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Source: *BioScience*, Vol. 39, No. 5 (May, 1989), pp. 314-320
Published by: American Institute of Biological Sciences
Stable URL: http://www.jstor.org/stable/1311114
Accessed: 16/07/2009 13:26

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Developmental Biology in Outer Space

Spaceflight provides the opportunity for new studies

George M. Malacinski, Anton W. Neff, Jeffrey R. Alberts, and Kenneth A. Souza

The constant and omnipresent gravitational force under which life on Earth has been evolving for more than 3.5 billion years has led many biologists to speculate that genetically based systems accommodate or even use gravity. Indeed, gravity may have been a key constraint in the evolution of many structures and functions that characterize present-day organisms.

Simple organisms, for example, are genetically adapted for gravity stress. The fruiting slime mold, *Dictyostelium,* synthesizes profuse amounts of slime (extracellular matrix) that facilitates upward growth, in which the fruiting body rises above the surface for more efficient spore dispersal. *Daphnia,* a freshwater microcrustacean, seems to possess gravity receptors in its antennal-socket setae. These receptors appear to aid in orientation: when subjected to changes in buoyancy in experiments where gravity is reduced, *Daphnia* exhibits abnormal movements (Meyers 1985).

Among insects, gravity adaptations vary. Moths, with their large wingspans, exhibit apparently normal flight in the reduced gravity (microgravity) of outer space; bees do not. Some vertebrates, such as amphibian and avian species, produce relatively large, yolk-laden eggs, which, after fertilization, rotate according to the gravity vector. Other terrestrial vertebrates have developed elaborate antigravity skeletal and muscular systems that facilitate erect posture and locomotion.

Developmental biology will help predict whether humans can expect to colonize outer space

For more than a century, researchers have wrestled with questions of whether gravity plays a direct role in either controlling the pattern of embryogenesis (e.g., axis formation) or regulating the development of tissues and organs (e.g., the balance mechanism of the vertebrate inner ear). W. Roux (1884) reported the first experiments designed to prevent frog eggs from orienting with respect to the gravity vector, to determine whether gravity plays a direct role in embryonic pattern formation. Those experiments have been repeated on several organisms by subsequent generations of embryologists, yet the results have always been ambiguous.

Ground experiments with microgravity can use a horizontal clinostat, an instrument that constantly rotates a specimen in an attempt to cancel the net gravity vector. Microgravity can also be achieved by buoyancy tests, drop-tower tests, and parabolic aircraft flight. For most experiments, however, no suitable conditions for creating microgravity exist on Earth, so the interpretation of data from ground-based experiments has usually been tenuous. Present-day spaceflight technology promises to help resolve the issue of gravity and embryogenesis.

Knowledge of how various organisms can function in the microgravity of outer space is improving. In this article, we focus on animal development, although there have also been spaceflight experiments with plants (Halstead and Dutcher 1984). Virtually all the types of adult animals that have been tested survived short-term (2–20 day) spaceflight, including several invertebrates such as brine shrimp (*Artemia*), nematodes (*Nematospiroides*), beetles (*Tribolium*), and fruit flies (*Drosophila*) and various vertebrates such as fish (*Fundulus*), frogs (*Rana*), rats (*Rattus*), monkeys (*Macacca* and other species), and humans (Klein 1981, Souza 1979).

Although these organisms certainly survived spaceflight, in many cases they were demonstrably affected by microgravity. The carefully monitored physiological changes astronauts experience during both short-term and long-term spaceflight have included fluid shifts toward the head, transient changes in red-blood-cell counts, vestibular disturbances of the

