

## Catecholamine Activity and Infectious Disease Episodes

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### **Abstract:**

The profile of 3-hydroxy-4-methoxy methoxy acid (VMA) excretion was studied in relation to reported acute infectious disease episodes. Daily VMA excretion levels and symptom reports were analyzed for a group of 47 volunteers over a four-week period. Results showed a tendency for elevated VMA levels to occur with greater frequency within three days prior to the onset of symptoms. These findings are interpreted as suggesting that elevated levels of catecholamine activity may increase susceptibility to disease by interfering with the immune response, and in the presence of an agent lead to an infectious disease episode.

**Index Terms:** catecholamines, stress, infectious disease, sympathetic nervous system, susceptibility to infection, VMA excretion, immune response.

### **Article:**

The influence of psychosocial stress on susceptibility to acute infectious diseases has received considerably less attention from investigators than the corresponding relationship for chronic diseases. Yet, the generally short latent (incubation) periods characteristic of many infectious disease conditions provide opportunities to study more directly the time relationship between suspected etiologic "stress" factors and onset of disease symptoms.

In animals stressful environmental conditions have been shown to contribute to higher rates of infection,<sup>1-3</sup> and in humans psychosocial factors have been associated with greater susceptibility to a variety of infectious diseases.<sup>4</sup> The mediating physiologic mechanisms for the influence of psychosocial factors may be the sympathetic nervous system and the pituitary-adrenal endocrine systems through their effects on the immune responses, although the supporting evidence is far from conclusive. Corticosteroids are widely used to suppress inflammation in humans. Rinehart, et al., reported reduced effectiveness of human monocyte function *in vivo* following three days of prednisone therapy.<sup>5</sup> Steven son reported that glucocorticoids *in vitro* stimulated random migration of macrophages away from cultured explants of spleen tissue, reducing the intensity of their inflammatory activity.<sup>6</sup> Monjan and Collector found that short-term (20 days) exposure of mice to noise stress depressed the lymphocyte-mediated cytotoxic response, and this depression paralleled increased plasma cortisol concentrations in a second group of mice.<sup>7</sup>

The catecholamines, too, have been suspected of influencing immune processes by their anti-inflammatory activity in both acute and chronic inflammation.<sup>8-10</sup> However, there is little evidence linking variations in the activity of these hormones, *in vivo*, with susceptibility to infectious diseases.

In a recent study Gruchow found higher levels of vanillylmandelic acid (VMA) excretion in respondents who reported chronic health problems, and lower levels in those who reported only nonchronic (infectious) conditions.<sup>11</sup> However, because this was a cross-sectional study the reported morbidity occurred at varying times up to one year prior to the interviews and the collection of urine specimens for VMA determinations. As a result, these values may not have accurately reflected the physiologic changes occurring at the time of infectious illness episodes.

The study reported here was a prospective follow-up to that previous study. The catecholamine activity levels and health statuses of a group of participants were measured daily over a four-week period. From this data it was possible to determine the profile of catecholamine activity prior to and during reported symptomatic infectious disease episodes.

## **METHODS**

Forty-seven volunteer university students (24 male, 23 female) were studied over a four-week period. All of these students were enrolled in university full time, were between the ages of 17 and 22, and resided in the same student-housing complex.

The study protocol included: (1) an initial self-report questionnaire requesting demographic information plus information on the respondent's health status during the previous 12 months, (2) the collection of urine specimens each morning for 28 days for VMA and creatinine analyses, and (3) daily report cards (diaries) on which the respondent indicated current health status and the presence of any illness symptoms during the 28-day study period.

At the beginning of the study the 130 male residents and 120 female residents of the complex received letters describing the study and inviting them to attend a briefing session during which they could enroll in the study. At this session, the initial questionnaire for demographic and health status information was administered to the 47 who volunteered, and a supply of urine specimen bottles and daily symptom report cards was provided to each participant. Oral instructions for obtaining specimens were given and identical written instructions were enclosed with the specimen bottles. It was emphasized that specimens should be obtained in the morning when the respondent "first (got) out of bed." This was to make the specimens as comparable as possible with respect to the time of collection. Each specimen bottle contained 1/2 gm. of sulphamic acid crystals\* to prevent bacterial growth in the urine, and to maintain the stability of catecholamine metabolites.

