Renin-Angiotensin-Aldosterone System During Chronic Thiazide Therapy of Benign Hypertension

By J. J. Bourgoignie, M.D., F. J. Catanzaro, M.D., and H. M. Perry, Jr., M.D.

With the technical assistance of Esther Schoepfle and Linda Kurz

SUMMARY
Activity of the renin-angiotensin-aldosterone system was investigated in 53 patients with benign essential hypertension treated with thiazides. Following acute (less than 3 weeks) exposure to thiazide, renin activity was increased in peripheral plasma, and sensitivity to infused angiotensin was decreased but only when dietary salt was simultaneously restricted. During chronic (more than 2 months) exposure to hydrochlorothiazide, 32 patients with unrestricted salt intake had normal renin activity in peripheral plasma (39 of 43 determinations), normal sensitivity to infused angiotensin (18 of 22 tests), and normal aldosterone excretion (nine of nine assays). Renin activity correlated well with angiotensin sensitivity ($r = 0.661; P < 0.001$). Therefore, chronic ingestion of thiazide apparently induces no change in the renin-angiotensin-aldosterone system and hence presumably neither secondary aldosteronism nor negative sodium balance.

Additional Indexing Words: Renin activity Angiotensin infusion Aldosterone excretion Angiotensinogen

The initial effect of thiazide diuretics is to increase the sodium lost in the urine. The resultant negative sodium balance leads to decreased exchangeable sodium and hence decreased plasma and extracellular fluid volumes. These in turn reduce cardiac output and thereby lower arterial pressure. In both man and experimental animals, negative sodium balance is associated with increased activity of the renin-angiotensin-aldosterone system.7-11 After several weeks or months of exposure to thiazide diuretics, exchangeable sodium, and with it plasma and extracellular fluid volumes return to normal levels.1-3, 5, 6, 12 Cardiac output also returns to normal,3 but the antihypertensive effect of the drug persists, indicating that at this stage of therapy peripheral resistance has been reduced.18 An effect on vascular walls has been invoked to explain this reduction in resistance.

When sodium balance returns to normal during prolonged administration of thiazide, the activity of the renin-angiotensin-aldosterone system would also be expected to return to normal; however this has not actually been observed. In the present study, this system was examined in patients exposed to hydrochlorothiazide, both chronically and acutely. To avoid the secondary hyperaldosteronism associated with malignant stages of hypertension,14 only patients with so-called benign hypertension have been studied. Activity of the renin-angiotensin-aldosterone system was evaluated in the following ways: circulating renin activity was measured in 53 patients; the pressor response to infused angiotensin

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was determined in 28 of them; and urinary aldosterone excretion was measured in nine.

**Group Studied**

Fifty-three patients with hypertension of several years' duration were studied. Twenty-three were males; 36 were Negroes; their ages ranged from 17 to 70 years (median, 45 years). At the time of study, none had acute cardiac, vascular, or renal complications; in particular, none had heart failure, exudative or hemorrhagic retinopathy, or more than 25 mg of urea nitrogen per 100 ml of plasma, although 14 had proteinuria. Six were considered to have chronic pyelonephritis on the basis of history, urinalysis, and roentgenographic studies; the others were treated for essential hypertension. The patients have been separated into two groups on the basis of the length of their exposure to hydrochlorothiazide.

When studied, 32 outpatients from the Washington University Hypertension Clinic had ingested 50 to 100 mg of hydrochlorothiazide daily for a median period of 18 months (range, 2 to 84 months). Hydrochlorothiazide was the sole antihypertensive agent used for 14 of them; it was combined with hydralazine for nine, with ganglioplegic agents for five, and with both hydralazine and ganglioplegic agents for four. In the clinic, 21 of these outpatients had average diastolic pressures below 100 mm Hg; six had average pressures between 100 and 110 mm Hg; and five had averages above 110 mm Hg. All 32 had at least 138 mEq of sodium per liter of plasma, and 27 had 140 mEq or more. Twenty-one patients had less than 3.5 mEq of potassium per liter of plasma. No patient's intake of sodium was restricted; the intake of potassium was specifically supplemented for only two patients, although all were instructed to drink fruit juice regularly every day.

