relocation of a particular lipid — phosphatidylserine — from the inner to the outer leaflet of the plasma membrane[6]. It is also envisaged that death induces the inappropriate surface localization of molecules from internal cellular compartments[7], which seems plausible given the violent membrane remodelling and changes in cell volume or density that occur as cells die. But none of the latter, potentially attractive, molecular signals has been identified.

Brown *et al.*[1] now provide evidence of an alternative sorting system that is based on negative, rather than positive, cues. They propose that repulsive impulses from healthy cells actively discourage the predatory phagocytes. But these impulses are disabled during cell death, and it is this that allows prolonged contact between predator and prey. Such long-lasting interactions assist the definitive recognition of attractive signals generated later on the dying cells by specialized receptors on the phagocyte surface[8].

The authors obtained clues to this mechanism by reconstituting, in a flow-chamber system, encounters between macrophages (a particularly efficient type of phagocyte) and leukocytes (a potential prey). Here, and consistent with previous observations made by video recording[9], macrophages methodically palpate any leukocytes that they encounter. If a leukocyte is healthy, it quickly detaches from the macrophage. But if it is dead or dying, the contact lasts long enough to allow the cell to be eaten.

What is the molecular basis for this interaction? Adhesion receptors are proteins that allow cells to contact other cells or their extracellular matrix, and are among the best candidates for the molecules that mediate the link between macrophages and dying cells, as well as the switch between attraction and repulsion. Brown *et al.* identified CD31 as the adhesion receptor in this case. CD31 is a widely expressed membrane protein that can be involved in a variety of interactions[10]. It binds to several different partners to modulate adhesiveness and cell activation, and can also interact with CD31 molecules on the surface of other cells. For instance, CD31 on leukocytes can bind to CD31 on cells of endothelial tissue layers, allowing the leukocytes to migrate across the endothelia towards a site of infection[11]. Here, a repeated shift from attachment to detachment — in response to bidirectional signalling through CD31 — is a key determinant of cell progression.

So what happens in our cellular life-or-death situation? Brown *et al.* first show that the predominant method by which leukocytes are tethered to macrophages involves a 'handshake' between their respective CD31 proteins. They also forced cells that do not normally express CD31 to do so and found that, when these cells were healthy, they first attached to and then detached from macrophages. But when they were dying, they remained attached. Brown *et al.* also engineered living leukocytes to express a mutant CD31 that could not anchor to the membrane or could not transmit signals into the leukocyte on binding to CD31 on macrophages. These leukocytes also remained attached. Other data hinted that CD31 signalling is naturally disabled in dying leukocytes, preventing detachment.

Thus, the idea is that when a healthy cell encounters a macrophage, signalling through the bound CD31 receptors leads to the cell's being repelled and detaching (although the molecular details of repulsion are not known). But in dying cells, signalling through CD31 is somehow disrupted; the cell is not repelled, and the balance is shifted towards its engulfment (Fig. 1).

Although it is not yet known how the CD31-mediated signal is disabled during cell death, this view of the burial procedure is immediately appealing. It seems intuitive and economically logical to associate death with the inactivation of pre-existing signalling circuits, rather than with the emergence of new molecular pathways. Moreover, the inactivation of existing circuits might be quicker than building up new pathways, which fits with the finding that patrolling macrophages select their prey well before any massive cellular modifications occur.

If the inactivation of repulsive signalling pathways is indeed an early event in cell death, then it might shed new light on studies of the nematode worm *Caenorhabditis elegans* in which cells that were 'almost alive' were eliminated[12,13]. These events have been interpreted as evidence that phagocytes can actively kill their prey, rather than simply consuming dead cells. But an alternative explanation is that a loss of repulsive signalling, and hence an attachment to phagocytes, occurs before the key apoptotic events — that is, before final commitment to cell death. In other words, phagocytes cross a 'point of no return' in their decision to eliminate dying cells before those cells are irrevocably committed to the decision to die. That suggestion is bolstered by the finding that CD31 does not seem to be destroyed by the apoptotic protein-degrading enzymes, hinting that the switch from repulsive to attractive signalling might become independent of definitive activation of the death machinery.

It is still possible, however, that negative sorting does not occur in invertebrates such as *C. elegans*, instead representing an upgrading of the death programme to vertebrates. Such fine-tuning might have emerged to deal more efficiently with the varied situations of cell death seen in more complicated multicellular organisms. ■

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Theoretical biology

Ants on a Turing trail

Peter Hammerstein and Olof Leimar

The behaviour of ants when dealing with their dead has parallels with biological pattern formation more generally, for instance as seen during development.

Social insects can build complex structures such as termite mounds that resemble skyscrapers, complete with air conditioning. But unlike human builders, they work without the help of an architect or a blueprint. This is similar to the process of morphogenesis, by which cells of a developing organism produce features on a scale much larger than their own size. The cells do not possess an internal representation of these features, be it the pattern on a seashell or the basic segmentation of a fruitfly.

Local activation and long-range inhibition[1–3] have traditionally been regarded as important characteristics of pattern formation, the general idea being that an elevated local concentration of a pattern-forming substance should induce further local build-up, and that a high local concentration in one place should also inhibit a build-up some distance away. There are few cases in biology where the actual mechanisms have been demonstrated. But, writing in *Proceedings of the National Academy of Sciences*, Theraulaz

et al.[4] present an example of such a process in social insects. Their careful experimentation has revealed how the behaviour of individual workers of the ant *Messor sancta* produces spatial patterns in a colony's disposal of corpses — the so-called ant cemeteries.

