light without photosensitizer nor α-crystallin kept in the dark with photosensitizer gave any significant fluorescence at these wavelengths. An increase in absorbance between 300 and 400 nm accompanied development of fluorescence in the photooxidized samples as Fig. 2 demonstrates.

Singlet oxygen-mediated photooxidation has been shown to have damaging effects on proteins (*20*). The principal mechanism of such damage is believed to be via photooxidation of the amino acid residues histidine, tryptophan, tyrosine, cysteine, and methionine (*21*). We have shown above that singlet oxygen has marked effects on bovine α-crystallins. In addition we have found that bovine β-crystallin is more sensitive to the cross-linking process than α-crystallin (see Fig. 1) and that human crystallins appear to be as sensitive as the bovine crystallins. Preliminary studies in our system with other proteins suggest that crystallins may be particularly susceptible to cross-linking.

The components necessary for singlet oxygen generation exist in the lens. Light and oxygen are present and the photosensitizers riboflavin and *N*-formylkynurenine (*22*) have been identified in the lens. Fluorescent derivatives of kynurenine isolated from human lens promote photooxidation of lens proteins in vitro by sunlight with production of increased blue fluorescence and pigmentation (*11*). This increase supports the hypothesis that singlet oxygen may be generated in the human lens and could be a causative factor in the changes associated with aging and nuclear cataractogenesis. The increase in vivo in blue fluorescence, pigmentation, and cross-linking is a very slow process, probably due to the presence of very high concentrations of the endogenous antioxidants glutathione and ascorbic acid in the lens (*23*). Ascorbic acid is a known $^1O_2$ scavenger (*24*), and we have demonstrated that glutathione inhibits cross-linking in our system (see Fig. 1). The fact that these cataractogenic changes occur predominantly in the lens nucleus may reflect the much lower concentrations of antioxidants in this part of the lens (*25*). In addition, since protein turnover is essentially absent in the lens nucleus (*26*), photooxidized protein molecules would tend to accumulate.

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Methylphenidate and Hyperactivity: Effects on Teacher Behaviors

Abstract. *Teacher interactions with hyperactive and comparison boys were observed during classroom activities. A double-blind, methylphenidate-placebo crossover design was used within the hyperactive group. With no knowledge of any child's diagnosis or drug status, the teacher was more intense and controlling toward hyperactive boys taking placebo than toward either medicated hyperactive boys or comparison boys; her behavior did not differ toward the latter two groups. Discussion focused on the need to consider the broad social ramifications of pharmacologic treatment programs.*

Challengers as well as champions of pediatric psychopharmacology agree that stimulant drugs have detectable and predictable effects on the classroom behaviors of children considered hyperactive. Although serious questions remain about the side effects and long-term outcomes of stimulant treatment during childhood, short-term gains for many children have been documented conclusively in double-blind, placebo-controlled studies (*1, 2*).

Almost nothing is known, however, about the social ramifications of methylphenidate—the impact of medication on a child's interpersonal environments. Recent laboratory studies indicate that children's medication influences maternal behavior patterns (*3*). It is important to assess the impact of stimulant medication on a teacher's behavior toward a child, as hyperactive children often have their greatest difficulties—and show the most dramatic medication-related improvements—in school environments (*4*). Further, information is needed about the complex interplay between teacher and child because teachers often serve as the primary evaluators of drug treatment. The present study addressed this question in a quasi-naturalistic classroom setting.

This study was part of an intensive assessment of hyperactive boys taking methylphenidate. In order to create a quasi-naturalistic environment, two 5-week morning enrichment programs were conducted during the summer months. Within each of the two identical summer sessions, there was a Monday-Wednesday class and a Tuesday-Thursday class, yielding four cohorts in all, each with 15 or 16 boys. The boys participated in laboratory components and field trips on the days they were not in class.

Twenty-two hyperactive boys were recruited through local pediatricians. All boys accepted for these studies were previously considered hyperactive by the referring physician, had no other

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medical diagnosis, had been taking methylphenidate for at least 3 months, and were judged to be positive drug responders by their physicians. This group ranged in age from 7 years, 8 months to 11 years [mean ($\bar{X}$) = 9 years, 7 months]. An unselected, heterogeneous group of 39 comparison boys, ranging in age from 7 years, 7 months to 11 years, 3 months ($\bar{X}$ = 9 years, 2 months), was recruited through advertisements to attend a university summer program.

After 2 weeks for familiarization, a series of different 2 by 2 experimental designs, each taking a full four-period morning, was implemented in each class. Each experiment varied two dimensions of classroom and teaching structure and was repeated in each of the four classes. There were four such experiments in the series, two of which are reported here. Data from all 4 days of each experiment were combined in the analyses. This report focuses on the teacher's behavior; summaries of the boys' classroom behaviors are reported elsewhere (*5*).

A randomly selected half of the hyperactive boys were assigned to the placebo group before experiment 1, while the other half continued taking their regular dose of methylphenidate. These conditions were reversed for experiment 2, which followed a 4-day drug wash-out period. Each boy's regular dosage, as prescribed by his own physician, was maintained. Morning dosage range was 5 to 40 mg ($\bar{X}$ = 12.3 mg) or 0.11 to 1.28 mg per kilogram of body weight ($\bar{X}$ = 0.41).

