Essential Hypertension: Abnormal Renal Vascular and Endocrine Responses to a Mild Psychological Stimulus

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SUMMARY We have assessed the influence of a mild emotional stimulus on arterial blood pressure, heart rate, renal blood flow, plasma renin activity (PRA), and plasma aldosterone concentration in 24 normal subjects, eight of whom had a parent with hypertension, and in 15 patients with essential hypertension. A nonverbal IQ test, Raven's Progressive Matrices, was employed as the stimulus. In 11 of the 15 hypertensives, arterial blood pressure rose transiently by 7 mm Hg or more, but in only three of 16 normal subjects ($\chi^2 = 7.23$, $p < 0.01$). Transient moderate increases in heart rate were also more common in the hypertensives ($p < 0.01$). Renal blood flow rose in 11 of 16 normal subjects and fell in each of the 15 patients with essential hypertension ($\chi^2 = 15.1; p < 0.005$). As opposed to the transient changes in arterial pressure and heart rate, the fall in renal perfusion was sustained. The PRA fell in 10 of the 16 normal subjects with a negative family history and rose in 14 of 15 patients with essential hypertension ($p < 0.005$). Changes in plasma angiotensin II concentration and in plasma aldosterone were in accord with the changes in PRA, but plasma cortisol did not change. Both the renal vascular response and the change in PRA were intermediate in normal subjects in whom family history was positive for hypertension. For the entire group of 39 subjects there was statistically significant agreement between the direction of the renal vascular response and the directional change in PRA: renal blood flow rose when PRA fell and fell when PRA rose ($p < 0.005$). We conclude that there is an abnormality in the control of both the renal circulation and of renin release in patients with essential hypertension in response to psychological provocation, and that a similar process is present in some normotensive subjects whose parents have hypertension. (Hypertension 3: 11-17, 1981)

KEY WORDS • emotions • renal vasculature • plasma renin activity • plasma aldosterone

ESSENTIAL hypertension remains a disease of unknown pathogenesis. As for many processes in which the cause is obscure and which may be exacerbated by stressful circumstances, investigators have repeatedly claimed that psychological, especially emotional, factors play a pathogenetic role — perhaps the key role.1-4 As reviewed recently,4-5 this conclusion has lacked credibility to many for a number of reasons: the conclusions were often based on subjective and uncontrolled observations and the stimuli employed were often gross and poorly reproducible. Moreover, the index employed was often only the pressor response, and because the blood pressure response to vasoconstrictor agents is also enhanced in essential hypertension,6 it has been reasonable to suspect that the enhanced pressor response to emotional stimuli was nonspecific.

Because psychological stimuli are difficult to apply in a controlled and even semiquantitative fashion, we attempted to deal with these limitations in this study by employing Raven's Progressive Matrices, a nonverbal IQ test first employed by Nestel7 for this purpose. The result was a stimulus too mild to produce a sustained increase in blood pressure. Our focus, however, was on the underlying renal vascular and related endocrine responses rather than the direct pressor effect of the stimulus.

Recent advances have again directed our attention to the kidney as a pathogenetic factor in sustaining hypertension whatever its cause.8-10 Two earlier studies have documented an accentuated renal vascular response to a major, disturbing stimulus in patients with hypertension.11,12 We have extended the documentation to both an enhanced renal vascular response and renin release provoked by even a mild stress similar in degree to those that form the fabric of our everyday lives. An unanticipated finding was that...
normotensive subjects whose parents had hyperten-
sion frequently demonstrated a renal response that
resembled that of patients with essential hypertension,
but smaller in magnitude and reduced in duration.
Viewed in the context of evidence that suggests an im-
portant inherited factor in the pathogenesis, this
observation is consistent with a hypothesis in which
the renal response in essential hypertension was not a
consequence of long-standing hypertension, but rather
could be present at its origin.