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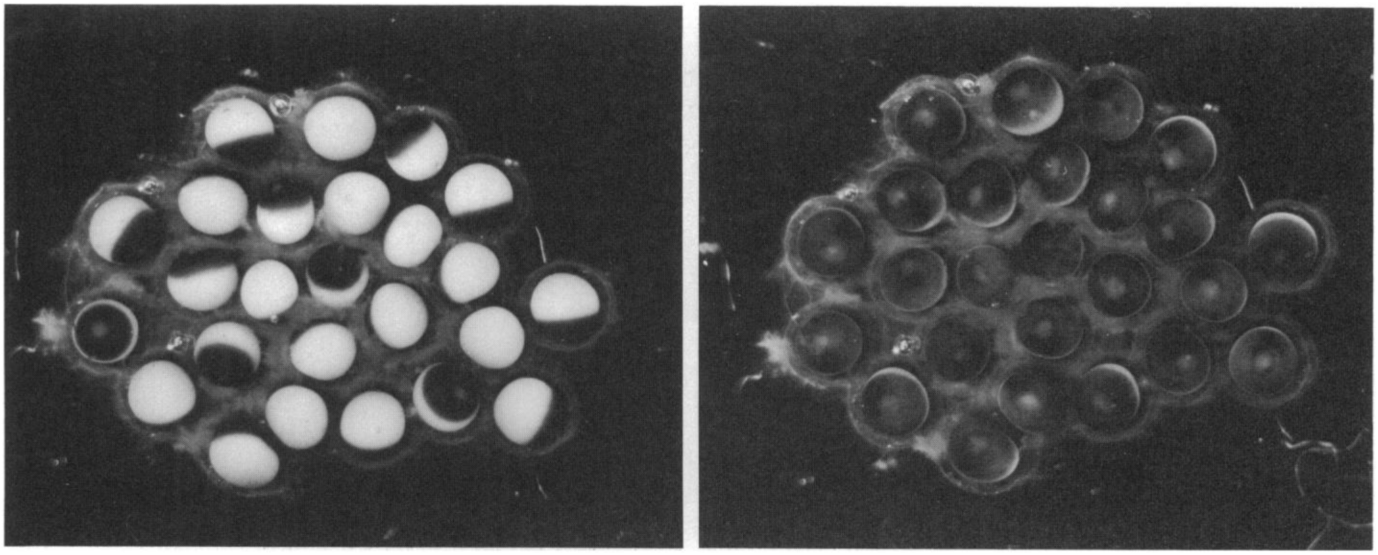

Figure 1. Frog eggs are spawned in a random orientation with regard to gravity (left). Like most amphibian eggs, these frog eggs (*Xenopus laevis*) are darkly pigmented in one hemisphere and lightly pigmented in the other. Within minutes after fertilization, they spontaneously rotate in their gelatinous capsules so that the darkly pigmented hemisphere faces up, away from gravity (right). These eggs are approximately 1.2 mm in diameter.

ear, and decreased bone, skeletal muscle mass, and strength (Nicogossian 1985).

Understanding of how animal embryos, rather than adults, fare in microgravity is much less comprehensive. Even though several types of embryos have been tested, relatively definitive information is only available for *Drosophila*. The 1962 Soviet manned satellites *Vostok 3* and *Vostok 4* provided the initial finding that fruit fly impregnation and fertilization, egg laying, and development proceed normally, although the one- to two-week flights were far too short to allow an entire generation of development (Antipov et al. 1965). More recent reports, however, state that adult fruit fly aging is accelerated in microgravity (Miquel and Philpott 1978). In spaceflight experiments with other types of embryos (e.g., fish, frog, and rat), some factor such as equipment limitation, shortness of flight, launch delay, premature termination, or mechanical failure has prevented the collection of definitive data.

Why study development in microgravity?

Several rationales exist for pursuing the study of embryonic systems in microgravity. First, biologists are interested in gravity's role in normal development. Eggs of some organisms display a natural orientation response to the earth's gravity. Amphibian eggs, which are darkly pigmented in one hemisphere and lightly pigmented in the other, are spawned in a random orientation, but after fertilization they uniformly rotate so that the darkly pigmented hemisphere opposes gravity (Figure 1). Developmental biologists suspect the egg-rotation phenomenon is an obligatory step in the establishment of the body axis.

Avian eggs also appear to respond to gravity. As the fertilized egg moves down the oviduct, it rotates. The antero-posterior axis of the embryo appears to be established by a downward movement (toward gravity) of blastodisc cells (Eyal-Giladi and Fabian 1980). The development of eggs that normally rotate according to the gravity vector is likely to be vulnerable to weightlessness and therefore disrupted during spaceflight. Even subtle defects, if introduced early into a developing system, might cascade during subsequent stages.

