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## Regeneration of Symmetrical Hindlimbs in Larval Salamanders

Abstract. *The complete circle rule of the polar coordinate model of pattern regulation was tested for regenerating hindlimbs of* Ambystoma *larvae. The hindlimbs were made symmetrical in the circumference of either the thigh or the shank, and their ability to regenerate from both levels was observed. Thighs composed of two anterior halves failed to regenerate, whereas thighs composed of two posterior halves often regenerated distally complete, correspondingly symmetrical limbs; shanks composed of either two anterior or two posterior halves regenerated distally complete, correspondingly symmetrical limbs. These results are in contrast to what is predicted by the complete circle rule and suggest a modification of this rule.*

French *et al.* (*1*) have proposed a polar coordinate model to account for epimorphic pattern regulation in insect imaginal disks as well as regenerating insect and amphibian appendages. The cells of these structures are hypothesized to respond to two components of positional information, one component corresponding to position around the circumference of the limb, the other to position along a radius of that circle. In amphibian limbs, the circumferential component is represented by a circular sequence of positional values, and the proximal-distal axis of the limb is represented by the sequence of values along the radius of the circular sequence. According to the model, regeneration of amphibian limbs is governed by two rules for cellular interactions. The shortest intercalation rule states that missing values in either the radial or circular sequences are filled in along the shortest route by intercalary regeneration. The complete circle rule states that distal transformation of blastema cells will take place only if these cells are derived from a limb stump possessing a complete circular sequence of positional values. A complete circular sequence is present after simple amputation or can be generated by shortest intercalation when normally nonadjacent positional values of the circular sequence are apposed.

Bryant (*2*) has shown that adult *Notophthalmus viridescens* upper arms made symmetrical in the circular sequence by grafting together either two anterior or two posterior halves fail to regenerate after amputation; this result provides evidence for the necessity of a complete circular sequence of positional values for distal transformation. I now report the results of similar experiments in which upper and lower hindlimbs of *Ambystoma* larvae were made symmetrical with respect to their anterior and posterior halves (hereafter called double anterior and double posterior limbs). Both double anterior and double posterior lower hindlimbs regenerate correspondingly symmetrical limbs. Double anterior upper hindlimbs fail to regenerate, but double posterior upper hindlimbs regenerate symmetrical limbs. The production of symmetrical regenerates by symmetrical hindlimbs is a result opposite that predicted by the complete circle rule of the polar coordinate model.

Hindlimbs of *Ambystoma mexicanum* or *Ambystoma tigrinum* (length from snout to tail, 60 to 80 mm) were made symmetrical in either anterior or posterior regions of the thigh or shank (Fig. 1). Controls consisted of longitudinally halving the thighs and shanks and putting the halves back together in the normal orientation. Grafts become revascularized within 3 to 5 days after the operation and, after an initial period of edema lasting about 1 week, became well integrated with the host tissues. After a healing period of 10 to 32 days, amputation was performed through the middle of the grafted region (mid-thigh or distal shank).

The limb skeletons were examined by methylene blue staining after a 25- to 50-day period of regeneration (Tables 1 and 2). No difference in the results was noted between the two species. All control limbs regenerated normally (Fig. 2A). Some of the symmetrical thighs and shanks also regenerated normally. No sign of the grafted half was observed in the latter cases at the end of the experiment, which suggests that it had resorbed. It is likely that the host stump tissue in these cases formed an oblique wound surface, which would encompass the normal stump circumference and thus allow normal regeneration to occur. This hypothesis is strengthened by two observations: (i) In all remaining cases the graft was still visible on the limb stump at the end of the experiment. (ii) I have often observed this mode of normal regeneration in half-upper or lower hindlimbs of axolotls of the size used in the present experiments. The half-hindlimb rounds off and regresses somewhat, and a blastema forms from the whole stump circumference at a 45° angle to the longitudinal axis of the limb. The blastema subsequently straightens by faster growth on one side.

