(which degrade critical ecosystem services) deserves more attention.

On the positive side, I think that the development of countryside biogeography as a framework for enhancing the preservation of biodiversity in human-dominated landscapes deserves attention alongside prospects for establishing large-scale reserves, which Wilson discusses very thoroughly. On a separate issue, I'm more sceptical about heritability estimates churned out by behavioural geneticists (often based on badly analysed twin studies) for such attributes as proneness to agoraphobia and fear of snakes. But these are trivial matters compared to the magisterial sweep of *The Future of Life*, and I find myself in total agreement with its major points.

Wilson was recently attacked viciously in the pages of *The Economist*. He was critical of Bjørn Lomborg's anti-environmental book *The Skeptical Environmentalist*, which the magazine and Cambridge University Press have been heavily promoting. In my view, Wilson had accurately pointed out that busy scientists were having to waste a huge amount of time replying to the book's distortions. *The Future of Life*, by coincidence, is Wilson's perfect response. It clearly lays out the reasons for his deep concern for the human future (shared by the vast majority of his colleagues) and why he thinks that scientists and society have no time to waste. It also reveals him to be a thoughtful, caring, life-loving human being. ■

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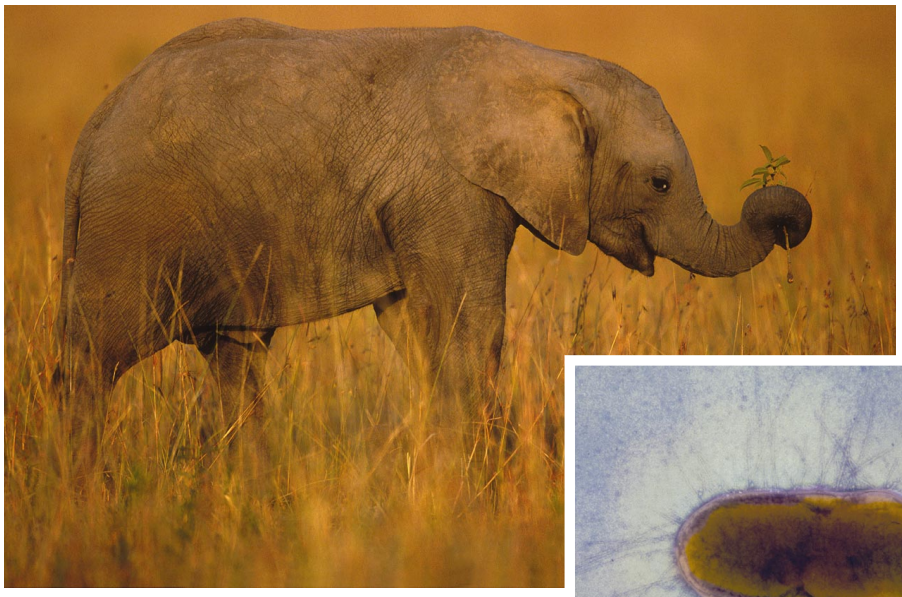
# From *E. coli* to elephants

Genes and Signals
by Mark Ptashne and Alexander Gann
*Cold Spring Harbor Laboratory Press: 2002. 208 pp. $59, £43 (hbk); $39, £28 (pbk)*

Kevin Struhl



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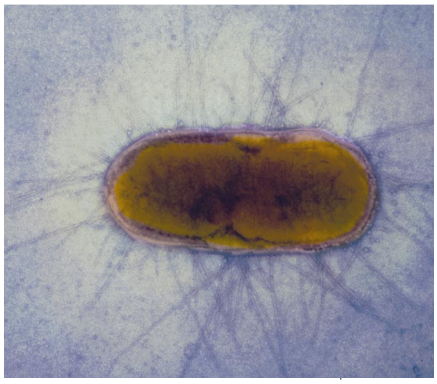

KWANGSHIN KIM/SPL

**The same, only more so: gene regulation is similar for organisms ranging from the elephant to the bacterium *Escherichia coli*.**

The regulation of gene expression is a fundamental aspect of biological phenomena such as the response to environmental conditions, the development of multicellular organisms, morphology and disease. Gene regulatory patterns are extraordinarily diverse and complex, yet the regulation of each gene is precise with respect to when and how much expression occurs. Gene regulation is also remarkably flexible, both to rapidly alter the constellation of genes expressed in response to new conditions, and to accommodate evolutionary demands. At most, a few thousand proteins account for the complexity and precision of gene regulation in humans. How is this accomplished?

