Chapter 2

TISSUE INTERACTIONS IN MAMMALIAN REGENERATION

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Introduction

WITH THE EXCEPTION of repair to the central nervous system, mammals are as capable of tissue regeneration as are lower vertebrates (13, 29). Their inability to replace histologically complex appendages (epimorphic regeneration), however, a developmental feat for which lower vertebrates are famous, remains to be explained (9). From the phylogenetic point of view, there would seem to have been little selective advantage in retaining the capacity to regenerate limbs in the course of evolving warm-blooded vertebrates from cold-blooded ones. Birds and mammals have a high metabolic rate that depends upon the frequent consumption of food. Even if they could regenerate limbs, it would probably take several months to develop a functional appendage, during which time a predator would probably have starved to death and the prey would have fallen victim. Higher vertebrates may have substituted sufficient intelligence to avoid debilitating injuries in place of their ancestors' capacity to regenerate lost parts of the body. One might predict that if mammals were to regenerate anything, it would be limited to those structures that are not required for survival but that are important enough to have afforded selective advantage to those individuals capable of replacing them.

Epimorphic regeneration requires the coordinated participation of all parts of the amputation stump for the production of a blastema and the communication of morphogenetic information to the developing regenerate. Although each histologic component of a limb is capable of tissue regeneration, the replacement of the entire appendage is a developmental phenomenon that is more than the sum of its parts. When an injured tissue repairs itself in an unamputated limb, it does so by reestablishing the continuity of the affected structures. This is a wound-healing phenomenon whether it occurs in the skin or in such internal tissues as bones, tendons, muscles, nerves, or blood vessels. Cases of tissue regeneration differ from epimorphic regeneration not in degree but in kind (2). The regrowth of an amputated appendage is a qualitatively distinct developmental phenomenon, the success of which depends upon the healing of the stump by epidermal migration, the accumulation of a blastema, and the differentiation of distal anatomical structures not represented by

counterparts in the stump. The influence of nerves or spinal cord is also essential to many examples of appendage replacement (30). Epimorphic regeneration, therefore, is not the separate regrowth of each individual tissue in the stump but is a process in which the participating tissues pool their resources in a developmental investment that gives rise to a structure that could not have been achieved without the cooperative interaction of the diverse tissues represented in the stump. Not surprisingly, the key to epimorphic regeneration, both in higher and lower vertebrates, lies in the coordinated responses of individual tissues to interruptions in their continuities.

Not so many years ago it was generally believed that mammals were incapable of epimorphic regeneration. It is now known that there exist some interesting exceptions to this rule, exceptions which prove that the general lack of regeneration in higher vertebrates is not attributable to being a mammal per se. These examples of mammalian regeneration are valuable for two reasons. One is that the mechanisms by which missing parts are replaced in mammals can be compared with similar events in lower forms, thus broadening our overall perspective of the range of regenerative phenomena in the animal kingdom. The other value of studying cases of regeneration in mammals is to make comparisons with nonregenerating structures in order to pinpoint how wound healing leads to the production of a blastema in some cases but to scar formation in others. The implications for the prospects of inducing regeneration in human appendages, e.g., fingertips (24), are inescapable (14).

Deer Antler Replacement

The earliest known example of mammalian regeneration was that of the annual replacement of deer antlers (1). These remarkable headpieces are shed each winter or spring, to be replaced by new outgrowths that may elongate at rates in excess of 2 cm per day in larger species. Antlers come in many forms, from the short unbranched spikes in the smallest species to the enormous racks that were grown each year by the giant deer *(Megaceros)* that became extinct in the Pleistocene. In some forms (moose, fallow deer) the antlers may become palmate. Antlers are grown only by males, except in reindeer and caribou in which both sexes possess them. The sequence of events in the regeneration of elk antlers is illustrated in Figures 2-1 through 2-6.

