

- understanding how plants are built and how to improve them. *Plant Physiol.* **123**, 423–425 (2000).
3. Rédei, G. P. in *Methods in Arabidopsis Research* (eds Koncz, C., Chua, N. H. & Schell, J.) 1–15 (World Scientific, Singapore, 1992).
 4. Fink, G. R. Anatomy of a revolution. *Genetics* **149**, 473–477 (1998).
 5. Pennisi, E. *Arabidopsis* comes of age. *Science* **290**, 32–35 (2000).
 6. Laibach, F. Zur frage nach der individualität der chromosomen im pflanzenreich. *Beih. Bot. Zentralbl.* **22**, 191–210 (1907).
 7. Laibach, F. *Arabidopsis thaliana* (L.) Heynh. als object fur genetische und entwicklungsphysiologische untersuchungen. *Bot. Archiv.* **44**, 439–455 (1943).
 8. Rédei, G. P. *Arabidopsis thaliana* (L.) Heynh. A review of the biology and genetics. *Bibliogr. Genet.* **20**, 1–151 (1970).
 9. Rédei, G. P. & Koncz, C. in *Methods in Arabidopsis Research* (ed. Koncz, C., Chua, N. H. & Schell, J.) 16–82 (World Scientific, Singapore, 1992).
 10. Rédei, G. P. *Arabidopsis* as a genetic tool. *Annu. Rev. Genet.* **9**, 111–127 (1975).
 11. Müller, A. Embryonetest zum nachweis rezessiver lethalfaktoren bei *Arabidopsis thaliana*. *Biol. Zentralbl.* **82**, 133–163 (1963).
 12. Ledoux, L., Huart, R. & Jacobs, M. DNA-mediated genetic correction of thiamineless *Arabidopsis thaliana*. *Nature* **249**, 17–21 (1974).
 13. Meinke, D. W. & Sussex, I. M. Embryo-lethal mutants of *Arabidopsis thaliana*: model system for genetic analysis of plant embryo development. *Dev. Biol.* **72**, 50–61 (1979).
 14. Koornneef, M. *et al.* Linkage map of *Arabidopsis thaliana*. *J. Hered.* **74**, 265–272 (1983).
 15. Chilton, M. D. *et al.* Stable incorporation of plasmid DNA into higher plant cells: the molecular basis of crown gall tumorigenesis. *Cell* **11**, 263–271 (1977).
 16. Koornneef, M. & van der Veen, J. H. Induction and analysis of gibberellin sensitive mutants in *Arabidopsis thaliana* (L.) Heynh. *Theor. Appl. Genet.* **58**, 257–263 (1980).
 17. Koornneef, M., Rolf, E. & Spruit, C. J. P. Genetic control of light-inhibited hypocotyl elongation in *Arabidopsis thaliana* (L.) Heynh. *Zeit. Pflanzenphysiol.* **100**, 147–160 (1980).
 18. Koornneef, M., Jorna, M. L., Brinkhorst-van der Swan, D. & Karssen, C. M. The isolation of abscisic-acid (ABA) deficient mutants by selection of induced revertants in non-germinating gibberellin sensitive lines of *Arabidopsis thaliana* (L.) Heynh. *Theor. Appl. Genet.* **61**, 385–393 (1982).
 19. Koornneef, M. *The Genetics of Some Plant Hormones and Photoreceptors in Arabidopsis thaliana* (L.) Heynh. Ph.D. thesis, Wageningen Agricultural University, The Netherlands (1982).
 20. Somerville, C. R. & Ogren, W. L. Phosphoglycolate phosphatase-deficient mutant of *Arabidopsis*. *Nature* **280**, 833–836 (1979).
 21. Somerville, C. R. & Ogren, W. L. Inhibition of photosynthesis in *Arabidopsis* mutants lacking leaf glutamate synthase activity. *Nature* **286**, 257–259 (1980).
 22. Leutwiler, L. S., Houghévans, B. R. & Meyerowitz, E. M. The DNA of *Arabidopsis thaliana*. *Mol. Gen. Genet.* **194**, 15–23 (1984).
 23. Bennett, M. D. & Smith, J. B. Nuclear-DNA amounts in angiosperms. *Phil. Trans. R. Soc. Lond. B Biol. Sci.* **274**, 227–274 (1976).
 24. Braam, J. & Davis, R. W. Rain-, wind-, and touch-induced expression of calmodulin and calmodulin-related genes in *Arabidopsis*. *Cell* **60**, 357–364 (1990).
 25. Chang, C., Bowman, J. L., DeJohn, A. W., Lander, E. S. & Meyerowitz, E. M. Restriction fragment length polymorphism linkage map for *Arabidopsis thaliana*. *Proc. Natl Acad. Sci. USA* **85**, 6856–6860 (1988).
 26. Cheng, C. L., Dewdney, J., Nam, H. G., den Boer, B. G. W. & Goodman, H. M. A new locus (*NIA 1*) in *Arabidopsis thaliana* encoding nitrate reductase. *EMBO J.* **7**, 3309–3314 (1988).
 27. Crawford, N. M., Smith, M., Bellissimo, D. & Davis, R. W. Sequence and nitrate regulation of the *Arabidopsis thaliana* mRNA encoding nitrate reductase, a metalloflavoprotein with three functional domains. *Proc. Natl Acad. Sci. USA* **85**, 5006–5010 (1988).
