Comparative Assessment of Stimuli That Release Neuronal and Adrenomedullary Catecholamines in Man

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SUMMARY We assessed the release of neuronal and adrenomedullary catecholamines in response to various stimuli of the sympathetic nervous system in normal subjects. Plasma catecholamines and their urinary metabolites, normetanephrine and metanephrine, were measured. Sodium restriction increased supine plasma norepinephrine by 37% and ambulatory plasma norepinephrine by 22%, with urinary normetanephrine excretion increased 29%. The sodium restriction did not elevate plasma epinephrine or urinary metanephrine. The most potent stimuli of norepinephrine were treadmill exercise, orthostasis, caffeine, the cold pressor test, sodium restriction and handgrip exercise, in descending order. Plasma epinephrine was increased by caffeine, treadmill exercise, the cold pressor test, handgrip exercise and the Valsalva maneuver, in that order. Syncope resulted in profound changes in plasma epinephrine but only modest changes in plasma norepinephrine. We conclude that in man, there is frequent dissociation between the effects of different stimuli on neuronal and adrenomedullary catecholamine release.

LOW CONCENTRATIONS of catecholamines in blood and the poor sensitivity of fluorometric techniques for measuring them have prevented full assessment of the value of plasma norepinephrine (NE) as a marker of sympathetic nervous activity until the development of sensitive enzymatic assay methods. The recent extension of these methods to epinephrine (E) and dopamine (D) permits better understanding of events at the neuronal and adrenomedullary levels.

Many physiologic maneuvers have been used to elucidate the function of the autonomic nervous system, including the Valsalva maneuver, the cold pressor test, static and dynamic exercise, and upright posture. Other stimuli, too, result in sympathetic neuronal or adrenomedullary discharge: low sodium diet, syncope, venepuncture, smoking and caffeine.

We compared the effects of these stimuli on plasma levels of NE, E and D in normal subjects by a sensitive enzymatic assay; we also assessed the effect of changes in sodium balance by measuring urinary normetanephrine and metanephrine with highly sensitive and specific stable isotope dilution assays. Because contradictory data in the literature may reflect different control conditions, we performed all our studies on patients in documented sodium balance who strictly avoided both tobacco and methylxanthine beverages.

Methods

The study subjects included one female and 14 male volunteers, 18–54 years old. Four were black and 11 were white. All subjects had a normal physical exam and no history of chronic or recent acute illness. No subject was on medication during the study. Volunteers abstained from methylxanthine and alcoholic beverages during the study, and the two who were smokers abstained from tobacco for 24 hours before and during the study. We excluded subjects who varied from their ideal weight by more than 10%. Serum creatinine, urea nitrogen, electrolytes, glucose, cholesterol and triglycerides were normal in all subjects. Urinalysis and baseline urinary normetanephrine and metanephrine levels were normal. Eleven subjects participated in the first six parts of the study, and seven subjects participated in the low-salt study.

Before the study, all subjects were brought into balance on a 150 mEq sodium diet provided in the Elliot V. Newman Clinical Research Center of Vanderbilt University Hospital. This usually required 3–5 days of sodium-controlled diet. We monitored urinary sodium, potassium and creatinine until balance was achieved. On the first day, the subjects remained flat in bed and took nothing by mouth after midnight. A 19-gauge heparin-lock needle was placed in the right forearm at 7:30 a.m. After a 30-minute rest in the supine posture, an 8:00 a.m. blood sample was taken to measure catecholamines. Next, the subject held 30% of his predetermined maximum handgrip capacity for 3 minutes; blood pressure and heart rate were measured before, during, and after. The application and use of the sphygmomanometer might alter circulating catecholamines, determinations of blood pressure and heart rate were monitored as the patient repeated this maneuver on the second day of the study. The patient was ambulatory from 8:05–11:00 a.m., when another catecholamine sample was taken and the heparin-lock needle removed.

On the second day the subjects were again kept supine after midnight and a heparin-lock needle was
placed in the right forearm. Thirty minutes later a catecholamine sample was taken via the heparin-lock needle and immediately thereafter another catecholamine sample was taken by venepuncture from the left antecubital fossa.