When studied, 21 hospitalized patients had ingested 50 to 100 mg of hydrochlorothiazide daily for a median period of 3 days (range, 3 to 21 days). Hydrochlorothiazide was the sole antihypertensive agent used for 12 of them; it was combined with hydralazine for six and with both hydralazine and guanethidine or alpha methylldopa for three. At rest in hospital, 13 patients had diastolic pressures below 100 mm Hg; seven had pressures between 100 and 110 mm Hg; and one had a pressure above 110 mm Hg. The intake of sodium was not limited for 10 patients, while for the other 11, dietary sodium had been restricted to less than 20 mEq daily for 2 to 5 days preceding the observations considered here. No supplemental potassium was administered.

**Methods**

**Determination of Renin Activity**

All patients were up and about immediately before 10 to 20 ml of blood was collected from an antecubital vein into dry heparinized tubes. The blood was immediately centrifuged at 1200 \times g for 10 min, and the plasma was quickly separated and stored at -18 C. The subsequent measurement of renin activity involved three steps: removal of angiotensin and any other small vasoactive molecules from plasma by means of dialysis, incubation of the renin and angiotensinogen present in the dialyzed plasma, and estimation of angiotensin produced during incubation with one or both of two bioassays. Of the 70 samples studied, 23 were assayed with the aortic strip and 47 were assayed in the nephrectomized rat.

At the beginning of the study, renin activity was measured with the aortic strip, using the method of Helmer and Judson to prepare the plasma. Following acidification to pH 5.5 with HCl, the plasma was dialyzed overnight against distilled water at 4 C; the dialyzed plasma was then rendered isotonic with saturated sodium chloride and incubated for 1 hr at 37 C; finally the constrictor activity of the dialyzed incubated plasma was assayed with a spirally cut strip of rabbit aorta.

Later in the study, preparation of the plasma was modified, and the assay was performed in the nephrectomized rat. Two to 5-ml aliquots of plasma were dialyzed at 4 C in Visking cellophane membrane no. 20 for 15 to 17 hr against approximately 40 volumes of an aqueous solution containing 0.10 M NaCl, 0.05 M NaH2PO4-Na2HPO4 (pH 5.7), and 0.005 M Na2HEDTA (ethylenediamine tetraacetate). Dialysis was repeated twice, once for 7 to 9 and once for 15 to 17 hr, against the same volumes of similar solution without EDTA. After dialysis, the plasma was centrifuged at 1200 \times g for 10 min at 4 C, and the supernatant was then stored at -18 C. Immediately prior to assay, the dialyzed plasma super-
pressor activity of the incubated plasma was assayed in an anesthetized (25 to 50 mg/kg pentobarbital intraperitoneally), ganglioneurotomic (25 mg/kg of pentolinum bitartrate intravenously) rat by injecting 0.05 to 0.2 ml into the jugular vein while the blood pressure was directly recorded from a cannulated carotid artery with a Sanborn electromanometer. Male rats of the Wistar strain, weighing between 150 and 250 g were used; they had been bilaterally nephrectomized 16 to 20 hr before assay. Each plasma was tested at least three times and in two rats.

With both bioassays, the renin activity of plasma was determined by comparing the response it produced with the responses from known amounts of synthetic angiotensin. Here and throughout this report synthetic angiotensin refers to 1-L-asparaginyl-5-L-valyl angiotensin octapeptide (Hypertensin*). The standards consisted of six successively doubled concentrations of synthetic angiotensin, with the lowest concentration being 195 ng per 100 ml of the phosphate buffer (without EDTA but with 0.2 g per 100 ml of neomycin sulfate) described above. Each unknown plasma was bracketed by a pair of consecutive standards, that is, the first equalling half the second, and the concentration of angiotensin in the plasma was calculated by linear interpolation.

To compare the results obtained with the two bioassays, renin activity was determined simul-

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Constrictor activity on aorta (ng%)</th>
<th>Presor activity in rat (ng%)</th>
<th>Ratio of constrictor activity to pressor activity</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>600</td>
<td>95</td>
<td>6.32</td>
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<tr>
<td>2</td>
<td>750</td>
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<td>3</td>
<td>600</td>
<td>127</td>
<td>4.72</td>
</tr>
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<td>600</td>
<td>150</td>
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<td>155</td>
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<td>1030</td>
<td>180</td>
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<td>630</td>
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<td>2485</td>
<td>2.17</td>
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<td>15</td>
<td>2300</td>
<td>789</td>
<td>2.92</td>
</tr>
<tr>
<td>Mean</td>
<td>2419</td>
<td>652</td>
<td>4.35</td>
</tr>
</tbody>
</table>

*Ciba Pharmaceutical Co., Summit, New Jersey.