 28. Last, R. L. & Fink, G. R. Tryptophan-requiring mutants of the plant *Arabidopsis thaliana*. *Science* **240**, 305–310 (1988).
 29. Nam, H. G. *et al.* Restriction fragment length polymorphism linkage map of *Arabidopsis thaliana*. *Plant Cell* **1**, 699–705 (1989).
 30. Meyerowitz, E. M. & Pruitt, R. E. *Arabidopsis thaliana* and plant molecular genetics. *Science* **229**, 1214–1218 (1985).
 31. Lloyd, A. M. *et al.* Transformation of *Arabidopsis thaliana* with *Agrobacterium tumefaciens*. *Science* **234**, 464–466 (1986).
 32. Estelle, M. A. & Somerville, C. R. The mutants of *Arabidopsis*. *Trends Genet.* **2**, 89–93 (1986).
 33. Meyerowitz, E. M. *Arabidopsis thaliana*. *Annu. Rev. Genet.* **21**, 93–111 (1987).
 34. Hauge, B. M. *et al.* An integrated genetic RFLP map of the *Arabidopsis thaliana* genome. *Plant J.* **3**, 745–754 (1993).
 35. Grill, E. & Somerville, C. Construction and characterization of a yeast artificial chromosome library of *Arabidopsis* which is suitable for chromosome walking. *Mol. Gen. Genet.* **226**, 484–490 (1991).
 36. Guzman, P. & Ecker, J. R. Development of large DNA methods for plants: molecular cloning of large segments of *Arabidopsis* and carrot DNA into yeast. *Nucleic Acids Res.* **16**, 11091–11105 (1988).
 37. Ward, E. R. & Jen, G. C. Isolation of single-copy-sequence clones from a yeast artificial chromosome library of randomly-sheared *Arabidopsis thaliana* DNA. *Plant Mol. Biol.* **14**, 561–568 (1990).
 38. Arondel, V. *et al.* Map-based cloning of a gene controlling omega-3-fatty-acid desaturation in *Arabidopsis*. *Science* **258**, 1353–1355 (1992).
 39. Giraudat, J. *et al.* Isolation of the *Arabidopsis* *Abi3* gene by positional cloning. *Plant Cell* **4**, 1251–1261 (1992).
 40. Feldmann, K. A. & Marks, M. D. *Agrobacterium*-mediated transformation of germinating seeds of *Arabidopsis thaliana*: a non-tissue culture approach. *Mol. Gen. Genet.* **208**, 1–9 (1987).
 41. Marks, M. D. & Feldmann, K. A. Trichome development in *Arabidopsis thaliana*. 1. T-DNA tagging of the *glabrous1* gene. *Plant Cell* **1**, 1043–1050 (1989).
 42. Feldmann, K. A., Marks, M. D., Christianson, M. L. & Quatrano, R. S. A dwarf mutant of *Arabidopsis* generated by T-DNA insertion mutagenesis. *Science* **243**, 1351–1354 (1989).
 43. Somerville, C. *Arabidopsis* blooms. *Plant Cell* **1**, 1131–1135 (1989).
 44. Yanofsky, M. F. *et al.* The protein encoded by the *Arabidopsis* homeotic gene *agamous* resembles transcription factors. *Nature* **346**, 35–39 (1990).
 45. Feldmann, K. A. & Marks, M. D. Rapid and efficient regeneration of plants from explants of *Arabidopsis thaliana*. *Plant Sci.* **47**, 63–69 (1986).
 46. Valvekens, D., van Montagu, M. & van Lijsebettens, M. *Agrobacterium tumefaciens*-mediated transformation of *Arabidopsis thaliana* root explants by using kanamycin selection. *Proc. Natl Acad. Sci. USA* **85**, 5536–5540 (1988).
 47. Bechtold, N., Ellis, J. & Pelletier, G. *In-planta Agrobacterium*-mediated gene transfer by infiltration of adult *Arabidopsis thaliana* plants. *C.R. Acad. Sci. Ser. III* **316**, 1194–1199 (1993).
 48. Weigel, D. & Meyerowitz, E. M. The ABCs of floral homeotic genes. *Cell* **78**, 203–209 (1994).
 49. Bowman, J. L., Smyth, D. R. & Meyerowitz, E. M. Genetic interactions among floral homeotic genes of *Arabidopsis*. *Development* **112**, 1–20 (1991).
 50. Haughn, G. W. & Somerville, C. R. Genetic control of morphogenesis in *Arabidopsis*. *Dev. Genet.* **9**, 73–89 (1988).
 51. Magnien, E., Bevan, M. & Planque, K. A European bridge project to tackle a model-plant genome. *Trends Biotechnol.* **10**, 12–15 (1992).
 52. Kaul, S. *et al.* Analysis of the genome sequence of the flowering plant *Arabidopsis thaliana*. *Nature* **408**, 796–815 (2000).
 53. Somerville, C. & Dangl, L. Genomics: plant biology in 2010. *Science* **290**, 2077–2078 (2000).
 54. Somerville, C. The twentieth century trajectory of plant biology. *Cell* **100**, 13–25 (2000).