After an additional 30 minutes in the supine position, the subjects performed the Valsalva maneuver by forcibly exhaling into a manometer to a pressure of 40 mm Hg for 20 seconds. Catecholamine samples were taken immediately before and after the maneuver. The time required to take the sample ranged from 30–90 seconds.

After another 30-minute rest, the subjects performed the isometric handgrip test described above, and control and experimental samples for catecholamines were taken before and afterwards.

Finally, after a further 30-minute rest, the subjects performed a cold pressor test by placing their left hand in a pan containing equal parts of water and ice at a temperature of 0–2°C for 60 seconds. Control and experimental catecholamine samples were taken before and after the test. Subsequently, the subjects were ambulatory for 1 hour and then performed a treadmill test, which consisted of 3 minutes of exercise at 4 mph with the grade adjusted according to the subject's weight to give a total of 10,000 footpounds of work. Blood pressure and pulse were monitored. Ambulatory (control) catecholamines were taken immediately before the treadmill test; immediately afterwards, a repeat blood sample was taken. Because of the rapid fluctuation in catecholamine concentrations after physical exertion, all subjects had the treadmill catecholamine sample drawn within 15 seconds after exercise, by venepuncture from a large vein.

On a subsequent day, while subjects were still in 150 mEq sodium balance, 24-hour urine samples were collected and metanephrine and normetanephrine concentrations were determined using a gas chromatography-mass spectrometry method which depends on selected ion monitoring with deuterated metanephrine and deuterated normetanephrine as internal standards. Deuterated normetanephrine is commercially available (Merck), while deuterated metanephrine was biosynthetically prepared from deuterated epinephrine using catechol-O-methyltransferase in a modification of the procedure of Axelrod. After addition of internal standard, urine was acid hydrolyzed at pH 0.9 for 45 minutes and then passed over a nonionic polymeric XAD-2 column (Mallinckrodt). The amines were immediately eluted with 0.1N HCl, brought to pH 10.0 and extracted into methyl ethyl ketone. The organic phase was aspirated and rotoevaporated to dryness, and the sample was then derivatized by adding 200 μl pentafluoropropionic anhydride (PFPP) and 200 μl ethyl acetate. This PFPP derivative was then blown to dryness with a gentle stream of dry nitrogen at 45°C, dissolved in 200 μl ethyl acetate and injected into the GC-MS system. We used a 6-foot OV-17 column in this analysis. Relative peak heights of ion current at m/z 458/460 were used to determine both substances. Relative peak heights at 445/446 served as a check against interfering substances. This assay is sensitive to the 100 pg range; the coefficient of variation is 2.5% for normal urine processed on different days.

Seven subjects were then brought into sodium balance on a 10 mEq sodium diet; this process usually required 5 days. When balance was achieved, the subjects remained supine and took nothing by mouth after midnight. As before, 8:00 a.m. supine and 11:00 a.m. ambulatory samples for catecholamine determination were drawn from a heparin-lock needle placed at 7:30 a.m. On a subsequent day, while still in sodium balance, subjects collected 24-hour urine samples which were analyzed as above.

The data and methods of our study of caffeine's effect on catecholamines were recently reported. In a study of the hemodynamic effect of nitroglycerin in the upright posture, sublingual doses of 0.4 mg nitroglycerin inadvertently resulted in syncope in two of us (DR and RMR) when intravenous cannulas permitted instantaneous sampling for blood catecholamines.

The simultaneous differential assay of NE, E and D by a radioenzymatic method has been described. In this assay a 50-μl aliquot of plasma without further extraction or deproteinization was added directly to incubates containing catechol-O-methyltransferase and S-adenosyl-L-methionine (3H-methyl) (New England Nuclear Corp, specific activity 8.1–11.5 Ci/nmol). The total incubation volume was 100 μl. To an identical incubation mixture containing a second 50-μl aliquot of the plasma sample we added 100 pg each of NE, E and D as internal standards. Blank tubes contained each of the above reagents except plasma. After incubation for 60 minutes at 37°C, the 3H-O-methyl catecholamines were extracted and then isolated using thin layer chromatography. Radioactivity in each catecholamine derivative was determined by scintillation counting. This assay is sensitive to 20 pg/ml of plasma.