Daily symptom reporting was by means of index cards on which were provided a checklist of ten health status items and a space to write in health problems not listed. The intent of the list was to elicit the reporting of acute respiratory symptoms and to distinguish these respondents from those who were without symptomatic health problems. Only respondents who reported they had a "cough," "sore throat," "cold" or "flu" on any given day were considered to have acute respiratory illness symptoms.

Collection points for the specimens and report cards were located conveniently in the lobby of each residence (one for males and one for females). Specimens and cards were collected and delivered to the laboratory each morning to minimize the possibility of mix-ups between days, or of participants providing two specimens from one day. Specimen bottles and cards were pre-coded for identification. Specimens were kept frozen until analyses.

Since neither specimen volumes nor collection intervals could be controlled in this study, urine specimens were analyzed for both VMA and creatinine concentrations to compensate for possible individual variations in renal function. The method of Pisano et al.<sup>12</sup> was used for VMA determinations, and creatinine determinations were made using the alkaline picrate method of Folin and Wu.<sup>13</sup> All further references in this paper are to creatinine-corrected VMA values. Although creatinine-corrected VMA values show a strong relationship to age,<sup>14</sup> the narrow range of the ages of the participants in this study obviated the need for age-corrections of the VMA determinations.

VMA was selected as the physiological measure rather than free catecholamines, because it is a more stable measure of catecholamine activity, in that the lag in excretion resulting from the metabolic breakdown process reduces the specificity of the VMA titre in relation to isolated short-term increases in catecholamine activity, and because the collection of urine specimens is less refractory than obtaining blood samples for serum measures of catecholamine activity. A primary disadvantage of utilizing VMA measurements is that

sympathetic nervous activity and adrenal medullary activity cannot be differentiated. The method of VMA assay used in this study has been shown to be relatively free from interference by dietary factors or drugs.<sup>12</sup>

## RESULTS

All of the 24 males and 23 females who agreed to participate in the study at the beginning continued their participation for the entire 28-day period. An average of 21 specimens and corresponding symptom reporting cards was received from each respondent during the 28 days (range = 11-27). There was no difference in response rates between males and females. The overall response rate based on a possible total of 1316 participant-days (47 X 28 = 1316) was 75 percent (987/1316).

During the four-week study period, 34 respondents (17 males and 17 females) reported common cold or flu symptoms on at least one day. The average number of days on which these symptoms were reported in this group was 5.5, with a range of from one day to twenty-two days. The average for males (7.5 days) was higher than for females (4.7 days), but there was wide variation within both groups and this difference was not statistically significant ( $t = 1.50, p < .20$ ).

### *Illness Episodes*

For the purposes of this study an illness episode was defined as two or more consecutive days of reported respiratory symptoms, at least three days after the beginning of the study period, and at least three days before the end of the study period. The three-day margins were necessary so that the profile of VMA excretion for three days before and after onset of symptoms could be ascertained for each episode. A sequence of two or more days of reported symptoms was considered to be a more reliable indicator of a respiratory illness episode than a single day. Seventeen respondents (10 males and 7 females) reported episodes of two- or more days, with an average duration of 6.4 (S.D.  $\pm 4.5$ ) days per episode. Two male respondents reported two episodes apiece, bringing the total number of episodes suitable for study to 19.

