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# SYMPATHOADRENAL RESPONSE TO GRAVITATIONAL STRESS *

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Space flight imposes upon man many stresses; i.e., thermal, irradiation, sensory deprivation, acceleration (exit), deceleration (re-entry), and so forth. Some of these stresses, such as sensory deprivation, cannot be adequately studied within the earth's atmosphere whereas others, such as acceleration and deceleration, lend themselves more easily to experimentation. Although the sympathoadrenal system is an integral part of the body's response to many of these stresses, it has not, however, been fully evaluated in terms of the stresses imposed by space flight. Therefore, the experiments herein described were designed to evaluate more precisely the role of the sympathoadrenal medullary system in one specific stressful situation, namely, gravitational stress (prolonged acceleration).

Noradrenaline is the neurohormone of the sympathetic (adrenergic) nerves (1–4) and is released as such at the nerve endings. Although noradrenaline is also found in the adrenal medulla, adrenaline is the chief hormone of the human adrenal medulla (3, 5, 6). Both of these hormones are released in increased amounts under a number of stressful situations; i.e., thermal burn (7), trauma (8), X-irradiation (9), severe muscular exercise (10), and so forth. There can also be a selected release of these hormones, as is seen in anxiety (11) and hypothalamic stimulation (3, 12). This increased release of adrenaline, noradrenaline, or both, is reflected in the urine by an elevation in the urinary output of free and conjugated adrenaline and noradrenaline (3); therefore, by measuring the urinary output of adrenaline and noradrenaline, one has a barometer of sympathoadrenal medullary activity.

## METHOD

Subjects were centrifuged, and urine was collected before and after centrifugation and bioassayed for adrenaline and noradrenaline. The details of the methods used are described in the following paragraphs.

### *A. Centrifugation*

*1. G tolerance experiments.* To determine the relationship of adrenaline and noradrenaline output to positive G (+ G) tolerance, subjects were centrifuged with 10 rides of 15 seconds each at the subjects' subthreshold blackout levels. All subjects were experienced Air Force personnel who had been previously classified as low, intermediate, or high G tolerance subjects.

The subject's response during each G run was evaluated by a system of peripheral and central flashing lights on a panel mounted in front of him in the centrifuge cab. The subject was required to respond to the flashing lights by turning them off as they flashed on. Failure to respond to peripheral lights was considered evidence of loss of peripheral vision, and lack of response to central lights was considered blackout.

Determination of the blackout level was accomplished by exposing the subject to a series of 15-second centrifugations at various G exposures. The exposure was so arranged that the subject was centrifuged 10 times within 1 hour with a 3-minute rest period between each ride. The G exposure was varied but so designed as to be just below the blackout level. As far as was practical, the centrifugation was designed to produce a maximal G exposure without causing the subject to black out.

*2. G variation experiments.* To determine the relationship of adrenaline and noradrenaline output to various G exposures, subjects were centrifuged at 2 G and again at 4 G. Each subject was tested on separate days. On each day, the subjects were given, within a 1-hour period, 10 consecutive rapid-onset centrifugations. (In rapid-onset centrifugations, the subject is rapidly accelerated so that peak G is reached and then the centrifuge decelerated within a 15-second period.) On any one experimental day, the subject was exposed to only one G level, either 2 G or 4 G. Hence, a subject would have 10 centrifugations at 2 G on one day and then 10 more at 4 G on another day. A 3-minute rest period occurred between the centrifugations.

The G levels used were well below the usual blackout threshold of the subjects; that is, the subjects, when exposed to a series of centrifugations in which the G level was progressively increased on succeeding rides, did not black out (loss of central and peripheral vision) below 4 G.

The subjects were not informed of the G level to which they would be exposed on any one day and were

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not told the profile of the centrifugation; i.e., all rides would be at the same G on any one day. The sequence of G levels was varied for the experimental group so that some subjects had a 4 G and others a 2 G profile on the first experimental day.

In addition to the above experiments, all subjects—low, intermediate, and high G tolerance—were centrifuged at 2.5 G. These subjects were given 10 consecutive rapid-onset centrifugations within a 1-hour period. The purpose of these latter experiments was to determine if there was any difference between the adrenaline and noradrenaline output of high, intermediate, and low G tolerance subjects when exposed to the same gravitational stress, a stress considerably below their blackout level.

