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THE EFFECTS OF RESERPINE ON EMOTIONAL BEHAVIOR OF NORMAL AND BRAIN-OPERATED MONKEYS

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THE EFFECTS OF RESERPINE ON EMOTIONAL BEHAVIOR OF NORMAL AND BRAIN-OPERATED MONKEYS

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The untamed rhesus monkey appears to be affected in much the same way by reserpine as it is by certain brain lesions. In its normal, untreated state, a monkey will invariably withdraw from human observers, usually grimacing or screeching loudly, will frequently attack if cornered, and cannot be petted unless actually physically restrained.

The following descriptions would never be applied to normal animals:

". . . the monkey can now be handled with little fear that he will strongly resist any manipulation to which he is submitted" (Earl, 1953).

"The physical and emotional response to a threatening situation was markedly reduced and the approach of another animal or human, which ordinarily would have evoked a defiant attack or prompt flight, was now amiably tolerated" (Plummer *et al.*, 1954).

". . . animals were markedly altered in their behavior with respect to man, permitting petting and handling without any visible excitement, or even approaching and reaching for observers" (Weiskrantz, 1953).

". . . the authors independently felt it safe to enter the animal's cage and 'petted him for a considerable time.' When the observer placed his hand in the animal's mouth, it was chewed very gently" (Pribram & Bagshaw, 1953).

The first two statements refer to animals treated with reserpine; the last two refer to monkeys who had been subjected to bilateral lesions in the anterior medial portion of the temporal lobes, including the amygdaloid complex and prepyriform cortex. Other similarities can be pointed out, among them an increase in gastrointestinal activity (Plummer *et al.*, 1954; Wilson, 1954), a decrease in rectal temperature (Plummer *et al.*, 1954; Pribram and Bagshaw, 1953), and awkwardness of posture (Plummer *et al.*, 1954; Weiskrantz, 1953).

The present report is an account of an attempt to compare directly the effects of these two independent variables the lesion and the drug, as well as to investigate whether the effect of reserpine is altered in an animal who has sustained an amygdala lesion. Since one of the most striking changes in gross behavior produced by either variable seems to be the tolerance of situations and stimuli which normally are strongly aversive, it was decided to study the behavior in a situation in which the aversiveness, or "punishing" strength of a stimulus could be carefully controlled. For this purpose, we used a variant of a situation first described by Sidman (Sidman, 1953) which, in addition to providing a quantitative measure of the animal's performance, permitted us to obtain a specification of how strong an electric shock was required for each animal to elicit reliable avoidance behavior.

Subjects

Seven immature rhesus monkeys (*Macaca mulatta*) were subjects. All were untamed and experimentally naive, except for brief participation in an earlier

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experiment involving food reward. Age range was estimated to be between one and two years. The animals were divided into Group I, with three animals, and Group II, with four animals.

Method

Apparatus. Two similar sets of apparatus were employed, Group I having been tested with one (Apparatus I) and Group II, with the other (Apparatus II). Both consisted of small cages in which a single manipulandum was available. In Apparatus I, this manipulandum was a small rectangular panel on the front wall of the cage. In Apparatus II, it was a protruding lever. Either the pushing of the panel or the depressing of the lever activated a microswitch which was connected with a recording device. Both apparatuses were soundproofed, the former by being placed within a large refrigeration room, and the latter by being placed within a small converted refrigerator. In both cases, there was a masking noise provided by air blowers. In neither instance was the refrigeration compressor unit functioning. Subjects could be seen through one-way vision windows. FIGURE 1 is a picture of an animal inside Apparatus II. For an illustration of Apparatus I, the reader is referred to an earlier study (Weiskrantz, 1953).

All experimental sessions were conducted automatically by means of relay and timer apparatus not shown in FIGURE 1. This apparatus was set up to operate according to the following contingencies: A push of the panel (or press of the lever) delayed the occurrence of a brief electric shock by 10 seconds. Regardless of when a push occurred, the next shock would not be delivered until 10 seconds after the *last* response. Hence, if an animal pushed the panel at least once every 10 seconds, he would never receive a shock. If, however, a shock was permitted to occur, the next one would occur, not 10 seconds later, but 2½ seconds later, until the animal responded once again, thereby delaying the next shock by 10 seconds. In Sidman's terminology, these contingencies consisted of a response-shock interval of 10 seconds, and a shock-shock interval of 2½ seconds. The apparatus automatically tabulated the number of responses made and the number of shocks delivered, as well as providing a cumulative graph of the animal's performance.

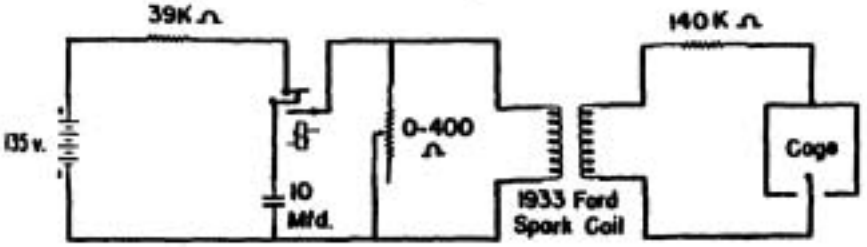
Shocks were delivered to the animal through a low resistance chain attached to an aluminum collar around the animal's neck. Both the chain and collar were permanently fixed to the animal. During experimental sessions, the animal's chain was attached to a beaded-chain swivel, which was connected to an insulated fixture on top of the cage. The cage itself provided one pole of the circuit. Wires supplying electrical charge were heavy-duty ignition cable.

The shock circuit is shown in FIGURE 2. The intensity of the shock could be varied by changing the variable resistor shunted across the primary coil. After preliminary work, it was decided to use six values of shock, calculated to give nearly equal increments in total electrical charge delivered to the animal. For convenience, we shall label these values from 1 to 6, 6 being the strongest value. The actual resistances corresponding to these values are ½, 1, 2, 4, 19, and 400 ohms. The only large deviation from equality of intervals occurs between shocks 5 and 6, this interval being only about one third the size of the others.

FIGURE 1. Monkey shown in Apparatus II.

Shock 1, to humans, feels like a very slight tingle. Shock 6, which is very painful, will jump an air gap of just under $\frac{1}{2}$".