Methods

Subjects

The 24 normal subjects were all potential kidney
donors ranging in age from 22 to 66 years (38.9 ± 3.9
years) and requiring selective renal arteriography as
part of their assessment. All were carefully screened
for cardiovascular, renal, or adrenal disease. In eight,
a history of hypertension in one or both parents was
obtained. The 15 patients with essential hypertension
ranged in age from 22 to 65 years (40.1 ± 4.0 years).
None had received antihypertensive medication for at
least 4 weeks prior to study.

All were admitted to a metabolic ward where a
thorough history and physical examination were ob-
tained and detailed laboratory investigation was per-
formed as described.12 The detailed assessment we use
to diagnose essential hypertension by exclusion has
been described.13 In brief, a thorough history and
physical examination were followed by a laboratory
investigation that included in the examination a fresh
urinary sediment, quantitative urine cultures, 24-hour
urine collections for the determination of excretion of
vanillylmandelic acid, metanephrines, 17 hydroxy and
17 keto steroids, protein, and the clearance of
creatinine. Serum electrolyte, urea nitrogen, crea-
tinine, glucose, uric acid, calcium determinations,
aldosterone, renin, and cortisol as well as a complete
blood count were obtained routinely. Routine ex-
amination also included a chest film, electrocar-
diogram, bolus high dosage intravenous pyelogram,
and renal arteriogram in all patients included in this
study. The clinical indications for arteriography were
those generally cited, with an unusual age of onset be-
ing the most common indication in this group and
previously undiagnosed essential hypertension in the
potential donor being next. Obtaining details of the
family history was facilitated by distributing a
ROCOM questionnaire (Roche Laboratories) prior to
admission, with instructions that multiple family
members be consulted concerning family history of
disease, which included hypertension.

Sodium intake was restricted to 10 mEq/day and
potassium intake fixed at 100 mEq/day in all of the
patients with essential hypertension. An identical
protocol was used in 14 of the normal subjects, includ-
ing the eight with a hypertensive parent, but because
of a wide range of plasma renin activity (PRA) in the
patients with essential hypertension, in five of the
potential kidney donors a 200 mEq sodium intake was
utilized to reduce PRA. In an additional five donors,
potassium intake was restricted to 40 mEq/day along
with restricted sodium intake, to provoke a higher
control PRA. All subjects were on the diet for at least
5 days, and were in balance at the time of the study.

Techniques

Urography, selective renal arteriography, and renal
blood flow assessed by the xenon washout technique
were performed according to methods we have
described.13 Arterial catheterization and aortography
were completed 60 minutes or more prior to initiating
the physiological studies. Arterial blood pressure and
the electrocardiogram heart rate were monitored con-
tinuously with a Statham P23 Dc Transducer con-
ected to the catheter and recorded on an Electronics
in Medicine polygraph. Blood pressures reported
represent the mean of a 1-minute sample taken at each
blood flow determination, assessed by an individual
who was not aware of either the patients’ diagnosis or
the protocol sequence. PRA, plasma angiotensin II,
aldosterone, and cortisol concentrations were
measured by radioimmunoassay.14 Plasma and
urine creatinine and sodium and potassium concen-
trations were measured by the autoanalyzer method.

Protocols

Written informed consent was routinely obtained
prior to this study. The subjects were told that we
know of an important interaction between the mind
and body, and that the object of the study was to
assess body function while the mind was otherwise
occupied. To that end we described a “game” designed
to occupy them, which would be played during the
study. The game would consist of a series of projected
slides that posed a question and demanded a spoken
answer. As long as they were answering questions,
they were told, we knew that their mind was occupied
with the game.

The slides were back-projected via a prism onto a
10 × 10 in. screen with a commercial system (Singer
Caramate). The slides shown during the first 6 minutes
consisted of optical illusions that the subjects were
asked to identify. During the next 20 minutes the sub-
jects were shown a series of slides derived from
Raven’s Progressive Matrices, a nonverbal IQ test
designed to free the assessment of IQ from education
and social factors. The matrices consist of a series of
spatial puzzles of increasing difficulty; the subjects
were to choose from among eight solutions provided
and were urged to answer as quickly as possible. Renal
blood flow was assessed at intervals through the
procedure (see fig. 1 for timing). Blood pressure and
heart rate were monitored continuously. Arterial
blood samples were drawn for determinations of
plasma angiotensin II, aldosterone, and cortisol con-
centrations and PRA prior to and at the end of the
study.

