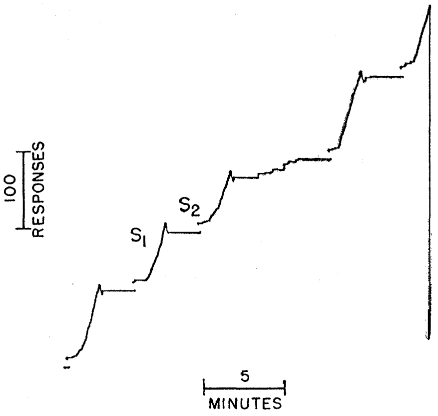

Fig. 3. Cumulative response curve for the chirp response of one chicken under a discrimination procedure.

the fixed-ratio schedule: 4 seconds of access to the food tray every 16 seconds. However, this periodic feeding was provided independent of responding. Figure 1 shows that the rate under periodic feeding (bar *D*) was less than 10 percent of the rate observed under fixed-ratio (20) (bar *C*). Apparently, it is the response requirement rather than the food presentation alone that is responsible for the high rate of responding under fixed-ratio schedule.

A fifth experiment demonstrated that the high rate of vocalizing obtained under fixed-ratio reinforcement was not simply the result of the stimulus change provided by response-dependent tray presentation. The procedure for this control condition was the same as that for the fixed-ratio condition, a 4-second tray presentation after every 20 responses, except that the food tray was now empty. The average rate of responding in the fifth hour under this condition is shown in Fig. 1, bar *E*. When a formerly neutral stimulus is paired repeatedly with a primary reinforcer it acquires a temporary control over responding which dissipates if the stimulus continues to be presented without further pairing (*8*). In the vocalizing experiments reported here, the food tray and the food were presented concurrently on thousands of occasions. The effect on the rate of chirping of discontinuing this pairing was slight initially. By the second experimental hour, however, presentation of the empty tray had, for the most part, lost its control over the rate of chirping (see Fig. 1). The terminal effect of the presentation of the empty tray may be compared to the effect of simple extinction—the sixth experimental condition—in which neither food nor tray is ever presented. Under the extinction procedure, the response rate fell to zero within a half hour.

In the final study, food was made contingent on responding during one stimulus and on not responding during a second stimulus. When a red light was on in the subject's compartment, food presentation was contingent on the first chirp after 2 minutes had elapsed. Following one reinforcement on this fixed-interval schedule (*7*), a green light was turned on and food presentation was then contingent on a pause in responding of at least 2 minutes. These conditions alternated. Each of the birds learned the stimulus discrimination within an hour. High rates of responding were observed during the stimulus that was paired with fixed-interval reinforcement ($S_1$) and low rates of responding were observed during the stimulus that was paired with reinforcement for not responding ($S_2$). When cumulative chirps in $S_1$ are plotted as a function of time, a pattern of responding is obtained that is typical of operant performance under fixed-interval schedules of reinforcement: the interval begins with a pause and the rate increases as the time of reinforcement approaches. Figure 3 shows a sample of the cumulative response record obtained during a stable discrimination performance (average rates for this session appear in Fig. 1, bars *G* and *H*). The average rate of responding during the fourth hour of training on the discrimination procedure was 22 responses per minute in $S_1$, and three responses per minute in $S_2$; the modal rate of responding in $S_2$ was zero.

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### References and Notes

1. Some anecdotal information has been available, however. See, for example, O. H. Mowrer, *Learning Theory and Personality Dynamics* (Ronald Press, New York, 1950), pp. 688–726.
2. Although the respondent-operant distinction is a behavioral one, it overlaps considerably with the distinction, in physiological terms, between autonomic and skeletal responses.
3. Skinner has suggested that "vocal behavior below the human level is especially refractory" to operant conditioning: B. F. Skinner, *Verbal Behavior* (Appleton-Century-Crofts, New York, 1957).
4. This research was supported in part by a grant from the National Science Foundation, and was carried out during the tenure of a predoctoral fellowship from the National Institute of Mental Health, U.S. Public Health Service.
5. The chicks were 5 weeks old at the start of this research. After 5 months there was a marked change in topography and decline in rate of chirping in the home cage and the experiments were discontinued. Because the chicks were growing during this 5-month interval, continued maintenance of 80 percent of their ad libitum body weight, as initially determined, would have resulted in starvation. Therefore, every month the birds were given free access to food in their home cage for 2 days and a revised "running weight" was computed.
6. Wirthmore Feeds, Inc., kindly contributed the chick starter for these experiments.
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## Descending Projections to Spinal Motor and Sensory Cell Groups in the Monkey: Cortex versus Subcortex