Second, biologists may be able to use microgravity experiments to generate new information about basic cellular processes. Most embryos contain cells that undergo remarkable changes (e.g., drastic shape changes, fusion, or migration over long distances). Cells and systems in a process of dynamic change are usually more susceptible to perturbations than are those in homeostasis. Thus, the cells and systems of developing organisms can be used as a kind of magnifying glass, exposing environmental effects, such as reduced gravity, that would be difficult to see and study in adults. The developmental biologist may therefore be able to investigate direct effects of microgravity on individual cells.

Third, several nations, including the United States, are formulating plans for a permanent manned space station and future colonization of the solar system (e.g., lunar and Martian bases [Payne 1986]). Any colonization will ultimately require multiple generations of plants and animals for food and the means for waste recycling. Because of the complexity of such a system, it is necessary to now focus on the ability of animals to reproduce and develop in microgravity, including lunar (0.16 g) and Martian (0.39 g) gravity, relative to Earth's 1 g.

Weightlessness and *zero g* are terms routinely used by space biologists, but it should be noted that, although gravity is substantially diminished during spaceflight, it is not completely eliminated. Microgravity of 10^{-3} to 10^{-4} g is regularly experienced. Yet 10^{-5} to 10^{-6} g may be required to completely eliminate sedimentation and thermal convection effects within

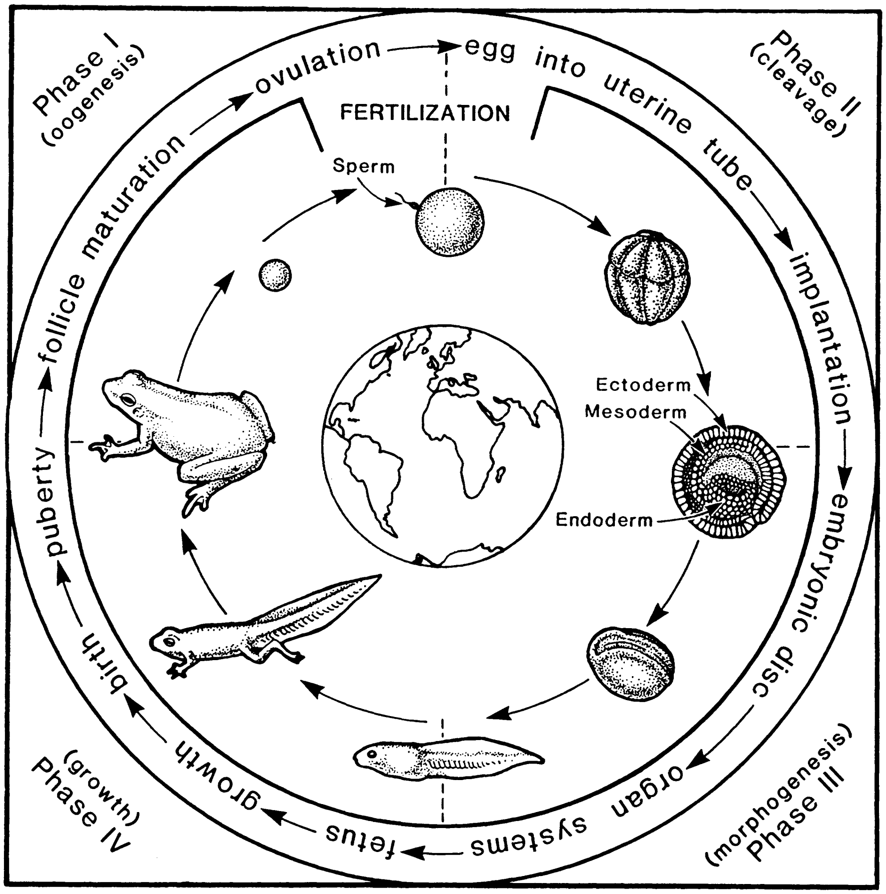

Figure 2. Developmental life cycles of amphibians (inner diagram) and mammals (outer circle). Each phase is thought to be sensitive, to some extent, to microgravity. Although some phases have been tested during spaceflight, technical constraints have so far prevented analysis of a complete life cycle. Phase I may be insensitive to microgravity, because there is no evidence that growing oocytes orient according to the gravity vector. However, phases II and III may be sensitive to microgravity, especially in amphibian and avian eggs, which rotate according to gravity. Phase IV is at least partially sensitive to microgravity, because muscle development in terrestrial vertebrates requires a load as a stimulus for maintenance of growth.

individual cells. Such low-gravity forces are not experienced on the National Aeronautics and Space Administration's (NASA) space shuttle, but they are expected on the higher-altitude orbiting manned space station and free-flying co-orbiting space platforms. A plethora of direct microgravity effects may await discovery once suitable technology for obtaining such low-gravity forces becomes available.