Preoperative Procedures. Initial training: All animals were first trained on the highest shock intensity, No. 6. Three of the animals had previously had experience with panel-pushing for food reward, and transferred quite readily to the new situation. Each of the other four animals was trained by first delivering a train of shocks until the animal merely approached the lever, then later touched the lever, and finally pressed the lever. This process took from four days to three weeks, with approximately half an hour of testing daily.



SHOCK CIRCUIT

FIGURE 2

"Avoidance threshold" training: Details of the testing schedule will not be described here, since they will be submitted in a future manuscript analyzing the effects of the lesions on the avoidance thresholds. After initial training, all animals, sooner or later, were tested on each of several shock intensities, starting from the weakest in the series. Each animal was run, 40 minutes per session, on a given shock value for several days, until his daily rate became stable. Stability was defined by establishing a criterion in which the number of presses and the number of shocks received could not vary by more than a certain amount in a five-day period. In the case of the weak shocks, an additional criterion was established which was satisfied if an animal received at least 200 shocks within a 30-minute period on 2 successive days. The avoidance threshold was arbitrarily defined as the lowest intensity of shock which was sufficient to elicit behavior which would keep the number of shocks in a 80-minute period *under* 200, or more than an average shock rate of 6.667/min. (If an animal did not respond at all, he received 24 shocks/min.)

A typical record obtained for one of the animals on shock No. 5 is shown in FIGURE 3. This record cumulated all the responses the animal made, each response having moved the pen vertically by a small increment. The paper was moved horizontally at a constant rate. The pen automatically reset to "0" whenever a complete vertical excursion was made. This curve indicates how many responses an animal made in a given period of time, and the slope of the curve is a direct measure of the animal's over-all rate. Each little pip on the line indicates a shock.

In FIGURE 4 is shown the response records of this same animal on the ascending series of shock intensities. Note the increase in rate of response, and concomitant decrease in number of shocks delivered as the shock intensity grew stronger.

Drug experiments: After completion of avoidance threshold training (which occupied a matter of some weeks), the animals were tested under the influence of reserpine (Serpasil), pentobarbital sodium (Nembutal), and, in addition, some animals were tested after administration of isotonic saline. Shock No. 5 was used for all animals except one (S-194) which was tested on No. 6, since his threshold was 5. These values were sufficient, in all cases, to produce a high rate of response, which kept the number of shocks down to a low number.

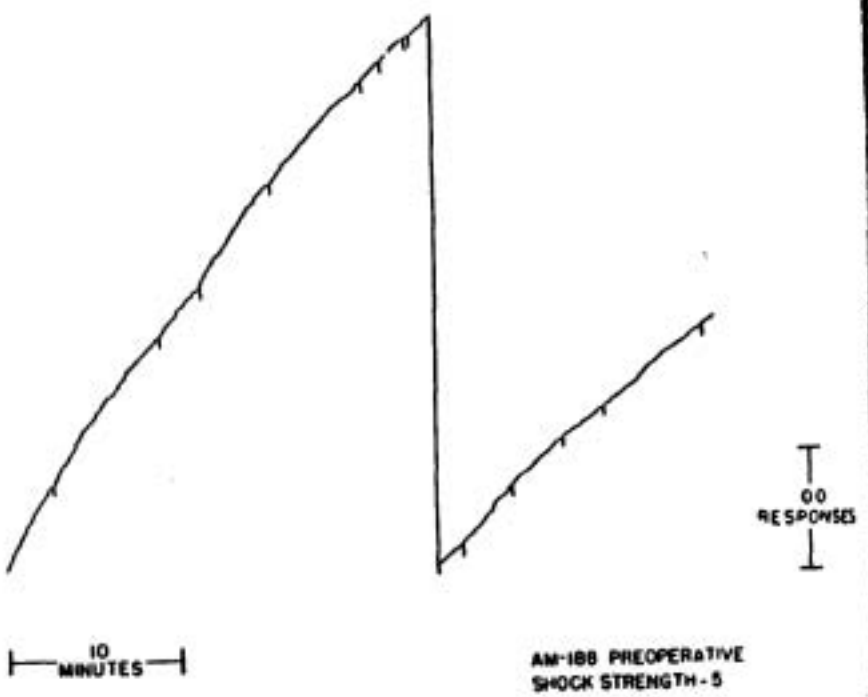


FIGURE 3. Typical cumulative performance record. See text for explanation.

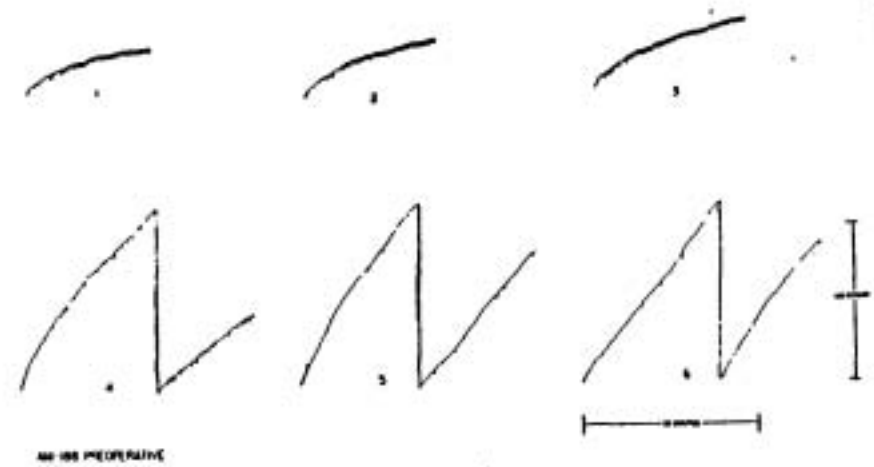


FIGURE 4

These experiments were conducted in the following sequence:

(1) First a normal control level was re-established by running the animals for two sessions.

(2) All animals were then tested following an intramuscular injection of reserpine (.75 mg./kg.). Each animal was tested when the drug seemed to have made it more docile and pettable, but before a deep state of sedation had been reached. This was accomplished within 150 to 245 minutes.

(3) A few days later, well after the gross effects of reserpine had worn off, Group I animals were run again in a normal session.

(4) All animals were next tested under pentobarbital, using an intramuscular injection of half the calculated anesthetic dose (18 mg./kg.). The criterion for desired depth of effect was that the animal should be staggering, but just well enough coordinated to grab a peanut held above his head. This was achieved within 45 to 90 minutes.

(5) Next, Group I was run following an intramuscular injection of isotonic saline solution, in volume the same as the pentobarbital dose (.30 cc./kg.). Animals were tested after the same interval following injection as they had been following pentobarbital.