*Abstract.* In rhesus monkeys, corticospinal fibers have been found to terminate in motor, sensory, and internuncial cell groups. The present study reveals that the subcorticospinal fibers terminate primarily on internuncial neurons. Possible mechanisms involved in transmission of cortical and subcortical influences on motor and sensory cell groups are discussed.

Previous neuroanatomical studies in the rhesus monkey (*1*) revealed that pre- and postcentral corticobulbar and corticospinal projections terminate in motor, internuncial, and sensory cell groups (Fig. 1*A*). The motor and internuncial cell groups receive precentral fibers primarily. The sensory cell groups of the spinal trigeminal complex and the spinal posterior horn receive postcentral fibers primarily, while the nuclei cuneatus and gracilis receive both pre- and postcentral fibers. The precentral fibers to motor and internuncial neurons subserve motor functions and in all likelihood represent "direct" and "indirect" corticomotoneuronal pathways (see *2*). The pre- and postcentral projections to the sensory nuclei, on the other hand, probably represent cortical sensory feedbacks. This hypothesis is supported by physiological demonstrations of a cortical influence on these sensory nuclei (*3*). Since the brain stem likewise influences the sensory nuclei (*3*, *4*), the cortical influence on these nuclei was first thought to be mediated through the reticular formation (*3*). However, in cats, a direct cortical pyramidal influence upon the nuclei cuneatus and gracilis (*5*) has been demonstrated physiologically, in striking agreement with the anatomical observations (*6*).

In view of the physiological findings of subcortical influences on sensory nuclei, subcorticospinal pathways were studied anatomically.

In nine rhesus monkeys, lesions were made in the medulla oblongata (level of hypoglossal nucleus). The sum of these lesions interrupted all the longitudinal bundles throughout the medullary *tegmentum*, leaving the pyramidal tract and its immediate vicinity untouched. The descending fiber degeneration was studied, by use of the Nauta-Gygax technique (*7*). As planned, this study revealed the terminal distribution of the descending fibers. Therefore, contrary to the classical approach, the descending fibers will be grouped strictly according to their termination. The origin of these fibers will be studied later.

Descending fibers were encountered throughout the tegmentum below the lesions. Among these fibers two types could be distinguished: (i) long fibers descending throughout the entire spinal cord; (ii) short fibers reaching the cervical levels.

The long bundles were encountered in the medial, ventral, and ventrolateral parts of the medullary cross sections. In the lateral parts of the tegmentum, medial to the spinal trigeminal complex, only short fibers were found.

From their terminal distribution (characteristically seen at a great distance from the lesion, for example, the lumbar region), two main groups of long descending systems could be distinguished. One was a lateral, long, subcorticospinal system, passing through the ventrolateral parts of the medullary cross section and descending through the lateral spinal funiculus (Fig. 1*B*, dotted area). This system, which contains undoubtedly many rubrospinal fibers, terminates primarily in the basal parts of the posterior horn and in the zona intermedia. The second main group was a ventromedial, long, subcorticospinal system, which passes through the ventral and medial parts of the medullary cross section and descends through the medial and ventrolateral spinal funiculi (Fig. 1*B*, area with crosses). This ventromedial system, which probably contains reticulospinal, vestibulospinal, and interstitiospinal fibers, terminates primarily in the medial and dorsomedial parts of the anterior horn and the adjacent parts of the zona intermedia. Extremely few of these long descending fibers terminate in the motoneuronal cell groups of the anterior horn or the nucleus proprius of the posterior horn. However, the most medial motor cell groups of the anterior horn might receive some long descending fibers.