Acknowledgements

We thank G. Dilworth, M. Dilworth, M. Clutter, D. Meinke and E. Meyerowitz for providing images and information about events mentioned herein.

 Online links

DATABASES

The following terms in this article are linked online to: **The Arabidopsis Information Resource (TAIR):** <http://www.arabidopsis.org>
FAD3

FURTHER INFORMATION

Affymetrix's Arabidopsis ATH1 Genome Array: http://www.affymetrix.com/support/technical/datasheets/arab_datasheet.pdf
Chris Somerville's lab: http://www.ciwddp.stanford.edu/research/research_csomerville.php
GARNET: <http://www.york.ac.uk/res/garnet/garnet.htm>
International Arabidopsis Symposium in Göttingen, Germany: <http://www.arabidopsis.org/ais/1965/contents01S.html>
Kazusa DNA Research Institute: <http://www.kazusa.or.jp/en>
Maarten Koornneef's lab: <http://www.dpw.wageningen-ur.nl>
MIPS: http://mips.gsf.de/proj/thal/proj/thal_overview.html
SciSearch: <http://lib-www.lanl.gov/www/citations/citations.htm>
Access to this interactive links box is free online.

TIMELINE

Conrad Hal Waddington: the last Renaissance biologist?

Jonathan M. W. Slack

Conrad Hal Waddington was a leading embryologist and geneticist from the 1930s to the 1950s. He is remembered mainly for his concepts of the 'epigenetic landscape' and 'genetic assimilation'. This article reviews his life and work, and enquires to what extent his ideas are relevant tools for understanding the biological problems of today.

Conrad Hal Waddington was a true twentieth-century polymath: he published research in palaeontology, population genetics, developmental genetics, biochemical embryology

and theoretical biology. No modern funding agency would allow any individual to undergo so many changes of interest and direction. It is therefore a sign of the changes that occurred in the biosciences during the twentieth century that Waddington was awarded a series of research fellowships and academic positions in the 1930s and 1940s, culminating in the directorship of the Institute of Genetics in Edinburgh, UK. Most biologists under 40 years old have probably not heard of Waddington, who died in 1975. But to many of us who are a little older, he is



Figure 1 | **Conrad Hal Waddington**. Reproduced with permission from REF. 1 © (1977) The Royal Society.

a dimly remembered figure from the past. Why do we remember the name? What did he discover? What were his ideas, and have any of them survived to the modern machine age of the post-genomic biosciences? Before the Second World War, Waddington's interests were in embryology and, in particular, the identification of inducing factors that are active in early embryonic development. Subsequently, his work shifted in the direction of genetics, but retained a distinctive character that was shaped by an awareness of developmental problems. In this article, I outline his work in a broadly chronological manner, pausing to examine more closely the more important themes.

Waddington's formative years
C. H. Waddington was born in 1905 (FIG. 1; REF. 1). His parents were tea planters in India, and he spent the first four years of his life there, but was later brought up in England by relatives. Like many other academic scientists, his childhood was spent collecting fossils, minerals and insects, or attempting chemical experiments. He attended the exclusive Clifton College School (a private high school) and was there taught chemistry by E. J. Holmyard, who was a noted writer of chemical textbooks and who interested Waddington not just in modern chemistry, but also in some of its

antecedents, such as Arabic alchemy and Alexandrian Gnosticism. In later life, he maintained that this interest in metaphysics had been seminal for his later scientific work². Waddington then went to the University of Cambridge and studied the natural sciences, specializing in geology. He recounts that he read little of the material that was required for his exams. Instead, he read much philosophy, particularly the ideas of A. N. Whitehead, a philosopher who had been at Cambridge in the early years of the century and who was concerned particularly with the reality of the perception of objects and the relations between objects. Waddington's unusual interests did not prevent him graduating with a first-class degree. He then began his Ph.D. research in palaeontology, studying the structure of ammonites. Interestingly, he simultaneously held two studentships for this work, one for palaeontology and the other for philosophy, the latter presumably a reward for his intensive studies of the ideas of Whitehead. By modern standards, he then irretrievably blotted his copybook by not finishing his Ph.D. thesis (although this would have been quite common at the time) and he remained 'Mr Waddington' until 1938, when he received a doctorate for his published work.

Embryology: the vertebrate organizer
Despite his curious interests, Waddington obtained a research fellowship in 1929 to work at the prestigious Strangeways Laboratory near Cambridge. He was not only an expert on ammonites and on the philosophy of science, but also evidently familiar with the recent German research in embryology that had led to the discovery of the 'organizer' by Spemann and Mangold in 1924 (REF. 3). The organizer is a region in the early amphibian embryo that has the property of inducing a second embryonic axis (that is, a second complete body) around itself, when grafted onto the ventral side of a host embryo. The new director of the Strangeways laboratory was Honor Fell, who was a pioneer in the techniques of organ culture *in vitro*. Waddington wondered if it would be possible to use these techniques to study the early embryonic development of higher vertebrates, such as mammals and birds, which are less amenable to microsurgical work than the amphibian embryos used by Spemann. He was successful in this and published a series of papers during the 1930s, in which he showed that there was indeed an organizer in mammals and birds. In higher vertebrates, the main body axis appears at an early stage as a condensation of cells called the 'primitive streak'. At the anterior end of the streak is a

region called Hensen's node. Waddington showed that the grafting of a duck node onto an early chick embryo (at the blastoderm stage) could induce the formation of a second body axis (FIG. 2). The most celebrated of his experiments was one on duck embryos in which he joined two blastoderms face to face and showed that each Hensen's node induced another primitive streak in the adjoining blastoderm⁴. He also showed that a node from a chick embryo could induce a second axis in a rabbit embryo, therefore indicating that the organizer signal, which emanated from the node, was the same in different classes of vertebrates⁵. Although, in his day, it was difficult to distinguish the graft from the host and hence determine exactly which parts had been induced, this could be done to some extent on the basis of the size of cells from the different species used. Waddington's conclusions on the organizer-like role of Hensen's node proved essentially correct, but in my view he was not credited sufficiently when interest in this question was re-awakened in the 1990s.

