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BIOCHEMICAL MEASUREMENTS OF THE HUMAN STRESS RESPONSE

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The threefold purpose of the study was (a) to identify biochemical response patterns to specific modes of stress, (b) to continue the search for suitable methods of quantifying stress in operational settings, and (c) to compare biochemical and psychophysiological stress indices. Three experiments were conducted using Air Force pilots as subjects. One experiment focused on the biochemical responses of student and instructor pilots who were involved in flight precautionaries or emergencies. A second experiment explored the biochemical response patterns to different modes of stress. The third experiment assessed the relationship between biochemical and psychophysiological indices

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Item 20 (*Continued*)

in pilots performing a task in a simulated hostile environment. When viewed in its entirety, data collected in the contract demonstrate a general response to a variety of stress modes, which is characterized by an increase in the excretion of epinephrine and norepinephrine, a decrease in the ratio of dopamine to norepinephrine, and an increase in the ratio of norepinephrine to serotonin. When examined individually, the experiments revealed the following. Although there were some excretion patterns common to all stress conditions, specific response patterns were also noted for various modes of stress. A battery of indices was identified which reflected the stress response across many modes of stress in a variety of field settings, and biochemical and psychophysiological indices did not show good agreement.

SUMMARY

Objectives

The objectives were (a) to identify neuroendocrine biochemical response patterns to specific modes of stress, (b) to develop a battery of biochemical indices that are sensitive to stress, and (c) to compare biochemical and physiological indices of stress.

Background/Rationale

Psychophysiological measures of stress have provided indices of moment-to-moment stress response, but the measures can be obtrusive and difficult to obtain in operational environments. The relations between psychophysiological and biochemical stress responses have not been determined. Knowledge of these relations can provide a step toward the development of a methodology that is both flexible and time specific for measuring response to stress.

Approach

Experiments were conducted using a battery of neurotransmitters and their metabolites as indices of stress response. The battery consisted of epinephrine, norepinephrine, dopamine, serotonin, vanillymandelic acid, 4-hydroxy 3-methoxyphenylglycol, homovanillic acid, 3, 4-dihydroxyphenyl-acetic acid, and 5-hydroxyindoleacetic acid. These measures were used to determine the stress response to flight, to simulated flight, and physical and mental work. (The report was reviewed additionally and endorsed for publication by personnel of the Crew Technology Division, USAF/SAM.)

Specifics

Three experiments were conducted using Air Force pilots. In Experiment One (40 subjects), stress response to in-flight "precautionaires" and "emergencies" was determined. The excretion of five neurotransmitters and metabolites into the urine during flight was used to measure the stress response of instructor pilots and student pilots. Immediately after the pilots landed, urine samples were collected for analysis. Significant main effects of both pilot's experience and event seriousness were found for the excretion rates for several biochemicals. Data show marked and measurable stress response (epinephrinergic) in both students and instructor pilots. Students showed a greater stress response to more serious precautionaries such as mechanical problems or smoke and fumes in the cockpit.

In Experiment Two, 10 subjects were examined on eight occasions. Biochemical measurements were taken of the stress response to submaximal and maximal physical stress (treadmill walking), to simulated landing on an aircraft carrier with and without secondary task loading, and to three aircraft training sorties. Data show four main results: (a) urinary rates of excretion of biogenic amines and their related metabolites can be used as an index of short-term stress, (b) increased norepinephrine and epinephrine values reflect an achievement-demanding situation, (c) the serotonergic system appears to produce a greater serotonin turnover in all training tests, and (d) decreased dopaminergic activity is generally responsive to selected tasks.

As a sideline to Experiment Two, both biochemical and physiological data were collected during the simulated carrier landing task. Physiological measures included brain coherence, cardiac inter-beat interval (IBI), change in reaction time to a secondary tone, and change in cardiac IBI over a 2-minute period. Analysis showed no correlation between biochemical and physiological indices.

In Experiment Three, stress response to simulated low altitude flight in a hostile environment was investigated using both biochemical and psychophysiological measures. Psychophysiological measures of stress were respiratory rate, cardiac IBI, change in respiratory rate, and change in IBI. Two groups of pilots served as subjects. The inexperienced

group (14 subjects) had just completed fighter lead-in training but had no actual fighter experience. The experienced group (20 subjects) consisted of pilots who were returning to the cockpit after a non-flying assignment. Both groups flew a sequence of simulated low altitude penetrations in an environment containing anti-aircraft artillery and surface-to-air missiles. Psychophysiological stress response was monitored during the missions. Immediately following the last low altitude penetration, urine was collected for the biochemical analysis. The two groups of pilots [illegible] significantly in their biochemical response to simulated combat. Biochemical and psychophysiological measures [illegible] response were largely uncorrelated.

Conclusions/Recommendations

1. Biochemical stress response patterns do vary with the mode and degree of stress.

2. A battery of indices has been identified that appears to reflect the stress response across many modes of stress in a variety of simulated field settings.

3. Biochemical indices and psychophysiological indices do not show good agreement. Data from experiments quantifying stress by one technique should not be simply and directly compared with those based upon the other technique.

PREFACE

This research represents a portion of the research program of the Air Force Human Resources Laboratory Technical Planning Objective 3, the thrust of which is air combat tactics and training. The general objective of this thrust is to identify and demonstrate cost-effective training strategies and training equipment capabilities for use in developing and maintaining the combat effectiveness of the Air Force aircrew members. More specifically, the research was part of the research program conducted under the Combat Mission Training Systems subthrust, which has as its goal to provide a technology base for training high level and quickly perishable skills in simulated combat environments. Work Unit 2313-T3-14 Stress Utilization Reduction in Flying Training, addressed a portion of this subthrust, namely, the effects factors affecting individuals' biochemical stress response. Dr Thomas Longridge was the project scientist and Dr Joe De Maio was the task scientist.

This research was conducted by the Human Performance Laboratory, Department of Health and Physical Education, and the Department of Chemistry of Arizona State University under the provisions of Contract F33615-80-K-0022 with the Air Force Human Resources Laboratory.

Special thanks are extended to the 96th Flying Training Squadron at Williams AFB. Without the cooperation and interest of the flight commanders, flight schedulers, instructor pilots, and students, the quality of the study would have been compromised.

We also gratefully acknowledge the financial support received from Arizona State University research funds and the unselfish assistance provided by Ms Nancy E. Bishop, Dr Joseph C. De Maio, and Mr Leonard C. Reuther.

This report has been reviewed by appropriate professional staff of the Crew Technology Division of the Air Force School of Aerospace Medicine and has been endorsed for publication with note that the studies reported contribute significantly to the development of biochemical indices of stress for application in operational environments.

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HUMAN STRESS RESPONSE

INTRODUCTION

Stress has long been recognized as an important component in learning and performance. Studies conducted by the Federal Aviation Administration's Stress Physiology Laboratory (Melton & Fiorica, 1971; Melton & Wicks, 1967) and by the United States Air Force School of Aerospace Medidine (Mefford, Hale, Shannon, Prigmore, and Ellis, 1971) indicate that flight training is quite stressful to student pilots. Fighter pilots report that the nature of their stress response is the most critical element in combat success (Griffith, 1979; Rictor, 1980).

The biochemical events that accompany stress alter perception, cognitive function, and motor responses (Frankenhaeuser, 1971, 1975; Frankenhaeuser & Patkai, 1964; Levi, 1972; Pitts, 1969; & Smith, 1973). Moderate levels of stress result in biochemical changes that enhance alertness and have an organizing effect on behavior. High levels of stress bias the subject's cognitive and motor processes toward readily accessible stored information and overlearned responses, respectively (Eysenck, 1976). In the pilot training environment, this behavioral rigidity may slow learning and increase the number of hours required to attain competence.

The degree to which a combat pilot is anticipating (ahead of) or reacting to (behind) events is to a large extent determined by the nature of the stress response (Griffith, 1979). The arousal that characterizes pronounced stress may take the form of attentiveness, aggressiveness, and euphoria; confusion, disorientation, and panic; or some yet different manifestation. A combat pilot in the former state would stand a good chance of coping with a combat engagement for which a novel response was required. The latter state is not conducive to successful operation of high performance man-machine weapons systems in any combat setting.

All perceptual, cognitive, and motor activity result from neuronal impulse transmission (Siegel, Albers, Katzman, & Agranoff, 1976). Three neurotransmitters which play a direct role in this process are norepinephrine (NE), dopamine (DA), and serotonin (5HT). The metabolic end products of these neurotransmitters are vanillylmandelic acid (VMA) and 4-hydroxy-3 methoxyphenylglycol (MHPG) for norepinephrine (and epinephrine); homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) for dopamine; and 5-hydroxyindoleacetic acid (5-HIAA) for serotonin. Neuronal transmission may also be indirectly influenced by NE and epinephrine (E) secreted by the adrenal glands during stress (Mason, 1968).

Stress has long been recognized as both a fundamental component of human behavior and a significant problem to pilot training and performance (Curran & Wherry, 1965; Hale, Duffy, Ellis, & Williams, 1965; Hartman, 1973; Krahenbuhl, Constable, Darst, Marett, Reid, & Reuther, 1980; Krahenbuhl, Darst, Marett, Reuther, Constable, Swinford, & Reid, 1981; Krahenbuhl, Marett, & King, 1977; Krahenbuhl, Marett, & Reid, 1978; Melton, Hoffman, & Delafield, 1969; Melton, McKenzie, Kellin, Hoffmann, & Saldivar, 1975; and Sarviharju, Huikk, Jouppila, & Kaerki, 1971). An integrated and functional definition of stress at the biochemical level is needed, however, before prediction and regulation can become a reality.

RATIONALE

Most investigations of the human stress response feature one or, at the most, several biochemical indices. These univariate studies have most often featured the adrenergic and noradrenergic systems. The dopaminergic and serotonergic systems have been examined more frequently in recent work, but the simultaneous examination of all these systems has not been undertaken. Attempts to explain stress and performance from the activities of a single system have not been fruitful; thus, the current study represented a significant expansion over earlier work in that four hormones/neurotransmitters and their metabolites were examined concurrently.

In lower animals, the study of neurotransmitters, their metabolites, and hormones may involve the analysis of urine, blood, spinal fluid, or brain tissue. Studies utilizing normal humans are typically limited to blood or urine. Blood analysis has the advantage of providing an event-specific glimpse at chemical levels in the bloodstream; however, it is an invasive technique not readily adaptable to field settings. The analysis of urine from a timed sample suffers because event-specific peaks and troughs are averaged, and an abstract of the total collection period is all that can be obtained. It has the advantage, however, of being a noninvasive method where, because of the efficiency of the kidney as a trap and the controlled outflow, an excretion rate can be calculated. Thus, while no one imagines that brain events are precisely measured in urine, timed excretion rates do indicate change by providing an integrated measure adaptable for use in field settings.

