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# THE RELEASE OF CATECHOLAMINES BY SHOCKS AND STIMULI PAIRED WITH SHOCKS[1]

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One monkey and five baboons were surgically prepared so that heart rate and blood pressure could be monitored continuously, and an extra-corporeal blood path was established to detect the secretion of epinephrine (adrenaline) and norepinephrine (noradrenaline). A respondent conditioning procedure was used in which a tone was paired with electric shocks. Epinephrine, but not norepinephrine was released by shocks, and a corresponding release was demonstrated by the tone alone. Heart rate and blood pressure changes were also elicited by shocks and by the tone.

Many physiological reactions can be conditioned to arbitrary stimuli through the procedure of respondent conditioning (Kimble, 1961; Bykov, 1957), and of these, cardiovascular responses have been extensively studied. For example, after an exteroceptive stimulus such as a light or sound has momentarily preceded an electric shock on several occasions, heart rate (Gantt, 1966) and blood pressure (Newton and Perez-Cruet, 1967) increase when that stimulus is presented alone. Paralysis of the subject with tubocurarine does not prevent this conditioning or its extinction (Black, 1965).

Some of these cardiovascular changes may be induced by the sympathetic nervous system, which is presumed to be activated during aversive conditioning. For example, as early as 1911 Cannon and de la Paz found that blood from a cat exposed to a barking dog contained a substance ("adrenal secretion") that relaxed an intestinal muscle strip. Mason, Mangan, Brady, Conrad, and Rioch (1961) measured release of catecholamines and other hormones during several different aversive conditioning procedures, using a fluorometric technique. They found an increase in the plasma concentrations of 17-hydroxycorticosteroids and of norepinephrine during an electric shock avoidance schedule, during a conditioned "anxiety" procedure, and release of epinephrine as well during an "ambiguous" stimulus that preceded either food reinforcement or aversive conditioning schedules in an irregular manner (*cf.* Brady, 1967).

We have used the continuous bioassay procedure developed by Vane (1964) to assess the release of catecholamines in primates during classical aversive conditioning procedures. Simultaneous recordings of heart rate and arterial blood pressure were also made.

## METHOD

### *Subjects*

One cynamologus monkey (*Macaca iris*) and five male baboons, weighing 5 to 10 kg, had continuous access to food and water.

### *Surgical Preparation*

The experiments were relatively complex and several problems were encountered in the first three, with the monkey and two baboons, the major one being formation of blood clots in the implanted arterial catheter. In the most successful experiments the catheter was pushed quite far down the artery, about 7 cm, so that

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there was turbulence around the tip, and the lumen of the catheter was partially filled by a nylon rod until the animal was used. The operative procedure was as follows. The baboon was anaesthetized with Phencyclidine (Sernylan, 2 mg/kg intramuscularly), supplemented, as needed, by pentobarbital sodium (Nembutal, 5 mg/kg intramuscularly). A skin incision was made in the neck over the region of the left external jugular vein, and that vein and the left carotid artery were exposed by blunt dissection. Two catheters, 25 cm in length, were made from Portex polyethylene tubing (internal diameter 2 mm, external diameter 3 mm) and a nylon rod of a diameter which just moved easily into the catheter was inserted down its whole length. A short, tight-fitting length of silicone-rubber tubing was tied as a cap to the end of the nylon rod, and formed a seal on the catheter by ligation. The space between the catheter and the rod was filled with strong heparin saline solution (5000 i.u./ml).

The carotid artery and jugular vein were cannulated and the catheters were inserted 7 cm down each vessel towards the heart. The distal end of each vessel was ligated. Next, a mid-line incision was made in the scalp, at the top of the head, in the same plane as the ears, and a trocar was passed under the skin from this incision to the neck wound. The two catheters were threaded through the trocar, which was then removed. Lengths of tubing of about 10 cm emerged from the scalp. The positions of the catheters were fixed only by the stitches in the scalp, which were also tied around them. The muscle layers and skin incision in the neck were closed by cat gut and nylon sutures as was the skin incision on the scalp. The whole operation was carried out under sterile conditions and, as a precaution, the animal was afterwards given benzyl penicillin (1 million units intramuscularly).

*Apparatus*

While the animal was still anaesthetized, it was placed in a restraining chair (Nicholson, 1965) where it had free access to food and water. The chair was inside a large wooden box (60 by 60 by 120 cm in height) which had a fan for air circulation, a loudspeaker for presenting the masking white noise and auditory stimuli, two white lights, and a hole to receive the lens of a television camera. Electromechanical equipment for presenting the various stimuli was in an adjoining room.

