Test sessions, beginning on day 61, were similar to the training session except that an avoidance contingency was added and the interval between trials increased to 60 seconds. A trial began with a 10-second warning period signaled by the onset of the houselights. If the mouse pressed the lever during the warning period the houselights were turned off and shock was not presented. If a response did not occur, the lights remained on and shock was delivered. Both the shock and lights were terminated as soon as the animal pressed the lever or after 1 minute. Twenty trials were given during each of 18 sessions (*10*) which were held between 0900 and 1400 hours. The number and latency of avoidance responses were recorded (*11*).

The results are presented in Fig. 1. An analysis of variance yielded a significant group effect [$F(3, 28) = 6.04$, $P < .003$] which, as shown in Fig. 1 and verified by post hoc analyses (*12*), is accounted for by the enhanced avoidance responding of fFf mice. The level of responding of mFm subjects was similar to that of males (mMm and fMf), for whom uterine position was without effect. As expected, all groups of animals increased their scores across sessions [$F(17, 476) = 2.68$, $P < .01$] (*13*). The group by session interaction was not significant, indicating that the rate of acquisition was similar for all groups and that uterine position influenced performance. It is possible, however, that had additional sessions been given the scores of groups mFm, mMm, and fMf would have reached that of fFf. The groups did not differ in their response latencies after onset of the warning signal or in their anticipatory responses, that is, lever pressing in the interval between trials.

It has been shown that female rats outperform males on various avoidance tasks (*14*) and that prenatal androgen is responsible for this difference (*15*). An overall gender difference in the direction of female superiority was found in our experiment when the data from mice of each sex were pooled across the uterine position variable [$F(1, 30) = 4.54$, $P < .05$]. We therefore conclude that the influence of male contiguity on the active avoidance responding of female mice is one of masculinization, apparently caused by stimulation of female fetuses by testicular androgen. Our findings demonstrate the efficacy of contiguity to two males, but we did not test females that had been located in utero between a male and a female (mFf). Previous research dealing with species-typical behavior, if applicable here, suggests that the avoidance behavior of mFf mice would be intermediate between that of males (fMf and mMm) and fFf females.

Our findings, and those of others (*1–3*), lead to an important question concerning polytocous mammalian species, those for which each pregnancy typically results in the birth of more than two offspring: What constitutes a "true" female? Is it any mammal possessing the XX genotype or only an animal with the XX genotype that has not been "contaminated" during fetal development by contiguous male siblings? This question requires consideration in assessments of the role of gender on those behavioral and physiological indices for which gonadal steroid hormones have been implicated.

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6. Rockland Swiss albino mice, bred in our facility, were kept as an outbred strain in a closed colony.
7. A total of 27 animals donated the 32 subjects. Five donors each provided two pups.
8. The apparatus (19 by 19 by 18 cm high) was constructed of clear Plexiglas. The lever, which operated with a force of 9 g, was centrally positioned on one wall, 10 mm above the floor, and protruding 15 mm into the chamber. The apparatus was housed in a sound-attenuating compartment.
9. Discontinuous shock sequences (0.5 second on, 0.5 second off) were used to facilitate the acquisition of avoidance behavior [M. R. D'Amato, D. M. Keller, L. DiCara, *J. Comp. Physiol. Psychol.* **58**, 344 (1964)].
10. The test session schedule was six consecutive days of testing followed by 1 day off and three periods of four consecutive tests each followed by 1 day off.
11. The operation of the apparatus as well as data collection were performed automatically by a microprocessing computer, thus virtually eliminating the possibility of experimenter bias.
12. Duncan's test with α set at 0.01 [G. Keppel, *Design and Analysis: A Researcher's Handbook* (Prentice Hall, Englewood Cliffs, N.J., 1973)].
13. Mice that did not avoid the shock pressed the lever as soon as the shock began; therefore, they never received a full minute of electric shock.
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Plasticity of Motor Behavior in Monkeys with Crossed Forelimb Nerves

Abstract. *Monkeys in which nerves innervating the flexor muscles of the forearm and hand (the ulnar or the median nerve) had been surgically cross-united with the nerve innervating the extensor muscles (the radial nerve), and vice versa, showed excellent (ulnar-radial crosses) to moderate (median-radial crosses) control of movement performance after regeneration. Antagonistic movement responses were seen occasionally, but these were corrected almost immediately. Stimulation of the crossed nerves showed that they had innervated the antagonistic muscle groups. The results reveal the capacity of the primate central nervous system to adapt to gross disturbances imposed on the execution of movements by changes in peripheral innervation.*