OBJECTIVES

The three objectives in this effort were (a) the identification of biochemical response patterns to specific modes of stress, (b) a search for methods suitable for evaluating stress responses in subjects under operational conditions, and (c) the comparison of simultaneously collected biochemical, psychophysiological, and behavioral responses in stressful settings. Three experiments were conducted to achieve these objectives.

The first experiment was designed to examine the biochemical responses of students and instructor pilots who experienced flight emergencies. The second experiment explored biochemical response patterns to different modes of stress. The third experiment was conducted in collaboration with another effort (Contract F33615-80-R-0020) and provided the opportunity to determine the association between biochemical and psychophysiological indices. A general hypothesis for these investigations was that distinct excretion patterns would emerge.

METHODS

The methods section has been divided into four sections. The first section contains the methods that were common to all three studies (generic). Each of the remaining sections details the procedures specific to the individual experiments.

Generic Methods

Subjects for all aspects of the project were Air Force personnel from whom informed consent was obtained. The research was conducted in conformance with the principles embodied in the Declaration of Helsinki.

For all experiments, timed urine samples were obtained from the subjects. Immediately prior to each collection period, subjects emptied their bladders and were encouraged to drink at least 250 ml of water, thereby reducing possible errors due to inadequate amounts of urine. At the close of the timed period (normally 30 minutes post-experimental conditions), the subjects again emptied their bladders and these specimens were collected for analysis. The exact length of time and total volume were noted. A 100-ml aliquot of each sample was stabilized with 1 ml of 10% EDTA-4% thioglycolic acid and stored at -90°C until analyzed. Basal excretion data were collected during similar time periods on two nonflying days selected to avoid academic and physical training requirements. These basal excretion rates were averaged to provide a more stable index of resting excretion rates.

To analyze all nine components, three different clean-up procedures were used. First, E, NE, and DA were analyzed according to the method of Riggin and Kissinger (1977) involving cation exchange chromatography followed by alumina adsorption. Dihydroxybenzylamine (DHBA) was the internal standard. The final alumina eluant was filtered and injected into a high-performance liquid chromatograph (HPLC) under condition A described in next paragraph. Second, DOPAC, MHPG, HVA, 5-HIAA, and VMA were determined by a modified method of Joseph, Kadam, and Risby (1981). Isovanillic acid was added as the internal standard. An organic extract of the sample was evaporated to dryness under N_2, and the residue, dissolved in H_2O, was injected into the HPLC under condition B described in next paragraph. Third, 5HT was analyzed by a modified procedure of Koch and Kissinger (1979). N-methyl serotonin was added as the internal standard and urine clean-up was achieved by ion exchange chromatography. The filtered eluant was injected into the HPLC under condition C described in next paragraph.

HPLC was carried out with a Waters μ-Bondapak C^{18} 300 x 3.9 I.D. mm 10 μ reverse-phase column, protected with a Whatman

Pell ODS (30-38 μm guard column) and a Whatman silicon gel precolumn (37-53 μm). Separation was achieved for condition A with a citrate-phosphate pH 3.0 mobile phase containing sodium octyl sulfate as ion pairing agent. Condition B used 0.1 M phosphate buffer pH 3.0 containing 14% methanol as the mobile phase. Under condition C, 0.5 M ammonium acetate buffer pH 5.1 containing 15% methanol was employed as the mobile phase. The biogenic amines and their related metabolites were measured on-line using electrochemical detection at +0.72 V and 5 nA with condition A, +0.76 V + 50 nA for condition B, and +0.5 V with 5 nA for condition C. The substances were quantified by comparing areas of the constituent amine and metabolite with their respective internal standard and to external standards. Duplicate determinations were run as a check of reliability.

Experiment One

The first experiment examined the biochemical responses of pilots and students who experienced in-flight incidents that were classified as "emergencies" or "precautionaries." The design of this study was ex post facto experimental. The independent variable was the classification of the in-flight event, and the dependent variable was the biochemical response.

The regimented nature of flight-line operations made this study feasible. Pilots leave for their flights at a precise time and void shortly before their departure. During a 4-month period, members of the research team met crews from returning flights that had been classified as "emergencies" or "precautionaries." Urine samples were collected from those subjects willing to cooperate and with certain recollection of the time they voided prior to their flight. Basal measures and specifics regarding the incident were gathered at a later date.

Experiment Two

The second experiment examined the biochemical responses of student pilots to differing modes of stress. The study featured a repeated measures, experimental, single group design. The independent variable was the mode of the stressor and the dependent variable was the biochemical response. The modes of stress studied included two intensities of exercise, a simulated aircraft carrier landing task, and three undergraduate pilot training flights.

Exercise Tasks. Two levels of exercise intensity were utilized: (a) 20 minutes of treadmill grade walking at 60% of the maximal aerobic capacity ($\dot{V}O_2max$), referred to hereafter as SUB EX (for submaximal exercise), and (b) treadmill grade walking to exhaustion, hereafter referred to as MAX EX (for maximal exercise).

The exercise tasks were administered by first determining each subject's maximal aerobic capacity utilizing the open-circuit method and a continuous incremental work test (Balke & Ware, 1959). Expired gas samples during exercise were collected in meteorological balloons through a breathing valve and collection system described by Daniels (1971). Gas samples were passed through a drying tube and analyzed for CO_2 and O_2 with the Beckman LB-2 and 4-digit OM-11, respectively. These instruments were calibrated before and after each test. Expired gas volumes were determined with a Parkinson-Cowen CD-4 gas meter. This test to exhaustion lasted from 21.5 to 25.0 minutes (with a mean of 23.3 minutes for the group). Oxygen consumption was determined for five submaximal workloads. A regression equation which related workload (criterion) to oxygen consumption (predictor) was constructed for each subject and used to predict a workload that would represent 60% of the subject's maximal aerobic capacity. These submaximal tests were each 20 minutes in duration.

Simulated Aircraft Carrier Landing Task. The simulated aircraft carrier landing task (SIM) used the hardware, software, and procedures previously described by Lindholm and Cheatham (1983), except that a single 25-trial session was used. The display was an out-the-window simulation of a Navy A-7 aircraft landing on a carrier deck. Physiological and performance measures were also gathered, again as previously described (Lindholm & Cheatham, 1983). The 25 trials included 5 trials on a tone task alone, 10 trials on the carrier landing task alone, and 10 trials attending to both the tone task and the carrier landing task. The physiological variables included brain coherence (the proportion of variance of N2 amplitude accounted for by the amplitudes of N1, P2, and P3), inter-beat interval (IBI) during the tone task, composite performance score for the carrier task performed alone, composite performance score for the carrier and tone tasks performed simultaneously, change in reaction time from the tone task alone to the carrier and tone tasks combined, and the percent change in IBI over 2-minute runs for the carrier task performed alone.

Undergraduate Pilot Training Flights. Three T-37 lesson units (Air Training Command, 1981) were selected for study. These were the first power-on-stall and spin recovery ride (C-2301), the first check ride (C-2790), and the first instrument ride (I-2001). These sorties will be referred to as SPIN, CHECK, and INSTR, respectively. The SPIN and CHECK rides were selected because earlier studies had found them to be stressful (Krahenbuhl et al., 1977). The INSTR ride was believed to be a "neutral" or relatively low-stress sortie, but did include the first experience at flying with the canopy darkened.

The experimental conditions selected for study allowed for the comparison of three modes of stress: exercise, simulated flight, and actual flight. The elements within these conditions were compared with one another and with basal conditions.

Experiment Three

The third experiment was originally planned to allow the simultaneous measurement of psychophysiological, biochemical, and performance indices of USAF pilots operating in a simulated high-threat environment. The experiment was planned as a descriptive single group design. The subjects obtained for the study, however, either were recent UPT graduates or were Air Force officers rotating from desk jobs back to fighter squadron assignments. This condition allowed for an ex post facto examination of the differences between these two groups.

The experimental condition represented a 50-minute lesson in the Advanced Simulator for Pilot Training (ASPT), which had been adapted to match the F-16 cockpit and programmed for a mission to destroy an enemy installation in a hostile zone. The subjects "flew" 10 missions each and received feedback indicating whether they were undetected, had been detected by radar, were being tracked by radar, or had been fired upon with a surface-to-air missile (SAM). Subjects were graded on their deviation from a prescribed attack, evasion, and escape sequence. They also received feedback on altitude, airspeed, and bomb error distance. Cardiac IBI and respiratory rate were monitored to provide indirect measures of arousal. SAM hits were noted as an additional performance variable.

RESULTS AND DISCUSSION

Results of the studies conducted under this effort will be presented in four parts. The first three sections will focus on the individual experiments. The final section examines the collected data, which is considered to be a composite examination of the biochemical response to stress.

Experiment One

Samples were gathered from 97 subjects over a 4-month period. These samples were not all suitable for use in the experiment. Some were mishandled by support personnel on casual status. Some possessed low volumes, which are known to affect validity. In a number of instances, a correlary basal measure could not be procured. Finally, it was concluded that some of the flights had been misclassified. This attrition was expected because of the reliance on unplanned occurrences as the treatment. The final acceptable data base represents an N of 40 (21 instructor pilots, 19 student pilots).

These data were analyzed in two ways. The first analysis (Table 1) consisted of the comparison between basal and flight incident conditions. Four indices were found to be significant. The excretion rate of E increased 61% over the basal value obtained from these subjects. (The excretion rate of 26.3 ng/min is 426% greater than what might be considered as a normal resting value.) This level of E excretion suggests pronounced activation of the organism.