For the symmetrical thighs, the most significant finding was a nonequivalence in the regenerative ability of double anterior and double posterior stumps. Although normal-looking blastemas often formed on double anterior thigh stumps and advanced as far as the late bud stage, they were able to redifferentiate only a conical cap of cartilage continuous with the tip of the femur or a short spike of cartilage that articulated with the femur (Fig. 2B). Several double anterior limbs


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were sectioned and stained by the Holmes silver nitrate method after blastemas had formed. All appeared normal in histological composition, which included the presence of an abundant nerve supply throughout the blastema. In contrast, all but one of the double posterior thighs underwent distal transformation. Five of these produced regenerates with normal axial asymmetry, but with a fibula and one or two toes missing (Fig. 2C), while 11 formed perfectly symmetrical double posterior regenerates (Fig. 2D). If it is assumed that each half of the stump gives rise to the corresponding half of the regenerate, the expected skeletal composition of symmetrical double posterior thigh regenerates would be two fibulae, nine tarsals in two mirror-image groups of four and one-half each, and five toes, with the third toe in the midline, flanked on either side by toes 4 and 5, in that order. This result was approximated in two of the 11 cases (Fig. 2D); but most of the cases (six of 11) had seven or eight tarsals and seven or eight toes (Table 2), with a single or duplicated toe 2 in the midline flanked on both sides by toes 3, 4, and 5, in that order.

One case formed only one tarsal and one toe (toe 5); one case three tarsals and three toes (toe 4 flanked on either side by toe 5); and the last case had toe 2 in the midline flanked by toe 5 on either side, but was missing toe 4 on either side. Two of the 11 cases had three fibulae, and three cases had one. Thus, there was a definite tendency in symmetrical double posterior or thigh regenerates for each half to produce slightly more than half the expected number of toes, with the first toe being consistently deleted. This is undoubtedly also true for the tarsal region, for despite the fact that an average of only 8.18 tarsals were regenerated, two cases formed 13 and 14 tarsals, and in most of the cases it was evident that what were counted as single tarsals in the midline were actually fusions of two tarsals.

An inverse relationship appears to exist between the length of time the double posterior thigh grafts were allowed to heal before amputation and the number of skeletal elements regenerated. Eight of the 11 double posterior thighs which produced double posterior regenerates had been allowed to heal for 10 to 14 days before amputation, and the other three were allowed to heal for 32 days. Those cases with the shorter healing time had an average of 2.13 fibulae, 9.25 tarsals, and 6.63 toes, while those healing for the longer time had an average of 1.33 fibulae, 5.33 tarsals, and 3.00 toes. In addition, the single case that failed to regenerate was also one in which the graft was allowed to heal for 32 days before amputation. Before amputation, four of the double anterior thighs were allowed to heal for 10 to 14 days and four for 32 days. In all cases, the length of the healing period had no effect on regeneration.

The nonequivalence in developmental potential was present, but it was not as evident in double anterior and posterior shanks as it was in the corresponding thighs; no effect of the length of the healing period on regeneration was observed. All of the double posterior shanks underwent distal transformation, and only three of the double anterior shanks failed to do so. The majority of the cases regenerated double anterior and double posterior limbs (Table 1), with double posterior shanks forming 17 percent more symmetrical regenerates than double anterior shanks. A nonequivalence in developmental capacity is also seen in the fact that the mean number of toes formed by double posterior regenerates is nearly twice that in double

Table 1. Types of regenerates formed after amputation of double anterior and posterior thighs and shanks.

| Graft type | Total cases | Normal | Abnormal asymmetric | Spike | Regenerates (No.) | Double anterior | Double posterior |
|---|---|---|---|---|---|---|---|
| Thigh | | | | | | | |
| Anterior control | 10 | 10 | 0 | 0 | 0 | 0 | 0 |
| Posterior control | 10 | 10 | 0 | 0 | 0 | 0 | 0 |
| Double anterior | 13 | 5 | 0 | 2 | 6 | 0 | 0 |
| Double posterior | 23 | 6 | 5 | 0 | 1 | 0 | 11 |
| Shank | | | | | | | |
| Anterior control | 5 | 5 | 0 | 0 | 0 | 0 | 0 |
| Posterior control | 5 | 5 | 0 | 0 | 0 | 0 | 0 |
| Double anterior | 22 | 3 | 2 | 1 | 3 | 13 | 0 |
| Double posterior | 17 | 3 | 2 | 0 | 0 | 0 | 12 |

