T he quest for better understanding for the pathophysiological basis of hypertension and atherosclerosis is ongoing. The complexity of hypertension and atherosclerosis and of the underlying mechanisms is becoming increasingly apparent. The number of candidate genes and molecular pathways that are involved is increasing in parallel. In the present issue of *Hypertension*, Tordjman et al 1 explore the role of the candidate gene, peroxisome proliferator-activated receptor (PPAR)–α (reviewed extensively and comprehensively in the Web site dedicated to PPAR: http://ppar.cas.psu.edu/), in the regulation of blood pressure and atherogenesis. The investigators follow up their previous observation that PPARα-deficient mice were protected from hypertension and atherosclerosis. 2 They currently report that, in a mouse experimental model of high renin and elevated angiotensin II levels in which the PPARα gene has been knocked out, hypertension and diet-induced atherosclerosis are averted.

PPARα is widely distributed in the vasculature, as well as in other tissues and organs. PPARα is a nuclear receptor, one in a family of at least 3 transcription factors that have been connected to cell metabolism and differentiation. The peroxisome, an intracellular organelle that is capable of self-replicating, is present in all eukaryotic cells that contain enzymes, some of which are oxidative enzymes. The effects of PPARα that we are currently dealing with, affecting blood pressure and atherogenesis, however, are thought not to be related to peroxisome proliferation or activation but rather to other intracellular pathways, some of which have been elucidated, whereas others remain to be clarified. 3 PPARα has pleiotropic effects and controls multiple gene targets that involve, among others, fatty acid oxidation, lipid metabolism, and inflammatory/vascular pathways. 3 As such, PPARα activity has been considered until now of benefit to the human organism.

In the current study, Tordjman et al 1 provide data that suggest that the absence of the human renin had been introduced along with the angiotensinogen gene, resulting in high renin–high angiotensin–high aldosterone hypertension. The investigators knocked out in this particular model of hypertension the gene encoding PPARα, resulting in genomic disruption, which led to a significant reduction in active renin and aldosterone and a parallel reduction in the level of blood pressure and cardiac hypertrophy. Additional findings in that study were diminished atherosclerosis at the aortic sinus and a reduction of foam cells in peritoneal macrophages. Fenofibrate, a PPARα activator, effectively increased blood pressure in the parental transgenic strain but did not affect blood pressure in the transgenic knockout strain. The investigators correctly concluded that, based on their findings in their specific mouse model, PPARα appears to fulfill a role in regulating blood pressure and atherogenesis. They further speculated that the mechanism whereby PPARα affects blood pressure involves the renin-angiotensin-aldosterone system.

The simplicity and straightforward nature of the study by Tordjman et al 1 needs to be commended: based on an incidental previous observation, the authors generated a tangible hypothesis, with a plausible association between 1 candidate gene and 2 phenotypes, blood pressure, and atherosclerosis. By knocking out the gene encoding PPARα in their high-renin model of hypertension, they successfully removed or attenuated the phenotype, whereas by amplifying the expression of the gene, they successfully enhanced the phenotype. These results and their interpretation must be addressed, however, with some caution and reservation. These data, derived from studies in a mouse model, infer that, contrary to the prevailing understanding, the presence of PPARα activity or stimulation/activation of PPARα might in fact be detrimental in terms of blood pressure and atherogenesis. Is such a provoking interpretation of the data valid? Is interpretation of data generated in the mouse also applicable to humans? The knockout model assumes that the PPARα gene had been singly knocked out, whereas the remaining genetic background of the Tsukuba hypertensive mouse remained unperturbed. Such assumption is necessary and acceptable when one strives to derive conclusions from studies in knockout models. The remote possibility does exist, however, that, in the knocking-out process, other genes had been affected as well and that the protective effect that Tordjman et al 1 observed in their knockout model might have been in fact related not to the absence of PPARα but to unintended and identified perturbation of one or more other gene. The issue of applicability of findings in the mouse to other strains and to humans is always a matter of
controversy that only direct hypothesis testing in humans can resolve.