The cells in the basal parts of the posterior horn and the zona intermedia, on which the lateral fibers terminate, are commonly regarded as propriospinal elements. The larger neurons in the medial and dorsomedial parts of the anterior horn, reached by the ventromedial fibers, are most likely of the same nature (*8*). In other words, both groups of long subcorticospinal fibers are distributed first and foremost to propriospinal neurons.

This distribution of the subcortical fibers to propriospinal neurons contrasts sharply with that of the cortical fibers which are distributed to sensory, motor, and propriospinal cell groups. As a consequence, while the cortical influence on the motor neurons and sensory cells in the posterior horn is direct, the influence of the subcortical centers on these cell groups (*9, 4*) must be exerted primarily through propriospinal internuncial neurons (Fig. 1*D*).

The internuncial nature of the nerve cells in the basal parts of the posterior horn and zona intermedia with respect to motor neurons is commonly accepted. A similar internuncial relation between those cells in the intermediary region and secondary sensory cells in the posterior horn previously has been assumed (*10*). The following anatomical findings likewise suggest such a relation. Lesions of the lateral tegmentum of the medulla oblongata revealed the existence of short fiber bundles, which descend into the lateral propriospinal bundles of the cervical segments. A great many of these fibers terminate in the lateral tegmentum and its spinal homolog, the zona intermedia. In addition, some of these fibers pass to local motor neurons (hypoglossal nucleus, upper cervical anterior horn) as well as to secondary sensory cells (spinal trigeminal complex), in agreement with previous observations in Golgi material