Nonprimate species such as rats or cats either do not adapt or adapt poorly to cross-union of flexor and extensor nerves and to muscle or tendon transposition (*1, 2*). Nonhuman primates seem to adapt better to nerve cross, but use "tricks" (*3*). Humans, however, can learn to use once-denervated muscles now supplied by a foreign nerve (*4*) and to adapt to muscle transposition (*1, 5*). We have found that, like humans, monkeys can adapt to major rearrangements in peripheral innervation of antagonistic muscle groups, after cross-union of flexor and extensor nerves of the distal forelimb.

Flexor muscles of the monkey and human forearm and hand are innervated by the median and ulnar nerves, and extensor muscles by the radial nerve (*6*). Eleven young Java monkeys (crab-eating macaque, *Macaca fascicularis* ssp.), all born and bred in the laboratory, were studied. Five received cross-anastomosis of the ulnar and radial nerves (U-R group), and the other six, of the median and radial nerves (M-R group). In some monkeys recordings were made before and after surgery of the electrical activity (EMG) of three muscles in the forearm; each muscle was innervated by a different nerve. Infants were weaned at 6 to 10 months of age and housed in individual cages. All were trained to retrieve small food rewards from a modified Klüver board (*7*) containing food wells of diminishing size, the smallest of these necessitating use of one finger only (the index) for successful retrieval of food (Fig. 1). Another board, developed especially to test such relatively independent finger movements in primates (*8*), contained narrow slots (Fig. 2A, extreme left, −6). When a small bait had been placed in one of these, it could be dislodged only by inserting the index on one side of the food and opposing the thumb on the other side in a precision grip (*9*).

Surgery was undertaken only when animals were fully proficient on these tests and after the normal movements had been recorded on video tapes or movie films. All surgery was bilateral to prevent the animals from using the normal limb only, which would have interfered with maximal recovery. Anesthesia was initiated with an intramuscular dose of ketamine (10 mg per kilogram of body weight) and maintained with small intravenous doses of barbiturates. The nerves were exposed just below the axilla, before the radial nerve turns around the humerus. Radial nerve branches supplying the triceps were not included in the cross. The nerves were cut, and the epineurium was sutured with interrupted stitches of 7.0 silk. All nerves were dissected free over such an extent that even fully stretching the arms would not put undue stress on the sutures, as postoperatively immobilizing the extremity in a splint for a few weeks was undesirable.

This denervation resulting from U-R or M-R cross was more extensive than that used by others (*6*) and included sensory fibers from cutaneous and other receptors as well. Therefore, we took care to prevent self-mutilation in the first postoperative weeks (*10*).

From the first day after the operation, the animals were encouraged to use their arms and hands. Initially, food was put on a flat surface in front of a hole in the cage front. After 2 months, the animals had usually recovered enough to use their hands to empty trays attached to the cage front (although occasionally feet or even tails were found to be quite handy for this purpose), and then the test boards were used.

Immediately postoperatively, the hands of U-R animals hung limp at the wrists, with the fingers and thumb flexed into the palm. Locomotion was bipedal or quadripedal, with the hands' dorsal surfaces facing downward. Over the next few weeks, wasting became evident in the denervated muscles. No *griffe* deformity of the hands, so common in humans, developed in any U-R animal. The animals retrieved food from a flat surface, raking it towards their mouths with flexed fingers. When presented with food in a well, they flung the arm forward, thus passively extending the wrist, and extended the fingers and thumb passively by dragging the hand across the board. Adduction of the thumb was aid-