Histogenesis and Development

The site at which antlers are destined to grow can be palpated in a fawn as a pair of exostoses on the frontal bone. These protuberances develop into the pedicles and the initial set of antlers during the deer's first year of life. The growth of the original antler is one of those rare instances in

Figures 2-1 through 2-6. Successive photographs of an elk during the course of antler regeneration, as seen several days (Fig. 2-1) and at monthly intervals (Figs. 2-2 through 2-6) after the old antlers were shed in late February.

nature in which something akin to regeneration occurs in the absence of epidermal wound healing. The histological origin of the pedicles lies in the periosteum, which overlies the frontal protuberances in fawns. Their development can be prevented by excision of the periosteum (23), but not of the overlying skin alone (19). Therefore, there is reason to believe that this periosteal tissue has the capacity to induce an outgrowth from the underlying frontal bone as well as the conversion of the overlying skin from that characteristic of the scalp to the velvetlike integument of the antler. Indeed, in a remarkable experiment carried out by Hartwig and

Schrudde (23), it has been shown that if the periosteum from the presumptive pedicle region is transplanted beneath the skin in the leg, there will develop at that site an ectopic pedicle and antler, the latter undergoing annual cycles of shedding and regrowth during subsequent years.

This original development of the pedicle in the fawn is promoted by the male sex hormone. Castration of a fawn precludes the later development of pedicle and antlers. Administration of estrogen also inhibits development. Conversely, the administration of testosterone to a spayed female promotes the outgrowth of pedicles from the frontal bone, although such pedicles do not normally give rise to antlers. It was Jaczewski who discovered that antler development can be induced from such pedicles simply by cutting off their ends (26, 27). Presumably this creates a wound necessary for the onset of antler growth per se. Indeed, it has been shown that if the end of the pedicle from which antlers are normally replaced is sealed with a full thickness layer of skin, antler growth is effectively inhibited (11).

An animal's first set of antlers is usually unbranched, but subsequent ones become increasingly elaborate until maturity, after which successive sets of antlers are replicas of each other. Following the shedding of the old antlers in the winter or spring, the raw pedicle stump is healed with skin and rounds up into an antler bud (10). During the spring and summer, this bud elongates and repeatedly bifurcates into the new rack of antlers, doing so by virtue of its apical growth zones. In these growing tips there is profuse proliferation of cells engaged in the synthesis of quantities of collagen fibers. The fibro-cellular growth zones at the tips of the elongating antler subsequently differentiate into cartilage. This cartilage is unique in that it is highly vascularized with veins that convey blood away from the growing tip. Later, the cartilage is replaced by bone. This bone is at first a spongy network of trabeculae, but with the maturation of the fully grown antler toward the end of the summer, appositional ossification on the trabeculae gives rise to the solid bone characteristic of the fully developed antler. The demise of the antler is presumably attributable to the vascular constrictions caused by the deposition of bone around the blood vessels. The arteries of an antler are located in the skin. Their impressions are often visible on the surface of the bony antler. With the interruption of blood flow, the velvety skin dies and is actively rubbed off by the deer. It has been shown that if skin from a growing antler is transplanted elsewhere on the body, it will survive indefinitely, suggesting that the death of the skin on the maturing antler is a case of murder, not suicide (11).

Hormonal Control of the Antler Cycle

These events, like so many others that regulate the annual changes in secondary sex characters, are controlled by fluctuations in the levels of sex hormones (31, 32). Castration of an adult deer in the fall or winter when he

has hard bony antlers results in their premature shedding several weeks later (5). This is followed by the regeneration of a new set of antlers, even at this atypical time of year. Although such antlers can grow to normal proportions, they are unable to complete their maturation in the sense of becoming densely ossified and shedding the velvet. They remain permanently viable, although in temperate regions they are vulnerable to freezing in the winter. The more severe the winter, the greater the amount of antler tissue that is frozen. With the coming of spring, this necrotic tissue is cast off, and the surviving stumps are stimulated to grow in the spring and summer. If the deer is kept indoors in the winter, his entire set of antlers may survive. In either case, new growth is promoted although the old antlers have not been lost. Consequently, the antlers of castrated deer develop rather bizarre outgrowths often taking the form of nodules produced along the sides of the shafts. The morphological characteristics of these overgrowths varies from one species to another, but in none is it more abnormal than in the castrated roe deer. In this species antler overgrowth is responsible for the production of a wiglike mass of amorphous antler tissue that may grow down over the sides of the head. In subsequent years the tumorlike growths become increasingly enlarged and grotesque. Although such structures are not known to be neoplastic, they may constitute a threat to the deer's health by infections, insect infestations, and the excessive accumulation of skin secretions. The only remedy is to inject testosterone. This promptly causes ossification, shedding of the velvet, and after the hormone has worn off, loss of the antlers. However, subsequent outgrowths may in due course become equally troublesome.

