shows that the locus determining response to dextran is not linked to the H-2 locus (linkage group IX), confirming this conclusion as based on the strain survey (Table 2).

The strain survey of the dextran response suggested that this locus was unlinked to the heavy chain allotype locus (C_H) as based on the response characteristics of CBA and BAB/14 (Table 2). The CBA strain is a low responder, yet has the BALB/c allotype, and BAB/14 is a high responder with C57BL/6 allotype. This conclusion, however, is not supported by the linkage analysis in the RI strains. Complete concordance is found for the strain distribution patterns of responsiveness and heavy chain allotype (*10*), demonstrating that the response locus is linked to the genes controlling the heavy chain constant regions. The response characteristics of CBA and BAB/14 mice are explainable if a recombinational event occurred between the locus for response to dextran and the genes coding for the heavy chain constant regions.

We favor the following interpretation of our results: A restricted response to dextran is due to selection of products of the germ-line $V_{\lambda(0)}$ gene or germ-line $V_{H(0)}$ gene or both. As the locus determining responsiveness is C_H-linked, if $V_{\lambda(0)}$ is necessary for response, the $V_{\lambda(0)}$ gene in mice is linked to the heavy chain locus. A recombinational event to explain the results in BAB/14 and CBA would then have occurred either between the locus for V_λ and the C_H locus or between the V_H and C_H loci. If response is determined by a $V_{\lambda(0)}$ gene, alleles of this gene (in unresponsive strains) code for the λ subunit of germ-line antibodies with different specificities.

It has been proposed that antibody variability is due to somatic mutation and selection; by this model a variety of germ-line antibodies exist prior to diversification equal to the number of germ-line V_L genes multiplied by the number of germ-line V_H genes (*11*). For example, if there are five different variable heavy chain genes and one lambda variable gene then five antibody specificities can be generated. The homogeneous response to dextran in certain strains of mice, such as BALB/c, suggests that such a germ-line antibody, $V_{\lambda(0)}V_{H(0)}$, is selected since it is unlikely that an identical antibody would be repeatedly generated by random somatic mutation. The low response in the kappa class in some strains, such as C57BL/6, suggests that they do not have a $V_{\lambda(0)}V_{H(0)}$ antibody with dextran specificity. The antibodies to dextran of these strains could be of the $V_{\kappa(0)}V_{H(0)}$ type (germ line) or these antibodies may have been selected for as a result of somatic diversification of germ-line genes. The light chain class of such somatically derived antibodies is more likely to be kappa since the ratio of germ-line V_κ genes to V_λ genes is at least 20 : 1 in the mouse (*2*).

Since high response is limited to a particular light chain class and idiotype, differences between strains must involve the bone marrow–derived cell. This is consistent with our initial results where immunizing C57BL/6 and BALB/c mice with sheep erythrocytes coupled to dextran B-1355S does not abolish the response difference. Both strains, because they respond well to SRBC, must have thymus-derived cells capable of recognizing the carrier determinants on SRBC. Difference in responsiveness to dextran in this case is due to differences expressed in the bone marrow–derived cell.

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Benzodiazepines: Anxiety-Reducing Activity by Reduction of Serotonin Turnover in the Brain

Abstract. *The anxiety-reducing effects of minor tranquilizers in the rat conflict test were mimicked by serotonin antagonists and by* p-*chlorophenylalanine, an inhibitor of serotonin synthesis; the depressant effects of the minor tranquilizers were mimicked by norepinephrine antagonists. Intraventricular injections of serotonin led to a suppression of behavior, and also antagonized the anxiety-reducing action of benzodiazeprines. Intraventricular injections of norepinephrine led to a release of punished behavior from suppression, and also antagonized the depressant action of benzodiazepines. The anxiety-reducing activity, and the decrease in serotonin turnover induced by benzodiazepines, were maintained over repeated doses, whereas depressant activity, and the decrease induced in norepinephrine turnover, both rapidly underwent tolerance. Tranquilizers may exert their anxiety-reducing effects by a reduction of serotonin activity in a behaviorally suppressive punishment system, and they may exert their depressant effects by a reduction of norepinephrine activity in a behaviorally facilitatory reward system.*

We attempt here to relate the behavioral actions of the minor tranquilizers (benzodiazepines, barbiturates, and meprobamate) to their recently discovered effects on monoamine turnover in the brain. Studies from several laboratories indicate that benzodiazepines and barbiturates decrease the turnover of norepinephrine, serotonin, and other biogenic amines in the brain (*1–3*). Because norepinephrine and serotonin play an important role in the control of behavior (*4, 5*), the decreased turnover of these substances may be at least partly responsible for some of the behavioral effects of tranquilizers. To test this idea, we varied the activity of norepinephrine and serotonin in the brain in several ways, and compared the behavioral effects of these changes with those of the benzodiazepines. On the assumption that

a decrease in monoamine turnover was involved, our chief aim was to determine whether the anxiety-reducing effects of tranquilizers are associated principally with a reduction of norepinephrine activity, or principally with a reduction of serotonin activity.

