Experimental Study on the Blood Pressure of Pregnant Hypertensive Rats*

II. THE MECHANISM OF THE FALL OF BLOOD PRESSURE AT LATE PREGNANCY IN EXPERIMENTALLY HYPERTENSIVE RATS

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EVIDENCE^{1,2,3,4,5,6)} that the high blood pressure of renal hypertensive rats reduced moderately at late pregnancy has been confirmed⁷⁾ in several other kinds of experimental hypertension such as DCA and Post DCA hypertension, adrenal regeneration hypertension, and salt hypertension and in spontaneous hypertension which was maintained in our laboratory⁸⁾.

From the above findings the blood pressure fall during pregnancy may be a phenomenon essentially associated with pregnancy and have no direct relation to the pathogenesis of the hypertension.

There have been about 4 hypotheses about the mechanism of this phenomenon; 1) anti-pressor activity due to placenta^{3,4,9)}, 2) anti-pressor activity due to fetus kidney^{5,10)}, 3) endocrine change during pregnancy^{2,11)} and 4) hemodynamic changes during pregnancy^{1,3,5,6,9,11)}, but the final clarification of this finding has not been attained.

So this study was designed to investigate the above mechanism by examining the effect of the following procedures on blood pressure of hypertensive rats; 1) fetal ablation of hypertensive pregnant rat, 2) new born kidney, liver, or spleen transplantation to peritoneum of hypertensive rat, and 3) placenta transplantation to peritoneum of hypertensive rat or parenteral administration of placental homogenate to hypertensive rat.

EXPERIMENTAL MATERIALS AND METHODS

Wistar strain rats supplied by the Animal Center of Kyoto University were used in this study. These rats were fed on boiled wheat and fish seasoned with a little salt (0.3% Na) and vegetable and tap water or 1% sodium chloride solution for drinking ad libitum. New born rats born from normal parents in our laboratory were used for transplantation experiments within 24 hours after delivery.

Renal infarction hypertension was induced by ligation of the bilateral posterior branches of the main renal artery as described by Loomis¹²⁾. Renal ablation hypertension was carried out by the method reported by Koletsky¹³⁾.

The systolic blood pressure was determined indirectly without anesthesia at the tail by the plethysmographic method^{8,14)}. The cuff width was 15 mm. The animals were kept for 10 min. in a box kept at 37°C, then put in the measuring box also at 37°C. Then 3–5 rounds of measurement were done and the most stable values were adopted. A level of 150 mm of mercury or greater was considered in the hypertensive range.

1. Fetal Ablation

Under light ether anesthesia uteruses of the 16th day of pregnancy in 6 rats with renal infarction hypertension were exposed through an anterior midline abdominal incision. Then a surgical needle was inserted into each amnion sac through the uterine wall and the head of the fetus was destroyed.

A similar sham operation except for the uterine manipulation was carried out as above described on 7 rats with renal infarction hypertension. The operation was kept as sterile as possible. After the opera-

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TABLE I EFFECT OF FETAL ABLATION ON

	Animal Number	Duration of Hyper- tension (days)	Number of Fetus or Young	Litter Weight (g)	Systolic Blood								
					Before Mating	After Mating							
						2	4	6	8	10	12	13	14
Fetal Ablation Group	R97	117	8		198	216	210	234	206	194	206	232	222
	R99	117	9		197	186	184	194	204	204	203	216	196
	R103	108	8		201	198	196	212	230	226	214	218	216
	R109	85	11		243	234	234	236	234	234	216	246	230
	R150	68	12		229	220	234	240	232	218	226	226	230
	R153	44	12		165	156	160	164	166	164	172	162	166
	R161	99	10		201	196	204	208	210	220	210	198	186
	Average	44-117	10 ±1		205 ±9	201 ±9	202 ±9	213 ±10	212 ±8	209 ±8	207 ±6	214 ±9	207 ±9
Sham Operation Group	R100	112	10	55	255	254	260	252	240	234	248	236	250
	R106	57	5	25	191	204	204	226	222	250	220	232	226
	R111	86	9	40	241	260	260	252	240	260	260	260	256
	R149	70	10	48	190	168	192	184	184	194	180	178	174
	R159	99	5	25	215	214	216	212	210	210	218	226	224
	R164	109	10	50	211	196	216	220	204	212	204	204	204
	Average	57-112	8 ±1	41 ±5	217 ±10	216 ±14	225 ±11	224 ±10	217 ±8	227 ±10	222 ±9	223 ±11	222 ±11

Note: ± Standard Error

tion dihydrostreptomycin sulfate, 0.02 gm; procain penicilline-G, 12,000 units; and penicillin-G potassium, 4,000 units were administered intraperitoneally. Again the next day the drugs were injected subcutaneously.