It is clear from the foregoing account that the onset of antler regeneration is triggered by a decrease in male sex hormone, whether it be the abrupt drop resulting from castration or the gradual decline that occurs in the spring after the breeding season. It is the rise in testosterone secretion toward the end of the summer that is responsible for the normal maturation of the antlers in preparation for the autumn mating season. Experiments have shown that if testosterone is administered to a deer in the spring before his old antlers have been lost, shedding and regrowth can be held in abeyance for as long as the hormonal treatments are continued (6). Injection of testosterone into an animal with antlers in velvet results in their premature maturation. Elongation ceases, mineralization occurs, and the velvet is shed several weeks later. Curiously, similar effects can be achieved by injections of the female sex hormone, estradiol benzoate.

The Effects of Seasonal Changes in the Photoperiod

The antler replacement cycle, and the reproductive cycle of which it is a part, are under the control of hormonal secretions that rise and fall with the seasons. These endocrinological changes are in turn regulated by

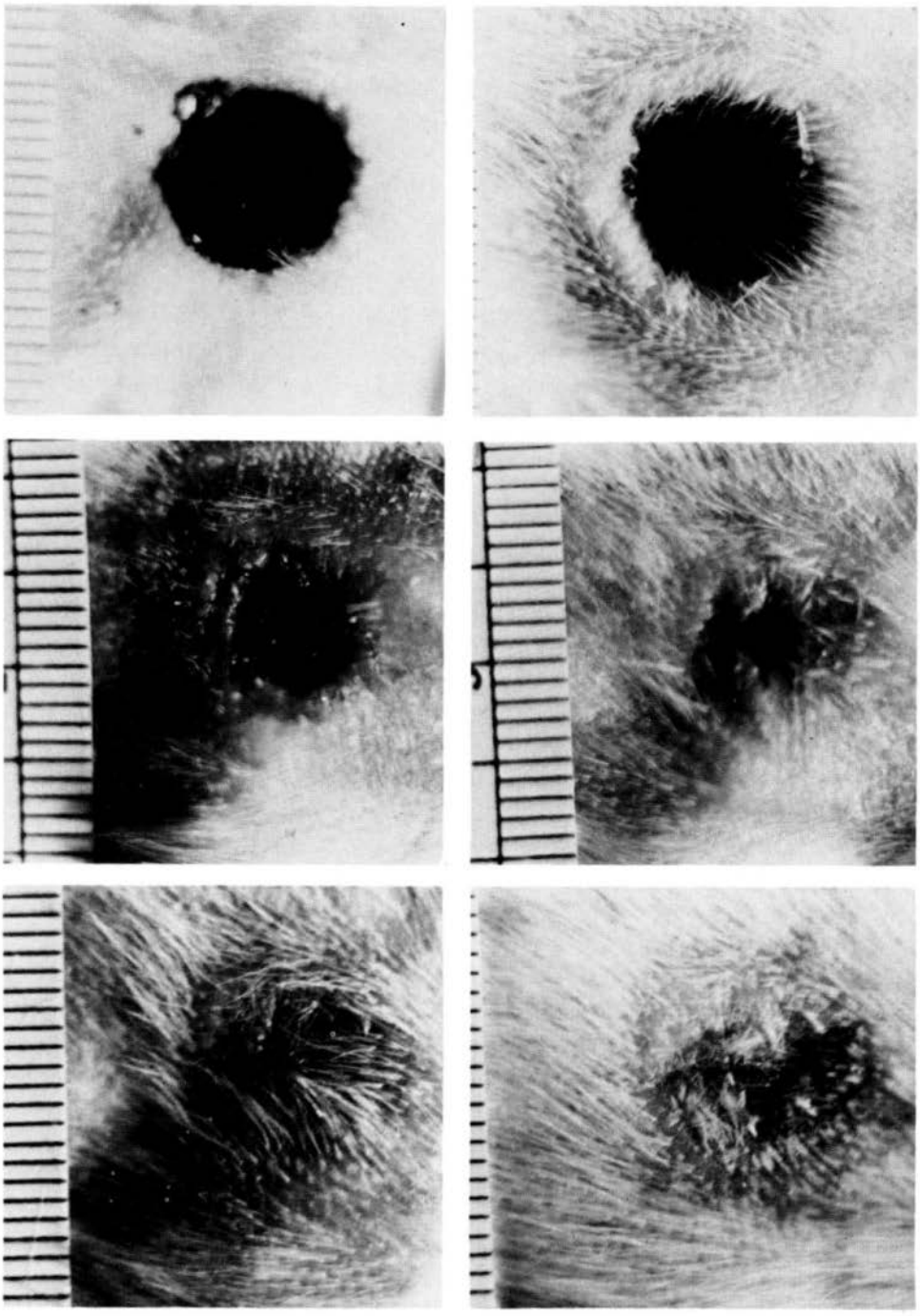
annual fluctuations in the photoperiod. Jaczewski (25) was the first to demonstrate that antler replacement is sensitive to changes in day length by inducing two sets of antlers to grow in one year by exposing red deer to two light cycles per year. Subsequent experiments have shown that deer are capable of producing as many as four sets of antlers a year if the light cycle is made to pass in only three months instead of twelve (7). This shows that it is the change in day length that triggers the recurrent loss and replacement of antlers. Indeed, if deer are held under artificial lighting conditions simulating those on the equator (12 hours of light, 12 hours of dark) they do not replace their antlers thereafter (8).