*B. Collection periods*

Urine collections were made in accordance with a 3-hour prerun period, a 1-hour run (centrifugation) period, a 1-hour postrun period, and a 3-hour post-postrun period. To insure an adequate urinary output during the 1-hour run and 1-hour postrun periods, approximately 250 ml of water was taken 10 minutes before the run period. Collections were made at the end of each period, the volume was determined, and the urine acidified to pH 2.0 to 3.0 with 2 N $H_2SO_4$.

*C. Preparation of urine extract*

The urine extract was prepared according to the procedure of von Euler and Hellner (13). The urine was

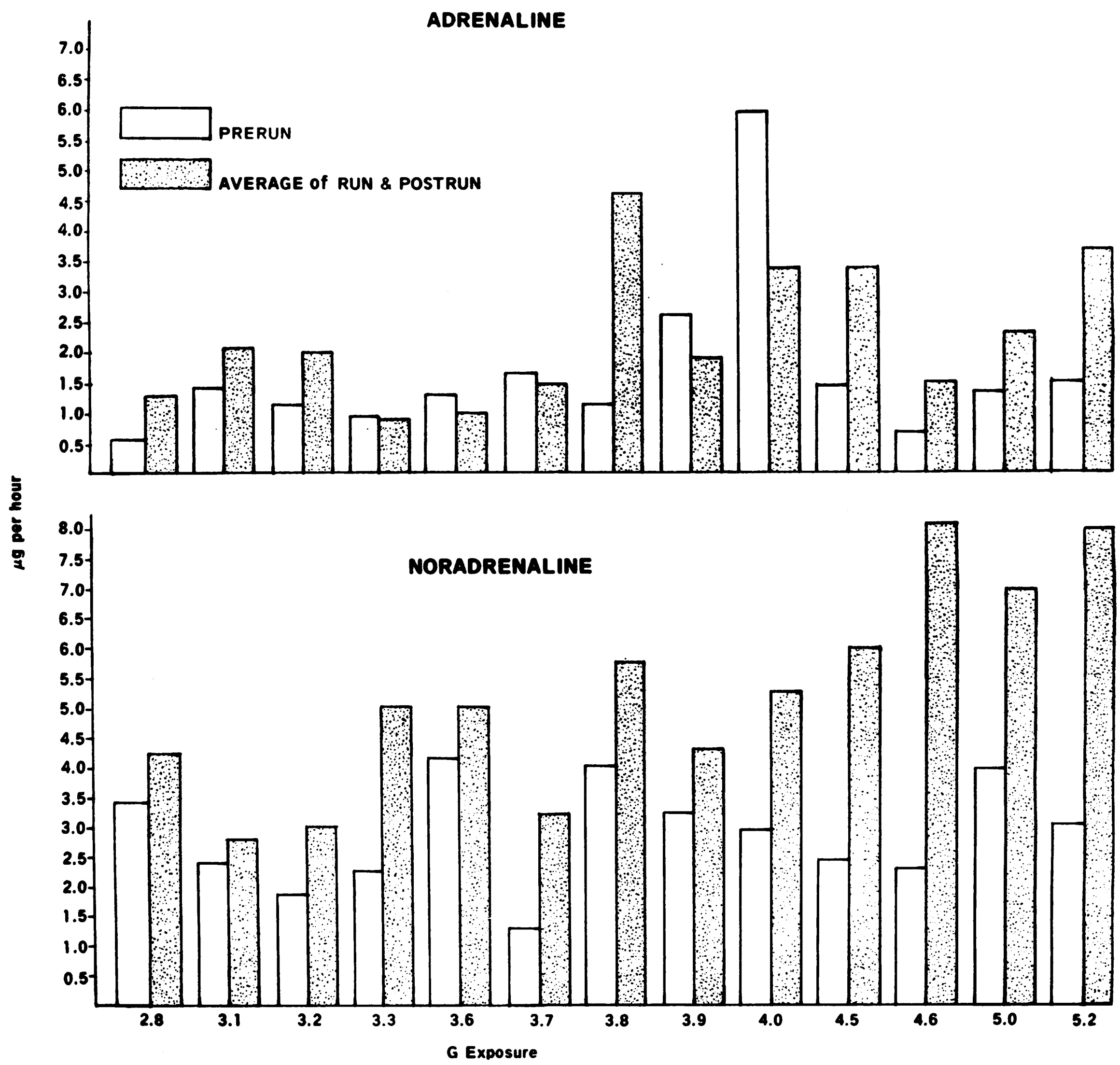


FIG. 1. URINARY OUTPUT OF ADRENALINE AND NORADRENALINE IN SUBJECTS OF LOW, INTERMEDIATE, AND HIGH G TOLERANCE CENTRIFUGED AT THEIR RESPECTIVE SUBTHRESHOLD BLACKOUT LEVEL. The normal output of adrenaline is 0.4 to 0.8 µg per hour and of noradrenaline is 0.8 to 3.0 µg per hour.

TABLE I

*Urinary output of adrenaline and noradrenaline* in subjects of low, intermediate, and high G tolerance centrifuged at their respective subthreshold blackout levels*

| Collection period | Low G tolerance (3.4 and below) | | | | Intermediate G tolerance (3.5 to 4.0) | | | | | High G tolerance (4.0 and above) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S.T. 2.8G | R.I. 3.1G | S.M. 3.2G | K.R. 3.3G | A.N. 3.6G | S.T. 3.7G | P.R. 3.8G | P.I. 3.9G | S.A. 3.8G | L.A. 4.0G | C.O. 4.0G | S.O. 4.5G | M.O. 4.6G | W.A. 5.0G | L.A. 5.2G |
