CATECHOLAMINE ACTIVITY AND REPORTED MORBIDITY

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Gruchow HW: Catecholamine activity and reported morbidity. Journal of Chronic Disease, 29:773-783, 1976.

Abstract:
Urinary VMA levels were measured in relation to the reporting of morbidity in an attempt to determine whether altered catecholamine activity is related to specific disease syndromes, or is a general characteristic of morbidity. The cross-sectional data show elevated VMA levels to be associated with the reporting of chronic disease conditions; non-chronic conditions and affective disorders were associated with lower VMA values, Although these findings are interpreted as supporting the hypothesis that psycho-social stimuli acting through the sympathetic-adrenal medullary system may be important in the etiology of chronic disease conditions, alternative explanations are discussed and the need for further longitudinal studies indicated.

Article:

INTRODUCTION

DURING the past several decades, the study of relationships between psychosocial factors and disease has led to better understanding of both the psychosocial events which may trigger or enhance disease processes, and the physiological mechanisms involved. Investigators are now in substantial agreement that psychosocial events can play an etiological role in a variety of different diseases. However, despite this progress, it is still unclear how these events are translated into disease states.

Two different approaches have generally been taken to study this problem. One approach holds that there is a degree of specificity in these relationships, with certain types of psychosocial events more often associated with one type of pathophysiologic condition than other types. This approach is illustrated by numerous studies which have successfully demonstrated that specific disease entities such as tuberculosis [1, 2], hypertension [3-5], coronary heart disease [6], cancer [7, 8], rheumatoid arthritis [9, 10], and even complications of pregnancy [11, 12] can be related to certain psychosocial events or to certain individual behavior patterns.

Other investigators have taken a second approach, in which the general nature of a person's interactions within the social environment is related to overall morbidity [13-17], and increased morbidity of all types has been related to perception of `...life situations as demanding, threatening and frustrating' [18].

A way to begin resolving this question of causality is to evaluate both the morbidity and the presumed psychosocial risk factors for a common physiological link. One such physiological intermediary appears to be the sympathetic—adrenal medullary system, Elevated levels of the catecholamines and their metabolites have been reported in experimental subjects associated with exposure to various types of psychosocial stimuli [19]. Furthermore, increased catecholamine levels have been reported for several disease states including angina [20], hypertension [21, 22] and gastric and duodenal ulcers [23, 24]. In addition, elevated catecholamine activity has been suggested as a possible factor in the etiology of diabetes [25, 26], and a beta adrenergic mechanism has been proposed as a central element in the development of bronchial asthma [27]. In contrast, decreased catecholamine levels have been found in some affective psychiatric disorders [28, 29].

From these reports and in view of the fact that the catecholamines are capable of directly influencing the functioning of many organs and tissues and of indirectly affecting still others, the argument for a generalized pathologic effect of adverse psychosocial events takes on added plausibility. The potential importance of such a relationship for the prevention, diagnosis, and treatment of disease is evident. However, no systematic attempt

has been made to describe the range of catecholamine levels in a representative non-institutionalized population and to correlate these levels with morbidity.

The present study looks at levels of the urinary catecholamine metabolite vanillylmandelic acid (VMA) in relation to the reporting of certain diseases in an attempt to determine whether altered catecholamine activity is related to specific disease syndromes, or is a general characteristic of sick persons.

METHODS

Study subjects

The data for this study were obtained as part of a comprehensive personal-interview health survey conducted on a probability sample of households in a Midwestern U.S. county [30]. The designated respondent in this survey was the 'female head-of-household', who usually was the wife of the male head-of-household. However, where there was no female head, the male head was interviewed. Interviews were administered anonymously by professional interviewers to 515 female and 37 male respondents over a six-week period. Information was obtained on the health status of each respondent, and in addition, respondents were requested to obtain and mail-in a specimen of their own urine for VMA determinations. The study sample was initially limited to the 307 respondents (56%) who returned urine specimens.

No significant differences were observed between respondents who returned specimens and those who did not, on the basis of age, sex, education, and size of household, However, significantly fewer respondents with less than S5000 yearly income returned specimens, compared to those with incomes above $5000 (Table 1). While this difference limits the generalizability of the results to the population of the survey area, it does not subsequently affect the comparisons between subgroups within the study population reported here.