Means have been presented with the standard error
of the mean (SEM) as the index of dispersion.
Statistical significance was assessed with the Student t
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test, or where indicated in the text, by analysis of variance or by nonparametric tests including the Fisher Exact Test, Wilcoxon Rank Sum Test, Mann Whitney U Test, or Chi square. The null hypothesis was rejected when a $p$ value of less than 0.05 was obtained. The protocols were approved by the Peter Bent Brigham Hospital and Harvard University Human Experimentation Committees, and written informed consent was obtained routinely.

Results

The normal subjects with a family history negative for essential hypertension, normal subjects with a positive family history, and patients with essential hypertension differed by analysis of variance in only one respect in the control period to the study (table 1). Mean arterial pressure, not surprisingly, was significantly higher in the patients with hypertension (98 ± 3.8 mm Hg; $p < 0.01$), than in either the family history negative (81 ± 2.7 mm Hg) or in family history positive (88 ± 4.6 mm Hg) normotensive subjects. The basal renal blood flow, PRA, angiotensin II concentration, aldosterone, and cortisol did not differ in any of the groups (table 1).

During performance of the game a clear difference in the pattern of the response between the normal subjects with a negative family history, the normal subjects with a family history positive for hypertension, and the patients with essential hypertension became apparent (figs. 1 and 2). Mean renal blood flow fell strikingly, by an average of 80 ± 14 ml/100 g/min, in the patients with essential hypertension ($p < 0.01$) and the fall was well-sustained (fig. 1). In the normal subjects with a negative family history, a small but statistically significant increase in renal blood flow occurred ($p < 0.01$). In the normotensive subjects in whom a family history of hypertension was present, renal blood flow fell, but tended to return toward control values as the game evolved (fig. 1).

When average values for mean arterial blood pressure and heart rate at the predetermined intervals were used, no change in mean arterial pressure was evident in any group (fig. 1). For the largest increase in blood pressure, however, averaged over 1 minute at these predetermined times, a clear difference was apparent; essential hypertensives showed a significantly greater tendency to a pressor response (fig. 2). Blood pressure rose by 7 mm Hg or more in 11 of 15 hypertensives, but in only three of 16 normal subjects ($x^2 = 7.23, p < 0.01$). A similar pattern was evident for the change in heart rate ($p < 0.01$).

Control PRA in the family history negative normal subjects (4.6 ± 0.69 ng/AI/ml/hr) differed neither from that in the normal subjects with a positive family history (3.6 ± 0.27 ng/AI/ml/hr) nor in the patients with essential hypertension (5.9 ± 1.1 ng/AI/ml/hr). As the game was played, however, a striking difference in the pattern appeared (figs. 2 and 3). The