Further investigation, however, has shown that the interpretation of these phenomena is not as simple as might have been suspected. For example, if deer are maintained on unchanging photoperiods in which the light and dark phases are not equal, antler replacement occurs at irregular intervals of about ten months (8, 18). Such cycles have been termed circannual rhythms because they approximate one year. Circannual antler cycles are expressed under constant lighting conditions in which the lengths of the light and dark periods differ by one hour or more (e.g., 13L/11D). For unaccountable reasons they are not expressed when the ratio of light to dark is close to one (12). Parenthetically, it is worth noting that deer native to the tropics replace their antlers every year, not on a circannual cycle but on an annual one. However, they do not do so in unison as is the case with temperate zone species, but each animal sheds and replaces his antlers at twelve-month intervals not necessarily synchronized with others in the population (5, 15).

Much has been learned over the years about the physiological factors involved in the growth of deer antlers. It is becoming apparent, however, that these structures are more than just zoological curiosities. They may reveal important clues about the nature of regeneration in mammals. They have been relatively neglected in the past, but it is hoped that as increasing attention becomes focused on various examples of regeneration in mammals, perceptive biologists will recognize the importance of learning more about the exception to the rule that mammals are not supposed to regenerate appendages.

Experiments on Rabbit Ear Regeneration

What is needed in our quest for the explanation of mammalian regeneration is a structure that regenerates in some forms but not in others. This would make it possible to compare the two systems step by step in order to determine at what point the regenerating structure differed from the nonregenerating one. The discovery that the rabbit ear is capable of regenerating from the margins of holes punched through its full thickness has made it possible to examine the histological sequence of events in



Figures 2-7 through 2-12. Regeneration of rabbit ear tissue from the margins of a 1 cm hole as seen one day (Fig. 2-7) and one, three, five, six, and twelve weeks (Figs. 2-8 through 8-12) after injury. By one week the margins of the hole are conspicuously swollen. New ingrowth is visible by the third week, and closure is achieved after two months.

comparison with those that occur in the nonregenerating ears of other species.

