BEHAVIORAL PHARMACOLOGY AND TOXICOLOGY[1,2,3]

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This is the fourth review in this series devoted to the broad area of behavioral pharmacology. Like our predecessors—Dews & Morse (1), Cook & Kelleher (2), Gollub & Brady (3)—we will treat only a few subtopics within the active research area covered by our title. Two recent developments attest to the rapid growth of this discipline. First, a Division of the American Psychological Association was formed in 1966; it already has almost 800 members. Second, the area has its first textbook, written by Thompson & Schuster and appropriately named *Behavioral Pharmacology* (4).

Two dominant themes in this review both grow out of the current search for correlations between brain chemistry and behavior. One is the role of adrenergic mechanisms in behavior. The other is the enhancement of learning by a drug originally claimed to affect RNA in the brain. Both surveys underscore the need to understand the behavioral mechanisms of drug action—our third theme. The fourth, behavioral toxicology, bears witness to a new concern by society and to the fact that much of what we call behavioral pharmacology is the study of selective toxicity, a point prominently featured in the previous sections. As in previous reviews, our selection of papers is meant to indicate trends, not to provide exhaustive coverage.

Neurochemical Correlates of Behavior: Adrenergic Systems

The past few years have been marked by an intensive effort to correlate neurochemical variables and behavior. Much of this activity stems from the growing belief that the key to behavior disorders such as schizophrenia and

[1] The survey of literature pertaining to this review was concluded in June 1968.

[2] The following abbreviations will be used: α-MMT (α-methyl-*m*-tyrosine); α-MT (α-methyl-*p*-tyrosine); DOPA (3,4-dihydroxyphenylalanine); DRL (differential reinforcement of low response rates); MAO (monoamine oxidase); PMH [pemoline (2-imino-5-phenyl-4-oxozolidinone) with magnesium hydroxide].

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depression lies in aberrant chemical processes and states within the nervous system [e.g., Schildkraut & Kety (5)]. Much of it arises from the conviction that new drugs which affect behavior can be developed only by understanding neurochemical mechanisms. At the same time, new methods in neurochemistry and new drugs affecting the chemical state of the nervous system have made it possible to pursue this goal more directly than was possible only a short time ago. There is now some optimism that correlations between behavioral and neurochemical variables can be established which will make it possible to explain drug actions and to formulate a pharmacological therapy of the behavior disorders. The bulk of this work has been directed toward the adrenergic substrates of behavior.

Most neuropharmacologists assume that within the central nervous system synapses operate by releasing chemical transmitter substances from their presynaptic nerve endings. Although the function of catecholamines as neurohumors has not yet been settled to everyone's satisfaction, the evidence in favor of such a role is most cogent. Catecholamines are found in the brain and have been localized within neurons. Histochemical fluorescence techniques have shown that norepinephrine and dopamine occur in what might be called adrenergic neuronal systems within the brain. It has also been amply demonstrated that the metabolic pathways for the synthesis and deactivation of catecholamines also exist within the brain. In the face of this evidence, it is almost impossible to deny to the catecholamines a major role as transmitters in neuronal systems. What is obscure is how they function as a behavioral substrate and how drugs which modify behavior interact with them to produce unique and specific effects. We have chosen, in this review, to focus on experiments which interfered with the normal functioning of catecholamine systems in the brain to see whether or not with the data at hand we can make any sense out of the interactions with behavior.

The biosynthesis of norepinephrine begins with the amino acid tyrosine, which, through the enzyme tyrosine hydroxylase, is transformed to 3,4-dihydroxyphenylalanine, or DOPA, and then, through the enzyme aromatic L-amino-acid-decarboxylase to 3,4-dihydroxyphenylethylamine (dopamine). The final stage, the conversion of dopamine to norepinephrine, is catalyzed by the enzyme dopamine β-hydroxylase. Alternative biosynthetic pathways also exist [cf., Iversen (6)]. Metabolic degradation of extraneuronal catecholamines seems to depend most heavily on O-methylation by catechol-O-methyltransferase. An alternative route, affecting intraneuronally stored forms, is oxidative deamination by monoamine oxidase. In assessing the action of drugs upon catecholamine function in the nervous system, we must take account of the fact that they can interfere with any one of these metabolic steps and, moreover, can affect release, action at the receptor surface, or the reuptake of transmitter released by nerve impulses. Given so many possibilities, plus the possibility that certain compounds have multiple effects, it is not surprising that the mechanisms of drug action on behavior,

as related to the status of adrenergic transmitters in the brain, should present us with so many difficult questions.

Depletion Studies

Impaired storage.—Certain drugs, such as reserpine, are able to deplete catecholamines from central nervous system sites. Several recent studies treat the long-term behavioral effects of reserpine. Levison & Freedman (7) found that a single dose of 1 mg/kg of reserpine to rats usually was sufficient to reduce the proportion of lever press shock avoidance responses to between zero and 50 per cent. It was roughly 12 days before the animals reached their predrug avoidance level. The authors point out that the prolonged effects of reserpine are consistent with data which show that approximately 2 weeks are necessary for brain amines to return to normal levels after such a dose. They also report, however, that increased shock intensities in later experiments produced a relatively more rapid recovery after reserpine. This is consistent with Sidman's 1956 report (8) and underlines the importance of behavioral parameters. Another aspect of long-term administration appears in a paper by Kulkarni, Thompson & Shideman (9). Experimental rats between the ages of 11 and 30 days received 0.1 mg/kg reserpine, intraperitoneally, each day and were then allowed to grow to adulthood. Reserpine lowered brain catecholamine levels to between 20 and 40 per cent of normal. These levels gradually increased to control levels after 3 weeks without reserpine. At 95 to 100 days of age, the rats treated with reserpine during infancy emitted relatively more responses on extinction after continuous reinforcement than control rats. Absolute frequencies, however, are not given. They may be an important factor not only in these results but in a later study with adult animals (10).

Pirch & Rech (11) investigated the behavioral adaptation reported to occur after chronically administering reserpine to rats. They used three behavioral criteria. One was spontaneous locomotor activity, another was the ability of rats to balance themselves on a slowly-rotating rod (rotarod), and the third was conditioned avoidance behavior in a shuttlebox. Successive administrations of 0.5 mg/kg reserpine 24 hr before each of the behavioral observations led to adaptation for locomotor activity but not for conditioned avoidance behavior and rotarod performance. In fact, after the tenth administration, the animals chronically treated with reserpine gave nearly twice as many activity counts in a 15-min period as the animals treated with saline.

Several new studies are attempts to correlate brain amine levels with behavior after depletion. Aprison & Hingtgen (12) compared tetrabenazine, a benzoquinolizine whose effects are similar to those of reserpine, but shorter-lasting; *p*-chloroamphetamine, a compound reported to decrease brain 5-hydroxytryptamine levels without markedly affecting norepinephrine; and 5-hydroxytryptophan, which they showed earlier (13) raises brain 5-hydroxytryptamine but lowers norepinephrine and dopamine. Only single

subcutaneous dose levels were used: 50 mg/kg 5-hydroxytryptophan, 2 mg/kg tetrabenazine, and 3 mg/kg *p*-chloroamphetamine. All three compounds disrupted performance on a positive reinforcement schedule (Variable Ratio 40). Only tetrabenazine also disrupted Sidman avoidance. Since only tetrabenazine reduced brain levels of both norepinephrine and 5-hydroxytryptamine, it might be tempting to offer this correlation as an explanation, but the authors believe that the time course of norepinephrine change argues against such a proposition. The two schedules, one maintained by shock, one maintained by food reinforcement, offer further interpretive problems, since we can't be sure whether the reinforcement schedule, per se, or the reinforcing stimulus was responsible for the differences. Single dose levels add to the difficulties. In a later study, Aprison & Hingtgen (14) used the compound α-methyl-*m*-tyrosine (α-MMT), which reduces brain amine levels via displacement by α-methyl derivatives of the parent compound. This time they studied pigeons maintained on a multiple reinforcement schedule. The standard dose was 100 mg/kg α-MMT. A disruption of the behavior was correlated with lowered levels of 5-HT (about 25 per cent), of norepinephrine (about 45 per cent), and of dopamine (about 85 per cent). During this same period, the levels of α-methyl-*m*-tyramines resulting from α-MMT decarboxylation increased from zero to a peak of about 1.0 μg/g. It clearly is not possible to single out one of these changes as the source of the behavioral disruption. Moreover, as Aprison & Hingtgen point out, previous experiments have shown that α-MMT in rats on operant avoidance schedules, rather than causing disruption, increases the output of behavior. It is not clear whether these are due to species, schedule, or dose differences.