The anxiety-reducing and depressant effects of tranquilizers may be measured in animals by the conflict test of Geller and Seifter (*6*). In this test, hungry rats perform a lever-press response to obtain a sweetened milk reward. The reinforcement schedule consists of punishment and nonpunishment components, alternating every 18 minutes. On the nonpunishment schedule (15 minutes), a response is rewarded with sweetened milk at infrequent and variable intervals—on the average, once every 2 minutes. On the punishment schedule (3 minutes), signaled by a tone, every response is rewarded with milk, but is also punished with a brief electrical shock (0.1 to 0.6 ma, 0.25 second in duration) to the feet. The rate of response in the tone period may be regulated by adjustment of shock intensity, and any degree of behavioral suppression may be obtained in well-trained animals. After several weeks of training, stable low rates of response are obtained during the punishment periods, and stable high rates in the nonpunishment periods. Drug-induced increases in the rate of punished responses are taken as an index of anxiety-reducing activity, while decreases in the rate of nonpunished responses are taken as an index of depressant activity.

If the anxiety-reducing effects of benzodiazepines depend on a reduction of norepinephrine activity, then other agents that reduce such activity ought also to exert an anxiety-reducing effect. Phenothiazine derivatives such as chlorpromazine exert strong central antiadrenergic effects, but do not release punished behavior from suppression (*6*). Since phenothiazines also antagonize other neurotransmitter actions, we tested the relatively selective α-noradrenergic antagonist, phentolamine, and the β-noradrenergic antagonist, propranolol. Both antagonists failed to release punishment-suppressed behavior in the rat conflict test. Intraventricular injections of propranolol (20 to 100 μg) had no obvious effect, but intraventricular injections of phentolamine (5 to 10 μg) strongly suppressed both punished and nonpunished behaviors (*5*). These experiments do not support the idea that anxiety-reducing activity depends on noradrenergic blockade. On the contrary, they suggest that α-noradrenergic blockade causes suppression of behavior.

Table 1. Effects of neurotransmitters in the rat conflict test. Results are expressed as means ± standard error of the mean. Experiment 1: Hydrochloride salts of the indicated substances were dissolved in 10 μl of Ringer-Locke solution, and were injected into the lateral ventricle immediately before the start of the 72-minute test. Abbreviations used, L-NE = L-norepinephrine. Experiment 2: Norepinephrine hydrochloride (5 μg) was injected in the lateral ventricle, 10 minutes before the test, either alone or followed by an intraperitoneal injection of oxazepam (10 mg/kg, suspended in 0.5 percent Tween 80) immediately before the conflict test. One week after the NE-oxazepam experiment the same rats were tested with oxazepam alone. Before this study, rats had received oxazepam only once.

Treatment	Rats (No.)	Responses per test	
		Punished	Nonpunished (hundreds)
	Experiment 1		
No injection	9	7.8 ± 1.1	14.1 ± 3.3
Ringer-Locke	9	11.4 ± 3.3	15.5 ± 2.9
L-NE (5 μg)	7	32.5 ± 9.0*	12.3 ± 2.2
L-NE (10 μg)	8	47.6 ± 8.0*	14.0 ± 3.1
D-NE (10 μg)	9	13.2 ± 4.4	13.7 ± 3.7
Dopamine (10 μg)	6	7.3 ± 1.6	11.4 ± 1.3
	Experiment 2		
No injection	7	3.9 ± 0.7	38.2 ± 10.1
Oxazepam	7	15.9 ± 7.6†	13.6 ± 5.4†
L-NE ‡	7	9.1 ± 4.7	30.7 ± 4.4§
L-NE ‡ + oxazepam	7	34.9 ± 7.3†§	25.4 ± 7.8†§

* Differs from Ringer-Locke, $P < .01$. † Differs from no injection, $P < .01$. ‡ Five micrograms injected 10 minutes before test. § Differs from oxazepam, $P < .01$.

