In a report in this week's issue, Saffran, Aslin, and Newport have proven that babies can learn (1). Eight-month-old infants exposed for only 2 min to unbroken strings of nonsense syllables (for example, "bidakupado,...") are able to detect the difference between three-syllable sequences that appeared as a unit and sequences that also appeared in their learning set but in random order. This result means that infants can use simple statistics to discover word boundaries in connected speech, right at the age when systematic evidence of word recognition starts to appear in real life (2). It is obvious that this is important; it may be less obvious to those outside the field why it flies in the face of received wisdom.

First, the nature of this learning is surprising: a purely inductive, statistically driven process, based on only 2 min of incidental input, with no reward or punishment other than the pleasure of listening to a disembodied human voice. Second, it contradicts the widespread belief that humans cannot and do not use generalized statistical procedures to acquire language (3–7). Noam Chomsky, the founder of generative linguistics, has argued for 40 years that language is unlearnable; he and his followers have generalized this belief to other cognitive domains, denying the existence of learning as a meaningful scientific construct:

"We may usefully think of the language faculty, the number faculty, and others, as 'mental organs' [that] develop in specific ways, each in accordance with the genetic program... multipurpose learning strategies are no more likely to exist than general principles of 'growth of organs' that account for the shape, structure and growth of the kidney" (3, pp. 138–139).

"I, for one, see no advantage in the preservation of the term 'learning'... we would gain in clarity if the scientific use of the term were simply discontinued" (7, p. 2).

"It is possible that the notion 'learning' may go the way of the rising and setting of the sun" (3, p. 245).

This belief is based on the famous "pov-
Crossing the Hydrophobic Barrier: Insertion of Membrane Proteins

Donald M. Engelman

Lipid bilayers are thin, flexible self-sealing boundaries that are used by cells to create regions of different composition and biochemical potential. To accomplish transmembrane functions, proteins inserted within and across the hydrophobic barrier must cope with hydrophilic interactions with the solutions inside and outside a cell or compartment and hydrophobic interactions with the membrane. Usually, proteins are assisted in their insertion by proteinaceous machinery. But can they insert spontaneously? The structure of α-hemolysin, reported by Song et al. in this issue of Science, reveals how a protein, in this case a toxin produced by a pathogenic bacterium, can penetrate a lipid bilayer (1)—by the spontaneous formation of an oligomeric β barrel (see figure).

It is much easier to understand the stability of observed transmembrane structures than to fathom the process by which they are positioned within a membrane. The membrane proteins whose high-resolution structures have been solved contain either bundles of α helices or β barrels in the regions presumed to span the lipid bilayer (2–5). One can rationalize each of these structures by recognizing that the main-chain hydrogen bonds need to be satisfied in an environment that lacks hydrogen bond donors or acceptors, and that the hydrophobic effect will stabilize the association of a transmembrane structure with the hydrophobic region of a lipid bilayer if the amino acid side chains contacting this region are predominantly apolar (6). Detailed knowledge of the final, folded state of a protein, however, does not inform us directly about the process of insertion, particularly if the protein in question is inserted into the membrane in a process catalyzed by cellular machinery. On the other hand, proteins whose functions require them to be stable in an aqueous environment and also capable of inserting themselves into membranes provide an opportunity to examine, biochemically and structurally, the determinants of an insertion event.

Spontaneous transmembrane insertions of both α helices and β barrels are found in the world of toxins, where the capacity to insert is packaged in a soluble molecule. Colicin A has a membrane-insertion domain that sequesters a hydrophobic helical hairpin whose insertion into the bilayer is postulated to be the primary step in colicin action (7). The α-hemolysin toxin studied by Song et al. is now shown to act by inserting β-barrel structures into bilayers, as previously surmised for aerolysin (1, 8). Other cases of spontaneous insertion have been documented, including the insertion of porins from denatured states in solution into lipid bilayers (9). Despite the fact that proteinaceous machinery is used for the insertion of many membrane proteins, a number of cases exist in which the insertion event does not require the participation of structures other than the inserting polypeptide and the lipid bilayer. How might this occur? Which intermediate states might one imagine?

The answer to the issue of intermediates will undoubtedly vary for specific cases, but three themes emerge in the examples we have thus far. The first is the role of oligomerization in the process. Both the α hemolysin and proaerolysin change oligomeric state in the process of insertion. α-Hemolysin binds to the membrane as a monomer, subsequently forms a heptamer, and then inserts. This sequence is based on studies of mutants that block steps in the process (10, 11). Thus, one wonders whether the energy of oligomerization may drive the process, producing an intermediate state that relaxes to the transmembrane form. The structure shows that a large surface area is buried in the oligomerization event; hence, a large amount of energy could be available. This is undoubtedly one of the directions that will be explored by Song et al.

A second theme is the exposure of regions of the protein that are kept sequestered in the soluble form of the molecule. The colicin A structure shows a hydrophobic helical hairpin surrounded by another structure, sequestering it from the aqueous environment (7). A body of work indicates that confor-