When examined by itself, the excretion rate for NE did not reflect a statistically significant change; however, when coupled with other substances in sums or ratios, NE was involved in three significant changes. The sum E + NE increased, the ratio DA/NE decreased, and the ratio NE/5HT increased. The increased excretion rate of E + NE was expected because it has been demonstrated in earlier studies (Krahenbuhl et al., 1977, 1978, 1980, & 1981). The decreased DA/NE ratio is consistent with the finding of Unger, Buu, Kuchel, and Schurch (1980) that DA may be converted to NE under stressful conditions. The increase in the NE/5HT

TABLE 1. COMPARISON OF EXCRETION RATES
BETWEEN BASAL AND FLIGHT INCIDENT CONDITIONS ($\bar{X} \pm SE$)

Variable	Basal	Flight Incident	Δ	Univariate F
E[a]	16.3 ± 2.9	26.3 ± 3.4	10.0 ± 4.9	4.16 *
NE[a]	39.2 ± 6.5	52.5 ± 5.2	13.4 ± 8.5	2.50
VMA[b]	2.27 ± 0.24	2.72 ± 0.20	0.44 ± 0.28	2.50
MHPG[b]	1.07 ± 0.20	0.85 ± 0.12	- 0.22 ± 0.21	1.10
DA[a]	245.1 ± 33.3	218.5 ± 23.2	-26.6 ± 44.8	0.35
HVA[b]	3.15 ± 0.32	3.09 ± 0.24	- 0.06 ± 0.40	0.02
DOPAC[b]	1.47 ± 0.27	1.00 ± 0.16	- 0.48 ± 0.29	2.62
5HT[a]	88.4 ± 8.8	86.3 ± 7.4	- 2.2 ± 10.8	0.04
5 HIAA[b]	3.22 ± 0.38	3.92 ± 0.20	- 0.30 ± 0.44	0.46
E + NE[a]	55.4 ± 9.2	78.8 ± 7.4	23.4 ± 1[illegible]	[illegible].30 *
VMA + MHPG[b]	3.34 ± 0.37	3.56 ± 0.25	0.22 ± 0.44	0.26
HVA + DOPAC[b]	4.62 ± 0.51	4.09 ± 0.33	- 0.53 ± 0.60	0.79
NE/E	2.79 ± 0.26	2.53 ± 0.21	- 0.26 ± 0.33	0.61
DA/NE	7.17 ± 0.52	4.92 ± 0.56	- 2.25 ± 0.81	7.67 **
NE/5HT	0.43 ± 0.04	0.64 ± 0.05	0.21 ± 0.06	13.32 **

[a] ng/min

[b] ug/min

* $p < .05$

** $p < .01$

ratio is also not surprising because NE has been associated with attentiveness and task-oriented responses (Frankenhaeuser & Patkai, 1964), whereas decreases in brain 5HT are associated with increased sensitivity and wakefulness (Seiden & Dykstra, 1977). Ellison (1975) suggests that a high NE/5HT ratio relates to excitement or anxiety, while a low ratio is found in low arousal and relaxation.

The second approach to examining the data from Experiment One was to apply a two-factor analysis of variance (ANOVA). An overview of the 2 x 3 factorial design is shown on Table 2. This analysis provided an examination of each main effect (GROUP: Student or Instructor; INCIDENT CLASSIFICATION: Low Order Precautionary, High Order Precautionary, or Emergency) and a test for interaction.

Incidents that were considered as Low Order Precautionaries included electrical malfunctions (gauges or warning lights not operating properly), control problems (loss of trim, stiff controls, etc.), and low EGT. Incidents considered as High Order Precautionaries included fumes and smoke in the cockpit and mechanical problems (malfunctions of the throttle, flaps, engine, landing gear, etc.).

The results of the ANOVA for each dependent variable are depicted in Table 3. The only differences for the main effect GROUP occurred for VMA and the sum VMA + MHPG. This result suggests that students experienced greater metabolism of epinephrine and norepinephrine. The percentage difference between instructors and students was 46% for VMA alone and 38% for the sum VMA + MHPG.

In comparing the responses of subjects to the three classifications of incident, significant ($p < 0.05$) main effect differences were found for eight indices (Table 4). The data for VMA and the sum VMA + MHPG suggest that greater metabolism occurred in the noradrenergic system during High

TABLE 2. FACTORIAL DESIGN USED TO EXAMINE VARIATION IN EXCRETION RATES[a]

GROUP	INCIDENT CLASSIFICATION			
	LOW ORDER[b]	HIGH ORDER[b]	EMERGENCY	
STUDENTS	8	7	4	19
INSTRUCTORS	9	8	4	21
	17	15	8	40

a number of observations shown

b precautionaries

TABLE 3. F RATIOS FOR THE GROUP X INCIDENT EXAMINATION OF BIOCHEMICAL RESPONSE[a]

Variable[b]	Main Effects		Group X Incident
	Group	Incident	Interaction
E	0.51	2.13	0.04
NE	0.99	2.39	3.26 *
VMA	9.34 **	4.22 *	1.13
MHPG	0.36	1.74	4.89 **
DA	0.04	5.57 **	1.53
HVA	2.75	10.34 **	2.39
DOPAC	2.12	2.64	1.71
5HT	0.65	3.15 *	1.89
5HIAA	0.12	5.57 **	1.98
E + NE	1.06	3.10	1.44
VMA + MHPG	9.39 **	6.25 **	4.96 *
HVA + DOPAC	3.45	5.63 **	1.68
NE/E	1.09	0.27	1.48
DA/NE	0.24	1.48	0.65
NE/5HT	1.25	3.15 *	1.93

[a] MANOVA F values for the nine primary measures were: Group, F=1.18, p=0.348; Incident, F=3.93, p=0.001; Interaction, F=1.81, p=0.050.

[b] Metabolites offse-

* $p < 0.05$

** $p < 0.01$

TABLE 4. DESCRIPTIVE VALUES FOR SIGNIFICANT MAIN EFFECTS CONTRASTS

MAIN EFFECT	VARIABLE	DESCRIPTIVE VALUES ($\bar{X} \pm SE$)			SIGNIFICANT CONTRASTS[a]
GROUP		A Students	B Instructors		
	VMA	3.26 ± 1.25	2.23 ± 1.08		A > B
	VMA + MHPG	4.17 ± 1.82	3.01 ± 1.08		A > B
INCIDENT		A Low Order	B High Order	C Emergency	
	VMA	2.27 ± 0.25	3.34 ± 0.36	2.50 ± 0.39	B > A
	DA	195.1 ± 20.3	299.9 ± 49.0	115.3 ± 23.6	A, B > C
	HVA	2.53 ± 0.24	4.20 ± 0.43	2.21 ± 0.37	B > A, C
	5HT	74.8 ± 6.9	108.3 ± 16.4	69.2 ± 8.5	B > C
	5HIAA	2.42 ± 0.21	3.68 ± 0.34	2.59 ± 0.44	B > A
	VMA + MHPG	3.04 ± 0.25	4.43 ± 0.51	3.04 ± 0.38	B > A, C
	HVA + DOPAC	3.18 ± 0.26	5.29 ± 0.49	3.76 ± 1.05	B > A
	NE/5HT	0.75 ± 0.06	0.59 ± 0.08	0.48 ± 0.07	A > C

[a] Planned contrasts of main effects indicated as significant in Table 3.

Order Precautionaries, but these data, along with those noted for the main effect group, are confounded by significant interaction (Figure 1). Examination of this interaction suggests that the noradrenergic responses of students and instructors were similar during the Low Order Precautionaries and Emergencies, but differed markedly during High Order Precautionaries. The data suggest a much greater response in students. An examination of the individual subject responses revealed that NE metabolism in every student was greater than for any instructor on the High Order Precautionaries that involved smoke and fumes in the cockpit.

The remaining INCIDENT differences are not confounded by an interaction effect. The lower excretion rate of DA in Emergencies is marked, but in the absence of an increase in NE (as shown by the DA/NE ratio) the significance in these lower DA values during Emergencies remains obscure. The excretion of DA metabolites (HVA + DOPAC) was highest during the High Order Precautionary incidents, suggesting that DA metabolism paralleled DA concentrations in the body tissues and fluids.

When considered in isolation, the data for 5HT and 5HIAA indicate greater serotonergic activity during High Order Precautionary incidents; however, Ellison (1975) has suggested that it is the ratio of NE/5HT that provides the most useful index of excitement. The mean values indicate that arousal and anxiety were greater during the Precautionary incidents than during the Emergencies.

It should be noted that these biogenic amines and their metabolites are known to be associated. The extent of these relationships is evident in the current data (Table 5). Interpretation of these results should not consider these substances as distinct and unrelated dependent variables.

In summary, the data collected during this experiment

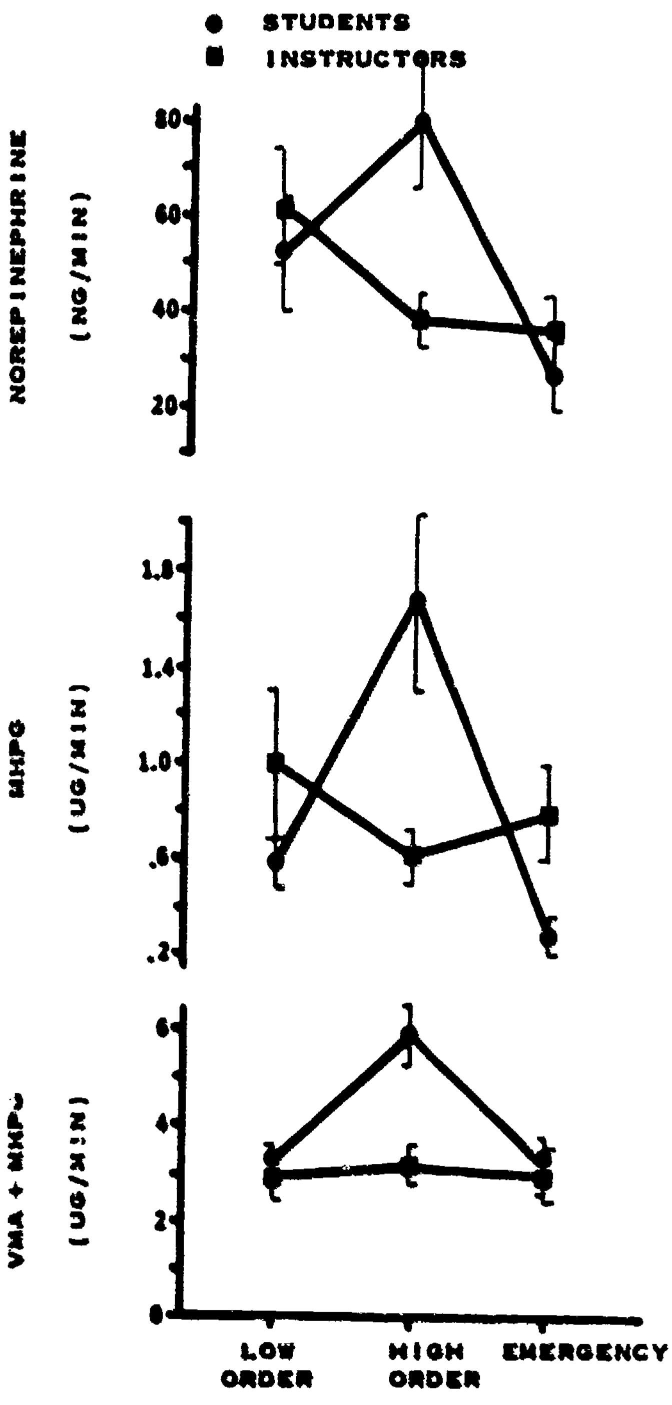

Figure 1. Interaction of GROUP and INCIDENT for the excretion rates of norepinephrine (top), MHPG (center), and the sum VMA+MHPG (bottom). Means and standard errors are plotted.