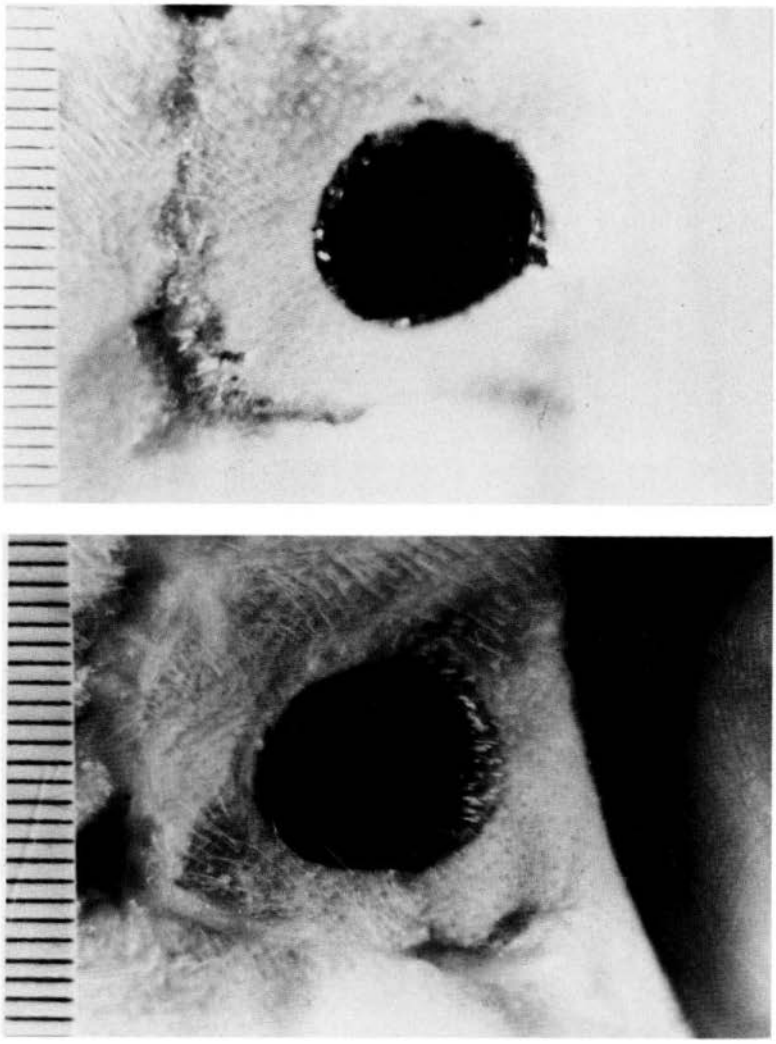
The rabbit ear consists of a sheet of cartilage sandwiched between the inner and outer skin. When a hole one centimeter in diameter is cut through these tissues, it heals by the migration of the inner and outer epidermis across the margins around the periphery of the hole (28). After the two layers of migrating epidermis have joined together, there begins to accumulate a mass of seemingly undifferentiated cells beneath the wound epidermis and off the end of the severed sheet of cartilage. These cells proliferate and give rise to a blastema extending around the margins of the hole. In several weeks, there is visible ingrowth from the periphery, after which chondrogenesis begins to occur in continuity with the original cartilage. There is thus established a growth zone around the circumference of the hole, the dimensions of which decrease as regeneration proceeds. After two months or so, the aperture is obliterated by the centripetal growth of new tissue (Figs. 2-7 through 2-12). Chondrogenesis is responsible for reestablishing the continuity of the original sheet of cartilage. Occasional hair follicles with sebaceous glands may develop in the integument.

The Role of Skin and Cartilage

Experiments have been carried out to explore the role of the ear skin in this kind of regeneration (16, 22). Accordingly, the skin on either side of the ear was replaced with grafts of belly skin from the same animal. Holes were then punched through the middle of the grafted areas so that the margins of the openings would be healed by belly skin instead of ear epidermis. Under these circumstances, only partial ingrowth occurred, and the new tissue that was formed lacked cartilage.

Other experiments have been carried out to determine how the cartilaginous sheet might affect the process of ear regeneration (16). This was achieved by reflecting the skin on one side of the ear, excising the sheet of cartilage thus exposed, and replacing the skin flap to yield an area of the ear in which the inner and outer layers of skin were not separated by cartilage. When holes were cut through this region, no regeneration occurred (Figs. 2-13, 2-14). These findings indicate that the cartilaginous sheet at the cut margins of a hole plays an indispensable role in the regenerative process.

