Heart “Sympathin”

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In view of the growing recognition of the pathogenic role of the adrenosympathetic humoral neurotransmitters in the heart muscle as chemical anoxia-producing agents, cardiac “sympathin” was extracted and assayed both colorimetrically and biologically, and some of its chemical and pharmacodynamic properties were studied in detail. It proved to be at least in part identical with nor-epinephrine (arterenol) and to exert effects analogous to those of epinephrine and nor-epinephrine upon blood pressure, heart rate and the electrocardiogram (depression or inversion of the T wave). Its action was intensified by cocaine and counteracted by nitroglycerine.

The presence of a cardioacceleratory substance or substances in the heart muscle was discovered independently by Demoor,1 Haberlandt,2 and Löwi3 in the years 1922, 1924 and 1926. While Haberlandt4 denied, apparently on insufficient evidence, a derivation of his “Herzhormon” from the adreno-sympathetic system, Löwi5 identified his “Akzeleransstoff” with epinephrine released from the stimulated cardiac sympathetic nerves. Likewise, Cannon and Lissak6 and Bacq and Fischer7 considered the sympathomimetic material, isolated by them from the myocardium of cats and man, as being epinephrine. Gaddum and Khayyal8 and Hoffmann, Hoffmann, Middleton, and Talesnik9 described the liberation of an “adrenalin-like” substance into the coronary perfusion fluid, especially under the influence of acetylcholine, and McDowall10 made similar observations with minced heart muscle treated with acetylcholine. The presence in the heart of sympathomimetic catecholamines other than epinephrine has been made probable by colorimetric findings of Shaw11 and of one of us.12 Von Euler,13 having studied active heart extracts very carefully, has come to the conclusion that “the biological effects as well as the chemical tests seem to leave no doubt that the substance responsible for the sympathomimetic actions in the heart extracts is different from adrenalin, and is, instead, intimately related to some substance resembling nor-adrenalin.” (Adrenalin and nor-adrenalin are identical with epinephrine and nor-epinephrine respectively.)

Attempts at a quantitative assay of sympathomimetic catecholamines in the heart have been undertaken with colorimetric and biologic methods by several investigators (table 1). In order to study the cardiovascular and electrocardiographic effects of the cardiac sympathomimetic amines in detail, as well as to correlate these effects quantitatively with the results of the colorimetric assay of these amines, the following experiments were carried out.

Methods

(a) For the chemical assay of the cardiac catecholamines the colorimetric method of Shaw11 was used on heart tissue and heart extracts in its modification by one of us.14

(b) Extracts of fresh hearts from cows, hogs and humans were prepared with a method, recently described by von Euler14 for the extraction of sympathomimetic amines from various tissues. It is based on the same principle of isolation of these amines through adsorption by and subsequent elution from aluminum hydroxide as Shaw’s colorimetric method and is, therefore, particularly well suited for quantitative comparison of the biological and colorimetric results. Before intravenous injection, the acid extracts were brought to pH 7.0 to 7.5. The dosage of the heart extracts was determined on the basis of their colorimetric readings and expressed in “gamma-equivalents,” each gamma-equivalent corresponding to the chromogenic effect of one gamma of epinephrine.

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(c) All biologic tests were carried out on atropinized cats under Nembutal anesthesia under artificial respiration and with the adrenals tied off. The extracts and other solutions were injected within 2 seconds into the left femoral vein in volumes of 4 to 6 cc. The blood pressure was recorded from a common carotid artery with a mercury manometer. Coincidence of the electrocardiograms with the blood pressure curve was established through a mechanical connection between the switch of the electrocardiograph and a time marker on the kymograph.