Table 1
Renin Activity Obtained with Two Different Bioassays

The correlation between the two methods was excellent, with a correlation coefficient of 0.894 (P < 0.001); however the absolute values on the aortic strips were about four times those obtained in the nephrectomized rat, with the use of the same synthetic angiotensin to standardize both. The relative insensitivity of the aortic strip to synthetic angiotensin has been observed before. Specifically Helmer18 reported that synthetic 1-asparaginyl angiotensin was only 25% as active on the aortic strip as either the naturally occurring angiotensin or the synthetic 1-aspartyl angiotensin, although all three were equally pressor in the pithed cat. Winer and Lubbe19 observed the same discrepancy for synthetic angiotensin between the constrictor activity on the aortic strip and the pressor effect in the ganglion-blocked rat. Whatever the reason for the discrepancy, we have equated the results of the two bioassays by quartering the values obtained on the aortic strip; we have thereafter treated the two sets of results in the same manner. Renin activity, determined by either assay, has been expressed as nanograms of synthetic angiotensin present per 100 ml of plasma, that is, ng%.

Both bioassays were dependent on the presence of excess angiotensinogen in the incubation mixture. Therefore it was possible that the apparently normal renin activity found after chronic exposure to thiazide was spuriously low following depletion of circulating angiotensinogen. This possible source of error was controlled by adding angiotensinogen-free human renin to 15 incubated plasma samples, reincubating and observing a marked increase in pressor activity of all samples tested. Human renin suitable for this purpose was prepared by Haas and associates' method,20 with the final dialysis performed against the phosphate buffer (without EDTA). Incubated alone, this preparation was without pressor activity in the nephrectomized rat, but when 0.01 ml was added to 0.5 ml of already incubated and tested plasma the mixture was incubated an additional 15 min. at 37 C and pH 5.7, the pressor activity of the plasma sample was always increased at least tenfold.

Using the nephrectomized rat, renin activity for 22 normal subjects ingesting an unrestricted diet averaged 322 ng% with a standard deviation of 66 ng%. Hence in this report the upper limit of normal for renin activity has been taken as 520 ng%, that is, mean plus three standard deviations.

Angiotensin Infusion Test

Immediately after blood was collected for renin assay, the pressor response to intravenously
infused angiotensin was determined for 28 patients, using the technique described by Kaplan and Silah\textsuperscript{21, 22} except that no saline was infused prior to angiotensin. In brief, 5\% glucose in water was infused into an antecubital vein while the arterial pressure in the other arm was recorded every 2 to 3 min. After the diastolic pressure had been stable for at least 10 min, the infusion was changed, without the patient's knowledge, to one containing 500 ng of synthetic angiotensin per milliliter of solution. The initial flow rate was chosen to deliver approximately 2 ng of angiotensin per kg of body weight per min. The rate was doubled every 6 min until a pressor effect was observed; it was then adjusted so that the diastolic pressure would be maintained 20 mm Hg above the base-line level for 5 minutes. Thereafter angiotensin-free fluid was again infused until the diastolic pressure had returned to its control value when the entire procedure was repeated. For a particular patient, the difference between the two pressor doses required to produce an increase of 20 mm Hg in diastolic pressure never exceeded 5\% of their average; this average dose is hereafter referred to as the critical dose and is expressed in ng/min/kg. We have previously considered patients with critical doses greater than 8.5 ng/min/kg as "angiotensin-insensitive" and those with lower critical doses as "angiotensin-sensitive."

