Adipsin expression at the protein and mRNA levels is greatly reduced in several distinct syndromes of obesity in the mouse: genetic obesity due to the db/db and ob/ob genes, and a chemically induced model secondary to neonatal exposure to monosodium glutamate. We considered first the possibility that the adipsin gene might be identical to the db or ob locus and the lowered expression of this protein might result from a mutation in this gene. We show here that the adipsin structural gene is located on chromosome 10 and hence is physically distinct from any obesity genes so far identified in the mouse. A major role for the adrenal gland and adrenal glucocorticoids in the aberrant regulation of adipsin in these models of obesity is indicated by several experiments. Adrenalectomy of the ob/ob mouse raises the circulating levels of adipsin protein and the amount of this mRNA in epididymal fat pads (5-fold), although neither is increased to the levels seen in lean controls. Exogenous administration of corticosterone completely blocks the effects of adrenalectomy on adipsin, suggesting that the effect of this endocrine ablation is through reduction of adrenal glucocorticoids. Corticosterone administration also causes suppression in the levels of adipsin mRNA and protein in lean mice, although this decrease is never as severe as that seen in obese mice. The effect of exogenous corticosterone in lean mice occurs within 2 days and hence is not secondary to the obesity which these hormones eventually elicit. These results indicate that glucocorticoids can regulate adipsin expression in vivo and strongly suggest that the hyperglucocorticoid state seen in certain obese models plays a significant role in lowering adiposin mRNA and protein levels. Quantitative analysis of these experiments suggests that other as yet unknown neuroendocrine factors also function to suppress adipsin in obesity.

Obesity, defined as excessive adipose mass, is a heterogeneous disorder that causes substantial morbidity and mortality. At the cellular level, obesity arises when there is an increased amount of lipid/fat cell and/or an increased number of adipocytes. Studies using experimental animals have shown that obesity can be produced either through hyperphagia (Rothwell and Stock, 1979) or through lesions which affect the efficiency of caloric utilization (Olney, 1969; Pizzi and Barnhart, 1976; Cameron et al., 1978). Genetically obese rodents, such as the ob/ob or db/db mouse, illustrate that single autosomal genes can regulate both appetite and energy efficiency (Bray and York, 1979).

The role of the adipose cell itself in the genesis and maintenance of the obese state has been the subject of considerable speculation. Adipocytes may play a largely passive role in obesity, proliferating or filling with lipid excessively under the control of systemic fuels and neuroendocrine factors. However, circumstantial evidence suggests that signals deriving from fat cells themselves may be important in controlling certain aspects of whole body energy balance, perhaps by influencing appetite or thermogenesis (Faust et al., 1977).

The rate of lipid accumulation in fat cells and the proliferation of preadipose cells are likely to be influenced by the genes expressed in these cell types. Indeed, fat cells express a program of proteins and mRNAs which is quite distinctive from other cell types (Siddhu, 1979; Spiegelman and Green, 1980) and undoubtedly determines, in large measure, the ability of these cells to carry out their specialized function of energy storage. The cloning of several genes activated in fat cell differentiation (Spiegelman et al., 1983; Bernlohr et al., 1984; Chapman et al., 1984) has enabled us to study how fat cell gene expression may be perturbed in the adipose tissue of obese rodents. The mRNA for glycerophosphate dehydrogenase and adipocyte P2 appeared to be expressed at similar levels in lean and obese mice, while that encoding the serine protease adipsin was severely reduced (100-fold) in obese animals (Flier et al., 1987). This reduction was observed in the genetically obese db/db and ob/ob mouse and the chemically induced MSG1 mouse model but was not observed in hyperphagic "cafeteria-fed" rats.

This decrease in adipins levels represented the first reported marked change in the expression of a fat cell-specific gene in obesity. Adding additional interest is the observation that this protein, which is a novel member of the serine protease family, is found in the circulation and has several properties expected of a putative systemic regulator of energy balance (i.e. an adipostat) (Cook et al., 1987). This raises two fundamental questions: why is adipsin expression reduced in obesity and what are the physiological consequences of this reduction? In

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The abbreviations used are: MSG, monosodium glutamate; kb, kilobase(s).
this report we first demonstrate that the adipsin gene is distinct from the ob or db loci, indicating that the reduced expression in obese models is not a direct result of a genetic mutation. Furthermore, we have investigated the regulation of adipsin mRNA and protein in lean and genetically obese mice and find that the adrenal gland and adrenal glucocorticoids play an important role in the aberrant expression of adipsin in obesity.