The boys were told at the beginning of the program that they would be "trying out different things," and thus no special explanations were required for the classroom experiments. Experiment 1 varied the amount of teacher supervision (regular or low) and the supply of task materials (sufficient or insufficient). Experiment 2 varied pacing (self-paced or other-paced activities) and ambient stimulation (quiet or noisy).

The teacher held an elementary teaching credential and had 3 years of experience in public school classrooms. She was completely unaware of the purposes of the study and thus blind to both the diagnostic and medication status of the students. Additional details about subject selection, medication procedures, and teacher background have been presented (*6*).

Teacher behaviors were coded from continuous videotapes of the entire classroom. The 32 videotapes (four periods for each of four cohorts for each of two experiments) were randomly assigned to individual raters such that no rater coded consecutive tapes from a specific cohort or experiment. No raters knew the purposes of the study; none knew the medication status of any of the boys.

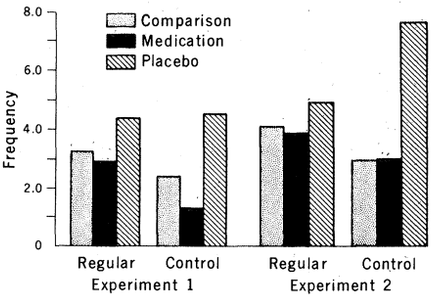

Fig. 1. Mean frequencies of teacher's regular and control contacts in the classroom.

For each experiment, the frequencies of each category were analyzed in a 3 (comparison, medication, and placebo group) by 2 (first classroom dimension) by 2 (second classroom dimension) analysis of variance design, and planned contrasts were done among the means for the placebo, medication, and comparison groups. The present report focuses on these group differences; procedures and results of the classroom variations and additional details about the analyses will be presented in a subsequent report.

Each teacher-child contact was coded as having either a regular function (conversation, information-giving, and small talk) or a control function (guidance, commands, and admonitions). Two raters independently coded approximately 40 percent of the tapes. The occurrence agreement index for function was .87.

Group means, presented in Fig. 1, indicate that in both experiments, the teacher engaged in more control contacts with boys given placebo than with those in either the medication or the comparison groups [experiment 1: placebo-medication contrast, F (1, 57) = 18.67, $P < .001$; placebo-comparison contrast, F (1, 57) = 12.78, $P < .001$. Experiment 2: placebo-medication contrast, F (1, 58) = 19.27, $P < .001$; placebo-comparison contrast, F (1, 58) = 28.30, $P < .001$]. There were no group differences for regular contacts.

The teacher's contacts were also coded for intensity (vigor, loudness, rapidity, and emotionality). Intense contacts were rare, occurring during only 1 to 2 percent of total interactions, and the interrater agreement index of 52 percent was somewhat lower than desirable. Despite these limitations, teacher intensity clearly distinguished the groups: almost all intense contacts were directed toward hyperactive boys taking placebo. In experiment 1, the mean for the placebo group was 0.31, in contrast to 0.08 for the medication group [F (1, 57) = 6.59, $P < .05$] and 0.08 for the comparison group [F (1, 57) = 10.66, $P < .01$]. In experiment 2, the placebo mean was 0.48, the medication mean was 0.04 [F (1, 58) = 14.20, $P < .001$], and the comparison mean was 0.05 [F (1, 58) = 19.81, $P < .001$].

The final category reported here is naming, coded whenever the teacher referred to an individual child by name. This category occurred during 33 to 42 percent of the interchanges and yielded an interrater agreement index of .84. The pattern for naming was similar to those for control and intensity. In experiment 1, the placebo mean was 4.04, in contrast to a medication mean of 1.78 [F (1, 57) = 14.49, $P < .001$] and a comparison mean of 2.43 [F (1, 57) = 12.18, $P < .01$]. In experiment 2, the placebo mean was 4.68, in contrast to a medication mean of 2.35 [F (1, 58) = 13.39, $P < .001$] and a comparison mean of 2.31 [F (1, 58) = 20.22, $P < .001$].

In addition to analyzing group averages, we examined the placebo-methylphenidate difference individually for the 22 hyperactive boys. Higher rates of control contacts were found under placebo conditions for 17 of these youngsters; there were no differences for three, and the medication rate was higher for only two. The corresponding figures for naming are 20, 0, and 2. Thus the teacher's responsiveness to medication status is apparent with a very substantial majority of the hyperactive group. Despite the relative rarity of intensity, the same pattern emerged: the placebo rate was higher than the medication rate for 11 of the 13 boys for whom this category was coded at all.

The teacher's global impressions, as reflected on Conners's short-form rating scales (*7*), were also obtained each day. These ratings, which are sensitive to drug effects, were substantially correlated with control contacts (r's = .49, .69), intensity (r's = .42, .63), and naming (r's = .51, .72), but not with regular contacts (r's = .26, .10).

