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-

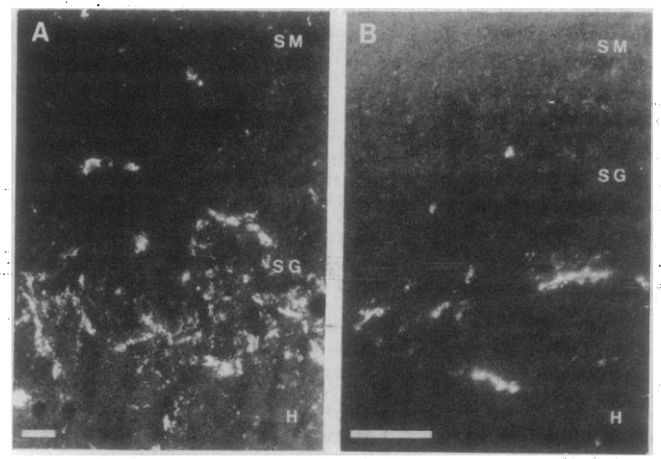

Fig. 1. Photomicrographs of the dentate hilar area of (A) female and (B) male rats transected as adults and prepared for fluorescence histochemistry 30 days later. Note that sympathetic fibers do not invade the molecular layer of the dentate in the male and that sprouted fibers are confined to the infragranular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

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age, may have a morphological basis.

To assess the axonal sprouting capacity of male and female rats, we transected the fimbria unilaterally between the posterior septum and anterior hippocampal formation with a stereotaxically placed knife. Six male and six female Sprague-Dawley rats (Hilltop Laboratories) each approximately 120 days old, were used in the first part of the study. The rats were killed by decapitation 21 to 30 days after the operation, their brains were removed and frozen on dry ice, and sections were prepared in a cryostat for fluorescence histochemistry (*4*).

We found that the central noradrenergic innervation of the hippocampal formation (*5*) and other brain regions is similar in males and females. In both, the anomalous axons enter the area dentata primarily at the dentatoammonic sulcus; a few also travel along vessels in the obliterated hippocampal fissure. Axons entering Ammon's horn apparently penetrate the pia adjacent to the extraventricular alveus.

However, we did find obvious differences between the groups in the extent of sympathetic ingrowth. In the females, sympathetic axons innervate the stratum oriens, stratum pyramidale, and stratum lucidum of CA3. Within the area dentata the axons extend to the supragranular layer, stratum granulosum, and the entire hilus (Fig. 1A). In contrast, in the adult males there is only limited growth into the infragranular hilus and stratum lucidum of CA3. There are many fewer axons and terminals in both cell layers, in the deep area of the hilus, and in the supragranular molecular layer at all septotemporal levels of the hippocampal formation (Fig. 1B). It is most likely that this difference in anomalous sympathetic innervation reflects a smaller number of terminals in the males, rather than less norepinephrine per terminal, since preliminary studies show that high-affinity uptake of [^{3}H]norepinephrine in the reinnervated animals is also less in the male group.

We also compared juvenile males and females for differences in their capacity for sympathetic sprouting in response to fimbrial lesions (Fig. 2). This group included two male and two female rats transected at postnatal day 13. In the young females, the pattern of sympathetic sprouting is similar to that of the adult females, except that the innervation of the entire area dentata and the stratum oriens is more dense. In the juvenile males there is also more sprouting than in the adult males with more fibers appearing in both cell layers, the stratum lucidum, and the infragranular hilus. A few fibers also appear in the supragranular molecular layer; however, the overall pattern is not as dense or extensive as in either female group.

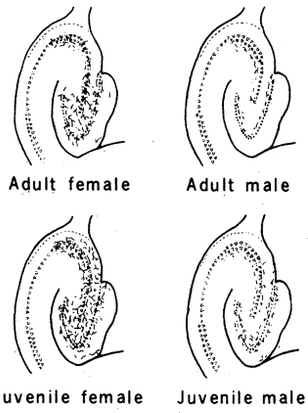

Fig. 2. Schematic drawing comparing the extent of sympathetic axon ingrowth (shaded areas) in adult and juvenile male and female rat hippocampal formations after fimbria transections. Axonal sprouting is more extensive in both younger groups; sprouting in both male groups is significantly less than in either female group.