Surgical procedure. Up to this point, to review briefly, all animals had avoidance threshold testing and testing on a high value of shock under the influence of reserpine and pentobarbital, and some animals were tested after injection of isotonic saline as well. Each animal was now given one of three brain lesions: an amygdaloidectomy (designated by AM); an inferior temporal convexity control lesion (IT); or a sham operation (S). In Group I, one animal was assigned to each of these three operate categories; in Group II, the animals were split evenly between AM and IT categories.

All lesions were bilateral and made in one stage, except for the sham lesion which was conducted in two stages. Intraperitoneal pentobarbital anesthesia was employed.

For the AM procedure, the zygoma was removed, the temporal muscle split and retracted, and temporal bone removed to expose the pole of the temporal lobe. The amygdala was visualized by gently retracting the lobe laterally. The lesion was made by means of suction, and was intended to include the entire amygdaloid complex and medial temporal pole.

In the IT procedure, the zygoma was left intact and the muscle cut slightly more posteriorly. The lesion extended dorsally to the superior temporal sulcus and ventrally into the fusiform gyrus, and was presumably limited to cortex.

The S procedure involved an exposure almost identical to the AM exposure. The orbital portion of the frontal lobes was gently retracted in an unsuccessful attempt to section the olfactory nerves.

Interrupted silk technique was used for closure of dura, muscle, and galea. Subcuticular continuous suture was used in the scalp. Animals were given a rest period of one week following surgery.

Histological analysis and reconstructions of the lesion are not yet available. FIGURE 5 shows reconstructions of lesions made in a recent study. These are ventral views of the brains with the two at the right showing an amygdaloid region lesion, with representative cross sections, while the two at the left show

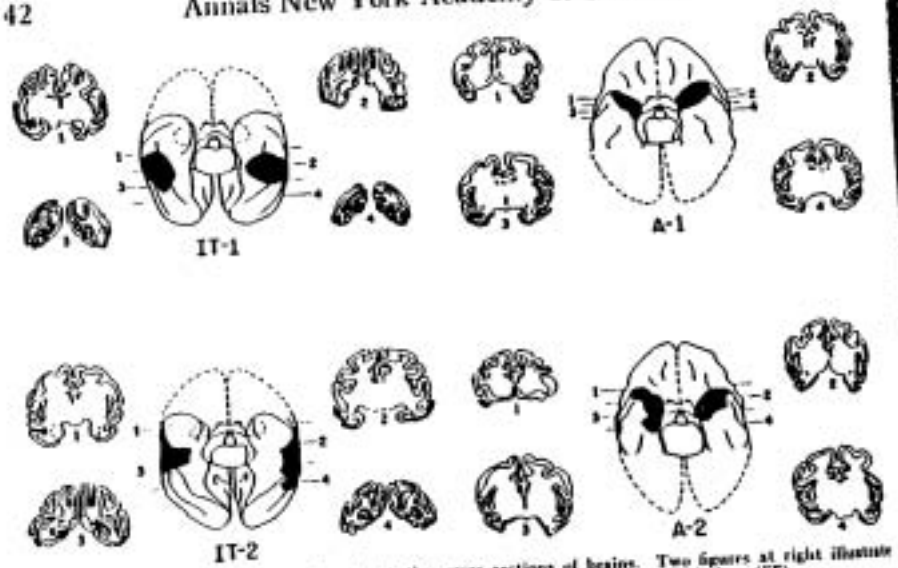


FIGURE 5. Reconstructions and representative cross sections of brains. Two figures at right illustrate amygdala region lesions (A), while two at left illustrate inferior temporal convexity lesions (IT).

inferior temporal convexity lesions. There is no reason to think that the lesions in this present study differ essentially from those illustrated in FIGURE 5, but detailed analysis of the behavioral changes due to the lesions awaits completion of the histological exa nination.

Postoperative training. All animals were rerun postoperatively on the avoidance threshold procedures, permitting a comparison with preoperative values. All drug procedures were repeated with the exception that no saline sessions were given.

In addition, because rather large changes were obtained in avoidance behavior following injection of reserpine, it was decided to test the animals in another situation not generally classified as "emotional." The three animals in Group 1 were trained in a situation where the panel-push did not delay a shock, but delivered a small pellet of food. The food was not delivered for each panel press but, rather, according to a random schedule, an animal being permitted a rewarded response once a minute on the average. Such a schedule produces a relatively stable rate of response, undisturbed by eating time or the effects of food satiation (Skinner, 1953). These animals were run for 30 minutes daily until their rates had stabilized to criterion, which all animals reached within 2 weeks. They were then run under reserpine, then again under normal conditions, and finally under pentobarbital.

Results

Effect of lesions on "avoidance thresholds." Only brief consideration will be given to the effects of brain lesions, *per se*, since, as has already been mentioned, histological examination has not yet been completed, and this paper, in any case, is primarily concerned with drug effects.

TABLE 1
AVOIDANCE "THRESHOLDS"

Animal	Preoperative	Postoperative	Difference
Group I			
AM—188	4	5	+1
IT—196	4	2	−2
S—194	5	3	−2
Group II			
AM—210	4	4	0 (+)
AM—205	3	3	0 (−)
IT—208	1	1	0 (−)
IT—207	4	1	−3

Summary for Groups I and II

	Increase	Decrease
AM	2	1
Control	0	4

The two cerebral lesions appeared to have had somewhat opposite effects. On the average, animals with amygdalectomies required a slightly more intense shock postoperatively in order to elicit avoidance behavior, while the inferior temporal controls (as well as the sham operate control) required considerably less intense shock. These results are listed in TABLE 1, together with a summary of the number in each group who increased or decreased their thresholds. When there was no difference in shock value (as indicated by "zero" in the "Difference" column), the sign indicates whether these animals received more or fewer shocks postoperatively, on the average, than they had preoperatively for that shock strength. It will be seen that two AM animals increased their thresholds, while one decreased slightly. All four controls decreased.