**EXPERIMENTAL PROCEDURES**

**Hybrid Cell Lines**—The construction and characterization of the mouse x Chinese hamster hybrid of series I, EAS, and EBS have been described (Francke et al., 1977; Francke and Taggart, 1979). Hybrid lines were subcloned and expanded in culture, and chromosomes were analyzed at the time of DNA extraction.

**Southern Blot Hybridization**—Genomic DNA was extracted from cultured cells as described (de Martinville et al., 1982; Baas et al., 1984). Ten micrograms of hybrid and parental control cell DNA were digested with a 4–fold excess of EcoRI in high-salt buffer (Maniatis et al., 1982) containing 4 mm spermidine HCl. DNA fragments were separated by electrophoresis in 0.8% agarose and transferred to Hybond-N (Amersham Corp.) by the methods of Southern (Southern, 1979). Filters were pretreated and hybridized with gel-purified 32P-labeled (Feinberg and Vogelstein, 1983) adipsin insert (pAD20, Spiegelman et al., 1983) as previously described (Barton et al., 1987).

**RNA Blot Hybridization**—Epididymal fat pad RNA was isolated as described (Flier et al., 1987). Electrophoresis, blotting, and hybridization with the adipsin cDNA (PAD-20) was as reported (Spiegelman et al., 1983).

**Immunoblotting with Antiserum to Adipsin**—Five-microliter aliquots of sera from experimental animals were electrophoresed in 10% sodium dodecyl sulfate-polyacrylamide gels. Transfer and reaction conditions with antipeptide antibodies directed toward adipsin are as described (Cook et al., 1987).

**Animals**—Mice of the ob/ob genotype on the C57Bl/6 background and their lean litter mates were obtained from Jackson Laboratories (Bar Harbor, ME) or were bred at the Sansum laboratory from ob/+ breeding pairs obtained from the Jackson Laboratories. Animals were between 2 and 12 weeks old at the initiation of experiments. All were fed the standard mouse diet (Purina 5015) ad libitum.

**Adrenalectomy**—Bilateral adrenalectomy or sham surgery was performed on 5–6-week-old mice with methoxyflurane anesthesia as described previously (Dubuc and Wilden, 1986). Following surgery, all mice were allowed access to 0.9% saline in addition to tap water. The effect of the surgery was confirmed by radioimmunoassay of corticosterone. All serum corticosterone levels were determined in duplicate using radioimmunoassay methods from Cambridge Medical Diagnostics (Billerica, MA).

**Corticosterone Administration**—Corticosterone (free base, Sigma) was given either by subcutaneous injections or by implantation of time release pellets. For injection, corticosterone was dissolved in corn oil and injected at daily intervals. Control adrenalectomized mice received diluent alone. Time release pellets of corticosterone or placebo pellets were inserted subcutaneously.

**Materials**—[35S]Labeled protein A and other radionuclides were obtained from Du Pont-New England Nuclear. Corticosterone and placebo pellets were from Innovative Research of America (Gaithersburg, MD).

**RESULTS**

The Adipsin Gene Is Located on Mouse Chromosome 10 and Is Physically Distinct from the ob and db Genes—Because the levels of adipsin mRNA are greatly reduced in the db/db and ob/ob obese mice, we considered first the possibility that adipsin mRNA may be reduced as a consequence of a direct lesion in this gene in either of these models. Adding some plausibility to this notion was the observation that the adipsin mRNA in the ob/ob mouse is approximately 100 bases larger than in lean litter mates (Flier et al., 1987). Since the chromosomal locations of the ob (chromosome 6) and db (chromosome 4) genes are known, we addressed this possibility by determining the chromosomal location of the mouse adipsin gene. Using genomic DNA from 17 well characterized mouse x Chinese hamster hybrid cell lines and one mouse x rat hybrid, Southern blotting analysis was carried out to determine the correlation between adipsin coding sequences and the presence or absence of particular chromosomes. A single strongly hybridizing 5.9-kb fragment was detected in EcoRI digests of mouse DNA (Fig. 1, lane M) and in all hybrid cell lines that had retained mouse chromosome 10 (e.g., Fig. 1, lanes 5 and 8). A cross-hybridizing fragment of 1.9 kb was present in Chinese hamster DNA (e.g., Fig. 1, lane CH) and in all Chinese hamster x mouse hybrids (Fig. 1, lanes 1–8). The rat EcoRI fragment was 3.0 kb (not shown). All mouse chromosomes besides chromosome 10 were ruled out as possible sites for adipsin sequences by at least three discordant hybrids (Table I). These results indicate the presence of a single gene for adipsin on mouse chromosome 10 and rule out the possibility of the adipsin gene being identical to the ob or db genes.