The average coefficient of variation was 3.2% for both NE and E, and 4.0% for D. The assay of catecholamines was facilitated by Cat-A-Kit (Upjohn Diagnostics).

Results

Venepuncture vs Heparin-Lock Sampling (table 1)

Mean plasma NE levels were 201 ± 49 (mean ± SEM) pg/ml after heparin-lock sampling and 228 ± 32 pg/ml a few seconds later in samples taken by venepuncture. Mean plasma E levels were 23 ± 4 and 29 ± 7, respectively, and the corresponding D levels were 38 ± 11 and 43 ± 9. None of these changes was statistically significant, and two of 10 subjects actually had higher values of NE and E after heparin-lock sampling than after venepuncture. The venepunctures in these healthy, nonobese subjects were relatively atraumatic, since all had easily approachable veins.

The Valsalva Maneuver (table 1)

During the Valsalva maneuver, heart rate increased an average of 20 beats/min (p < 0.001) as pulse
pressure decreased significantly. This was associated with a mean rise in plasma E from $29 \pm 5$ pg/ml to $36 \pm 4$ pg/ml ($p < 0.01$). Plasma NE rose from $212 \pm 50$ pg/ml to $224 \pm 43$ pg/ml but this was not significant. D showed no consistent change.

The Isometric Handgrip Test (table 1)

Plasma NE rose 27% after 3 minutes of handgrip exercise ($p < 0.05$), while E rose 67% ($p < 0.05$). In two subjects, plasma NE and E were unchanged. Again, there was no significant change in D. The pulse increase during the handgrip test averaged 11 ± 4 beats/min, while blood pressure rose 17 ± 4 mm Hg ($p < 0.005$).

The Cold Pressor Test (table 1)

Most volunteers found the cold pressor test to be the most difficult maneuver to perform. There was a mean increase in blood pressure of $24 \pm 7$ mm Hg ($p < 0.001$) and a mean increase in pulse of 10 ± 2 beats/min ($p < 0.05$). Plasma NE rose from $205 \pm 39$ pg/ml to $343 \pm 64$ pg/ml ($p < 0.01$), while plasma E rose 112%, from $24 \pm 2$ pg/ml to $51 \pm 8$ pg/ml ($p < 0.01$). Only one subject failed to increase NE and E significantly after this maneuver. The slight increase in plasma D was not significant.

Treadmill Testing (table 1)

The control samples for the treadmill test were taken while the subject was ambulatory rather than supine. With exercise there was a rise in NE from $368 \pm 69$ pg/ml to $896 \pm 105$ pg/ml ($p < 0.01$), while E rose from $39 \pm 7$ pg/ml to $90 \pm 20$ pg/ml. A mean 29% increase in D was not significant since it fell in two of 10 subjects and did not change in another two subjects. All subjects showed an increase in both NE and E with exercise.

Upright Posture (table 2)

We compared catecholamines in the supine posture and during ambulation. Plasma NE rose from $210 \pm 11$ pg/ml to $443 \pm 47$ pg/ml ($p < 0.001$). Plasma E was $29 \pm 9$ pg/ml supine and $42 \pm 12$ pg/ml ambulatory (NS). D levels were $55 \pm 16$ pg/ml and $61 \pm 13$ pg/ml, respectively (NS).

### Table 1. Sympathoadrenal Stimuli

<table>
<thead>
<tr>
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<th>E (pg/ml)</th>
<th>NE (pg/ml)</th>
<th>D (pg/ml)</th>
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<td>(mean ± SEM)</td>
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<tr>
<td>I</td>
<td>Heparin-lock sampling</td>
<td>23 ± 4</td>
<td>201 ± 50</td>
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<td>Venepuncture sampling</td>
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<td>After Valsalva</td>
<td>36 ± 4*</td>
<td>224 ± 43</td>
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<tr>
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<td>28 ± 4</td>
<td>216 ± 47</td>
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<td>47 ± 8*</td>
<td>275 ± 40*</td>
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<td>24 ± 2</td>
<td>205 ± 30</td>
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<td>90 ± 20*</td>
<td>896 ± 105†</td>
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*p < 0.05.
†p < 0.01.
‡p < 0.001.