Another way to produce amine depletion in the brain is to make circumscribed lesions. In a series of studies recently reviewed by Heller & Moore (15) it has been shown, for example, that a lesion of the medial forebrain bundle in the cat reduces norepinephrine substantially in the telecephalon but hardly at all in the diencephalon and midbrain. Sheard, Appel & Freedman (16) observed the effects of such lesions on behavior in the rat. After operation, the rats were trained to escape from foot shock by turning a cylindrical wheel. Animals with medial forebrain lesions in the lateral hypothalamus and with lesions in the posteromedial hypothalamic midbrain junction responded much less frequently than control animals, who, according to the figures, continued to emit responses even in the absence of shock. Although this suggests that amine depletion might be the cause of the behavioral deficit, another possibility is that the decrement in behavior is due to an effect of the lesion independent of the fall in brain amines. Harvey & Lints (17) have shown that animals with medial forebrain bundle lesions in the lateral hypothalamus show a progressive increase in sensitivity to foot shock. Perhaps, as Sheard et al. point out, this increased sensitivity is responsible for the disruption of behavior, although reserpine seems to reduce sensitivity, at the same time depleting norepinephrine and 5-hydroxytrypta-

mine. Medial forebrain bundle lesions also make rats more susceptible to the depressant effects of reserpine, as shown by Harvey (18) in animals trained to lever press for water.

Despite the understandable tendency to talk in terms simply of depression or impairment, the behavioral effects of catecholamine depletion, via release or displacement, are not unidimensional. Some kinds of behavior are simply not as susceptible as other kinds. Some parameters of an experimental situation can be manipulated to overcome drug-induced deficits. A thorough behavioral analysis of these interdependencies would be a valuable contribution.

Impaired synthesis.—Agents such as reserpine, tetrabenazine, and α-MMT release or displace catecholamines from their storage sites. The discovery that tyrosine hydroxylase subserves the rate-limiting step in the biosynthesis of norepinephrine (tyrosine → DOPA), and the development of tyrosine hydroxylase inhibitors such as α-methyl-*p*-tyrosine (α-MT), has generated a series of studies exploring the effects on behavior of depleting biogenic amines by retarding their synthesis. In one of the early studies with α-MT, Weissman & Koe (19) trained rats to avoid foot shock by leaping onto a platform mounted above the grid floor of an experimental chamber. They found no disruption at doses up to lethal levels (178 mg/kg i.p.). Doses up to 562 mg/kg (i.p.) of α-MMT, α-methyl dopa and L-tyrosine also failed to disrupt avoidance behavior. Other behavioral measures displayed a similar insensitivity. In contrast, Moore (20) reported that α-MT at a dose of 80 mg/kg (i.p.) produced a severe reduction of avoidance performance in guinea pigs. Moore, however, used a shuttlebox, and instead of a single trial, each set of observations consisted of 20 trials. The time course of the behavioral depression was not well correlated with the presence of α-MT in the brain, and it was far from perfectly correlated with the reduction in norepinephrine. Moore pointed to the difference in behavioral measurements as the source of the conflicting data between his experiment and that of Weissman & Koe.

Later, Rech, Borys & Moore (21) extended these studies to rats, and to other kinds of behavior, and provided dose-response data. Their behavioral assays consisted of a conditioned shuttlebox avoidance response, rotarod performance, and spontaneous locomotor activity. Their chemical assays examined the dopamine content of the telencephalon, the norepinephrine content of the brain stem, and brain α-MT. With intraperitoneal doses of 30, 100, 200, and 300 mg/kg of α-MT the authors found a dose-related impairment of conditioned avoidance behavior and noted that with a dose of 200 mg/kg the maximal decrease in brain catecholamines occurred 8 hr after injection. Because at the higher doses many of the animals exhibited overt toxic symptoms, the authors also examined the effect of a single oral administration of 200 mg/kg. The fall in avoidance performance was approximately as great as after the same dose given intraperitoneally in a suspension. Overt toxic signs, however, such as weight loss and impaired renal

function, did not appear. The decline in motor activity paralleled the fall in norepinephrine while rotarod performance and avoidance performance more nearly paralleled dopamine levels. These observations were further extended by administering three injections of 50 mg/kg (i.p.) every 4 hr. Overt toxic signs were not apparent after this regimen, except for ptosis and loss of muscle tone, but there was a complete loss of avoidance behavior 12 hr after the first injection. Although the authors believe that this amount of overt toxicity should not disrupt behavior, such a conclusion has not been satisfactorily established.

Two experiments by Hanson (22, 23) do little to clarify the issue of whether or not α-MT produces selective effects. Although in the first he reported a decline in avoidance performance in cats, the dose levels he used were close to lethal, because several of the animals died. The same toxicity problems also are apparent in his rats. The "behavioral" data are still reported. In view of the toxicity demonstrated in his own paper, we are puzzled that Hanson came to the conclusion, "The data thus support the view that catecholamine neurones in brain play a role in conditioned avoidance response." The later study compared the methylester hydrochlorides of α-MT and 3,α-dimethyl-tyrosine, which, unlike α-MT, is not converted to α-methyl analogues. Both cats and rats were again used. Doses of 3,α-dimethyl-tyrosine in doses up to 500 mg/kg, which proved toxic to cats, had little effect on conditioned avoidance response performance. With the rats, too, no clear differences in conditioned avoidance response performance were seen until dose levels that produced obvious toxic symptoms. This compound produced falls in brain dopamine and norepinephrine considerably smaller than those produced by α-MT.

These papers, together with the one by Moore, Wright & Bert (24) which deals specifically with the toxicology of α-MT, suggest a considerable lack of specificity and that the depression of conditioned avoidance performance is due to generalized toxic effects of the drug. An important point of Moore et al. is that α-MT produces kidney damage which impedes its excretion. The main contribution of the studies reviewed is perhaps to show that the indices of impairment correlate roughly with the amount of catecholamine depletion. Such a result, however, does not as yet possess much behavioral significance, especially without controls for the role of peripheral catecholamine depletion. Two clinical trials with humans, one by Charalampous & Brown (25), one by Gershon et al. (26), show, in fact, only a sedative effect, with no significant amelioration of psychotic symptoms.

Drug Interactions

Despite the burdens of logic, interpretation, and sheer experimental effort that they impose, drug interaction studies can be illuminating if not pushed to extremes of polypharmacy. Studies of the adrenergic correlates of behavior frequently have used amphetamine because of the evidence that it interacts with catecholamines to produce its effects. Some workers have

performed interaction studies in order to test the mechanism of action of amphetamine. Others have, as it were, examined the mirror image of this process, using amphetamine as a tool with which to probe the significance of adrenergic mechanisms in behavior. Reserpine has served as an intermediary from both standpoints.

Drug interactions with catecholamine depletion.—Earlier work on reserpine-amphetamine combinations [Smith (*27*)] led to a series of experiments on the locomotor activity of grouped mice (*28*) in attempts to correlate the effects of various drugs with the brain content of norepinephrine, dopamine and 5-hydroxytryptamine. In the experiments with reserpine, mice were pretreated with a rather sizable dose—5 mg/kg—24 hr before the administration of various doses of *d*-amphetamine. Despite the fact that this dose reduced spontaneous activity to extremely low levels, 3 mg/kg of *d*-amphetamine produced a rise in activity level to approximately twice that observed after administration of the same dose to mice in control groups. The dose of *d*-amphetamine which caused the maximal increase in locomotor activity (10 mg/kg) significantly decreased brain norepinephrine levels and increased brain 5-hydroxytryptamine levels. But 3 mg/kg *d*-amphetamine, which also increased locomotor activity, produced a slight, though not statistically significant, increase in brain norepinephrine. This same dose produced the maximal increase in brain dopamine. Together with the fact that both pipradrol and cocaine also increased locomotor activity, although neither had appreciable effects upon brain amines, Smith was led to conclude that release of brain norepinephrine need not accompany increased locomotor activity and that *d*-amphetamine acts directly on the central nervous system.