The blood pressure was determined every other morning during the first half of pregnancy and in the postpartum period (for 12 days) and every day in the second half of pregnancy. The prepregnancy level of blood pressure was calculated as an average value of three determinations during the week before pregnancy. The duration of hypertension of the rats in this experiment was less than 4 months.

2. Transplantation Experiments

1) New born kidney transplantation to peritoneum. In 7 rats with renal infarction hypertension and 3 rats with renal ablation hypertension, total new born kidneys of one litter were transplanted to the peritoneum without anesthesia as follows (principally according to the method reported by Muirhead et al.¹⁵⁾).

a) The new born kidneys of one litter were removed without anesthesia through dorsal incision.

b) The kidneys were placed in Gey's solution (3-4 ml) in a small Waring blender without any manipulation and the blender was operated for 30 sec..

c) The mixture was filtered through a siliconized sieve (32 meshes per inch) into a beaker. A small volume of Gey's solution was added through the sieve to assist in this procedure.

d) The suspended bits of tissue were centrifuged in a glass tube (2,000 r. p. m.), washed once in abundant Gey's solution by agitating them back into sus-

pension, then recentrifuged.

e) The final cell suspension was made up to 0.5-2.0 ml. To this suspension an antibiotic mixture was added so as to contain in the final volume the following: polymyxin B sulfate, 2,000 unit; neomycin sulfate, 2.5 mg.

f) The final suspension was injected into the peritoneal cavity of the renal hypertensive rat. The entire procedure, from removing the new born kidney to the injection, required about 15-25 minutes.

2) New born liver or spleen transplantation to peritoneum. In 8 rats with renal infarction hypertension, the livers of one or half a litter were transplanted to the peritoneum. In 2 rats with renal infarction hypertension, the spleens of one or 4 litters were also transplanted to the peritoneum. Both tissues were prepared as were the new born kidneys.

3) Placenta transplantation to peritoneum and parenteral injection of placental homogenate. In 4 rats with renal infarction hypertension, the placentas of one litter were transplanted to the peritoneum. The placentas of the last day or 18th day of pregnancy of normal females were handled as were new born rat kidney. The placental homogenate was prepared as follows.

a) Placenta of the last days of pregnancy was removed, segmented in a small block, and then placed in Gey's sol. (equivalent to 2 times the wet weight of placenta in volume) in a small Waring blender for 2 min..

b) The mixture was filtered through a siliconized sieve (32 meshes per inch).

c) The filtrate was mixed with antibiotic mixture as in the above. This placental homogenate was administered intraperitoneally or subcutaneously once

THE BLOOD PRESSURE OF HYPERTENSIVE RAT

Pressure (mmHg)															
(Days)															
15	16	17	18	19	20	21	22	23	24	25	26	28	30	32	34
230	234	192	228	182	208	224	222	230	240	228	212	216	216	234	231
198	210	186	196	210	198	200	204	210	200	196	194	192	206	208	208
226	228	190	216	226	210	190	216	200	216	220	222	224	208	186	226
230	254	228	224	248	226	212	214	256	238	230	246	204	220	210	230
234	226	210	210	210	218	224	220	224	226	220	226	230	242	232	240
158	156	160	158	162	156	160	160	150	154	164	164	156	164	160	162
200	190	206	214	186	206	206	176	204	200	204	216	216	200	220	220
211	214	196	207	203	203	202	202	211	211	209	211	205	208	207	217
±10	±11	±8	±8	±10	±8	±8	±9	±12	±11	±7	±9	±9	±8	±9	±8
250	250	200	210	192	146	154	186	226	240		228	226	260	256	256
224	220	232	232	242	210	158	172	182	214		220	220	244	250	226
258	256	260	244	200	154	133	158	186	226		232	220	246	256	260
180	186	172	162	170	168	138	152	162	200		186	190	200	186	190
206	192	210	196	222	192	186	204	212	206		228	200	232	232	240
202	200	200	200	210	196	176	176	200	206		206	214	220	200	210
220	217	212	207	206	178	158	175	195	215		217	212	234	230	230
±11	±11	±11	±11	±9	±9	±8	±7	±9	±6		±7	±5	±8	±11	±10

a day for 2-7 days, sometimes twice a day. The homogenate from placentas of 3 litters were injected into 3 renal hypertensive rats.