A more complete analysis of the behavior is given in TABLE 2. This analysis is concerned not with the threshold values, but with the animal's total performance at *all* values tested. Each entry is an average of an index comparing postoperative and preoperative performance for each shock intensity, computed according to the formula given. The responses/min. and shocks delivered/min. have been computed separately. (An average of merely the *ratio* of postoperative to preoperative performance would have been simpler, but the ratio suffers from the difficulty of approaching a limit of infinity at one extreme and tends to make, in addition, a rather biased average because of its skewed distribution. The index shown in TABLE 2 avoids such difficulties.) At the top of the table are the data for Group I; below, for Group II. A positive index means a higher postoperative rate than preoperative rate; a negative index means just the opposite. The table also summarizes the number of positive and negative indices for the two operate groups. Thus, all AM animals were slower in their responding postoperatively, while all controls were faster. Two of the three AM operates had a higher shock delivery rate postoperatively, while all controls had a lower delivery rate.

TABLE 2

Average Rate Indices

$$\Sigma\left(\frac{\text{Postop Rate}_i - \text{Preop Rate}_i}{\text{Postop Rate}_i + \text{Preop Rate}_i}\right) \Big/ N$$

Animal	Responses	Shocks
Group I		
AM 188	−.222	+.183
IT 196	+.220	−.562
S 194	+.154	−.338
Group II		
AM 210	−.110	+.206
AM 205	−.020	−.069
IT 208	+.088	−.787
IT 207	+.504	−.990

Summary for Groups I and II

	Responses		Shocks	
	Increase	Decrease	Increase	Decrease
AM	0	3	2	1
Control	4	0	0	4

One important fact should be stressed. While it required a higher shock to elicit avoidance behavior in the AM operates, on the average, the avoidance performance of these animals at very strong intensities was very rapid and adequate. In no sense was the habit "lost" following operation. These ani-

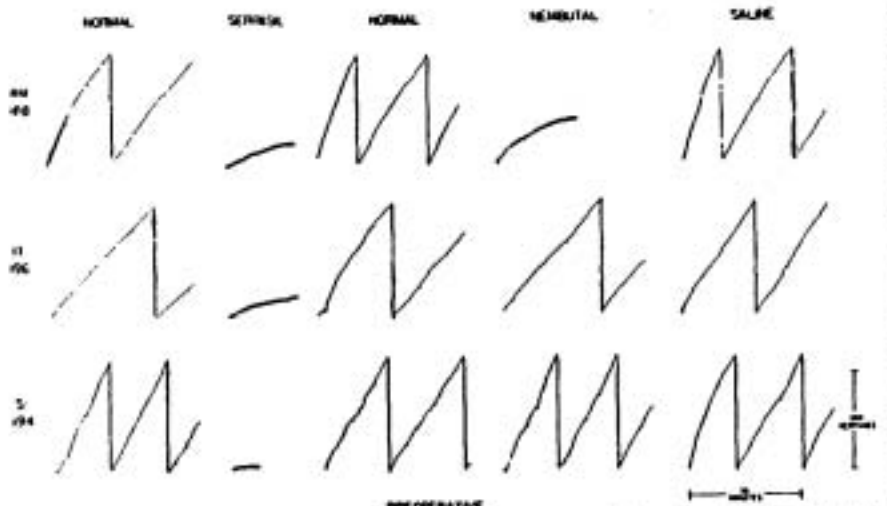


FIGURE 6. Preoperative performance records of Group I under normal conditions and under influence of drugs.

mals merely required stronger "electrical prodding," relative to controls, to demonstrate sustained avoidance behavior.

Effects of drugs on avoidance behavior. Preoperatively: The effect of the lesions on avoidance behavior, while definite, is dwarfed when compared with the effect of reserpine. FIGURE 6 shows the preoperative performance records for Group I. Note the low rates of response under reserpine. Pentobarbital had a rather pronounced effect in one animal, but still not as severe as the reserpine. Saline, it is interesting to note, had a slightly enhancing effect on rate.

FIGURE 7 shows the performance records for Group II. Essentially the same effects were obtained.

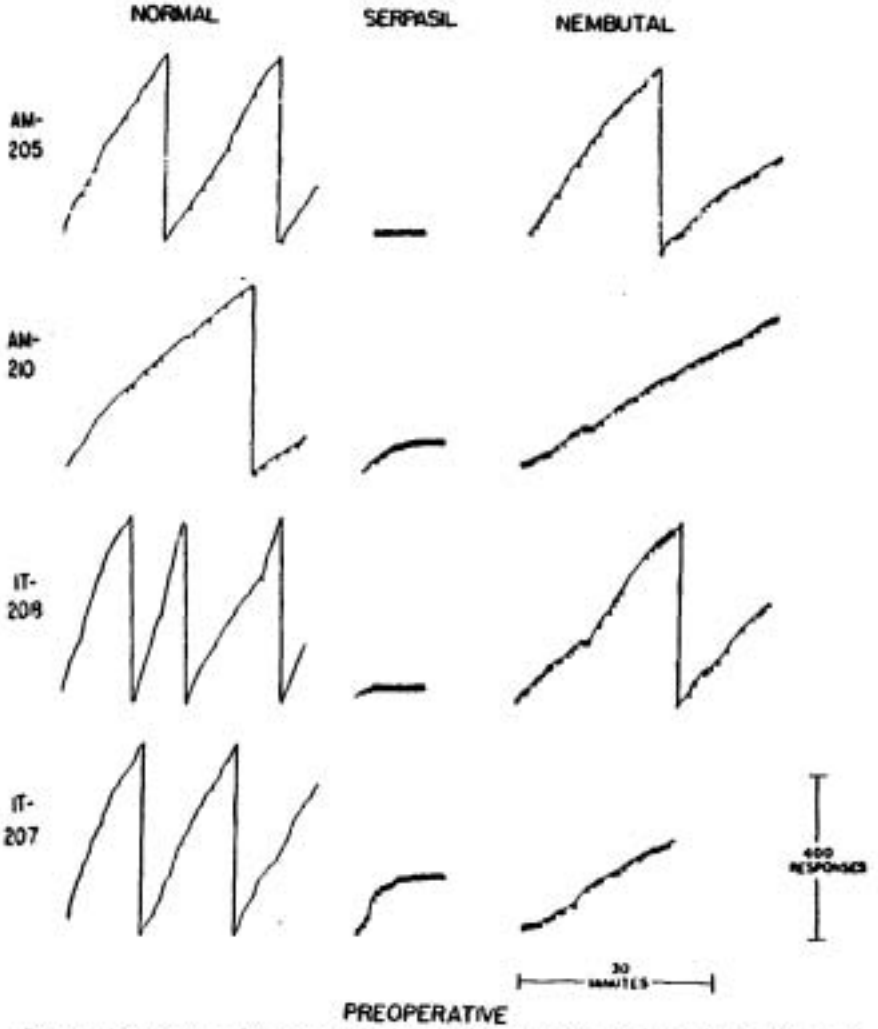


FIGURE 7. Preoperative performance records of Group II under normal conditions and under influence of drugs.