Stolk & Rech (*29*) extended these data on locomotor activity to rats, using more dose levels of *d*-amphetamine and longer observation periods. Reserpine, in a dose of 2 mg/kg, reduced locomotor activity maximally at 3 hr postdrug, which corresponds to maximal amine depletion [Glowinski & Baldessarini (30)], with recovery from that point to 43 per cent of control activity by 24 hrs. At that point a dose of 2 mg/kg of *d*-amphetamine to the rats pretreated with reserpine produced a rapid rise in activity, the peak being reached within a half hour and attaining a value more than twice that of animals pretreated with saline only, in which, moreover, the peak effect occurred after 2 hrs.

Other investigators have used L-DOPA to try to reverse the behavioral effects of reserpine. Seiden & Hanson (31) trained cats on conditioned avoidance in a shuttlebox, then administered 0.1 mg/kg reserpine. At 19 to 23 hr later, the cats were given varying doses of L-DOPA. After reserpine, avoidance performance fell to 25 per cent, and escape responding was impaired. There was a sharp recovery after L-DOPA (different doses), but the exact time course is unclear. The figures suggest that 1 to 2 hr seems to be the approximate latency to the maximum effect of L-DOPA. L-DOPA had little effect, however, on norepinephrine levels but increased dopamine.

The distribution of dopamine after L-DOPA appeared to follow that of aromatic L-amino-acid-decarboxylase, which may be responsible for the fact that high levels of dopamine were observed in the hypothalamus, as well as the striatum. Unfortunately, no data on L-DOPA alone were presented. These data suggest that in certain situations dopamine may play a key role in the behavioral depression brought about by reserpine. In a later study, Hanson & Utley (32) confirmed these results with L-DOPA-methylester HCl, which is soluble. Further evidence for a correlation between the time course of L-DOPA reversal of behavior depressed by reserpine and the rise of dopamine levels was provided by Seiden & Peterson (33) in an experiment with two strains of mice, DBA-1 and C57Bn/10, trained on a conditioned avoidance response in a shuttlebox. Reserpine was administered in a dose of 2.5 mg/kg 20 hr before the next session in the shuttlebox on the day after having reached a criterion of 18 avoidance responses out of 20 trials. L-DOPA was injected in a rather large dose—400 mg/kg (i.p.) In both strains of mice, reserpine virtually eliminated conditioned avoidance response performance. In both strains of mice the injection of L-DOPA produced an immediate partial restoration of performance within 5 min, which lasted longer in the DBA strain. Brain dopamine analyses for both strains showed an immediate and rather spectacular rise, from close to zero to a peak of about 7 μg/g, which is about seven times the normal level. There are two difficulties in trying to relate the effects on the conditioned avoidance response to the restoration of brain dopamine. First, although the two strains differed in the time course of restoration, brain dopamine levels did not differ. Second, performance was restored to about half of normal levels only, while dopamine determinations indicated a rise above normal levels of more than 700 per cent. Again, it is unfortunate that dose-response data for L-DOPA were not provided.

Conditioned avoidance behavior has also been used by Rech (34) to study the reversal by *d*-amphetamine of reserpine-induced depression. Two and a half hours after the administration of 2 mg/kg of reserpine, the proportion of avoidance responses had fallen nearly to zero and remained at that level up to 72 hr postdrug [cf., Levison & Freedman (7)]. A dose of 0.5 mg/kg of *d*-amphetamine produced substantial restoration 24, 48, and 72 hr after reserpine administration.

More extensive behavioral studies on the interactions of drugs with behavior in animals depleted of amines by reserpine-type drugs have been conducted by Smith (27) and McKearney (35). Smith's pigeons were trained to peck a key in an experimental chamber and were studied on a multiple reinforcement schedule with two components, a Fixed Interval of 300 sec and a Fixed Ratio of 33. The reserpine-pretreated animals were injected with 0.1 mg/kg 16 to 18 hr before the beginning of each experimental session for 7 days prior to the drug interaction studies. *d*-Amphetamine exerted its usual effects; at moderate dose levels it increased responding during the Fixed Interval component and decreased Fixed Ratio response

rates at dose levels above 3 mg/kg. Imipramine, pipradrol, and cocaine showed similar patterns of effects. In the pigeons pretreated with reserpine, *d*-amphetamine markedly increased the rate within the Fixed Interval component. These effects appeared not only as increases at the beginning of the interval but as increases in rate toward the end, an effect not seen with *d*-amphetamine alone, which tends to depress high rates. None of the other three drugs showed this pattern of effect. The reserpine-*d*-amphetamine combination also increased response rates during the Fixed Ratio component, again, a phenomenon not observed with amphetamine alone. Such a demonstration argues against simplistic neurochemical hypotheses about the effects of reserpine and amphetamine on the adrenergic substrates of behavior.

McKearney (35) also used operant behavior techniques to examine the antagonistic effects of certain drugs to the suppression induced by reserpine and similar agents. He used tetrabenazine, in order to produce only short-term effects, and studied the countervailing effects of *d*-amphetamine, imipramine, and harmaline—a short-acting MAO inhibitor. McKearney trained different groups of rats under different procedures. One group was trained under a 1-minute Fixed Interval reinforcement schedule. Another group was trained under a Variable Interval reinforcement schedule, with punishment and nonpunishment components. Two other groups of rats were trained under a Fixed Ratio 5 schedule, with water or escape from electric shock as reinforcement. Tetrabenazine, at 2 mg/kg, reduced response rates on all of these reinforcement schedules. At 1 mg/kg, *d*-amphetamine completely antagonized the effects of tetrabenazine on all schedules, restoring response rates to control levels. Harmaline was less successful in this respect, and imipramine was not successful at all. In additional experiments with chronically administered desmethylimipramine and reserpine, these earlier results were confirmed. McKearney points out that those investigators who, in the rat, had reported that imipramine or desmethylimipramine antagonized the effects of benzoquinolizines on motor activity or on gross behavior, typically used much higher doses than those used in these operant experiments. But even with higher doses, McKearney observed that desmethylimipramine did not antagonize the rate-suppressing effects of tetrabenazine. Again, as with Smith's study, there are some interesting drug-behavior interactions with implications for future research. In combination with TBZ, amphetamine did not exert nearly so pronounced an effect on responding during the first part of the Fixed Interval as during the last part. Such a complex interaction of situational variables and drug effects again calls into question any simplistic assumptions about the relationship between brain chemistry and behavior based on gross observations.

Drug interactions with impaired catecholamine synthesis.—In their original study, Weissman & Koe (19) also measured the effects of α-MT in combination with amphetamine. In a later paper [Weissman, Koe & Tenen (36)], they dealt at length with the matter of amphetamine antagonism.

One of their criteria was the increase in activity produced by amphetamine in mice. Intraperitoneal doses of 10, 32, and 100 mg/kg α-MT significantly reduced the increased activity resulting from 5 mg/kg of amphetamine, although even the highest dose, 100 mg/kg, still was not large enough to reduce activity to baseline levels. Chlorpromazine showed a much steeper dose-response gradient, and, at 10 mg/kg, reduced activity to baseline levels; α-MMT, at a dose level of 1000 mg/kg (i.p.), did not produce a significant reduction (although it must have profoundly reduced brain norepinephrine). On a Sidman avoidance schedule, a dose of 32 mg/kg of α-MT was able to antagonize the enhancing effects of 1 mg/kg amphetamine. Weissman et al. also tried to correlate the potency of a number of compounds in inhibiting tyrosine hydroxylase with their potency in counteracting the effects of amphetamine on certain aspects of gross behavior. They found a rough correlation, but, unfortunately, the gross behavior they tried to quantify quite clearly is multidimensional. In view of the complex interactions that we pointed out earlier in the studies of Smith (*27*) and McKearney (35) between situational variables and drug effects, and the discrepancies between effects on well-controlled behavioral processes versus the general appearance of animals, a further exploration of this correlation with more advanced behavioral techniques would serve a useful function.