Abbreviations: E = epinephrine; NE = norepinephrine; D = dopamine.

### Table 2. Sympathoadrenal Stimuli

<table>
<thead>
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<th>NE (pg/ml)</th>
<th>D (pg/ml)</th>
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<td>534</td>
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</table>

*p < 0.05.
†p < 0.01.
‡p < 0.001.

Abbreviations: E = epinephrine; NE = norepinephrine; D = dopamine.
Salt Restriction (table 2)

Plasma catecholamines measured in both the supine posture and after ambulation increased with alteration of sodium balance from 150 mEq/day to 10 mEq/day. Supine NE rose from 206 ± 10 pg/ml to 282 ± 27 pg/ml (p < 0.05). Supine E was not significantly altered, with levels of 30 ± 8 and 35 ± 10, respectively. Ambulatory NE rose from 440 ± 45 to 535 ± 52 (p < 0.01), but E was not significantly changed. D was not affected by sodium balance.

Urinary excretion of normetanephrine increased significantly with the lower salt diet, from 379 ± 17 μg/24 hr to 488 ± 33 μg/24 hr. Urinary metanephrine did not change significantly (fig. 1).

Ancillary Studies

The above maneuvers were selected because they have been thought to stimulate adrenergic neurotransmitter release, although some had a significant adrenomedullary component. Caffeine ingestion and syncope seem to cause an even more significant adrenomedullary discharge.

In a systematic study of caffeine, we observed a greater-than-twofold elevation in plasma E (p < 0.001) but a less-than-twofold increase in plasma NE (p < 0.001) after the ingestion of 250 mg of caffeine.

Pre-syncope was induced in one of the authors and syncope in another during an investigation of the hemodynamics of nitroglycerin: Eightfold elevations in plasma E were seen in blood samples taken immediately after syncope or pre-syncope while the increase in plasma NE was less than twofold. D was slightly increased.

Discussion

In many experimental and clinical situations, assessment of the activity of the autonomic nervous system is of great interest. Baseline blood pressure and heart rate are the parameters most frequently used to estimate the level of sympathetic function in such clinical situations as myocardial infarction and shock. Efforts to determine the functional capacity of the sympathetic nervous system in such disorders as idiopathic orthostatic hypotension generally depend on activating it by stimuli such as the Valsalva maneuver,20 the cold pressor test,9 and isometric exercise,21 and observing changes in heart rate and blood pressure. Other stimuli such as upright posture and treadmill exercise have also been assumed to provide information about sympathetic functional capacity.

A major difficulty in interpreting blood pressure and heart rate data lies in the interdependent and opposing effects of sympathetic and parasympathetic stimulation on both these parameters. Thus, an elevation in pulse rate may be due to increased sympathetic tone, reduced parasympathetic tone, or a combination of both which yields an overall rise in rate. Reliance on blood pressure is fraught with similar difficulties. Furthermore, the most widely used measure of the pressure component of the baroreceptor reflex, the Valsalva maneuver, requires arterial puncture, which limits the repeated assessment required in pharmacologic studies. More reliable and less invasive parameters are necessary.

The measurement of blood or urinary catecholamines may provide a more direct reflection of their net release from neurons and the adrenomedulla. Under baseline conditions the circulating concentration of NE represents a balance between the amount of NE which is released and escapes re-uptake into nerve terminals and the amount of NE which is being eliminated by excretion and metabolism. The plasma concentration of E represents a balance between adrenomedullary release, excretion and metabolism. With stimulation of the sympathetic nervous system there is increased release of catecholamine into the circulation without a corresponding increase in removal from the circulation.

In the present study we attempt to document the
magnitude of the response of catecholamines to a number of sympathetic stimuli. Since most blood E is derived from adrenal medulla22 while most blood NE derives from sympathetic nerve terminals,22 it is possible by separate measurement of the E and NE to discern the relative stimulation of the adrenal medulla and the sympathetic nervous system proper.