TABLE 5. INTERCORRELATIONS AMONG THE NINE PRIMARY DEPENDENT VARIABLES

	E	NE	VMA	MHPG	DA	HVA	DOPAC	5HT	5HIAA
E	--	.456[c]	.443[c]	.152	.485[c]	.233	.073	.385[a]	.038
NE	.456[c]	--	.602[d]	.135	.295	.462[c]	.030	.590[d]	.308
VMA	.443[c]	.602[d]	--	.133	.284	.741[d]	.444[c]	.542[d]	.509[d]
MHPG	.152	.135	.133	--	.331[a]	.174	-.016	.268	.237
DA	.485[c]	.295	.284	.331[a]	--	.403[b]	-.057	.618[d]	.203
HVA	.233	.462[c]	.741[d]	.174	.403[b]	--	.388[a]	.728[d]	.706[d]
DOPAC	.073	.030	.444[c]	-.016	-.057	.338[a]	--	.021	.338[a]
5HT	.385[a]	.590[d]	.542[d]	.268	.618[d]	.728[d]	.021	--	.500[d]
5HIAA	.038	.308	.509[d]	.237	.203	.706[d]	.338[a]	.500[d]	--

[a] $p < 0.05$
[b] $p < 0.01$
[c] $p < 0.005$
[d] $p < 0.001$

suggest that flight-line incidents result in a marked and measurable stress response in both students and instructor pilots. The stress evidenced in these two groups is more similar than different with the exception of High Order Precautionaries, where it appeared that students experienced a greater stress response. When the types of incidents were compared with one another, it appeared that the High Order Precautionaries (smoke and fumes in the cockpit or mechanical problems) caused a greater stress response than occurred during incidents classified by the USAF as either Low Order Precautionaries or Emergencies.

Experiment Two

In Experiment Two, 10 students were examined on eight occasions. Two basal measures were taken and averaged. Timed samples were also obtained for submaximal exercise (SUB EX), maximal exercise (MAX EX), during a simulated landing on an aircraft carrier (SIM), and during the C-2301 (SPIN), C-2790 (CHECK), and I-2001 (INSTR) rides (Air Training Command, 1981).

The treatment of data from Experiment Two is presented and discussed in three parts. The initial section will compare basal and stress conditions, ignoring the mode of stress. The remaining sections will focus specifically on exercise stress and piloting stress, respectively.

Basal and Stress Excretion Patterns. A comparison of basal and stress conditions was made by averaging the two basal excretion rates and contrasting these with the excretion rates from the six stress conditions monitored in this study. The results of this analysis reveal significant differences in nine of the 15 variables selected for study (Table 6). Increased excretion rates for E, NE, the sum E + NE, and a decrease in the NE/E ratio altogether suggest

TABLE 6. COMPARISON OF BASAL AND STRESS CONDITIONS IGNORING THE MODE OF STRESS ($\overline{X} \pm SE$)

Variable	Basal	Stress	Δ	Univariate F
E[a]	7.1 ± 0.6	19.9 ± 1.9	12.8 ± 1.6	63.68 **
NE[a]	47.2 ± 3.4	74.3 ± 6.2	27.1 ± 7.2	14.13 **
VMA[b]	4.19 ± 0.16	4.16 ± 0.25	- 0.03 ± 0.20	0.18
MHPG[b]	2.06 ± 0.44	2.04 ± 0.53	- 0.02 ± 0.37	0.00
DA[a]	285.8 ± 23.5	252.5 ± 13.4	-33.3 ± 24.7	1.82
HVA[b]	4.46 ± 0.16	3.68 ± 0.24	- 0.77 ± 0.22	12.18 **
DOPAC[b]	1.06 ± 0.05	1.03 ± 0.06	- 0.02 ± 0.08	0.07
5HT[a]	9.97 ± 1.9	83.4 ± 3.9	-16.2 ± 3.5	21.16 **
5HIAA[b]	4.29 ± 0.28	3.77 ± 0.26	- 0.53 ± 0.32	2.82
E + NE[a]	54.3 ± 3.8	94.3 ± 7.3	40.0 ± 8.0	25.00 **
VMA + MHPG[b]	6.26 ± 0.57	6.21 ± 0.70	- 0.05 ± 0.45	0.01
HVA + DOPAC[b]	5.12 ± 0.42	3.65 ± 0.24	- 1.47 ± 0.45	10.69 **
NE/E	8.55 ± 0.57	4.97 ± 0.62	- 3.58 ± 0.81	19.45 **
DA/NE	6.58 ± 0.37	4.13 ± 0.24	- 2.45 ± 0.30	68.56 **
NE/5HT	0.50 ± 0.04	1.00 ± 0.11	0.50 ± 0.11	19.18 **

[a] ng/min excreted

[b] ug/min excreted

* $p < .05$

** $p < .01$

pronounced activation of the adrenergic and noradrenergic systems. All changes were in the direction noted in earlier research on student pilots (Krahenbuhl et al., 1977, 1979, 1980, 1981).

The dopaminergic system evidenced three significant changes. HVA and HVA + DOPAC excretion rates decreased, as did the DA/NE ratio. It has been suggested that the noradrenergic system inhibits the dopaminergic system (Geyer & Segal, 1974; Kellogg & Wennerström, 1974), and as noted earlier, Unger et al. (1980) reported that DA may be converted to NE under stress. Either or both of these possibilities agree with the current data.

There were two significant changes in the serotonergic system: a decrease in 5HT and an increase in the NE/5HT ratio. These data agree with the results from Experiment One and support the notion that the NE/5HT ratio provides a useful index of arousal.

Exercise Related Excretion Patterns. The sympathoadrenal response to physical exercise has been thoroughly studied. Reviews of the literature by von Euler (1974) and Galbo (1983) lead to the conclusion that the concentrations of catecholamines in plasma and the urine excretion of catecholamines increase during exercise. The increase for norepinephrine is closely related to the relative intensity of the work (Howley, 1976). For epinephrine, the response is minimal during light exercise, but is much more pronounced as one approaches maximal exertion.

In contrast to the wealth of literature on the catecholamines, data are almost nonexistent on exercise-induced responses in the dopaminergic or serotonergic systems. There are also very limited data from experiments wherein the responses to exercise of these hormones/neurotransmitters and their metabolites were measured simultaneously.

The characteristics of the subjects are provided in Table 7. There was noted homogeneity on age, $\dot{V}O_2max$, and the length of time it took the subjects to exercise to exhaustion. This condition is desirable because it indicates a similar level of fitness for physical work. The variation in body weight was more normal (less homogeneous).

The excretion rates for E and NE and their metabolites (VMA, MHPG) are depicted in Figure 2. The variation among trials was significant ($p < 0.05$) for E, NE, and VMA. Post-hoc tests demonstrated that E excretion during submaximal exercise did not exceed basal values. The excretion of E during exercise to exhaustion, however, was significantly elevated over both the basal and submaximal rates. The excretion rate of NE closely paralleled changes in workload. The data for both E and NE agree with earlier work reported by others (see the reviews by von Euler (1974) and Galbo (1983).

The excretion rate of VMA was significantly ($p < 0.05$) lower during submaximal exercise than during either basal conditions or maximal exercise. This may indicate that the increased <u>ex</u>cretion of NE during submaximal work is, in part, due to reduced metabolism rather than increased <u>se</u>cretion.

The excretion rates for DA and its metabolites (HVA, DOPAC) are featured in Figure 3. The only significant ($p < 0.05$) differences occurred for HVA, where the excretion rate for maximal exercise was reliably below the levels found during resting conditions.

The excretion rates for 5HT and its metabolite (5-HIAA) are illustrated in Figure 4. The only significant difference occurred for 5HT, where the excretion rate for submaximal exercise was reliably lower than the levels found during basal conditions.

TABLE 7. EXERCISE RELATED DESCRIPTIVE CHARACTERISTICS OF THE SUBJECTS (N=10)

Characteristic (units)	Mean	Min-Max
Age (years)	22.2	21-23
Weight (lbs)	178.1	148-218
$\dot{V}O_2max$ ($ml \cdot min^{-1} \cdot kg^{-1}$)	50.6	45.6-54.6
Max test length (min)	23.3	21.5-25.0