Table 2. Mean number of skeletal elements redifferentiated by symmetrical regenerates.

| Graft type | Femur | Tibia | Fibula | Tarsals | Toes |
|---|---|---|---|---|---|
| Thigh | | | | | |
| Anterior control | 1.00 | 1.00 | 1.00 | 9.00 | 5.00 |
| Posterior control | 1.00 | 1.00 | 1.00 | 9.00 | 5.00 |
| Double posterior | 1.00 | 0.00 | 1.91 | 8.18 | 5.64 |
| Shank | | | | | |
| Anterior control | | 1.00 | 1.00 | 9.00 | 5.00 |
| Posterior control | | 1.00 | 1.00 | 9.00 | 5.00 |
| Double anterior | | 2.00 | 0.00 | 4.69 | 1.92 |
| Double posterior | | 0.00 | 2.00 | 5.09 | 3.58 |

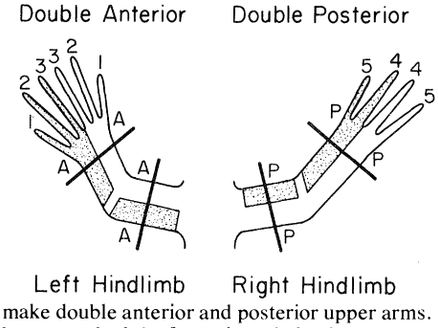


Fig. 1. Method of making double anterior and double posterior thighs and shanks (dorsal view). Host tissues are white, graft tissues stippled. Symmetrical thighs were made by removing the anterior half of the flexor and extensor muscles plus overlying skin from the right hindlimb and the posterior half of the flexor and extensor muscles plus overlying skin from the left hindlimb and exchanging the two halves. The femur was left intact in both limbs because it is difficult to halve it longitudinally. The axial definitions and the method are comparable to those used by Bryant (*2*) to make double anterior and posterior upper arms. The possibility that different results might have been seen had the femur been halved or removed cannot be ruled out, but it would seem unlikely since stump cartilage is not the sole source of regenerate cartilage (*9*) and, in fact, need not be present at all for regeneration of a complete skeleton distal to the amputation plane (*10*). Symmetrical shanks were made by first making a midline cut between the tibia and fibula from the point between the third and fourth toes to the knee joint in both right and left limbs. The tibia is located anterior to the midline of the shank and the fibula posterior to the midline. The anterior half of the right shank was then removed by making a second cut perpendicular to the midline at the knee joint, and the posterior half of the left shank was removed by making a similar cut. The two halves were then exchanged, making a six-digit double anterior shank on the left hindlimb and a four-digit double posterior shank on the right hindlimb. Normal axial orientations of the grafts were always maintained. Heavy lines indicate planes of amputation. Abbreviations: *A*, anterior; *P*, posterior.

anterior regenerates (Table 2). Double anterior shanks most frequently regenerated only a single toe (toe 1), while double posterior shanks most frequently regenerated three to four toes (Fig. 2, E and F). In the latter regenerates, the first, second, and third toes were consistently missing, with a single or duplicated fourth toe situated in the midline, flanked on either side by the fifth toe. The number of tarsals and toes formed by double posterior shank regenerates was about 60 percent that of corresponding thigh regenerates, which demonstrates that there is also a nonequivalence in developmental capacity between double posterior thighs and double posterior shanks in this regard.

The nonequivalence in regenerative potential of double anterior and double posterior thighs and shanks does not fit the prediction of the complete circle rule (*1*) that limbs with half or double half circular sequences should be unable to undergo distal transformation. The data suggest a modification of this rule, namely, that the extent of distal transformation of a limb sector is proportional to the fraction of the circular sequence of positional values carried by that sector, or that distal transformation cannot occur unless a threshold fraction of the circular sequence is present in a sector, or both. The spacing of the values would be different in the thigh and the shank, so that most of them would be carried in the posterior half of the thigh (*3*) but be more evenly distributed between the anterior and posterior halves of the shank.