The blood pressure curve, heart rate curve and curves representing the variations of the amplitude of the T wave above and below the electrocardiographic base line, were reconstructed on coordinate paper. Lead II and the chest leads CR1 and CR4 or V1 and V4 were registered, but only those leads where the T wave was frankly positive at the beginning of the experiment were used for the final analysis.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Species from which material was obtained</th>
<th>Method used</th>
<th>Calculated gamma per gram of heart muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Löwi (5)</td>
<td>Frog</td>
<td>Response of frog heart</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Shaw (11)</td>
<td>Frog</td>
<td>Colorimetry*</td>
<td>0.3-1.2</td>
</tr>
<tr>
<td>Shaw (11)</td>
<td>Rabbit</td>
<td>Colorimetry*</td>
<td>0.015-0.04</td>
</tr>
<tr>
<td>Cannon and Lissak (6)</td>
<td>Cat</td>
<td>Cat blood pressure</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Raab (12, 50)</td>
<td>Rat</td>
<td>Colorimetry*</td>
<td>0.3-1.9</td>
</tr>
<tr>
<td>Raab &amp; Humphreys (32)</td>
<td>Cat</td>
<td>Colorimetry*</td>
<td>0.9-1.8</td>
</tr>
<tr>
<td>Raab (14)</td>
<td>Man</td>
<td>Colorimetry*</td>
<td>0.3-1.1</td>
</tr>
<tr>
<td>Raab (51)</td>
<td>Cow</td>
<td>Colorimetry*, cat bl. pr.</td>
<td>1.2-2.0</td>
</tr>
<tr>
<td>Bacq and Fischer (7)</td>
<td>Man</td>
<td>Nictitating membrane</td>
<td>0.3†</td>
</tr>
<tr>
<td>von Euler (13)</td>
<td>Cow, horse, cat</td>
<td>Cat blood pressure</td>
<td>5.0</td>
</tr>
</tbody>
</table>

* Based on color units equivalent to 0.001 gamma of epinephrine (see Comment, Chemical nature).
† Up to 54% had been lost during the extraction procedure.

(d) Paper-chromatography was applied to several extracts in an attempt to identify the chemical nature of the active substance, obtained from the heart, by means of the method described by James.16 The paper strips were developed with potassium ferricyanide. These tests were carried out by Dr. Wm. v. B. Robertson.

(e) The serum potassium concentration was determined with a flame photometer in specimens, withdrawn from the right femoral artery through polyethylene tubing. These assays were also carried out by Dr. Robertson.

**Results**

**Blood pressure.** Usually, the pressor effect of freshly prepared heart extracts was equal or near equal to that of amounts of epinephrine which gave qualitatively and quantitatively the same colorimetric readings (fig. 1). Analogous amounts of dl-nor-epinephrine produced pressor effects similar to those elicited by epinephrine (figs. 1 and 2). In several experiments the cardiovascular effects of the heart extracts were compared only with those elicited by dl-nor-epinephrine (identical with dl-arterenol) (figs. 2 and 3, and table 2).

As a rule, the elevation of the blood pressure caused by the heart extracts was preceded by a more or less marked transient fall of blood pressure, ranging from −10 to −45 mm. Hg.
especially when larger doses were used (figs. 2, 3, and 7); the peak of the blood pressure curve was reached somewhat later and the descent of the curve was slower than after injection of epinephrine or nor-epinephrine (figs. 2 and 3). In some experiments, the pressor effect of the heart extract appeared considerably weaker than that of an equi-chromogenic amount of epinephrine or of an analogous amount of nor-

of 10-30 (average 22) gamma equivalents, the accelerations ranged from 16 to 65 (average 38) beats per minute. The degree and duration of this cardioacceleratory effect corresponded closely to that produced by equi-chromogenic doses of epinephrine and by analogous doses of nor-epinephrine (table 2). A brief initial period of bradycardia was due to cooling of the sinus node by the injected fluid.

**Table 2.**—Comparison of the Cardiovascular Effects of Sympathin-Containing Heart Extracts with Those of Epinephrine and dl-Arterenol in Seven Representative Experiments