In these transplantation experiments, the blood pressure was usually determined every day after transplantation for a week. The first determination was usually at 12-15 hours after transplantaion. In the experiment on placental homogenate, the blood pressure was measured once a day (usually at 12-15 hours after injection) for 8-10 days after the first administration of placental homogenate. The pre-treatment level of blood pressure was expressed as the average value of 3 determinations obtained during the week before the treatment. The change of blood pressure after new born kidney transplantation was expressed not only as an absolute value but also as a percentage value to the pretreatment level of blood pressure. In the experiments with new born kidney transplantation, the mean value and the standard error were calculated for the measured blood pressure, etc. In these experiments, any change over 20 mmHg was considered significant.

Morphologic Observation

The uterus including its contents on the last day of pregnancy after fetal ablation and peritoneal transplants were fixed in 10% formalin and stained with hematoxylin and eosin.

RESULTS

1. Fetal ablation and the blood pressure of pregnant hypertensive rats.

As shown in Table I and Text-Fig. 1, in 6 renal hypertensive rats with fetal ablation on the 16th day of pregnancy the blood pressure did not change at any stage of pregnancy, though

the blood pressure was very carefully determined every other day or daily.

On the other hand, 7 renal hypertensive rats which had the sham operation showed a definite fall in blood pressure at late pregnancy.

The above findings suggest that fetuses in pregnant hypertensive rats might play a determinant role in the change of blood pressure during pregnancy.

In rat R161, a hysterectomy was performed at the last day of pregnancy under light ether anesthesia. Histological study of the uterus content revealed the surviving placenta and degenerated embryo (Fig. 1, 2).

Text-Fig. 1. The Effect of Fetal Ablation on the Blood Pressure of Hypertensive Rat.

Each Value in These Two Groups is the Average of Determinations in These Experimental Animals-6 Rats in Fetal Ablation Group and 7 Rats in Sham Operation Group.

M.: Mating S. O.: Sham Operation
F. A.: Fetal Ablation D.: Delivery

2. New born kidney transplantation to peritoneum.

As shown in Table II, the blood pressure declined more than 20 mmHg except in case RA8. The extreme value was usually observed at the first measurement of blood pressure after the transplantation, namely at 12–15 hours after it. It took 2 to 15 days (average 7 ± 1 days) to recover the pre-experimental level of blood pressure. The mean fall of blood pressure (37 ± 4 mmHg, $19.4 \pm 2.2\%$) was caused by a mean wet weight of 0.34 ± 0.03 g of new born kidney given per 100 gm body weight. The typical patterns of this experiment are seen in Ri1 and R47 (Text-Fig. 2).

3. New born liver or spleen transplantation to

peritoneum.

The blood pressure was not influenced significantly by liver or spleen transplantation as shown in Table III. A few examples are presented in Text-Fig. 2.

4. Placenta transplantation to peritoneum.

The blood pressure was not influenced significantly by placenta transplantation except for case Ri4 in which the blood pressure change 15 hours after the transplantation was 23 mmHg. (Table III, Text-Fig. 2).

5. Parenteral injection of placental homogenate.

In rat RA10, the blood pressure fluctuated but did not show any definite tendency to decrease as did the blood pressure in the other 2