In some animals, conditioning was begun on the day after the operation and mean blood pressure and heart rate were measured during the session. Blood pressure from the carotid arterial catheter was recorded with a Statham P23Db strain gauge attached either to a Beckman Offner Dynograph or to a Texas Rectiriter recorder. Heart rate was either recorded on a second channel of the Dynograph with a heart rate input coupler, using the pulse pressure from the strain gauge as a trigger, or counted manually.

*Hormone Assay Procedure*

On the last day of each experiment, catecholamines in the blood stream were measured, using the blood-bathed organ technique. Blood from the carotid arterial catheter was pumped at a constant rate by a roller pump so that it superfused a strip of muscle from the rat stomach (Vane, 1957) and a longitudinal section of chicken rectum (Mann and West, 1950). (In several experiments, a section of rat colon was also used, to detect angiotensin (Regoli and Vane, 1964) but no evidence of changes in blood concentration of angiotensin was obtained.)

Heparin (Pularin, Evans, 1000 i.u./kg intravenously) was injected into the animal before the external circulation of blood was started. After superfusing the tissues, the blood was returned through the cannula in the jugular vein. With these organs superfused in series, it was possible to distinguish between the release of epinephrine and norepinephrine (Armitage and Vane, 1964). The rat stomach strip relaxes both to epinephrine (adrenaline) and to norepinephrine (noradrenaline), whereas the chick rectum relaxes only to epinephrine. If there is a relaxation of both, it is necessary to match the relaxation on the chick rectum with a control injection of epinephrine. If this matching injection also gives a matching effect on the rat stomach strip, there could not have been any norepinephrine release. However, if the relaxation of the rat stomach strip is greater than is shown by the control, there must also be some norepinephrine present. Our experience with this method shows that it is unlikely to detect less than 10% of norepinephrine in a mixture but would certainly detect more than 15%. The amounts of cate-

cholamines released were determined by comparing the responses of the blood-bathed organs with the effects of intravenous injections of epinephrine and norepinephrine. Generally, the technique could estimate the release of less than 200 ng epinephrine/kg body weight. The movements of the assay organs actuated auxotonic levers (Paton, 1957) attached to "Ether" strain gauges, and were displayed on two or three channels of the Dynograph. Blood pressure, heart rate, and the presentations of conditioned and unconditioned stimuli were also displayed on the Dynograph.

When blood was being withdrawn to superfuse the assay tissues, nylon tubing (1-mm external diameter) was inserted down the arterial catheter via a Y-junction piece, and was connected to the Statham pressure transducer.

Electric shocks were delivered via silver coin electrodes strapped to the animal's shaved tail by elastic bandage. Redux electrode paste helped maintain a good electrical contact. Voltage (50 Hz) was adjusted with a variable transformer, and current was monitored.

*General Procedure*

Several different methods of pairing tones with electric shock were used. With the exception of the first subject (a Cynamologus monkey), all preparations were short term. The subject was received on Monday or Tuesday of the week of the experiment and was placed in the restraining chair; the operation described above was performed the next day. Preliminary conditioning, with recording of blood pressure and heart rate only was, in some cases, performed on the following day and, in all cases, the cannulae were tested; for some subjects, a second day of recovery and conditioning was allowed. The measurement of catecholamine release and cardiovascular change was conducted the next day. The specific stimuli, and pairing procedures used, varied among the subjects, and are therefore described in detail for each baboon for which data are presented.

## RESULTS

In the three fully successful experiments, the animal was healthy and appeared fairly normal throughout; cannulae were sufficiently patent to allow the withdrawal of blood rapidly enough for the assay tissues, and blood pressure records were obtained. The results from the other experiments were similar in all respects, but were intermittently marred by technical difficulties, such as occlusion of the catheter by a clot.

The first successful experiment, with a 10-kg baboon, showed elicitation of heart rate and blood pressure changes and of release of epinephrine to a tone paired with shock as well as to shock alone. On the day after the operation, a discriminative training procedure was used. Two tones (1500 Hz and 2700 Hz, each of 11-sec duration) were presented, but only one of them (1500 Hz) preceded the electric shock (1-sec duration, 6 ma).