<table>
<thead>
<tr>
<th>Substance injected</th>
<th>Dosage</th>
<th>Maximal rise of: Blood pressure (mm Hg).</th>
<th>Heart rate (beats per min.)</th>
<th>Maximal depression (mm) of T wave in leads:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart extract (sympathin)</td>
<td>10 gamma equ.*</td>
<td>+15</td>
<td>+18</td>
<td>−−</td>
</tr>
<tr>
<td>Heart extract (sympathin)</td>
<td>10 gamma</td>
<td>+62</td>
<td>+15</td>
<td>−−</td>
</tr>
<tr>
<td>Heart extract (sympathin)</td>
<td>30 gamma equ.*</td>
<td>+45</td>
<td>+20</td>
<td>−−</td>
</tr>
<tr>
<td>Heart extract (sympathin)</td>
<td>30 gamma</td>
<td>+125</td>
<td>+15</td>
<td>−−</td>
</tr>
<tr>
<td>dl-Arterenol</td>
<td>30 gamma equ.*</td>
<td>+5</td>
<td>+45</td>
<td>−−</td>
</tr>
<tr>
<td>dl-Arterenol</td>
<td>30 gamma</td>
<td>+85</td>
<td>+25</td>
<td>−−</td>
</tr>
<tr>
<td>Heart extract (sympathin)</td>
<td>20 gamma equ.*</td>
<td>+50</td>
<td>+65</td>
<td>−−</td>
</tr>
<tr>
<td>Heart extract (sympathin)</td>
<td>20 gamma</td>
<td>+56</td>
<td>+70</td>
<td>−−</td>
</tr>
<tr>
<td>dl-Arterenol</td>
<td>15 gamma equ.*</td>
<td>+82</td>
<td>+30</td>
<td>−−</td>
</tr>
<tr>
<td>Heart extract (sympathin)</td>
<td>15 gamma</td>
<td>+86</td>
<td>+32</td>
<td>−−</td>
</tr>
<tr>
<td>dl-Arterenol</td>
<td>10 gamma equ.*</td>
<td>±0</td>
<td>+45</td>
<td>−−</td>
</tr>
<tr>
<td>dl-Arterenol</td>
<td>10 gamma</td>
<td>+65</td>
<td>+35</td>
<td>−−</td>
</tr>
</tbody>
</table>

* Colorimetrically determined.

Electrocardiogram. The changes of the electrocardiogram, elicited by the heart extracts, showed a striking analogy with those produced by corresponding amounts of epinephrine or nor-epinephrine* (figs. 2 and 3, and table 2). They consisted, as a rule, of a depression and/or inversion of the T wave between the 10th and 40th to 150th seconds, sometimes followed by a transient elevation of the T wave. A frequently occurring oscillation of the T wave within the first few seconds after injection is unspecific, as it was also seen after injection of plain Ringer solution. It seems to have been due to cooling of the subendocardial ventricular
muscle layers through the injected fluids, which were kept at room temperature."

In four out of sixteen experiments there was no significant depression of the T wave during the period of the 10th to the 150th second. In these instances, the T wave remained un-

The analogy of the electrocardiographic effects of the heart extracts with those produced by epinephrine and nor-epinephrine was not affected by the presence in the heart extracts of depressor impurities which interfered in varying degrees with their pressor action (fig. 3).

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**Fig. 2.** — The effect of sympathin, extracted from the heart muscle, upon the direction and amplitude of the T waves above and below the electrocardiographic baseline (Leads V1 and V4) and upon the heart rate of the atropinized cat is practically identical with that of equi-pressor amounts of nor-epinephrine (identical with arterenol). Time given in seconds from the beginning of the injection. Separate time scales for the kymogram and the plotted curves. (Cont'd on facing page)

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changed or became even temporarily elevated. The blood potassium, which was determined in three such experiments, showed an increase which approximately coincided with the elevation of the T waves (fig. 4). Similar reactions had been observed in some experiments with epinephrine and nor-epinephrine, but with increasing doses the typical depression of the T wave could be elicited.

**Nature of interfering depressor material.** The following findings seemed to support the assumption that the usual initial fall of the blood pressure, as well as the occasional marked weakening of the pressor effect of the heart extracts or its replacement by outright depression, might be caused by the presence of histamine or of a histamine-like substance in the heart extract:
(1) Injection of a combination of nor-epinephrine with histamine acid phosphate produced blood pressure curves which were very similar in shape to the curves produced by depressor heart extracts, containing an equivalent amount of colorimetrically determined cardiac sympatlin (fig. 5). Two to twenty gamma of histamine base per gamma of nor-epinephrine increased the depressor and enhanced the pressor effect of otherwise depressor heart extracts (fig. 6) but did not eliminate the depressor action. (Neohetramine is incapable of counteracting large doses of histamine⁸ [fig. 6]).

