Results from experimental studies in regenerating and developing amphibian limbs have led us to conclude that growth and pattern formation are coordinately controlled (French et al., 1976; Bryant et al., 1981; Bryant et al., 1987). This conclusion is based on two propositions: (1) cells possess information about their position in the limb (i.e. cells have positional values); and (2) whenever discontinuities exist in the array of positional values, interactions between adjacent cells with different positional values will result in the stimulation of growth and in the intercalation of appropriate intervening positional values. Consequently, growth will cease when all positional disparities have been resolved. As we discuss below, cellular interactions resulting in the stimulation of growth can occur during normal development as a result of cell rearrangements within the limb field, during regeneration as a result of cell migration associated with wound healing, or in experimental situations as a result of grafting to bring cells with disparate positional properties (e.g. anterior and posterior) into contact. Hence, this view can account for the initiation, maintenance and termination of limb growth and patterning during normal development, after amputation, as well as after a variety of experimental manipulations.

The view that growth and pattern formation are coordinately regulated by properties and behaviors intrinsic to cells is consistent with the idea that growth to final size of tissues and organs is, under normal conditions, controlled by mechanisms that are intrinsic to those tissues or organs. This idea is not new, and is supported by extensive experimental data in a variety of organisms (see Bryant and Simpson, 1984 for review). For example, developing amphibian limbs transplanted between small and large species develop to the size characteristic of the donor species, in disregard of the environment provided by the host (Twitty and Schwind, 1931). More recently, Sessions and Bryant (1988) demonstrated that limb regenerative ability in Xenopus, involving both growth and pattern formation, is also an intrinsic property of limb tissues. They observed that limb buds capable of normal regener-
ation can regenerate even when grafted to an older stage tadpole whose limbs have lost that ability. Conversely, blastemata from later stages did not regain regenerative properties when grafted onto a host that can regenerate a normal limb pattern. These results indicate that in addition to whatever growth permissive factors are provided by the host (e.g. hormones, growth factors, nerves), limbs develop and regenerate under the control of mechanisms intrinsic to the limb tissues.

The intrinsic nature of growth and pattern regulation has also been demonstrated quantitatively in experimental studies of both developing and regenerating limbs. In such studies, the nature and degree of cellular interactions have been manipulated experimentally so as to either stimulate or inhibit growth. In both cases, the amount of growth and the extent of the pattern formed are coincident. An example of the experimental stimulation of excess growth and pattern is provided by the well-known ability of contralateral limb bud or blastema transplants to engender the formation of supernumerary limbs (see Muneoka and Bryant, 1984). Additional growth and pattern are stimulated when cells from disparate positions are brought together; whereas identical procedures, but without the confrontation of cells from different limb positions, do not lead to any additional growth or patterning. Other experimental procedures that also generate the formation of well developed supernumerary limbs (see Tank and Holder, 1981; Maden and Holder, 1984; Egar, 1988), also involve either the deliberate juxtaposition of cells with different positional values or extensive wound healing, which as we discuss below, results in the confrontation of cells from opposite sides of the wound. Therefore, all situations in which excess growth is stimulated involve an increased probability of interactions between cells with disparate positional values.

Position-dependent growth and patterning can be negatively regulated in experimental situations by the juxtaposition of cells with similar positional values. A normal upper arm or leg stump is asymmetrical and possesses positional values for anterior, posterior, dorsal and ventral positions. Symmetrical stumps can be created by surgery such that one set of positional values is removed (e.g. anterior or posterior) and one set is represented twice in a symmetrical arrangement. If amputation of symmetrical upper arms or legs is performed close to the time of grafting, we have found that in the early regenerate each half of the limb is spatially isolated from the other (unpublished observations). Therefore immediate amputation of symmetrical limbs does not provide a test of the consequences of interactions of cells with similar positional values across the wound surface. However, when grafts are allowed to heal together for long periods of time (30-60 days), subsequent amputation leads to dramatically reduced growth and patterning, resulting in small spikes or no new structures at all (Bryant, 1976; Bryant and Baca, 1978; Stocum, 1978; Tank, 1978). Control experiments in which limbs have been grafted to make symmetrical limbs, and then regrafted to make normal but reversed limb stumps show that such limbs regenerate as expected, indicating that the procedures involved in creating symmetrical limbs and in allowing them to heal for long periods do not interfere with regenerative ability (Bryant and Baca, 1978). Furthermore, grafts of