Adipsin Expression in Adrenalectomized ob/ob Mice—The chromosomal mapping data imply that adipsin mRNA is reduced in obese mice because of aberrant regulation, as opposed to a direct genetic lesion. A role for the adrenals has been examined because the three mouse models showing aberrant adipsin regulation (db, ob, and MSG) have all been shown to have elevated glucocorticoid levels (reviewed in Bray and York, 1979; Tokuyama and Himms-Hagen, 1986), and adrenalectomy has been demonstrated to have marked effects on the adiposity of genetically obese rodents (Saito and Bray, 1984; Smith and Romsos, 1985; Tokuyama and Himms-Hagen, 1987).

Adrenalectomy was carried out on male ob/ob mice, and serum adipsin levels were determined by immunoblot assay 7 days later. Adrenalectomy was confirmed by radioimmunoassay of circulating corticosterone. As previously reported, adipsin levels were reduced in intact ob/ob mice (Flier et al., 1987), being 15% of those observed in the lean controls (Fig. 2). Adrenalectomy raised these levels to 60% of those seen in the lean animals. This experiment was performed on three separate sets of animals, and although there was some variability in the quantitative difference between adipsin levels in lean versus obese (obese ranging from 5 to 25% of control), adrenalectomy brought adipsin levels up in the ob/ob to approximately half that observed in the lean animals in every case. This experiment was also performed on female mice, and the same results were obtained (data not shown).

The effect of adrenalectomy on adipsin mRNA levels was also examined in a separate series of experiments. One week after adrenalectomy, epididymal fat pads were removed, and

**Fig. 1.** Southern blot analysis of EcoRI-digested Chinese hamster (CH), mouse (M), and mouse x Chinese hamster hybrid (lanes 1–6) DNAs using the adipsin cDNA as a probe. A single 5.9-kb fragment was detected in mouse DNA and in all hybrids retaining mouse chromosome 10 (lanes 5 and 8). The 1.9-kb cross-hybridizing Chinese hamster fragment serves as control in the lanes that are negative for the mouse fragment.
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Correlation of sequences detected by adipsin cDNA with mouse chromosomes in mouse x Chinese hamster somatic cell hybrids

Numbers of hybrids that are concordant (+/-) or discordant (+/+ or -/-) with the presence of mouse adipsin sequence are given for each chromosome. Hybrids in which a particular chromosome was structurally rearranged or present in fewer than 10% of cells were excluded.

| Hybridization/ Mouse chromosomes |
|-----------------------------|------------------|
| chromosome                  | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   | 12   | 13   | 14   | 15   | 16   | 17   | 18   | 19   | 20   |
| +/+                         | 4    | 4    | 1    | 2    | 0    | 3    | 4    | 2    | 3    | 3    | 0    | 5    | 1    | 1    | 4    | 2    | 4    | 4    | 4    |
| -/-                         | 6    | 5    | 6    | 8    | 7    | 6    | 4    | 6    | 10   | 11   | 11   | 8    | 9    | 7    | 3    | 6    | 3    | 9    | 6    | 4    |
| +/-                         | 0    | 1    | 4    | 3    | 5    | 2    | 1    | 3    | 2    | 0    | 5    | 0    | 3    | 3    | 1    | 1    | 1    | 2    | 1    | 0    |
| -/+                         | 5    | 7    | 6    | 4    | 3    | 5    | 7    | 5    | 2    | 0    | 1    | 3    | 3    | 5    | 9    | 6    | 9    | 3    | 5    | 7    |
| Total discordant            | 5    | 8    | 10   | 7    | 8    | 7    | 8    | 8    | 4    | 0    | 6    | 3    | 6    | 8    | 10   | 7    | 10   | 5    | 6    | 7    |
| Total informative           | 15   | 17   | 17   | 17   | 15   | 16   | 16   | 16   | 17   | 14   | 17   | 16   | 16   | 15   | 17   | 15   | 16   | 15   | 16   | 15   |