TABLE 1. COMPARISON OF URINE SPECIMEN RETURN RATES, BY INCOME, EDUCATION, AND SEX OF RESPONDENT.

	Yearly family income*		Education (years of school)			Sex of respondent	
	Under $5000	Over $5000	<9	9–12	>12	Male	Female
Returned specimens:	43 (41)	264 (59)	30 (52)	157 (55)	120 (58)	18 (49)	289 (56)
Total:	105 (100)	447 (100)	58 (100)	288 (100)	206 (100)	37 (100)	515 (100)

*$\chi^2 = 10.71$, 1 *df*, $P < 0.01$.
Numbers in parentheses are corresponding percentages.

Morbidity reporting

The health status of each respondent was assessed by measures of morbidity constructed from the survey responses. These included: (a) 'any long-term illness, disability or health problem'; (b) illnesses which restricted 'normal activities for at least two days' during the past year and (c) health problems for which medications were taken 'on a regular basis'. Reported conditions were defined as 'chronic' in accordance with the list of chronic conditions set forth in the U.S. National Health Survey [31]. All other morbidity, which in this study consisted of upper-respiratory tract infections, influenza (`flu') type illnesses, and acute genitourinary tract infections, was considered 'non-chronic'.

Urine specimens

At the close of each interview, respondents were given a 60 cm' plastic urine specimen bottle enclosed in a pre-addressed, stamped mailing carton. Oral instructions for obtaining specimens were given by the interviewers, and identical written instructions were enclosed with each bottle. It was emphasized that specimens should be obtained the following 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 g of sulphamic acid crystals* to prevent bacterial growth in the urine. Approximately 95% of the specimens were received with a pH of 4.0 or lower, and when necessary additional sulphamic acid crystals were added to lower the pH to 3.0. No evidence of bacterial contamination was apparent on gross inspection of any of the specimens received. Specimens were stored at -12°C prior to analysis.

VMA determinations

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 variation in renal function. The method of Pisano, *et al*, [32] was used for VMA determinations, while creatinine determinations were made using the alkaline picrate method of Folin and Wu [33], modified for the single-channel Technicon Autoanalyzer.** All further references in this paper are to creatinine-corrected VMA values.

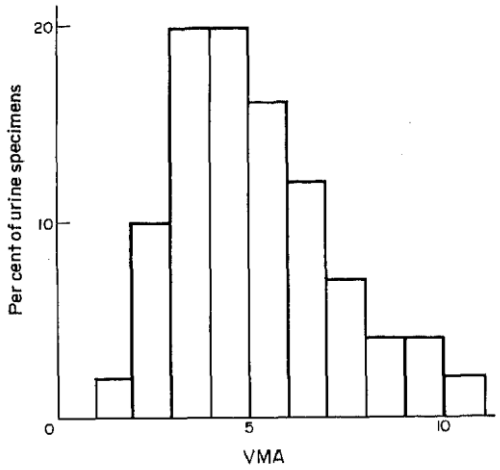

FIG. 1. Per cent distribution of vanillylmandelic acid (VMA) values, corrected for creatinine (μg VMA/0.5 mg creatinine) for study sample ($N = 307$).

VMA was selected as the physiological measure rather than free catecholamines, because it is a more stable measure of catecholamine activity, and because the collection of urine specimens is less refractory than obtaining blood samples for serum measures of catecholamine activity, both of which are important considerations in this type of survey study. A primary disadvantage of utilizing VMA measurements is that sympathetic nervous activity and adrenal medullary activity cannot be differentiated.

TABLE 2. VMA VALUES (μg) BASED ON AGE AND SEX OF RESPONDENTS

	Age of respondent (yr)				
	18–30	31–45	46–60	>60	Total
Males	(6) 3.71	(4) 3.87	(1) 4.11	(7) 4.89	(18) 4.31
Females*	(100) 4.31	(85) 4.80	(63) 5.59	(41) 7.24	(289) 5.19

*For females only: $F_{3,285} = 11.17$, $P < 0.01$.
Numbers of respondents in each category are given in parentheses.

