Angiotensin Skin Tests

By Benjamin Jablons, M.D.

Many attempts have been made to establish the relationship between angiotensin, human hypertension, and experimental hypertension. Three groups have reported the successful demonstration of a pressor material in varying amounts in the blood of patients with benign and malignant hypertension.\textsuperscript{1-3} Boucher, Biron, and Genest\textsuperscript{2} claim that the material they isolated gave pressor reactions, chemical reactions, and chromatographic and electrophoretic findings similar to those of pure angiotensin. They have also reported the presence of a depressor fraction in blood. The isolation of a relatively small amount of angiotensin in normotensives and the presence of this depressor fraction suggest that the homeostatic regulation of blood pressure involves, in some measure, the antagonistic activity of these components. The depressor material demonstrated in the blood by Boucher et al. is too small, however, to enable comparison with the antipressor material isolated from the kidney by Jablons.\textsuperscript{4,5}

Angiotensin Skin Test

The above concept suggested that there might be a varied response in individuals, depending on their relative balance of pressor material (angiotensin) and depressor material (angiotensin “inhibitor”). The availability of pure angiotensin II\textsuperscript{*} made it feasible to explore this possibility.

Twenty normotensive subjects, aged 13 to 80 years, were injected intradermally with 0.1 \( \mu \)g. of angiotensin II in saline solution. The duration of the persistence of the wheal that was produced by the angiotensin II was noted. The characteristic blanching reported by Wilkins and Duncan\textsuperscript{6} 20 years ago was similarly obtained with angiotensin II. When it is injected as indicated above, angiotensin II produces a circumscribed, localized, indurated area of blanching that persists for varying periods of time (fig. 1). A different type of skin reaction is produced by epinephrine (fig. 2), norepinephrine, vasopressin, mephentermine, or aldosterone. Norepinephrine produces an irregular area of blanching with a central ecchymotic area or even necrosis. Such a reaction has never been observed following the use of angiotensin. This material is not open to the objection leveled against natural angiotonin, which has been shown to contain varying amounts of angiotensin I, angiotensin II, other unidentified peptides, and the vasodilator Factor V of Halvorsen, Fasciolo, Calvo, and Chionetti.\textsuperscript{7} Repeated tests with synthetic angiotensin have yielded reproducible results when injected into the skin of 17 patients. In 22 normotensives, the local blanching and induration resulting from the intradermal injection of 0.1 \( \mu \)g. of angiotensin II persisted for an average of 17\( \frac{1}{2} \) minutes (range 5 to 120). In 21 untreated hypertensives, the skin tests persisted for an average of 119 minutes (range 5 to 720) (fig. 3). In a smaller group of treated hypertensives, the persistence of the skin reaction followed a similar pattern. In a subsequent group of hypertensive patients with renal impairment, as indicated by blood urea nitrogen levels of 30 mg. per cent or more, skin tests persisting for periods up to 1,440 minutes were observed.

Angiotensin Skin Tests in Experimentally Induced Angiotensin Hypertension

In studying the blood pressure-raising effect of angiotensin II in normotensives, it appeared of interest to observe the skin reaction to angiotensin II during a control period when 5 per cent dextrose and water was being infused, as compared with a period when the blood pressure was elevated by the

\textsuperscript{*}Supplied as Hypertensin CIBA.

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Figure 1

Note the characteristic, circumscribed area of blanching and induration produced by intradermal injection of 0.1 µg. of angiotensin II.

Figure 2

Note the irregular character of the wheal produced by the intradermal injection of epinephrine. In center of wheal is a punctate, ecchymotic area.
intravenous infusion of angiotensin II. In 8 normotensive individuals, the skin test during the control period averaged 17½ minutes and, during the period of hypertension, averaged 61 minutes (fig. 4 and table 1). Skin tests 20 minutes after the subsidence of the elevated blood pressure behaved similarly to the control tests. Skin tests made with angiotensin during a hypertensive period, induced by the infusion of norepinephrine, persisted for periods not exceeding 20 minutes. This finding and the fact that the angiotensin skin test persists for significantly longer periods when angiotensin blood levels are increased are further evidence of the differential diagnostic value of this test. This test has proved of value in a group of labile hypertensives in whom blood pressure elevation is not constant. Patients in this group have usually been designated as transient hypertensives, and various tests have been suggested to aid in their differentiation from normotensives. The response of blood pressure to immersion of the hand in cold water, the cold pressor test of Hines and Brown, is widely used for this purpose.

Cold Pressor Test and the Angiotensin Skin Test

The value of the cold pressor test to single out hyper-reactors is variously estimated by different investigators. A comparison of the cold pressor test with the angiotensin skin test (A.S.T.) was made in 31 individuals, 18 males and 13 females, aged 35 to 86 years. Ten were normotensive and 21 hypertensive. The hypertensive group was further sub-

### Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>During angiotensin-induced hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.M.</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td>L.T.</td>
<td>35</td>
<td>90</td>
</tr>
<tr>
<td>S.J.</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>G.C.*</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td>F.D.</td>
<td>25</td>
<td>105</td>
</tr>
<tr>
<td>C.J.</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>B.E.</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>McC.</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>Average</td>
<td>17.5</td>
<td>61</td>
</tr>
</tbody>
</table>

*See figure 4.

- **Figure 3**

Scattergram showing distribution of time duration of persistence of angiotensin II skin tests. Note the majority of tests in normotensives are 15 minutes or less and, in the hypertensives, persist for 60 minutes or more. Treated hypertensives scatter in same pattern as untreated hypertensives.

The normotensive group, the A.S.T. persisted for 30 minutes or less in 8 of the 10 and 60 minutes in 2. The cold pressor test (C.P.T.) was positive in 6 and negative in 4. Thus, the A.S.T. was within the normotensive range (30 minutes or less) in 80 per cent and the C.P.T. in only 40 per cent. In the untreated hypertensive group, the A.S.T. persisted from 90 to 220 minutes in 10 of the 11 subjects tested, and 1 had an A.S.T. time of 30 minutes (90.9 per cent.) The C.P.T. was positive in 7 and negative in 4 (63.0 per cent). In the treated hypertensive group, the A.S.T. persisted for 45 to 220 minutes in 8 and 30 minutes in 2 (80 per cent). The C.P.T. was positive in 4 and negative in 6 (40 per cent) of these patients. The A.S.T. in this series appears to be a more consistent and a more reliable indicator of the prehypertensive and hypertensive states.

**Summary**

The studies reported above indicate that the angiotensin skin test (A.S.T.) is a simple practical measure which has proved of value in differentiating between normotensive and hypertensive individuals. The duration of the blanching of skin by the test differs significantly in normotensives as compared with hypertensives. The test has served as an index
of differentiation between an emotionally induced elevation of blood pressure and one which may go on to an established hypertensive state. The A.S.T. is a more reliable test in the diagnosis of the latent, labile, or prehypertensive state than is the cold pressor test. Angiotensin-induced hypertension induces a prolongation of the A.S.T. as compared with control periods.

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References

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