TABLE II EFFECT OF THE NEW BORN KIDNEY TRANSPLANTATION TO PERITONEUM ON THE BLOOD PRESSURE OF HYPERTENSIVE RAT

Animal Number	Sex	Body Weight (g)	Duration of Hypertension (days)	Wet New Born Kidney Weight per 100 g Body Weight (g)	Systolic Blood Pressure Before Transplantation (mm Hg)	Minimal Systolic Blood Pressure After Transplantation (mm Hg)	Fall of Blood Pressure		Duration of Blood Pressure Fall (days)
							(mm Hg)	(%)	
Ri 1*	♂	190	25	0.37	181	144	37	20.4	7
Ri 2	♂	195	22	0.32	165	136	29	17.6	13
R 10	♀	180	92	0.48	171	110	61	35.6	5
R 25	♀	220	199	0.27	219	186	33	15.1	6
R 35	♀	195	139	0.31	206	176	30	14.6	5
R 37	♀	220	95	0.45	204	164	40	19.6	15
R 47	♀	155	93	0.19	175	132	43	24.6	10
RA8*	♀	220	139	0.18	205	190	15	7.3	2
RA16	♀	180	120	0.42	189	156	33	17.5	7
RA17	♀	185	110	0.40	197	150	47	23.8	4
Average		194 ± 6	22–199	0.34 ± 0.03	191 ± 5	154 ± 8	37 ± 4	19.4 ± 2.2	7 ± 1

Note: *R, Ri; Renal Infarction Hypertension + RA; Renal Ablation Hypertension ±; Standard Error

TABLE III EFFECT OF THE NEW BORN LIVER OR SPLEEN OR PLACENTA TRANSPLANTATION TO PERITONEUM ON THE BLOOD PRESSURE OF HYPERTENSIVE RAT

Organ for Transplantation	Animal Number	Sex	Body Weight (g)	Duration of Hypertension (days)	Wet Tissue Weight per 100 g Body Weight (g)	Systolic Blood Pressure (mm Hg)							
						Before Transplantation	After Transplantation (days)						
							1	2	3	4	5	6	7
Liver	R40	♀	145	43	0.45*	188	182	192	184	180	180	186	178
	R45	♀	145	43	0.45*	180	186	180	184	192	194	188	184
	R155	♀	245	126	0.69	197	192	194	200	200	186	210	194
	R166	♀	210	55	1.42	181	178	186	184	190	178	184	176
	R168	♀	205	55	1.42	203	204	208	218	202	192	196	220
	R170	♀	195	69	1.00	189	186	196	184	200	196	192	
	R171	♀	210	68	0.71	193	184	184	170	192	200	192	
	R172	♀	245	126	0.69	170	166	178	172	172	164		174
Spleen	Ri 3	♂	260	107	0.19+	172	168	156	186	178	168	176	180
	R169	♀	200	68	0.07	175	174	180	172	176	176	174	
Placenta	Ri 4	♂	260	125	$1.67 \pm$	193	170	180	194	190	194	192	186
	R48	♀	185	12	$3.27 \pm$	173	162	172		170	184		
	R164	♀	250	148	$2.14 \pm$	197	182	184	196	186	192	190	
	R174	♀	220	21	$2.74 \times$	163	170	170	164	160		166	

Note: * Liver from Half a Litter + Spleen from 4 Litters

$\pm$ Placenta of the Last Day of Pregnancy $\times$ Placenta of the 18th Day of Pregnancy

TABLE IV EFFECT OF INTRAPERITONEAL OR SUBCUTANEOUS INJECTION OF PLACENTAL HOMOGENATE ON THE BLOOD PRESSURE OF HYPERTENSIVE RAT

Animal Number	Sex	Body Weight (g)	Duration of Hypertension (days)	Wet Placenta Weight per 100 g Body Weight (g)	Number of Injection	Systolic Blood Pressure (mm Hg)									
						Before Injection	After the Onset of Injection (days)								
R 37	♀	225	85	2.46	5 (3)* in 4 days	199	182	190	184	200	192	212	198	202	
RA7	♀	205	69	1.46	3 (2) in 2 days	194	186	184	190	208	192		200	198	
RA10	♀	205	68	3.90	7 (3) in 7 days	193	166	206	202	164	196	202	166	192	186 186

Note: *The Number in Bracket Shows the Times of Subcutaneous Injection

animals (Table IV, Text-Fig. 2).

6. Morphologic Observation of transplants.

In new born kidney transplantation, there were some white or grey granules less than 1mm in size scattered over the peritoneum (such as the mesentery, or the undersurface of the diaphragm). Microscopic observation showed that the granules, even 34 days after transplantation, contained some viable epithelial cells in tubular structures or clumps embedded in a vascular stroma (Fig. 3). Epithelial cells in tubular pattern were also discovered in the peripancreatic lymph node (Fig. 4). In new born liver, spleen, and placenta transplantation, however, no definite viable structures of these organs were observed in any peritoneal surface or lymph node.

