# THE EXCRETION OF HIPPURIC ACID IN SUBJECTS WITH FREE ANXIETY

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During the war, many patients were encountered among the combat troops who suffered from the effects of long continued anxiety which manifested itself by a variety of somatic signs and symptoms such as tremor, sweating, tachycardia, dilated pupils, restlessness and weakness. Even after successful alleviations of the psychological stress of combat which acted as a constant excitation for anxiety, many patients continued to exhibit the somatic signs of anxiety (1). Such observations suggested that the anxiety induced by some psychological stress can set off a train of events which persist even after the alleviation of the specific stress. In order to investigate this possibility, a variety of studies were started to determine the influence of anxiety on various visceral functions. The present report is concerned with observations on the conjugative function of the liver in subjects with anxiety.

## DESCRIPTION OF SUBJECTS

In a hospital devoted to the care of men with post-combat neuroses, patients with much "free anxiety" were numerous as contrasted with the patient population of civilian psychiatric hospitals. The stimuli of combat were so excessive that the evoked anxiety could be mastered or "bound" only with great difficulty (1). In civilian life, except for the traumatic neuroses which develop after a sudden overwhelming threat to life or limb in an unexpected accident, the anxieties are less intense and less sudden in appearance, permitting a considerable degree of mastery by various psychological defenses. Since there are no quantitative psychologic tests for anxiety, the degree of "free anxiety" can be estimated only on the basis of the symptomatology presented by the patient. For such reasons a single observer (RRG) evaluated clinically and classified each patient independently of those performing the physiological measurements.

Four groups of subjects were studied: a group of physically healthy individuals with varying degrees of "free anxiety" (I), another group of physically healthy individuals who showed some anxiety symptoms but in whom most of the anxiety was "bound" (II), a third group of physically healthy individuals with a variety of neuropsychiatric disorders, chiefly psychotic depressions (III) and finally, a "normal" group consisting of mentally and physically healthy persons (IV).

The "free anxiety" group consisted of patients who suffered with fears of internal origin which they could not control or diminish by any psychological maneuver. Usually some physiological expression of anxiety could be observed in tenseness, restlessness, sleeplessness, anorexia, loss of weight, sweating, tremor, etc. Subjectively, these patients felt an internal dread, apprehension or fear before which they helplessly quaked.

Illustrative of Group I is S. S., a 37 year old male barber who complained of fear of death, suffocating sensations, numbness of hands and lips and panic attacks. His symptoms began about one year prior to his first visit after a saphenous vein ligation. At first he had a great deal of pre-occupation with the possibility of embolism about which he had read, but gradually his anxiety became generalized. There developed a generalized foreboding and apprehension which was present constantly, becoming irregularly worse in attacks of panic during which he would show all the somatic manifestations of acute anxiety such as dilated pupils, tremor of the facial muscles and hands, pallor of the face, tachycardia and hyperpnoea and he would be impelled to run from his shop into a doctor's office. Physical examination was essentially negative. Psychodynamic studies revealed that the patient's nuclear anxiety was related to a strict and forceful father who compelled the patient to leave school and become a barber, which he detested, in the father's shop. Strong unconscious hostility to the father, protected by passive homosexual and submissive attitudes toward him, was accentuated by the operation which symbolized punishment (castration) and his ego was constantly deluged by signals of danger (anxiety) indicat-

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ing that the disturbing hostility was approaching consciousness. No defensive maneuvers against the anxiety were possible.

The group classified as having "bound anxiety" included those patients who defended themselves from anxiety by obsessive and compulsive thoughts and rituals, who avoided external symbolic stimuli by counterphobic flight, who expressed the anxiety provoking conflict in hysterical conversion symptoms, who complied with anxiety provoking conscience forces by depression, who projected the responsibility for unacceptable feelings or attitudes in paranoid ideas, who dispelled their inner fears by aggressively attacking the external environment, or who prevented conscious feeling of conflict by developing psychosomatic expressions in organic dysfunctions. That these syndromes represent mastery or "binding" of anxiety becomes clear when it is demonstrated that removal of the defensive symptoms is accompanied by release of subjective or "free anxiety" (1).

Illustrative of Group II is B. C., a 19 year old female who had, two months prior to hospital admission, developed spasmodic twitchings of the entire body. These began after being awakened suddenly by children of her employer who frightened her. Neurological examination revealed no evidence of disease of the nervous system. The past life was full of evidences of rejection by mother and grandmother. In adolescence she had been sent to a reform school on the false charge of having sexual relations. After discharge she really became promiscuous and was sentenced to a house of correction. Later she fell in love with her employer and with his wife lived out a triangular sexual arrangement. The patient's twitching represented a conversion symptom reminiscent of jerkings of her body while being whipped at reform school. Under pentothal the patient admitted a fear that her present life would evoke punishment from her mother and a return to reform school. This fear was expressed only in her symptoms although the symptoms themselves evoked secondary apprehension and crying. Anxiety here was protected from becoming conscious by the conversion symptom.