His other main line of work in the 1930s was pursued in collaboration with Joseph and Dorothy Needham on the chemical

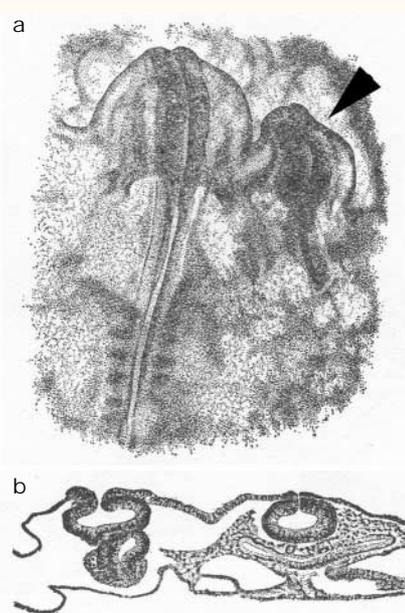


Figure 2 | **The existence of an organizer in higher vertebrates.** **a** | Graft of a duck node (indicated by an arrowhead) onto a chick blastoderm. The original embryo body is on the left, and the induced secondary embryo is on the right. **b** | The neural tube of the secondary embryo — a cylindrical structure that runs through the midline of the embryo — can be seen clearly in the section on the right. Panels **a** and **b** reproduced with permission from REF. 20 © (1956) Cambridge University Press.

“Waddington was the only one who seems to have thought through the problem and understood that the ‘organizer effect’ could not simply arise from one substance.”

basis of the organizer. Some of this work was done in Germany, as he obtained a research fellowship to visit Berlin. It is there that he met Otto Mangold, husband of the short-lived Hilde Mangold of the famous organizer paper, and a leading embryologist in his own right. A famous paper in the journal *Naturwissenschaften* had been published in 1932, showing that organizer tissue that was killed by heating or freezing had some inducing activity and that the inducing signal was therefore likely to be a chemical substance⁶. Several groups raced to identify this miraculous substance⁷. Most laboratories tended to assume that the nature of the organizer would be that of a simple neural inducer, because the most prominent feature of the second body axis that was induced by the organizer was the neural tube. By contrast, Waddington was the only one who seems to have thought through the problem and understood that the ‘organizer effect’ could not simply arise from one substance. This is because a whole secondary body is induced, containing many tissue types in a complex pattern. Waddington distinguished between ‘evocation’ — the unleashing of one of two possible pathways of development by the application of a substance — and ‘individuation’ — the production of a complex pattern by the inducing signal. The modern equivalent of ‘individuation’ is the formation of many specified regions in response to a concentration gradient of the inducer, to which the responding tissue has several threshold responses. Although this particular mechanism was proposed by Dalcq and Pasteels in 1937 (REF. 8), it did not become widely accepted until the 1980s. The ‘gold rush’ for the organizer is a well-known story⁷. Different groups isolated different active fractions from their starting material, including nucleic acid, the cephalins (a group of phospholipids) and glycogen. In the case of Waddington and the Needhams, they found that the neural-inducing activity (‘the evocator’) purified with the “unsaponifiable fraction of lipids”, that is,

the steroids⁹. We now know that the biochemists of the 1930s had no chance at all of purifying the inducing factors from early embryos: they are growth factors, present in picomolar concentrations, and cannot be purified without kilos of starting material and costly modern fractionation equipment. However, growth factors are notorious for their high specific activity and for sticking to a wide variety of other substances, so it is possible that all of the competitors had obtained contaminating traces of activity in their favourite chemical fraction, making it seem like the real organizer substance. It might also be noted that steroids had become increasingly popular by the mid-1930s. It had recently been discovered that sex hormones, the cardiac glycoside drugs and at least one important vitamin (vitamin D) were all steroids. Their chemical relatives, the polycyclic aromatic hydrocarbons, were being discovered to be potent carcinogens. Not for the last time would a fashionable class of compound be suspected of other glamorous activities and scientists be primed to expect such additional roles.

Perhaps it is because Waddington understood that the organizer effect was more complex than a simple response to one substance that he was involved in the final debacle of the gold rush. At the time, it was thought that organizing centres in the embryo might be high points of oxidative metabolism. Waddington investigated this by treating embryos with the dye methylene blue, which is an electron acceptor and so accelerates the rate of respiration. Alas, methylene blue did not affect the respiratory rate of the embryos, but it did induce neural tissue¹⁰! As it was an obviously unnatural compound, this led to the idea that embryonic induction was unspecific and that it would never be possible to purify the active organizer molecules by biological activity. Although there is certainly some non-specificity in newts, this is not true of other amphibians, such as *Xenopus*. It is more likely that the methylene blue was creating some tissue damage and liberating some growth factors as a result. The exaggerated pessimism about specificity remained in force until the 1980s, when the inducers were finally identified as members of the transforming growth factor- β and fibroblast growth factor families¹¹.