Moore & Rech (*37*) also studied the antagonistic effects of α-MT and amphetamine on avoidance. Rats were injected with 50 mg/kg of α-MT three times at 4-hr intervals. Four hrs after the last dose they were tested, then injected with either 100 mg/kg L-DOPA, 0.5 mg/kg *d*-amphetamine, or saline. L-DOPA and *d*-amphetamine significantly restored avoidance performance. It would have been useful to study other dose levels of L-DOPA and amphetamine and also to examine combinations of the two, since Weissman et al. (36) reported that DOPA pretreatment did not prevent or overcome the reduction by α-MT of amphetamine-induced changes in gross behavior. Hanson (38) attempted to do so. After 0.1 mg/kg of reserpine, 20 to 26 hr before, he found that avoidance responding by trained cats decreased to 40 per cent. After the combination of this dose of reserpine with 50 mg/kg of α-MT methylester HCl, it completely disappeared. Amphetamine in a dose of 2 mg/kg counteracted this effect of reserpine, but was unable to counteract the combined actions of reserpine and α-MT except in animals treated with small doses of L-DOPA (12.5 or 25 mg/kg). These data are presented rather obscurely and tersely, and it is not possible to determine the time course of the effect with any precision. Experiments by Stolk & Rech (*29*) and others suggest that this is an important parameter of drug interactions, and perhaps one source for the conflict with Weissman et al. Another series of interaction studies aimed at the mechanisms by which α-MT depresses behavior were reported by Moore & Rech (*39*) in which they directed their attention to MAO inhibitors. As they point out, these depressant effects on behavior could result from the depletion of brain catecholamine stores, from a direct depressant action of α-MT,

or from some yet undetermined action of the drug. A cumulative dose of 150 mg/kg of α-MT caused a fall in avoidance responding which reached its lowest point 4 hr after the last of the spaced injections. The MAO inhibitors—β-phenylisopropylhydrazine HCl (JB516) and tranylcypromine—reduced the fall in avoidance and rotarod performance induced by α-MT, and restored norepinephrine levels. Dopamine remained below the normal range. Since behavior was not fully restored, these data again suggest a fundamental role for dopamine. Weissman & Koe (40) studied several agents in combination with MAO inhibitors to contrast α-MT and *m*-iodo-L-α-methyl-tyrosine versus the amine releasers α-MMT and tetrabenazine. In grouped mice pretreated with 100 mg/kg of the MAO inhibitor nialamide 18 hr before drug administration, α-MMT and tetrabenazine profoundly enhanced activity. The two tyrosine hydroxylase inhibitors showed no such effect. Confirming Moore & Rech, MAO pretreatment also enhanced norepinephrine concentration in brain. But the depression in activity caused by the two tyrosine hydroxylase inhibitors was not restored by MAO treatment. The discrepancies between these two groups could lie in any one of a number of variables. Multiple versus single doses could be one. The differences in the behavioral assay may be another. The mode of MAO pretreatment apparently is not one, since the time interval was approximately the same and the increased brain levels of norepinephrine produced by the MAO inhibitors were approximately equal.

Rech, Carr & Moore (41) reasoned, like Hanson (38), that if the depression of performance demonstrated in rats after α-MT were due to a depletion of catecholamines, the prior administration of reserpine, which has the same effect, should enhance the action of α-MT. They confirmed this prediction. Their data indicate that the effects on depletion were additive, and that a threshold had to be reached to produce behavioral effects. Further behavioral evidence for the additive effects of these two compounds comes from a second study in the same paper, in which 50 mg/kg of α-MT was repeatedly given to animals originally injected with a large dose of reserpine (2 mg/kg). Even after 15 days there was still a significant fall in avoidance performance after α-MT. Rotarod performance recovered more rapidly, and spontaneous locomotor activity even more quickly. By 14 days, norepinephrine still had not recovered to more than half of control values, although dopamine levels recovered to a greater extent, perhaps three-quarters of normal.

Given what appear to be the large surplus stores of neurohumors in the brain, it seems reasonable that a depression in performance will occur only when a substantial proportion of the total stores has been eliminated. (A parallel sort of effect is seen with the behavioral effects of anticholinesterases. Depletion of acetylcholine levels to less than half of normal typically is necessary if any behavioral effects are to be observed [cf., Weiss & Heller (42)].) Necessary controls for the hypothesis that reserpine and α-MT act synergistically would be dose levels of these drugs that individu-

ally deplete catecholamine levels to the values produced by the combination. Earlier data by this group of authors indicate that if this is done, behavioral impairment is comparable (e.g., 21). The main difference observed in the present study is that the effects produced by α-MT occurred much more rapidly than is typically the case.

Sulser et al. (43) studied the actions of amphetamine and desmethylimipramine on spontaneous locomotor activity in rats after the reduction of brain norepinephrine by α-MT or by α-MMT. A rather large dose of α-MMT (500 mg/kg) 6 hr before did not alter the increased activity produced by 3 mg/kg—again, a rather large dose—of *d*-amphetamine. Pretreatment with 50 mg/kg of α-MT 2.5 hr beforehand blocked the action of *d*-amphetamine. In contrast, the hyperactivity evoked by combination of desmethylimipramine and tetrabenazine was not modified by α-MT but was reduced by α-MMT. At these dose levels, α-MT produced a maximum depletion of 50 per cent of brain norepinephrine 4 hr after administration, and α-MMT a maximal depletion of 80 per cent. This is a rather crucial difference, looking back at the paper by Rech et al. (41). It would have been more useful for the authors to present dose-response data for the two amine depletors as both antagonists and sole agents.

The work of Sulser et al. (43), who used a dose of 10 mg/kg of desmethylimipramine in rats, exemplifies a chronic problem. Kornetsky (44), in a study of operant behavior, also with rats, found that small doses of both desmethylimipramine (1 mg/kg and 2 mg/kg) and imipramine (2 mg/kg and 4 mg/kg) increased the rate of responding on a reinforcement schedule (DRL) which differentially reinforced long intervals between responses (15 sec or more). Doses of 4 mg/kg and more of desmethylimipramine produced severe reductions in rate, an obvious toxic effect, and at a dose level less than half of that employed by Sulser et al. On Sidman avoidance, Kornetsky found that doses of 2 mg/kg or more of desmethylimipramine depressed avoidance rate. Bernstein & Latimer (45), studying Sidman avoidance in rats, reported that a dose of 10 mg/kg desmethylimipramine (used by Sulser et al.) plus 2 mg/kg of amphetamine induced ". . . extreme excitation and toxic side effects; therefore, the dose was diminished to 2.5 mg/kg . . ." The comparison of these doses with those in the paper by Sulser et al. illustrates the problem. Neuropharmacologists frequently use drug dose levels considerably higher than those at which significant behavioral effects are obtained. Perhaps these are necessary to produce reliable biochemical changes, but they disturb scientists interested in pursuing correlations with behavior, especially those who try to find some specificity in the behavioral effects. Javoy et al. (46), for example, measured norepinephrine turnover in brain, by their intracisternal method, after 5 mg/kg of *d*-amphetamine and called this "a small dose." A dose of 5 mg/kg of *d*-amphetamine probably eliminates most operant behavior, however. The experiment was aimed at another problem, we grant, but it helps achieve the ultimate goal of neuropharmacology—namely, explanations of behavior—for neuro-

pharmacologists to use dose levels of drugs small enough to make behavioral sense.

Monoamines and operant behavior.—The experiments of Marley & Morse (47) on young chickens are relevant from the standpoint of the role postulated for the α-methylated forms of catecholamines; it has been suggested that α-MT may owe its action, in part, to the fact that its decarboxylation products, e.g., α-methyl-norepinephrine, displace norepinephrine from its storage sites, a role certainly fulfilled by α-MMT. The young chicken is particularly useful for studies of this kind because it seems to possess no effective blood-brain barrier, and moreover, as Marley & Morse (48) demonstrated in an earlier paper, chicks can easily be trained on complex intermittent reinforcement schedules. In the present study Marley & Morse studied α-methyl-norepinephrine (nordefrin), α-methyl-phenethylamine (*d*-amphetamine), and α-methyltryptamine. The young chickens were tested between 8 and 19 days of age, on multiple reinforcement schedules containing Fixed Interval and Fixed Ratio components. Pecking was reduced in the Fixed Interval component, but not the Fixed Ratio component, by 2.5 and 5 μM/kg (i.p.) of α-methyl-norepinephrine. These effects were counteracted by the injection of phenoxybenzamine 3 days previously. Pecking was, therefore, differentially responsive under the two different schedules. Fixed Interval response rates increased after *d*-amphetamine, while rates on Fixed Ratio showed decreases. Thus, the administration of amphetamine to an organism with an ineffective blood-brain barrier is no different from its effects in organisms with a fully developed barrier.