This modification suggests that there is an unequal contribution of blastema cells to the regenerate by different sectors of the thigh. The data suggest that only the femur and perhaps the tibia of the regenerate is derived from the posterior half. This would account for the fact that double anterior thighs regenerated only cones of femoral cartilage and, infrequently, a single cartilage distal to the femur that might be interpreted as a tibia; double posterior thighs formed distally complete double posterior regenerates, each mirror half of which often contained close to the normal number of tarsals and toes. That asymmetrical regenerates produced by the double posterior thighs contained near normal complements of toes but only one fibula is also consistent with this scheme. In the shank, the contribution of anterior and posterior halves of the stump would be more equal; thus both double anterior and posterior shanks would form distally complete, although nonequivalent, double anterior and double posterior regenerates. Other evidence consistent with this view is that longitudinal halves of lower arms or legs of the adult newt regenerate half limbs after transverse amputation (*4*). Likewise, longitudinal halves of young upper arm blastemas of larval *Ambystoma maculatum* develop into distally complete half-regenerates when grafted to the dorsal fin in a way that prevents regulation in the anterior-posterior axis (*5*). The fact that anterior halves of blastemas form distally complete regenerates might seem at variance with the inability of double anterior stumps to regenerate. It should be kept in mind, however, that these halves are derived from blastemas that have received cellular contributions from both the anterior and posterior halves of normal limb stumps, whereas the blastemas formed on double anterior limb stumps do not receive the normal cellular contribution.

Singer *et al.* (*6*) have presented evidence that the developmental potential of the anterior and posterior halves of *N. viridescens* upper arm stumps is equivalent but that their actual contribution to the regenerate is greatly influenced by