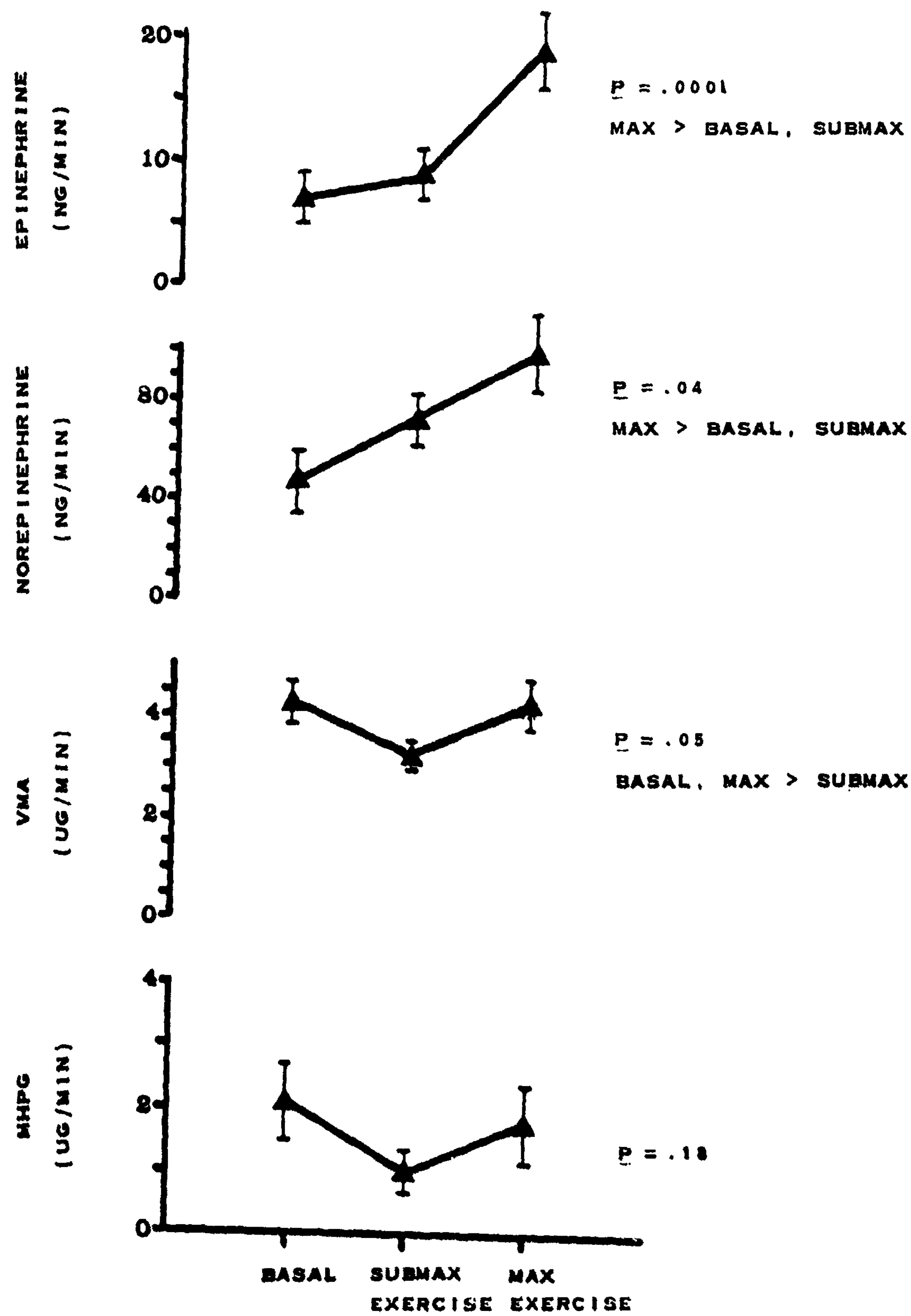

Figure 2. Excretion rates for epinephrine, norepinephrine, and their metabolites. Means and standard errors are plotted.

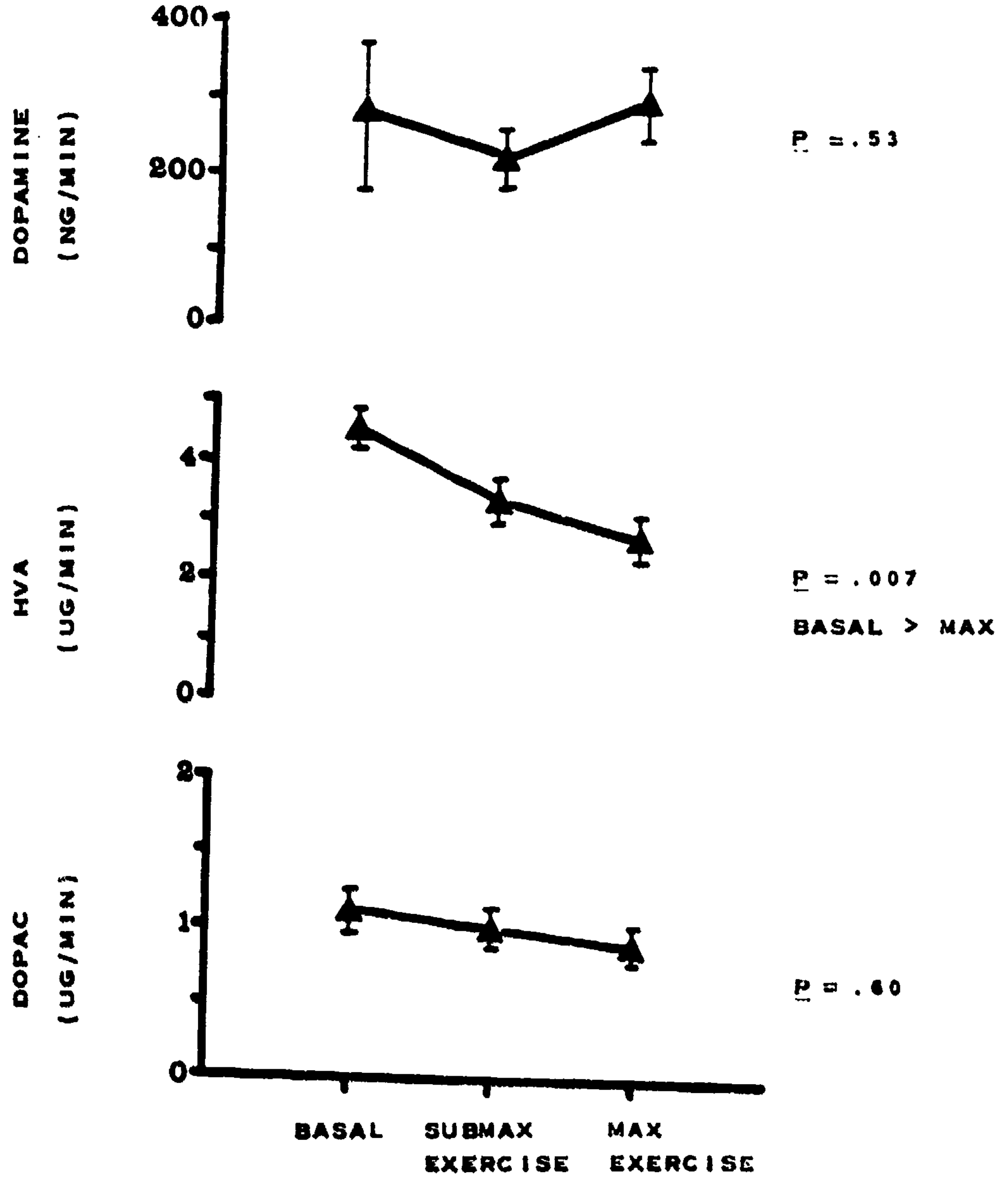

Figure 3. Excretion rates for dopamine and its metabolites. Means and standard errors are plotted.

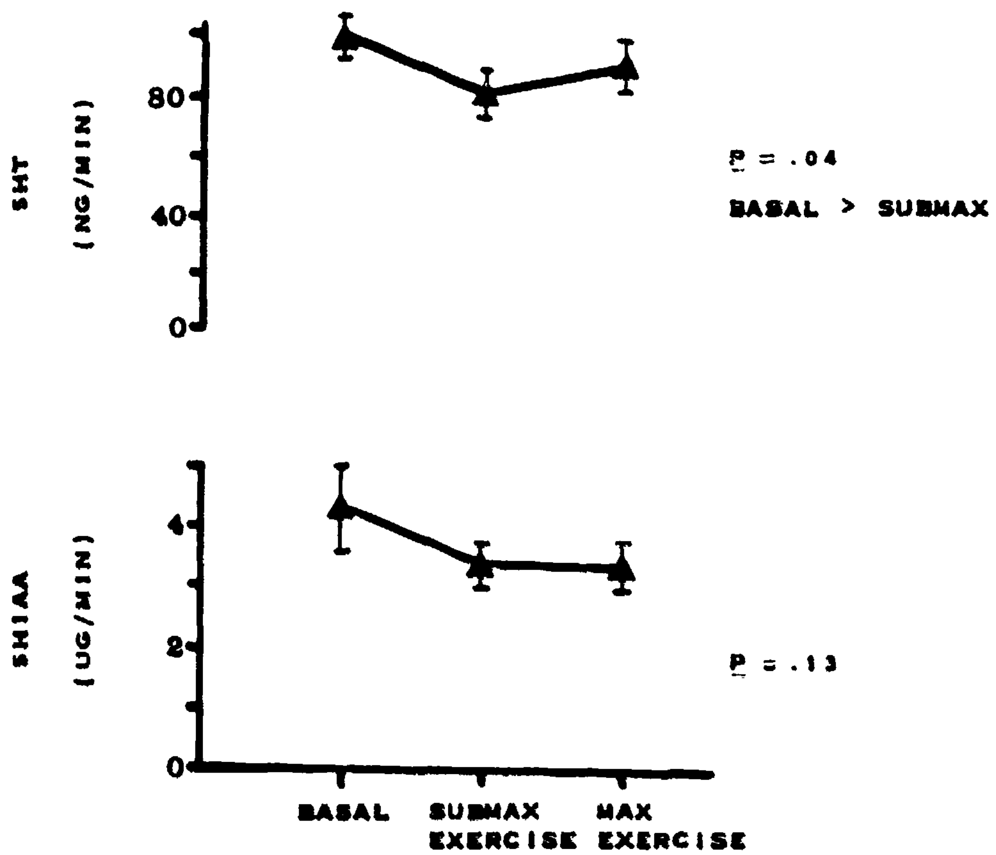

Figure 4. Excretion rates for serotonin (5HT) and its metabolite. Means and standard errors are plotted.

The DA/NE ratio decreased and the NE/5HT ratio increased significantly for both modes of exercise. The NE/E ratio remained unchanged.

For the modes of exercise considered singly, then jointly, the following excretion patterns were noted:

1. Submaximal exercise was characterized by (a) a greater responsiveness to NE than E, (b) an elevated NE/E ratio, (c) a decrease of excretion rate of VMA and perhaps MHPG, and (d) a decrease in the ratio of each metabolite to each respective precursor with the exception of the dopaminergic system.

2. Maximal exercise was characterized by (a) a decrease in NE/E ratio, (b) no change in VMA and MHPG excretion rate, (c) an increase in NE and E, and (d) a greater decrease in the ratio of each metabolite to each respective precursor.

3. Both maximal and submaximal exercises showed similarities in (a) a lack of change in the excretion rate of DOPAC and a significant reduction in HVA, (b) a reduction in DA/NE ratio to one-half of basal, (c) a decrease in 5HT excretion rate, and (d) a lower 5HT/NE ratio.

Pilot Training Excretion Patterns. This aspect of the investigation replicates and expands upon earlier studies (Krahenbuhl et al., 1977, 1978, 1980, 1981) with student pilots formerly limited to measurements of NE and E now to include seven additional components. The use of the urinary excretion as an index for various forms of stress in this study was limited to three selected in-flight training lessons and a laboratory simulator test (SIM).