## METHODS

All subjects were given a careful medical examination and studied psychologically by interviews, by tests and through continual observation by attendants. All subjects except those comprising the "normal" groups were hospitalized. The latter individuals, however, carefully conformed to the regimen outlined below. All subjects received a nutritious diet without known deficiencies. At the end of a two week period, the efficacy of this diet was assessed by performing a three day nitrogen balance study on representative individuals from each group. Nitrogen equilibrium was considered to indicate nutritional adequacy.

The hippuric acid test was performed according to Quick (2). After an overnight fast, 1.77 grams of sodium benzoate were administered by intravenous injection and, after one hour, the urine collected was analyzed for hippuric acid by the precipitation method of Quick (3) and by the extraction method of Quick as modified by Snapper (4). Results obtained on all assays by these widely different methods agreed within 2 per cent.

The psychiatric treatment given some of the patients in the "free anxiety" group (I) and some of the other mentally ill persons in the other groups consisted of electric shock therapy followed by psychotherapy, insulin shock therapy followed by psychotherapy, or psychotherapy alone.

## RESULTS

### *Excretion of Hippuric Acid in Subjects with "Free Anxiety"*

It is apparent from Table I that patients with "free anxiety" (Group I) have a greater excretion of hippuric acid after the intravenous administration of sodium benzoate than do the subjects in the other three groups. Analysis of variance (5) revealed a statistically significant difference between the groups ($P < 0.01$); that the difference between the groups was due to a difference between Group I on the one hand and Groups II, III and IV on the other hand ($P < 0.001$); and that there was no difference in the excretion of hippuric acid by the subjects in Groups II, III and IV. The statistics revealed that the probability that

TABLE I

*Hippuric acid excretion after intravenous injection of 1.77 grams sodium benzoate*

| Group | Number of subjects | Urine volume* | Mean hippuric acid excretion* | Analysis of variance† | | |
|---|---|---|---|---|---|---|
| | | | | $F_1$ | $F_2$ | $F_3$ |
| | | *ml./hr.* | *grams/hr.* | | | |
| Group I ("Free Anxiety") | 17 | 125 ±94.2 | 1.93 ±0.68 | | | |
| Group II ("Bound Anxiety") | 14 | 131 ±27.2 | 1.37 ±0.24 | | | |
| Group III ("Depression") | 10 | 116 ±70.4 | 1.23 ±0.19 | 8.65 | 26.38 | |
| Group IV ("Normals") | 11 | 92 ±46.4 | 1.27 ±0.19 | | | 1.52 |

* In terms of group mean ± S.D.

† $F_1$—Mean variance among all groups/mean variance within all individuals.

$F_2$—Mean variance between Group I and Groups II, III, IV/mean variance within all individuals.

$F_3$—Mean variance among Groups II, III and IV/mean variance within all individuals in these groups.

the difference between Group I and Groups II, III and IV could be due to chance is less than 1 in 1000.

It was noted that the amount of hippuric acid excreted by individuals with "free anxiety" after the injection occasionally exceeded that which could be anticipated from the complete conversion of the test dose of benzoate. Thus, whereas the complete conversion of 1.77 grams sodium benzoate can yield 2.20 grams of hippuric acid, three of the 17 patients in Group I were found to excrete 2.49, 2.80 and 3.99 grams respectively. Similar occasional supertheoretical excretions of hippurate have been noted by others (6).

Such observations led to the possibility that the high results obtained in the patients with "free anxiety" might be the result of a very high level of endogenous excretion rather than an increased rate of conversion of the administered sodium benzoate. In order to evaluate the influence of endogenous hippuric acid excretion on the quantity excreted subsequent to the administration of sodium benzoate, the endogenous hippuric acid excretion was determined in six members of Group I and in a similar number from Group IV. The endogenous excretion was determined for the period immediately prior to the administration of benzoate. A number of preliminary observations had demonstrated no hourly changes in endogenous hippuric acid excretion in the fasting subject for as long as six hours. It was therefore assumed that the rate of endogenous excretion would continue unchanged after administration of benzoate and that the total hippuric acid excretion after benzoate could be corrected for the endogenous excretion calculated from the determination prior to the administration of the test dose. The difference between these values was assumed to be the amount of hippurate excreted as a result of the conversion of the administered benzoate by the liver.

TABLE II

*Hippuric acid excretion corrected for endogenous excretion*

| Group | Patient | Endogenous (A) | After benzoate (B) | Corrected (B)-(A) |
|---|---|---|---|---|
| | | *grams/hr.* | *grams/hr.* | *grams/hr.* |
| I "Free Anxiety" | 1 | 0.16 | 2.16 | 2.00 |
| | 2 | 0.23 | 1.66 | 1.43 |
| | 3 | 0.07 | 1.87 | 1.80 |
| | 4 | 0.05 | 1.93 | 1.88 |
| | 5 | 0.10 | 1.74 | 1.64 |
| | 6 | 0.10 | 1.55 | 1.45 |
| IV "Normals" | 7 | 0.11 | 1.42 | 1.31 |
| | 8 | 0.03 | 1.35 | 1.32 |
| | 9 | 0.04 | 1.38 | 1.34 |
| | 10 | 0.04 | 1.10 | 1.06 |
| | 11 | 0.04 | 1.37 | 1.33 |
| | 12 | 0.07 | 1.44 | 1.37 |
| Significance of difference between groups | | | $F = 21.713$ ($P < 0.001$) | $F = 15.126$ ($P < 0.01$) |