TABLE 3. COMPARISON OF AGE-ADJUSTED VMA VALUES* BY SEX OF RESPONDENT

Sex	*N*	Mean age-adjusted VMA values (μg)
Male	18	4.31†
Female	289	5.19†

*Age adjustment was achieved by dividing the VMA value for each respondent by the mean VMA value for the appropriate age category. This ratio was then multiplied by the overall population mean (5.10 μg/0.5 mg).
†Values for males and females significantly different, $t = 2.133$, 305 *df*, $P < 0.025$.

RESULTS

VMA determinations

The distribution of VMA values for the study population is shown in Fig. 1. The population mean was 5.10 μg VMA/0.5 mg creatinine, with a standard deviation of 1.77 *μg/0.5* mg. For both male and female respondents VMA values increased with age, although this increase was statistically significant only for females (Table 2).

In addition, values were higher for female than male respondents in every age category, and the age-adjusted mean VMA value for females was significantly higher than the corresponding value for males (Table 3). As a result of this observed sex difference, and because the small number of male specimens (18) precluded their separate consideration, further analysis of reported morbidity in relation to VMA levels was limited to the 289 female respondents.

Reported morbidity and VMA values

In response to the questions on morbidity, 39.8% (115) of the 289 female respondents reported at least one chronic (24.9%) or non-chronic condition (12.5%), seven respondents (2.4%) reported both chronic and non-chronic conditions, and 174 (60.2%) reported 'no disease'.

The reporting of chronic conditions increased progressively with age, from 10% of the 18-30 yr-olds to 51.3% of those over-60 (χ^2 = 48.7, 3 *df*, P < 0,001), while the reporting of non-chronic conditions decreased from 20% of the 18-30 yr-olds to 3% of those over-60 (χ^2 = 20.15, 3 *df*, P < 0.001), These findings are in general agreement with most other morbidity surveys, in which the incidence of chronic diseases increases markedly with age, while the incidence of non-chronic conditions tends to remain stable or decrease with age [31, 34].

The VMA values associated with the reporting of morbidity are given in Table 4. Respondents who reported chronic conditions had significantly higher age-adjusted VMA values than those who reported `no disease', while those who reported non-chronic conditions had significantly lower values. That these differences reflected variations in VMA excretion rates, and not a systematic bias in creatinine levels, is indicated by the lack of a statistically significant difference between the mean creatinine levels for respondents with chronic conditions and the other respondents (1.23 mg/cm^3, and 1.31 mg/cm^3, respectively, t = 0.941, 287 *df*, P > 0.10).

TABLE 4. COMPARISON OF AGE-ADJUSTED VMA VALUES BASED ON REPORTED MORBIDITY STATUS

Condition	*N*	VMA values (μg)
Chronic, only	72	5.66*
'No disease'	174	5.08*†
Non-chronic, only	36	4.44†
Both chronic and non-chronic	7	5.85
Total	289	5.10

*t = 2.008, 244 *df*, P < 0.05.
†t = 2.298, 208 *df*, P < 0.05.

Respondents who reported both chronic and non-chronic conditions had VMA values within the chronic condition range. It appears, therefore, that higher VMA values are associated with chronic conditions, and lower values with the absence of these conditions.

It is uncertain what interpretation should be given to the VMA values of the no disease' respondents, except to suggest that this group may have included some respondents with unreported conditions (both chronic and non-chronic) thereby resulting in an aggregate VMA value which was intermediate between those observed for the two groups of reporting respondents.

When morbidity was compared on the basis of VMA values, the reporting of chronic conditions was found to increase from slightly more than 20% of respondents with VMA values less than 6.00 μg, to 42.9% of those with values over 6.00 μg (Table 5). In contrast, the percentages of respondents reporting only non-chronic

conditions decreased progressively from 21.5 to 4.8% over the same range of VMA values. Stated in other terms, respondents with the highest VMA values (over 6.00 µg) were twice as likely to have reported a chronic condition as those with lower values, while those with the lower values (less than 6.00 *ug)* were 3.5 times more likely to have reported only a non-chronic condition. No significant trend based on VMA values was observed for the 'no disease' respondents.