In Tables 8 and 9 the results are summarized. Table 8 shows the effect of four modes of short-term flight training stress on urinary excretion rates of biogenic amines and their metabolites. The basal excretion rates for NE and E parallel those of earlier reported results (Krahenbuhl et al.,

TABLE 8. EFFECT OF FOUR MODES OF SHORT-TERM IN-FLIGHT TRAINING STRESS ON URINARY EXCRETION RATES OF BIOGENIC AMINES AND METABOLITES ($\overline{X} \pm SE$)

	Mean ± S.E.M.				
	Basal (ng/min)	SIM (ng/min)	SPIN (ng/min)	CHECK (ng/min)	INSTR (ng/min)
EPI	5.92 ± 1.19	15.5 ± 2.5 [b]	24.3 ± 3.8[b]	23.7 ± 2.3 [bd]	20.8 ± 3.3 [bd]
NE	39.6 ± 4.1	45.5 ± 5.67	63.3 ± 7.5[ad]	60.9 ± 5.8 [bd]	70.4 ± 14.4 [bc]
DA	229. ± 22.	233. ± 19.8	260. ± 14.	235. ± 16.	238. ± 22.7
5HT	102. ± 3.4	80.3 ± 7.5[b]	79.4 ± 3.5[b]	75.3 ± 6.5 [b]	100. ± 15.
	(µg/min)	(µg/min)	(µg/min)	(µg/min)	(µg/min)
VMA	4.19 ± 0.41	3.51 ± 0.23[a]	3.35 ± 0.19[a]	3.79 ± 0.26	4.59 ± 0.56[c]
MHPG	0.95 ± 0.20	0.35 ± 0.19[b]	0.93 ± 0.15[c]	0.56 ± 0.11[a]	2.17 ± 0.53[bc]
DOPAC	1.05 ± 0.13	0.86 ± 0.13	1.11 ± 0.09	0.98 ± 0.09	1.24 ± 0.23
5HIAA	3.74 ± 0.43	3.57 ± 0.33	3.40 ± 0.34	3.02 ± 0.30	4.40 ± 0.72
HVA	4.46 ± 0.41	3.69 ± 0.28[a]	3.46 ± 0.38[b]	3.48 ± 0.35[b]	5.29 ± 0.98[c]
VMA + MHPG	5.14 ± 0.44	3.86 ± 0.26[b]	4.28 ± 0.29[a]	4.35 ± 0.25[a]	6.76 ± 0.61[ac]
HVA + DOPAC	5.51 ± 0.45	4.55 ± 0.31[b]	4.57 ± 0.45[a]	4.46 ± 0.42[b]	6.53 ± 1.18[c]

[a] $p < .05$ between BASAL and test values (SIM, SPIN, CHECK, or INSTR)

[b] $p < .01$ between BASAL and test values

[c] $p < .01$ between BASAL and In-Flight Tests (SPIN, CHECK, or INSTR)

[d] $p < .01$ between SIM and In-Flight Tests

TABLE 9. RATIO OF INDIVIDUAL VALUES OF URINARY EXCRETION RATES OF BIOGENIC AMINES AND METABOLITES ($\overline{X} \pm SE$)

	Basal	SIM	SPIN	CHECK	INSTR
NE/E	8.71 ± 1.5	3.22 ± 0.28[b]	3.16 ± 0.50[b]	2.68 ± 0.23[b]	3.51 ± 0.51[b]
5HT/NE	2.82 ± 0.29	2.01 ± 0.31	1.44 ± 0.19[bc]	1.27 ± 0.08[bd]	1.67 ± 0.21[b]
DA/NE	6.47 ± 0.95	5.76 ± 0.69	4.77 ± 0.69[a]	4.08 ± 0.40[bd]	4.33 ± 0.60
DA/E	54.2 ± 11.8	18.6 ± 2.9 [b]	16.4 ± 4.9 [b]	10.8 ± 1.3 [bd]	13.6 ± 1.9[bd]
DA/5HT	2.26 ± 0.23	3.09 ± 0.33[d]	3.34 ± 0.24[b]	3.28 ± 0.39[b]	2.65 ± 0.26
5HT/E	24.8 ± 5.1	6.61 ± 1.38[b]	4.65 ± 1.24[b]	3.41 ± 0.38[bd]	5.55 ± 0.74[b]
DA/NE + E	5.61 ± 0.84	4.36 ± 0.55	3.51 ± 0.59[b]	2.93 ± 0.29[bd]	3.21 ± 0.42[bd]
5HIAA/5HT	36.1 ± 3.5	47.5 ± 5.6 [b]	42.6 ± 3.4	42.1 ± 5.3	47.9 ± 7.9 [a]
A	27.4 ± 4.6	20.7 ± 2.3	18.1 ± 2.5 [b]	19.0 ± 1.8 [b]	26.8 ± 4.1
MHPG/E	29.9 ± 13.4	24.4 ± 3.0	58.0 ± 18.9 [c]	31.1 ± 9.2	157.0 ± 72. [c]
MHPG/NE	27.3 ± 6.5	7.8 ± 1.0 [b]	16.4 ± 3.1 [ad]	11.0 ± 2.8[b]	43.1 ± 19.4 [d]

$A = \frac{HVA + DOPAC}{DA}$

[a] $p < .05$ between BASAL and test values (SIM, SPIN, CHECK, or INSTR)

[b] $p < .01$ between BASAL and test values

[c] $p < .01$ between BASAL and In-Flight Tests (SPIN, CHECK, or INSTR)

[d] $p < .01$ between BASAL and In-Flight Tests

1977, 1978, 1980, 1981). Significant increases in the rates of excretion of NE were obtained in the CHECK, SPIN, and INSTR rides, whereas NE excretion in the SIM test was nonsignificantly increased over the basal rate.

MHPG, the major metabolite of brain NE, had a basal rate of excretion of 0.95 ± 0.20 μg/min which compared with a basal value of 1.56 μg/min reported for normal college students (Wehr et al., 1980).

Markedly increased rates of excretion of MHPG paralleled the increases in NE and in E in the INSTR test. Significant decreases in MHPG rates were obtained with the CHECK and SIM tests which had increased rates of NE and E. In the SPIN test, MHPG was unchanged, whereas the rates of excretion of NE and E were significantly increased. Ratios of urinary excretion rates of metabolites/biogenic amines are given in Table 9. The MHPG/NE ratio increased twofold in the INSTR test but was markedly reduced in the SPIN and CHECK rides and in the SIM test.

The rates of excretion of E (Table 8) were significantly elevated over basal values: in the SIM test 211%, in the INSTR ride 330%, in the SPIN ride 440%, and in the CHECK ride 425%. E increases were markedly greater than those of NE. This is clearly noted in the NE/E ratio (Table 9) which, with a value of 8.7 in the basal state, decreased to around 2.7 for the CHECK, 3.5 for the INSTR, and 3.2 for both the SPIN and SIM tests. The SPIN NE/E ratio obtained in this study was similar to that reported earlier (Krahenbuhl et al., 1978). VMA rates of excretion showed a significant decrease in the SPIN and SIM tests, nonsignificant decreases in the CHECK ride, but a nonsignificant increase in the INSTR ride compared to the BASAL rate. Whereas the anticipated elevations in the rates of excretion occurred with NE and E, the rate of DA excretion did not change significantly.

Basal excretion of 4.46 μg/min of HVA, considered to be a major metabolite of DA in humans, is in the range reported earlier (Elchisok, Polinsky, Ebert, and Kopin, 1982). Rates of excretion of HVA decreased significantly in the SIM, SPIN, and CHECK tests but increased slightly, albeit not significantly, in the INSTR test.

Rates of excretion of DOPAC, also a metabolite of DA, on the other hand, showed no significant change over BASAL values for all of the tests, but the sum of HVA and DOPAC excretion rates showed significant decrease in the SIM, SPIN, and CHECK tests and a nonsignificant increase in the INSTR test.

Rates of excretion of 5HT were significantly decreased in SIM, CHECK, and SPIN tests, but were unchanged in the INSTR ride. Basal rate of the major 5HT metabolite 5-HIAA at 3.74 ($\pm$ 0.41) μg/min was similar to that earlier reported for human controls; i.e., 3.4 ($\pm$ 0.76) μg/min (Himwich, 1970).

The rate of 5-HIAA excretion paralleled the decrease in 5HT excretion rate in both the CHECK and SPIN rides and in the SIM test. While no change of 5HT excretion rate was obtained in the INSTR ride, there was a nonsignificant increase in 5-HIAA rate of excretion. The ratio of 5-HIAA/5HT indicates an increase in serotonergic activity in all of the tests but most significantly in the SIM and INSTR tests.

In the several training lessons known to be stressors for student pilots (Mefford et al., 1971), the acute stress response was indicated by a marked increase in the rates of both NE and E excretion but a decrease in the rate of 5HT excretion. In the present study, NE urinary pattern was similar to, but the E, DA, VMA, and HVA urinary patterns differed from, those observed in long-term stress of space flight (Tigranian, Kvetnansky, Kalita, Davydova, Pavlova, & Vorekin, 1980; 5HT and its metabolite were not measured in that study. That DA (or DA-SO_4) may under conditions of stress contribute to the formation of NE was offered as an explanation for the decreased urinary excretion rate of DA observed by Unger et al. (1980), and accounts for the urinary increases of NE.

In flight tests, stress effectors which increased NE rates may reflect enhanced sympathetic-adrenomedullary activity. It might be noted that short-term stress influences tyrosine hydroxylase, and the subsequent synthesis of catecholamines, differently in the brain as compared to the adrenals (Oka, Ashiba, Kiss, & Nagatsu, 1982). The non-airborne laboratory simulator (SIM) test did not effect the significant increase in NE that was noted in flight tests. Higher urinary excretion of both NE and E is seen in an achievement-demanding situation in males (Bergman & Magnusson, 1979); this may reflect the difference in the flight and nonflight tests. Further, it has recently been reported that NE is increased with outward expression of anger, whereas E increases with anger retained inward (Ostruff, Gitler, Bonesek, Ebersole, Harkness, & Mason, 1982). The INSTR ride differed from all of the tests with a nonsignificant decrease in 5HT.

The INSTR, generally viewed as a neutral flight, proved to contain elements of stress involving essentially the adrenergic and noradrenergic systems but was not accompanied by any significant change in dopaminergic or serotonergic systems. This test which involved flying blind, that is with canopy darkened and use only of instruments, may reflect sensory deprivation that is inherent to the task and/or results from the restriction from conducting visual checks (which normally precede landing) until the very last moment. The test appeared to induce an anxiety state that was reflected by increased sympathetic-adrenomedullary response.

