LSD 334

(1957).

EXCRETION OF EPINEPHRINE AND NOREPINEPHRINE IN VARIOUS EMOTIONAL STATES*

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RESPONSES of the adrenal gland to stress have been the subject of much research (1). Unlike the adrenal cortex, the adrenal medulla as a part of the sympathetic nervous system is intimately connected with the expression of the emotions (2). A study was undertaken to determine the excretion of epinephrine (E) and norepinephrine (NE) of normal and psychiatric patients in various emotional states. Data were obtained on: (a) subjects in both sleeping and waking states, (b) professional hockey players and their coach before and after the game, (c) amateur boxers before and after the contest, (d) neuropsychiatric patients appearing at staff conference, (e) normal subjects in anticipatory states, (f) psychiatric patients receiving the psychotomimetic agent, lysergic acid diethylamide (LSD), and (g) psychiatric patients on whom mental status and Malamud-Sands rating scale records were obtained during the collection period.

The excretion rates of E and NE were studied after graded doses of E and NE were infused. These data were used to estimate the secretion of the amines in the various stress conditions studied.

METHODS

After acid hydrolysis (3), the urine was extracted by the alumina adsorption method of von Euler and Hellner (4) and bioassayed by a modification of the method described by Gaddum and Lembeck (5). The bioassay is based on the quantitative inhibition by the catechol amines of the contraction induced with acetylcholine in an *in vitro* preparation of rat colon and rat uterus. E and NE are approximately of equal potency in their effect on the rat colon, whereas E is some one hundred times as potent as NE in its effect on the rat uterus (6, 7).

Received July 21, 1956.

* Aided in part by a grant from the Army Medical Research and Developmental Board, Contract No. DA-49-007-MD-438, The Ford Foundation, and the Scottish Rite Committee of Research for Dementia Praecox of the National Association for Mental Health.

RESULTS

Infusion experiments

Figure 1 depicts the data of 10 E infusions and 9 NE infusions in doses of 0.05, 0.10, and 0.20 micrograms per kilogram per minute (μg./Kg./min.). Pre-infusion urine was collected from 9:00 A.M. to 10:00 A.M., at which time the infusion was started and continued for thirty minutes. The infusion collection represented the period ranging from 10:00 A.M. to approximately 11:00 A.M. Figure 1 shows the hourly excretion for each dosage rate above its control level. In the case of E, only 0.5–1.0 per cent of the total dose infused appeared in the urine, but in the case of NE from 3.0–5.0 per cent of the total dose appeared in the urine in excess of the control level (8). For the NE infusions the relationship of excretion-above-control and dosage seemed to be essentially linear. However, in the case of E infusion, there was a sharp change in the slope at doses above 0.10 μg./Kg./min. Although there was a two-fold increase in the excretion rate with the doubling of the dose from 0.05 to 0.10 μg./Kg./min., there was a seven-fold increase in the excretion rate on subsequent doubling from 0.10 to 0.20 μg./Kg./min. These data served in estimating the approximate secretion rates of E and NE in the studies reported.

Diurnal variation

Six normal subjects consisting of physicians and laboratory personnel who were conducting their usual daily activities, were studied. Each col-

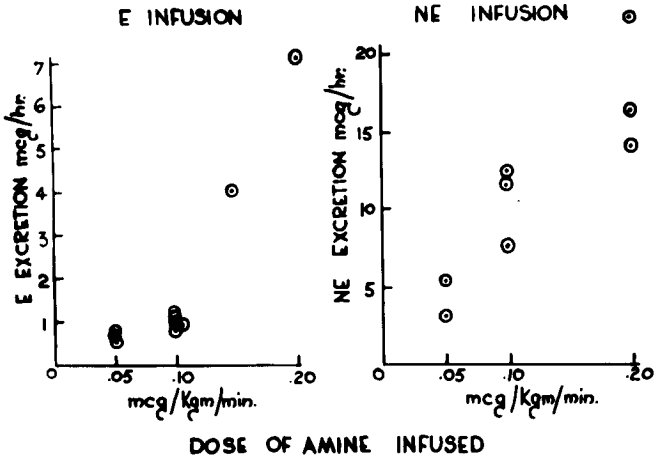

FIG. 1. The excretion of epinephrine (E) and norepinephrine (NE) above control levels after thirty-minute infusion of E and NE in doses of 0.05, 0.10 and 0.20 μg. Kg./min. (*see* text).

