CC/NUMBER 3
JANUARY 20, 1986

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Wolpert L. Positional information and the spatial pattern of cellular differentiation. *J. Theor. Biol.* 25:1-47, 1969.
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Patterns of cellular differentiation may be generated by the cells, first having their position specified as in a coordinate system, and then interpreting this in terms of their genetic constitution and developmental history. The coordinate system may be universal. [The SCI® indicates that this paper has been cited in over 545 publications since 1969.]

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November 14, 1985

In the early 1960s, I had been working during the summers with Trygve Gustafson on the cellular basis of sea-urchin morphogenesis.[1] While we were interested in cellular forces, I was very conscious of the long-standing Swedish interest in gradients and regulation of sea-urchin embryo, particularly that of Rünnstrom and Hörstadius, but I couldn't understand how these gradients could specify pattern or how they were regulated. In fact, apart from Meryl Rose and C.H. Waddington, no one thought much about spatial organization. Cell differentiation and induction were the dominant interests. I, however, was primarily concerned with the ability of the sea-urchin embryo to develop a spatially normal pattern over an eight-fold size range. When I got married and found it difficult to travel to Sweden for the summers, I chose to work with Gerry Webster on *Hydra* regulation as a model. In order to formulate the problem more formally, I invented the French Flag Problem: how a line of similar cells could form a pattern such that one-third was blue, one-third white, and one-third red. I was collaborating with two theoreticians, Mary Williams and Michael Apter. Apter was keen on the obvious solution—number the cells from each end, and the cells can thus compute which third of the line they are in! For some time, I resisted this solution as being too complex but suddenly realized that, in more general terms, if cells knew their position, then a larger number of pattern problems could be accounted for. I was particularly encouraged that it could account for Curt Stern's experiments on genetic mosaics in *Drosophila*.[2]

Part of the stimulus for my work was Waddington's Theoretical Biology Meetings at Bellagio, and I presented the idea there at Easter 1968, where it was sympathetically received. But at Woods Hole, in the same year, the reception was rather hostile. However, I was encouraged, particularly by Sydney Brenner, to write it up fully.

The paper has frequently been cited because, I hope, it both defined the general field of pattern formation and provided a particular conceptual framework. The idea of positional information is now quite widely used in developmental biology.[3] The most interesting application is the model for epimorphic regulation developed by French, Bryant, and Bryant,[4] which suggested that there is a set of positional values specified in terms of polar coordinates. They put forward a set of rules for how the system regulates that can explain a wide variety of results. Our own work has concentrated on positional information in the chick limb bud.[5-7]

1. **Gustafson T & Wolpert L.** Cellular movement and contact in sea urchin morphogenesis. *Biol. Rev.* 42:442-98, 1967. (Cited 200 times.)
2. **Stern C.** Gene expression in genetic mosaics. *Genetics* 61:199-211, 1969.
3. **Wolpert L & Stein W.** Positional information and pattern formation. (Malacinski G M & Bryant S V, eds.) *Pattern formation. A primer in developmental biology.* New York: Macmillan, 1984. p. 3-21.
4. **French V, Bryant P J & Bryant S V.** Pattern regulation in epimorphic fields. *Science* 193:969-81, 1976. (Cited 310 times.)
5. **Summerbell D, Lewis J H & Wolpert L.** Positional information in chick limb morphogenesis. *Nature* 244:492-6, 1973. (Cited 175 times.)
6. **Tickle C, Summerbell D & Wolpert L.** Positional signalling and specification of digits in chick limb morphogenesis. *Nature* 254:199-202, 1975. (Cited 120 times.)
7. **Tickle C, Alberts B, Wolpert L & Lee J.** Local application of retinoic acid to the limb bud mimics the action of the polarizing region. *Nature* 296:564-5, 1982.