Experiments with L-norepinephrine supported this idea. Intraventricular injections of the transmitter produced large increases in the rate of punished responses (Table 1); indeed, the anxiety-reducing activity of norepinephrine administered intraventricularly compares favorably with that of the benzodiazepines administered systemically. Neurochemical specificity is suggested as D-norepinephrine and dopamine produced only negligible effects. Significantly, intraventricular injections of norepinephrine increased rather than decreased the punishment-lessening activity of systemically administered benzodiazepines (Table 1); this finding again contradicts the idea that the anxiety-reducing activity of tranquilizers depends on a reduction of noradrenergic activity. At the same time, norepinephrine antagonized the depressant effect of oxazepam on nonpunished behavior (Table 1); this supports the suggestion that the depressant action of tranquilizers may be mediated by reduction of norepinephrine activity.

If reduction of serotonin, rather than norepinephrine, turnover is involved in the anxiety-reducing activity of benzodiazepines, then antagonists of serotonin or inhibitors of its synthesis should counteract the suppressive effects of punishment. Such seems to be the case. Graeff and Schoenfeld (*7*) observed very large increases in the punished response rates of pigeons after intramuscular injection of the serotonin antagonists, methysergide and D-2-bromolysergic acid diethylamide; the effect "was of the same magnitude as that produced by chlordiazepoxide, diazepam, and nitrazepam" (*7*). We also have obtained punishment-lessening effects with methysergide in the rat conflict test (*5*). There are also reports of large releases of punishment-suppressed behavior after administration of the serotonin synthesis inhibitor, *p*-chlorophenylalanine (PCPA) (*5, 8*). The time courses of behavioral release and of serotonin depletion after PCPA injection coincide closely, and repletion of serotonin by administration of its precursor 5-hydroxytryptophan reverses the punishment-lessening effect of PCPA (*5, 8*).

Consistent with these findings, elevation of the concentration of serotonin in the brain by combined administraton of 5-hydroxytryptophan and an inhibitor of monoamine oxidase causes suppression of food-rewarded behavior in the pigeon (*9*). Furthermore, the long-lasting, serotonin agonist, α-methyltryptamine, active in the central nervous system, suppresses punished and nonpunished behaviors in the pigeon (*7*) and rat (*5*). These findings with serotonin agonists, antagonists, and PCPA support the possible existence of a behaviorally suppressive serotonin "punishment" system, whose activity may be

Table 2. Effects of single and repeated doses of oxazepam on turnover of serotonin and norepinephrine. Rats were injected in the lateral ventricle with [^{14}C]serotonin (1.1 μg, 0.35 μc) and [^{3}H]norepinephrine (1.1 μg, 0.26 μc) dissolved in 10 μl of Ringer-Locke solution, 10 minutes before a single or the sixth daily intraperitoneal dose of oxazepam (20 mg/kg), and were killed 3 hours later. Control groups received single or repeated doses of saline instead of oxazepam; means of control groups did not differ significantly and were combined. No significant effects on monoamine turnover were found in the diencephalon-forebrain region with the dose of oxazepam studied. However, the saline group included one animal in which all diencephalon-forebrain determinations substantially exceeded the range of the other nine animals. If this case was excluded, the resulting means in the saline group for total ^{14}C and [^{14}C]5HT were significantly smaller than the corresponding means of either oxazepam group. For details of chemical analysis, see (*5*). Results are expressed as means ± standard error of the mean. Abbreviations used: [^{14}C]5HT, [^{14}C]serotonin; [^{14}C]5HAA, [^{14}C]5-hydroxyindoleacetic acid + neutral metabolites; [^{3}H]NE, [^{3}H]norepinephrine; [^{3}H]NMN, [^{3}H]normetanephrine; *N*, number of rats.

	Number of disintegrations per minute per milligram of midbrain-hindbrain region		
	Saline ($N = 10$)	Oxazepam	
		Single dose ($N = 8$)	Repeated doses ($N = 6$)
Total ^{14}C	20.7 ± 1.48	31.9 ± 1.71*	27.1 ± 1.08*
[^{14}C]5HT	10.1 ± 0.77	15.0 ± 0.90*	13.4 ± 0.41*
[^{14}C]5HIAA	10.6 ± 0.76	16.8 ± 0.99*	13.6 ± 0.71*
Total ^{3}H	28.4 ± 2.11	42.6 ± 3.66*	33.1 ± 2.25
[^{3}H]NE	9.5 ± 1.10	16.6 ± 1.99*	10.9 ± 0.92
[^{3}H]NMN	10.3 ± 1.14	14.7 ± 1.51*	12.3 ± 1.02

* Differs from mean of saline group at $P < .05$.

decreased by benzodiazepines and other anxiety-reducing agents.