On the first trial, the 1500-Hz tone was presented alone, and there was no change either in blood pressure or heart rate. Nine conditioning trials were then given, during each of which the systolic and diastolic blood pressures increased by about 10 mm Hg and then returned to base line over the next minute. Concurrent with the increase in blood pressure was a sharp fall in heart rate of between five and 10 beats per minute from a basal level of about 200 per minute. By the sixth trial the heart rate and blood pressure changes occurred during the tone and simply continued after the shock had been presented. On the ninth trial the 1500-Hz tone was presented alone and changes in blood pressure and heart rate were essentially the same as on the preceding trials. Because no evidence of differential responding was seen after about a dozen interspersed presentations of the 2700-Hz tone, the procedure was changed to use only the 1500-Hz tone.

On the next day the blood-bathed organ method was used to determine catecholamine outputs during further trials. Blood was superfused at 10 ml/min over a rat stomach strip, a rat colon, and a chick rectum and was then returned intravenously. During the period in which the assay organs were stabilizing, tones and shocks were presented to the baboon. Changes in heart rate and blood pressure were small compared with those obtained on the previous day and there was no observed behavioral response to the shock. We believed that the mechanical pressure on the tail by the straps holding the shock electrodes had been tight enough to cause a mechanical anaesthesia. Therefore, with this subject only, shocks were delivered via light clip electrodes, one

attached to each ear. The cardiovascular responses were then similar to those obtained on the previous day, and there was also a release of catecholamines when shocks were given. The cardiovascular response consisted of a rise in both systolic and diastolic pressure of about 20 mm of mercury and a fall of heart rate of 10 to 15 beats per minute. The first paired presentation of tone and shock released some catecholamines into the circulation. By calibration with known amounts of catecholamines, the material released was shown to be 5 $\mu$g of epinephrine. The second pairing elicited a similar release of epinephrine. On the third trial, only the tone was presented. The cardiovascular changes were very similar to those obtained before, but the release of epinephrine was reduced to 3 $\mu$g. Two more paired presentations each induced the release of about 5 $\mu$g epinephrine and a smaller release was again obtained with the tone alone. A further pairing trial 35 min later released 5 to 7 $\mu$g of epinephrine. The injection of 7-$\mu$g epinephrine intravenously induced blood pressure and heart rate changes almost identical to those seen on a conditioning trial. As in all these experiments, successive trials were conducted only when all technical aspects of the experiments were judged to be appropriate. This criterion included return to baseline and stable movements of the assay tissues, and of heart rate and blood pressure. The intertrial intervals were therefore irregular, and were at least 8 min, and as much as 30 min.

Figure 1 was taken from a later stage in the experiment. In the left part of the figure, the effects of intravenous injections of epinephrine (7 and 3.5 $\mu$g), and norepinephrine (8 $\mu$g) are shown. The rat stomach strip (top tracing, RSS) relaxed after all three injections, whereas the chick rectum (second tracing, CR) relaxed only after epinephrine. Due to the time taken for the blood to reach the assay tissues, the effects of catecholamines upon them occurred about 35 to 45 sec after the drugs were given, whereas the cardiovascular effects of these drugs were more sudden, beginning within 10 sec. Later in the experiment, by running the paper at 10 times the normal speed, it was possible to see that the rise of blood pressure started within 2 sec of the conditioned stimulus and the fall of heart rate within 4 sec. Note that the third event shown was the presentation of the tone alone (CS). This produced a relaxation of the assay tissues similar to that produced by 3.5 $\mu$g of epinephrine, but a change in heart rate and blood pressure which were somewhat larger.

The right-hand section of Fig. 1 shows the effects of presenting the tone and shock stimuli both alone and in sequence. Each presentation of the tone alone released about 3.7 $\mu$g of epinephrine; paired presentation of tone and shock released 5.5 $\mu$g, and shock alone released 6.6 $\mu$g. The difference between the effect of shock alone and shock preceded by tone was greater as estimated from the response of the chick rectum than from the rat stomach strip.

In these experiments, the release of epinephrine was estimated by injecting calibrating doses of epinephrine in one shot intravenously. The shape of the curves of relaxation of the assay tissues following these injections and following release from the adrenal glands shows that the medullary release must also have reached the venous circulation in a similar sudden burst.

At the end of the experiment, the tone was presented alone on a number of trials. On each successive presentation there was a smaller epinephrine release, and smaller changes in heart rate and blood pressure, until, after 11 trials, all responses to the tone were extinguished.