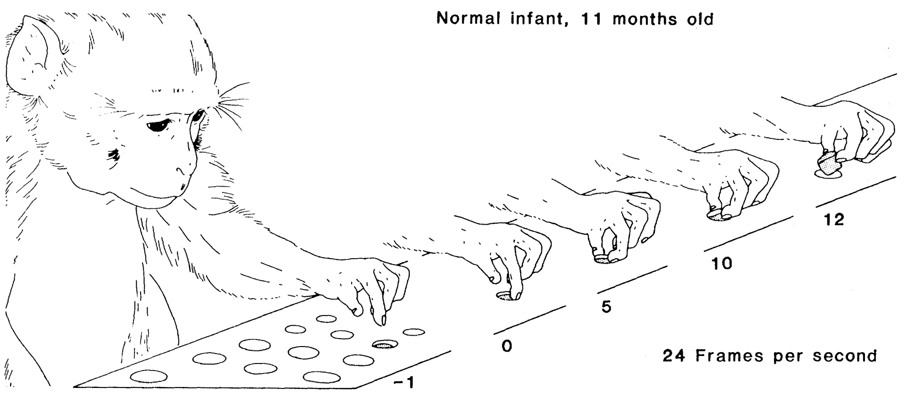

Fig. 1. Drawings taken from a movie film of a young monkey retrieving a food reward from a small well in a modified Klüver board (*3*). Numbers refer to the number of the frame before (−) and after (0) the fingers first touched the board. In approaching the food, the hand and fingers assumed a precision grip posture with extension of the index and extension and partial opposition of the thumb; the other fingers were kept flexed and out of the way throughout the movement sequence. Retrieval of the food was achieved by opposition of the thumb against the tip of the index finger.

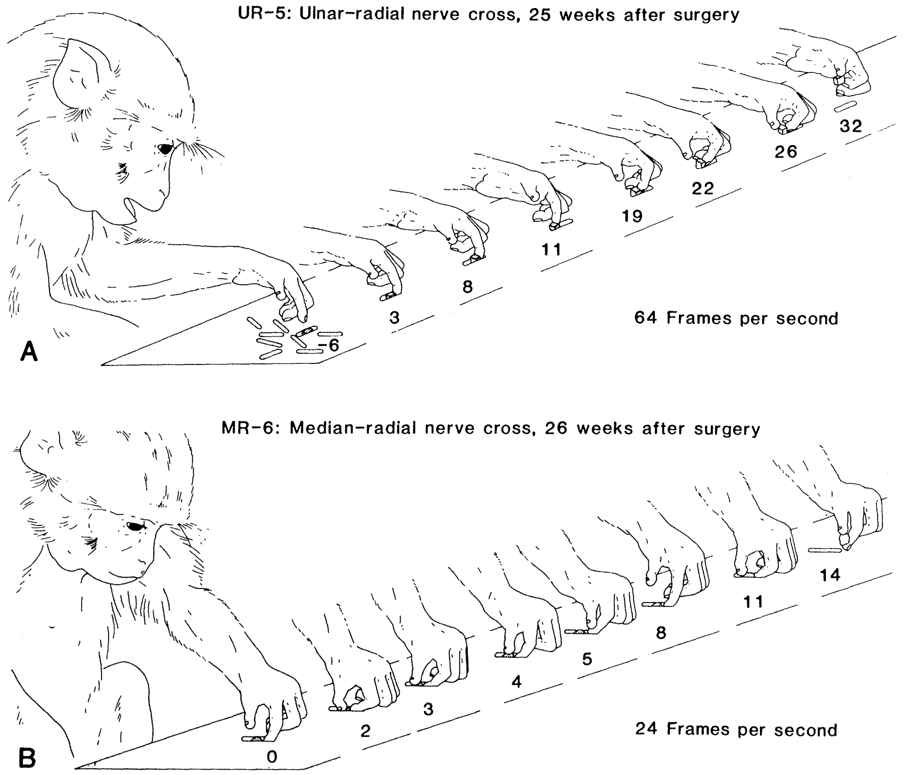

Fig. 2. Drawings taken from high-speed movie film of a monkey retrieving a food reward from a narrow slot after nerves to flexor and extensor muscle groups of the forearm and hand were crossed. (A) Ulnar and radial nerves crossed. Food retrieval was achieved by partially dislodging the food from the slot with the extended index, followed by opposition of the thumb. The other fingers were kept flexed and out of the way until the food had been recovered. The wrist was kept stable in an extended position. (B) Median and radial nerves crossed. The wrist was dorsiflexed, the index inserted on one side of the food, and the thumb opposed on the other side. The animal failed to dislodge the bait at the first attempt (frame 5) and repeated the movement sequence correctly without antagonistic movements.

ed by then pushing the hand slightly forward, and the food would be dislodged. After a period of 5 to 7 weeks, depending on the size of the animal, some evidence of reinnervation could be seen: a more stable and extended wrist position or small extension movements at the metacarpophalangeal joints of the fingers. Reappearance of EMG activity in flexor carpi ulnaris occurred simultaneously with that of ulnar deviation movements at the wrist. Thereafter, progress was often rapid and the animals' movements became more and more coordinated. With one exception, no U-R animal showed signs of antagonistic movement responses. Occasional "slips," if slips they were, were remedied immediately. Progress continued at an observable rate for 5 to 6 months after surgery, when most animals had achieved movement control comparable to that found preoperatively (Fig. 2A). The animals were not handicapped outside the test situation. Locomotion was normal and plantigrade, grooming skillful, and in play, dorsiflexion of the wrist and full finger extension were commonly seen.