In one of the few experiments dealing with the effects of monoamines on operant behavior, Dews (49) compared L-norepinephrine, isoproterenol, normetanephrine, mescaline, and metanephrine on Fixed Interval responding in pigeons. Except for normetanephrine, these drugs, as dose levels were raised, caused a reduction in response similar to that produced by L-norepinephrine in earlier studies from Dews's laboratory.

The Search for Neurochemical Correlates

It is obvious that we comprehend very little about the role of adrenergic systems in behavior, and we hope the present review has helped define some of the problems. There are still others. For example, many studies employ drug interactions to test hypotheses about the relationship between behavior and underlying biochemical states. Although these studies may have a rational basis, one must be cautious about interpretations; the fact that desmethylimipramine and tetrabenazine may so interact as to increase the output of spontaneous motor activity should not lead to immediate assumptions about the role of adrenergic mechanisms in this interaction. Amphetamine, for example, interacts with a wide variety of drugs. Rushton & Steinberg (50) recently showed that the activity of rats in an unfamiliar environment is greatly enhanced by a mixture of *d*-amphetamine and chlordiazepoxide. Similar results have been reported by this group and others for amphet-

amine-barbiturate combinations, and, as they point out, amphetamine interacts in a variety of ways with different centrally-acting drugs, depending on the doses and the kinds of behavior studied. These include atropine, ethanol, MAO inhibitors, reserpine, etc. Perhaps it is true that a common biochemical mode of action underlies all of these synergistic interactions. It is far from certain, however, and until more detailed and specific information is available, interpretations of behavioral changes produced by drug combinations in terms of biochemical mechanisms is still highly speculative. Another caution has been cited by Karczmar & Scudder (51) in a review of their work on brain catecholamine levels and behavior in mice. Different strains and genera of mice differ widely in parameters such as spontaneous motor activity. They also differ widely in brain levels of biogenic amines. The correlation between brain amines and level of spontaneous activity is virtually zero.

A most salient difficulty in interpreting the data on brain amines and behavior lies in the constricted range of behavioral situations employed. So far, for example, the most advanced technique employed in studies of the behavioral effects of α-MT has been avoidance conditioning. These situations certainly have their place as behavioral assays, but we must make better use of the power and subtlety of operant conditioning techniques. This is simply to say that we must have the best possible understanding and control of the conditions which lead the behavior to occur. To quote Dews (49), "To express a preference for working with conditioned behavior is thus merely to express a preference for working with well-controlled situations rather than vague ones" (page 145). The central role that must be played by an experimental analysis of behavior is only underlined by the data currently available on α-MT. So far, they mostly show that impairing catecholamine synthesis depresses behavior. If this is the only behavioral defect produced by interference with such a key neurochemical mechanism, then attempts to relate neurochemical mechanisms at this level to the subtle details of behavior disorders are destined for failure. It may be, of course, that specific neurohumoral systems are deployed within the brain in a variety of roles assigned by independent evolutionary processes, and that correlating brain chemistry with complex behavior will be impossible. But the first order of business is to see whether or not the first step can be taken. Several decades of development in the experimental analysis of behavior should not be permitted to languish while we refine and embellish our chemical procedures. A microanalysis of brain chemistry must be accompanied at every step of the way by a corresponding microanalysis of behavior.

Behavioral Effects of Pemoline with Magnesium Hydroxide

We are in the midst of a search for new drugs that promise to speed learning, increase the ultimate amount learned and remembered, or enhance the quality of performance. Its main impetus is the growing interest in the biochemistry of behavior, and a significant fraction of the work stems di-

rectly from speculation about the role of RNA in learning and memory. We shall devote this section to a single agent, pemoline with magnesium hydroxide (PMH), a drug that attracted interest because of its purported relation to RNA.

Pemoline was synthesized in Europe and reported to have mild performance-enhancement properties in human subjects [e.g., Dureman (52)]. All of the work to be reported here employed an equimolar combination of pemoline (which is 2-imino-5-phenyl-4-oxozolidinone) and magnesium hydroxide, a combination asserted to be more potent than pemoline alone [Plotnikoff & Meekma (53)]. Interest in the behavioral effects of PMH was stimulated by two papers from Abbott Laboratories published together in *Science,* in February, 1966, by Glasky & Simon (54) and by Plotnikoff (55). In the first, Glasky & Simon reported that PMH stimulated RNA polymerase in rat brain, both *in vivo* and *in vitro.* [For reviews of the possible role of RNA in memory retention, see Booth (56) and Gaito (57).] Reasoning that such an effect would enhance learning and memory, they predicted such an enhancement by PMH. Plotnikoff, in the second paper, confirmed this prediction by reporting that PMH "enhances the acquisition and retention of a conditioned avoidance response in rat" (page 703). Interest in the drug was further heightened because a prominent psychiatrist, Cameron (58), reported that PMH improved memory in intellectually-deteriorated older patients. [Cameron et al. (59) had previously reported that yeast RNA produced a similar improvement—an effect that Nodine et al. (60) could not confirm.] Since at least mild deficiencies in memory are universal afflictions, especially among professors, and since the drug appeared to have a theoretical rationale for its apparent success in assuaging these afflictions, additional investigators began work almost immediately.

It was soon clear that the original claims for the drug had to be greatly modified. Even its biochemical rationale evaporated when both Morris, Aghajanian & Bloom (61), and then, from Abbott itself, Stein & Yellin (62), failed to confirm the original report of Glasky & Simon. We shall here first examine studies of human behavior and then studies on other animals. We devote so much space to this drug because it can be considered prototypical of many agents that have appeared and will appear as the biochemical revolution continues to promote the search for drugs that affect learning and memory.

Studies of Human Behavior

Acquisition and retention.—Cameron's clinical success was outlined in an oral report and has not been published (58). Talland, Hagen & James (63) attempted to duplicate his success with amnesic patients, using various tests of acquisition and recall in double-blind studies of patients with Korsakoff syndrome. For instance, they read the patient a newspaper report of an unusual incident, then determined how much of it he could recall immediately and on the following morning. The authors used very small

groups, usually four subjects, single doses of 25 or 50 mg PMH, and a 3-week course of 25 mg per day. They found no marked changes in performance. In a final study they used ten patients, each as his own control, and looked at the effect of a 3-week course of either 50 mg per day PMH or placebo. The drug regimen had no discernible effect upon several measures of learning and recall. These studies can be faulted on the basis of the small numbers of patients studied, but they were apparently done with care, and the absence of even the slightest trend toward a drug effect seems to justify the negative conclusion to which the investigators were led: "In the light of our observations, we must, therefore, regretfully conclude that the day that offers a pharmacological remedy for severe memory disorders has not dawned yet, and it is unlikely that Cylert [PMH] will prove to be the much-hoped-for cure" (page 429).

PMH apparently does not affect learning in normal human subjects—at least not the several examples that have so far been studied. Burns and co-workers (64) gave doses of 6.25 to 25 mg 2.5 to 3 hr before measuring the rate of acquisition of a complex discrimination. The subject faced a row of eight small lights, each of which signaled that one of eight response keys should be pressed. A correct response was followed immediately by the next trial, while an incorrect response also produced a brief tone. During an experimental session, subjects gradually learned to respond to the cue lights with appropriate key presses. The rate at which the subject acquired this skill was not affected by the PMH. (A group that received 15 mg of *d*-amphetamine—a rather substantial dose—was included for comparison; its learning rate also did not differ from that of the placebo group at an acceptable level of significance.) The groups consisted of only six subjects each, but since the trend of the data indicated a decrease in learning rate after treatment, it is difficult to argue that the addition of more subjects would have produced evidence for a positive effect of PMH.