The suppressant effects of intraventricular serotonin in the rat self-stimulation test generally support these conclusions (*5, 10*). However, for reasons that are not yet clear, the action of serotonin in the conflict test is complex and apparently triphasic (*5*). Doses of 1 to 20 μg of serotonin lead to an initial phase of intense behavioral suppression, that lasts for 10 to 20 minutes, a longer secondary phase of normal response, or, frequently, behavioral facilitation (including release of punished behavior), and, finally, a prolonged period of behavioral suppression, which may persist for 2 days with high doses. Similarly, intracarotid administration of serotonin induces biphasic effects on the electroencephalogram [a brief arousal pattern followed by a longer phase of hypersynchrony (*11*)] and iontophoretic application of serotonin to some spinal neurons causes biphasic changes in their spontaneous firing rate (*12*). These findings, on a reduced time scale, resemble the behavior seen in our experiments, although the acute nature of these preparations makes it difficult to evaluate the possibility of a third phase.

To further test the idea that the anxiety-reducing effects of tranquilizers are mediated by reduction of serotonin activity, we tried to antagonize the punishment-lessening action of oxazepam by intraventricular administration of serotonin. Eight rats received intraventricular injections of either serotonin hydrochloride (5 μg), L-norepinephrine hydrochloride (5 μg), or Ringer-Locke solution (10 μl) immediately before receiving intraperitoneal injections of oxazepam (10 mg/kg). All rats received all drug combinations during 10 days of testing, but in different sequences. We focused attention on performance in the first programmed punishment period, 3 to 6 minutes after the injections, because the acute suppressant effect of serotonin lasts only about 15 minutes. In six out of the eight rats, serotonin decreased the anxiety-reducing action of oxazepam, whereas in seven out of the eight rats L-norepinephrine increased the anxiety-reducing effect of the tranquilizer (mean punished responses: Ringer-Locke, 8.0; serotonin, 3.4; norepinephrine, 14.6—Ringer-Locke versus serotonin or norepinephrine, $P < .05$).

In biochemical experiments, we compared the effects of single, and of repeated, doses of oxazepam on the turnover of norepinephrine and serotonin. The anxiety-reducing and depressant actions of benzodiazepines follow different courses during their chronic administration; the depressant action rapidly undergoes tolerance after a few doses (*13*), while the anxiety-reducing action fails to show tolerance, and may even increase with repeated doses (*14*). If these behavioral effects were mediated by decreases in turnover of serotonin and norepinephrine, as we suggest, then it might be possible to show that benzodiazepine-induced decreases in serotonin turnover will persist with repeated doses, while the decrease in norepinephrine turnover will undergo tolerance.

We modified the methods of Chase, Katz, and Kopin (*3*) for measuring benzodiazepine effects on serotonin turnover to permit concurrent determinations of norepinephrine turnover. Twenty-four rats, with permanent cannulas in the lateral ventricle of the brain, were injected intraperitoneally either once or daily for six consecutive days with oxazepam or saline. Ten minutes before the single or sixth dose of oxazepam (or saline), rats in all four groups received an intraventricular injection of [^{14}C]serotonin and [^{3}H]norepinephrine. Three hours after the injection of the radioisotopes, the rats were killed by decapitation. The brains were removed, and were divided into forebrain-diencephalon and midbrain-hindbrain pieces by a vertical knife-cut caudal to the mammillary bodies and rostral to the superior colliculus (the cerebellum was discarded).

The effects of single or of repeated doses of oxazepam on the turnover of [^{14}C]serotonin and [^{3}H]norepinephrine in the midbrain-hindbrain region are reported in Table 2. In rats treated with a single dose of oxazepam, the total amount of ^{14}C and ^{3}H exceeded that of the saline controls; this is consistent with previous reports (*1, 3*) and reflects significant elevations in the concentration of [^{14}C]serotonin and [^{3}H]-norepinephrine and their major metabolites, [^{14}C]5-hydroxyindoleacetic acid and [^{3}H]normetanephrine (*15*). In rats treated with repeated doses of oxazepam, there were significant increases only in the concentration of [^{14}C]serotonin and metabolites labeled with ^{14}C, but not of [^{3}H]norepinephrine or metabolites labeled with ^{3}H. Thus, a decrease in norepinephrine turnover in the midbrain-hindbrain region was no longer detectable after six doses of oxazepam, although serotonin turnover was still substantially reduced. In the conflict test, the depressant action of this dose of oxazepam similarly disappears after six daily injections, whereas its anxiety-reducing action persists (*16*).