| Adrenaline output as related to G tolerance ($\mu g/hr$) | | | | | | | | | | | | | | | |
| Prerun | 0.6 | 1.4 | 1.2 | 0.9 | 1.3 | 1.7 | 1.1 | 2.6 | 0.4 | 1.2 | 5.9 | 1.4 | 0.7 | 1.3 | 1.5 |
| Run | 1.6 | 2.7 | 2.3 | 0.9 | 1.0 | 2.5 | 5.0 | 1.9 | 2.5 | 4.0 | 4.9 | 4.9 | 1.6 | 2.6 | 3.9 |
| Postrun | 1.0 | 1.5 | 1.7 | 0.8 | 0.9 | 0.3 | 4.1 | 1.7 | 1.5 | 1.0 | 1.8 | 1.8 | 1.4 | 2.1 | 3.3 |
| Post-postrun | 0.3 | 0.7 | 0.9 | † | 0.2 | 1.0 | 3.6 | 1.3 | 1.3 | 0.5 | 0.6 | 2.0 | 0.7 | 1.4 | 1.7 |
| Noradrenaline output as related to G tolerance ($\mu g/hr$) | | | | | | | | | | | | | | | |
| Prerun | 3.4 | 2.3 | 1.8 | 2.2 | 4.1 | 1.3 | 4.0 | 3.1 | 3.9 | 3.2 | 2.9 | 2.4 | 2.2 | 3.9 | 3.0 |
| Run | 5.2 | 3.2 | 1.4 | 5.8 | 5.9 | 4.9 | 6.0 | 4.7 | 6.9 | 5.1 | 5.2 | 6.9 | 7.1 | 7.8 | 10.5 |
| Postrun | 3.1 | 2.3 | 4.4 | 4.0 | 3.9 | 1.3 | 5.4 | 3.9 | 3.8 | 4.4 | 5.1 | 4.9 | 9.0 | 6.0 | 5.5 |
| Post-postrun | 3.1 | 2.9 | 1.1 | † | 4.4 | 5.7 | 4.0 | 3.8 | † | 1.7 | 2.0 | 5.1 | 2.7 | 4.7 | 2.0 |

* Normal output: adrenaline, 0.4 to 0.8 $\mu g$/hr; noradrenaline, 0.8 to 3.0 $\mu g$/hr.
† Destroyed.

hydrolyzed by boiling for 20 minutes at pH 2.0. The adrenaline and noradrenaline were adsorbed on aluminum hydroxide and filtered. The precipitate was washed with distilled water and redissolved with 2 N $H_2SO_4$. The remaining salts were precipitated from the solution by mixing the extract with alcohol and acetone and then filtered. The final filtrate was concentrated under vacuum with a rotary evaporator.