A second baboon, was prepared surgically, exposed to conditioning procedures with measurement of heart rate and blood pressure on the next day, and to the full experimental procedure on the third. On the second day, the mean blood pressure was 90 mm of mercury and the mean resting heart rate was about 118 per min. A 1500-Hz tone, 7-sec long, was paired with a 7-10 ma shock, 1-sec long, to the tail. After the fifth trial, the tone alone produced increases in heart rate of 24 beats per minute and increases in systolic and diastolic blood pressure of about 20 mm of mercury.

On the next day, the circulating catecholamines and cardiovascular function were assessed. Further conditioning trials were conducted and presentations of tone alone and shock alone were also given. The results with this subject were similar to those described above. There was release of epinephrine only, of about 1 to 2 $\mu$g, an increase in blood pressure of about 12 mm of mercury, and an increase in heart rate of about 20 beats per minute. Calibrating intravenous injections of

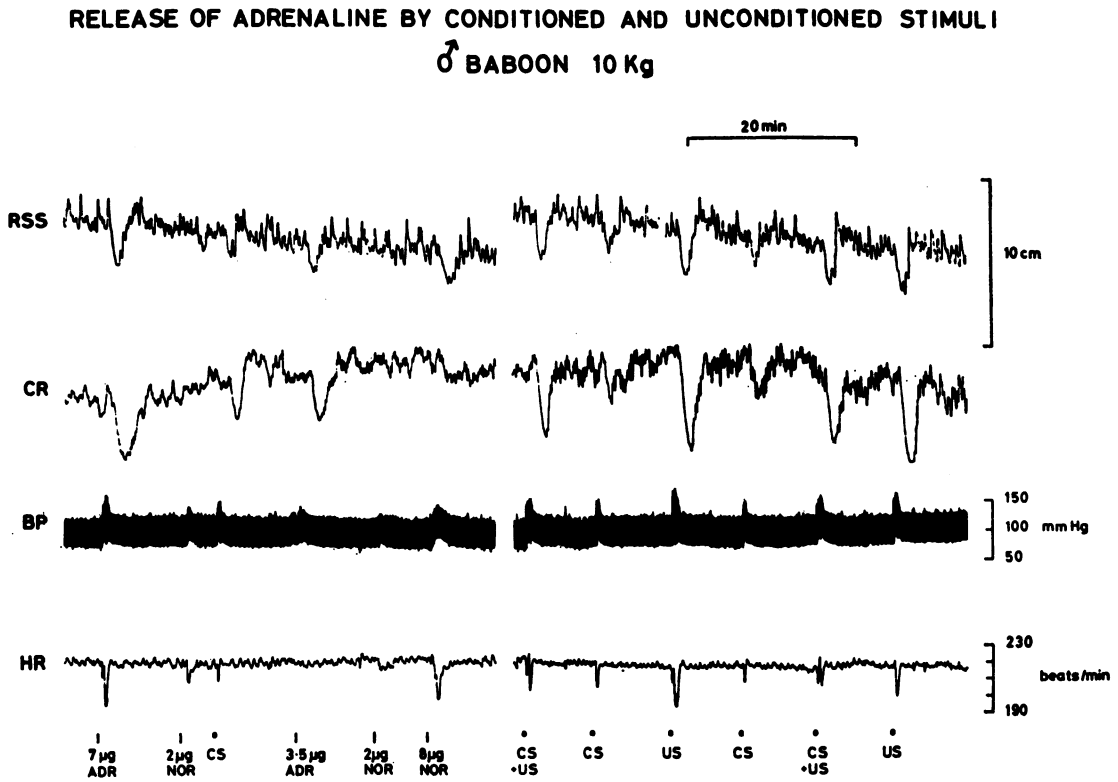


Fig. 1. Two sections of polygraph recordings from a male baboon (10 Kg). Records are, from top, movement of rat stomach strip muscle (RSS), movement of section of chick rectum (CR), arterial blood pressure (BP), and heart rate (HR). Scales on top and to right of records indicate absolute values. Time of occurrence and types of event are indicated at bottom of record: introduction of epinephrine (adrenaline-ADR) and norepinephrine (noradrenaline-NOR) into venous blood catheter, presentation of tone (CS) and electric shock (US).

epinephrine (1 to 5 $\mu$g) decreased the heart rate when the blood pressure was increasing, implying that the increased heart rate during the conditioning trials was not due to circulating epinephrine but must have been due to stimulation of sympathetic nerves to the heart or to vagal inhibition.