As a group, the M-R animals never achieved the recovery of the U-R group. In part, the not-infrequent discrepancies in size between the median and radial nerves and the resulting difficulties in obtaining a good junction of the cut ends may have been responsible; but even with better matching, return of function to the large number of muscles normally innervated by the median nerve was incomplete. Immediately after surgery, wrist drop was not prominent. The hand resembled a loose fist. Locomotion was bipedal or quadripedal with flexed fingers and with the ulnar side of the hands on the floor. Muscle wasting became obvious in a few weeks, and, especially in the first three fingers, the skin became smooth and shiny and the fingers like matchsticks. The M-R animals often developed some muscle contracture that affected especially the metacarpophalangeal joints of the fingers. Most striking was their inability to pronate, but all animals soon learned to use the intact ulnar-innervated muscles, flexing the little and ring fingers around food and adducting the thumb (and thenar pad) against the hypothenar eminence. The first signs of reinnervation (including EMG's) occurred at 4 to 7 weeks, most commonly in the thumb, which would no longer be kept adducted or tucked flat into the palm. Finger flexion movements, wrist extension, and pronation reappeared. Appreciable improvement continued over a period of 10 months, although minor improvement could be seen after longer periods. All animals, because of contractures, continued to walk with their fingers flexed. Effective use of the hand depended mostly on the recovery of thumb movements—especially flexion of its distal phalanx and extension of its metacarpophalangeal joint—both necessary for effective precision grip. Such recovery occurred in one-third of the 12 M-R preparations (Fig. 2B). Regardless of their state of recovery, as a group the M-R animals did not show antagonistic movement responses.

The good-to-fair recovery seen in U-R and M-R animals, however, need not be due to reorganization at higher levels of the central nervous system: nerve fibers could have made functional reconnections with their original target muscles. Therefore, once maximum recovery had occurred, each animal was anesthetized, and the crossed nerves were exposed and stimulated proximal to the suture line. They had innervated the wrong set of muscles, with one exception—an M-R cross in which a mixed extension-flexion response was obtained from median nerve stimulation. This hand showed the most pronounced deficit and could not be used purposefully. These experiments indicate that the observed plasticity in motor behavior is genuine and central.

Another possibility is that the animals had learned to use intact rather than the crossed nerves, perhaps simply suppressing the involvement of the latter—that is, they would resort to tricks (*6*). In two U-R and one M-R monkey, the hitherto intact nerves were cut and sutured bilaterally. All animals were impaired in their movements, but no antagonistic responses were ever seen, and the recovery of the U-R animals paralleled that of a control monkey with only the median nerve cut and sutured. These data and the fact that recovery after nerve cross was generalized and extended to behavior outside the test situation favor real adaptation rather than trick movements.

In all animals, the recovery may have been favored by their young age. The effect of age was studied in one 10-year-old adult pigtail macaque (*M. nemestrina* ssp.) with an U-R cross. She was treated as the juveniles were. Regeneration required more time. Reinnervation was not seen until 11 weeks after surgery and became obvious only at 19 weeks. Recovery continued to a level close to normal at 15 months after surgery. The adult animal differed from all but one of the juveniles, however, in that 28 weeks after surgery, antagonistic movement responses were seen: extension of the third to fifth fingers when these should have been kept flexed and out of the way of the thumb and index to facilitate precision-grip food retrieval. This response was not present consistently, and after another 3 weeks was no longer seen. The juvenile U-R animal that displayed a similar antagonistic response learned to suppress it even faster—within a few days—and on a particular day, after a few trials.

These experiments contrast with earlier reports (*3*) in showing that the primate central nervous system can adapt to severe changes in the arrangement of its outputs (and inputs) through the cross anastomosis of peripheral nerves. At present, how and where these adaptations take place is unknown.

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