Genetics and development
Despite his heavy involvement in embryological research during the 1930s, Waddington was also interested in genetics, particularly through his friendship at Cambridge with Gregory Bateson (son of

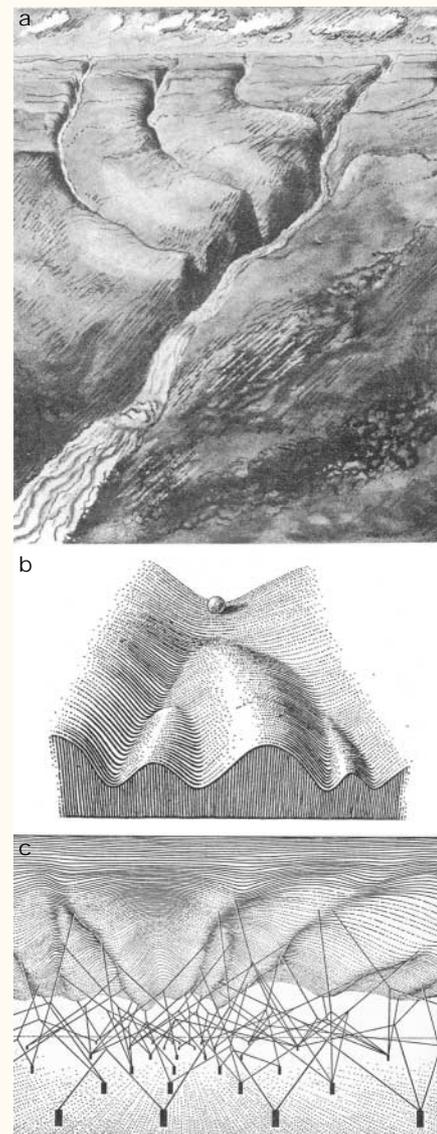


Figure 3 | The epigenetic landscape. **a** | This is a painting by John Piper that was used as the frontispiece for Waddington's book *Organisers and Genes*. In the picture, which is intended to represent the epigenetic landscape, the developmental pathways that could be taken by each cell of the embryo are metaphorically represented by the path taken by water as it flows down the valleys. The water is supposed to be flowing away from the viewer, towards the sea in the distance. But the bifurcations of the valleys look so unnatural that the flow of water actually appears to be towards the viewer. **b** | A later depiction of the epigenetic landscape. The ball represents a cell, and the bifurcating system of valleys represents the ‘chreodes’ or bundles of trajectories in state space. **c** | A rare view behind the scenes of Waddington's landscape. Each valley in the landscape is formed by tension on guy ropes that are attached to complexes of ‘genes’, represented as pegs stuck in the ground. Panel **a** reproduced with permission from the frontispiece of REF. 12 © (1940) Cambridge University Press; panels **b,c** reproduced with permission from REF. 13 © (1957) Geo Allen & Unwin.

Box 1 | Dynamical systems theory and the epigenetic landscape

Waddington formulated the concept of the epigenetic landscape, published in its mature form in 1957 (REF. 13), to represent the way that developmental decisions are made. His model was influenced by the tradition of dynamical systems theory, which was particularly associated with the name of Henri Poincaré and was ultimately derived from nineteenth-century work on celestial mechanics. A dynamical system comprises a series of relationships that describes the evolution of system variables in time, and their dependence on each other. At any one time, the system can be represented by a single point in a multidimensional state space, the axes of which represent the values of each of the system variables. Every point in state space is associated with a vector, representing the direction and velocity of evolution of the system from that point. A few isolated points will be 'attractors' to which the system will move spontaneously, given enough time. Waddington's epigenetic landscape is a metaphor for a dynamical system, one in which the axes represent concentrations of all the substances, or all the gene products, in the cell. All the cells in the embryo would evolve according to the same laws, but because of the existence of inducing signals, cells in different regions would follow different pathways ('chreodes') and end up at different attractors, which can be elegantly associated with different states of terminal differentiation.

In certain simple physical systems, it is possible to predict the evolution of the system by computing the potential energy that is associated with it. In such cases, the system will evolve spontaneously to a local minimum of potential energy. René Thom in his 'catastrophe theory'¹⁹ proposed that it would be possible to compute a generalized 'potential surface' for any dynamical system. As these surfaces can be somewhat folded, movement 'down' the surface can lead to discontinuous changes in one or more of the system variables. This is a so-called 'catastrophe', representing an abrupt, discontinuous change in a system that is governed by smooth continuous dynamics. There is an obvious similarity between this formulation and Waddington's epigenetic landscape, and he helped to publicize catastrophe theory through the Serbelloni symposia (see main text).

Whether in a general sense of arbitrary n -dimensional complex systems, or in its specific manifestation of catastrophe theory, dynamical systems theory has been popular in the social sciences. However, it has been more useful in providing an imagery and language for discussion than it has in formulating concrete theories that have real predictive value. So far, it has made little impact in developmental biology, where most scientists insist on the primacy of data and in finding out what is actually there. A form of dynamical systems theory that might be more applicable to developmental problems is offered by Boolean networks, in which all variables can take just the two values 0 or 1 (REF. 21). This corresponds well to the idea that a gene is either 'on' or 'off'. Such systems are computationally more tractable than those based on differential equations, but so far biologists have shown little interest in them.

the evolutionary theorist William Bateson, and a leading geneticist in his own right). In 1939, he went to the United States and worked at Caltech with Sturtevant and Dobzhansky on *Drosophila* wing development. In 1940, one of his most influential books, *Organisers and Genes*¹², was published, in which he discussed at length the importance of 'competence' — the ability of cells or tissues to react to an inducing signal. At the time, the nature of genes was still unclear but it was known that they were involved in the production of enzymes and, perhaps, other substances. Waddington was impressed by the similarity between the qualitative decision points found in both inducing-factor action and gene action. For example, the ectoderm of an amphibian embryo would become epidermis without the neural-inducing factor but would switch its fate to neuroepithelium in its presence. The *Drosophila* antenna (a sensory

appendage on the head) would form an arista (a bristle on the distal end of the antenna) under the influence of the wild-type allele of the gene *aristopedia*, but would become switched to a terminal leg segment (tarsus) under the influence of a mutant allele. (*aristopedia* is an example of a homeotic gene, mutations of which can convert one body part into another.) Reasoning from such examples, he presented development as a series of branching decisions, taken under the control of genes. This book also introduced, for the first time, the idea of the 'epigenetic landscape' to describe the process of decision-making in development (FIG. 3a).