Fig. 2. The effect of adrenalectomy on circulating adipsin in ob/ob mice. ob/ob mice and their lean litter mates were obtained from Jackson Laboratories. Obese mice were adrenalectomized (ob/ob ADX) or sham operated (ob/ob) as described, and serum was collected 7 days later. Immunoblotting with antibodies to mouse adipsin and 125I-protein A was performed as previously described (Cook et al., 1987). The signal within the bracket reflects adipsin immunoreactivity, while the band above this is a nonspecific artifact of the reaction with this antisemur. Each sample represents a single mouse.

Fig. 3. The effect of adrenalectomy and replacement corticosterone on adipsin mRNA levels in ob/ob mice. The ob/ob mice were adrenalectomized as in Fig. 2, and epididymal fat pad RNA was isolated (Flier et al., 1987) 1 week after adrenalectomy from pools of four mice for each group. Some adrenalectomized mice were given daily subcutaneous injections of 200 or 500 μg of corticosterone. Blot hybridization with probes for B-actin and adipsin was as previously described (Flier et al., 1987). Ten micrograms of total mRNA were electrophoresed per lane. Lane 1, lean intact; lane 2, ob/ob intact; lane 3, ob/ob adrenalectomized, injected with corticosterone diluent alone; lane 4, same as lane 3 with daily 200-μg corticosterone injection; lane 5, same as lane 3 with daily 500-μg corticosterone injection.

RNA was purified and assayed by blot hybridization for levels of adipsin mRNA. The obese mice had adipsin levels reduced 50-fold compared to their lean litter mates (Fig. 3, lanes 1 and 2). Adrenalectomy stimulated a 5-fold increase in the level of this message (lane 3). This is true when adipsin mRNA is expressed per unit of total RNA and is also valid when normalized to the actin signal used as a hybridization control.

To assess whether glucocorticoids are responsible for all or part of this effect of adrenalectomy, some adrenalectomized animals received daily injections of replacement corticosterone. It is apparent that these corticosterone injections can completely reverse the effects of adrenalectomy on adipsin mRNA levels (Fig. 3, lanes 4 and 5). In other experiments (not shown), glucocorticoid injections also suppressed the rise in adipsin protein due to adrenalectomy.

Exogenous Corticosterone Can Suppress Adipsin Levels in Lean Animals—The experiments above indicate that adrenalectomy can achieve a partial reversal of the suppression of adipsin mRNA and circulating protein in the obese mouse. We next asked whether chronic corticosterone administration (for 2 weeks) could cause suppression of adipsin levels in lean animals. A clear suppression in adipsin mRNA level is seen with 10-mg pellets, and a 90% reduction is seen at the 25- and 50-mg doses (Fig. 4). This amount of adipsin mRNA is still approximately 10-fold higher than that observed in the ob/ob animals. In addition to assays of adipsin mRNA and protein, fat pad weight and circulating corticosterone values were also determined. Chronic glucocorticoid administration also caused a dose-dependent reduction in circulating adipsin from 10- to 50-mg doses (Fig. 5), but even at the highest corticosterone treatments (50 mg of pellet/animal), adipsin levels did not decrease to the low levels seen in the obese mice. In addition to the quantitative decrease in adipsin, it is...
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clear that this treatment also decreases the heterogeneity of this protein’s mobility on sodium dodecyl sulfate gels, as is also observed with the ob/ob sample (Flier et al., 1987). That the glucocorticoid treatment was effective in increasing adipose mass and circulating corticosterone levels can be observed in Fig. 6. A dose-dependent increase in fat mass was seen up to a dose of 50 mg/animal, where epididymal fat pads were approximately twice as heavy as in placebo controls. Similarly, serum corticosterone was elevated in animals receiving the glucocorticoid pellets, reaching values of 20 µg/dl with the 10-mg pellets to over 60 µg/dl at the 50-mg doses. Higher doses of corticosterone (100 mg) caused toxicity, and adipsin levels could not be analyzed.