(3) Histamine did not interfere with the cardioacceleratory and with the characteristic electrocardiographic effects of nor-epinephrine.
which had been subjected alone to the identical procedure, could not be recovered in the final extracts by means of the colorimetric method of Rosenthal and Tabor.\textsuperscript{19} Whether another histamine-like substance which cannot be de-

![Diagram](image)

**Fig. 3.**—The effect of sympathin, extracted from the heart, upon the T wave (Lead II) and heart rate is independent of the inhibition of its pressor effect, due to the presence of contaminating depressor substances with histamine-like action (nor-epinephrine derivatives?). Comparison with nor-epinephrine. Time in seconds.

ected with this method is involved, would have to be investigated with a different technic.

Attempts to destroy the interfering depressor material by incubating either the heart muscle or the final extracts with histaminase-containing tissue extracts at pH 7.5 gave inconclusive results, as the added extracts produced strong depressor effects by themselves.

The fact that von Euler's heart extracts (after having been purified from other contaminants) appeared to be relatively free from depressor actions, has been attributed by him\textsuperscript{20} to the difference in dosage, in that his experiments were carried out with much smaller doses than those which we needed in order to provoke electrocardiographic responses.

In view of the existence of N-alkyl-homologues of epinephrine with similar cardioacceleratory and T-wave depressing,\textsuperscript{21–23} as well as chromogenic, properties, but with a vasodepressor action,\textsuperscript{21, 24–25} the possible presence of such substances in the heart extracts was also taken into consideration. However, this appears most unlikely, as the combined injection of such substances (N-isopropyl- and N-ethyl-epinephrine) with nor-epinephrine produced blood pressure curves which differed significantly from those produced by partly depressor heart extracts, in that the depressor effect occurred always belatedly after an initial elevation.

Finally, the possibility of the presence of unidentified depressor derivatives from nor-epinephrine must be considered.\textsuperscript{57}

**Modification of cardiovascular effects of heart sympathin by cocaine.** In four experiments, heart extracts (5–30 gamma equivalents) were injected before and after cocaine (30–50 mg. intraperitoneally). An intensification of the pressor effect (fig. 7) like that which is characteristic for both epinephrine and nor-epinephrine,\textsuperscript{13} and a rather insignificant increase of cardiac acceleration were observed, as far as interfering arrhythmias (atrioventricular block, ventricular fibrillation and cardiac alternans which occurred only after cocaine pretreatment) permitted. In two experiments, the T-wave depressing effect of the heart extracts was markedly intensified after cocaine; in two other experiments, with an elevation of the T wave, this was slightly to markedly diminished in two leads.

**Modification of cardiovascular effects of heart sympathin by nitroglycerine.** In view of the fact that nitroglycerine had been found to weaken not only the pressor but also the cardioacceleratory and T-wave depressing effects of epinephrine and nor-epinephrine,\textsuperscript{26} three experiments
were carried out in which heart extracts were injected alone and simultaneously with nitroglycerine (4–6 mg. intravenously), as well in that the T-wave depressing effect of heart sympathin (5–30 gamma equivalents) was weakened or entirely abolished.

**Figure 4.**—The occasional absence of a distinct depression of the T wave and its replacement by an elevation may be explained by a transient increase of the arterial serum potassium level, as has also been seen after injection of epinephrine or nor-epinephrine (arterenol). (The potassium levels at different stages of the experiment are indicated by the symbol K⁺ m. equ.)

as equal amounts of nitroglycerine alone as control. The results were similar to those obtained with epinephrine and nor-epinephrine. Stability of heart sympathin. In the intact dead heart, or in mash made from fresh heart muscle, the effectiveness of the cardiac sym-
Heart sympathin began to decline after about twenty-four hours in the refrigerator, and it almost disappeared within forty-eight hours, while the acid extracts remained fully active for several days.