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the Subjects Prior to Study</th>
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<tbody>
<tr>
<td>BP (mm Hg)</td>
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<tr>
<td>Family history negative</td>
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<tr>
<td>81 ± 2.7</td>
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<tr>
<td>Family history positive</td>
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<td>88 ± 4.6</td>
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<td>Subjects with essential hypertension</td>
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<tr>
<td>98 ± 3.8*</td>
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<td>RBF (ml/100 g/min)</td>
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<td>Family history negative</td>
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<tr>
<td>332 ± 19</td>
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<tr>
<td>Family history positive</td>
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<tr>
<td>305 ± 14</td>
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<tr>
<td>Subjects with essential hypertension</td>
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<tr>
<td>319 ± 25</td>
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<tr>
<td>PRA (ng AI/ml/hr)</td>
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<tr>
<td>Family history negative</td>
</tr>
<tr>
<td>4.6 ± 0.69</td>
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<tr>
<td>Family history positive</td>
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<tr>
<td>3.6 ± 0.27</td>
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<tr>
<td>Subjects with essential hypertension</td>
</tr>
<tr>
<td>5.9 ± 1.11</td>
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<tr>
<td>AII (pg/ml)</td>
</tr>
<tr>
<td>Family history negative</td>
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<tr>
<td>32.3 ± 4.9</td>
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<tr>
<td>Family history positive</td>
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<tr>
<td>41.0 ± 6.4</td>
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<tr>
<td>Subjects with essential hypertension</td>
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<tr>
<td>35.8 ± 4.4</td>
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<tr>
<td>Aldosterone (ng/dl)</td>
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<td>Family history negative</td>
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<td>25.4 ± 8.8</td>
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<tr>
<td>Family history positive</td>
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<td>14.3 ± 2.1</td>
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<td>18.6 ± 3.0</td>
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<tr>
<td>Cortisol (µg/dl)</td>
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<td>12.73 ± 1.6</td>
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<td>Family history positive</td>
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<td>22.2 ± 6.0</td>
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<td>Subjects with essential hypertension</td>
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<tr>
<td>13.4 ± 2.5</td>
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<td>No. of subjects</td>
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<td>Family history negative</td>
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<tr>
<td>16</td>
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<tr>
<td>Family history positive</td>
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<tr>
<td>8</td>
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<tr>
<td>Subjects with essential hypertension</td>
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<td>15</td>
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</table>

*p < 0.01.

BP = blood pressure; RBF = renal blood flow; PRA = plasma renin activity; AII = angiotensin II.
PRA was unchanged or fell in 10 of the 16 normal subjects with a negative family history and rose in 14 of the 15 patients with essential hypertension (MWUT; p < 0.005). A correlation was found (fig. 3) between the control PRA (X) and PRA at the end of the game (Y) in the family history negative normoten-
sive subjects (Y = 0.82X + 0.30; r = 0.91; F = 65.4; p < 0.01) and in the patients with essential hyperten-
sion (Y = 1.44X + 0.88; r = 0.96; F = 183; p < 0.001). The slope from these equations differed significantly, rising in the essential hypertensives (1.44 ± 0.10 SD) and falling in the normal subjects (0.82 ± 0.01 SD; t = 16.3; p < 0.02).

For the entire group of 39 patients, there was agreement between the direction of the renal vascular response and the directional change in PRA: among the subjects in whom renal blood flow fell, PRA rose in 88%. Conversely, PRA fell in 72% of those in whom renal blood flow rose (χ² = 7.90; p < 0.005).

The changes in plasma angiotensin II concentration were in accord with the results of PRA. Plasma angiotensin II fell in 10 of the 12 normal, family history negative subjects in whom the determination was available, which differed significantly from the rise that occurred in 13 of 15 patients with essential hypertension (+ 7.9 ± 2.8 pg/ml; p < 0.005).

Plasma aldosterone also fell significantly during the game in the family history negative normal subjects, to 15.1 ± 4.05 ng/dl (p < 0.01). A tendency for plasma aldosterone to rise in the patients with essential hypertension (to 21.1 ± 7.7 ng/dl) did not achieve statistical significance, but was significantly different from the pattern of the response in the normal subjects (p < 0.01). As for PRA, the control plasma aldosterone concentration was a determinant of the response (fig. 3). In contrast, no significant changes in plasma cortisol occurred in any group.

The normotensive subjects who had a parent with hypertension showed intermediate responses (fig. 2). Renal blood flow rose in only 3 of 8, vs 11 of 16 with a negative family history (p < 0.01). The PRA rose in 6 of 8, but in only 5 of 16 with a negative family history (p < 0.05). The difference in the pressor pattern did not achieve statistical significance.