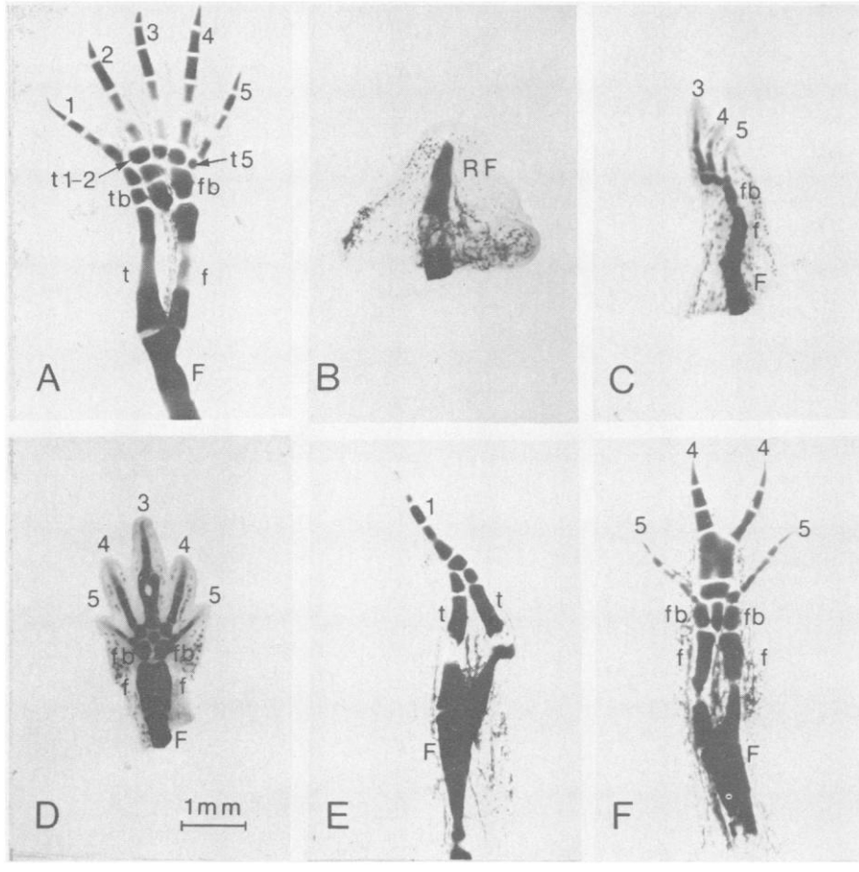


Fig. 2. Regenerates obtained after amputation of control and experimental limbs, methylene blue stained. Numbers refer to toes, in anterior to posterior order. Abbreviations: *F*, femur; *t*, tibia; *f*, fibula; *tb*, tibiale tarsal; *fb*, fibulare tarsal; *t1-2*, tarsal articulating with metatarsal 1 and 2; *t5*, tarsal articulating with metatarsal 5; *RF*, femoral cartilage. [Nomenclature follows that of Francis (*11*).] (A) Double anterior control, 50 days after amputation through the thigh. A completely normal limb regenerated. Double posterior thigh control regenerates as well as double anterior and posterior control shank regenerates present a similar appearance. The large tarsal located between the tibiale and the fibulare is the intermedium. (B) Double anterior thigh regenerate 44 days after amputation. A long cone of femoral cartilage regenerated in continuity with the remaining femur. (C) Asymmetric regenerate formed on a double posterior thigh stump, 28 days after amputation. A single fibula regenerated, plus four tarsals and three toes. This is essentially a posterior half regenerate. (D) Symmetric double posterior regenerate formed on a double posterior thigh stump 32 days after amputation. The symmetry is nearly perfect, with the first and second toes of the foot and the intermedium and tarsal 1-2 of the tarsus deleted. The metatarsals of the third toe are present in the midline twice, and share a single set of phalanges. Tarsal 3 and the central tarsal are shared by the two halves in the midline. (E) Symmetric double anterior regenerate formed on a double anterior shank stump, 32 days after amputation. Two tibiae, three tarsals, and the first toe regenerated. Note the increasing convergence of skeletal elements in the midline with increasing distance from the amputation plane. (F) Symmetric double posterior regenerate formed on a double posterior shank stump 35 days after amputation. The intermedium and tarsal 4 are shared by the two halves in the midline, with tarsal 1-2 and 3 deleted. The first, second, and third toes are deleted, and the metatarsals of the fourth toes are fused along their median borders.

the pattern of innervation to the limb. Thus, they have found that upper arm regenerates are derived mainly from the posterior and ventral sectors of the stump, in which the major nerve trunks are concentrated. A nonuniform distribution of nerves in the blastema could therefore account for the nonequivalence of regenerates arising from double anterior and double posterior half limbs. This possibility cannot be ruled out, for blastemas derived from those limbs are heavily innervated throughout [see also (*2*)]. Why then, do both double anterior and double posterior hindlimb stumps not form normal regenerates? The most likely answer is that the halves of symmetrical hindlimbs in some way interact with one another in an inhibitory fashion so that each is prevented from regenerating other than its original prospective significance. This hypothesis is supported by the fact that double posterior half limbs allowed to heal for 32 days before amputation produce fewer tarsals and toes than do those which healed for only 10 to 14 days.

Although the idea of differential contributions to the blastema by different stump sectors is consistent with the results reported here, it is not consistent with inability of both double anterior and double posterior upper arms of adult newts to undergo distal transformation (*2*). However, we cannot discount the possibility that positional information may be arranged or generated in different ways in forelimbs and hindlimbs, in limbs of different genera, or in embryonic and postembryonic limbs. For example, Carlson (*7*) has shown that amputation after 180° displacement of tissues relative to one another in the upper arm of *A. mexicanum* results in about 80 percent of the regenerates having multiple digits, whereas the same experimental manipulations in the hindlimb result in multiple digits in only 10 percent of the cases (*8*). It would be instructive in this regard to do a comparative study which might lead to a more unified concept of the process of pattern formation and regulation in amphibian appendages.