TABLE 1. DIURNAL VARIATION OF NE AND E EXCRETION IN 6 NORMAL SUBJECTS*

	NE (μg./hr.)	E (μg. hr.)
Sleep	1.2 ±0.14	0.02 ±0.01
Morning	2.3 ±0.49	0.10 ±0.02
Day	2.4 ±0.60	0.21 ±0.07

* *See* text for times of collection.

lected a sample representing the period of sleeping, a second sample from the time of waking to about 10:00 A.M., and a third sample from 10:00 A.M. to the time of retiring at night. The results are listed in Table 1. NE excretion increased two-fold, and E excretion by five to ten-fold on waking.

Professional hockey

This sport entails considerable aggressive activity in attack and defense. The game is fast and involves marked physical activity and man-to-man contact. Pre-game samples of urine were collected at ten to thirty minutes before game time, and post-game samples were collected some three hours later. The latter samples included urine formed during the contest. Game time was 8:00 P.M. In Table 2 are listed the values for pre-game and post-game collections (20 samplings in six games) of defensemen and forwards who do the skating. The data are presented in terms of creatinine because it was not always possible to obtain timed samples. For samples taken following the game, there was a six-fold increase in NE excretion over the control level, with a moderate increase in E excretion. Two players were sampled before the game, but on physical examination by the trainer, they were not permitted to participate. In the same table are presented the data of these players, indicating no post-game increase in NE but an appreciable increase in E. Both players sat in the press box and watched the game.

The goal tender skates very little but is in constant vigilance in front of the net ready to defend the goal. The coach remains on the bench directing strategy. Data obtained on the goal tender in three games, and on the coach in six games are presented in Table 3. There was a marked increase in both NE and E excretion in the goal tender, but on the average there were no significant changes in the excretion of either amine in the coach.

TABLE 2. EXCRETION OF NE AND E IN MEMBERS OF A PROFESSIONAL HOCKEY TEAM DEFENSEMEN AND FORWARDS VERSUS NON-PARTICIPATING PLAYERS

Urine collection	Number of hockey players sampled	NE (μg./100 mg. creatinine)	E (μg./100 mg. creatinine)
		*Active hockey players (defensemen and forwards)**	
Pre-game	20	2.7 + 0.43	0.36 + 0.07
Post-game	20	15.3 + 2.20	0.95 + 0.21
		$t = 5.66$ P = less than .001	$t = 2.68$ P = less than 0.05, greater than 0.01
		Two players who did not participate in the game†	
Pre-game	#18	2.2	0.23
Post-game		3.3	0.75
Pre-game	#10	5.6	0.78
Post-game		5.3	1.42

* The approximate hourly excretion is 10% less than the figure given in terms of 100 mg. creatinine when corrected by creatinine coefficient.[1]

† Due to their physical condition.

[1] Data in terms of μg./100 mg. of creatinine may be computed in terms of μg. hr. if the weight of the subject is known. Since the weight of the athletes is highly correlated with muscle mass, and creatinine excretion is dependent on muscle mass, the computation of the formula for creatinine coefficient would furnish the creatinine excretion per unit time for a particular weight (24).

$$\text{Creatinine Coefficient (18-32 for males)} = \frac{\text{Mg. creatinine per 24 hrs.}}{\text{Body wt. in Kg.}}$$

For example, using a creatinine coefficient of 26, it was calculated that the subject weighing 200 pounds would excrete approximately 100 mg. hr. Since the average weight of the hockey players was 180 pounds, the estimate in terms of μg. hr. would be 10 per cent less than that presented in terms of μg./100 mg. of creatinine.