Previous studies have also demonstrated that axonal sprouting in a variety of central structures is more vigorous in lesioned neonatal or juvenile animals than in lesioned adults (*2*, *6*). The remaining axons may sprout into actively growing regions, resulting in expansion of terminal fields. This may therefore reflect dendritic growth as well as axonal invasion of novel territory, as is more likely the case in adults. By contrast, in the present studies the juvenile females showed greater termination of sprouted fibers within the same regions as in the adults—without expansion into additional fields.

Regulation of eventual terminal distribution of the anomalous sympathetic afferent fibers is probably a complicated process involving at least three factors: (i) maturity of the sympathetic innervation of the vasculature, (ii) maturity of the damaged afferent system, and (iii) maturity of the receptive neurons. We know that the sympathetic innervation of the extracerebral arteries is already present as early as the second postnatal day. The significance of the maturity of the damaged afferent system is less clear. Ingrowth of the anomalous sympathetic axons is dependent on damage to axons originating in or passing through the medial septal nucleus (*7*). The septal innervation of the hippocampal formation is quite well developed by postnatal day 13 in the rat, as suggested by the pattern of acetylcholinesterase (AChE) staining (*8*). Interestingly, two of the latest features to mature are the darkly staining suprapyramidal and supragranular layers, both of which are heavily innervated by the anomalous sympathetic axons. Since these regions only mature after day 14, our lesions on day 13 may have deafferentated an immature septal system in the process of synaptogenesis.

The postsynaptic neurons are also immature morphologically. In addition, cholinergic receptor binding activity is higher in the young rat than in the adult (*9*). This suggests that a larger number of receptors or postsynaptic sites may become available to form contacts with the sympathetic axons in the younger lesioned animals. This or the immaturity of the septal afferent fibers could account for the increased density of sprouted axons after the lesions in the juveniles.

The mechanisms underlying the reduced axonal sprouting in the lesioned males are even less clear than those controlling the differences in young and adult rats of the same sex. At no age was the sprouting in the males as extensive as in the females. There may be a sex difference in the normal septal projection to the hippocampal formation; however, this remains to be ascertained. Another interesting possibility is suggested by the fact that the septum and hippocampal formation both contain sex-steroid binding sites (*10*). Thus testosterone or its derivatives may in some way inhibit axonal sprouting in the male animals. This could be accomplished by binding of circulating hormone in the adult or by a more permanent alteration as a result of early exposure of the hippocampus to sex steroids during development. Of course, an alternative hypothesis—that the males lack some factor that facilitates sprouting in the females—cannot yet be dismissed.

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Clinical Radioimmunodetection of Cancer with Radioactive Antibodies to Human Chorionic Gonadotropin

Abstract. *Injection of iodine-131-labeled goat immunoglobulin G antibody to human chorionic gonadotropin (hCG) into patients with hCG-secreting trophoblastic and germinal tumors permitted tumor detection and location by external gamma-ray scintigraphy. Excision of one of the metastatic tumors located by this method indicated a tumor/nontumor ratio of 39.29. The method appears to offer a new clinical tool for precisely locating hCG-producing tumors in the body, even when tumor identification by other clinical methods has failed.*

Human chorionic gonadotropin (hCG) was one of the first tumor markers used to monitor disease activity in patients with hCG-producing neoplasms, such as trophoblastic and germ-cell tumors (*1*). Recently it was shown that serum hCG levels were elevated in a group of patients with a diverse array of cancers (*2*). The finding that tumors producing carcinoembryonic antigen (CEA) can be detected and located in humans in vivo by administering a radioactive foreign antibody to CEA and performing total-body scanning with a gamma-ray scintillation camera (*3*) suggests that this method of cancer radioimmunodetection can also be applied to hCG-containing neoplasms. Indeed, Quinones *et al.* (*4*) demonstrated that human choriocarcinomas grown in hamsters could take up 2.8 times more radioactively labeled antibody to hCG than the animals' livers. We report here that hCG-producing tumors in man can be detected and located by radioimmunodetection after administration of ^{131}I-labeled goat antibody to hCG, revealing tumor sites not demonstrated by other diagnostic techniques.