Molecular studies of gene regulation were pioneered by François Jacob and Jacques Monod in the early 1950s. By the mid-1960s, three basic types of specific DNA sequence that determine the level of expression under particular physiological conditions were defined in the bacterium *Escherichia coli*. Such regulatory DNA sequences turn out to be specific binding sites for RNA polymerase, repressor proteins and activator proteins. Regulation of an individual gene is determined by the quality of its polymerase binding site, the particular activator and/or repressor proteins that bind in the vicinity of RNA polymerase, and the physiological conditions that modulate the function of the activators and/or repressors.

Monod once wrote that "anything that is true of *E. coli* must be true of elephants, except more so". In a lucid and provocative book, Mark Ptashne, a leading figure in the field for nearly 40 years, and Alexander Gann argue for a unifying principle of gene regulation that centres on the concept of regulated recruitment by means of adhesive interactions between proteins. They go on to argue that such regulated recruitment is a general strategy used by many other biological mechanisms involving enzyme specificity, regulatory precision and evolutionary flexibility.

Using a few well-chosen examples, Ptashne and Gann first describe three distinct mechanisms of transcriptional activation in bacteria. In one mechanism, DNA-binding activator proteins stimulate gene expression by recruiting RNA polymerase to the promoter sequences that lie just upstream of the gene. Recruitment is mediated by short 'adhesive' surfaces between the activator and polymerase, and the adhesive properties *per se* are sufficient for activation. In a second mechanism, the activator induces a conformational change in an inactive polymerase already bound at the promoter, thereby stimulating transcription. And in a third mechanism, the activator induces a conformational change in the promoter, effectively changing it from an inactive to an active form. This section of the book presents the key experiments and arguments for these mechanisms in a manner that is exceptionally lucid and beautifully illustrated. It is understandable to the non-expert, for whom it was intended, and is a 'must read' for anyone interested in gene regulation.

Armed with these lessons from bacteria, Ptashne and Gann consider yeast, a single-celled eukaryote, and conclude that activation occurs by regulated recruitment of the transcription machinery (which contains more than 50 proteins and so is much more complex than bacterial polymerases). Again, the authors use the device of a well-chosen example for clarity, the brief is convincingly argued, and the end result is illuminating to both the expert and the novice. The emphasis on regulated recruitment is important for the overall theme of the book, and it is certainly true that this mechanism predominates in yeast cells.

However, in emphasizing the fundamental similarities between bacteria and eukaryotes, Ptashne and Gann have made an unconventional choice in classifying chromatin-modifying activities as part of the transcription machinery. Chromatin and chromatin-modifying enzymes affect all eukaryotic processes involving DNA, and are typically considered as part of the DNA template, rather than the transcription machinery. So although activators and repressors use adhesive surfaces for regu-

lated recruitment of chromatin-modifying activities, such recruitment does not directly affect transcription and indeed is analogous to (although mechanistically distinct from) the bacterial mechanism in which activators modify promoter structure. In eukaryotes, the basic chromatin structure renders core promoters inherently inactive in the absence of an activator, whereas bacterial promoters are generally accessible to the polymerase. In my view, chromatin fundamentally affects the logic of gene regulation in eukaryotes, but fundamentalism is in the belief of the beholder.

The only disappointing part of the book is the brief section on higher eukaryotes. Unlike the rest of this book, and unlike Ptashne's previous influential monograph *A Genetic Switch*, this section covers many different phenomena (all very interesting and important) in a rather sketchy fashion. This subject calls for another book, although it is probably premature to write one at the level to which we have become, and wish to remain, accustomed.

In the grand scheme, the principles of regulated recruitment through weak, adhesive interactions between proteins are applied to other examples of enzyme specificity and regulation (such as splicing, proteolysis and signal transduction), where diversity, precision, and evolutionary flexibility are paramount. Some may consider this section to be a statement of the obvious, namely that protein–protein interactions are important in biology. However, I agree with Ptashne and Gann that this concept is fundamental to understanding specificity in biology, and is, in historical context, a revolutionary idea. Until recently, enzyme specificity and protein function were thought of in terms of precise active sites with near-unique substrate recognition. Regulation in this view occurs by allostery, a mechanism in which a signalling molecule alters the enzyme in a structurally precise manner.

In this context, the emerging picture that a great deal of biological specificity is mediated by simple adhesive interactions involving limited and modular protein surfaces is neither obvious nor intuitive. But the concept has the undeniable virtue of explaining the apparently contrary notions of precision and flexibility. In addition to the exposition of this major theme, the final section of the book and the afterword are full of interesting insights.