Although oxazepam may have exerted small effects on serotonin turnover in the diencephalon-forebrain region (Table 2), the greatest effects of the drug were concentrated in the midbrain-hindbrain region. This result seems consistent with the observation that intraventricularly administered serotonin is selectively accumulated in the central

gray area of the midbrain (*17*), a region frequently associated with punishment and aversive behavior (*18*). Such considerations focus attention on serotonergic synapses in this central gray area as possible sites of action for the anxiety-reducing effects of benzodiazepines and related tranquilizers.

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16. Although the reduction of serotonin turnover decreased slightly after repeated doses of benzodiazepines, the anxiety-reducing activity actually increases (*14*). Such increase may be due partly to progressive unmasking of the anxiety-reducing action as tolerance to the depressant action develops, and partly to supersensitivity to norepinephrine, which may develop as a result of drug-induced disuse of noradrenergic synapses.
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Locomotion: Control by Positive-Feedback Optokinetic Responses

Abstract. *Several species of arthropods perform forward locomotory movements when restrained in place and exposed to a pattern of stripes moving backward at normal locomotory velocities. Locomotory effort varies directly with stripe velocity. In nature such locomotory reactions would increase the visual stimulus that elicits them; hence, the reactions represent a new class of optokinetic responses employing positive visual feedback. Stabilizing mechanisms include response decrement during constant stripe velocities.*

When an animal is placed within a rotating, vertically striped cylinder, it turns in the same direction as the cylinder (*1*). The stimulus, or input, for this optokinetic reaction is relative motion in the animal's visual field. The response, or output, is eye or body movement that tends to stabilize the stripes in the visual field. In terms of control theory (*2–4*), the output of this optokinetic system reduces the visual input, and hence the feedback is negative. In nature this response is presumed to help maintain an animal on a "desired" locomotory course despite external disturbances and bilateral asymmetries within the organism (*1*).

In contrast, we now describe a new class of optokinetic responses in which the visual feedback is positive. That is, the output (locomotory movement) increases the input (relative motion in the visual field), and thus the response is self-reinforcing. Our data suggest that positive-feedback optokinetic responses play an important role in controlling normal locomotory activity and that such responses are of widespread occurrence in the animal kingdom.

The positive-feedback optokinetic responses were elicited by exposing an animal to a pattern of stripes painted on the moving belt of a treadmill (Fig. 1A). Specimens were restrained in place above the treadmill and separated from it by a transparent Plexiglas platform; they could therefore see the moving stripes, but were unable to feel the movements of the belt. Lateral mirrors, mounted at an angle of 45°, reflected the ventral stripes to provide additional visual stimulation from both sides of the animal. The treadmill was bolted to a thick plate of stainless steel that rested on rubber feet within a Plexiglas aquarium. The aquarium was in turn enclosed within a Faraday cage that was supported on a table by vibration-proofed mounts. The treadmill was attached by a long, flexible drive shaft to a variable-speed electric motor outside the cage. During the experiments, which lasted from one to several hours, the animals were maintained at constant temperatures and viewed under constant illumination through a one-way mirror mounted in the front of the Faraday cage.

Species studied include the lobster (*Homarus americanus*), crayfish (*Procambarus clarkii*), locust (*Shistocerca vaga*), cockroach (*Periplaneta americana*), blowfly (*Sarcophaga bullata*), and sphinx moth (*Manduca sexta*). In all of these animals, movement of the stripes from front to rear induced forward locomotory movements [however, see (*5*)].

The detailed properties of the positive-feedback optokinetic responses have been examined in the lobster. Here, forward walking typically began within 1 or 2 seconds following the onset of stripe movement, increased in strength during the first few stepping cycles, and then showed marked decrement (Fig. 1, B and C). These responses could be eliminated by covering the moving belt with a stationary pattern of stripes, showing that the moving visual stimulus caused the responses. The optokinetic responses were often labile, but ones like those shown in Fig. 1 were obtained from the majority of the 35 lobsters used in this study.

The optokinetic responses involve more than one motor system, each recruited at a specific and relatively stable optokinetic threshold. In Fig. 1D, for example, walking movements were elicited at a treadmill speed of 2.5 cm/sec, while rhythmic, locomotory movements of the abdominal swimmerets were not initiated until the stripe velocity reached 11 cm/sec. Each time the treadmill speed was increased the responses of both locomotory systems increased and then decreased simultaneously to about the same degree. The decrement may have resulted from adaptation in the visual input common to both motor systems (*6*).

In the lobster not only are several motor systems involved in the optokinetic responses, but in addition the activity within a given motor system varied directly with the movement velocity of the stripes. In the walking system, for example, increasing the treadmill speed increased the stepping frequency (that