Hyperimmune goat antiserum was prepared with purified urinary hCG. The antiserum to hCG was absorbed with human urinary protein, using an automated chromatography system with a solid-phase (Sepharose 4B, Pharmacia) immunoadsorbent column (*5*). The immunoglobulin G (IgG) fraction of the absorbed antiserum was chromatographically purified with *O*-(diethylaminoethyl)cellulose and then concentrated to 7.35 mg of protein per milliliter by ultrafiltration through a membrane (Amicon PM30). The purity and immunoreactivity of the IgG were determined by immunodiffusion and immunoelectrophoresis against hCG and against donkey antibody to goat serum and IgG. The titer of the goat IgG antibody to hCG, as determined by radioimmunoassay with half of maximum binding used as the endpoint, was 5×10^5.

The goat antibody to hCG was labeled with ^{131}I (Amersham/Searle) by the chloramine-T method (*6*). The labeled antibody (specific activity, 5 to 10 Ci per gram of IgG protein) was diluted with 1 percent human serum albumin (Hyland) in physiological saline and filtered with a 0.22-μm sterile filter. Chromatographic analysis with a Sephadex G-200 gel indicated that 90 to 95 percent of the ^{131}I-labeled antibody cochromatographed with the IgG. Individual lots of ^{131}I-labeled goat IgG antibody to hCG were tested by an independent testing laboratory (Scientific Associates) and determined to be sterile, pyrogen-free, and nontoxic in short-term tests.

Subjects were patients with an hCG-secreting tumor or a tumor thought to have areas of hCG production. Their informed consent was first obtained. Also, before injecting the labeled antibody, we tested the subjects for anaphylactic hypersensitivity to goat IgG. To reduce thyroid uptake of ^{131}I, potassium iodide solution (Lugol's solution, Purepack Pharmaceutical) was administered (five drops twice daily, orally) to the patients as soon as they entered the study and until completion of scanning.

The ^{131}I-labeled IgG antibody to hCG was administered intravenously (2 to 3 μg per kilogram of body weight; total radiation per patient, 1.20 to 1.80 mCi) in 20 ml of sterile 0.9 percent NaCl over a period of 10 to 15 minutes. To subtract blood-pool activity and any free iodine activity secreted in the stomach and urinary bladder, 0.5 mCi of $^{99m}TcO_4^-$ (E. R. Squibb & Sons) and 0.5 mCi of ^{99m}Tc-labeled human serum albumin (Union Carbide) were injected intravenously 30 and 5 minutes before imaging, respectively. Images of the anterior, posterior, and lateral chest and abdomen were made with a gamma-ray scintillation camera (LFOV, Searle) at various intervals after application of the radioactive antibody, but usually after 24 and 48 hours. Scans

Table 1. Photoscanning results for four patients with benign or malignant tumors. (+) Denotes tumor identified; (−), tumor not identified; and (0), tumor excised. The activity concentration ratio (T/NT) represents ^{131}I counts in tumor compared to an equivalent area of the same organ or body region, and the activity count ratio [T/NT(S)] denotes the same relation after subtraction of the ^{99m}Tc image from the ^{131}I picture, both computations made 24 hours after injection of labeled goat IgG antibody to hCG. Numbers in parentheses indicate number of sites positive for tumor. N.A., not available.

Patient no.	^{131}I Dose (mCi)	Primary diagnosis	Serum hCG (ng/ml)	Radioimmunodetection findings		T/NT	T/NT(S)
				Primary site	Secondary sites		
200	1.20	Embryonal carcinoma	0	0	−, Lungs (5)	1.00 to 1.20	1.20 to 2.30
228	1.74	Hydatidiform mole (preoperative)	34,700	+*		2.87*	8.65*
228	1.74	Hydatidiform mole (postoperative)	N.A.	0		1.40	1.07
230	1.80	Teratocarcinoma	117	0	+, Pelvis (1)	2.20	38.30
231	1.25	Embryonal carcinoma with choriocarcinoma	1,721	0	+, Lungs (2)	1.02 to 1.28	7.68 to 11.34
					+, Abdomen (1)	2.20	14.19

*One hour after the injection of labeled antibodies (preoperative).

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