The conclusion that PMH has no beneficial effect upon human learning is buttressed by two other reports—one by Smith (65) and one by Talland & McGuire (66). Smith found no changes in the rate at which his young adult subjects learned to recite lists of short words, and to maneuver a stylus along a curved track while watching the track only in a mirror. He used three groups of 12 men, matched on a general intelligence test, and gave his drug groups either 25 or 37.5 mg PMH 3 hr before the test. Smith also made 24-hr post drug retention tests that were completely negative. In addition, he included a series of tests of short-term memory, classical conditioning, steadiness, and reaction time, all of which yielded negative results. Moreover, subjects receiving the higher dose of the drug performed significantly worse throughout the task than members of the other two groups. This point is important, since it makes it unlikely that a higher dose would have produced improvement.

Talland & McGuire used a display of 127 pushbuttons laid out in a homogeneous field. Thirty of these made up a path through the field. Only

the start of this path was labeled, and the subject's task was to find the path by trying buttons. A dose of 25 mg PMH, given orally 90 min previously, did not change the number of trials needed to meet the criterion of two consecutive faultless performances. Talland & McGuire also found no effect on two tests of recall.

Signal detection.—The work described above leads us to believe that PMH has no important effect on either acquisition or retention in humans. However, the drug may affect performance, particularly on tasks demanding sustained alertness. Talland (67) studied adults who monitored a display of numbers in order to detect the presence of a particular signal. Displays changed every 1.25 sec and remained in view for only 0.5 sec. About one of 12 was a signal consisting of a display equal in number to the display it replaced. Thus, signals occurred about once every 15 sec. The subjects worked on this task for 24 min, then for another 24 min on a more complex variant of the same task with the signal now consisting of a display of digits that matched in number the display two steps back. The task was presented 125 min after the subjects took an oral dose of 25 mg PMH (or a placebo). Five min before the subjects started the task they took another pill, again either a placebo or a 25 mg dose of PMH. However, if the subject had received PMH for his first dose, he now received placebo. Thus, comparisons could be made between the effects of PMH given either 5 min or 2 hr before the start of the monitoring task. The drug appeared to be more active when tests started 5 min after administration than when they started 2 hr later, a result that is difficult to reconcile with the data of Gelfand et al. (68) cited below. As the author himself points out, the stimulus complexity comparison was confounded with time after drug, since the more complex task always came second.

The type of task used by Talland (67), in which the subject responds to occasional signals, is usually quite sensitive to amphetamine [e.g., Talland & Quarton (69)], and it is unfortunate that the investigator did not include amphetamine as a drug control [cf., Weiss & Laties (70); Laties & Weiss (71)]. PMH does resemble amphetamine on another task that has been used to study both drugs. Holliday & Devery (72) showed that amphetamine could improve performance on simple arithmetic problems, over long periods of time, after the subjects had been deprived of one night's sleep. Gelfand et al. (68) showed that PMH would do the same. They used oral doses of 25, 50, and 100 mg PMH, as well as doses of 15 mg *d*-amphetamine and 20 mg methylphenidate, and watched the development of the drug effects over a 4-hr period. The 100 mg dose produced a statistically reliable increase over the performance level of the control group. The other two drugs also enhanced performance, to about the same extent.

Studies of Animal Behavior

Plotnikoff's first experiment (55) appeared to demonstrate that PMH increased the rapidity with which rats learned to avoid an electric shock to

the feet by jumping out of a box onto a small platform. The rat was placed in the box and allowed to remain undisturbed for 15 sec. Then a buzzer came on for 15 sec. During the last 5 sec of the buzzer, the metal grid floor was electrified. Apparently in an effort to simulate the type of organism used in the human studies, only "slow learners" were used—rats that, in a series of three preliminary trials, left the box only after the shock came on. Plotnikoff found that these rats required a mean time of about 26 sec to jump out of the box on the first of the ten acquisition trials started 30 min after drug (or vehicle) was administered orally; i.e., they usually waited until the shock began. Improvement came slowly for the control subjects; they reached a mean of 16.7 sec on the tenth trial. At that time, rats that had received, for example, 10 mg/kg PMH, were leaving the box within an average of 4.3 sec, not even waiting for the start of the buzzer. Doses of 5 and 20 mg/kg were also effective. On the following day the rats were each given ten more trials without drug. Neither buzzer nor shock were present, the rat merely being placed in the box for a maximum of 30 sec. The rats that had been brought to a high level of performance by the PMH did not change. For example, the 10 mg/kg group started their second batch of trials with a time of 5.7 sec and ended it with a time of 5.7 sec. (The 5 mg/kg and 20 mg/kg groups yielded similar results.) The control group started with 15.3 sec and ended with 23.0 sec. The drugged animals, therefore, did not extinguish. Plotnikoff also included some representative results (for single doses) of experiments with methamphetamine (0.1 to 2.0 mg/kg) and methylphenidate (2.5 to 20.0 mg/kg). These two drugs affected neither acquisition nor subsequent performance of an avoidance response, a surprising finding in view of the numerous studies that have reported improved avoidance learning and performance of various types with amphetamine and many other locomotor stimulants, e.g., Hearst & Whalen (73), Rech (74), Stone (75), Verhave (76).

Plotnikoff's paper stimulated a lot of controversy. The first emendation came in a letter to *Science* from Bowman (77). Plotnikoff considered the trials given 24 hr after original learning as a measure of retention or "memory." Bowman pointed out that such a measure is valid only if both drug and control groups are originally brought to equal levels of performance. This was not done; drugged animals escaped from the box much more rapidly than control animals. Thus, on the retention test, animals drugged during learning were at a distinct advantage. Next, Frey & Polidora (78) reported an experiment in which these levels were held constant. Instead of receiving a fixed number of training trials, their rats were trained until they made three consecutive avoidance responses, each occurring less than 10 sec after being placed in the box. The use of this criterion wiped out the differences in retention reported by Plotnikoff.

Frey & Polidora also offered alternative explanations for Plotnikoff's learning data. They pointed out that the "slow learners" used by Plotnikoff were most probably rats that learned to minimize the shock; maintaining

contact with, rather than jumping around on, the electrified grid minimizes circuit "makes" and "breaks" and reduces current density. Frey & Polidora demonstrated that PMH helped rats that had learned to "freeze" more than those that had not. Unfortunately, these authors apparently used a different criterion than Plotnikoff in choosing their "slow learners," namely, "failure to leave the apparatus in a 3-trial test session." These rats thus were even more resistant to shock than those used by Plotnikoff, which usually left the box when the shock came on. Moreover, the method the authors used to manipulate freezing admits a second interpretation of the data. They varied shock level, and pointed out the possibility that the drug increased reactivity to the shock itself or to the stimuli paired with the different shock intensities. The relevance of this explanation is shown by the work of Beach & Kimble (79) and by the fact that the ability of amphetamine and other locomotor stimulants to improve avoidance performance seems to depend in part on their ability to break up freezing; this effect, in turn, may depend upon the drug increasing motor activity [Doty & Doty (80), Hearst & Whalen (73), Krieckhaus (81), Krieckhaus, Miller & Zimmerman (82), Pearl, Aceto & Fitzgerald (83), Rech (74), Stone (75, 84, 85), Verhave (76)].

Beach & Kimble (79) examined the effect of PMH on the activity of rats before, during, and after a 15-sec presentation of a buzzer. Originally, both drugged rats and controls reacted to the buzzer with about equal increases in activity. But after repeated presentations, the control rats reacted much less than the PMH-treated animals. Such a failure to habituate probably is related to the increase in spontaneous motor activity shown to occur by Boitano & Boitano (86).

