamine	10												NS
Phenindamine	25												NS
Diphenhydramine	25												NS
Chlorpheniramine	4												NS
Fluphenazine	1												NS
Chlorcyclizine	50												*
Promethazine	25												*
Chlorpromazine	25												*
Amylobarbitone	100												*

FIG. 1.—Percentage changes in mean cff produced by centrally-acting drugs, compared with identical placebo under double-blind conditions. They were determined in several different experiments with different subjects and cannot therefore strictly be compared with each other. Their significance at the 5 per cent. level is indicated by an asterisk.

FIG. 2.—Mean cff before and at 1, 2 and 3 hours after administration of a placebo and amylobarbitone 50 and 100 mg. in six subjects. 95 per cent. confidence limits were all of the same order and are shown only for 100 mg. at 3 hours.



### Comparison of Drugs within Same Chemical Group

Piperazine phenothiazine derivatives have less sedative effects than aliphatic derivatives in clinical practice. A comparison of the aliphatic compound chlorpromazine with the piperazine derivative fluphenazine showed that chlorpromazine has a significant depressant effect on cff compared with fluphenazine, confirming this clinical observation (Turner, 1966). Besser, Duncan, and Quilliam (1966) showed similar effects in a comparison of chlorpromazine and perphenazine on auditory flutter fusion threshold which is the auditory counterpart to the visual critical flicker frequency.

### Combinations of Drugs

A proprietary mixture of dexamphetamine sulphate 5 mg. and amylobarbitone 32.4 mg. (Drinamyl, "purple-heart") is claimed by its manufacturers to produce a therapeutic effect "without the drowsiness that accompanies the use of barbiturates alone, and without the irritation or anxiety that may accompany the use of stimulants alone". A comparison of the effects of amylobarbitone 100 mg., amylobarbitone 100 mg. + dexamphetamine 15 mg., and a placebo showed that, whereas amylobarbitone produced a significant fall in mean cff over 4 hours, the amylobarbitone-dexamphetamine mixture did not significantly differ from the placebo in its effects (Turner, 1965c).

### Time Course of Drugs

The rate of excretion of amphetamine is markedly dependent on urinary pH (Beckett, Rowland, and Turner, 1965; Asatoor, Galman, Johnson, and Milne, 1965). A low pH results in the rapid elimination of the drug, whereas an alkaline urine delays its excretion. Retention of a drug within the body does not necessarily imply prolonged action, however, but a comparison of the duration of action of amphetamine on cff under conditions of urinary acidity and alkalinity showed that the magnitude and duration of elevation of cff was significantly greater under alkaline than under acid conditions (Smart and Turner, 1966).

### Discussion

It is generally recognized that there is a need for accurate methods of assessing the action of drugs on central nervous function, which will be acceptable and readily learnt by the subject. These results show that measurement of cff permits such an evaluation of the effects of centrally-acting drugs. Whereas previous investigators had often used large doses to obtain such effects, the method described, using the adaptation phenomenon, seems more sensitive and changes are found with modest therapeutic doses of many drugs. The accuracy of these observations is supported by the dose-response curves which may be obtained with two or more doses. Cff also allows a comparison of drugs within the same therapeutic or chemical class, for example the antihistamine and phenothiazine drugs. Studies of drug interaction and combination, and of the time course of drugs under different conditions may also be carried out using cff.

It is important to have a placebo control in each experiment, as the use of the adaptation phenomenon is associated with a consistent fall in cff over time (Turner, Sneddon, and

Smart, 1967), and this must be taken into account in the analysis of the drug effects. In any case, spontaneous variations between subjects, between days and between times must be assessed in order to obtain a true indication of the action of a drug.

The stability of the adaptation phenomenon already referred to has been further confirmed in these studies, in which no drug has influenced the adaptation of cff to intermittent light of varying frequency, even though the mean cff may have been elevated or depressed. The psychological implications of the phenomenon have been discussed elsewhere (Turner, 1965a).

### Summary

The measurement of critical flicker frequency after adaptation to intermittent light of varying frequencies has demonstrated changes in visual discrimination after modest therapeutic doses of centrally-acting drugs. It is a valuable test in the study of interaction and duration of action of these drugs, and allows a comparison to be made of central activity between members of the same pharmacological or chemical class.

The adaptation of critical flicker frequency to intermittent light is not modified by any of the drugs which have been studied.

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