These experiments indicate that experimentally increased levels of circulating glucocorticoids cause suppression of endogenous levels of adipsin mRNA and protein but even at very high doses do not cause the level of suppression in adipsin that is observed in the genetically obese mice.

**The Effect of Acute Corticosterone Administration**—The experiments presented above involved 2 weeks of glucocorticoid administration. In order to ascertain how quickly adipsin gene expression responds to glucocorticoids, lean mice were injected daily with 4 mg of corticosterone, and epididymal fat pads were harvested at 8 h and 2 days after the first injection. Fig. 7 illustrates that the decrease in adipsin mRNA cannot be observed 8 h after the first injection but becomes clearly visible by 2 days after the injections began. Adipsin mRNA decreases by day 2 to 32% of the level observed in control mice based upon loading equivalent amounts of total RNA. When normalized to the actin signal, the signal obtained from the treated mice is 43% of the control value. These data indicate that adipsin mRNA begins to drop well before any increase in fat pad weight is detectable and indicates that the change in adipsin levels is not secondary to the change in adiposity that this hormone stimulates.

**DISCUSSION**

The role of the fat cell in obesity has come under much discussion. While adipocytes clearly play a role as the major site for energy storage in most vertebrates, some physiological studies have suggested that fat cells play a significant role as a regulator of systemic energy balance (Faust et al., 1977). Such “adipostat” models have hypothesized a fat-produced circulating regulator of energy metabolism, but compelling evidence for such a molecule has been lacking. We have suggested that a systemic regulatory role for adipsin is possible because it is produced predominantly by fat, circulates in the bloodstream, and its mRNA level is regulated consistently during metabolic perturbations. In addition, adipsin belongs to a protein family (serine proteases; Cook et al., 1985, 1987) whose members play regulatory roles in other systemic functions such as blood clotting, blood pressure, and resistance to infections. The fact that adipsin is also profoundly reduced in some (but not all) models of rodent obesity suggests that an improved understanding of adipsin’s regulation in normal and obese animals could prove extremely useful to our understanding of gene control and energy balance.

We have used the cloned adipsin cDNA to assign the chromosomal locus for adipsin (Adn) to mouse chromosome 10. Loci associated with genetic obesity which have been mapped in the mouse include obese (ob, chromosome 6), diabetes (db, chromosome 4; Holmes, 1976) and adult obesity and diabetes (Ad, chromosome 7; Wallace and McSweeney, 1979). Adipsin expression is reduced greatly in ob/ob and db/db mice (Flier et al., 1987). Since the mapping data presented here demonstrate that the ob and db mutations are asyntetic with the adipsin structural locus, it is clear that the level of expression of adipsin mRNA is affected by several mutations at distinct genetic loci.

These genetic data imply that adipsin expression is reduced in certain obesities because of some regulatory disturbance in the pathways that control adipsin expression. The potential involvement of glucocorticoids in adipsin expression was suggested by the fact that the three mouse models of obesity in which reduced adipsin has been demonstrated (db/db, ob/ob, and MSG injection) have higher levels of glucocorticoids than their lean controls (Bray and York, 1979; Tokuyama and Himms-Hagen, 1986). While the genetically obese mice are also hyperinsulinemic, hyperglycemic, and hyperphagic, the MSG model does not show these characteristics (Bray and York, 1979; Cameron et al., 1978).

The adrenal ablation experiments together with corticosterone administration studies argue persuasively that glucocorticoids play a significant role in the reduced adipsin expression in the ob/ob mouse. First, adrenalectomy causes an increase in the levels of circulating adipsin protein and adipsin mRNA in the epididymal fat pads. Second, glucocorticoid injections completely reversed this adrenalectomy effect, with levels of adipsin mRNA (Fig. 4) and protein (not shown) matching the intact obese animals. This strongly suggests that the effects of the adrenalectomy on adipsin expression can be largely explained by the loss of glucocorticoids as a result of this surgery. Finally, if the hyperglucocorticoid state of the obese animals plays a significant role in the suppression of adipsin expression, it might be expected that exogenous administration of glucocorticoids could significantly lower
adipsin levels in lean animals. Figs. 6 and 7 illustrate that a major reduction in adipsin mRNA levels can be brought about in the lean litter mates of obese mice by the implantation of glucocorticoid pellets or daily injection of glucocorticoids. An effect of the latter treatment is visible within 2 days, considerably before major effects on fat pad weight are seen. This argues that the effects of glucocorticoids on adipsin expression are unlikely to be secondary to alterations in fat cell size.