Beach & Kimble also repeated Plotnikoff's experiment and did not find the same striking difference between drugged and undrugged rats. On the first test trial, the three drug groups [5, 10, and 20 mg/kg (i.p.)] left the box in mean times of 14.0, 15.1, and 11.7 sec, respectively, while the control group averaged 17.8 sec. On the tenth trial, the means were 8.5, 3.2, 11.8 and, for the controls, 13.7 sec. These data are for "slow learners." Again, the criterion was changed; while Plotnikoff defined "slow learners" as animals that "escaped only to applied shock during the last 5 seconds of the 30-second sequence," Beach & Kimble defined their slow learners as "subjects showing at most one avoidance during the three trials, jumping onto the escape platform only after the grid floor was electrified." These differing criteria may lie behind the differing initial performances: Beach & Kimble's "slow learners" left the box on the average in about 15 sec, while Plotnikoff's left in about 26 sec. Beach & Kimble also pointed out that if performance was gauged by the percentage of trials on which shock was avoided, rather than latency, the difference between drug and control groups washed out completely: 19 of the 24 "slow learners" successfully avoided the shock on the first of the ten test trials; 23 of the 24 did so on the last of the ten trials. However, the rats in the drug groups tended to

leave the box before the sound of the buzzer that preceded the shock. This fact fits well with the idea that responsivity to stimulation may be the controlling factor in this situation.

One other possible source of the latency differences between Plotnikoff (55) and Beach & Kimble (79) may lie in the rate at which the trials were executed; Beach & Kimble spaced their trials 10 min apart. Thus, the data were collected over a 100-min period that started 30 min after drug administration. The time-effect curve of the drug is thus confounded with the acquisition curve. To what extent this influenced Plotnikoff's experiment cannot be determined, for the temporal spacing of trials was not mentioned. [The same type of criticism, concerning the time-effect curve of drug action, can be made of another experiment by Plotnikoff (87) on the effects of electro-convulsive shock on memory.]

The critics of Plotnikoff's original retention data pointed out that final performance differed for the control and various PMH groups [Bowman (77), Frey & Polidora (78)], and that the drug may have affected some factor involved in the original situation, such as responsivity or motor activity, that was irrelevant to hypotheses concerned with learning and memory [Beach & Kimble (79), Boitano & Boitano (86)]. Plotnikoff (88) answered his critics with an experiment that apparently demonstrated that PMH had the ability to enhance retention of an avoidance response even when given after, rather than before, the original learning, presumably by modifying a consolidation process [cf., McGaugh (89)]. He used "fast learners" in this experiment—rats that had learned to jump out of the box "within the first 15 secs. by the second and third" preliminary trials—and gave them the PMH (5 to 20 mg/kg orally) within 2 min of the last of ten conditioning trials. On the tenth trial the six rats in the control group averaged 3.3 sec in leaving the box. When they were retested one week later (with no buzzer or shock present), they averaged 19.6 sec, about the same as at the start of the ten original trials. Six rats in one of the PMH groups averaged 2.6 sec on their tenth acquisition trial; a week later they averaged 3.3 sec. No comparable data for other drugs were presented. This type of facilitation by a post-trial treatment has been reported for several other drugs, so the effect is not unique to PMH. Furthermore, the procedure has its own pitfalls and the reader is referred elsewhere for critical reviews of this area [Gollub & Brady (3), McGaugh & Petrinovich (90]. We wish only to add one more possible explanation to those that have been put forward. Rats avoid a trap that has been baited previously with food that made them sick; and sickness-producing X-rays that have been paired with saccharin lead to saccharin aversion or avoidance of the place where the symptoms occur [Kimeldorf & Hunt (91)]. Exposure to a box that is paired with an injection of PMH (or any drug, for that matter, that may produce peculiar or aversive internal stimuli) may lead rats to jump out of that box in the future more rapidly than untreated rats.

Several studies have examined the effect of PMH in other avoidance

paradigms. Both Filby, Szara & Salzman (92) and Kulkarni (93) studied free operant lever-pressing avoidance situations and found that PMH increased the rate at which rats learned to avoid shock by pressing a lever. Filby, Szara & Salzman also found that *d*-amphetamine [3 mg/kg (i.p., 30 min before the session] did about as well as 40 mg/kg PMH (i.p.), the only dose used. Kulkarni found a reliable increase with an intraperitoneal dose of 5 mg/kg PMH, and Soumereu-Mourat & Cardo (94) found that they could hasten the acquisition of an avoidance response more closely related to that used by Plotnikoff with an oral dose of 20 mg/kg PMH. Thompson & Knudson (95) also reported positive results with both 1- and 2-way avoidance shuttlebox tasks; in the first instance the rat was picked up and replaced in the avoidance chamber each time it moved out, while in the second instance the rat started each trial in the box it had escaped to on the previous trial. Thompson & Knudson used 20 mg/kg PMH (i.p.). Powell, Martin & Kamano (96) used the same dose with a 2-way shuttlebox task and also reported more rapid learning of conditioned avoidance. Cyert, Moyer & Chapman (97) could not detect the effects of an oral dose of 10 mg/kg on 1-way shuttlebox avoidance.

Positively reinforced behavior.—Because Plotnikoff's *Science* paper (55) was based on a conditioned avoidance situation, most subsequent investigations used a similar situation. One of the few studies of positively-reinforced behavior was conducted by Filby & Frank (98), who examined the rate at which rats came under control of the contingencies of reinforcement on a differential reinforcement of low response rates (DRL) schedule, a schedule on which animals must pause at least a specified length of time (here, 20 sec) between responses on a lever before the second response of a pair will be reinforced. This reinforcement schedule has the great virtue, in this context, of not simply rewarding increased activity. The investigators argued that drug-induced improvement in central associative mechanisms should lead the animals to show more rapid adaptation to the schedule. However, groups of animals treated with 5, 10 or 20 mg/kg PMH (i.p.), 30 min before each of 15 1-hr sessions, did not improve in performance more than control animals. In fact, rats receiving 10 mg/kg or more PMH responded more frequently, and therefore received fewer reinforcements than controls. This effect is similar to that found in the rat after amphetamine [Sidman (99), Kelleher et al. (100), Laties et al. (101], and meprobamate [Kelleher et al. (100)], among other drugs.

Grosser, Sprinthall & Sirois (102) also examined the acquisition of positively reinforced behavior. They reinforced every lever response made by experimentally naive rats and found that those given 20 mg/kg PMH (p.o.) 20 min beforehand made about the same number of responses during a 1-hr session as rats given only the vehicle. During a 1-hr extinction session a week later, rats given 20 mg/kg PMH before the session invariably (eight of eight) made more responses during this period than they had a week earlier, while control rats usually (six of eight) made fewer. This

could be interpreted as "memory" enhancement—subjects do more of what they have been taught to do if given PMH first. Or such an effect could, we suppose, be considered "learning" impairment, since the rats were not adjusting to their changed circumstances as rapidly as they did under control conditions. Seeming contradictions such as these illustrate the hazards involved in using such loose general terms rather than describing the behavior itself. Another study of response rate after PMH was reported by Gurewitz et al. (103). They showed that 20 mg/kg PMH (i.p.) led water-deprived rats to make more responses when each response (a lick from an electrified water dish) was punished with shock. These three studies suggest, again, that any effects PMH may have on learning and performance are most probably mediated by processes far removed from the ones, such as memory storage, often invoked to explain the empirical findings.

General comments.—PMH, like all other drugs, has multiple effects. It is an inescapable fact of life that teasing out and describing its behavioral properties will be a lengthy and laborious task. But the most striking characteristic of the pemoline literature is that not a single intensive study of its behavioral properties has yet appeared. Also, since few of the studies cited here report on comparisons with other drugs, one cannot as yet conclude much about the uniqueness of PMH's effects.

With very few exceptions, the literature on PMH is confined to journals specializing in short reports and rapid publication. We seem to have here a clearcut case of the medium used by the investigator helping to determine the message communicated to the reader. And the price paid by the reader for brevity and speed has been high. For instance, since the equipment used in most of these studies is not standard, and since procedural detail in this field is frequently of crucial importance, more than casual description is necessary if replication—or even interpretation—is to be possible. Such description is simply not possible if the space limitations are too great. The original *Science* article that started much of the work on PMH failed to include the size of the avoidance apparatus, the parameters of either the electric shock or the buzzer used as stimuli, or the temporal spacing of the trials, among other vital details.