The assay organs in this experiment reliably detected intravenous injection of less than 2-$\mu$g epinephrine. However, during some of the conditioning trials, even though the changes in heart rate and blood pressure were fairly regular, there was not always a detectable output of epinephrine to the tone or shock. There appeared to be no other difference between this animal and the others which would account for the difference in hormonal output.

Because the two complete experiments reported above, and the preceding ones which were technically less satisfactory, were consistent in showing cardiovascular changes and output of epinephrine during the delay conditioning procedure, a different procedure was used in the next experiment. The baboon was received on a Monday, cannulated on Tuesday, and recordings of heart rate and blood pressure were made on Wednesday and Thursday. On these two days, appetitive delay conditioning, in which food (apples) was paired with a tone (1500 Hz), was performed. The animal readily accepted the food, and oriented its head toward the place where the food was delivered when the tone was turned on. But there were no detectable changes in heart rate or blood pressure as a function of any of the experimental manipulations, which included presentation of food alone, presentation of auditory stimulus alone, paired presentations, and a final series of trials with tone and no food (extinction).

On the third post-operative day, the animal would not accept pieces of apple, probably because it had been given too much food,

including apples, on the night before. Two conditioning procedures with shock were, therefore, used. First, a delay conditioning procedure, similar to that used with the other two baboons, was instituted. The auditory stimulus was a 4000-Hz tone and electric shock was applied to the tail. Changes in blood pressure, heart rate, and epinephrine release were again demonstrated for presentations of paired tone and shock, shock alone, and tone alone. The pattern of heart rate changes was, however, different from that described for the other animals. In this case, there was an initial momentary decrease in heart rate followed by an increase.

Later in the experiment a different conditioning procedure was instituted in which a 2-min auditory stimulus (4000 Hz) was presented and was sometimes accompanied by eight irregularly spaced electric shocks to the tail. On some trials, no auditory stimulus was presented, but eight irregularly spaced electric shocks were presented over a 2-min interval. Figure 2 shows a comparison of the effects produced by eight shocks which are and are not accompanied by a specific exteroceptive stimulus. During the first period shown, shock was presented alone; about 2 $\mu$g of epinephrine was released and blood pressure and heart rate increased. A similar effect was produced by the second unaccompanied series of shocks. The third series of shocks was accompanied by a tone which had been associated with the chain of eight shocks on previous trials. There was a smaller increase in heart rate during this series of shocks and also a smaller output