In a number of cases, a rather special kind of behavior under reserpine was noted. FIGURE 8 shows an enlarged view of one of the records. Note the even sparing between shocks. What this animal was doing was pushing the lever immediately after the shock had been delivered, thereby delaying the next

FIGURE 8. Performance record of animal S-194 under reserpine. Evenly spaced shocks are separated by 10 seconds.

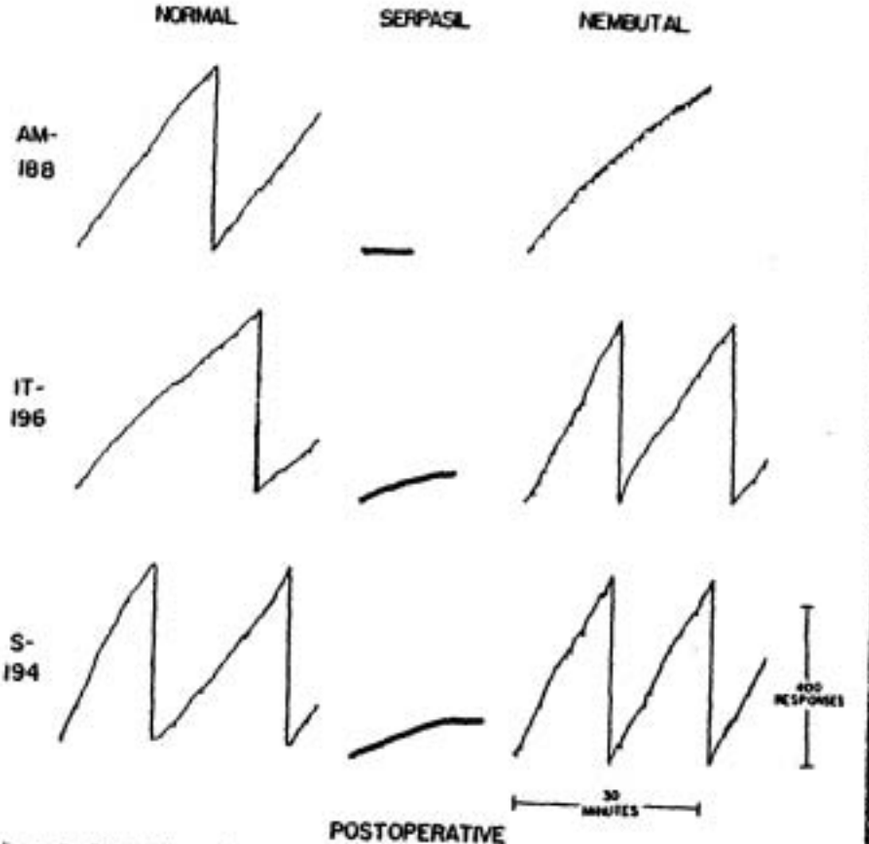


FIGURE 9. Postoperative performance records of Group I under normal conditions and under influence of drugs.

shock by 10 seconds. But, he only rarely pressed in between or in "anticipation of" shocks. Hence, he regularly received a shock almost every 10 seconds. This change in behavior can be characterized as the loss of avoidance or anticipatory responses, while escape responses remain intact. Later, as occurred *inevitably* under reserpine, this animal stopped responding completely.

Such a sustained regularity of shock intervals under pentobarbital was never observed. In many cases, the records indicate a decrease in rate of response. If one were able, however, to count all of the attempted responses made by the animals under pentobarbital, the total would probably indicate an increase rather than a decrease in rate for all animals, since many of the animals' swipes at the bar were clean misses or insufficient in force to depress it.

The reserpinized animals presented a markedly contrasting picture. In all

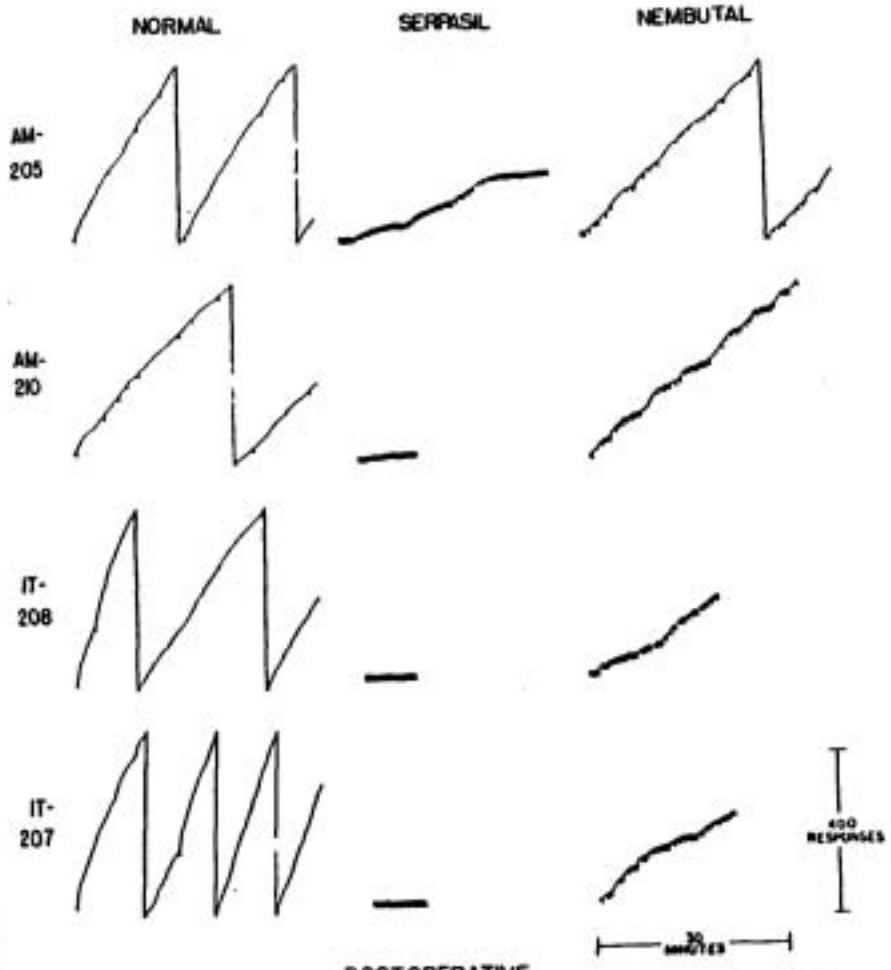


FIGURE 10. Postoperative performance records of Group II under normal conditions and under influence of drugs.

instances, they jumped vigorously whenever a shock was delivered, but then seemed quite unconcerned. Between shocks, they sat quietly in a hunched over position. While there may have been an analgesic effect, there was no question that they responded to the shocks.