The epigenetic landscape. This is perhaps the idea for which Waddington is best remembered and that is described in detail in a second influential book, *The Strategy of the Genes*¹³. The landscape refers to a surface

down which a ball rolls (FIG. 3b). At various points, there are branches in the possible path the ball can take, and so by the time it has rolled to the bottom it will have made several binary choices. The ball represents a cell in an embryo and, at each developmental branchpoint, it is nudged down one path or the other by the action of embryonic inducing factors and/or homeotic genes. It is not clear from Waddington's earlier works exactly what the folded surface of the landscape represents, and scientists are still confused by this today. In *The Strategy of the Genes*, he explicitly states that the landscape represents a surface embedded in a multidimensional state space of cellular metabolism — that is, a space for which there is one axis representing the concentration of each substance in the cell. The pathways are the permitted trajectories ('chreodes') that can be taken by cells (BOX 1). In reality, the permitted pathways would be unlikely to form a two-dimensional surface, but this is the form that lends itself to a diagram on the printed page. Most amusingly, he showed us a view of the 'underside' of the landscape, revealing its hypothetical relationship to the genes (FIG. 3c). Genes are visualized as pegs stuck in the ground, each with a guy rope attached to a sheet of fabric, which makes up the landscape. The idea is that individual genes have quantitative effects and their individual actions cooperate to produce the landscape as a whole. This conception of the landscape seems to derive from the philosophical heritage of Whitehead, as Waddington describes the action of many genes as forming a 'conrescence', a typical Whiteheadian concept. Nonetheless, the guy rope arrangement indicates that there might be some individual genes that could change the topology of the landscape if mutated to inactivity and therefore give rise to discrete changes in developmental pathways. These are, of course, the homeotic genes, such as *aristopedia*, which Waddington had encountered in his studies of *Drosophila*.

It should be noted that the landscape incorporates some of Waddington's developmental concepts, for which he introduced new terms (BOX 2). For example, the pathways themselves are called 'chreodes'. The term 'canalization' means that, up to a certain threshold, any genetic variation or environmental noise will be 'buffered' and not affect the pathway, but above this threshold, the cell would flip over into an adjacent pathway. By representing a pathway as a valley in a surface, Waddington provided a simple mechanical analogy for the rather complex biochemical-genetic buffering that occurs in organisms during development.

Box 2 | A Waddingtonian glossary

In all his books, Waddington's philosophical background comes to the fore through his eagerness to define new terms to express the essential underlying phenomena of development. The most important are listed here.

Evocation

The effect of an inductive signal, the action of which on the responding tissue selects one of a few possible developmental pathways. At a local level, we now understand that all inductive signals are evocators, but Waddington emphasized the distinction between evocation, which might arise from the application of a single substance, and potentially more complex processes.

Individuation

The early organizer experiments made it seem that the signal was calling into existence a whole complex body plan. Waddington called such complex events 'individuation'. Today there are well-characterized signals that, by themselves, create a pattern; for example, a morphogen gradient that has several threshold responses produces an ordered pattern of induced structures. However, each individual local induction is an evocation.

Competence

The capacity to respond to an inductive signal. Waddington did not invent this term, which is a translation of the German 'Reaktionsfähigkeit', but he did write at length on the importance of competence.

Epigenetic landscape

A visual depiction of a set of developmental choices that is faced by a cell in the embryo. (See FIG. 3 and main text of article.)

Canalization

A valley in the landscape represents a cluster of similar trajectories through state space. The idea of canalization indicates that most trajectories will exist as clusters; in other words, a small external or internal perturbation will not affect the pathway.

Chreode

Chreodes are the buffered pathways in the landscape.

Homeorhesis

A counterpoint to the 'homeostasis' (maintenance of a stable state) concept of Claude Bernard. Homeorhesis indicates a situation of stable flow.

Epigenetics

To Waddington, 'epigenetics' meant the "causal analysis of development". In the 1960s, he persuaded the UK Medical Research Council to support an epigenetics sub-institute of his establishment in Edinburgh. However, the spirit of the times meant that it became simply another building full of molecular biologists.

Now that developmental biology has become a mature science, the only two of Waddington's terms that have lasted are 'competence' and 'epigenetics'. Neither term was actually introduced by Waddington, and 'epigenetics' today tends to be used in the narrower sense of gene regulation by chromatin modification. However, his distinction between 'evocation' and 'individuation' is preserved in the modern theory of the morphogen gradient.

The epigenetic landscape was a completely original contribution to developmental biology, although the idea was derived from Sewall Wright's 'fitness landscape', which was applied to evolutionary theory. The latter is a multidimensional state space in which the axes are all the attributes of the organism and the surface represents the fitness. Sewall Wright's image was mainly used to argue that there would be local 'peaks' of fitness from which organisms could not easily reach higher peaks, as they would have to get there through a 'valley' of lower fitness.

One rather worrying feature of *The Strategy of the Genes* is the curious vagueness

about the molecular nature of the gene, especially as the book was published four years after Watson and Crick's revelation of the structure of DNA. This must partly be due to the fact that much of the book is based on manuscripts written in the 1940s, but also indicates that Waddington probably did not appreciate just how much this discovery would revolutionize biology in the future.