Quantitative aspects of the chronic glucocorticoid administration experiments are also consistent with the notion that the level of these hormones observed in intact ob/ob mice is sufficient to bring about a reduction in adipsin expression. Glucocorticoid assays yielded quite reproducible results for both lean (approximately 1–3 μg/dl) and obese animals (approximately 15–20 μg/dl). The fact that adipsin mRNA was suppressed at the first dose to raise circulating corticosterone values above the intact obese level (10-mg pellets gave 20 μg/dl) suggests that the hormone levels seen in the ob/ob may be sufficient to suppress this message, particularly since the ob/ob animals appear to have increased sensitivity to glucocorticoids (Tokuyama and Himms-Hagen, 1987). A more precise quantitative relationship between corticosterone values and adipsin levels in obese and lean animals will require more investigations.

While these studies are consistent with a major role for glucocorticoids in adipsin regulation, it is apparent that the hyperglucocorticoid state alone cannot fully explain adipsin suppression in the obese mice. Although adrenalectomy causes a major rise in adipsin expression in the ob/ob animals, it does not reach the lean levels for either the protein or the fat pad mRNA. Adrenalectomy brings glucocorticoid levels down to those seen in the ob/ob mouse, in addition to high levels of glucocorticoids. However, this suppression in the obese mice. Although adrenalectomy causes a major rise in adipsin expression in the ob/ob animals, it does not reach the lean levels for either the protein or the fat pad mRNA. Adrenalectomy brings glucocorticoid levels down to those seen in the lean mice. This was also seen when animals were killed 1 week later than those used in Figs. 3 and 4, which were killed 1 week after adrenalectomy. Chronic corticosterone treatment of lean animals also failed to suppress adipsin mRNA levels to those seen in the ob/ob mice. This suppression was 90% in animals receiving 50-mg pellets, which were effective in greatly raising serum corticosterone and stimulating a major increase in fat mass. However, even with doses so high that they occasions some toxicity (100 mg/mouse), further decreases in adipsin levels were not observed and they did not approach the 99% reduction seen in ob/ob animals (not shown). Taken together, these data suggest that other factor(s) contribute to the suppressed adipsin expression in the ob/ob mouse, in addition to high levels of glucocorticoids.

How do glucocorticoids affect adipsin expression? In theory, this could be a direct effect on adipsin expression through the action of a specific receptor in fat cells. Glucocorticoid-responsive genes have been demonstrated in cultured adipocytes (Nechushtan et al., 1987). However, we have been unsuccessful to date in demonstrating any effect of dexamethasone or corticosterone on adipsin mRNA levels in either cultured 3T3 adipocytes or primary rat fat cells. Furthermore, no consensus glucocorticoid regulatory sequence element is apparent in the first 500 base pairs upstream of the start of transcription in the mouse adipsin gene (Min and Spiegelman, 1986; Phillips et al., 1986). If the effect of glucocorticoids seen in vivo is not direct, this suggests that these hormones may influence other physiological systems which could directly control adipsin. Presumably, a role for other factors may also help explain why adrenalectomy cannot completely normalize adipsin expression in ob/ob mice. In this regard, we have recently found that the sympathomimetic amineephedrine strongly stimulates adipsin mRNA levels in MSG-induced obese mice (data not shown). This is particularly interesting since there have been suggestions that the high glucocorticoid levels in ob/ob mice may play a role in blunting sympathetic nervous activity (Vander Tuig et al., 1984; Tokuyama and Himms-Hagen, 1987). Whether glucocorticoids control adipsin expression in vivo by altering sympathetic nervous tone is not yet clear, but this may be tested using a variety of well characterized sympathetic agonists and antagonists.

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