Experimental questions and microgravity effects

Researchers have posed a number of experimental questions about developmental animal systems in space. Does microgravity directly affect individual somatic cells? Can developmental and reproductive cycles of a variety of animal species be completed in microgravity? If not, what gravity levels are necessary? Do aquatic organisms with buoyant (gravity-unloaded) skeletons display the same responses to microgravity as terrestrial organisms, which have gravity-loaded skeletons? Do developing animals display phenotypic adaptive responses to long-term spaceflight? What sorts of genetic adaptations will be displayed by species that reproduce in space?

To formulate specific hypotheses, it is useful to define a developmental life cycle in terms of a series of phases, as in Figure 2, where development is viewed in terms of sequential, irreversible stages. As the cycle proceeds, the structural and functional complexities of the organism increase. Certain stages might be expected to be more vulnerable to microgravity than other stages, and some organisms such as *Drosophila,* which has already been shown to successfully complete early development (fertilization and embryogenesis) during spaceflight, may be less sensitive than other organisms. Amphibian and avian eggs would be expected to be much more sensitive to microgravity since, unlike the typical insect egg, they rotate along the gravity vector and are substantially larger.

Direct effects. Initial experiments on cultured human embryonic lung cells revealed no major differences between growth during spaceflight and growth at 1 g (Montgomery et al. 1978). Given the variety of other embryonic cells that have since been observed to grow normally during spaceflight, it is unlikely that microgravity alone interferes directly with normal cell division.

More recent experiments, however, indicate that lymphocytes, which unlike lung cells or embryonic cells do not adhere to a solid substrate, display diminished growth stimulation by the mitogen (mitosis stimulator) concanavalin in a microgravity environment (Cogoli et al. 1984). Some single-celled organisms, including bacteria, were found to grow to higher-than-normal population densities in microgravity, indicating the possibility that for some organisms microgravity stimulates cell growth (Bechler et al. 1986).

The important issue of whether gravity affects single cells in a multicellular organism requires further investigation. The direct effects of gravity might include alterations in metabolic rate, changes in cell morphology, or modifications in intracellular organelles. To date, convincing evidence is lacking. Analyses of differentiation in cultured mammalian somatic cells or the study of behavior of unusual cells (e.g., giant single cells) during spaceflight might be valuable experimental approaches.

Indirect effects. Several varieties of indirect effects of gravity can be described. First, given that all animals evolved in a 1-g environment, it is perhaps not surprising that load-bearing tissues and organs display substantially less structural mass in microgravity. Mammalian skeletal muscle has been shown repeatedly to atrophy during orbital spaceflight, whereas bone growth in young rats seems to virtually cease during microgravity exposure (Gazenko et al. 1980, Morey-Holton and Arnaud 1985). Such alterations should be considered indirect effects of microgravity because to a large extent they can be replicated at 1 g; for example, the hind limbs of rats can be suspended so they never bear a load (Steffen and Musacchia 1984).

Second, sensory-mediated effects, which are the result of stimulation of the nervous system, are indirect effects of microgravity. Early embryos (e.g., through phase III in Figure 2) lack sensory perception mechanisms, so they are excellent model test systems for direct gravity effects. But during the latter part of gestation, the development of sensory systems may permit the fetus to detect a microgravity environment. The vestibular system in numerous vertebrates begins to function during a prenatal period. In late embryos, microgravity may trigger a chain of events, such as hormone release or nervous stimulation, leading to alterations in various body tissues and systems that themselves are not otherwise directly influenced by microgravity. In placental mammals, it is also possible that the fetus may be stimulated by some aspect of the mother's gravity-related behavior.

Stress-related changes in developing animals, especially mammals, should also be included along with indirect microgravity effects. Physiological alterations have been observed in male rats that have been flown in space (Gazenko 1980, Souza 1979). Changes in female rats, although not yet documented, are certainly expected. If a pregnant female responds to weightlessness with changes in hormone levels, glucocorticoids may be transmitted across the placenta to the developing embryo and suppress many developing organ systems. Microgravity-related stress effects may be subtle and therefore difficult for the scientist to monitor.