Because venepuncture is a mildly uncomfortable procedure, a study of its effect on catecholamines was made. This is primarily a technical concern: If venepuncture significantly alters catecholamines, as was suggested by Carruthers,23 then meaningful data must always be obtained by sampling from an indwelling catheter. In the present study, the small difference in catecholamines obtained by the two methods was insignificant.

Although the Valsalva maneuver produces a substantial reduction in arterial pressure,24 it did not significantly elevate NE levels in plasma. This probably reflects the brevity of the sympathetic discharge, which does not persist long enough to permit accumulation of NE to apparent steady state concentrations. As the half-life of NE is 1–2 minutes,25, 26 any increased level of neurotransmitter output will not be reflected by a new steady state until more than 4 minutes have elapsed (assuming that 90% of steady state levels would be achieved in 3–4 half-lives). Thus, the accumulation kinetics of NE predicts that maneuvers which elicit more sustained neurotransmitter release (upright posture and exercise) will yield considerably higher levels of plasma NE than the more transitory release evoked by the Valsalva maneuver. Most subjects find the Valsalva maneuver moderately stressful; the rise in E suggests that this stress was great enough to induce some minimal adrenomedullary discharge.

With isometric handgrip exercise, the early phase of the blood pressure and heart rate response is primarily mediated through vagal withdrawal, but sympathetic stimulation supervenes after 30 seconds.22 The delineation of the components of the cold pressor response are less well-defined but may be similar. Both studies were moderately stressful to most subjects and the latter was severely stressful to a few subjects. While all subjects in this investigation were able to complete both these procedures satisfactorily, from past experience we have noted that about 5% of people are unable to endure 60 seconds of the cold pressor test. (The highly motivated subject may do much better than this; some workers have used cold pressor tests of 5–10-minute durations.) NE, E, pulse and blood pressure all increased significantly with both maneuvers. The cold pressor test had a more potent effect than handgrip exercise on both NE and E as well as blood pressure, but the rise in heart rate was greater with handgrip exercise. Again, as with the Valsalva maneuver but to a greater extent, some degree of adrenal discharge is implied.

Handgrip exercise is standardized by the subject’s maximum demonstrated effort. Since the “maximum” is dependent on motivation, stress and emotion, the response to 30% of that maximum will vary widely. In those people who have a much greater sympathetic response than others to handgrip exercise, this stress might elicit a greater response than the other maneuvers we tested.

By far the most potent stimulus of NE was treadmill testing. All subjects generated a heart rate of at least 125 beats/min during this study. The NE rose 243% above the standing control sample and 427% above the supine control. There was a comparable 229% rise in E above the standing control. Similar results have been reported by others.5, 27, 28 Minor differences in reported NE increments probably reflect differences in levels of effort required. Among our subjects a regular jogger registered the smallest increase in both NE (61%) and heart rate after exercise, while at the other extreme one subject had a 786% rise in NE. It would be expected that the best-trained subjects would have the least sympathetic stimulation while performing the same amount of external work; thus, conditioning may account for part of the person-to-person changes in NE levels observed in our study.

As impressive as these changes are, the changes in NE response associated with orthostasis are almost as dramatic. Ambulatory NE is 211% greater than supine NE. In contrast, no orthostatic change in E occurs, suggesting that the adrenal medulla is stimulated by treadmill exercise but not by change from the supine to ambulatory postures. Similar responses of catecholamines to orthostasis have been reported.29, 30 Ambulatory catecholamine levels have generally been somewhat lower than levels taken within 5–10 minutes of assuming upright posture.31

The relationship of sodium intake to hypertension has been recently reviewed.32 The observation that many hypertensive patients lower their blood pressures when maintained on a low-salt diet has been repeatedly documented.33 For this reason, the interaction of sodium balance with the autonomic nervous system is of particular interest. In this study 150 mEq and 10 mEq sodium balances were achieved with an average weight differential of 1.7 kg. While this represented less than a 2% weight loss during 10 mEq sodium balance, NE rose significantly in both postures while E remained stable. That the elevation in plasma NE reflects an increased level of neurotransmitter release and not an alteration in elimination of NE from plasma was confirmed by the demonstration that excretion of its metabolite, normetanephrine, is also increased. For those changes in catecholamine release which, like sodium deprivation, are more than transient, combined assessment of NE concentration in plasma and measurement of the excretion of its metabolite strengthen the validity of this approach in quantifying sympathetic function (fig. 1). The sensitivity and specificity of the present method for measuring urinary normetanephrine and metanephrine should facilitate their assessment in investigations that involve measurements within the physiologic range.