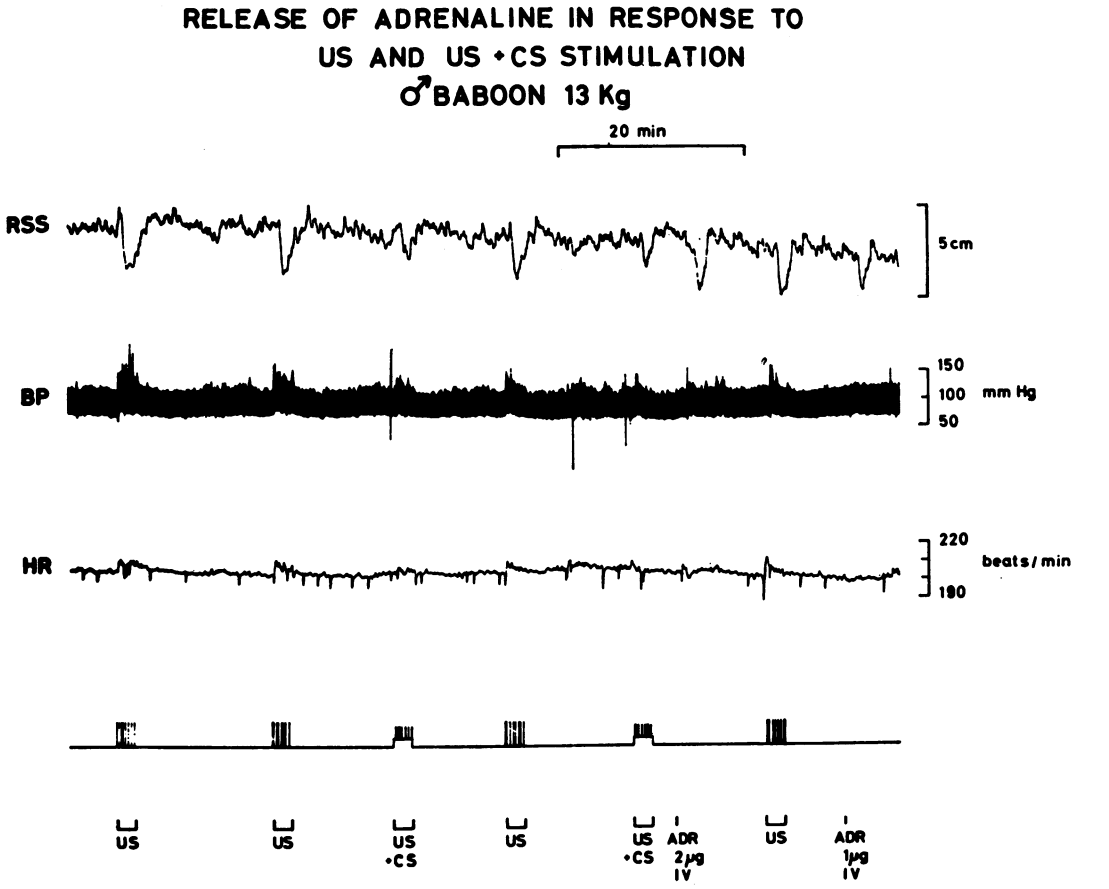


Fig. 2. Polygraph recording from experiment with male baboon (13 Kg). From top, records are movement of section of rat stomach strip (RSS), arterial blood pressure (BP), and heart rate (HR). Scales are shown at the top and to the right of the recordings. Events are indicated on the bottom tracing and by symbols below: administration of epinephrine into the venous blood return (ADR) presentation of electric shocks alone (US) and presentation of electric shocks accompanied by a continuous tone (US + CS). Single large excursions on the BP record are artifacts due to movements by the animal which constricted the arterial catheter.

of epinephrine into the circulation. Next, the shocks were given alone and the increase of heart rate and output of epinephrine were once again larger.

Shocks with tone again produced a smaller change in epinephrine secretion and in heart rate. Intravenous injections of 1 and 2 $\mu$g of epinephrine showed that the previous releases had been within this range. This section of tracing shows that when the series of shocks was paired with a tone to which the animal had been conditioned, there was less output of epinephrine into the circulation than when the shocks were given without warning.

## DISCUSSION

These experiments showed that increases in systolic and diastolic blood pressure and in heart rate were elicited by an auditory stimulus paired with electric shock, and by shock alone. Because no explicit test was made to rule out sensitization or pseudo-conditioning, it cannot be concluded unambiguously that the response to the tone was specifically conditioned rather than being due to pseudo-conditioning. The procedure followed was a delayed conditioning paradigm, which has previously been shown to produce cardiovascular changes. Such changes have been widely reported in dogs (*e.g.*, Gantt, 1966), and increases in heart rate and blood flow under similar procedures have been reported in monkeys (Smith and Stebbins, 1965). As in the experiments of Smith and Stebbins (1965) and Stebbins and Smith (1964), visual observation of the animals did not reveal any substantial increases in gross body movement during the conditioned stimulus. In fact, there was often a lessening of activity during the tones. Although undetected increases in muscle tension might have developed during the conditioned stimulus, successful cardiovascular conditioning has been obtained or maintained in dogs when muscle activity has been abolished by crushing anterior spinal nerve roots (Royer and Gantt, 1966) or by the use of neuromuscular blocking agents (*cf.* Black, 1965). The cardiovascular responses elicited by the tone were, therefore, unlikely to have been artifacts of, or dependent on, an operant skeletal response, but, most likely, were conditioned respondents (*cf.* Rescorla and Solomon, 1968).