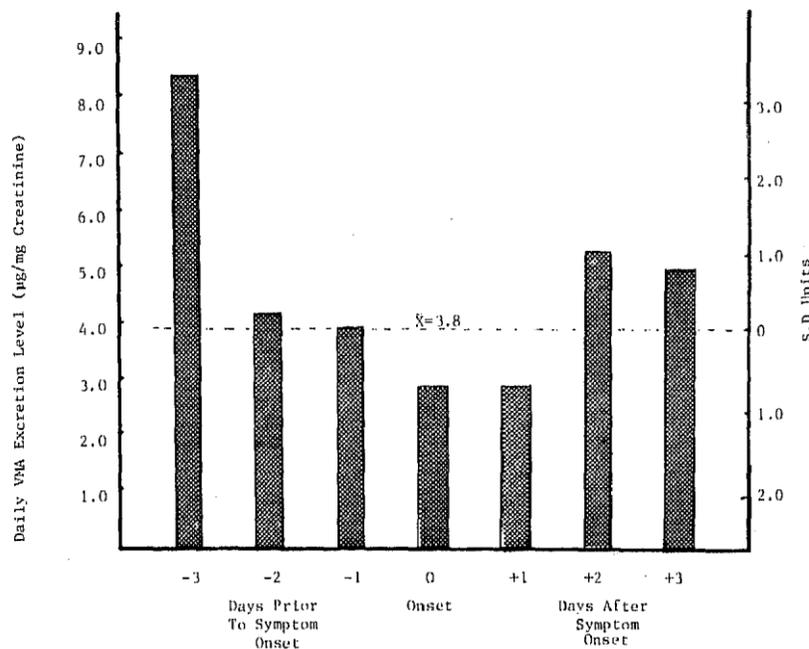


Fig. 1. Sample individual pattern of VMA excretion (respondent #14). S.D. units are based on the four-week mean value ( $3.8 \mu\text{g}/\text{mg}$ ) for this respondent.

### *VMA Profiles*

A characteristic pattern of variation in VMA values was observed to coincide with the onset of reported symptoms in 13 of the 19 (68 percent) episodes. The nature of this pattern was that of a peak, or spike, in VMA values of a single-day duration, one or more standard deviation (S.D.) units above the individual mean within three days prior to the onset of symptoms (Fig. 1). The spike was generally followed by a decrease to near- or below-average values around the time of symptom onset. This pattern is further reflected in the average daily

VMA values surrounding the onset of symptoms for respondents with illness episodes, which shows substantially elevated values preceding onset, and a below average value one day after onset (Fig. 2).

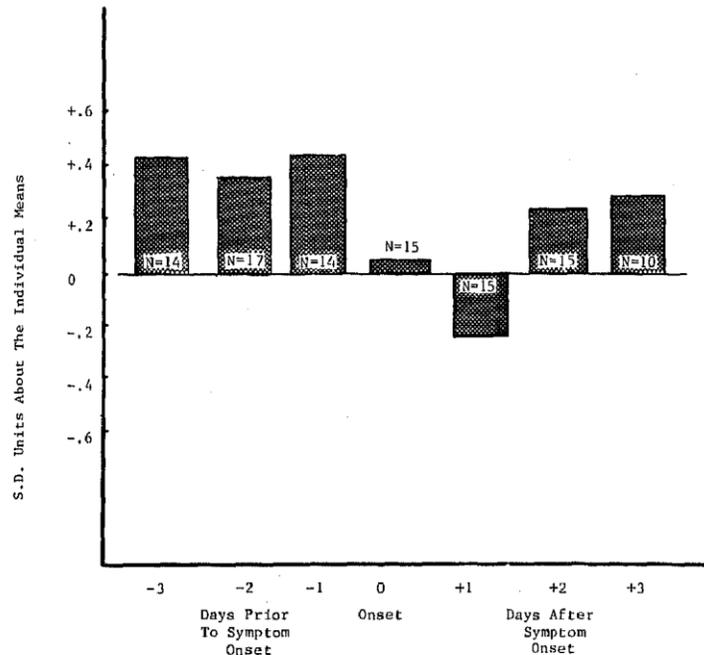


Fig. 2. Average VMA values expressed in S.D. units for respondents with illness episodes on days surrounding onset of symptoms. Values are expressed in S.D. units to correct for the differences in individual mean values during the study period.

However, considerable variation was observed in the individual values on any given day, owing primarily to differences in the days preceding onset on which the VMA spikes occurred. The tendency for peak VMA values to occur with greater frequency prior to the onset of symptoms, and with a lower frequency after onset, is illustrated by the bar graphs in Fig. 3. The top graph shows the proportion of respondents with illness episodes who had VMA spikes on days before and after onset of symptoms (Fig. 3A). The lower graph shows the distribution of VMA spikes for a "control" group of respondents who were matched to the illness-reporting group on sex and date of "symptom onset" (Fig. 3B). Since some of the respondents in the control group reported single-days of respiratory symptoms (but not episodes of two or more days), pairing was done in such a way that controls were asymptomatic on the study dates corresponding to those surrounding the illness episodes of their matched counterparts.