TABLE 3. EXCRETION OF NE AND E IN PROFESSIONAL HOCKEY PLAYERS - GOAL TENDER AND COACH

	Number of samples	Urine collection	NE (μg./100 mg. creatinine)	E (μg. 100 mg. creatinine)
Goal tender	3	Pre-game	3.3 + 0.7	0.45 + 0.20
		Post-game	9.2 + 1.8	1.30 + 0.81
Coach	6	Pre-game	1.8 + 0.5	0.38 + 0.09
		Post-game	3.7 + 0.9	0.43 + 0.21

Amateur boxing

Six amateur boxers were sampled in the finals of a national tournament. Each boxer was engaged for three rounds, or a total of fifteen minutes from the beginning to the end of the contest. The results in this case were also expressed in terms of creatinine because of the difficulty of obtaining timed urine samples. In Table 4 are presented the results for each boxer studied.

TABLE 4. EXCRETION* OF NE AND E IN AMATEUR BOXERS

Boxer	Urine collection	NE (μg./100 mg. creatinine)	E (μg./100 mg. creatinine)
Ch	Pre-contest	17.9	1.64
	Post-contest	—	—
Sm	Pre-contest	38.1	1.78
	Post-contest	32.4	0.67
Br	Pre-contest	4.2	0.40
	Post-contest	7.0	0.87
Pe	Pre-contest	6.7	0.22
	Post-contest	2.8	0.41
Why	Pre-contest	1.7	1.67
	Post-contest	—	—
Bra	Pre-contest	—	—
	Post-contest	15.9	1.70

* The approximate hourly excretion is 25 per cent less than the value given in terms of 100 mg. of creatinine when corrected by the creatinine coefficient.

Unlike the pre-game E values for the hockey players, the pre-contest E values for the boxers were elevated, with or without further elevation after the contests. The NE excretion was varied; elevated values were observed both before and after the contest. The pre-contest E values in this study were the highest obtained in the so-called "control" samples of all our studies.

Neuropsychiatric patients during staff interview

The conditions of the interview were in marked contrast to those encountered by the athletes. The patient sits across from the psychiatrist doing the interviewing in the presence of some 20 members of the hospital medical staff. All participants are seated and the exchange in this case is

strictly verbal. The setting is serious and to the patient it is very important, because on the basis of his performance decisions are made by the staff which affect his immediate future. Eleven subjects were studied, on 8 of whom control samples were obtained. The interviews took place on Thursday mornings and the control sample was obtained at the same time

TABLE 5. EXCRETION OF NE AND E DURING STAFF CONFERENCE INTERVIEW OF 11 NEUROPSYCHIATRIC PATIENTS

	Number of samples	NE (μg./hr.)	E (μg./hr.)
Interview day	11	2.6±0.4	0.50±0.14
Control day	8	2.3±0.2	0.27±0.12
			P = less than .001

on the next day—Friday. The results are listed in Table 5. There were no changes in NE excretion when the interview day was compared with the control. However, in every subject on whom a control was obtained there was an elevated excretion of E during the interview. As might be expected, there were marked individual variations in this increase. The subjects in general were self-effacing and on their best behavior with no aggressive or active emotional display.

Normal subjects in anticipatory states

Urine collections were made on 11 normal subjects before they underwent the usual insulin tolerance test and the methacholine (Mecholyl) test described by Funkenstein *et al.* (9). The subjects consisted of laboratory personnel and students. There was a varying degree of knowledge and understanding as to the nature of these tests among the group. In Table 6, the variability of the excretion rates may be seen. The subjects who were familiar with the nature of the tests and the hospital setting were quiet and waited patiently; they had normal excretion rates of E and NE. On the other hand, the students and personnel unfamiliar with the tests and the setting were restless, asked many questions of the attending nurse and physician, and were quite anxious about the experiments. Subjects Gi and Dm had very high excretions of NE with normal values for E, and Subjects Ms and Sm had high values for both amines in each instance.