What this role might be has been investigated by the selective irradiation of the tissue components of the ear (20). Preliminary investigations proved that exposure to 3,000r x-rays was more than enough to inhibit regeneration from the margins of holes punched through the rabbit ear. Using this dosage, further experiments were undertaken in which the cartilage in an area of ear was removed while the skin was irradiated before replacement



Figures 2-13 and 2-14. No regeneration occurs in rabbit ear holes in the absence of cartilage. Figure 2-13: appearance of hole one day after cutting through a region of the ear from which the cartilaginous sheet had been removed several weeks earlier. Figure 2-14: same hole twelve weeks later, showing complete lack of regeneration.

of the cartilage; or the cartilage was irradiated and grafted back into the unirradiated ear. When just the skin was irradiated while the cartilage had been shielded, regeneration occurred from the margins of holes cut through such regions. In the reciprocal experiment, however, only partial ingrowth occurred, and this did not include chondrogenesis. These results strongly suggest that the differentiation of new cartilage depends upon the existence of healthy cartilage in the surrounding ear from which differentiation can proceed. Other experiments indicate that the sheet of

cartilage in the ear exerts little morphogenetic influence on the cartilage that may regenerate from it. For example, if an extra sheet of cartilage is grafted to an ear, and a hole punched through the region with double layers of cartilage, only a single sheet differentiates in the subsequently regenerated region (21).

Although cartilage regularly differentiates in the regenerating parts of the ear, it is not capable of tissue regeneration per se. If the skin of the ear is reflected and the underlying cartilage removed followed by replacement of the skin flap, the missing portion of the cartilage is not regenerated. These results are reminiscent of what happens in amphibian limbs. If a skeletal element is removed from an unamputated limb, it is not replaced. However, if it is removed with the rest of the limb by amputation, it may be replaced as the entire limb regenerates distal to the level of amputation (4). In the rabbit ear, the cartilaginous sheet is differentiated only when it does so in conjunction with the regrowth of the full thickness of the ear. This may be taken to indicate that regeneration of the cartilage depends upon its proximity to a healing epidermal wound.

Epidermal Downgrowths

Close examination of the sequence of events following perforation of the ear confirms the possibility of an interaction between the healing epidermis and the subjacent cartilaginous sheet. As indicated earlier, the margins of a hole cut through the full thickness of the rabbit ear are healed by epidermal migration from the inner and outer skin. Even before these two sheets of migrating epidermis meet in the middle, they develop conspicuous downgrowths into the underlying dermal connective tissue (16). These tongues of epidermal cells may extend as deep as 1 mm and are usually evident by about five days after injury. They eventually undergo epidermal differentiation, leading to the keratinization of their innermost cells. This results in their modification into an infolding toward the latter part of the second postoperative week. In the meantime, blastema cells accumulate between the epidermal downgrowths from the inner and outer skin, leading to the aggregation of a mass of undifferentiated cells off the end of the cut cartilaginous sheet. As a blastema swells, it pulls the infolded epidermis out into a flat sheet on the surface of the regenerate. Thus, epidermal downgrowths are seldom seen after twelve days or so.

The possible role of the epidermal downgrowths in promoting regeneration is suggested by the time and place of their formation. They are present at precisely that period when the blastema begins to form. They are located in exactly the right location to constitute a possible barrier between the dermis of the original skin and the margins of the hole where the blastema must form if regneration is to occur. Nevertheless, these

coincidences do not prove that the epidermal downgrowths are in any way responsible for the production of a blastema instead of a scar.