The quantitative differences in values for NE and E, and possibly MHPG, between the in-flight tests and the nonflight simulator test may reflect a cochleo-vestibular response to noise and vibration exposure in the flight tests. Previous reports have indicated that young subjects with good hearing and balance have lower excretion levels of NE and E, compared to those with impaired hearing (Manninen, 1980). However, in the present study with subjects 21 to 23 years of age who have passed a rigorous physical examination, hearing and balance have been presumed to be good.

Although MHPG is reported to be a major CNS metabolite of NE (Glowinski, Kopin, & Axelrod, 1965), only 20% of MHPG from this source appears in the urine, the remainder being converted to VMA (Blombery, Kopin, Gordon, Markey, & Ebert, 1980).

HVA is considered to be a major metabolite of DA in humans, albeit excretion of HVA has been used less frequently than cerebrospinal fluid HVA as an index of CNS DA turnover. This despite reports that more than 33% to 50% of urinary HVA originates from CNS DA (Brown, Ebert, Hunt, & Rapoport, 1981). Although no significant change was noted in DA rates in all of the tests, the significant decrease in its metabolite HVA and in the sum of HVA + DOPAC in the SIM, SPIN, and CHECK tests suggest that DA nevertheless may be involved. The dopaminergic system has been shown to be associated with voluntary motor behavior; this may be reflected in the present results. NE did not increase over the basal value in the nonflight SIM test, but did increase in the flight (SPIN, CHECK, and INSTR) tests. E increased only 100% over BASAL in the SIM test but 300% to 400% in the flight tests. These differences may reflect the challenge of the in-flight tests and the effort made to achieve test objectives lacking in the simulator test, or the difference may reflect cochleo-vestibular responses.

As seen in Table 9, the percentage of ratios of specific biogenic amines, as well as ratios of specific biogenic amines, to their metabolites reflect relative responses of synthesis and inactivation compared to the control (BASAL) group.

Stress is associated with activation of the sympathetic-adrenal system and the hypothalamic-pituitary-adrenal axis. Renal elimination of the biogenic amines and their metabolites is one indicator of this activation. Differences in the amount of excreted biogenic amines and their metabolites and in the ratio of renal excretion of the individual components reflect differences among the various stressors and can be used to follow changes resulting from these stressors. In this connection, problem solving used as a stressor stimulus gave urinary catecholamine values which correlated well with plasma values (McCubbin, Richardson, Langer, Kizer, & Obrist, 1983).

In reviewing the primary changes that occurred during these flight training tasks, four main points are noted:

1. Urinary rates of excretion of nine components of the biogenic amines and their related metabolites can be a useful noninvasive index of short-term stress response in human subjects.

2. Increased NE and E values, in agreement with earlier reported results with flight tests, reflect an achievement demanding situation.

3. The serotonergic system appeared to be involved with a greater 5HT turnover in all of the training tests.

4. Decreased dopaminergic activity, as reflected in the HVA and in the sum of HVA and DOPAC results, appeared to be responsive in the SIM, SPIN, and CHECK but not in the INSTR tests.

5. The responses to different stress stimuli are not identical, and distinct differences exist between the non-flight simulator test and the in-flight tests.

Biochemical and Physiological Responses. As a sidelight to Experiment Two, both biochemical and physiological data were collected during the SIM test. The basic biochemical indices were correlated with four physiological indices. As noted in the methods section, these items were brain coherence (COH), cardiac inter-beat interval (IBI), change in reaction time to a tone task during simulated carrier landings (ΔRT), and change in the cardiac IBI over a 2-minute trial on the carrier landing task (ΔIBI). The eventual mean UPT score from six check rides was taken as a criterion of student piloting ability (ABIL) and also related to the biochemical data. A summary of the significant ($p \leq .05$) Spearman Rho correlations is located in Table 10. A review of that table reveals no discernible pattern to the biochemical and physiological indices; however, a number of the biochemical excretion variables showed significant relationship with students' eventual prowess as a pilot (ABIL), as demonstrated from their records on check rides during pilot training.

Experiment Three

Samples for Experiment Three were gathered from 34 subjects, 14 of whom were recent UPT graduates; i.e., fighter inexperienced (INEXP), and 20 of whom had formerly held fighter assignments but were at the time of the experiment transferring from desk jobs back to fighter assignments; i.e., fighter experienced (EXPER). Limited availability of the subjects caused the basal and experimental measurements to be taken on the same day. This resulted in biased basal data which cloud the interpretation of results in this experiment.

TABLE 10. SPEARMAN RHO RELATIONSHIPS BETWEEN CHANGES IN BIOCHEMICAL INDICES DURING STRESS AND SELECTED PHYSIOLOGICAL AND PERFORMANCE VARIABLES*

Biochemical Variables	Physiological Variables				UPT Performance
	COM	IBI	ΔRT	ΔIBI	ABIL
E	--	--	--	--	.571
NE	--	--	--	--	.906
VMA	--	--	.604	--	.584
MHPG	--	--	--	--	--
DA	--	--	--	--	--
HVA	--	--	--	--	.553
DOPAC	--	--	--	--	--
5HT	--	--	--	--	--
5HIAA	--	--	--	--	--
E + NE	--	--	--	--	.778
VMA + MHPG	--	--	--	--	--
HVA + DOPAC	--	--	.565	--	--
NE/E	--	--	--	--	--
DA/NE	--	--	--	--	-.602
NE/5HT	--	--	--	--	--

* Only statistically significant ($p < 0.05$) are shown.

Data from this experiment were analyzed three ways. The simplest analysis contrasted "BASAL" and STRESS data. The second approach consisted of a comparison of the INEXP and EXPER groups. The third item examined was the relationship between biochemical data and physiological data collected during the same time period on these subjects. As with Experiment One, these biogenic amines and their metabolites are known to be associated. The extent of these relationships is noted in Table 11.

Basal and Stress Excretion Patterns. The first analysis (Table 12) consisted of the comparison between basal and treatment excretion patterns. The treatment consisted of 11 simulated sorties flown against an enemy position. Statistically significant ($p < .05$) differences were noted on four of the biochemical indices. The stress condition increased E, NE, the sum E + NE, and the NE/5HT ratio. As noted in earlier sections, these are all indicative of a pronounced stress response.

Experienced and Inexperienced Pilots. The results of the two factor (Experience x Trial) ANOVA are depicted in Table 13. The outstanding element to be noted is the interaction between the main effects. These interactions have been illustrated in Figure 5. It is interesting to note that in every instance excretion rates decrease for the INEXP group and increase for the EXPER group. There were no statistically significant results on the experience factor that were not confounded by this interaction. The clearest picture appears for the serotonergic system where the excretion of both the parent neurotransmitter and its metabolite increased in the EXPER group and decreased in the INEXP group. A belabored discussion of these data will not be attempted because the basal (reference) values are suspect.

TABLE 11. INTERCORRELATIONS AMONG THE PRIMARY DEPENDENT VARIABLES (N=34)

	E	NE	VMA	MHPG	DA	HVA	DOPAC	5HT	5HIAA
E	--	.320	-.154	-.200	.586[d]	-.095	-.084	.101	.018
NE	.320	--	-.067	.009	.468[c]	-.044	-.108	.091	.021
VMA	-.154	-.067	--	.602[d]	.102	.515[c]	.608[d]	.363[a]	.402[a]
MHPG	-.200	.009	.602[d]	--	.081	.212	.830[d]	.148	.638[d]
DA	.586[d]	.468	.102	.081	--	.237	.199	.437[b]	.273
HVA	-.095	-.044	.515[c]	.212	.237	--	.413[a]	.778[d]	.424[a]
DOPAC	-.084	-.108	.608[d]	.830[d]	.199	.413[a]	--	.385[a]	.698[d]
5HT	.101	.091	.363[a]	.148	.437[b]	.778[d]	.385[a]	--	.333
5HIAA	.018	.021	.402[a]	.638[d]	.273	.424[a]	.698[d]	.333	--

[a] $p < 0.05$
[b] $p < 0.01$
[c] $p < 0.005$
[d] $p < 0.001$

TABLE 12. COMPARISON OF BASAL[a] AND STRESS CONDITIONS IN EXPERIMENT THREE ($\bar{X} \pm SE$)

Variable	Basal	Stress	Δ	Univariate F
E[b]	12.2 ± 1.9	30.5 ± 3.9	18.3 ± 3.5	26.83 **
NE[b]	57.1 ± 8.0	78.9 ± 9.4	21.77 ± 8.8	6.05 *
VMA[c]	3.35 ± 0.31	3.86 ± 0.26	0.51 ± 0.39	1.74
MHPG[c]	0.86 ± 0.11	1.04 ± 0.20	0.18 ± 0.19	0.86
DA[b]	234.7 ± 20.5	241.9 ± 17.4	7.2 ± 23.4	0.10
HVA[c]	3.78 ± 0.36	4.18 ± 0.42	0.41 ± 0.41	1.00
DOPAC[c]	0.96 ± 0.08	1.16 ± 0.11	0.19 ± 0.13	2.22
5HT[b]	83.3 ± 7.8	84.2 ± 6.4	0.9 ± 7.8	0.01
5HIAA[c]	3.83 ± 0.41	4.10 ± 0.35	0.27 ± 0.46	0.34
E + NE[b]	69.4 ± 8.9	109.4 ± 11.3	40.1 ± 11.2	12.74 **
VMA + MHPG[c]	4.23 ± 0.37	4.90 ± 1.96	0.67 ± 1.99	0.49
HVA + DOPAC	4.09 ± 0.26	4.01 ± 0.36	- 0.08 ± 0.33	0.07
NE/E	7.81 ± 1.90	7.68 ± 2.40	0.13 ± 1.72	0.01
DA/NE	6.50 ± 1.09	6.09 ± 1.25	- 0.41 ± 1.34	0.10
NE/5HT	0.66 ± 0.07	1.04 ± 0.13	0.38 ± 0.14	7.62 **

[a] Not true basal conditions

[b] ng/min excreted

[c] ug/min excreted

* $p < .05$

** $p < .01$

TABLE 13. F RATIOS FOR THE EXPERIENCE X TRIAL EXAMINATION OF BIOCHEMICAL RESPONSE

Variable	Main Effects: Experience[a]	Main Effects: Trial[b]	Experience X Trial Interaction
E	0.02	24.23**	0.83
NE	0.00	4.73*	3.82
VMA	1.89	0.81	10.82*
MHPG	0.24	0.44	2.40
DA	0.11	0.01	4.95*
HVA	0.06	0.46	3.89
DOPAC	1.33	1.28	6.35*
5HT	2.41	0.11	6.95*
5HIAA	6.35*	0.01	10.96*