In the first series of Theraulaz and colleagues' experiments, the ants had access to a circular arena in which ant corpses were homogeneously distributed along the perimeter. The ants had a strong tendency to follow the wall of the arena — so this is effectively a one-dimensional situation, which facilitates mathematical analysis of the process. The authors monitored the formation of clusters of dead ants and the dynamics of their spatial distribution. The result that emerged was puzzling. Instead of quickly choosing one or a few fixed locations for piles of corpses, the ants formed many clusters, some of which grew while others disappeared after some effort had already been made to build them. The number of clusters first grew, reaching a maximum after three hours. Later it decreased and remained constant when a stable spatial pattern was finally established. Subsequent experiments were performed to estimate the parameters of individual ant behaviour, such as the probabilities that a given ant would pick up or drop a corpse, or would make a U-turn while carrying a corpse along the perimeter. For this purpose the authors manipulated cluster size.

The observations indicate that a mechanism of short-range activation and long-range inhibition is at work. The activation would consist of a behavioural tendency to drop corpses with a probability that increases with the density of corpses in the immediate neighbourhood. This mechanism leads to local amplification of corpse density, unless it is overridden by the inhibitory process. Inhibition occurs through the ants' tendency to pick up corpses and carry them for considerable distances, leading to the long-range depletion of the clusters.

Theraulaz *et al.* developed a mathematical model for the process of ant cemetery construction. This model is similar to one by Gierer and Meinhardt[2] that has been applied to seashell pattern formation[3]. The ant cemetery model explained not only the final formation of a stable distribution of large piles but also the intermediate occurrence of clusters that then disappear. For the dynamics of how the average number of clusters changes with time and when its maximum is reached, the model predictions were in close agreement with the experiments. Furthermore, as the inhibition–activation structure of the model suggests, cluster formation did not occur if the initial density of corpses was too low. Results such as these show that pattern formation can be understood at a deep level and that the behavioural mechanisms behind it are very simple.

What general insights do we gain about the ants? Given that their behaviour followed the mathematical model so closely, it seems as though they have no mental concept of the large-scale process in which they participate. When they move corpses in the cemetery, their actions are guided mainly by aspects of the local temporal and spatial environment, and possibly by chance, but not by foresight and planning. One could then say that the structures simply appear as a by-product of the ants' shortsighted way of dealing with corpses. Would this be adaptive in the evolutionary sense? At first glance the ants seem to act inefficiently. But it might well be a better use of a small brain not to attempt to be an excellent architect. The robustness of the procedure that structures the cemetery could outweigh a certain waste of time and energy.

Ants in the wild do not have access to a circular arena, but the same mechanisms that lead to periodic patterns in the arena are likely to be operating. The structures of the natural cemeteries of *M. sancta* have not been studied systematically, so it is not known whether they sometimes consist of several piles or whether the ants' behavioural mechanisms usually produce a single pile. Nevertheless, the experiments with the circular arena reveal how simple mechanisms can act to create structure in a controlled and simple world for which it is easy to compare theoretical and empirical findings.

This is notable because the results reported by Theraulaz *et al.*[4] are likely to have parallels in other collective processes. For instance, decisions in morphogenesis are made by cells, which are difficult to envisage in the role of architects. Organisms and 'superorganisms' of social insects thus share a problem, so ants might teach us valuable lessons about morphogenesis. The potential of this analogy was recognized 25 years ago by Deneubourg[5]. We now know that various cases of patterns on seashells[3] and the formation of piles in ant cemeteries might be explained by similar underlying principles. These principles exemplify the basic conceptual model of activation and inhibition that Gierer and Meinhardt[2] created to make Turing's[1] abstract ideas about morphogenesis amenable to observation and experiment. The ants may indeed be on a Turing trail. ■

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100 YEARS AGO

A few examples of the practical application of scientific education in Germany are given in the *Journal* of the Society of Arts. The sugar industry is the first illustration of the progress of industry through science. In 1840, 154,000 tons of beetroot were crushed, from which 8000 tons of raw sugar were produced, showing about 5½ per cent. of raw sugar extracted from the root. Twenty years later, 1,500,000 tons were treated which produced 128,000 tons of sugar, or about 8 per cent. Last year about 12,000,000 tons were crushed, which produced 1,500,000 tons of raw sugar, raising the percentage to 13. This advance is due entirely to scientific treatment. The production of dry colours, chemicals and dyes in Germany shows a corresponding increase in production and dividend-paying capacity... A great advance has also been made in the scientific instrument industry. The value of the exports from Germany of scientific instruments in the year 1898 was about 250,000*l.* — three times what it was in 1888 — and the work gave employment to 14,000 people.
From *Nature* 10 July 1902.

50 YEARS AGO

***The Mitotic Cycle.* By Dr. Arthur Hughes.**
It is rightly emphasized on the dust-cover of this valuable monograph that the process of cell division presents one of the most difficult problems the experimental biologist has yet attempted to solve, and if this present account of the mitotic cycle is not an easily flowing and well-balanced narrative, the reflexion is not on the author but on the present state of our knowledge of the subject. There is a large and widely scattered literature of unequal relevance and of uneven quality. The lines of advance have been largely dictated by considerations of the materials and techniques available, and a strong medical bias is also evident. Thus we now have an extensive knowledge of the early cleavage of a certain few eggs, of the growth in culture media of a certain few tissues, of the methods of induction of cancerous growths, and of the methods of mitotic inhibition by a multitude of diverse substances. The obvious questions posed by the mitotic activity of normal animal and plant tissues have been almost entirely neglected, although very recently a start has been made towards their solution.
From *Nature* 12 July 1952.