Thus, while engaging in everyday classroom activities, the teacher was clearly responsive to the medication status of her hyperactive pupils. Teacher-student contacts were more frequently control-oriented and intense for hyperactive boys taking placebo than for those taking medication or for the com-

parison group. Boys taking placebo were also contacted by name more frequently than their peers. Regular contacts did not distinguish the groups, and there were no significant differences between the medication and comparison groups for any category.

These placebo-related differences in teacher behaviors are particularly noteworthy in the context of previously reported differences in the boys' behaviors during the classroom experiments. Once again, the medication and comparison conditions yielded no significant differences. Boys taking placebo, however, differed markedly from their peers in several response domains, including task attention, energy bursts, verbalization, noisiness, movement, and disruptive activity (*5*). In terms of the specific behaviors observed in this series of studies, methylphenidate apparently normalizes both hyperactive children's classroom behaviors and teacher-student interchanges. Medication-related changes in children's behaviors have real-life consequences; teacher and child behaviors covary predictably.

One implication of these results is that medication may redirect the ongoing streams of transaction in the classroom. The teacher makes a substantial—though often inadvertent—contribution to the child's treatment program, and this contribution may either enhance or attenuate the outcome. Moreover, changes in teacher behaviors impinge on the other children in the classroom, for example, by redistributing teacher attention; no information is available on such spillover effects. These findings, if replicated in regular classrooms, suggest the need for more extensive monitoring of treatment outcomes than is typically the case. Our results complement previous documentation of methylphenidate effects on children and underscore the need to consider the social ecological context of pharmacologic treatment (*2*).

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Sexual Dimorphism in Extent of Axonal Sprouting in Rat Hippocampus

Abstract. *Sympathetic axons, normally innervating the extracerebral vasculature, sprout into denervated regions of the hippocampal formation after lesions of the medial septal nucleus or fimbria in adult female rats. Similar lesions in adult males also elicit the sympathetic ingrowth; however, the number of anomalous axons is greatly reduced and their distribution is altered. In adult males the sympathetic axons do not send out collaterals within the stratum oriens of region CA3 or the molecular layer or deep hilar regions of the area dentata, as they do in adult females. Lesions in juveniles of both sexes result in more vigorous sprouting than in their adult counterparts. In the young males the anomalous axons are distributed more extensively into the dentate molecular layer; in the young females the axons merely send out more collaterals within the same regions as in the adults. This sexually dimorphic response to central nervous system damage suggests either that the sprouting is affected by the hormonal environment of the mature hippocampal system or that this brain region, like the hypothalamus, may express permanent morphological or physiological differences as a result of exposure to sex steroids during development.*

The nervous system retains much of its growth potential in adult mammals. This is reflected in the capacity of many central nervous system structures to sprout after lesions are made. In the hippocampal formation, partial deafferentation by removal of the entorhinal cortex results in reorganization of the remaining afferents to the fascia dentata (*1*, *2*). Loy and Moore (*3*) described the ingrowth of an anomalous afferent system after damage of the fimbria. After such lesions were made in adult female rats, sympathetic, norepinephrine-containing axons grew into the area dentata and CA3 region of Ammon's horn from their normal sites of innervation along the extracerebral hippocampal arteries.

Although the precise mechanisms governing the elicitation and extent of axonal sprouting after either lesion is not known, we hypothesized that the hormonal environment may play some role in the growth process. This report describes an apparent hormonal effect on sympathetic axonal sprouting: sprouting was less in male animals than in their female counterparts. This suggests that sex differences in some nonreproductive behaviors, or in responses to brain dam-

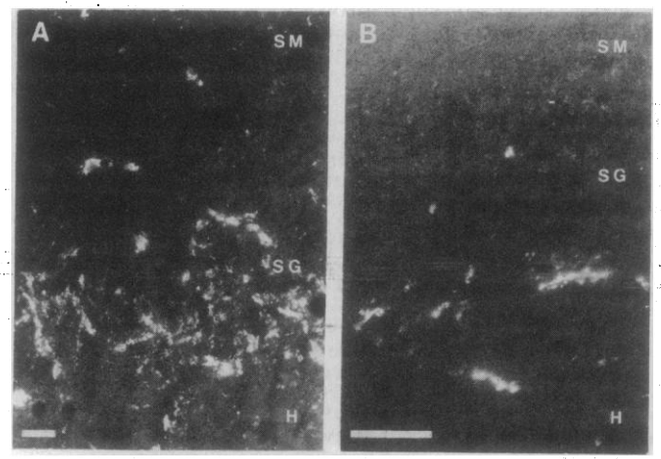

Fig. 1. Photomicrographs of the dentate hilar area of (A) female and (B) male rats transected as adults and prepared for fluorescence histochemistry 30 days later. Note that sympathetic fibers do not invade the molecular layer of the dentate in the male and that sprouted fibers are confined to the infragranular hilus. Abbreviations: *H*, hilus; *SG*, stratum granulosum; *SM*, stratum moleculare (scale bars, 40 μm).

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