To evaluate the validity of the Tordjman et al\textsuperscript{1} findings, it is vital to examine whether the results of the current investigation as to the role of PPAR\(\alpha\) in hypertension and atherosclerosis are consistent with what has been reported previously in the medical and scientific literature, both in experimental models and in humans. The authors of the article acknowledge that previous studies in rats have yielded inconsistent results with regard to blood pressure and other effects of PPAR\(\alpha\) manipulation. In fact, a significant number of studies provide evidence that activation of PPAR\(\alpha\) prevents or attenuates hypertension, findings that are seemingly opposite to those currently reported by Tordjman et al.\textsuperscript{1} Diep et al,\textsuperscript{4} eg, demonstrated that PPAR\(\alpha\) activation with docosahexanoic acid (DHA) attenuated the development of angiotensin II–induced hypertension in Sprague Dawley rats. Engler et al\textsuperscript{5} fed spontaneously hypertensive rats with a diet containing DHA for 6 weeks and found a significant reduction in blood pressure. Williams et al\textsuperscript{6} reported in male and female Sprague-Dawley rats that chronic PPAR\(\alpha\) agonist treatment reduces salt-dependent hypertension produced by endothelin \(\beta\) receptor blockade. In humans, Prisco et al\textsuperscript{7} showed that 4 g/d of highly purified eicosapentaenoic acid together with DHA ethyl esters favorably affected BP in mild hypertensive subjects. Mori et al\textsuperscript{8} found in mildly hyperlipidemic men that 4 g/d of DHA for 6 weeks significantly reduced daytime and 24-hour ambulatory blood pressure. If DHA activates PPAR\(\alpha\), and if PPAR\(\alpha\) activation reduces blood pressure, then why did knocking out of PPAR\(\alpha\) in the study by Tordjman et al\textsuperscript{1} paradoxically prevent rather than worsen hypertension? Could it be that DHA in the other studies did not exert its blood pressure–lowering effect by activating PPAR\(\alpha\) but instead by promoting prostaglandin synthesis through the effects of DHA on steroid and eicosanoid metabolism? Engler et al\textsuperscript{5} were cautious in their conclusion by stating that it remains to be established whether indeed PPAR\(\alpha\) or some other mechanisms contribute to the antihypertensive effect of PPAR\(\alpha\) activators. Interestingly, data that have linked PPAR\(\alpha\) activation to the prevention of hypertension extend beyond DHA and can also be found when scrutinizing the effects of fenofibrate in other models of hypertension. Diep et al\textsuperscript{5} showed that fenofibrate prevented the development of angiotensin II–induced hypertension in Sprague-Dawley rats. De Ciuceis et al\textsuperscript{8} provided similar evidence by showing that combined low doses of PPAR\(\alpha\) (fenofibrate) and PPAR\(\gamma\) (rosiglitazone) activators attenuated the development of hypertension in the same model of angiotensin II–infused Sprague Dawley rats. Are there any data in the literature that support the findings of Tordjman et al\textsuperscript{1}? In animal models, Iglarz et al\textsuperscript{11} found that, in deoxycorticosterone-acetate (DOCA)–salt–treated animals, fenofibrate did not prevent the development of hypertension. In humans, Subramanian et al\textsuperscript{12} treated normotensive subjects with fenofibrate for 21 days and found a small increase in 24-hour systolic blood pressure but no change in diastolic blood pressure; in the same study, fenofibrate did not prevent the development of hypertension in patients who were administered dexamethasone for 3 days. Such results, however few, are consistent with those of Tordjman et al.\textsuperscript{1} It might also be of relevance to note that several clinical studies (elegantly reviewed by Brown and Plutzky\textsuperscript{3}) based on therapeutic agents that activate PPAR\(\alpha\), including fibrates, have yielded in large disappointing results in terms of end-point cardiovascular events, possibly suggesting the lack of an inherent hypotensive effect of PPAR\(\alpha\) activation and perhaps even an opposite effect, as suggested by the current study. It may thus be that the present report by Tordjman et al\textsuperscript{1} is indeed of clinical relevance to humans.