[a] EXPER vs. INEXP

[b] BASAL vs. STRESS

* $p < 0.05$

** $p < 0.01$

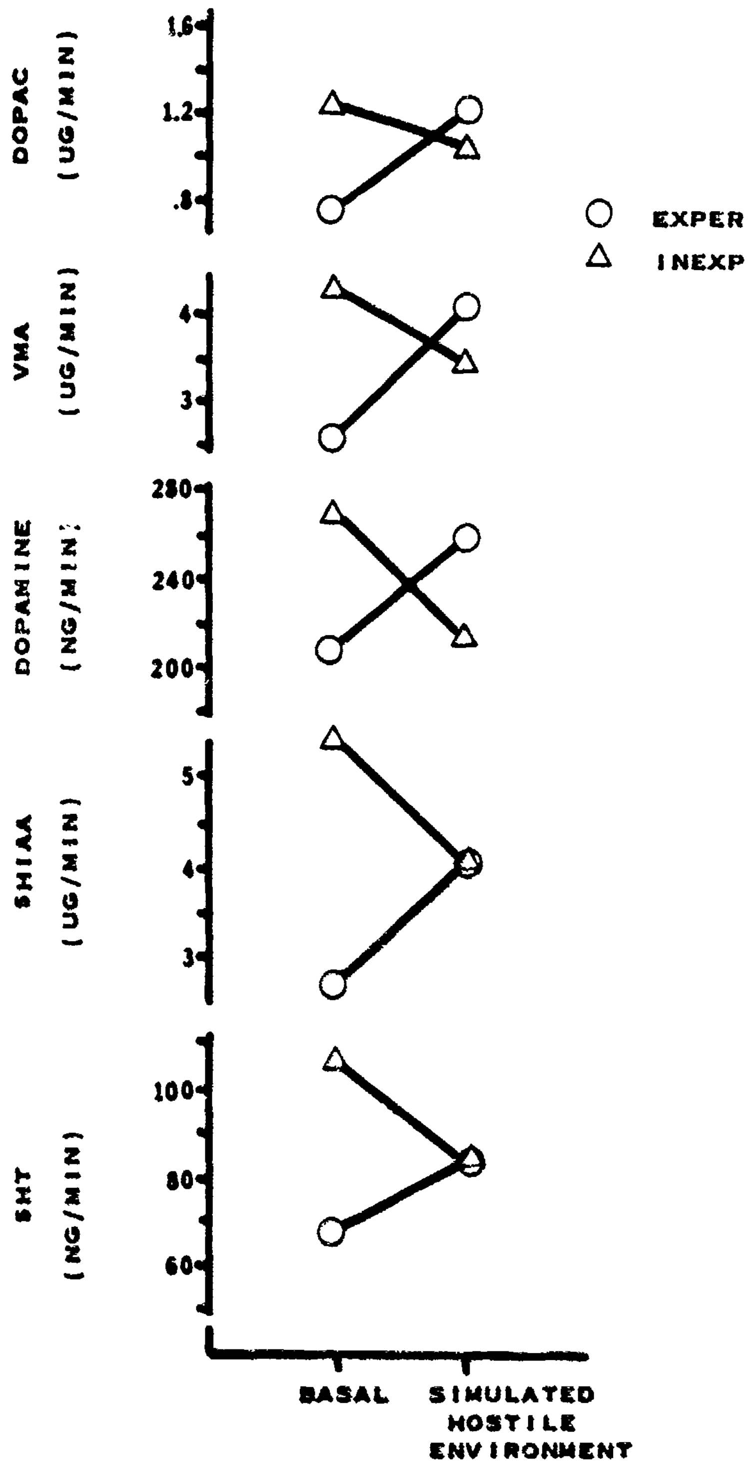

Figure 5. Interaction of Experience and Trial for the excretion rates of DOPAC (top), VMA (second from top), Dopamine (middle), 5HIAA (second from bottom) and 5HT (bottom). Mean values are plotted.

Biochemical and Physiological Correlation. The physiological variables selected for comparison with the biochemical indices were respiratory rate, cardiac IBI, change in respiratory rate, and change in IBI. The only performance variable available in time for the preparation of this report was the number of trials out of 10 that ended with a surface-to-air missile strike (SAM HITS). The statistically significant ($p < 0.05$) coefficients are depicted in Table 14. Although some of the relationships are significant, no pattern of statistical significant is evident. It should also be noted that when this many correlations are computed, approximately four coefficients would be expected to be significant by chance alone (Games, 1971). It must be concluded from these data that the physiological and biochemical data are measuring different aspects of arousal or stress.

Overview

When the data from all experiments are collated and analyzed as a simple examination of the human response to stress, a large number of indices are significant (Table 15). Across all experiments (N=134), exposure to stress caused a 121% increase in E, a 46% increase in NE, a 60% increase in the sum E + NE, and an 18% decrease in the sum HVA + DOPAC; also, a 26% decrease in the NE/E ratio, a 28% decrease in the DA/NE ratio, and a 73% increase in the NE/5HT ratio. Interpretation and discussion of these changes has been provided in earlier sections.

Table 16 has been prepared in an attempt to provide an overview for all aspects of the effort reported on herein. The data base for the changes noted was drawn from Tables 1, 5, 10, and 13. It would appear from this summary that the human stress response manifests itself with the following biochemical patterns:

TABLE 14. PEARSON PRODUCT MOMENT CORRELATION COEFFICIENTS BETWEEN CHANGES DURING STRESS IN BIOCHEMICAL INDICES AND SELECTED PHYSIOLOGICAL VARIABLES* (N=27)

Biochemical Variables	Physiological Variables: Respiratory Rate	IBI	Δ Respiratory Rate	Δ IBI	SAM HITS
E	--	--	--	--	--
NE	--	--	--	--	--
VMA	--	--	--	--	--
MHPG	--	--	--	--	--
DA	--	--	--	--	--
HVA	--	--	--	--	--
DOPAC	--	--	--	--	--
5HT	--	--	--	--	--
5HIAA	--	--	.324	.335	--
E + NE	--	--	--	--	--
VMA + MHPG	--	--	--	--	--
HVA + DOPAC	--	--	--	--	--
NE/E	.339	--	--	--	--
DA/NE	--	--	--	--	--
NE/5HT	--	--	-.343	--	--

* Only statistically significant ($p < 0.05$) relationships are shown.

TABLE 15. COMPARISON OF BASAL AND STRESS CONDITIONS IN ALL EXPERIMENTS ($\bar{X} \pm SE$) N=134

Variable	Basal	Stress	Δ	Univariate F
E[a]	11.1 ± 1.1	24.5 ± 1.7	13.4 ± 1.9	51.41 **
NE[a]	47.3 ± 3.2	69.0 ± 4.1	21.6 ± 4.7	21.53 **
VMA[b]	3.41 ± 0.15	3.65 ± 0.15	0.25 ± 0.16	2.46
MHPG[b]	1.46 ± 0.21	1.43 ± 0.25	0.03 ± 0.18	0.02
DA[a]	260.7 ± 15.4	239.6 ± 10.2	-21.0 ± 18.3	1.32
HVA[b]	3.89 ± 0.16	3.63 ± 0.17	- 0.26 ± 0.19	1.90
DOPAC[b]	1.16 ± 0.09	1.05 ± 0.06	- 0.10 ± 0.10	1.02
5HT[a]	92.2 ± 3.4	84.5 ± 3.2	- 7.7 ± 4.1	3.46
5HIAA[b]	3.86 ± 0.20	3.60 ± 0.16	- 0.26 ± 0.22	1.30
E + NE[a]	58.5 ± 4.0	93.5 ± 4.9	35.1 ± 5.9	35.28 **
VMA + MHPG[b]	4.87 ± 0.31	5.77 ± 0.60	0.90 ± 0.57	2.53
HVA + DOPAC[b]	4.71 ± 0.25	3.87 ± 0.17	- 0.84 ± 0.28	8.70 **
NE/E	6.65 ± 0.59	4.93 ± 0.69	- 1.72 ± 0.59	8.41 **
DA/NE	6.73 ± 0.36	4.86 ± 0.38	- 1.87 ± 0.44	17.98 **
NE/5HT	0.52 ± 0.03	0.90 ± 0.06	0.38 ± 0.06	34.93 **

[a] ng/min excreted

[b] ug/min excreted

* $p < .05$

** $p < .01$

TABLE 16. SUMMARY OF CHANGES FROM BASAL TO STRESS CONDITIONS IN THE STUDY[a]

Variable	Change: Experiment One[a]	Change: Experiment Two[b]	Change: Experiment Three[c]	Change: All Data[d]
E	INCREASED	INCREASED	INCREASED	INCREASED
NE	*	INCREASED	INCREASED	INCREASED
VMA	--	--	--	--
MHPG	--	--	--	--
DA	--	--	--	--
HVA	--	DECREASED	--	--
DOPAC	--	--	--	--
5HT	--	DECREASED	--	--
5HIAA	--	--	--	--
E + NE	*	INCREASED	INCREASED	INCREASED
VMA + MHPG	--	--	--	--
HVA + DOPAC	--	INCREASED	--	INCREASED
NE/E	--	DECREASED	--	DECREASED
DA/NE	DECREASED	DECREASED	**	DECREASED
NE/5HT	INCREASED	INCREASED	INCREASED	INCREASED

a From Table 1
b From Table 5
c From Table 10
d From Table 13
* p = .12 for NE, .06 for E+NE. In all likelihood these would have been statistically significant given true basal excretion levels as the reference for determining change.
** p = .76. Nonsignificant decrease noted. True basals may have resulted in a statistically significant change.

1. E, NE, and their sum, E + NE, all increase as a result of stress.

2. The ratio of DA to NE decreases.

3. The ratio of NE to 5HT increases.

These patterns were seen in every experiment and although not statistically significant in every case (exceptions are noted in Table 14), there is reason to believe that true basal measures would have provided a totally coherent picture. These patterns have been identified individually in previous studies, but this project represents the first occasion when they have been demonstrated in concert.

CONCLUSIONS

There were three basic objectives to this research effort. In respect to those purposes, it may be concluded that

1. Biochemical response patterns vary with the mode of stress.

2. A battery of indices has been identified which seems to reflect the stress response across many modes of stress in a variety of field settings.

3. Biochemical and physiological indices do not show good agreement. Data from experiments quantifying stress by one technique should not be simply and directly compared with those based on the other technique.

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