Elevated blood levels of catecholamines and 17-hydroxycorticosteroids have been previously reported in monkeys undergoing conditioning by Mason *et al.* (1961).[5] In that experiment, monkeys were exposed to several different aversive conditioning procedures, *i.e.*, a shock avoidance schedule, a conditioned emotional response procedure (an auditory stimulus that preceded shock was occasionally presented while the monkey was working for food reinforcement), and a multiple schedule in which a waiting period preceded, on an irregular and unpredictable basis, exposure to an avoidance schedule, to food reinforcement, to shock punishment, or to the conditioned emotional response procedure. Plasma levels of epinephrine and norepinephrine were determined by the Weil-Malherbe and Bone method using chemical separation and fluorometric identification, and of corticosteroids (17-OH-CS), by the Nelson-Samuels method, on blood samples withdrawn immediately before an experimental session, and after 10 and 30 min. They reported: "While norepinephrine and 17-OH-CS elevations occurred in virtually all the conditioned emotional disturbances investigated in this study, the instances in which marked epinephrine elevations occurred–that is levels above 2.5 $\mu$g/l., were relatively rare". The only situation that produced consistent increases in epinephrine level was the "ambiguous" waiting period. The authors suggest that norepinephrine is released under "stereotyped, predictable situations, in which the conditions associated with the administration of the noxious stimulus to the animal are unambiguous and familiar" (P. 352), whereas, epinephrine is released in conditions which "all possess an appreciable degree of uncertainty, novelty, or unpredictability" (P. 350).

That finding differs considerably from the present results, but so do the methods. At no time during the present experiments was a release of norepinephrine detected, and even with a mixed output of epinephrine and norepinephrine the latter would have been detectable in proportions of 10 to 20%. The blood-bathed organ method primarily detects phasic releases of hormones, and relatively stable levels, or a very slow release, are less

[5]See also the recent supplement to *Psychosomatic Medicine*, Vol. 30, No. 5, Part II, which summarizes a variety of research by Mason and his colleagues on endocrine changes accompanying various conditioning procedures.

easily seen. In the experiment by Mason *et al.* (1961), norepinephrine increased to as much as 13.6 μg/l., a level which, had it occurred in the present study, would have been detected easily.

Almost every detail of the present experimental procedure was different from those of Mason *et al.* (1961), *e.g.*, different species, methods of conditioning, amounts of exposure to conditioning procedures, and time intervals. It would therefore be fruitless to speculate as to which one distinguishing variable is at the root of the difference. One can conclude, however, that an emphasis on the degree of unpredictability or ambiguity of the conditioning procedure is not generally applicable to the present results. It might be relevant to note Mason, Tolson, Brady, Tolliver, and Gilmore (1968) on urinary levels of catecholamines in monkeys under an avoidance schedule. In that study, levels of epinephrine in trained monkeys approximately tripled, whereas those of norepinephrine increased by only 30% during the first 24 hr of an avoidance session. Even though the original data (Mason *et al.*, 1961) on differences in catecholamine output were collected in the same laboratory and in a similar conditioning situation, these authors also acknowledge the presumed importance of the many small differences in procedure that could have produced these markedly different results.

The present study represents perhaps a third pattern of adrenal hormone release, to a third set of behavioral conditioning procedures. We can conclude that shocks and tones paired with shocks in this experiment elicited epinephrine alone, or a mixture of epinephrine and not more than 10 or 15% of norepinephrine. The lower limit of sensitivity to a hormone mixture is at the mean relative level of norepinephrine output detected in the urine of monkeys under avoidance training by Mason *et al.* (1968). The possible congruence of these results should not be overlooked. Altogether, the involvement of the adrenal medulla in response to aversive conditioning procedures seems well established, although the specific variables controlling different types of hormone release are not at all known.

One additional result of the present experiment that deserves some comment was the tendency for lower cardiovascular and hormonal response when a conditioned stimulus preceded the shock than when the shock occurred alone. Similar findings have been reported for the GSR conditioning in man (Kimble, 1961). Rats or dogs also spend more time in a compartment in which shocks are preceded by a stimulus, than in one in which equally frequent shocks are presented alone (Lockard, 1963; Perkins, Levis, and Seymann, 1963; Wagner, 1966). Katcher and Turner (1968) reported, however, that neither heart rate nor blood pressure in curarized dogs differed to signalled and unsignalled shocks. The generality of this finding requires further research.

It also remains to be determined what the interaction is between the cardiovascular and hormonal responses described in this paper and other activities of the organism. Recent work by Miller and his colleagues (Miller, 1969) seriously calls into question any distinction among recordable activities on the basis of type of effector tissue or innervation. The present procedure describes a method for measuring on-line activity of the adrenal medulla, for application of either respondent or operant conditioning procedures. Whether the activity of the adrenal medulla or related autonomic processes during operant avoidance or escape conditioning of some other behavior plays any important role is still largely a matter of speculation (*cf.* Herrnstein, 1969).

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