DISCUSSION

Many speculations about the mechanism of the fall of blood pressure at late pregnancy were reported but only a few experiments to investigate this mechanism have been preformed.

Goldblatt et al.¹⁰⁾ reported that most of the hypertensive dogs that became pregnant showed a moderate fall of blood pressure and that pregnant animals frequently withstood a degree of constriction of the renal artery which would kill a nonpregnant animal. They speculated that this might be a compensatory effect of the normal kidneys of the fetuses. Harrison et al.⁵⁾ and Grollman⁶⁾ also ascribed the fall of blood pressure at late pregnancy to the antihypertensive action of normal fetal kidney or the hemodynamic change at such a period. Page⁹⁾ suggested from his experimental study of the effect of fetal ablation on the blood pressure that the beneficial effect of pregnancy in renal hypertensive animals might be due to the presence of placenta, not fetus, and the increased destruction of angio-

Text-Fig. 2. A Few Example of Blood Pressure Change by Transplantation of New Born Tissue or Placenta or Parenteral Injection of Placental Homogenate.

R47, Ri1: New Born Kidney Transplantation

R45: New Born Liver Transplantation

Ri3: New Born Spleen Transplantation

R164, Ri4: Placenta Transplantation

RA10: Parenteral Injection of Placental Homogenate

tonin by angiotonase of placental origin or hemodynamic change during pregnancy. He⁷⁾ also administered the several hormones related to pregnancy such as estrone, progesterone, chorionic hormone and lactogenic hormone to experimentally hypertensive rat and found no definite change in blood pressure. Dill et al.¹⁶⁾ reported that the injection of sex hormones to hypertensive rabbit had no effect on blood pressure, al-

Fig. 1. The survived placenta of the last day of pregnancy in R161 after the fetal ablation. Well grown trophoblasts are shown.
H-E stain $\times 100$

Fig. 2. The degenerated embryo of the last day of pregnancy in R161 after the fetal ablation. Degenerated or necrotic embryonic tissue with some calcification may be seen.
H-E stain $\times 100$

though Armstrong¹⁷⁾ reported that progesterone moderately lowered the blood pressure of renal hypertensive rat. Foa et al.²⁾ suggested that the endocrine change at late pregnancy might cause the change of blood pressure at such a period. Dodson⁴⁾ stated that this phenomenon might be due to the presence of placenta judging from his experimental results on fetal ablation in rat. Summarizing the above reports, the cause of this phenomenon might be 1) antipressor substance or enzyme of placenta, 2) antipressor substance of fetus kidney, 3) endocrine change during pregnancy or 4) hemodynamic change during pregnancy.

The experimental data in this study on the effect of fetal ablation on the blood pressure during pregnancy are quite opposite to Dodson's and Page's. In my hypertensive pregnant rats with fetal ablation there was no definite fall in

Fig. 3. Tubules and clusters of epithelial cells in peritoneal granule on the 34th day after the new born kidney transplantation.
H-E stain $\times 400$

Fig. 4. Tubules of epithelial cells in peripancreatic lymphnode. Some viable epithelial cells in tubular structure are seen in medullary lymph sinus. H-E stain $\times 400$

blood pressure at late pregnancy such as seen in the sham operated group. The operation for fetal ablation was done with great care to prevent shock or infection after it. This result seemed to show that fetus, not placenta, was of importance in the definite fall of blood pressure at late pregnancy, although the cause of this discrepancy between this result and theirs is obscure and cannot be fully explained. The viable placenta as well as the degenerated embryo were ascertained after the operation by morphologic observation. As suggested by Haterius¹⁸⁾ and Kirsch¹⁹⁾, the placenta even after the fetal ablation apparently survived and functioned normally till term.