The validity of using the response to a single specific dose of angiotensin as the sole measure of sensitivity to angiotensin has been challenged.\textsuperscript{24} Likewise the meaning of a parameter like critical dose, that is, the amount of angiotensin required to raise the diastolic pressure a single specific increment, has been questioned, the question being how closely the amount of angiotensin required to produce some smaller increase in diastolic pressure was related to critical dose. Figure 1 indicates that, with changes in diastolic pressure greater than 8 mm Hg, there is a linear relationship between the dose of angiotensin and the increment in blood pressure. It must be emphasized that the 14 patients considered in the figure were carefully chosen as representatives of rather homogeneous groups of either "angiotensin-sensitive" or "angiotensin-insensitive" patients; patients of intermediate sensitivity were omitted. Although the purpose of the figure is to show the validity of using critical dose, it also indicates that patients acutely exposed to thiazide tend to be angiotensin-insensitive and patients chronically exposed tend to be angiotensin-sensitive.

**Measurement of Urinary Aldosterone**

During the 24 hr before blood was drawn for renin assay, urine was collected from nine ambulatory patients for aldosterone assay. The determinations were made by Bio-Science Laboratories, by the method of Kliman and Peterson.\textsuperscript{25} For this laboratory the mean value for normal subjects is 14.0 $\mu$g/24 hr with a standard deviation of 6.7 and a range of 3 to 27.

**Results**

**Renin Activity**

Renin activity in peripheral venous blood was measured 43 times for 32 patients who had been ingesting a normal diet plus 50 to 100 mg of hydrochlorothiazide daily for more than 2 months. The mean circulating renin activity was 250 ng/\% with a standard error of 34 ng/\%. Following such chronic exposure to thiazide only four patients had definitely elevated renin activities (fig. 2). Three of the four had relatively short exposures when originally tested (2, 2, and 5 months), and all three had normal renin activities (337, 276, and 251 ng/\%) when retested later (after 4, 5, and 8 months of exposure). The fourth, a 65-year-old man with a cystic lesion in the lower pole of one kidney, had a renin activity
of 634 ng% after ingesting hydrochlorothiazide for 7 years.

In contrast, many of the patients tested following acute exposure to thiazide had elevated renin activities in peripheral venous blood. Specifically the mean activity of 27 samples from 21 patients who had ingested from 50 to 100 mg of hydrochlorothiazide daily for 3 weeks or less was 611 ng%, with a standard error of 91 ng%. The difference between the mean activity for patients with chronic exposure and the mean activity for patients with acute exposure was highly significant ($P < 0.001$).

We have not attempted to restrict dietary sodium in chronically treated patients, but our patients beginning therapy with diuretics have been about equally divided between those whose dietary sodium has been restricted to 20 mEq daily and those with no limitation. It must be emphasized that only patients with restriction of sodium had elevated renin activities. Thus the mean renin activity of 13 samples from salt-restricted, acutely exposed (to thiazides) patients was 882 ng%, and the mean was 360 ng% for 14 samples from chronically exposed patients without salt restriction. The difference between these two means was statistically significant with $P < 0.005$. Among patients with unrestricted dietary sodium, on the other hand, there was no significant difference between the group chronically, and the group acutely, exposed to thiazide, with $P > 0.2$.

**Figure 2**

Renin activities in peripheral plasma of hypertensive patients ingesting hydrochlorothiazide for less than 3 weeks (acute) and more than 2 months (chronic). The acutely exposed patients included a salt restricted and an unrestricted group, while the chronically exposed patients were all unrestricted. Renin activity is indicated by a solid dot if measured with the nephrectomized rat and by an open circle if measured with the rabbit aorta, the latter values all having been divided by four before being plotted (see "Methods"). The normal mean value ± 1, 2, and 3 times the standard deviation is indicated for 22 normal subjects without dietary restriction.

**Figure 3**

Critical doses of angiotensin for hypertensive patients ingesting hydrochlorothiazide for less than 3 weeks (acute) and more than 2 months (chronic). For the acute group, eight patients were studied 10 times, and for the chronic group, 20 patients were studied 22 times. Only three patients were on salt restricted diets and they accounted for three of the four very high critical doses in the acute group.
Sensitivity to Infused Angiotensin

Sensitivity to angiotensin was measured 22 times in 20 patients who had been ingesting a normal diet plus 50 to 100 mg of hydrochlorothiazide daily for more than 2 months (fig. 3). The mean critical dose was 6.3 ng/min/kg with a standard error of 0.8 ng/min/kg. Only four patients had critical doses greater than 8.5 ng/min/kg which we have previously used as the upper limit of normal. Two of the four simultaneously had elevated peripheral renin activities; these patients were not subsequently retested when their renin activities had become normal, nor was angiotensin infused into the other two patients with elevated renin activities.