**Fig. 5.**—In some heart extracts, the pressor action of sympathin (determined colorimetrically) seems to be entirely overshadowed by depressor contaminants. The depressor curve, elicited by these extracts, can be imitated by the combination of analogous amounts of nor-epinephrine (arterenol) with histamine. (Top curve, cow heart sympathin [10 gamma equ.]; middle curve, dl-arterenol [10 gamma] + histamine acid phosphate [600 gamma]; bottom curve, dl-arterenol [10 gamma].)

**Paper chromatography of heart extracts.** This procedure gave definite evidence of the presence of nor-epinephrine in the heart extracts. The 

\[ R_f \]

value and the color, obtained upon development, were identical with those of nor-epinephrine. Since no quantitative evaluation of the nor-epinephrine, detected by paper chromatography, has yet been undertaken, the question remains open as to whether the chromogenic and biologically active material in the heart muscle consists entirely of nor-epinephrine or whether some other undefined related substances are also present. However, no other catecholamines, including epinephrine, which are capable of forming adrenochromes, could be demonstrated in the heart extracts.

**Comment**

Our results confirm the statements of other investigators regarding the presence in the...
heart of sympathomimetic amines (heart "sympathin"), possessing chromogenic and biologic properties similar to those of epinephrine and particularly of nor-epinephrine. The cardiovascular effects of heart sympathin, as well as its chemical nature and pathophysiologic significance, have been studied in further detail.

**Cardiovascular effects.** In addition to the pressor and cardioacceleratory effects, the action of cardiac sympathin upon the electrocardiogram was found to be practically identical with that exerted by equi-chromogenic and equipressor amounts of epinephrine and by analogous amounts of nor-epinephrine, even in those instances in which the pressor effect was partially or entirely masked by contamination of the heart extracts with depressor impurities.

The characteristic depression and/or inversion of the T wave, elicited by extracted and injected cardiac sympathin, like those elicited by injected epinephrine and nor-epinephrine, or by stimulation of the cardiac sympathetic nerves (sympathin discharge), are attributable to the specific action of these sympathomimetic amines and their derivatives upon the myocardial cell metabolism. This chemical action results in excessive, wasteful oxygen consumption by the heart muscle and in consecutive myocardial hypoxia, despite simultaneous coronary dilatation which does not suffice to compensate fully for the rapid consumption of oxygen. Recent observations have shown a remarkable degree of independence of the electrocardiogram from the coronary blood flow.

According to Kisch, the stimulation of oxygen consumption is not due solely to epinephrine itself, but rather to a quinoid oxidation product of epinephrine (omega adrenochrome) which is formed through enzymatic interference in the tissues. This view seems to be compatible with our recent observation that doses of adrenochrome which exert only a slight pressor activity can elicit a T-wave inverting (hypoxia-producing) effect on the electrocardiogram.

In a few instances, the sympathin-containing heart extracts failed to depress the T wave. This was probably due to a simultaneous increase of serum potassium which is known to elevate the T wave. Epinephrine mobilizes potassium from the liver and the same seems to be true regarding cardiac sympathin (fig. 4).

Like the cardiovascular effects of epinephrine and nor-epinephrine, those of cardiac sympathin were partly accentuated by cocaine (fig. 7) and weakened or abolished by nitroglycerine (blood pressure, T-wave depression).

**Chemical nature.** As far as the chemical identity of the chromogenic and biologically active heart sympathin is concerned, it can be stated on the basis of paper-chromatographic tests, that nor-epinephrine constitutes at least a substantial part of it and may possibly be identical with it in its entirety. This would be compatible with the pharmacodynamic and colorimetric tests, carried out by von Euler. However, if we do assume a total identity of the chromogenic and sympathomimetic material, extracted from the heart, with nor-epinephrine, there remains a discrepancy to be explained, in that the maximally pressor extracts appeared both equi-chromogenic and equi-pressor with epinephrine, while the color effect of pure nor-epinephrine is weaker (about one third) and its pressor effect stronger (about twice) compared with those of epinephrine. It is pos-
sible that even the maximal pressor effects, produced by heart extracts, were the results of a compromise between a per se stronger nor-
epinephrine action and the counteraction of interfering vasodepressor contaminants which, in some instances, were, in fact, powerful enough to dominate the picture.

