common to different phyla, we often forget that these genes encode proteins that act within cells; it is the changes in cell shapes and numbers that actually constitute morphogenesis. The chapter on costs and constraints (also well done) wrestles with one of the most difficult problems facing the field: How does one select for a complex developmental process? Exploring the answer to that key question will require studies designed to measure variation and selection on complex traits.

This is the third evo-devo book to appear within a year; it follows volumes by Sean Carroll *et al.* (*7*) and Eric Davidson (*8*) [reviewed in *Science* by Wray (*9*)]. Of the trio, Wilkins's book offers by far the most comprehensive exploration of the field. The other two focus primarily on promoter analyses and the genetic regulatory pathways themselves and, in places, pay little attention to how the processes may be important in evolution. However, unlike Wilkins, they use color illustrations, which are almost imperative for explaining complex patterns of gene expression in space and time. Carroll *et al.*'s text seems the best for teaching undergraduates. It is simple enough to appeal to students who are new to the field, yet it offers enough detail for them to understand the model systems. Wilkins's account should be an easy read for aficionados, but whether it is accessible to undergraduates remains to be seen. (I plan to use the three texts in classes at various levels next year.)

In any case, *The Evolution of Developmental Pathways* would be great to read in a seminar class for graduate students or within a lab meeting. It will certainly generate discussions about data, terminology, and interpretations—matters so important to rigorous science. And it can help train a new generation of students to study how complex morphologies can evolve within the framework of developmental gene networks. If we are to understand how genomes create unique animals from single fertilized eggs, then we will have to grapple with the many complex issues Wilkins raises in this book.


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**BOOKS: PHILOSOPHY**

# Knowledge and Social Norms


**Alvin I. Goldman**


Philosophers of science and practitioners of the social studies of science have been at loggerheads over how to approach science and how to evaluate it as a knowledge-producing enterprise. Philosophers focus on the evidential grounds and cognitive merits of science. Sociologists highlight the nonevidential considerations that influence science: the professional and ideological interests, the discursive networks, and so forth. Philosophers feel that social studies of science either ignore the question of whether science yields legitimate knowledge or draw unwarranted negative conclusions from their case studies. Sociologists feel that the normative issues raised by philosophers provide little or no purchase on the actual conduct of science. According to Helen Longino, both sides suffer from a misplaced "dichotomizing" drive. They assume that science is either rational and not social or social but not rational; the rational and the social are mutually exclusive. Her mission in *The Fate of Knowledge* is to show how science can be social and produce knowledge.

**The Fate of Knowledge**
*by Helen E. Longino*
Princeton University Press, Princeton, NJ, 2002. 245 pp. $49.50, £35. ISBN 0-691-08875-6. Paper, $16.95, £11.95. ISBN 0-691-08876-4.

This is a sensible piece of ecumenism. Longino, however, is not unique in pursuing this course, as she sometimes seems to imply. In recent years, a number of epistemologists and philosophers of science have highlighted the social framework of the epistemic conduct of science and other fact-finding arenas (*1*). Longino often conflates disagreements with her on other matters with a weakness for dichotomizing. If, by her lights, a philosopher favors an excessively "reductivist" approach to the social, she sees this as perpetuating the dichotomizing tradition. But one can reconcile the rational and the social under many interpretations of the social.

The most important question, though, is how Longino herself effects the reconciliation between the social and the rational. As in earlier work, she proposes social "norms" for social knowledge. These norms require communities to be governed by critical discursive interactions. Publicly recognized forums for the criticism of evidence and methods must exist. There must be "uptake" of criticisms (beliefs and theories must change in response to critical discourse). There must be publicly recognized standards by reference to which theories are evaluated. Lastly, communities must be characterized by "tempered equality" of intellectual authority (all members must be considered capable of contributing to the dialogue). Insofar as a community satisfies these conditions, Longino says, it is a knowledge-productive community. Because the norms call for social interactions, Longino touts the approach as an emphatically social brand of epistemology. There can be no quarrel there. What is questionable is Longino's claim that communities satisfying her four conditions will necessarily produce knowledge. It is especially doubtful that these conditions capture what is distinctive about scientific knowledge.

Consider a test case. Members of a religious community form beliefs about the universe by appeal to a sacred text ("evidence"). They often disagree in interpreting the text, so they engage in critical interactions. The criticisms take place in publicly recognized forums. Members are genuinely influenced by the criticisms they receive. There are public standards for interpreting the text. And the community is governed by qualified equality of authority, where greater weight goes to those with more training in the community's seminaries. This community satisfies Longino's four conditions, but does it automatically qualify as a knowledge-producing community? Surely not. Still less does it qualify as a community producing scientific knowledge. Longino is not oblivious to such examples; she adduces some of them herself. But how does she answer the worries?

One response is to tighten the requirements. The community must be open to all perspectives: "no claim or belief can be held immune to criticism." The religious community will presumably violate this requirement because it is dogmatic about its standards, e.g., that theories are to be judged by the sacred text. But this move creates a threat from the opposite direction. Instead of excessive looseness, the approach is imperiled by excessive tightness. Isn't science also "dogmatic" in insisting on scientific or statistical methods? Researchers aren't invited to challenge those methods when they submit their research papers. Indeed, general questions of scientific standards are usually relegated to philosophy journals rather than published in scientific journals. Even if a statistical method is challenged, the challenge is assessed by appeal to logic and


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mathematics. And aren't those standards dogmatic in some sense? I am not arguing that science is dogmatic in any objectionable way. The point is that adding antidogmatism at the level of standards may impose so severe a constraint that no knowledge-producing community can meet it.