The post-war period

During the Second World War, Waddington worked for the Royal Air Force Coastal Command, where he used the new method of 'operational research' (the use of mathematical

modelling to improve procedures) to increase the effectiveness of anti-U-boat measures. In 1944, he became deputy director of a new research institute for animal breeding and genetics, and took with him some of his operational research team. A measure of his perceived importance is that the institute was originally due to be sited in Oxford, but was actually set up in Edinburgh so that Waddington could also occupy the Chair of Genetics at that university. After some reorganization of the departments in the institute, Waddington ended up as Honorary Director of the Institute of Genetics, the focus of which was on basic science, separate from the applied animal breeding section.

Apart from some trips to the United States in the 1970s, Waddington stayed in Edinburgh until his death in 1975. The experimental work that he carried out in the 1950s and 1960s was mostly a disappointment, considering the enormous intellectual promise he had shown before the war. Much was focused on the use of electron microscopy to look more closely at eggs and embryos, and on isotopic tracers to follow embryonic biosynthesis and the transport of materials.

The inheritance of acquired characteristics. His last memorable experimental work, done in the late 1940s and early 1950s, concerned the phenomenon of 'genetic assimilation'. This is a Darwinian mechanism that mimics the inheritance of acquired characters. Fifty years ago, the issue of the inheritance of acquired characters was particularly important because of the dominance of T. D. Lysenko in the USSR¹⁴. Lysenko was a plant breeder who managed to use his political influence to acquire a senior position in Soviet science. He espoused a theory involving the inheritance of acquired characters and was able to use the repressive machinery of the Soviet state to dispose of his scientific opponents. He had made some real discoveries relating to the 'vernalization' of crops (whereby treatments applied to winter crop varieties allow them to be sown in the spring, therefore increasing overall yield), and did help Soviet agriculture in the dark days of the Second World War. However, his overall influence was profoundly negative and set back Soviet genetics for many decades¹⁴. Waddington was closely associated with a group of left-wing scientists, including Blackett, Bernal, Hogben, Pirie and the Needhams. This group, working in Cambridge and London, covered a breadth of scientific interests ranging from physics through protein crystallography to metabolic biochemistry. The rise of Lysenko was a



Figure 4 | The callosities on the ventral surface of the ostrich. The callosities are depicted by arrows. How did they become assimilated into the genome? Reproduced with permission from REF. 13 © (1957) Geo Allen & Unwin.

source of extreme embarrassment to them because anyone who supported the USSR was expected also to support Lysenko. Waddington himself never had any sympathy for Lysenko's views, and in the end only Bernal of the British group actually attempted to defend him in public.

The type of phenomenon that Waddington sought to explain had previously been called 'pseudoexogenous adaptation'. A celebrated example is represented by the prominent callosities on the ventral skin of the ostrich (FIG. 4). Callosities of the epidermis can be produced by prolonged rubbing, and when the ostrich sits down, it will rub two particular places on its ventral surface. These spots bear prominent callosities; however, surprisingly, they do not arise during life but are formed during embryonic development, so they are already present at the time of hatching. The question in the early years of the century was: Did rubbing the skin of ancestral ostriches bring about a change in their genes such that the callosities were produced spontaneously? The ostrich is not a convenient model organism for experimental genetics, but Waddington was able to obtain very similar effects in the laboratory using *Drosophila*. His key idea was that a

qualitative morphological change can be produced by an external treatment, but the competence to respond to the treatment is a quantitative variable that depends on many loci. If the treatment is applied, and a proportion of individuals show the morphological effect, then selective breeding from this group can eventually produce a population in which the morphological change arises spontaneously without the treatment. A clear example of this is Waddington's experiments with the **crossveinless** phenotype in *Drosophila*^{15,16}. There is a small transverse ('cross') vein in the middle of the *Drosophila* wing, and this can be made to disappear by briefly exposing flies to a high temperature during pupation. If the individual flies that lack the cross-vein are bred, and the temperature shock and selection is repeated for a few generations, then a population arises in which a high proportion has the spontaneous crossveinless phenotype. Waddington emphasized the key role of his concept of 'canalization' (BOX 2) in understanding genetic assimilation, because the essentially quantitative variation becomes converted into qualitative change through a switch in the developmental pathway.

Waddington's association with the political left has given rise to a colourful but inaccurate legend concerning the 'commune' founded in Edinburgh for the staff of his new institute. This was Mortonhall House, on the outskirts of Edinburgh. It was rented by the then Agricultural Research Council in 1947 to provide housing for members of the new institute, as housing was practically unobtainable in Edinburgh after the war. Ten families moved in, along with some single people in the attic. Meals were taken at a common table, and there was a domestic staff of three to do the cooking and cleaning. Altogether, it sounds more like a Cambridge College than a hippie commune. Apparently, the experiment was not very successful as the hierarchy of work was brought back to the home, creating some tensions. After the first couple of years, the families began to move out, and the house was closed after six years.

Although Waddington's later experimental work was not so interesting, he became increasingly active in promoting theoretical biology. This culminated in the holding of four symposia at the Villa Serbelloni on Lake Como in Italy, under the auspices of the Rockefeller Foundation (which had also funded his early work on inducing factors). The symposia were published as four volumes by Edinburgh University Press and contain a bizarre miscellany of articles about whether

there can be general theories in biology, and some specific speculations about development and evolution¹⁷. Out of these meetings came Lewis Wolpert's positional information theory¹⁸, according to which regional specification in development works by cells first acquiring information about their position in the embryo, and then interpreting this condition as a particular pathway of differentiation. In addition, they also helped to popularize the 'catastrophe theory' of René Thom¹⁹ (BOX 1).

