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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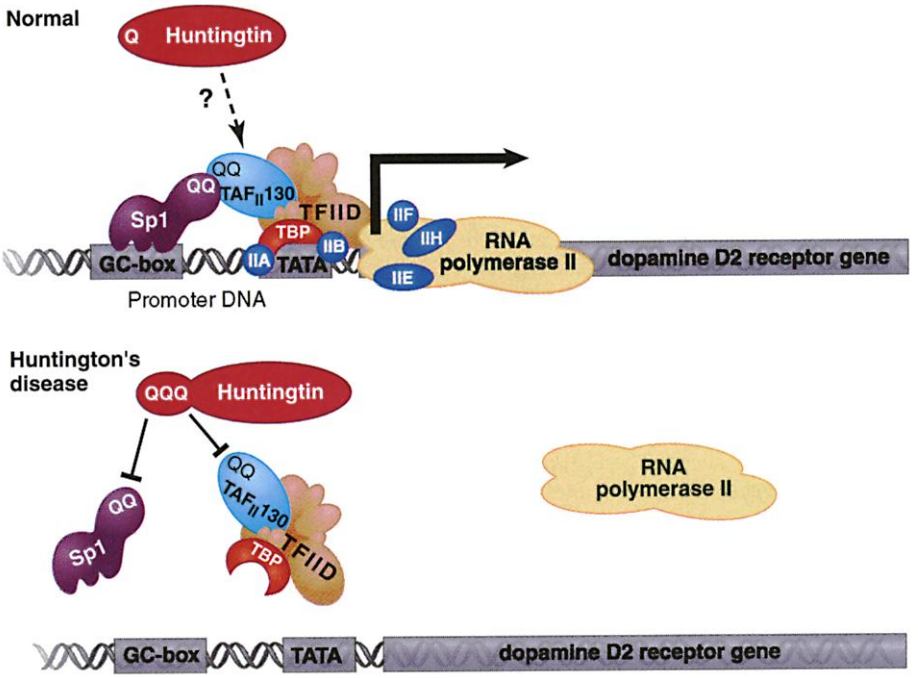

Blocking interfaces. Mutant huntingtin disrupts transcriptional activation by Sp1 and $TAF_{II}130$ in HD. **(Top)** The transcription factor Sp1 binds to DNA elements called GC boxes in cellular promoters. A specific protein-protein interaction between the glutamine-rich (QQ) regions of Sp1 and the $TAF_{II}130$ subunit of TFIID is required for recruitment of the general transcriptional machinery, which includes transcription factors TFIIA, B, D, E, F, and H. This glutamine interface serves to bridge Sp1 to the machinery required to recruit RNA pol II. Once correctly targeted to the dopamine D2 receptor gene, RNA pol II initiates transcription of an mRNA copy of this gene. **(Bottom)** In HD, the glutamine expansion in huntingtin disrupts transcriptional activation by Sp1 and $TAF_{II}130$. An amino-terminal fragment of huntingtin, containing an expanded polyglutamine tract, accumulates in the nucleus. Here, this mutant protein associates with Sp1 and $TAF_{II}130$, preventing Sp1 from binding to the GC box, and ultimately disrupting the ability of Sp1 and $TAF_{II}130$ to interact. Without proper targeting by the general transcriptional machinery, RNA pol II cannot properly locate the dopamine D2 receptor promoter region and the gene cannot be transcribed. The deregulated expression of this gene, as well as of many others, may be an early step in the neurodegenerative process taking place in the HD brain.

deleterious effects of mutant huntingtin disrupt Sp1-mediated transcription in HD brain cells. Mutant huntingtin decreases the expression of several Sp1-dependent neuronal genes, including the dopamine D2 receptor gene, whose expression is known to be compromised in HD brains.

Third, and perhaps most striking, overexpression of both Sp1 and its normal target coactivator $TAF_{II}130$ was required to overcome inhibition of dopamine D2 receptor gene expression by mutant huntingtin; neither alone was sufficient to restore normal transcription. Finally, concomitant overproduction of Sp1 and $TAF_{II}130$ reversed the cellular toxicity associated with the mutant huntingtin protein in brain cells. These findings suggest that by harboring extra glutamines, huntingtin becomes a hyperactive glutamine-rich corepressor that usurps the normal interactions between the transcriptional activator Sp1 and its cognate coactivator $TAF_{II}130$ (see the figure). Such disruption of Sp1-mediated transcription may be one of the earliest deleterious consequences of accumulating mutant huntingtin in the HD brain.

Both the direct and specific interference of transcription by mutant huntingtin and the indirect consequences to gene expression are implicated in HD pathology (*9*). Protein aggregates called neuronal intranuclear inclusions that contain mutant huntingtin as well as other regulatory proteins have been observed in the nuclear compartment of HD brain cells (*10*). Given that this is the cellular compartment where transcription occurs, these aggregates may nonspecifically alter gene expression. The Dunah *et al.* work suggests instead that mutant huntingtin can specifically disrupt Sp1/$TAF_{II}130$-dependent transcription in HD cells. However, these findings do not preclude the possibility that neuronal intranuclear inclusions may also contribute to the pleiotropic deregulation of gene expression. Because these two models are not mutually exclusive, it will be important to identify the consequences of sequestering different transcription factors in the intranuclear inclusions observed in the nuclei of HD brain cells. In fact, mutant huntingtin targets and abrogates the function of the transcriptional coactivator CBP (*11, 12*). Taken together, these studies suggest that mutant huntingtin may simultaneously disrupt transcription by different transcriptional pathways in affected HD neurons. But a number of questions remain unanswered—for example, why do only brain cells (and not other cells in the body) become crippled by the deregulation of transcription in HD, and how does aberrant transcription lead to severe neurodegeneration?

Several other genetic diseases are caused by glutamine expansions in various proteins (*2*). Shimohata *et al.* have described a glutamine expansion in dentatorubral-pallidoluysian atrophy (DRPLA), a neurodegenerative disease similar to HD (*13*). Mutant DRPLA protein (also called atrophin-1), like huntingtin, contains an expanded polyglutamine tract that, remarkably, also targets $TAF_{II}130$ and disrupts transcription by CREB. CREB, like Sp1, is a transcriptional activator protein known to engage $TAF_{II}130$ as a coactivator partner. Disruption of the interaction between $TAF_{II}130$ and its cognate activators may be a common theme in diseases caused by glutamine expansions.

With such specific molecular mechanisms in hand, investigators can now address the possibility of targeting one or more of these selective protein-protein interactions for therapeutic intervention. It may eventually be feasible to develop drugs that alleviate the negative effect of glutamine expansions on specific pathways of gene expression. For example, Steffan *et al.* have shown that inhibitors of histone deacetylase enzymes can arrest neurodegeneration in models of polyglutamine diseases in *Drosophila*, presumably by altering gene expression patterns (*14*). Such therapies in humans may delay or reduce the clinical symptoms of HD and other glutamine expansion diseases. Intensive biochemical, genetic, and clinical studies will be required to bring such an important goal to fruition.

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