### *D. Bioassay of adrenaline and noradrenaline*

The various modifications of the fluorometric method in current use for measuring the adrenaline and noradrenaline are not entirely satisfactory because the urine contains many known and unknown constituents which are fluorometrically active and, therefore, impart an error to the determination (14). For these reasons and because the bioassay measures the biological activity of the naturally occurring isomers of adrenaline and noradrenaline, the bioassay was used in preference to the fluorometric method.

The bioassay method of measuring adrenaline and noradrenaline has been described by a number of investigators (7, 13, 15). In this method, the cat's blood pressure is used in conjunction with the fowl's rectal caecum; the former is sensitive to noradrenaline and the latter to adrenaline. The cat's blood pressure was recorded from the carotid artery and injections of adrenaline, noradrenaline, and urine extracts made via the femoral vein. The hen's rectal caecum was suspended in Tyrode's solution within a water bath. Injections of adrenaline, noradrenaline, and the extract were made into the bath and the degree of caecal relaxation recorded.

After the activity ratio of adrenaline and noradrenaline on the cat's blood pressure and the hen's rectal caecum and the activity of the urine extract in terms of *l*-noradrenaline had been determined, it was then possible to calculate the amount of *l*-noradrenaline and *l*-adrenaline in the extract (3, 7, 10).

## RESULTS

*A. G tolerance experiments.* Subjects of high, low, and intermediate G tolerance were centrifuged as described under Section A of Method, and the urines collected in accordance with the schedule described under Section B of Method.

The urines were bioassayed for adrenaline and noradrenaline and the results are described in Table I and Figure 1. Upon centrifugation, there was an increase in the adrenaline output of 2 to 12 times that of the control values. This elevation in adrenaline output was greatest during the run period, but also occurred during the prerun as well as the postrun periods. The increase in adrenaline output upon centrifugation could not be correlated with the degree of centrifugation, since subjects of low, intermediate, and high G tolerance showed no significant difference in output of adrenaline during the run period or the postrun period.

The prerun output of adrenaline varied greatly from subject to subject. This prerun elevation of adrenaline appeared to be related to the anxiety associated with the anticipation of being centrifuged. Noradrenaline output (release), on the other hand, did not appear related to the anxiety associated with anticipating centrifugation, but was more closely akin to the physical stress of centrifugation; i.e., the hemodynamics, cardiac changes, and so forth. This was attested to by the fact that there was no significant elevation in the noradrenaline output in the prerun samples but a large increase in the noradrenaline output in the run and postrun samples.

The noradrenaline elevation in the run and the postrun periods was 2 to 5 times above prerun levels and appeared to parallel the degree of G tolerance; the greater the G tolerance, the greater the output of noradrenaline. Stated somewhat differently, subjects of high G tolerance centrifuged at their sub-blackout threshold level showed a greater output of noradrenaline than those subjects of low G tolerance centrifuged at their sub-blackout threshold. Subjects with an intermediate G tolerance, in general, showed a noradrenaline output level between that of the high and low subjects. This greater output of noradrenaline in the subjects of high G tolerance is in all probability related to the greater physical stress imposed by the higher G centrifugation rather than to any difference in the subjects' G tolerance (see Table II).

The fact that an elevated adrenaline and noradrenaline output is also found in the post-postrun period probably represents a delay in the renal clearance of these hormones produced during the run period rather than any prolongation of their production. As would be expected, the greatest adrenaline and noradrenaline output generally occurred during the run period.

*B. G variation experiments.* From the preceding results on G tolerance, it would seem that subjects of high G tolerance, when centrifuged at their subthreshold G level, characteristically show a greater output of noradrenaline than those of intermediate or low G tolerance. To determine if this increased output of noradrenaline was a characteristic of the high G subjects or was related to the physiologic demand imposed by higher centrifugation, G variation experiments were undertaken.

Subjects of high G tolerance were centrifuged at 2.0 G and 4.0 G (see Method). As before, the urines were collected on a 3-hour prerun, 1-hour run, 1-hour postrun, and 3-hour post-postrun schedule, and bioassayed for adrenaline and noradrenaline. The results of these G variation exposures are described in Table II. The noradrenaline output was significantly elevated during the run and the postrun periods and the degree of elevation paralleled the G exposure; i.e., the greater the G exposure, the greater the noradrenaline output; subjects centrifuged at 4.0 G excreted more noradrenaline than the same subjects centrifuged at 2.0 G.