All stimuli discussed so far — except venepuncture and the Valsalva maneuver — had major effects on NE. In contrast, syncope induced a primarily
adrenomedullary discharge: The percent increase in $E$ was five times that of $NE$. Caffeine ingestion has also been shown to cause predominantly adrenomedullary stimulation. 17

Stimuli tested in this study can therefore be ranked by selective potency of stimulation (table 3). Caffeine ingestion and treadmill exercise appear to be the most potent, clinically useful tests of the capacity of adrenomedullary function, and treadmill exercise and orthostasis are the most potent stimuli of sympathetic nervous function. Of the three most commonly used tests of sympathetic function in clinical practice (Valsalva, cold pressor and handgrip), the cold pressor test was most potent in raising $NE$, $E$ and mean blood pressure.

There are problems in interpreting selective catecholamine data, especially if urinary parameters are being monitored. Infusion studies have shown that 1.5–4.0% of $NE$—but only 1% of $E$—is excreted by the kidney. 34, 35 Furthermore, the fractional excretion of administered epinephrine increases at higher rates of infusion. 35 Finally, urine pH affects the amount of catecholamine excreted. 36 The extent to which these limitations are circumvented by applying specific determination of urinary metanephrine and normetanephrine levels remains uncertain.

Our method for measuring catecholamines and their metabolites greatly facilitates the assessment of adrenergic function in various disease states.

Acknowledgments

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References

21. Lind AR, Taylor SH, Humphreys PW, Kennely BMN,
Effects of Volume Expansion and Contraction in Normotensive Whites, Blacks, and Subjects of Different Ages

FRIEDRICH C. LUFT, M.D. CLARENCE E. GRIM, M.D., NAOMI FINEBERG, PH.D., AND MYRON C. WEINBERGER, M.D.

SUMMARY We studied the blood pressure, natriuretic, kaliuretic and humoral responses of 347 normal subjects after volume expansion and volume contraction to examine possible differences among whites, blacks and subjects of different ages. According to outpatient 24-hour urine collections, blacks excreted less sodium and potassium than whites. After similar states of sodium intake were achieved among all subjects, 2 liters normal saline were given i.v. Blacks and subjects ≥ 40 years excreted less sodium than whites or subjects < 40 years, over a 24-hour period. In addition, blacks excreted less potassium. The delay in sodium excretion occurred during the first 12 hours after the salt load. Blacks had a greater suppression of plasma renin activity than whites 24 hours after saline. Blacks also had higher blood pressures than whites after saline administration; their pressure remained elevated until furosemide was given. Furosemide, 120 mg over 24 hours, evoked greater natriuresis, but less kaliuresis in blacks than in whites. The greater prevalence of hypertension in both blacks and older subjects may be related to relatively blunted natriuretic responses when these groups engage in the high sodium-low potassium intake characteristic of our society.

ALTHOUGH ELEVATED BLOOD PRESSURE may result from a variety of causes,1 most hypertensive persons have no immediately known or identifiable cause of their blood pressure elevation.2 Dietary fac-

utors, particularly sodium and potassium, have been implicated in human hypertension on the basis of circumstantial evidence.3-5 Guyton and associates6 have recently emphasized that the kidney functions as the final common pathway of blood pressure regulation in both the normotensive and hypertensive state through its control of the excretion of salt and water. They suggest that factors which operate on the kidney and influence its excretion of salt and water are responsible for the development of hypertension. Aberrancies in the handling of salt and water in the normotensive state may have bearing on the development of hypertension, particularly in individuals in societies that consume diets high in sodium and low in...
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