TABLE III

*Effect of psychotherapy on hippuric acid excretion*

| Subject | Elapsed time (weeks) | Grams hippuric acid | | | Clinical remarks |
|---|---|---|---|---|---|
| | | Before | After | Change | |
| JR* | 5 | 1.69 | 1.25 | 0.44 | Marked decrease in free anxiety |
| HW* | 3 | 1.87 | 1.70 | 0.17 | Not much clinical improvement |
| WB | 26 | 2.16 | 1.61 | 0.55 | Marked decrease in free anxiety; some still present |
| SS | 35 | 2.20 | 1.55 | 0.65 | Marked decrease in free anxiety; patient learned to bind anxiety successfully |
| AR* | 45 | 2.49 | 1.73 | 0.76 | Marked decrease in free anxiety; some still present |
| JE† | 10 | 3.99 | 1.95 | 2.04 | Marked decrease in free anxiety; good deal of anxiety still present. Patient was most anxious of series |

* Electric shock therapy.
† Insulin shock therapy.

A summary of these studies appears in Table II. It is evident that the difference in hippuric acid excretion between the two groups is highly significant ($P < 0.01$) even when the values are corrected for endogenous excretion. It thus appears justifiable to attribute these differences in excretion rates to differences in the rate of conversion of benzoate. No explanation of the supertheoretical quantities excreted in the three patients noted above could be found.

Machella, Helm and Chornock (6) demonstrated that the hippuric acid excretion consequent to the intravenous injection of sodium benzoate is not influenced by body weight but is influenced by the volume of urine excreted during the test period. Since the volume of urine passed during the test period by the subjects comprising our various groups varied markedly and seemed

to be greater in the patients with anxiety, it became pertinent to analyze the influence of this variable. For such purposes we employed an analysis of covariance (5) of the data and found that the differences between the groups noted above was not conditioned by the variations in the volume of urine excreted during the test period.

*Effect of Psychotherapy on Hippuric Acid Excretion*

The influence of psychotherapy on the excretion of hippuric acid by some of the subjects composing Group I is indicated in Table III. Every patient in whom the "free anxiety" was markedly reduced showed a concurrent reduction in the quantity of hippuric acid excreted subsequent to the administration of sodium benzoate. One individual (H. W.) who showed no clinical reduction in "free anxiety" also showed no reduction in hippuric acid excretion. In contrast, is the observation that normal controls who were retested over a period of as long as 39 weeks, showed no significant alteration in hippuric acid excretion (Table IV). However, the number of subjects with "free anxiety" that were studied in this manner is too small to establish the statistical significance of these changes.

TABLE IV

*Variation of hippuric acid excretion in normal controls*

| Subject | Elapsed time (weeks) | Grams hippuric acid | | |
|---|---|---|---|---|
| | | Before | After | Change |
| JG | 3 | 1.05 | 1.10 | 0.05 |
| MS | 14 | 1.30 | 1.29 | 0.01 |
| RF | 39 | 1.38 | 1.39 | 0.01 |
| SG | 1 | 1.42 | 1.45 | 0.03 |
| HA | 17 | 1.52 | 1.55 | 0.03 |
| MF | 2 | 1.52 | 1.58 | 0.06 |
| CS | 17 | 1.52 | 1.48 | 0.04 |

## DISCUSSION

Hyperexcretion of hippuric acid consequent to the administration of sodium benzoate has been observed by Quick (7, 8) and by Rosenberg and Soskin (9). The former offered no explanation for this phenomenon while the latter noted that the hyperexcretion occurred in patients with a mild degree of hepatic damage. On the basis of other observations that the first effect of a noxious agent upon the liver is to increase its irritability (10), Rosenberg and Soskin suggested that the hyperexcretion of hippuric acid may be due to an increase in the conjugating function of the liver during the early stages of hepatic damage.

Accordingly, our observations that patients with "free anxiety" show an hyperexcretion of hippuric acid and that with a diminution of the "free anxiety" there may be a concurrent restitution to the normal level of hippuric acid excretion, suggest the possibility that such patients may have an increase in the functional capacity of the liver insofar as the conversion of sodium benzoate is concerned.

It is conceivable that in patients with liver damage, the increase in the conjugating properties of the liver during the early phases of the damage represents a mechanism whereby the organism increases its capacity to combat the toxic agent. Consequently, it may be postulated that the increase in the conjugating property of the liver of the patients with "free anxiety" belongs to the general category of changes which ensue when an organism is exposed to a situation which induces fear (11). In other words, irrespective of whether the stimulus for the fear is endogenous or exogenous in origin it may well be that one of the physiological responses is an increase in the conjugating properties of the liver.

## CONCLUSION

Patients with "free anxiety" as defined herein demonstrate a statistically significant hyperexcretion of hippuric acid consequent to the administration of sodium benzoate. With reduction of the "free anxiety" there appears to be a concurrent reduction in hippuric acid excretion.

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