When subjects of low, intermediate, and high G tolerance were centrifuged at the same G (i.e., 2.5 G), no significant difference was noted in the noradrenaline output (see Table III). There was no correlation between the noradrenaline output and the G tolerance, since all subjects showed approximately the same output of noradrenaline; when the run and postrun noradrenaline was averaged, it varied between 3.2 and 5.7 μg per hour (Table III). The noradrenaline results would again indicate that the noradrenaline output was closely related to the physical stress of centrifugation rather than to any variation in the G tolerance of the subject. The adrenaline output, on

TABLE II

*Correlation of urinary adrenaline and noradrenaline to G variation*

| Collection period | Subject* 1 | | Subject 2 | | Subject 3 | | Subject 4 | | Subject 5 | | Subject 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | A | B | A | B | A | B | A | B | A | B |
| | | | | | Adrenaline output† (*μg/hr*) | | | | | | | |
| Prerun | 0.5 | 0.6 | 1.2 | 0.7 | 1.8 | 2.7 | 1.5 | 1.7 | 3.1 | 0.9 | 1.2 | 1.0 |
| Run | 1.9 | 2.4 | 1.8 | 2.0 | 1.8 | 2.9 | 1.8 | 3.1 | 1.3 | 2.9 | 3.1 | 2.5 |
| Postrun | 3.9 | 1.7 | 2.0 | 0.9 | 2.5 | 3.9 | 2.4 | 5.5 | 1.8 | 2.6 | 2.5 | 1.3 |
| Post-postrun | 1.1 | 0.7 | 1.8 | 1.2 | 1.1 | 1.6 | 1.0 | 1.5 | 1.7 | 1.7 | ‡ | 1.8 |
| | | | | | Noradrenaline output† (*μg/hr*) | | | | | | | |
| Prerun | 1.0 | 1.9 | 3.5 | 1.9 | 3.1 | 4.1 | 1.7 | 3.9 | 2.8 | 3.3 | 1.8 | 2.0 |
| Run | 1.4 | 3.1 | 4.1 | 5.8 | 3.5 | 4.5 | 4.0 | 5.6 | 5.9 | 7.0 | 2.5 | 3.8 |
| Postrun | 1.9 | 1.6 | 3.6 | 5.7 | 5.1 | 6.8 | 2.6 | 3.8 | 2.0 | 2.1 | 2.8 | 5.7 |
| Post-postrun | 3.2 | 1.5 | 3.4 | 0.6 | 3.8 | 4.9 | 3.0 | 3.3 | 3.4 | 3.0 | ‡ | 1.5 |

* Subjects of high G tolerance centrifuged at 2.0 G (A) and 4.0 G (B).
† For normal output, see footnote to Table I.
‡ Destroyed.

TABLE III

*Urinary output of adrenaline and noradrenaline in subjects of various G tolerance centrifuged at 2.5 G*

| | Low G tolerance (3.4 and below) | | | Intermediate G tolerance (3.5 to 4.0) | | | | | High G tolerance (4.0 and above) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Collection period | S.T. 2.5 G | K.R. 3.0 G | K.O. 3.3 G | C.O. 3.6 G | S.R. 3.7 G | P.R. 3.8 G | S.A. 3.9 G | P.I. 3.9 G | C.G. 4.0 G | S.I. 4.3 G | E.V. 4.4 G | S.O. 4.5 G |
| | | | | | | Adrenaline output (*μg/hr*) | | | | | | |
| Prerun | 0.6 | 0.3 | 0.9 | 2.1 | 1.7 | 1.0 | 0.4 | 2.6 | 5.9 | 0.8 | 5.9 | 1.4 |
| Run | 1.6 | 1.0 | 0.9 | 2.2 | 2.5 | 5.0 | 2.5 | 1.9 | 4.9 | 1.8 | 6.2 | 4.9 |
| Postrun | 1.0 | 0.7 | 0.8 | 1.1 | 3.1 | 4.1 | 1.5 | 1.7 | 1.8 | 2.7 | 2.2 | 1.8 |
| Post-postrun | 0.3 | 0.1 | 2.6 | 0.8 | 1.0 | 3.6 | † | 1.3 | 0.6 | 0.9 | 1.1 | 2.0 |
| | | | | | | Noradrenaline output* (*μg/hr*) | | | | | | |
| Prerun | 3.4 | 2.4 | 2.2 | 3.0 | 1.3 | 3.9 | 3.9 | 3.1 | 2.9 | 1.9 | 3.0 | 2.4 |
| Run | 5.2 | 6.8 | 5.8 | 3.7 | 4.9 | 6.0 | 6.9 | 4.7 | 5.2 | 3.6 | 2.2 | 6.9 |
| Avg. (Run and Postrun) | (4.1) | (5.3) | (4.9) | (3.5) | (5.3) | (5.7) | (5.4) | (4.3) | (5.2) | (3.2) | (5.8) | (5.9) |
| Postrun | 3.0 | 3.7 | 4.0 | 3.1 | 5.7 | 5.4 | 3.8 | 3.9 | 5.1 | 2.8 | 9.5 | 4.9 |
| Post-postrun | 3.1 | 1.4 | 6.9 | 2.2 | 1.3 | 4.0 | † | 3.8 | 2.0 | 3.4 | 7.0 | 5.1 |