Postoperative: The effects of both reserpine and pentobarbital were roughly the same postoperatively as preoperatively. Figures 9 and 10 show the performance for Groups I and II postoperatively. In figures 11 and 12, pre-

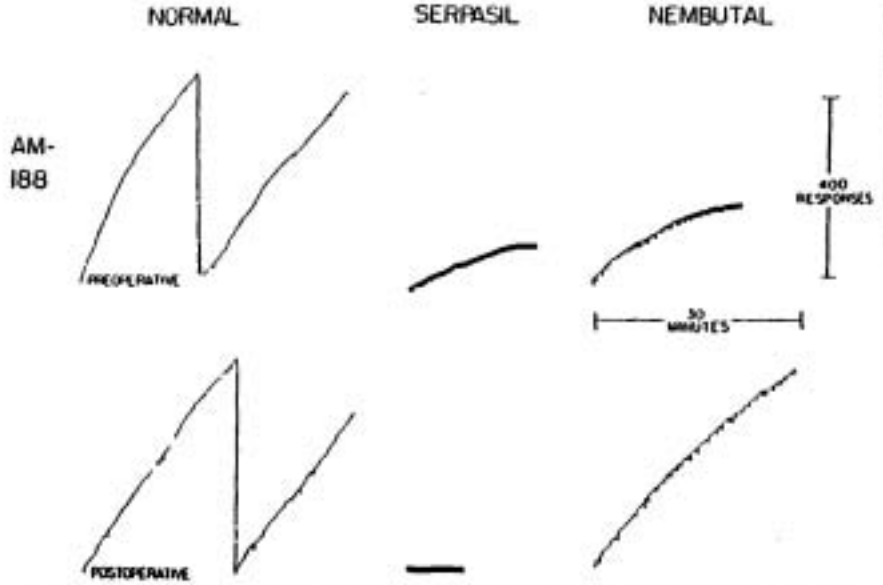


FIGURE 11. Comparison of preoperative and postoperative performance records for animal AM 188.

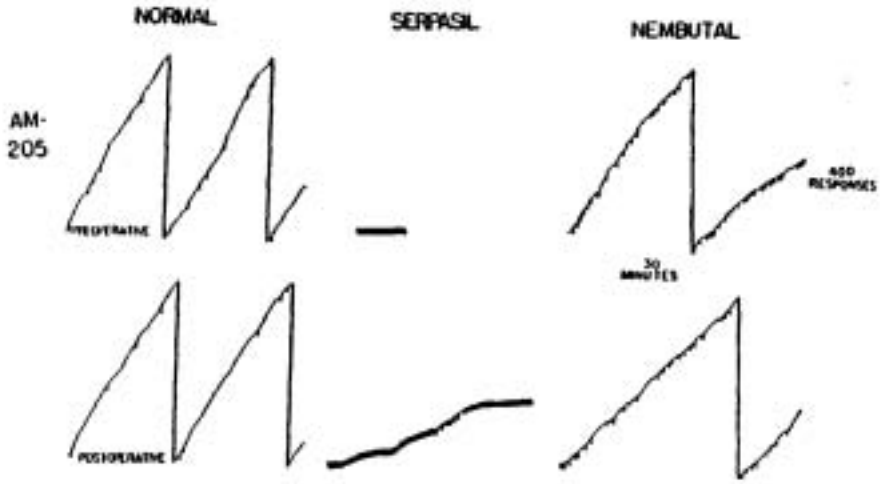


FIGURE 12. Comparison of preoperative and postoperative performance records for animal AM-205.

TABLE 3
GROUP I
RATIO OF RATES UNDER VARIOUS CONDITIONS TO NORMAL RATES

Animal	(Normal Rates)		Reserpine / Normal		Normal / Normal		Pentobarbital sodium / Normal		Saline / Normal	
	Preop	Postop	Preop	Postop	Preop	Post-op	Preop	Postop	Preop	Post-op
Responses										
AM—188	19.700	19.280	.238	0	1.328	—	.334	.749	1.220	—
IT—196	15.067	20.867	.328	.265	1.199	—	1.396	1.257	1.493	—
S—194	24.700	23.121	.139	.196	.955	—	1.231	1.272	1.063	—
Average	19.822	21.089	.235	.154	1.161	—	.987	1.093	1.259	—
Shocks										
AM—188	.150	.313	81.407	77.450	.447	—	83.333	8.201	.330	—
IT—196	.167	.193	86.299	69.083	.796	—	.599	1.036	.171	—
S—194	.216	.173	99.208	65.659	2.005	—	1.236	3.468	.191	—
Average	.178	.226	88.971	70.731	1.083	—	28.389	4.325	.231	—

operative performance is compared with postoperative performance for two individual animals. There is no evidence that an amygdaloidectomy made any difference to the effectiveness of reserpine. The occurrence of the evenly-spaced "escape" responses under reserpine was also frequently noted post-operatively.

It is not really proper, of course, to compare directly the preoperative and postoperative performance rates under a drug, since the operation itself had some effect on the control level of rate. In TABLE 3, therefore, we have compared for Group I animals, the drug rates with normal control rates both preoperatively and postoperatively. The first column shows the preoperative and postoperative normal rates, while successive columns show the ratio of rates under various conditions to these normal preoperative and postoperative rates. The upper table shows the data for responses made per minute, while the lower shows the shocks received per minute.

Note, as we have already seen, that reserpine was effective *both* preoperatively and postoperatively in producing marked reductions in response rate with concomitant increases in shock rate. Note also that, while the average ratio in *response* rate under pentobarbital is close to one, the shock rate is much higher than one, reflecting perhaps the effect of incoordination. Also note the slight increase in response rate under saline.