Respondents who reported illness episodes had the highest frequencies of spikes on days "-3" and "-2" prior to symptom onset, and the lowest frequency on the day after onset. This pattern was not observed in the control group, nor was there the same extent of variation in the relative frequency of spikes from day-to-day among the controls. The elevated frequencies in the illness-reporting group on days "-3" and "-2," and the depressed frequency on day "+1" were all significantly different from the control group values ( $p < .05$ ). Although the data are less complete, the frequencies of VMA spikes in the illness group earlier than three days prior to symptom onset and beyond three days after onset do not show notable variations.

To further assess the degree of relationship between peak VMA values and reported acute respiratory symptoms, the frequencies of VMA spikes were cross-tabulated for all respondents throughout the study period with the occurrence of respiratory illness symptoms. These results are listed in Table 1. One out of every five VMA spikes during the study period was followed within three days by the onset of an episode of acute respiratory symptoms. Forty-two percent of these spikes were followed by at least one day of reported

respiratory symptoms within three days, and nearly half (48.5 percent) by at least one day of symptoms within five days.

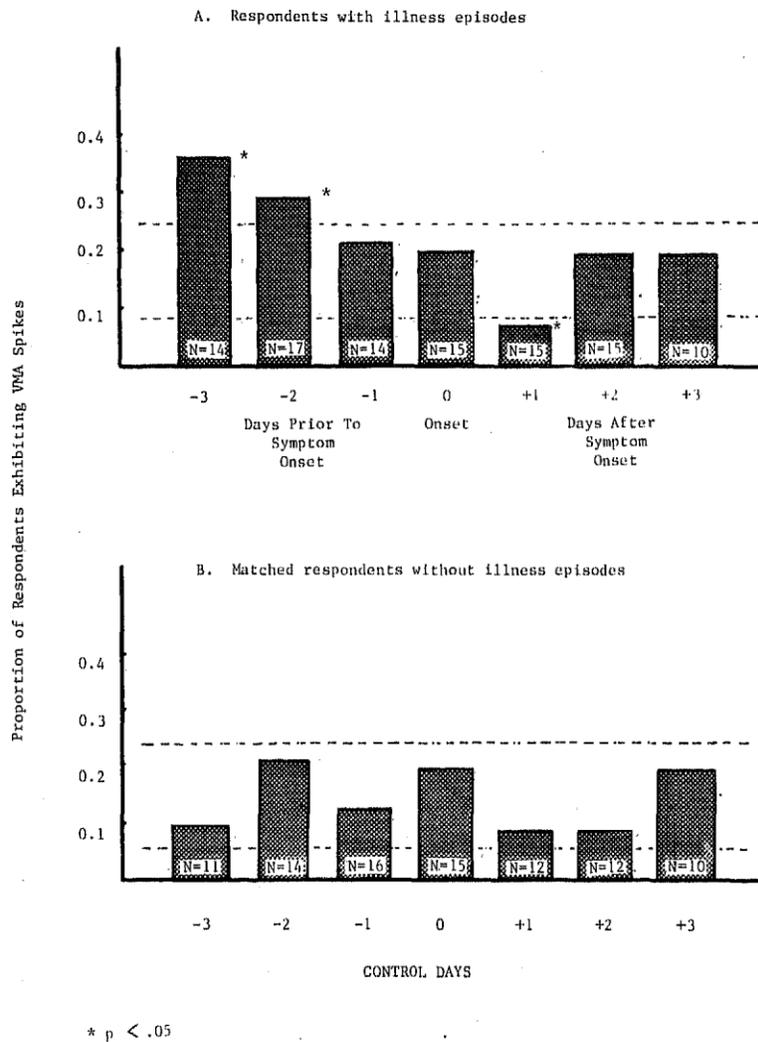


Fig. 3. Frequency of VMA spikes one or more S.D. units above individual means for (A) respondents reporting illness episodes, and for (B) respondents matched on sex and date of "onset" without illness episodes. Broken lines represent 95% confidence intervals for the overall frequency in the control group. (See text)