* For normal output, see footnote to Table I.
† Destroyed.

the other hand, varied from subject to subject and was elevated during the run as well as the prerun periods.

## DISCUSSION

It has been shown that various forms of stress activate the sympathoadrenal medullary system and this is reflected by an increase in the urinary output of the sympathetic neurohormone, noradrenaline, and the adrenal medullary hormone, adrenaline (7–11, 16). Furthermore, Goodall and Berman (11) showed that, under high gravitational stress, the increased adrenaline release was largely related to emotion, anxiety associated with being centrifuged. The experiments herein described corroborate their findings. From Tables I–III, it is apparent that no correlation can be drawn between the adrenaline output and the extent of centrifugation or the G tolerance of the subjects. The fact that the adrenaline output was generally increased before as well as during centrifugation would certainly seem to indicate that the adrenaline release was more closely associated with the anxiety or fear of being centrifuged than to the physical changes produced by centrifugation.

The noradrenaline release, on the other hand, appeared closely related to the actual physical stress of centrifugation and unrelated to the emotions involved in centrifugation. This is borne out by the fact that there was no significant increase in noradrenaline output in the prerun period but a markedly increased output during and immediately after centrifugation (see tables and figure).

The question naturally arises as to the possible relationship of G tolerance to noradrenaline output; i.e., do subjects with high G tolerance actually release more noradrenaline than those with low G tolerance and thereby protect themselves from greater G stress? Table I and Figure 1 would seem to indicate this. However, since all of the subjects referred to in Table I and Figure 1 were centrifuged at their respective sub-blackout threshold levels, it could mean that those with a high G tolerance were in this instance stressed to a greater extent than those with a low G tolerance and, because of this greater gravitational stress, released a larger amount of noradrenaline. To prove this latter point, subjects of high G tolerance were centrifuged at 2 G and again at 4 G. The results of these latter experiments clearly show that the physical stress of 4 G was greater than that of 2 G and was reflected by a greater noradrenaline output at 4 G than at 2 G (Table II). In view of this last finding, all subjects—low, intermediate, and high G tolerance—were centrifuged at 2.5 G. These 2.5 G experiments indicate that there was little or no difference in the noradrenaline output when subjects of various G tolerance received the same centrifugation pattern (Table III). In brief, it seems that the noradrenaline output is dependent upon the physical stress imposed by centrifugation and has no direct relationship to the G tolerance of the subject.

SUMMARY

1. Subjects were centrifuged, and urine was collected before and after centrifugation and bioassayed for adrenaline and noradrenaline. The urinary output of adrenaline and noradrenaline was correlated to the G tolerance of the subject and to various G exposures.

2. Adrenaline output was increased before centrifugation as well as during and immediately after centrifugation. This increased adrenaline release was shown to be largely related to the emotions; i.e., anxiety associated with the anticipation of being centrifuged, rather than to the physiologic changes produced by centrifugation.

3. The output of noradrenaline was elevated only during centrifugation and during the period immediately following centrifugation. This increased noradrenaline output appeared to be dependent upon the physical stress imposed by centrifugation and had no direct relationship to the G tolerance of the subject.

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