In *Genes and Signals*, Ptashne and Gann have written a unique book that is driven by ideas and broad concepts, yet is based on solid information. It is accessible to undergraduates with some knowledge of biology, yet it is also valuable to experts in the field. I highly recommend it. ■

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## Science in culture

### Seeing stains

**Mary Osborn's immunofluorescence images of cellular structures.**

*Martin Kemp*

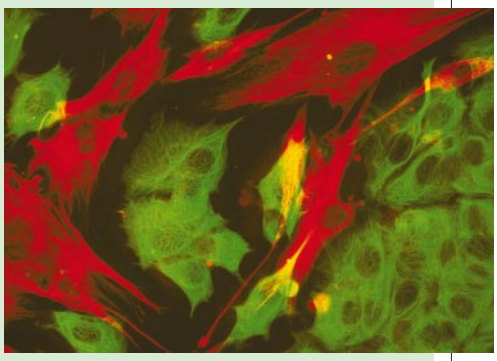
Stains (and those who have pioneered their use) are the unsung heroes of microscopy — well known to microbiologists, certainly, but not generally enjoying a high public profile. New instruments for seeing ever smaller details seem to present more eye-catching examples of scientific advance.

The story began with the progress from the primitive microscopes of the seventeenth century, in the hands of such pioneers of discriminating seeing as Anthony von Leeuwenhoek and Robert Hooke, and the gradual refining of optical resolution to its theoretical limits. Then came the non-optical revelations of electron microscopes, as developed by Vladimir Zworykhin and others, and the molecular marvels disclosed by the scanning tunnelling microscope devised by Gerd Binning and Heinrich Rohrer. Yet without selective staining and other marking techniques we would not be able adequately to differentiate key components in the tiny structures.

One of the most elegant and widely applicable techniques, immunofluorescence, has, as its name suggests, ingeniously adopted techniques from immunology. Albert Coons used it to reveal pneumococci in infected mouse tissues in 1942. But its power in visualizing intracellular structures was only realized in 1974 when Elias Lazarides and Klaus Weber (then at Cold Spring Harbor Laboratory in New York state) used it to reveal microfilament bundles in cells. The basic technique works as follows.

Given a protein (antigen) that is of interest, an antibody is made. Once the cell has been made permeable, the antibody invades and binds itself to the antigen. The unbound antibody is then washed away. A second antibody carrying a fluorescent marker (such as green fluorescein or red rhodamine) recognises the first, and the process of washing away the excess is repeated. It is rather like doubling the process in conventional photographic printing with 'hypo', in which the excess developer must be fully washed out if the image is to be become clearly defined. The final step of immunofluorescence is to view the marked protein using a microscope with a light source and filter set.

A pioneer of the technique, Mary Osborn of the Max Planck Institute of Biophysical Chemistry in Göttingen, Germany, is the European winner of the 2002 L'Oreal/UNESCO Prize for Women in Science, awarded for international scientific excellence. She has also been in the vanguard of promoting the status of women scientists. Her work demonstrates that the results of immunofluorescence are both scientifically potent and visually beguiling to a high degree. Osborn, working at times together with Weber, has used immunofluorescence to disclose microtubules and intermediate filaments as functional components in cells.



**Colour coding: an immunofluorescence micrograph of epithelial and fibroblastic cells.**

The story of the microtubules vividly shows how optical and electron microscopy need to work hand in hand, and how the greater magnification of the latter does not necessarily deliver fully coherent results when visualizing the structural continuities of forms that extend across the cell. In the late 1970s there was an acrimonious debate about the length and number of microtubules. Weber and Osborn were even accused of "painting white lines" on their images. Only when the same cell was visualized by the Göttingen group, both with immunofluorescence staining for tubulin and as a whole mount in electron microscopy, did the evidence of extended microtubules speak unequivocally for itself.

The intermediate filaments have proved to be particularly useful in routine pathology and cytology, acting as highly effective markers of cell type. As Osborn explains, "human tumours retain the intermediate filament typical of their origin. Intermediate-filament antibodies can be of particular use in certain differential diagnoses when the pathologist or cytologist is unsure of the diagnosis by conventional staining."

The micrograph shown here was made by Osborn in 1987, and shows a mixture of epithelial and fibroblastic cells growing in culture stained with antibodies against two intermediate filament proteins, keratin and vimentin. The keratin antibody decorates the intermediate filaments present in the epithelial MCF7 cell line (in green) whereas the vimentin antibody decorates the filaments in the fibroblastic HS27 cell line (in red), thus distinguishing the two cell types.

Alongside the technical achievements lies a sheer love of looking at the perpetually varied topography of stained cells. As Osborn says, "I can still stare down the microscope for hours. Not only because they are beautiful but also because every cell shows subtle differences in the arrangement and distribution of the three filament systems." ■

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