Gravity may also affect the highly specific contacts between mother and newborns necessary for offspring survival and normal development. The hallmark of early life in mammals is the nursing relationship. On Earth, mother rats nurse their infants by lying over or alongside a huddle of pups. The coherence of this mother-litter system is maintained, in part, by gravitational force. From the huddle of bodies, the infants use their olfactory, vestibular, and tactile senses to detect the mother by waving their heads through coordinated scanning movements until they locate and grasp a nipple (Figure 3). A variety of gravity-oriented actions is involved that could well be disrupted in a weightless world. When such maternal-offspring interactions are prevented in laboratory experiments on Earth, pups develop abnormal social behavior.

These distinctions between direct and indirect effects of microgravity should be recognized as somewhat arbitrary. They will, however, facilitate analyses designed to identify the target cells or tissues involved in a microgravity response. This work is important for both pure and applied research.

Adaptation to microgravity

Short-term adaptation to microgravity appears to involve a variety of physiological and behavioral adjustments. Those already observed in adult humans (e.g., headward fluid shifts and changes in red-blood-cell counts) are likely to occur in developing embryos as well. Gravity may actually serve, at least indirectly, to guide the development of systems that control muscular movements fundamental to normal physiological function. Muscle growth and function in turn affect bone development. The adaptation of developing animals to accommodate sensory perception of lack of gravity load may influence the neuromuscular events that underlie behavior. The extent to which animals adapt to microgravity by altering behavior patterns remains to be

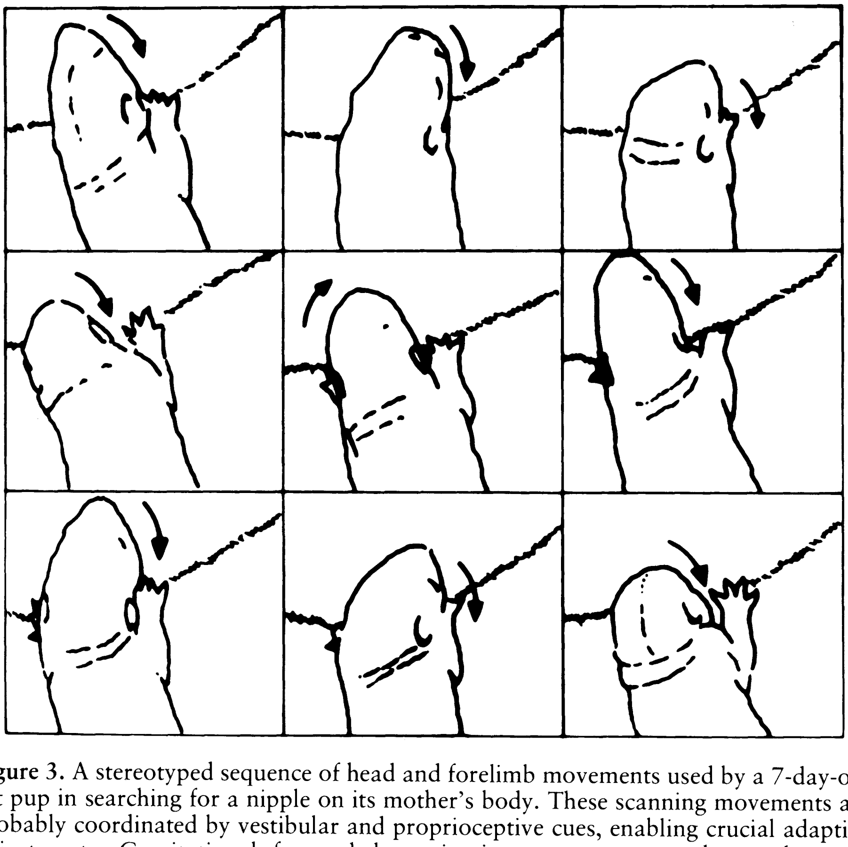

Figure 3. A stereotyped sequence of head and forelimb movements used by a 7-day-old rat pup in searching for a nipple on its mother's body. These scanning movements are probably coordinated by vestibular and proprioceptive cues, enabling crucial adaptive adjustments. Gravitational forces help maintain contact among the mother and offspring and provide vestibular cues that coordinate their interactions. The figure is taken from Alberts and Cramer (1988) and is composed of sequential frames (left to right, top row to bottom row) from a video recording adapted from Pedersen and Blass (1981).