Conclusions

Waddington is a unique figure in the history of twentieth-century biology. Apart from the scientific work that is the subject of this article, he was also a connoisseur of the arts and was personally acquainted with many of the leading artists, sculptors and architects of the day. His first wife, 'Lass' Lascelles, was an artist, and his second wife, Justin Blanco White, an architect. He was also a Morris dancer (practitioner of an eccentric form of English traditional dancing) and squire (leader) of the Cambridge Morris Men in the 1930s. His scientific legacy is represented by two important discoveries: the organizer in higher vertebrates, and the phenomenon of genetic assimilation. In addition, there is his promotion of theoretical biology and the colourful metaphor of the epigenetic landscape. I, myself, was greatly stimulated by his book *Principles of Embryology*²⁰ when I entered developmental biology in the early 1970s. Although the terminology that he introduced never became popular, he did discover the mammalian organizer and he did pioneer the use of dynamical systems approaches to thinking about genetic networks and development. He is not well known to younger biologists because his work lies to one side of the mainstream of molecular biology. However, one of the biggest challenges of today is how to relate a vast and rapidly growing mass of genomic information to a relatively much smaller number of key biological phenomena. Some form of theoretical biology will have to be devised to meet this challenge and, whether attributed or not, Waddington's ideas will doubtless re-surface in the process.

Jonathan M. W. Slack is in the Developmental Biology Programme, Department of Biology and Biochemistry, University of Bath, Bath BA2 7AY, UK.
e-mail: j.m.w.slack@bath.ac.uk

doi:10.1038/nrg933

1. Robertson, A. Conrad Hal Waddington 8 November 1905–26 September 1975. *Biogr. Mem. Fellows R. Soc.* **23**, 575–622 (1977).
2. Waddington, C. H. in *Towards a Theoretical Biology* Vol. 2, 72–81 (Edinburgh Univ. Press, UK, 1969).

3. Spemann, H. & Mangold, H. Über Induktion von Embryonenanlagen durch Implantation artfremder Organisatoren. *Arch. Microsk. Anat. EntwMech.* **100**, 599–638 (1924).
4. Waddington, C. H. Experiments on the development of chick and duck embryos cultivated *in vitro*. *Phil. Trans. R. Soc. Lond. B Biol. Sci.* **221**, 179–230 (1932).
5. Waddington, C. H. Experiments on determination in the rabbit embryo. *Arch. Biol.* **48**, 273–290 (1937).
6. Bautzmann, H., Holtfreter, J., Spemann, H. & Mangold, O. Versuche zur Analyse der Induktionsmittel in der Embryonalentwicklung. *Naturwissenschaften* **20**, 971–974 (1932).
7. Witkowski, J. A. Optimistic analysis — chemical embryology in Cambridge 1920–42. *Med. Hist.* **31**, 247–268 (1987).
8. Dalcq, A. & Pasteels, J. Une conception nouvelle des bases physiologique de la morphogénèse. *Arch. Biol.* **48**, 669–710 (1937).
9. Waddington, C. H., Needham, J. & Needham, D. M. Studies on the nature of the amphibian organisation centre. I. Chemical properties of the evocator. *Proc. R. Soc. Lond. B Biol. Sci.* **117**, 289–310 (1935).
10. Waddington, C. H., Needham, J. & Brachet, J. Studies on the nature of the amphibian organisation centre. III. The activation of the evocator. *Proc. R. Soc. Lond. B Biol. Sci.* **120**, 173–198 (1936).
11. Slack, J. M. W. Inducing factors in *Xenopus* early embryos. *Curr. Biol.* **4**, 116–126 (1994).
12. Waddington, C. H. *Organisers and Genes* (Cambridge Univ. Press, UK, 1940).
13. Waddington, C. H. *The Strategy of the Genes* (Geo Allen & Unwin, London, 1957).
14. Medvedev, R. *The Rise and Fall of T. D. Lysenko* (Columbia Univ. Press, New York, 1969).
15. Waddington, C. H. Canalization of development and the inheritance of acquired characters. *Nature* **150**, 563–565 (1942).
16. Waddington, C. H. Selection of the genetic basis for an acquired character. *Nature* **169**, 278 (1952).
17. Waddington, C. H. (ed.) *Towards a Theoretical Biology* Vols 1–4 (Edinburgh Univ. Press, UK, 1968–1972).
18. Wolpert, L. Positional information and the spatial pattern of cellular differentiation. *J. Theor. Biol.* **25**, 1–47 (1969).
19. Thom, R. *Structural Stability and Morphogenesis* (Benjamin, Reading, Massachusetts, 1975).
20. Waddington, C. H. *Principles of Embryology* (Cambridge Univ. Press, UK, 1956).
21. Thomas, R. Boolean formalisation of genetic control circuits. *J. Theor. Biol.* **42**, 563–585 (1973).

Acknowledgements

I am grateful to A. McLaren, C. Stern and L. Wolpert for comments on the manuscript, but I know they do not necessarily agree with all my statements.

Online links

DATABASES

The following terms are linked online to:
LocusLink: <http://www.ncbi.nlm.nih.gov/LocusLink/ristapediala> | [crossveinless](#)

FURTHER INFORMATION

Jonathan Slack's lab: <http://www.bath.ac.uk/bio-sci/slack.htm>
 Access to this interactive links box is free online.