Administration of lysergic acid diethylamide (LSD)

Fourteen psychiatric subjects were given from 150 to 300 micrograms of LSD orally. Seven were chronic schizophrenics, 4 were manic-depressive

TABLE 6. PRE-TEST NE AND E EXCRETION OF 11 NORMAL SUBJECTS*

Normal subjects	Before insulin test		Before methacholine test	
	NE (μg. hr.)	E (μg. hr.)	NE (μg./hr.)	E (μg./hr.)
Ba	3.4	0.35	1.7	0.13
El	3.2	0.16	4.9	0.17
El	4.1	0.17	—	—
Fo	0.9	0.02	—	—
Ma	1.2	0.10	2.8	0.18
Sp	1.5	0.05	1.0	0.20
Zi	1.9	0.15	3.2	0.51
Gi	3.7	0.22	7.7	0.17
Dm	—	—	8.9	0.07
Ma	4.2	0.52	3.2	0.80
Sm	9.0	1.82	3.5	0.96
Pa	—	—	3.2	0.07

* Adapted from data of Elmadjian *et al.* (19).

patients and 3 had involutional depression. The control collection was made from 10:00 A.M. to 2:00 P.M., at which time the LSD was administered. The LSD collection was made from 2:00 P.M. to 10:00 P.M. In this series, the chronic schizophrenics showed no reaction to the LSD in mood, affect or perception. As seen in Table 7A there were no significant changes

TABLE 7. EFFECT OF ADMINISTRATION OF LSD ON NE AND E EXCRETION IN 14 NEUROPSYCHIATRIC SUBJECTS

	Number of samples	NE (μg./hr.)	E (μg./hr.)
		A. *Non-reactors*	
Chronic schizophrenia:			
Control	7	2.3±0.4	0.14±0.02
LSD	7	2.0±0.8	0.20±0.03
		B. *Reactors*	
Manic depressive state:			
Control	4	2.8±0.5	0.21±0.09
LSD	4	16.7±3.7	1.54±0.58
Involutional depression:			
Control	3	5.6±0.2	0.21±0.05
LSD	3	3.2±1.5	1.24±0.78

in either E or NE excretion. On the other hand, in the manic-depressive patients and those with involutional depression there was a marked increase in E excretion (Table 7B). In the manic-depressive group there was also an increase in NE excretion, but in the involutional depression group there was no change in NE values. In contrast to the schizophrenics, the other two groups manifested marked psychiatric changes following administration of LSD.

Psychotic subjects on whom Malamud-Sands rating scale records were obtained

In 10 psychiatric patients a study was made of the relationship between results of Malamud-Sands rating scale tests and the excretions of E and NE. This scale (10) rates the patient in 22 categories and the data are recorded on a check sheet. On the rating scale each item scored appears on the left-hand side. A designated base line appears through the center of the rating scale. Going from the base line to either the left or the right, the deviations are observed (Table 8). In the preliminary analysis of the data in the 22 categories rated, motor activity and hostility reactions were abstracted and a composite score including these two items was computed. In Figure 2 is shown the relationship of this score to NE excretion. Patients with active aggressive emotional display had higher NE excretions; those with passive self-effacing emotional display had normal levels of NE. In Figure 2, when a line appears through the circles, it indicates that these subjects also had a high excretion of E. The subject indicated by an asterisk had normal NE excretion, but the excretion of E was 2.75 μg. per hour, which is extremely high. This subject showed periodic bursts of excitement with expressions of fear and guilt.

TABLE 8. PORTION OF THE PSYCHIATRIC RATING SCALE OF MALAMUD AND SANDS (10)

FUNCTION	6	5	4	3	2	1	BASE LINE	1	2	3	4	5	6
APPEARANCE	Bizarre		Decorative		Over-meticulous		NEAT — CARELESS	Slovenly		Untidy	Incontinent		Smearing
MOTOR ACTIVITY	Excited		Agitated		Restless		ACTIVE — QUIET	Under-active		Retarded	Stuporous		
MIMETIC EXPRESSION	Incongruous		Dramatising		Exaggerated		ANIMATED — RESTRAINED	Stiff		Waxy-flexibility	Mask-like		
RESPONSIVITY	Anaklitic		Suggestible		Dependent		FLEXIBLE — RIGID	Stubborn		Resistive	Negativistic		
HOSTILITY REACTIONS	Destructive		Combative		Belligerent		AGGRESSIVE — SELF-EFFACING	Self-deprecating		Self-mutilating	Suicidal		

The ratings obtained for the functions, "motor activity" and "hostility reactions," were added in computing the total scale. When a subject was rated as being agitated and combative the total score would then be 8 to the left of the base line. On the other hand, a subject rated as self-deprecating and retarded would have a score of 5 to the right of the base line.