Attempts to shed further light on this problem by experimental means have strengthened the suspicion of a causal relationship between epidermal downgrowths and regeneration. If this suspicion is correct, one might predict that these structures would not develop in nonregenerating ears. There are two ways to prevent the regeneration of rabbit ears. One is by exposure to x-rays, the other by removing the cartilaginous sheet. Examination of the healing margins of holes cut through irradiated ears or ones lacking cartilage have proved that epidermal downgrowths do not develop under these circumstances. Further, they have not been found in the healing margins of holes cut through the ears of those nonregenerating species thus far examined (e.g., sheep and dogs). Finally, it has been shown that if wounds are made in the skin alone, they heal without the development of epidermal downgrowths such as occur on the margins of holes through the entire ear. It would appear that these epidermal downgrowths develop in relation to the cut edges of an underlying sheet of cartilage. It may be possible that they are instrumental in the development of a blastema, if not the initiation of chondrogenesis from the cut edge of the original cartilaginous sheet.

Regeneration in Other Ears

Rabbits are not the only animals whose ears can regenerate. Other lagomorphs have been found to be capable of filling in holes that are cut through their external ears. Not only does the hare regenerate ear tissue, but the pika does likewise. The latter animal is a short-eared lagomorph that inhibits mountainous rock slides at high altitudes. Like its long-eared relatives, it is capable of regenerating tissues from the margins of holes cut through its ears, including chondrogenesis.* Why it is that the lagomorphs are so uniquely endowed with such regenerative powers is not known.

Ear regeneration has been shown not to occur in the vast majority of animals thus far tested. Negative results have been obtained in sheep, dogs, deer, guinea pigs, chinchillas, gerbils, hamsters, rats, mice, opossums, and armadillos. Even the patagonian cavy, a remarkably rabbitlike rodent from South America, is unable to fill in holes cut through its long ears. Nevertheless, there remain a few other species that, like the rabbit, can regenerate ear tissue. One such example is the domestic cat in which holes several millimeters in diameter can be filled in by new tissues, including cartilage. Whether or not epidermal downgrowths are present in this regenerating system remains to be determined.

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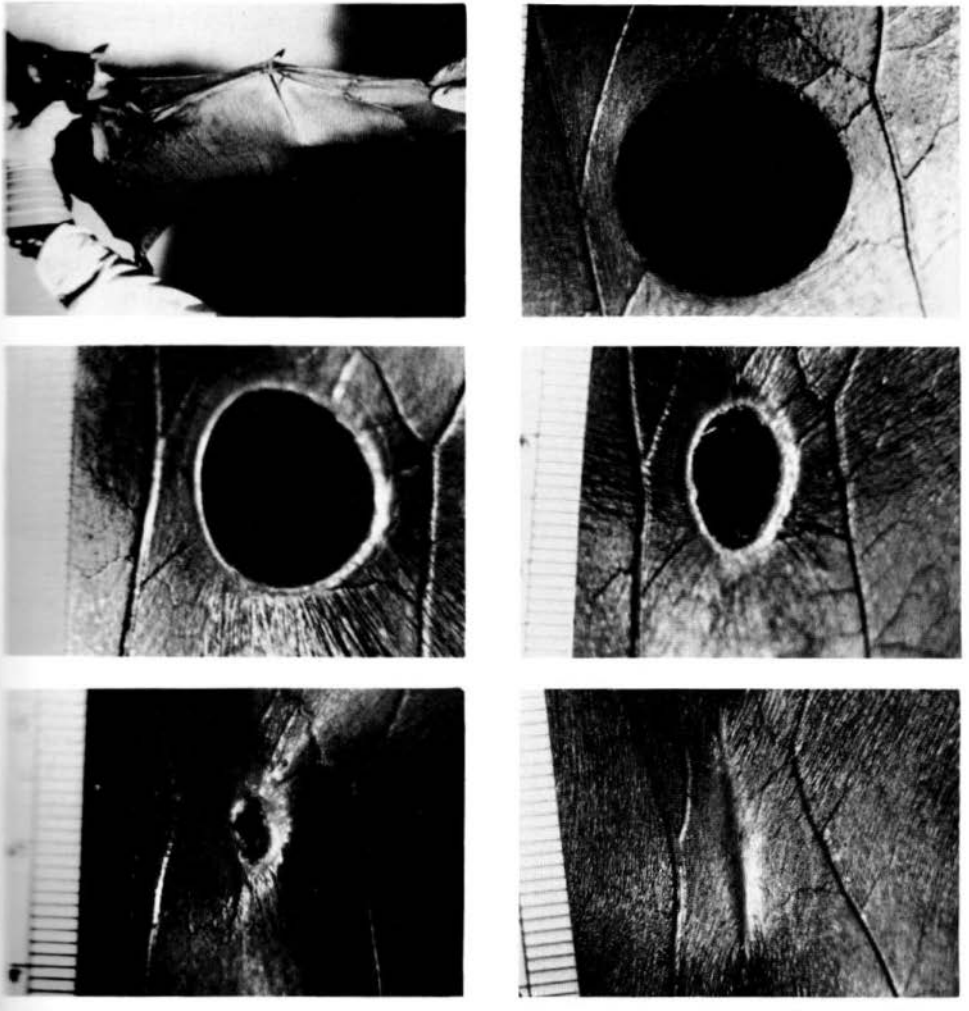
* The author is indebted to Dr. Preston Somers and Ms. Carolyn Engel of the Department of Biology at Fort Lewis College, Durango, Colorado for their cooperation in our studies of pika ear regeneration.