Now, it is of great importance and interest to study which organ in the fetus plays the decisive role in the fall of blood pressure at late pregnancy. For this purpose, a series of transplantation experiments as described previously

was planned. Only in those experiments involving new born kidney transplantation did the blood pressure of the experimentally hypertensive rats show a definite fall. And in this case some viable kidney cells were visible in the peritoneal granule or lymph node by histologic examination. Judging from these results, fetus kidneys might play an important role in this phenomenon. They may secrete some antihypertensive substance to reduce the high blood pressure of the experimentally hypertensive rats as suggested previously by Goldblatt¹⁰⁾ and Grollman⁶⁾. This situation may be analogous to that in diabetes mellitus which, according to some authors^{20, 21, 22)}, improves as the fetal pancreas begins to function.

There have been many reports about the antihypertensive action of adult kidney. Antihypertensive action of normal adult kidney had been studied mostly by transplantation of normal kidney to the hypertensive animal as follows. Kolff et al.²³⁾ reported a lowering of blood pressure in renoprival hypertensive dogs when the blood of the hypertensive animals was perfused through normal kidneys. Muirhead et al.²⁴⁾ demonstrated that grafting a normal kidney to the neck of a dog with sustained renoprival hypertension was followed by prompt lowering of arterial pressure in the hypertensive recipient, frequently to control level. Kolff²⁵⁾ observed the reduction of high blood pressure in experimental renal hypertensive dog by a similar method. Gomez et al.²⁶⁾ demonstrated a prompt lowering of arterial pressure in rats having hypertension induced by figure-of-eight ligature of kidney or DCA when the kidney of a normal rat was grafted to the groin of the hypertensive one. Muirhead et al.¹⁵⁾ reported that if the kidneys were removed and reimplanted immediately into the peritoneum as cell suspension, the development of renoprival hypertension was completely prevented in dog. Merrill et al.²⁷⁾ observed a decrease in the blood pressure of hypertensive man following the homotransplantation of a kidney from his twin brother. Tóth et al.²⁸⁾ reported that two intact kidneys, in the presence of two ischemic ones, prevented the development of hypertension in both parabiotic rats.

My experiments indicate that even the new

born kidney is able to display antihypertensive action similar to that of an adult one. When all the small new born kidneys in a litter are gathered, their total weight is about the same as an adult kidney. So it is not unreasonable that the new born kidneys from a litter supply as much antihypertensive action as an adult kidney.

Neither the injection of placental hemogenate nor placenta transplantation was significant in lowering the blood pressure in this study, though Sisson et al.^{29, 30)} isolated a hypotensive, smooth muscle-contracting principle from fetal placenta of the rabbit. They suggested it was a kind of polypeptide. Similarly Ichikawa³¹⁾ found a smooth muscle stimulating and hypotensive substance-arachidonic acid-in human placenta.

The effect of endocrine or hemodynamic change during pregnancy on blood pressure was not actively studied in this experiment but it is speculated that their role might not be so important.

On the other hand, Misrahy³²⁾ reported that histamine and adenosine were endogenously produced by the chick embryo during its development and that the content of histamine and of adenosine in the rat fetus is quite similar to that of chick. Kahlson et al.^{33, 34)} reported that urine excretion of histamine in rat greatly increased at late pregnancy and sharply decreased after delivery and that this increase of histamine excretion disappeared after fetal ablation. His experiment³⁵⁾ also presented fetal liver as the principal site of histamine formation. But, before one can discuss whether histamine or adenosine metabolism of pregnant rat including fetus has some relation to the blood pressure fall at late pregnancy or not, further investigations are required.

SUMMARY

The mechanism of the fall of blood pressure during pregnancy in experimentally hypertensive rats was studied in this report.

1. Fetal ablation carried out on the 16th day of pregnancy without damage to the placenta interfered with the fall of blood pressure in hypertensive rats with renal infarction.

2. Intraperitoneal transplantation of new

born kidney, liver, spleen or placenta as cell suspension or parenteral injection of placental homogenate to renal hypertensive rats was performed and the changes of blood pressure by these procedures were studied. In these studies, only new born kidney transplantation led to a definite fall of blood pressure. Histologically, the viable epithelial cells of new born kidney assumed a tubular structure or irregular cluster in the peritoneal granule or lymphnode.

3. Judging from these data, the fetus kidneys may play an important role in the fall of blood pressure at late pregnancy in experimentally and spontaneously hypertensive rats, that is, the fetus kidney may secrete some antihypertensive substances which can lower the blood pressure of pregnant hypertensive rat.

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