mia. The Rivera study clearly demonstrates that the compartments of the secretory pathway and their regulated sorting sites can be adapted to achieve rapid and efficient secretion of engineered therapeutic proteins.

This new technology may provide a simple platform from which to regulate secretion of therapeutic proteins in any type of cell. However, there remain intriguing scientific challenges that will need to be overcome if the systematic success of this approach is to be assured. Protein folding and accumulation are constantly monitored by the ER (*14*). Proteins that fail to assume a transport-competent conformation are targeted for removal by an ER-specific degradative pathway (*15*). Although both peptide signals and sugar modifications play a role in regulating protein stability (*14*), the exact mechanisms by which proteins are selected for degradation are unknown. Moreover, accumulation of unfolded proteins in the ER requires that both the size of the ER and its accessory components undergo continuous adjustment. This is achieved through signaling pathways from the ER to the nucleus whose components include the ER-associated transmembrane proteins Ire1, PERK (PKR-like ER kinase), and potentially other signaling receptors (*16, 17*). These pathways trigger the synthesis of a variety of resident ER and cytosolic proteins, which are required for proper protein folding, regulation of translation, membrane lipid synthesis, and transport. In a number of cases, signaling pathways from the ER can induce apoptosis of cells and tissue degeneration associated with diseases such as liver cirrhosis, peripheral neuropathies, and perhaps Alzheimer's disease (*2, 17*). Intriguingly, mobilization of the ER—although clearly observed by Rivera and colleagues as an expansion of the ER in response to accumulation of engineered proteins—did not cause programmed cell death, the activation of PERK, or degradation of the FKBP12-fusion protein.

Indeed, it is becoming increasingly apparent that transient protein aggregation is a normal intermediate step in the folding and assembly of a variety of proteins, enabling the ER machinery to cope with a heavy or unbalanced protein synthesis load. Such aggregation allows for the temporary sorting and storage of specific proteins without the induction of protein degradation or the programmed death of cells. An example would be the accumulation and release of immunoglobulin from the distended ER of mature B cells. Cells can compensate for inefficient protein transport by accumulating proteins and expanding the ER (this is seen in some forms of congenital hyperthyroid goiter) (*2*). Furthermore, normal tissue homeostasis can be controlled by endogenous circulating molecules that trigger ER export of accumulated protein. For example, C reactive proteins stored in the ER are rapidly released during tissue injury. Therefore, under certain conditions the ER can avoid activation of unwanted stress signaling pathways, which are usually mobilized in response to protein aggregation and accumulation.

A better understanding of the events that direct ER export and its integration with degradative and stress signaling pathways will no doubt improve our ability to generate "designer" cargo target proteins and to control their secretion. The Rivera *et al.* study represents a promising step in this direction. Furthermore, it confirms the importance of selective protein export from the ER as a key step in regulating cellular, tissue, and body homeostasis (*5, 7*).

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PERSPECTIVES: BEHAVIOR

Measuring Beelines to Food

Thomas Collett

Many decades ago, von Frisch (*1*) showed that honeybees are able to measure the distance that they fly from their hive to a foraging site. Knowing this distance helps bees to return to the site and also enables them to communicate the location of the site to other bees. A forager bee imparts this information on its return to the hive by performing a waggle dance (see the figure). A missing piece to this story is an understanding of the way in which bees measure this distance. Led by the bees' errors when flying with tail winds or against head winds, von Frisch supposed that the bees' estimate of distance was derived from the energy they expended during a flight—a curiously unreliable tape measure for bees to use.

The issue was reexamined by two groups in the mid-1990s, one in Notre Dame headed by Esch and another at the Australian National University led by Srinivasan, who reports his latest findings on page 851 of this issue (*2*). Both groups rejected the energy consumption hypothesis. They showed instead that bees monitor distance visually. Bees integrate over time the motion of images crossing the retina as they fly through a landscape. By this means they can both measure and control the distance that they travel. The experimental proofs of both groups depended on a fundamental limitation of the insect neural system that measures self-generated image motion (optic flow). This system is ignorant of the distance of features in the world that generate image motion on the retina. Consequently, flying a short distance close to the ground will generate the same integrated motion signal as flying a longer distance high above the ground.

Esch and Burns (*3*) trained bees to forage from the top of a 50-m-high building to a feeder placed on the roof of another tall building 230 m away. The waggle dances of these bees indicated a distance that was about half the length signaled by bees traveling the same distance from a hive to a feeder on the ground. Srinivasan *et al.* (*4*) took a different tack. They analyzed the search behavior of bees that were trained to fly several meters down a narrow, well-lit tunnel and to forage at a feeder partway along its length. When the feeder was absent, bees searched persistently at the expected location. Evidence for the use of optic flow came from testing these trained bees in tunnels of different widths. Making the tunnel narrower than the standard 22 cm caused bees to search closer to the entrance. When the tunnel was widened, bees searched further from the entrance. To maximize the perceived image motion, the tunnel was decorated with black and white vertical stripes on the walls (see the cover of this issue). But if the stripes were horizontal, so that there were no contrast changes to activate the motion detection system, bees did not know where to search when the feeder was missing and flew from one end of the tunnel to the other without stopping in the middle. Srinivasan and his colleagues have now woven these two strands of research together, and in this issue of *Science* they pre-