TABLE 4 shows comparable data for Group II animals. The table at the bottom is a summary for all seven animals. It shows the number of animals in each group in which reserpine had either an increased or decreased effect postoperatively as compared to preoperative ratio values. There is no consistent direction of change. From this summary table we conclude that reserpine is just as effective in an operated as an unoperated animal.

TABLE 4
GROUP II DATA
RATIO OF RATES UNDER VARIOUS CONDITIONS TO NORMAL RATES

Animal	(Normal rates)		Reserpine / Normal		Pentobarbital sodium / Normal	
	Preop	Postop	Preop	Postop	Preop	Postop
Responses						
Group II						
AM—205	25.960	22.184	.031	.194	.555	.300
AM—210	13.250	14.463	.435	.080	.719	.816
IT—207	29.267	42.480	.373	0	.296	.155
IT—208	34.667	25.200	.099	0	.460	.440
Average	25.786	26.082	.234	.068	.508	.528
Shocks						
Group II						
AM—205	.234	.283	103.598	49.678	9.401	4.947
AM—210	.867	.350	17.745	60.151	7.074	16.908
IT—207	.017	.017	855.588	1426.000	393.588	642.352
IT—208	.133	.033	143.218	734.606	27.120	225.909
Average	.313	.171	280.037	567.608	109.296	220.029

Summary for both Group I (see TABLE 3) and Group II (above)

	Responses		Shocks	
	Increase	Decrease	Increase	Decrease
AM	3	2	1	2
Control	1	3	2	2

Food reward results. The results of the food reward experiment with Group I animals, conducted after the other experiments were completed, are shown in FIGURE 13. Reserpine depressed the food responses almost entirely. No animal, at the end of the session, would pick up and ingest food when the experimenter delivered it to the food dish, but if it were actually held in front of his mouth, he might chew the food for a while. Notice the only slight effect of pentobarbital. It should be mentioned that previous investigation has shown that amygdala operates are not altered in their rates of response to this same schedule of food reward (Weiskrantz, 1953).

Discussion

Little question remains that, under the conditions of this study, reserpine has a severely depressing effect on avoidance behavior of the rhesus monkey. We have not attempted to study the effects of different doses or different time intervals on behavior; obviously, a whole set of parametric relationships re-

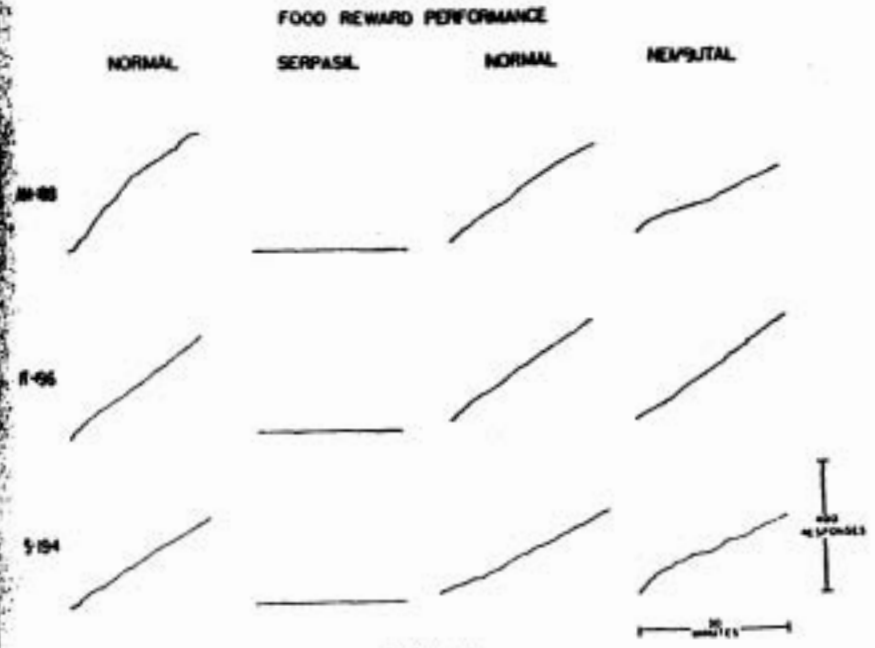


FIGURE 13

mains to be explored. It should be repeated, however, that the animals were tested at a time when the gross effects of the drug had not approached their maximum degree, and it seems highly probable that even what little behavior was observed in this project would have been completely depressed had a longer time interval been permitted to elapse between injection and behavioral testing.

The evidence, however, that food rewarded responses are also depressed would seem to indicate that the drug has a rather general effect on behavior, although it is likely that a hierarchy of behaviors could be established with further investigation, employing, for example, the type of multiple schedule recently developed by Ferster (Ferster, 1954). The fact that, in a number of cases, the rather special type of reserpine response record was obtained in which animals responded only *after* a shock had occurred, but did not avoid subsequent shocks, suggests that behavior occurs only when there is strong external stimulation to maintain it. Even well-established patterns of behavior seem incapable of maintaining themselves without such external control e.g., an animal might chew a few times on a bit of food, but then "forget" that it is in its mouth. A new piece of food might start off a few more chews. In view of the observed lack of anticipatory responses, an interesting question arises. Assuming that animals will fail to respond to conditioning procedures while under the influence of reserpine, will they also fail to exhibit the *memory* of them once the sedating effects have worn off; *i.e.*, does reserpine merely depress *performance*, or does it also depress *learning* capacity? Investigation is now in progress regarding this question.

Although many similarities in behavior exist between a reserpinized animal and an amygdala operate, the effect of the present investigation has been to point out some essential differences. For one thing, the amygdala operate is still capable of well-maintained avoidance behavior, albeit higher intensities of shock are required relative to controls.* It is perfectly possible that, with higher shock intensities, reserpinized animals would also exhibit avoidance behavior. Nevertheless, within the limits tested here the operation has less of an effect than the drug. Second, the depressing effects of amygdala lesions have to date been demonstrated only for "emotional" behavior. In other situations, such as responding for food on a random reward schedule, discriminating visual patterns for food reward, or delayed response tasks, amygdala operates fall within normal limits (Pribram and Bagshaw, 1953; Weiskrantz, 1953). Reserpine, on the other hand, seems to be more general in its behavioral effects; responding for food on a random reward schedule, at least, is severely depressed. This difference was also apparent in gross observations of the two types of animals. Reserpinized animals are much more sluggish and inactive than amygdala operates, except, perhaps, for the latter's first 48 postoperative hours.