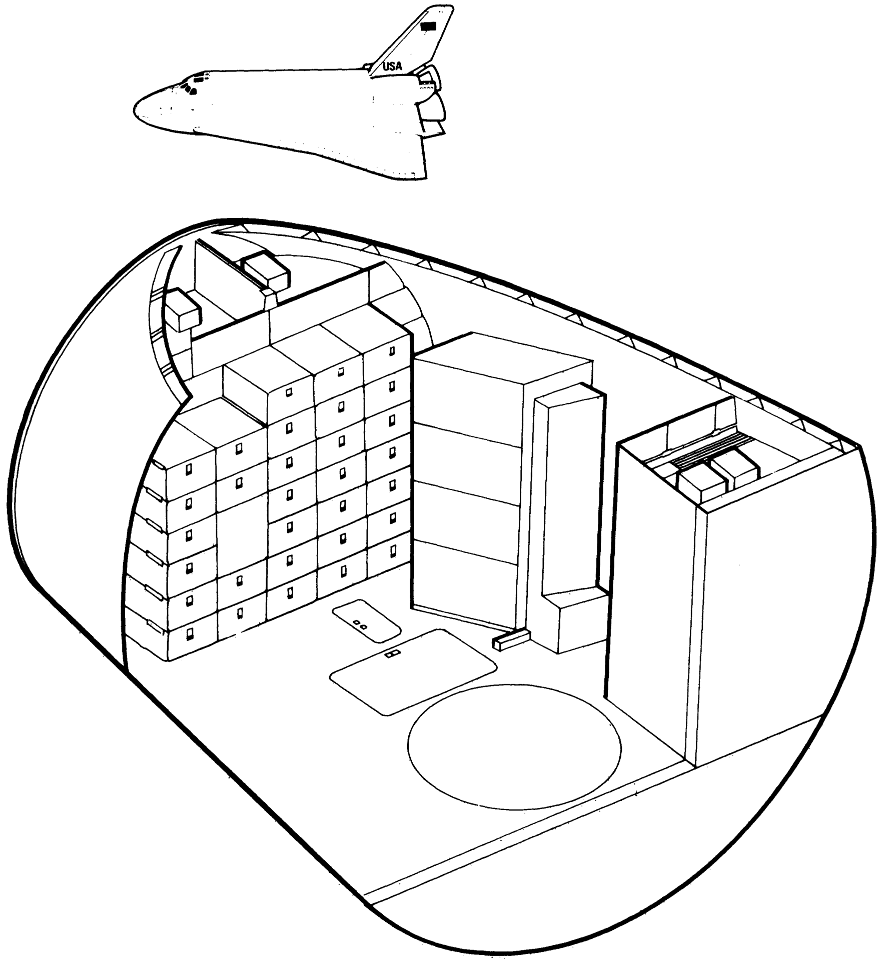

Figure 4. Interior of the space shuttle's middeck. Banks of lockers containing experiments are depicted on the left. Each locker is approximately 17 inches wide, 20 inches deep, and 10 inches high.

discovered.

In contrast to those short- or medium-term physiological and behavioral adaptations, long-term genetically based changes need also be considered. Once a permanent space station or more extended orbital flights are available, it should be possible to determine whether microgravity is a force for natural selection. Organisms with relatively short generation times (e.g., *Drosophila* and the nematode *Caenorhabditis elegans*) are currently being tested in short-term flights, with the aim of eventually determining the extent to which multiple generations in space alter the organism's gene pool.

Model systems

The ideal experimental system for developmental biology studies in space is easier to define than to produce. Small animals with rapid life cycles are preferred, as are those that can be maintained on simple diets and in ordinary laboratory habitats. Relevance to mammalian embryonic development is also desirable. At a minimum, space studies call for an organism that has been thoroughly described from the embryological standpoint. Finally, those large embryos which display ground-based gravity effects (e.g., amphibian and avian eggs), although not directly relevant to mammalian embryos, may be the most interesting.