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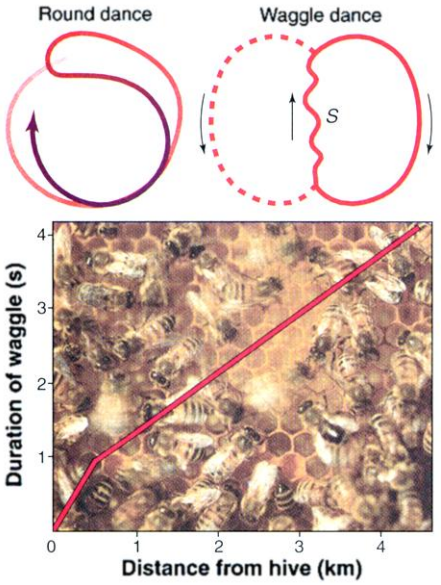

Flight of the honeybee. The round and waggle dances are performed by foraging bees on an area of vertical comb close to the entrance of the hive to signal the availability of food. When food is close to the hive, foragers perform a round dance, which gives no indication of the direction in which the food is located. For sites more distant than about 50 m, the direction of food with respect to the sun's azimuth is signaled by the angle of the waggle component (*S*) relative to gravity, and the distance of the food from the hive is signaled by the duration of the waggle component. Duration increases nonlinearly with distance.

sent an analysis of the dances that bees perform after flying through the tunnel (*2*).

The 11-cm-wide and 6.4-m-long tunnel was lit by skylight through the top. It was placed a few meters from the hive. Honeybees typically do not perform the waggle dance when the feeder is closer than 50 m from the hive. Instead, they signal through the round dance that food is nearby (see the figure). Bees returning from a feeder at the entrance to the tunnel performed the expected round dance. The feeder was then placed 6 m into the tunnel. When the tunnel had horizontal stripes that generated minimal image motion, bees continued to perform a round dance. In contrast, if the tunnel walls were covered with a random texture generating abundant image motion, bees performed a waggle dance that indicated a greatly magnified distance between hive and feeder of about 200 m. Flying a short distance through a narrow tunnel thus turns out to be equivalent to flying a distance 30 times further over open ground. Srinivasan *et al.* infer from these data that in the outdoor environment in which the bees were tested, features generating image motion were about 170 cm away from the bees' eyes. As the perceived image motion depends strongly on details of the terrain, the bees' measuring tape will be route dependent. This shortcoming does not matter if the principal use of the measuring tape is to gather and transmit information about a particular route.

The slope of the relation between waggle duration and distance becomes less steep with distances greater than about 500 m (see the figure). The shallower slope at greater distances might result either from saturation of the system that integrates optic flow, or because bees fly higher over longer journeys (*5*) and so are at a greater mean distance from objects generating optic flow. The great advantage of measuring the waggle dance of bees that have flown through the tunnel is that the optic flow in the tunnel is well defined. It thus becomes possible to test for the linearity of the integrator, provided, of course, that workshop and bees cooperate in building and flying the much longer tunnels that would be needed.

Different insects have to contend with different ecological problems so that image motion is unlikely to be the only cue that insects use for measuring distance. Because bees fly and are subject to unknown winds, ground speed and distance are most reliably controlled and measured through image motion. But insects that walk on the ground and are not subject to passive transport by wind can do better. Rather than relying on optic flow, with its unavoidable uncertainties, walking insects can, with advantage, use proprioceptive information or some kind of step counting to monitor the speeds and distances that they travel. Indeed, desert ants keep a precise record of the distance that they walk to and from their nest, and they seem to make little if any use of optic flow in monitoring these distances (*6*).

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PERSPECTIVES: BIOSYNTHETIC PATHWAYS

Biosynthesis Meets Bioinformatics

David E. Cane

Natural products continue to be a fertile ground for chemical and biochemical inquiry and serve as an invaluable source of some of the most widely used agents in human medicine, such as the antibiotics erythromycin, tetracycline, and penicillin, the anticancer agent taxol, and the cholesterol-lowering drug mevinolin, not to mention plant extracts used widely in dietary supplements and traditional medicine. Studies of the biosynthesis of natural products have revealed the origins of many of these biologically important and chemically complex substances and have been an invaluable tool for the discovery of new biochemical reactions. Traditionally, these studies have relied primarily on incorporation experiments with isotopically labeled precursors and on isolating new enzymes catalyzing individual transformations in multistep biosynthetic pathways. Two recent publications (*1*, *2*) illustrate the continuing role of biosynthetic studies in unearthing new biochemistry and highlight the increasing role of molecular biology and genomics in this quest.

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Until about 10 years ago, mevalonic acid was widely regarded as the common precursor of the more than 30,000 naturally occurring terpenoids. Inhibition of mevalonic acid biosynthesis by fungal-derived metabolites such as mevinolin has become a widely used and effective method for the therapeutic control of serum cholesterol levels. It therefore came as a surprise when the research groups of Rohmer in Strasbourg and Arigoni in Zürich independently discovered that certain bacteria, algae, and higher plants can use an entirely different pathway for the biosynthesis of the universal isoprenoid building block isopentenyl diphosphate (IPP) [for a review, see (*3*)]. The discovery of this mevalonic acid–independent pathway initiated intensive investigations aimed at identifying the relevant enzymes and metabolic intermediates. The pathway is now known to begin with the conversion of the glycolytic intermediates pyruvate and glyceraldehyde-3-phosphate (**1**, G-3-P) to the five-carbon sugar 1-deoxyxylulose phosphate (**2**, dXP) in a thiamin diphosphate (TPP)–dependent reaction (*4*, *5*) (see panel A in the figure). Interestingly, dXP is also a precursor for thiamin and vitamin B_6 in bacteria such as *Escherichia coli*.