These differences, together with the finding that reserpine was just as effective in depressing avoidance behavior in an operated as in a normal animal, evidently rule out the amygdaloid region as a critical site of action of reserpine. There is another possibility closely related by experimental anatomy to that of the amygdaloid complex. It has been shown by strychnine neuronographic techniques that the amygdaloid complex (at least the cortical nucleus of the complex) is part of a larger system consisting of the prepyriform cortex, anterior insula, anterior temporal pole, and posterior orbital frontal areas, in addition to the amygdala (Pribram and MacLean, 1953). When all or almost all of this system is damaged experimentally, the effects on gross behavior are almost indistinguishable (at least, to us) from those produced by reserpine in a normal animal. At this stage, it is still impossible to state whether a mass relationship is important in assessing the results of these lesions (with the implication that an amygdaloid region lesion alone does not destroy enough of this system) or whether a *focus* exists which is actually outside the amygdaloid complex. In the latter connection, it is significant that Turner has reported that relatively small lesions which just touched the boundary of the amygdala, but remained outside its main body, produced a much greater tameness in monkeys than lesions restricted to the amygdala (Turner, 1954). Furthermore, it has been observed in our laboratory that lesions that are placed in the prepyriform cortex and anterior insula, but which just *exclude* the amygdala, produce a reserpinelike animal. Moreover, it is of great interest to note that the *acquisition* of avoidance behavior of animals with large lesions in the orbito-insula-temporal system is very much more depressed in a shuttle-box situation than is true with more restricted amygdaloid region operates (Pribram and Weiskrantz, 1955). We, together with Pribram, are currently testing such operates in the avoidance *performance* situation described in this paper.

* Arguing against, incidentally, the claim that only the *acquisition* and not the *maintenance* of avoidance behavior is affected by amygdala lesions (Brady *et al.*, 1954).

Although an early hypothesis regarding the site of action of reserpine pointed to the hypothalamus, subsequent research has led to the notion that some of the effects are "probably due to a blockade between afferent and efferent neurones," rather than to a "direct depressant effect" on hypothalamic centers (Schneider, 1954; Hein, 1953). We do not feel that the evidence is really substantial enough to rule out direct involvement of hypothalamic centers. Even if the "blockade" notion is accepted, it is almost meaningless to make the assumption of a "purely efferent" hypothalamus, which seems to be an implicit assumption in the "blockade" hypothesis as enunciated thus far. "Blockade" could still have a hypothalamic locus. Furthermore, the finding that reserpine (heavy doses, at least) affects nonhypothalamic neural activity does not rule out the possibility of a dose-time hierarchy giving hypothalamic areas priority. Finally, while the evidence derived from hypothalamic lesions does not exclude the possibility that an extrahypothalamic control center might still be the principal site of reserpine action, the strong similarity of behavioral changes produced by lateral hypothalamic lesions in the monkey (Ranson, 1939) and by reserpine is too striking to pass unmentioned.

Nevertheless, the preliminary findings with orbito-insula-temporal lesions are of some interest with respect to the idea that reserpine might somehow prevent impulses from an extrahypothalamic modulating or activating center from reaching the hypothalamus. There is good evidence that the amygdala and orbital frontal areas of the monkey send direct fibers to the ventral medial nucleus of the hypothalamus (Adey and Meyer, 1952; Clark and Meyer, 1950), which has been implicated in emotional behavior (Wheatley, 1944) and metabolic activity (Hetherington and Ranson, 1942) of cats and rats. Stimulation of the cat's amygdala yields a cortical "arousal" or "activation" pattern (Feindel and Gloor, 1954), which suggests that it might have an "activation" role somewhat analogous to that proposed for the reticular formation.

Analysis of the possible site of reserpine action has mainly followed the following pattern: As an independent variable, reserpine is administered, and certain consequences are either noted or measured as dependent variables, *e.g.*, "relaxation," "sedation," blood pressure changes, miosis, *etc.*; or else the effect of reserpine is noted on some other independent-dependent variable relationship, *e.g.*, carotid sinus reflex, decorticate sham rage, avoidance behavior, *etc.* Once these are established, a given part of the nervous system is isolated (brainstem section) or "activated" (hypothalamic stimulation) or destroyed (ciliary ganglion destruction; amygdala lesion) and changes in the consequences or in the relationships noted.

Of all the dependent variables employed for these studies, the behavioral ones are among the most difficult and complex. Yet they are certainly among the most important. The widespread use of reserpine in clinical psychiatry is based almost entirely on its behavioral effects. In a more general sense, our understanding of the mechanism of action will not be achieved *without* reference to the behavior of the affected organism. No matter how many physiological steps are filled in concerning the action of reserpine, the causal chain will not have been completed until the behavioral consequences have been determined.

This is tantamount to saying that the behavioral consequences *must* be studied sooner or later and, fortunately, can be studied independently of and prior to the investigation of physiological mechanisms. Indeed, the present state of our knowledge indicates that the analysis of behavior is very likely to *suggest* physiological loci of action, given knowledge of the effects of lesions and electrical stimulation of the central nervous system on behavior. The hypothalamic hypothesis was based largely on the similarity of the reserpine behavior to behavior produced by hypothalamic lesions and stimulation. Our present hypothesis concerning the possible role of the orbito-insula-temporal areas is based on similar evidence. Given the importance of behavioral research, it should follow that the same scientific rigors that apply to other disciplines must apply here. Gross observations are important, but they can scarcely be given the status of more than preliminary observations which may guide subsequent analytic research.

Summary

Seven thesus monkeys were tested in an avoidance performance situation under normal conditions and following injection of reserpine (Serpasil) and pentobarbital sodium (Nembutal). Animals were then retested following a bilateral amygdalaoidectomy, a bilateral control lesion in the inferior temporal convexity, or a control sham operation. In addition, three of the animals were tested postoperatively in a food reward situation under normal conditions and under drug conditions. The following results were obtained:

(1) Amygdaloidectomized animals required a stronger electric shock relative to control operates to display avoidance behavior under normal conditions.

(2) Both in the preoperative and postoperative animal, reserpine depressed avoidance behavior very severely, while pentobarbital depressed it only slightly or not at all.

(3) Reserpine, in some cases, produced a unique pattern of responding in which shocks were "escaped" but not "avoided."

(4) Food rewarded responses were almost entirely depressed by reserpine, while pentobarbital only slightly depressed such responses.

Similarities and differences between the effects of lesions and drugs are discussed as well as hypotheses regarding the possible site of action of reserpine.

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