**Discussion**

Various stimuli have been used in attempts to provoke an emotional response in man. For some, such as serial subtraction or the Stroop Color Test, it must be clear to the participants that the aim of the maneuver is to provoke or unsettle them. Our experience was that serial subtraction was too sensitive to the mood and personality of the investigator and the subject to serve as a reproducible stimulus. Our subjects were instructed that we were playing a game the purpose of which was to occupy their attention while we made certain physiological measurements; at no time were the terms stress or test employed. Nonetheless, patients with essential hypertension appeared to perceive the maneuver as stressful. Because we interpreted their comments in an open rather than coded fashion, we have not subjected the data to formal analysis. A prospective, controlled study designed to assess the subjects' perception of the maneuver would be worthwhile, and is planned. One element in our results might indicate that the stress provoked by recognition of an IQ test was not central to the response: the optical illusions, which we in-
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FIGURE 3. Influence of control plasma renin activity and plasma aldosterone concentration on these indices at the end of the procedure. The slopes relating the control and final values were significantly steeper in patients with essential hypertension for both plasma renin activity (p < 0.01) (left) and plasma aldosterone concentration (p < 0.02) (right). Only the normal subjects without a family history of hypertension have been included.

PLASMA RENIN ACTIVITY

PLASMA ALDOSTERONE

INCLUDED AS A RELATIVELY NEUTRAL INTRODUCTION TO THE PROCEDURE, ELICITED AN ALMOST COMPLETE EXPRESSION OF AT LEAST THE RENAL VASCULAR RESPONSE. THE STIMULUS, THEREFORE, COULD HAVE REPRESENTED UNDIFFERENTIATED AROUSAL INDUCED BY A DISCRIMINATION TASK.

FEW INVESTIGATORS IN THE FIELD TODAY ARE PREPARED TO ACCEPT HYPERTENSION AS A VEGETATIVE CONCOMITANT OF CHRONIC EMOTIONAL TENSION OR OF SPECIFIC PSYCHOLOGICAL TRAITS, THE SIMPLEST ASSUMPTION UNDERLYING MUCH OF THE EARLIER WORK IN THIS FIELD. ACCORDING TO ALEXANDER ET AL.21 “THE NUMBER OF VARIABLES IS SO GREAT AND THEIR MUTUAL CORRELATION IS SO COMPLEX THAT ONE CAN ARBITRARILY SELECT PSYCHODYNAMIC PATTERNS WHICH ARE CLEARLY DEMONSTRABLE IN ONE GROUP OF PATIENTS, BUT WHICH ARE ALSO PRESENT AND DEMONSTRABLE IN MANY OTHERS . . . ANXIETY, DEPENDENT NEEDS, FEAR, ENVY, JEALOUSY, HOSTILE IMPULSES, DISILLUSIONMENT, PROGRESSIVE AND REGRESSIVE TRENDS (OCCUR) IN EVERY PATIENT, WHETHER HE SUFFERS FROM ORGANIC OR PURELY PSYCHOLOGICAL SYMPTOMS. WE ALSO FIND THESE PATTERNS IN NORMAL INDIVIDUALS.”

Thus the conflicting reports as to whether a characteristic “hypertensive” personality and emotional response to provocation exists may not be surprising. Some investigators have described a reduced, insufficiently expressed emotional response,1, 2, 18 for example, whereas others have described hypertensives as being less well controlled and more impulsive,19 even tending to express more fear and anger than normotensive controls.19, 20 All investigators appear to agree that the emotional responses are maladaptive although there has been no unanimity as to the specific nature of the response.20-25

Another methodologic problem may have contributed to the confusion. An important element of selection is built into the referral process,4 as is most clearly seen in the early literature on hypertension; patients selected for referral to a psychiatrist are not a random sample. Even among patients with hypertension, the forces that determine whether a patient will be referred to a medical center for a detailed clinical evaluation may well include their personality. In this study, six of the 15 hypertensives came to evaluation not because of their hypertension, which had not been diagnosed, but rather as potential kidney donors. The response in this subset differed in no way from the group as a whole; moreover, the similar response in normotensive subjects with a positive family history also suggests that we did not study a selected subset of hypertensives.