TABLE 5. PERCENTAGES OF STUDY POPULATION REPORTING CHRONIC AND NON-CHRONIC CONDITIONS BASED ON AGE-ADJUSTED VMA VALUES

	VMA values (µg)				
Condition	<4.00 (N = 79)	4–6.00 (N = 126)	>6.00 (N = 84)	χ^2	P
All chronic	21.5	20.6	42.9	12.13	<0.01
Non-chronic, only	21.5	13.4	4.8	9.86	<0.02

Specific chronic conditions and VMA values

Having observed that respondents who reported chronic diseases had higher VMA values, the distribution of age-adjusted VMA values for each of the twelve chronic conditions reported by the study population was examined to determine if higher VMA values were associated only with certain conditions, or with chronic conditions in general. As seen in Table 6, the VMA values for different chronic conditions ranged from 5.22 µg (hyperthyroidism) to 7.22 *µg* (complications of pregnancy). Although pregnancy itself was not considered a chronic condition, pregnant respondents without complications also had relatively high VMA values (N = 6, mean VMA = 5.6 *µg).* However, even after adjusting the pregnancy mean to that of the total population, the mean VMA value for complications of pregnancy (6.02 µg) was still well above the mean for chronic conditions.

TABLE 6. AGE-ADJUSTED VMA VALUES FOR SPECIFIC CHRONIC CONDITIONS

Condition	Number of respondents	Mean VMA values (µg)	±SE
Complications of pregnancy	6	7.22	1.111
Multiple sclerosis	2	6.52	1.315
Gastrointestinal disorders	9	6.20	0.393
Arthritis	15	6.15	0.256
Diabetes	5	5.85	1.127
Allergies, hay fever and sinus trouble	12	5.66	0.334
Asthma	4	5.56	0.913
Hypertension	22	5.52	0.206
Coronary heart disease	6	5.36	0.728
Anemia	7	5.31	0.503
Chronic lung disease	4	5.25	0.391
Hyperthyroidism	10	5.22	0.552
All chronic conditions	102*	5.82	
All persons with chronic conditions	79	5.68† (5.21–6.15)	0.236
All persons with non-chronic conditions, only	36	4.44† (3.95–4.93)	0.247

*More than one condition per respondent possible.
†Significantly different, t = 4.77, 113 df, P < 0.005.
Confidence intervals (95%) are in parentheses.

Since some individuals reported more than one chronic condition, the values given in Table 6 are not necessarily specific for each condition; nevertheless, the entire range of VMA values associated with these chronic conditions is above the upper 95% confidence interval for the non-chronic conditions. Therefore, it appears that higher VMA values are characteristic of all of the chronic conditions reported in this study.

Affective disorders

Affective disorders *(N* = 9, VMA = 4.03 µg) were not included in Table 6 because of the indeterminate nature of the health problems included in this category, and also because the relationship between catecholamine

activity in the brain and VMA excretion may differ from that of the somatic sympathetic-adrenal medullary system. However, the lower VMA values of respondents who reported these disorders are consistent with the findings of other investigators that certain affective disorders may be associated with lower levels of catecholamine activity [28, 29].

TABLE 7. COMPARISON OF AGE-ADJUSTED VMA VALUES FOR TREATED (MEDICATED) AND UNTREATED (UNMEDICATED) CHRONIC CONDITIONS

Chronic condition	VMA values (μg)			
	Treated	(N)	Untreated	(N)
Gastrointestinal disorders	5.74	(2)	7.14	(3)
Arthritis	5.73	(7)	6.50	(8)
Hypertension	5.64	(21)	3.05	(1)
Chronic lung disease	4.78	(2)	5.72	(2)
Hyperthyroidism	5.03	(9)	7.00	(1)
Allergies, hayfever and sinus trouble	5.12	(7)	6.41	(5)
All conditions	5.46*	(52)	6.35	(20)

*Significantly different from the mean VMA value for non-chronic conditions of 4.44 μg ($t = 3.26$, 86 df, $P < 0.005$).