Epinephrine was not demonstrable by paper-
chromatography in the hearts of animals which had been killed rapidly in the slaughterhouse. In case of an identity of all cardiac sympat
thin with nor-epinephrine, the colorimetric readings, obtained with the method of Shaw\textsuperscript{11, 12, 14, 22, 59, 54}
would have to be multiplied by three, and, thus, would closely approach the figure given by von Euler\textsuperscript{23} (see table 1).

\textit{Origin.} The original formation of cardiac sympathin or of its immediate precursors takes place, in all likelihood, within the ganglia and postganglionic fibers of the cardiac sympathetic nerves, from which it is discharged through a process of “neurosecretion” into the myocardial effector cells. Stimulation of the cardiac sympathetic nerves has been shown to be followed by an increase of the myocardial sympathin concentration,\textsuperscript{32} cardiac denervation, on the contrary, by a partial depletion.\textsuperscript{52} The fact that this depletion is never a complete one, seems to support the contention that neurosecretory sympathetic structures exist also inside the heart muscle itself, as suggested by both morphologic\textsuperscript{53–56} and biologic\textsuperscript{34, 37, 49} findings. Finally, the heart muscle possesses an outstanding ability to absorb and accumulate epinephrine and related compounds from the circulating blood.\textsuperscript{14} Nor-epinephrine has only recently been recognized as forming a substantial part of the adrenal medullary secretion.\textsuperscript{54–56}

An increase of the concentration of epineph-
rine-like substances in the heart has been ob-
served colorimetrically not only after injection of epinephrine, but also after physical exercise, exposure to cold, and administration of agents which are known to elicit the discharge of epi-

nephrine and nor-epinephrine (acetylcholine,\textsuperscript{47} insulin\textsuperscript{14}) finally also in thiamin deficiency.\textsuperscript{48}

\textit{Pathogenic significance.} The presence in the heart of relatively large quantities of such a powerful and potentially injurious hypoxia-pro-
ducing agent as nor-epinephrine, must be con-
sidered as being of fundamental significance for the understanding of many physiologic and pathologic functional states of the heart.\textsuperscript{46}

Abnormally high concentrations of catechol-
amines, either identical with or related to nor-
epinephrine and epinephrine, have been demonstrated colorimetrically in the hearts of individuals who had died in uremia,\textsuperscript{42} in congestive cardiac failure\textsuperscript{44} or who had succumbed to a sudden, otherwise unexplained cardiac death.\textsuperscript{43–45}

The probable role of sympathomimetic amines in the heart muscle in the pathogenic mechanism of thyrotoxic heart disease and of angina pectoris has been discussed elsewhere.\textsuperscript{46}

\textbf{SUMMARY}

The heart muscle of cattle, hogs and humans was shown to contain relatively large amounts of pharmacodynamically potent sympathomimetic material ("sympathin") which was found to be at least in part chemically identical with nor-epinephrine (arterencl), and which may be possibly identical with nor-epinephrine in its entirety.

When extracted from heart muscle and injec-
ted into atropinized cats in colorimetrically determined doses, heart sympathin elicited cardio-
vascular effects (elevation of blood pressure, cardiac acceleration, depression and/or inver-
sion of the T wave) equivalent to those of equi-pressor and equi-chromogenic doses of epi-

nephrine or analogous doses of nor-epinephrine. In some extracts, the vasopressor effect was largely masked by histamine-like-acting de-
pressor contaminants which, however, were not identical with histamine (nor-epinephrine der-
ivatives?), and which did not interfere with the specific cardiac effects of heart sympathin.

The action of heart sympathin was modified by cocaine and by nitroglycerine in the same manner as that of epinephrine and nor-epineph-

The neurosecretory origin and the patho-
physiological significance of heart sympathin were briefly discussed, with particular emphasis on the widely disregarded ability of epinephrine and nor-epinephrine to elicit hypoxia of the heart muscle by chemically inducing an ex-
cessive and wasteful oxygen consumption in
the myocardium, irrespective of coronary blood flow.

Acknowledgments

We are indebted to Dr. William v. B. Robertson for carrying out the paper-chromatographic tests and serum potassium determinations, and to Dr. M. L. Tainter of the Sterling-Winthrop Research Institute for the supply of dl-arterenol (dl-nor-epinephrine).

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