Earlier studies have demonstrated a potentiated renal vascular response to emotional stress in patients with hypertension,1, 11 an observation confirmed and extended by this study. This study has documented, in addition, that a stress too small to induce a sustained blood pressure increase will provoke a striking and well-sustained reduction in renal blood flow in patients with essential hypertension. It may be important to recognize that the setting in which this study was performed, following arteriography in a cardiovascular catheterization laboratory, may have contributed to the results. The studies were performed at least 1 hour after the acute discomfort of arterial catheterization and aortography had waned and attempts were made to provide a neutral setting free of fear and discomfort; although overt emotional reactions were not evident, the situation is clearly potentially stressful. Indeed, it is reasonable to ascribe the increase in renal blood flow and fall in PRA and aldosterone concen-
The intense renal vasoconstriction raises at least three interesting questions. First, what mediators could have been responsible for the response? Second, is there any precedent for vasoconstriction involving the renal vasculature preferentially? Third, could the renal response play a pathogenetic role in the development of hypertension? Only partial answers are available for each. Nestel,⁷ who employed the same stimulus, documented an increase in urinary catecholamine excretion that paralleled the pressor response: norepinephrine, via local neural release, could certainly have been responsible for the renal response, although the stimulus as we employed it was not pressor. As an alternative, local angiotensin formation as a consequence of the enhanced renin release could have been responsible for the renal vasoconstriction. Both possibilities are amenable to direct assessment with specific antagonists.

Whether the renal response was mediated directly by the action of norepinephrine on the renal vascular alpha receptors, or indirectly by angiotensin formation, it seems likely that the link between the emotional or psychotic stimulus and the renal response was neural. The past two decades have seen the accumulation of evidence that suggests that discrete, focal responses to activation of different central neuron pools are common, and that diffuse firing occurs only when near maximal activation of the system is required.⁸¹ ³⁰ Indeed, the blood supply of the kidney, in particular, is subject to separate, independent central nervous system control.⁸¹ ³⁰ In view of the intense renal vasoconstriction without a systematic change in arterial blood pressure, an offsetting reduction in cardiac output or vasodilatation in other vascular beds must have occurred. Again, a substantial precedent for this exists: for example, dilatation in the vasculature of skeletal muscle is well documented during an emotional response.¹¹ A reduction in cardiac output to account for the unchanged arterial blood pressure is less likely.¹²

Reasonable but unproved speculation would place the response in the category mediated by the "defense reaction:" certainly emotional factors can activate this area and, as recently reviewed,⁸⁸ important elements in that response include transient, mild pressor changes, a sharp reduction in renal blood flow, and striking renin release — as occurred in the patients with hypertension and some of the normotensive children of hypertensives studied. In their basal state, however, the characteristics of hypertensives are thought to be more characteristic of their coping style than of the emergency defense reaction.⁸⁷

Investigators who have approached the problem of the pathogenesis of hypertension from widely differing viewpoints have found it difficult to achieve a synthesis without invoking a renal component.⁶ ¹⁰ The abnormal responses documented in this study could play pathogenetic roles in one or more of several ways. Renal vasoconstriction, especially in concert with enhanced aldosterone release, could modify the state of sodium balance. Angiotensin formation could lead not only to a pressor response directly, especially in the presence of a somewhat expanded total body sodium, but has also been demonstrated to enhance the vascular response to sympathetic nervous system activation.³⁸ The fact that the response occurred to a stimulus so mild, and that a qualitatively similar
response occurred in normotensive subjects whose parents had hypertension, provides an easy link between these observations and pathogenesis. How can we weave these observations into our current understanding of the pathogenesis of hypertension in this syndrome? Psychological factors are best seen as one of a host of factors that interact with a predisposition, which at least in part is genetically predetermined. The fact that PRA and aldosterone concentration rose most strikingly in those who already carried the highest levels, for example, suggests that a biological amplification system was at work, enhancing responses rather than initiating them. To the extent that a reduced ability to cope with a stressful situation occurs in patients with essential hypertension, their response expressed in cardiovascular, renal, and endocrine indices is enhanced. The nature of the predisposition is likely to vary from person to person, or perhaps from family to family. The ease of application of the test and the excellent indices provided by measurement of PRA and aldosterone make prospective studies in the children of individuals with essential hypertension attractive. Will those who show this pattern of response go on to develop hypertension?

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