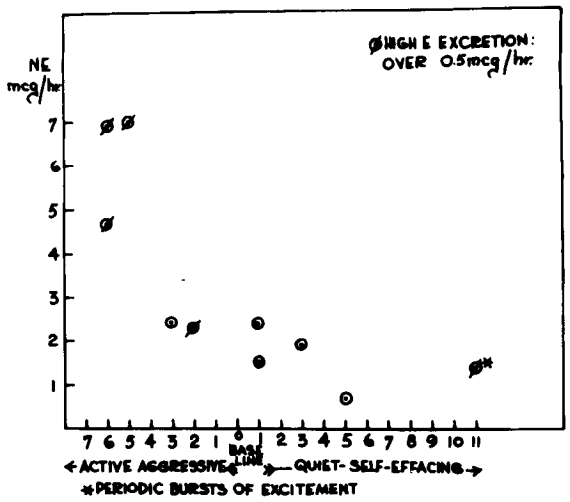

FIG. 2. The relation of norepinephrine excretion to emotional state of neuropsychiatric patients. (The abscissa depicts the composite score for the functions of motor activity and hostility reactions from the Malamud-Sands rating scale, and the ordinate represents the excretion of norepinephrine in μg. per hour during the observation period.)

DISCUSSION

In our studies, three general excretion patterns were evident during emotional states: 1) elevated NE excretion with normal E values, 2) elevated E excretion with normal NE values, and 3) elevated excretions of both NE and E. The diurnal variation data presented in Table 1 may be considered as normal excretion rates with which to compare excretion rates during various stresses.

In anticipatory states (*e.g.*, Subjects Dm and Gi, Table 6) and in hockey players during a moderately tense game, we observed high NE excretion with slight elevated E excretion. In the involutional-depressive patients receiving the psychotomimetic agent, LSD, and in the neuropsychiatric patients during an interview, there was elevated excretion of E with little elevation in that of NE. Finally, when an intense emotional display was evident, such as in manic-depressive patients treated with LSD, hockey players, amateur boxers, and disturbed neuropsychiatric patients, both NE and E excretions were elevated. When increased excretion of NE was present, there was ample evidence of aggressive, active emotional display. In cases of tense, anxious but passive display, the excretion of E was frequently elevated.

In studies of airmen, von Euler reported that during the air-borne period there was increased excretion of E, regardless of whether ground personnel

or pilots were sampled (11). This result is similar to the excretion patterns obtained when subjects operated the Werthessen-Hoagland pursuitmeter which simulates the operation of controls of a plane (8). As might be expected, the degree of increase was much smaller in the latter study. Further reports from von Euler's laboratories indicate that increased NE and E excretions are found in athletes who participate in skiing and running events (12). In surgical shock, there is high NE excretion with or without elevated E excretion (13).

The question arose during our studies whether NE excretion could be due to motor activity per se. This is highly unlikely, since several subjects with marked emotional disturbances who were lying down or sitting had high NE excretion with or without elevated E excretion (*e.g.*, Gi, Dm, Sm; Table 6 and Fig. 2). Furthermore, in terms of physical movement (generalized exercise), the goal tender in the hockey study remained in one place during the whole playing time, yet he manifested a marked increase in NE excretion. To test the effect of generalized exercise, experiments were then conducted in which Subject El raked grass for two hours; this work involved considerable walking and movement of the muscles in the shoulders and arms. This subject was not emotionally involved and, at the end, he was physically tired. The excretion of NE was normal (2.2 μg. per hour), but the excretion of E was elevated (0.35 μg. per hour). Two-hour samples were obtained on 2 laborers—1 who worked at mixing mortar and carrying bricks, and 1 who unloaded trucks and was a pick-and-shovel man. The former had an NE excretion of 3.2 μg. per hour and an E excretion of 0.54 μg. per hour, whereas the latter had an NE excretion of 5.7 μg. per hour and an E excretion of 0.12 μg. per hour. It may be concluded that exercise per se (that is, without marked emotional involvement) is not a major factor in determining the high NE values observed, such as those in the boxers or in the hockey players.