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## Cholecystokinin Inhibits Tail Pinch–Induced Eating in Rats

Abstract. *Peripheral administration of the COOH-terminal octapeptide of cholecystokinin in doses from 1 to 100 micrograms per kilogram of body weight (0.25 to 25.0 micrograms per rat) significantly antagonized tail pinch–induced eating in rats, an animal model for stress-induced human hyperphagia. Centrally administered cholecystokinin was effective only in high doses (3 micrograms into the cerebral ventricle). The finding that the minimal effective dose of cholecystokinin in suppressing stress-induced appetitive behavior is smaller after peripheral than central administration suggests that the peptide is acting on peripheral, as opposed to central nervous system, substrates.*

Antelman and associates (*1*, *2*) and others (*3*) have reported that mild tail pinch reliably induces eating in sated rats. This is particularly interesting in view of observations that eating behavior in both humans and animals increases during stress (*4*). We now report that administration of the active core (COOH-terminal octapeptide) of cholecystokinin (CCK) (*5*), an intestinal peptide hormone reported to induce satiety (*6*, *7*), antagonizes tail pinch–induced ingestive behavior in rats.

The tail pinch method (*1*, *2*) was used in our experiments. Naive adult male Sprague-Dawley rats weighing about 250 g were screened by placing them in a stainless steel surgical bowl (33.8 cm in diameter) in the presence of 5 g of rat chow (45-mg pellets, Noyes) and applying a 2-minute tail pinch about 5 cm from the tail tip with a 25-cm surgical hemostat insulated at the tips with foam rubber. This procedure produced a positive response in 66 percent of animals tested; approximately the same response rate was obtained by applying a pressure of 70 to 100 pounds per square inch (psi) with a calibrated pressure cuff. Positive responders were defined as those that exhibited continuous chewing and eating during the 2-minute test period. Nonresponders were excluded from further experimentation and responders were used on subsequent days as follows. In experiments examining the effects of peripheral peptide administration on tail pinch–induced ingestive behavior, rats were injected intraperitoneally with various doses of the COOH-terminal octapeptide of CCK (*8*) or vehicle (0.9 percent NaCl, *p*H 7.5). Five minutes later each rat was placed in a surgical bowl as described above and a continuous 10-minute mild tail pinch was applied. At the end of the test period, the amount of food consumed was calculated. In experiments on the effects of central administration of CCK on tail pinch–induced eating, rats with implanted lateral ventricular cannulae (1.4 mm lateral and 0.5 mm posterior to the bregma and 3.5 mm from the top of the skull) (*9*) were treated with CCK or vehicle (10 $\mu$l) and tested 5 minutes later as described above. Other experiments were performed to determine the effects of CCK administration on tail pinch–induced gnawing behavior. In these studies rats received either CCK or vehicle intraperitoneally and were placed in a surgical bowl containing wood chips. Gnawing behavior was quantified by counting jaw movements

Table 1. The effect of intracerebroventricular administration of cholecystokinin on tail pinch-induced eating in rats. Rats were injected through lateral ventricular cannulae with 10 $\mu$l of vehicle (0.9 percent NaCl, *p*H 7.5) or CCK dissolved in vehicle; 5 minutes later they received a 10-minute continuous tail pinch. Mean food consumed by control rats was 1.82 ± 0.19 g. Student's *t*-test (two-tailed) was used to compute statistical differences. Although the total number of control animals is shown, computation of statistical differences was made between experimental and control groups ($N \geq 6$) for each experiment. Food consumption is given as mean percentage of control ± standard error of mean; N.S., not significant.

| Treatment | *N* | Food consumed (% of control) | *P* |
|---|---|---|---|
| Vehicle | 30 | 100.0 ± 10.0 | |
| CCK, 0.3 $\mu$g | 6 | 92.4 ± 19.1 | N.S. |
| CCK, 0.5 $\mu$g | 13 | 72.2 ± 12.9 | N.S. |
| CCK, 1.0 $\mu$g | 6 | 59.6 ± 19.0 | N.S. |
| CCK, 3.0 $\mu$g | 8 | 22.16 ± 6.9 | < .01 |


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