In contrast for 10 determinations in eight patients who had ingested 50 to 100 mg of hydrochlorothiazide daily for 3 weeks or less, the mean critical dose of infused angiotensin was 10.4 ng/min/kg with a standard error of 1.5 ng/min/kg (fig. 3). The intake of sodium was limited to 20 mEq daily for only three patients, and all three had critical doses of angiotensin exceeding 15 ng/min/kg; whereas it was unrestricted for five patients, three of whom had normal critical doses and normal circulating renin activities. The difference between the 22 infusions to patients chronically exposed to hydrochlorothiazide and the 10 infusions to patients acutely exposed, including both the salt-restricted and the unrestricted, was near the limit of statistical significance (P < 0.02), but again there was no significant difference if only the unrestricted patients were considered.

Aldosterone Excretion

The urinary excretion of aldosterone was determined for nine (ambulatory) patients who had ingested a normal diet plus 50 to 100 mg of hydrochlorothiazide daily for more than 2 months (table 2). No patient excreted more than 27 μg/24 hr, the upper limit of normal. The simultaneously determined renin activities were well within normal limits for all nine patients.

Table 2
Aldosterone Excretion and Simultaneously Determined Renin Activity in Peripheral Plasma for Nine Patients Chronically Ingesting Thiazide

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urinary aldosterone (μg/24 hr)</th>
<th>Peripheral renin (ng%)</th>
<th>Duration of ingestion (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.F.</td>
<td>26</td>
<td>297</td>
<td>2</td>
</tr>
<tr>
<td>A.K.</td>
<td>27</td>
<td>267</td>
<td>36</td>
</tr>
<tr>
<td>A.T.</td>
<td>20</td>
<td>292</td>
<td>27</td>
</tr>
<tr>
<td>E.V.</td>
<td>16</td>
<td>188</td>
<td>18</td>
</tr>
<tr>
<td>M.D.</td>
<td>22</td>
<td>337</td>
<td>2.5</td>
</tr>
<tr>
<td>G.C.</td>
<td>18</td>
<td>164</td>
<td>60</td>
</tr>
<tr>
<td>E.W.</td>
<td>14</td>
<td>162</td>
<td>2</td>
</tr>
<tr>
<td>M.L.</td>
<td>11</td>
<td>278</td>
<td>36</td>
</tr>
<tr>
<td>M.B.</td>
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<td>367</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>17.4</td>
<td>261</td>
<td>20.5</td>
</tr>
</tbody>
</table>

Relationship Between Renin Activity and Angiotensin Sensitivity

Simultaneous measurements of renin activity in peripheral plasma and the critical dose of infused angiotensin were made 32 times for 28 patients. The correlation co-

Figure 4
Correlation between renin activity in peripheral plasma and critical doses of infused angiotensin simultaneously determined in 32 separate instances for 28 hypertensive patients ingesting hydrochlorothiazide for less than 3 weeks (squares) or more than 2 months (circles). Solid symbols indicate that renin activity was measured in nephrectomized rats; open symbols, that it was measured in the rabbit aorta. Since similar significance (P < 0.005) was obtained when the critical dose of angiotensin was plotted against renin activity measured with the rabbit aorta (r = +0.625; N = 23), or with the nephrectomized rat (r = +0.613; N = 22), only the value obtained in the rat was plotted in the 10 instances when both were available.
efficient was highly significant when the entire group with acute and chronic exposure to hydrochlorothiazide was considered \((r = +0.661; P < 0.001)\) (fig. 4). The coefficient remained significant, although smaller, when only the 22 instances involving patients chronically exposed to hydrochlorothiazide were considered \((r = +0.473; P < 0.05)\), the decrease being due to the narrower ranges of values for such patients.