The secretion rate levels of the catechol amines E and NE may be estimated by comparing the excretion data obtained during the various stresses with those of the infusion experiments (Fig. 1). Under certain conditions of stress, such as hockey players during the game, the output of NE is of the same order as that during infusion of 0.2 μg. of NE per Kg. per minute, and the output of E is of the same order as that during infusion of from 0.10 to 0.20 μg. of E per Kg. per minute. These data are comparable to those presented by von Euler (14).

Since doubly adrenalectomized humans excrete little or no measurable amounts of E, it seems safe to assume that practically all the E appearing in the urine in normal subjects is secreted from the adrenal medulla (8, 15). NE values for subjects with the adrenals removed are within the normal range. Furthermore, in studies in which the diurnal variation of adre-

nalectomized subjects was determined, there was an increase in NE excretion in the waking state over that in the sleeping state– similar to the increase observed in normal subjects (8). These results indicate that, in all probability, most of the NE excreted is extra-adrenal in origin. Data presented by von Euler on the relative concentrations of E and NE in the adrenal medulla and peripheral postganglionic fibers of the sympathetic nervous system indicate that there is ten times more E than NE in the human adrenal, and that practically all of the neurohormone present in the peripheral nerves is NE. The demonstration of NE secretion following stimulation of postganglionic nerves also adds to the evidence that NE is the peripheral neurohormone of the sympathetic nervous system (16, 17).

Qualitative differences of sympathico-adrenal discharge have been demonstrated by varying the intensity of electrical stimulation of the hypothalamus (18). Evidence also seems to indicate that the central sympathetic representation involved with the secretion of E is different from that involved with the secretion of NE. Hypoglycemia induced by administration of insulin selectively increases the excretion of E without concurrent elevation in the excretion of NE (19, 20). On the other hand, during the hypotension induced by administration of methacholine, although there is no significant increase in E excretion there is a distinct increase in NE excretion when compared with the NE excretion observed followihg an insulin test in the same subject (20). Changes from the recumbent to the standing position result in an increased excretion of NE with no change in E (21). Experimental data of Gellhorn support the view that hypotension induces secretion of NE (22).

With a brief review of experimental data available, one may speculate as to the location of the areas of central sympathetic representation concerned with NE and E excretion. Evidence that electrical stimulation of the posterior hypothalamus induces a sharp increase in blood pressure is well established (23). That this occurs in the absence of the adrenal has also been noted. Hyperglycemia which is induced by stimulation of the lateral hypothalamic region depends on the integrity of the adrenal medulla, since it does not occur when the splanchnic nerve is cut. The inference may be drawn that the posterior hypothalamus is concerned more with secretion of NE, whereas the lateral hypothalamus is concerned more with secretion of E. However, the vasomotor center in the medulla oblongata the region of the floor of the fourth ventricle—is by far the most sensitive area related to E secretion (2).

SUMMARY

The excretion of epinephrine (E) and norepinephrine (NE) was determined in athletes (hockey players and boxers), normal subjects in anticipa-

tory states, and psychiatric subjects. In the last group, mental status and rating scales were also studied. The results support the hypothesis that active, aggressive emotional displays are related to increased excretion of NE, with or without increased excretion of E, whereas tense, anxious but passive emotional displays are related to increased excretion of E in association with normal excretion of NE.

From infusion studies it was found that, under the foregoing conditions of stress, secretion rates of NE rose to levels comparable to those during infusion of 0.2 μg. of NE per Kg. per minute, whereas the highest E levels were comparable to those during infusion of 0.1 μg. of E per Kg. per minute.

The sources of the NE and E are discussed, as well as the central autonomic representations controlling their secretion.

Acknowledgments

The authors wish to express their gratitude to Dr. Thomas A. Kelley, Mr. Lynn Patrick and Mr. Milton Schmidt of the Boston Bruins Hockey Team and to the players who made the study possible; and to Mr. Hammy Moore and Mr. Wynn Green, the trainers, who actively participated in the conducting of the study.

To Mr. William Downing, President of the New England Chapter of the National Amateur Athletic Union, and to the boxers who participated, the authors express their appreciation.

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