Another pressing problem for Longino is to show why her favored procedures guarantee knowledge production. What is knowledge, anyway? Along with most epistemologists, she says that knowledge involves truth (or a gussied-up version of truth called "conformance," but the differences don't matter here). This leaves us with the question: Why would compliance with her list of procedures generally yield true beliefs? Longino implies that an adequate social epistemology would show why the distinctively social aspects of inquiry are of special help in attaining knowledge. But she doesn't show how this works for the social procedures she embraces. How exactly do public forums for criticism guarantee that any random community, starting from any epistemic principles (e.g., "believe the tea leaves"), will either succeed in getting to the truth or be forced to abandon its initial principles? It is especially unclear how the requirement of interactive criticism picks out everything distinctive to science. Doesn't more have to be said about the types of evidence distinctive to science (experimental evidence, presumably) and how, specifically, the evidence is deployed (methods of inference)? These dimensions are not adequately captured by the abstract and otherwise unconstrained requirement of interactive criticism.

*The Fate of Knowledge* usefully interprets and evaluates a wide range of contributions to the debate over science and the social. The quality of interpretation, however, runs the gamut from excessive charity to ill-founded criticism. Longino laudably attempts to make sense of the clash between empirical sociologizers and normative rationalizers by distinguishing different senses of knowledge and of key concepts such as individualism and relativism. But some of these attempts are less than transparent or amply motivated.

**Note**

1. This work includes my own *Knowledge in a Social World* (Oxford Univ. Press, Oxford, 1999), which Longino overlooks.



PERSPECTIVES: NEURODEGENERATION

# A Glutamine-Rich Trail Leads to Transcription Factors

**Richard N. Freiman and Robert Tjian**

Huntington's disease (HD) is an inherited neurodegenerative disorder characterized by progressive motor and cognitive deficits, leading to death. Decades of intense research have led to the identification of a mutant form of the huntingtin protein as the cause of HD (*1*). Expansion of CAG trinucleotide repeats in the HD gene results in an expanded stretch of glutamine amino acids in mutant huntingtin. The age of onset of HD correlates with the length of the glutamine expansion. Although increased trinucleotide repeats are a hallmark of several human diseases (*2*), we still do not know what normal huntingtin does in cells or how its function is altered by glutamine expansion. However, recent work, including the report by Dunah *et al.* (*3*) on page 2238 of this issue, suggests that glutamine expansion may enable mutant huntingtin to corrupt normal transcription in neurons in the human brain.

Transcription of DNA into messenger RNA is one of the most highly regulated processes in the cell. Transcriptional regulation depends on a complex molecular machine consisting of more than 100 proteins (*4*). Genes are switched on and off through the carefully orchestrated interplay of large numbers of proteins that interact with each other and with regulatory DNA elements that specify the activity of each gene in the genome. Before transcribing a given gene, the enzyme RNA polymerase II (RNA pol II) must first be instructed by a complex ensemble of regulatory proteins, called transcription factors, to bind to a specific region of DNA (see the figure). Composite regulatory DNA sequences (promoters) adjacent to and upstream of the transcriptional start site contain small patches of DNA elements recognized by specific DNA binding proteins that activate transcription by recruiting RNA pol II.

In the early 1980s, specificity protein 1 (Sp1) became the first of many sequence-specific transcriptional activators to be isolated from human cells (*5*). Extensive biochemical and molecular characterization of Sp1 revealed that it targets specific genes by binding to GC-box DNA elements present in cognate promoters. Also, Sp1 contains distinctive glutamine-rich activation domains that are typical of an extensive family of transcriptional activators conserved in multicellular organisms. The glutamine-rich activation domains of Sp1 selectively bind and target core components of the transcriptional machinery such as TFIID, a multiprotein complex composed of the TATA-box binding protein (TBP) and multiple TBP-associated factors ($TAF_{II}$s) (*6*). Sp1-dependent transcription requires various TAF subunits of TFIID, illuminating the importance of coactivators for potentiating transcription. There is a specific interaction between the glutamine-rich activation domains of Sp1 and a glutamine-rich subunit of TFIID called $TAF_{II}130$ (*7*). Association of glutamine-rich proteins thus represents a major class of protein-protein interfaces that enable transcription factors to signal one another about regulating the expression of specific genes.

Recent studies including that of Dunah *et al.* (*3*) reveal the intriguing convergence of the parallel tracks of transcription regulatory mechanisms and HD. A recent paper (*8*) reported a specific interaction between huntingtin and Sp1 in the brains of genetically engineered HD mice. Expanding on this study, Dunah *et al.* now reveal the ability of mutant huntingtin in human HD brain cells not only to associate with Sp1 but also to disrupt a specific activator-coactivator interaction. These two studies suggest that an early step in the development of HD may involve deregulation of specific transcriptional programs in brain neurons. By blocking the specific interaction of Sp1 with $TAF_{II}130$ in brain cells, Dunah and colleagues found that mutant huntingtin carrying an expanded glutamine repeat interferes with the normal patterns of Sp1-mediated gene expression (see the figure).

These investigators report a number of important links between the glutamine expansion in mutant huntingtin and a negative effect on Sp1-dependent transcription in brain cells (*3*). First, there is enhanced association of mutant huntingtin with Sp1 in extracts from the brains of asymptomatic HD individuals. Second, the association of Sp1 with $TAF_{II}130$ is reduced in HD brains compared with brains from healthy individuals. The enhanced association of mutant huntingtin with Sp1 also blocked the binding of Sp1 to promoter DNA (*3, 8*). Such

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