Practical considerations associated with spaceflight, however, often require that a compromise be struck between the hypothesis to be tested and the capacity of the spacecraft. Figure 4 illustrates the interior of the space shuttle's middeck. In addition to space limitations governing the experiment's hardware, time constraints restrict the extent of astronaut involvement. The ideal experiment is one which is self-contained, requires a relatively small volume, is fully automated with minimal power needs, and can be flown in a space shuttle middeck locker and not require the large pressurized module, Spacelab, which must be flown in the space shuttle cargo bay (Figure 5). Several developmental animal systems have been flown under Spacelab conditions.

The recent flight of the Soviet satellite *Cosmos 1514* provided an opportunity to study the effects of microgravity on rodent development. Soviet scientists launched 10 pregnant rats into orbit for 5 days during the last trimester of their 22-day pregnancy. During this period, fetal brains normally undergo major stages of de-

Table 1. Organism systems tested in microgravity studies

Organism	Flight	Result	Reference
Fruit fly eggs	*Cosmos* biosatellite series	Normal embryogenesis	Souza 1979
Fish eggs	*Cosmos* biosatellite series; *Apollo/Soyuz*	Fertilization difficulties	Scheld et al. 1976
Frog eggs	US biosatellite; *Gemini*	Normal embryogenesis	Young 1976
Prenatal rats	*Cosmos 1514*	Short delay in neural development, but eventual intact sensory function	Keefe et al. 1986, Alberts et al. 1986
Human cell cultures	*Apollo*	Normal growth for embryonic lung cells, decreased mitogen stimulation for lymphocytes	Montgomery et al. 1974, Cogoli et al. 1984

Figure 5. Interior of the European-built Spacelab illustrating the pressurized laboratory module, which flies in the space shuttle's cargo bay.

velopment and exhibit limited function. After the capsule landed, US and Soviet scientists studied the state of brain development in fetuses taken from five of the females sacrificed on landing (Keefe et al. 1986). Also analyzed from the same flight were the behavior, sensory function, and brain development of pups from some of the rats that completed their pregnancy after return to Earth and that delivered their pups (Alberts and Cramer 1986). Histological analyses of fetal rat brains collected immediately after the flight revealed that development of their nervous systems had slowed down; some brain characteristics were 24–36 hours delayed in appearance. But by the time of birth—about five days after the five-day flight—these signs of developmental delay had disappeared, and sensory and behavioral function appeared normal.

Table 1 summarizes the results of several experiments on a variety of model systems. So far, no major catastrophic effects of microgravity on embryogenesis have been observed. Several explanations are possible: eggs and the maternally inherited developmental programs of the early embryo may be overbuilt and therefore not easily perturbed by the absence of 1 g; many externally developing eggs (e.g., fish and amphibian) naturally develop in an aqueous, buoyant environment, so they could be largely insensitive to microgravity; and, finally, early embryos lack sensory perception organs, so they may not recognize a microgravity environment.

Various limitations characterize the experiments so far. In most cases, fertilized eggs provided the starting point for experimentation, so egg-activation events such as those involved in establishing embryo symmetry had all occurred at 1 g, before lift-off. Most shuttle flights have been of short duration, so only brief periods in life cycles have been examined. Finally, the near-zero-g forces that may be required to eliminate intracellular effects have not yet been achieved.

Opportunities

Clearly, the fundamental question of whether entire developmental and reproductive life cycles can be accomplished in microgravity has yet to be answered. Exciting opportunities for developmental biologists exist, because the answer to that question affects the broader issue of whether humans can realistically expect to permanently colonize outer space.

NASA funds basic research in developmental biology through its Space and Gravitational Biology Program, under the auspices of the Life Science Division at NASA headquarters in Washington, DC. Research proposals for ground-based experimentation as well as spaceflight trials are routinely solicited. Attention is currently directed to research formats suitable for the space shuttle and the long-term orbiting space station.

Conclusions

Several benefits accrue from studying the capacity of developing systems to tolerate microgravity. First, insights into fundamental biological issues such as egg and embryonic pattern specification promise to emerge. Second, novel information at the interface of medicine, behavioral psychology, and embryology will no doubt accumulate. Finally, scientific imagination is stimulated by considerations of the logistics—conceptual, technical, and human—of colonizing outer space.

Acknowledgments

The research of G.M.M. and A.W.N. is supported in part by NASA grant NAG 2-323. J.R.A.'s research is also partly supported by NASA contracts.

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