**TABLE 1**  
VMA SPIKES AS PREDICTORS OF  
ACUTE RESPIRATORY SYMPTOMS

Reported Morbidity	VMA Spikes One S.D. Above Mean	
	Frequency	Percent
Illness episode within 3 days	13	19.7
Single day of symptoms within 3 days	15	22.7
Subtotal, all reported morbidity within 3 days	28	42.4
Illness episode or single day of symptoms within 5 days	4	6.1
Subtotal, all reported morbidity within 5 days	32	48.5
No reported morbidity within 5 days	34	51.5
Total	66	100.0

## DISCUSSION

### *VMA Spikes*

The characteristic pattern of VMA spikes observed prior to the onset of symptoms is consistent with the hypothesis that psychosocial factors increase susceptibility to disease by altering sympathetic-adrenal medullary activity. The increased catecholamine activity reflected in the higher VMA values may temporarily reduce the effectiveness of immune responses, thereby increasing susceptibility to infectious disease agents. Qualliotine et al., in a series of studies with human lymphocytes *in vitro* infected with pneumococci, found that the catecholamines reduced the bactericidal activity of leukocytes.<sup>15,16</sup> Subsequently, Ignarro and Colombo have shown that catecholamines and cAMP inhibit the osmotic release of Bglucuronidase from leukocyte lysosomes.<sup>17</sup> However, increased susceptibility associated with higher catecholamine levels by itself would not be sufficient unless a disease agent was also present. This might account for the fact that illness episodes did not follow every VMA spike observed. Furthermore, catecholamines may not increase susceptibility to all agents, and there may be other, or multiple, hormonal influences besides the catecholamines which determine the onset of symptoms.

Underreporting of illness symptoms could also have contributed to this deficit, although the diary method of reporting used in this study has been found to be less affected by underreporting than other methods.<sup>18</sup>

Another alternative explanation might be that the observed increases in VMA values reflect a sympathetic response to the invasion of an infectious agent, and in fact result from infection. Because the spikes occurred within the incubation periods (1-3 days) of the presumed respiratory conditions studied,<sup>19</sup> this possibility cannot be ruled out. To support this position it might be argued that tissue trauma caused by invading organism(s) could precipitate a generalized sympathetic response. However, there is no evidence of which I am aware to indicate that the invasion of an infectious agent results in an elevation of catecholamine activity. The argument would be less tenable if a specific preceding psychosocial event could be identified as a potential cause of the observed VMA spikes. Unfortunately, the present study does not provide this evidence.

The possibility that the observed clustering of VMA spikes prior to illness episodes was within the range of normal probabilities was also considered and ruled out. The expected relative frequency of observing a value one S.D. above or below the mean in a normal distribution is 0.317, and for a value one S.D. above the mean only 0.159.<sup>20</sup> This expected probability is not substantially different from the overall seven-day frequency observed in the control group (0.144), but is significantly lower than the overall frequency for the three days prior to onset in the illness group (0.289,  $p < .02$ ).

### *Onset Depression*

The decreased frequency of VMA spikes and the below average VMA values for the day following onset might represent either a temporary depletion of catecholamine substrate resulting from the preceding overproduction, or the effect of an active process to reduce catecholamine activity. There is no empirical basis for further interpretation of this finding. Theoretically, the relationship between decreased VMA values and onset of symptoms is consistent with the known antagonism of the catecholamines to the immune response. Since the reported respiratory symptoms are the manifestations of an active inflammatory process, lower VMA values in the presence of an infection could be expected to result in a more symptomatic condition.

## CONCLUSION

The VMA profiles surrounding the onset of reported respiratory symptom episodes observed in this study point to a possible association between catecholamine activity and susceptibility to infectious disease in humans, whereby higher levels of catecholamine activity increase susceptibility to infectious diseases. The nature of this possible association is consistent with the known antagonism between catecholamines and immune competency. Questions raised by these data include whether the VMA spike precedes or follows invasion of the infectious agent, and uncertainty over the mechanism leading to decreased excretion levels following the VMA spike and coinciding with the onset of symptoms.

## Notes:

\*Practical grade sulphamic acid crystals, (NH<sub>2</sub>SO<sub>3</sub>H. mot. wt 97.09), obtained from Eastman Kodak Co., Rochester, New York.

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