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Pleiotropy: what do you mean? Reply to Zhang and Wagner

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It is a testament to the conceptual slipperiness of pleiotropy that thoughtful people can reasonably disagree about its meaning and extent. Zhang and Wagner [1] raise important issues in response to our recent Opinion article [2], and readers will do well to consider their critique. Here, we offer a brief counterpoint to the objections that they raise.

First, Zhang and Wagner argue against our categorization of pleiotropy into three distinct forms. At some level, this point is semantic, because we could as well have described a single kind of pleiotropy in three contexts: molecular genetics, developmental genetics, and evolutionary genetics. Our central goal, however, is to discourage inappropriate applications of data from one context to theory from another. Zhang and Wagner's analogy to dominance illustrates our concern. As they note, a single mutation can have different dominance with respect to different phenotypes. Where the term 'dominance' appears in evolutionary population genetics, however, it refers exclusively to dominance with respect to fitness. Given that phenotypes may vary nonlinearly with fitness, data on dominance in the context of development may be misleading about the role of dominance in the evolutionary fate of mutations. The same holds for pleiotropy.

Next, Zhang and Wagner argue that lethal gene deletions are uninformative because they cannot contribute to evolution. This is our point. If the goal is to estimate the pleiotropy of null mutations to answer questions about evolution, then those mutations too pleiotropic to ever contribute to evolution are exceedingly relevant. They demonstrate that pleiotropy constrains evolution. Zhang and Wagner suggest that the patterns of pre-lethality developmental pleiotropy exhibited by such mutations are informative, but we reiterate the importance of distinguishing developmental from selectional pleiotropy in such cases. Embryonic lethals all have the same pattern of selectional pleiotropy.

The third point of disagreement is whether subtle allelic effects that lie below thresholds for statistical detection are biologically important. We believe that the weight of empirical data decisively favors an affirmative answer, and we invite readers to revisit our notes on this point in the original Opinion [2]. We share with Zhang and Wagner the view that the development of methods to measure pleiotropy without dependence on statistical thresholds is an important goal.

Finally, Zhang and Wagner suggest that the way forward is more data. As empiricists, we echo this point. However, data alone are not sufficient. We need data that are relevant to our hypotheses. Zhang and Wagner suggest that the examples we offer of successes in the study of pleiotropy (the *cis*-regulatory theory of morphological evolution and the antagonistic pleiotropy model of aging) are themselves in dire need of such data, and we do not doubt that they remain hypotheses. Their virtue, from our perspective, is that they are well-posed hypotheses, such that the relevant data are precisely defined. In our Opinion, we argue that many questions about pleiotropy are ill posed, and that greater attention to conceptual foundations will improve our empirical progress.

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