Irrespective of whether the data generated by Tordjman et al\textsuperscript{1} with regard to the effects of PPAR\(\alpha\) on blood pressure and atherosclerosis are consistent with or different from those published by others in parallel studies, these are credible experimental data that cannot be refuted. Do these results, however, make sense from the physiological/biological point of view? Could they have been predicted just by sheer knowledge on the mode of action of and pathways in which PPAR\(\alpha\) is involved? Could one have foreseen the effect of blocking (or knocking out) or stimulating PPAR\(\alpha\) on blood pressure and atherogenesis? A glance at the enormous complexity of the pathways in which PPAR\(\alpha\) is involved (see Figure) reveals that prediction of the phenotype resulting from knocking out the PPAR\(\alpha\) gene would have been next to impossible or, at best, unfounded guess work. The very large number of pathways to which PPAR\(\alpha\) is connected and its known effect on an even greater number of genes perhaps helps explain why, under different sets of circumstances and conditions, the phenotypic expression of the gene might vary. In the model used by Tordjman et al,\textsuperscript{1} the expression of knocking out the gene was a reduction in blood pressure and atherosclerosis. In other models, it is quite plausible that diminished expression of the gene might have resulted in a different phenotype, including an opposite phenotype consisting of an increase in blood pressure and augmented atherogenesis. The large number of pathways in which PPAR\(\alpha\) is involved also raises the question of whether the effect of PPAR\(\alpha\) on blood pressure and atherosclerosis is indeed mediated by the renin-angiotensin-aldosterone system, as suggested by Tordjman et al,\textsuperscript{1} because other pathways, as shown in Figure 1, might be no less involved, and Tordjman et al\textsuperscript{1} do not provide any evidence to the contrary.

Assuming that the results of the study by Tordjman et al\textsuperscript{1} and their interpretation are valid and applicable to humans, this study becomes of prime clinical relevance and of major scientific importance. From the clinical point of view, the data generated raise challenging questions as to the potentially detrimental effects of fibrates. Fibrates, which are commonly used in the treatment of hyperlipidemia, stimulate PPAR\(\alpha\). If knocking out the PPAR\(\alpha\) gene reduces blood pressure and attenuates atherosclerosis, the possibility must then be taken into account that, conversely, stimulating the PPAR\(\alpha\) gene might increase blood pressure and paradoxically promote atherosclerosis. Acti-
vation of PPARα might then be considered detrimental to human health. From the scientific point of view, the question could be raised of whether the data generated by Tordjman et al. in their current study shed more or new light on the pathophysiology of hypertension and of atherosclerosis in humans in general and on the role of PPARα in particular. After evaluating the data provided, it appears that the only conclusion that can, at present, be definitively drawn from this investigation is that, in the mouse, under conditions in which renin is very elevated, PPARα is in some way involved in blood pressure regulation and atherogenesis. Such involvement might not necessarily apply to other forms of hypertension, including essential hypertension, or to atherosclerosis in humans or other species. Nevertheless, a stimulating and controversial hypothesis has been raised as to the role of PPARα in the regulation of blood pressure and atherogenesis, one that remains to be tested.

In conclusion, the current study by Tordjman et al. is of prime importance, because the investigators have successfully focused our attention on a controversy that involves PPARα. This central molecule which action had been considered until now beneficial and a prime therapeutic target, may in fact turn out to be a candidate gene for hypertension and for atherosclerosis and, thus, a foe to human health. More in-depth research is required to establish if, when, and how PPARα might indeed be involved in the generation of high blood pressure and atherosclerosis in humans, issues that remain, at present, unresolved.

Disclosures
None.

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