Effects of medications on VMA values

Since many respondents with chronic conditions reported taking medications, the possibility existed that the higher VMA values associated with these conditions were due to the effects of medications, rather than to some other factor(s) associated with the conditions. To evaluate this possibility, respondents in each of the chronic condition categories were divided into 'treated' and 'untreated' groups, according to whether or not they reported taking medications for their conditions. All of the respondents with diabetes, asthma, coronary heart disease, anemia, affective disorders, and complications of pregnancy reported taking medications, so that for these conditions, there was no untreated group for comparison. However, for the six other conditions comparisons could be made (Table 7).

It was observed that while the treated respondents had lower VMA values for every condition (with the exception of one person with hypertension) the mean value for these respondents was still significantly higher than that for the respondents who reported only non-chronic conditions. It should be noted in this context, that some of the medications which these respondents were receiving probably had direct effects on catecholamine activity, although the nature of these effects undoubtedly varied, depending on the particular biochemical actions of the drugs. However, despite the uncertain and probably mixed effects of medications on catecholamine activity, their net effect in this study was to decrease VMA values. Therefore, the observed higher VMA values for chronic conditions could not be attributed to medications.

CONCLUSION

The results of this study reveal that elevated VMA levels are associated with all of the chronic disease conditions reported, independent of age or of medications; lower VMA levels are associated with the reporting of non-chronic conditions and affective disorders. While these findings support the hypothesis that psychosocial stimuli can lead to chronic disease morbidity via alteration of sympathetic-adrenal medullary function, the data fall short of relating all morbidity to increased catecholamine levels.

However, there are also other possible explanations for the observed relationships. One alternative is that respondents with chronic conditions may have higher levels of sympathetic activity either as a result of the disease processes, or because of greater anxiety associated with their knowledge of these conditions, as opposed to less debilitating non-chronic conditions. This could lead to higher VMA values for chronic conditions, as observed, and might also explain the elevated VMA values found for pregnant women without complications. Another possibility is that respondents with pre-existing higher VMA values may perceive illness as more threatening, and therefore may be more prone to report the existence of chronic conditions, although in fact their morbidity experiences may be similar to other respondents.

Also, these results do not necessarily imply that the manifestation of non-chronic conditions is unrelated to increased catecholamine activity. There are several reasons for this. First of all, the morbidity reported in this study occurred at varying times up to one year prior to the interviews and the collection of specimens for VMA determinations. As a result, the recorded VMA values may not accurately reflect the physiological changes occurring at the time the reported non-chronic episodes occurred. This reporting interval is less important for chronic conditions since the persistent nature of these conditions makes them more directly relatable to physiological measures, such as VMA, made at a single point in time.

Secondly, while there is less evidence to link catecholamines with the type of non-chronic infectious diseases reported in this study, anti-inflammatory properties of catecholamines have been described [35, 36]. Qualliotine [37, 38] reported that catecholamines reduced the bactericidal activity of leukocytes, and Ignarro and Colombo [39] have shown that catecholamines and cyclic-AMP inhibit the osmotic release of /3-glucuronidase from leukocyte lysosomes. Therefore, it would appear from these studies that if catecholamine activity does alter susceptibility to infectious diseases, higher, not lower, VMA values should be associated with an increased incidence of these conditions.

The cross-sectional nature of the data reported here is not sufficient to determine causal relationships, nor to rule out the alternative explanations. To adequately resolve these questions longitudinal studies are needed to measure catecholamine activity prior to and during episodes of both chronic and non-chronic (infectious) conditions. The results of this study do, however, show that higher catecholamine activity may be a risk factor for a large number of chronic diseases, and they provide an empirical basis for further investigations of the hypothesis that events in the social environment can have a general pathologic effect on the human organism resulting from the increased activity of the sympathetic-adrenal medullary system.

Notes:

*Practical grade sulphamic acid crystals, (NH_2SO_3H, mol. wt 97.09), obtained from Eastman Kodak Co., Rochester, New York, 14650, U.S.A.

**Technicon Autoanalyzer Method N-1.11).

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