**Discussion**

Negative sodium balance enhances the activity of the renin-angiotensin-aldosterone system,\(^7-11, 26\) Increased activity of circulating renin has been reported in man during the initial period of exposure to diuretics, but only in the presence of concomitant restriction of dietary sodium\(^7, 9, 27\); Gifford and associates\(^8\) found changes in plasma volume but not in exchangeable sodium or aldosterone excretion while studying patients on unrestricted diets. The normal renin activities of most of our patients with acute exposure to thiazides and no dietary restriction of sodium can be reasonably explained by postulating the absence of significant negative sodium balance at the particular time when renin was measured.

If treatment with thiazide continued, adaptive “escape” from the natriuretic action of the drug occurs, positive sodium balance appears, and extracellular fluid and circulating blood volumes increase toward pretreatment levels.\(^{28}\) Uncertainty remains whether these volumes and total exchangeable sodium return to normal\(^11\) or toward normal but remain somewhat low.\(^{28}\) Our observations on patients chronically exposed to thiazide do not support the hypothesis that production of aldosterone, the final effector substance of the system, remains elevated,\(^{20}\) since all nine patients studied excreted normal amounts of aldosterone, although excretion was at the upper limit of normal in several instances.

For hypertensive patients, except those with primary aldosteronism, renin activity correlates well with aldosterone production.\(^{11, 30}\) In agreement with the observed normal excretion of aldosterone, renin in peripheral plasma eventually became normal in 27 of 28 chronically treated patients. The normal renin activity could not be explained by depletion of circulating angiotensinogen; furthermore Peters\(^3\) found no direct effect of thiazide on the velocity of angiotensin production from angiotensinogen. An excess of circulating angiotensinase is more difficult to exclude as a cause of spuriously low or normal renin activity since the latter is measured by the angiotensin it produces. The normal sensitivity to infused angiotensin observed in 16 of 20 patients chronically ingesting thiazide would seem to make excess angiotensinase less likely, particularly since the synthetic angiotensin used appears to be more sensitive in vitro to angiotensinase than the natural angiotensin formed during incubation of plasma.\(^{32}\)

It is not known precisely what physiological parameter the angiotensin infusion test measures; it is not yet evident that it is an indirect measure of circulating angiotensin, as originally proposed\(^2\); nevertheless empirically the angiotensin infusion test correlates well with the renin activity of peripheral plasma.\(^{2, 33}\) Therefore normal sensitivity to infused angiotensin would not favor an abnormal renin-angiotensin system nor secondary aldosteronism. For 20 patients chronically exposed to thiazides, the mean critical dose of angiotensin was 6.3 ng/min/kg which agreed closely with the 5.6 ng/min/kg previously observed by us for 28 patients with benign essential hypertension but no exposure to thiazide.\(^23\)

**Acknowledgment**

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**References**


Circulation, Volume XXXVII, January 1968


Parry’s Recapitulation
on Angina Pectoris (1799)

It may be advantageous to place under one view the general conclusions which have been drawn from the preceding enquiries into the nature and causes of the Angina Pectoris. From these it appears,

I. That it is a case of Syncope, preceded by a notable anxiety or pain in the region of the heart.

II. That so far as the most accurate observation has hitherto gone, the tendency to this disorder arises from mal-organization in the heart itself; which mal-organization seems to be chiefly induration of the coronary arteries.

III. That this mal-organization acts by diminishing the energy of the heart.*

IV. That the chief symptoms of the disease are the effect of blood retarded and accumulated in the cavities of the heart and neighbouring large vessels.

V. That the causes exciting the paroxysms are those which produce this accumulation;

1. By mechanical pressure; or

2. By stimulating in an excessive degree the circulating system; in consequence of which, the heart, weakened by the mal-organization, readily sinks into a state of quiescence, while the blood continues to advance in the veins. Whence it follows, that, the power of the heart being given, the disposition to paroxysms will be directly as the momentum of the blood in the veins; and that, on the contrary, the momentum of the blood in the veins being given, the disposition to paroxysms will be inversely as the power of the heart.

VI. That after a certain approach towards quiescence, the heart may recover its irritability, so as again to carry on the circulation in a more or less perfect degree, from the operation of the usual stimuli; but

VII. That death may at length ensue from a remediless degree of inirritability in the heart.—Caleb Hillier Parry: An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris. London, Cadell and Davies, 1799, p. 140.

*By the energy of the heart I mean not merely the readiness, but also the degree of irritability or excitability.
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