Many of the studies cited above reported on only a single dose level of PMH, usually chosen on the basis of work by other investigators. These studies also frequently used rats from a different source than that of their reference study or even, in some cases, rats of a different strain. The potential hazard in such a switch, when not accompanied by a dose-response curve, has been outlined for other drug, strychnine, by Petrinovich (104). He showed that a dose of 0.125 mg/kg yielded a facilitory effect on maze learning in Long-Evans rats while doses above 0.25 mg/kg did not do so. McGaugh & Petrinovich (105) had previously shown that a dose of 1.0 mg/kg was effective in the Tryon strain. Other investigators had chosen to use the latter dose, had switched strains from Tryon to Long-Evans, and consequently, it now appears, missed the effect they were looking for.

There is still another factor that may have determined, to an unknown extent, the results of some of these experiments. Only Frey & Polidora (78), among those reporting latencies in the "jump-out box" avoidance task, stated that they kept the person who collected the data ignorant of whether or not the rats had been drugged. This precaution may have been especially important because none of these experiments gave details on how the time measurements were made. Presumably, a clock was started when the rat was placed on the grid floor and stopped when the rat reached the platform outside the box. None of the reports that used "jump-out" boxes described whether this occurred automatically or whether a person made the measurement. In the latter case, "blind" measurements would be essential.

Behavioral Parameters of Drug Action

Kelleher & Morse (106) have lucidly examined the present status of research aimed at key behavioral parameters of drug action. They emphasize the major problem areas that seem most likely to provide us with general principles of drug-behavior interaction. We can do little more here than refer to one of these. The previous sections of this review clearly demonstrate how the lack of such general principles hampers the search for correlations with neurochemistry.

The rate-dependency hypothesis.—One parameter that seems to be of prime importance in determining response to drugs in a free operant situation is the baseline rate of response [Dews (107)]. For instance, amphetamine may tend to lower high rates of response while increasing low rates. Other drugs seem to have their own complex relationships to the baseline rate. Many recent experiments have been devoted to such relationships [e.g., Clark & Steele (108), Dews (109), Gibson (110), Hearst (111), McKearney (35), McMillan (112), McMillan & Morse (113), Morse (114), Ray & Bivens (115), Smith (27), Steinman (116), Vaillant (117], and one enduring problem is that of manipulating rate while keeping constant other potentially important variables, such as reinforcement density and schedule of reinforcement. Gibson (110), for instance, compared behavior under control of a Fixed Ratio schedule, during which each 50th response was reinforced, with behavior under the control of a DRL schedule, during which only the first response made at least 15 sec after the immediately prior response was reinforced. Pigeons worked more than ten times as rapidly on the former as on the latter schedule. Doses of *d*-amphetamine that decreased the high Fixed Ratio rate increased the low DRL rate. Although rates differed, so did schedule, making a rate interpretation ambiguous.

Steinman (116) worked within one schedule of reinforcement by putting together three Fixed Interval components in a chained schedule. Only a response at the end of the third interval produced the delivery of grain. The first response made after the end of the other two intervals merely changed the key light color to that appropriate to the subsequent interval. This

schedule typically leads to a low response rate during the initial interval, a higher one in the intermediate interval, and the highest rate of all in the interval that is closest to the grain reinforcement. Appropriate doses of *d*-amphetamine increased the response rate when it was low and decreased it when it was high. The experimental situation is not completely unambiguous, however, for behavior during the three intervals leads to conditioned reinforcement of different strengths, and drugs can change the conditioned reinforcing properties of stimuli controlling performance [cf., Thomas (118)].

A third way to examine dependencies on the baseline rate is to measure it within a schedule such as the Fixed Interval [Dews (119), McMillan (112), Smith (27)]. The experiment by McMillan can be used to illustrate this technique. McMillan used pigeons that worked on a multiple schedule with Fixed Interval of 5 or 15 min and Fixed Ratio 30 components. He made the usual comparisons between Fixed Interval and Fixed Ratio rates, but he also assessed the changes within successive minutes of the interval component. Response rate was, of course, low near the beginning of the interval, intermediate near the middle, and high near the end. The same rate dependency occurred for amphetamine, considering these rates, as with rates generated by different schedules. Again, interpretation of this result, standing alone, would not be completely unambiguous, since position within an interval may be associated with factors other than rate. However, the similarity of findings generated by many different techniques is heartening and argues strongly for the basic strength of the rate-dependency hypothesis.

Future work should probably aim at devising manipulations which can maintain constancy in other potentially important parameters while varying rate. Much work also remains to be done in elucidating the ways in which baseline rate interacts with other factors. For example, many drugs affect how well discriminative stimuli maintain control of behavior [Blough (120), Dews (121)]; the importance of the baseline rate may well vary with the type of this stimulus control [Dews (121), Gatti (122), Laties & Weiss (123, 124)].

Behavioral Toxicology

For the first time, the chapter on behavioral pharmacology in this *Annual Review* includes specific references to behavioral toxicology. We do this in order to recognize explicitly that such a discipline is coming into existence. Many studies of the behavioral effects of drugs can be conceived of as attempts to determine selective toxicity in the context of a therapeutic aim. Behavioral toxicology is the study of this selective toxicity as a direct aim. The increasing prominence of both academic and industrial toxicology [Michaelson & Hodge (125)], the cries of society for help in solving problems of environmental pollution [cf., President's Science Advisory Committee (126)] and the consequent pressures for the expansion of toxi-

cology [Brodie, Cosmides & Rall (127)] mean that the role of toxicology and, within it, the role of behavioral toxicology, is certain to widen.

European toxicologists seem to have been more receptive to, and more aware than their American counterparts, of the contributions that behavioral methods can make. There are active behavioral laboratories in many countries, with an especially intense interest in behavior in the Soviet Union [Medved, Spynu & Kagan (128)]. As the United States Toxicology Delegation to the U.S.S.R. reported [Magnuson et al. (129)], "Conditioned reflex responses are the prime tools of investigators in the toxicology and pharmacology laboratories" (page 19). At Zurich, Grandjean & Bättig are actively pursuing a program exemplified by their work on trichlorethylene, the widely used industrial solvent (130). American toxicologists have by no means been inactive, however. Goldberg, Johnson & Knaak (131), for example, have investigated the interactions of an anticholinesterase pesticide with several psychopharmacological agents on avoidance behavior. Bullock et al. (132) recently reported a maze study on tetraethyl lead. Reynolds & Back (133), in a pilot study, tried to study the effects of a hydrazine on primate performance.

Both abroad and in America, however, most of the experiments still seek to demonstrate rather gross, generalized toxic effects. There is a trend, however, to adopt the methodology proven so valuable in behavioral pharmacology. We have space for only a few examples. Armstrong et al. (134) investigated the effects of mercury vapor on the behavior of pigeons trained on a multiple schedule of reinforcement and found it possible to produce reversible changes in the behavioral baseline before they could detect any gross changes or overt pathology. Mercury possesses a unique history as an industrial hazard and CNS poison, and further research with modern behavioral techniques should help us understand why. Hanson, Witoslawski & Campbell (135) examined the effects of pheniprazine, a MAO inhibitor, on red-green color blindness in pigeons. The drug had previously been shown to cause this visual type of selective toxicity in humans. The investigators trained their birds to peck a key when it was illuminated with light of either 570 or 610, but not 550, 590, or 630nm. Chronic dosing (never given just before an experimental session) disrupted the discrimination in four of the six birds at doses that did not abolish responding. Withdrawal of the drug led to recovery of the behavioral baseline.

Although the problems of air pollution are stirring up a lot of publicity and governmental attention, remarkably little has been published on how any air contaminant affects behavior. One exception is the recent study by Beard & Wertheim (136) of the effects of carbon monoxide upon time discrimination in humans. They managed to detect the effects of 50 ppm with a 90-min exposure to the gas. They also could detect the effects of low concentrations of CO on the performance of rats working on a spaced-responding reinforcement schedule. The concentration of CO necessary to produce a given change in performance was a function of the pause between re-

sponses demanded by the schedule. With a 30 sec pause required, about 10 min of exposure to 100 ppm was enough to decrease response rate more than two standard deviations below that of the control period. With a 10 sec pause required, about 40 min of exposure was necessary to produce the same decrement in performance. This type of parametric variation is just as essential to behavioral toxicology as it is to behavioral pharmacology [Boren (137)]. In fact, the emphasis on the unity of pharmacology and toxicology by NIH, and the emphasis in the new toxicology on specific mechanisms of action, may make the need for advanced behavioral technology even more pressing.

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