Figures 2-15 through 2-20. Regeneration in fruit bat wing membrane. Figure 2-15 is a specimen of *Pteropus* to show the extensive webbing of its wing. The closure of a hole 1.5 cm in diameter is illustrated in Figures 2-16 through 2-20, photographed one day and two, three, four, and seven weeks after injury. Although considerable contraction is revealed by the approximation of the two blood vessels on either side of the perforation, this is supplemented by the regeneration of new tissue at the margins of the hole.

Probably the most valuable and important ears of any mammal are those of bats that fly by echolocation. Investigations of a variety of species, including the insectivorous little brown bat *(Myotis lucifugus)* and several Central American fruit bats,* have confirmed that their ears are capable of filling in holes 2 mm in diameter (which is a large hole in relation to the size

* My thanks to Dr. Alvin Novick in Yale University for kindly making various species of fruit bats available to me for experimentation.

and thickness of the ear). Unlike cats and rabbits, however, these animals fill in ear holes with skin and connective tissue, in the absence of chondrogenesis. Bats that fly by night vision rather than echolocation, such as the old world fruit bats *(Pteropus)* fail to regenerate ear tissue from the margins of holes. The contrast between these two types of bats strongly suggest that ear regeneration in mammals is an adaptive phenomenon.

Equally adaptive is the regenerative ability of bat wing membranes. Despite their maneuverability in flight, it is not uncommon for bats to tear or puncture their wings. When this happens, the surrounding tissues contract. In addition, there is considerable production of new tissue at the edge of the wound that grows in from all sides to reestablish the original continuity (Figs. 2-15 through 2-20). In fruit bats, holes as much as 3 cm in diameter can be filled in after a couple of months.

Conclusions

There now exists a sufficient number of mammalian structures known to be able to regenerate for meaningful comparisons to be made. It would seem that the capacity for epimorphic regeneration in mammals may have evolved independently in a variety of structures and species. Thus, there is no guarantee that the developmental mechanisms by which regeneration is achieved in one system necessarily applies to the others. On the other hand, such attributes as may prevail in all known cases may be assumed to have fundamental importance for the regenerative process per se. For example, there can be no regeneration in mammals, or in other forms, without a healing epidermal wound. The role of nerves, however, appears not to be universal. Although neurotrophic influences are essential for the regeneration of many appendages in lower vertebrates (30), nerves have been shown not to be required for the replacement of antlers in deer (33), the ingrowth of tissue from the margins of rabbit ear holes (22), or the repair of bat wing membranes (3). The importance of epidermal downgrowths in the healing of wounds needs to be explored further to determine if this phenomenon, which appears to be so important in rabbit ears, also occurs in other regenerating mammalian systems.

Clearly, the mechanisms by which regeneration occurs in those mammalian structures thus far discovered must be investigated more thoroughly in the years ahead. It is hoped that additional examples of mammalian regeneration may be added to the list. Only by the exploration of such naturally occurring examples of regeneration will it be possible to understand this interesting phenomenon in sufficient detail to be able some day to promote regeneration where nature never intended.

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