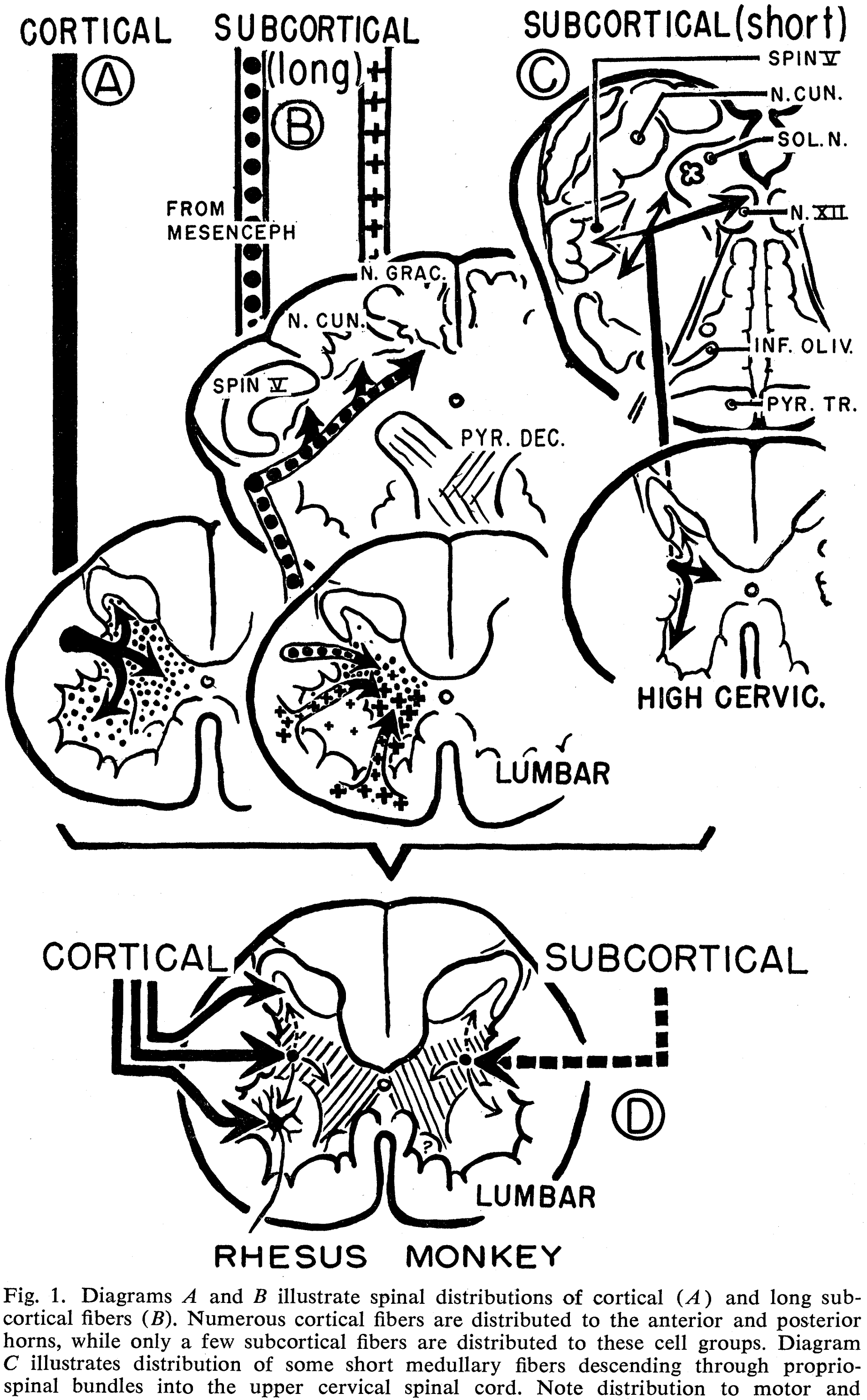

Fig. 1. Diagrams *A* and *B* illustrate spinal distributions of cortical (*A*) and long subcortical fibers (*B*). Numerous cortical fibers are distributed to the anterior and posterior horns, while only a few subcortical fibers are distributed to these cell groups. Diagram *C* illustrates distribution of some short medullary fibers descending through propriospinal bundles into the upper cervical spinal cord. Note distribution to motor and sensory cell groups. Diagram *D* emphasizes differences in termination of cortical and subcortical fibers in the spinal cord, with special reference to the influence on sensory and motor neurons. Crosshatch indicates area of interneurons.

(*11*) (Fig. 1*C*). These short fiber bundles apparently constitute the most rostral components of the lateral propriospinal system, adjoining the spinal gray matter on the lateral side. As such, the distribution of these fibers may exemplify the distribution pattern of the entire lateral propriospinal chain, originating in the lateral tegmentum and the zona intermedia and distributing among others to motor and sensory cell groups.

Were this supposition correct, we might predict that the long lateral subcorticospinal system terminating in this very zona intermedia would influence the activity of the secondary sensory cell groups in the posterior horn, in addition to its commonly accepted influence on the motor neurons. This prediction is in striking agreement with the actual findings of a systematic physiological investigation of the medullary cross section (*12*). In that study (*12*) it was found that the points from which the sensory cells in the posterior horn could be influenced dromically were located in the ventrolateral parts of the cross section, an area occupied by the lateral subcorticospinal system. Furthermore, this long, lateral, subcorticospinal system apparently also transmits a subcortical influence on the sensory nuclei cuneatus and gracilis. This is suggested by findings in additional experiments, in the rhesus monkey and the cat, with lesions in the mesencephalon. In these cases, the lateral subcorticospinal system was degenerated and some of its fibers were found to distribute to the basal parts of the nuclei cuneatus and gracilis. On the other hand, some physiological studies (*3*) suggest that the medial bulbar reticular formation influences "all" the sensory nuclei: the spinal posterior horn as well as the nuclei cuneatus and gracilis. In regard to this conclusion some reservations seem necessary (see *5*, *12*). Moreover, in the present material a distinct fiber system from this part of the reticular formation to the region of "all" these sensory nuclei could not be demonstrated. However, this does not allow us to rule out the possibilities of a transmission of reticular activity to the posterior horn through the mediation of the cells in the dorsomedial parts of the anterior horn, which receive long reticulospinal fibers (*13*).

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## Possible Two-Stage Mechanism in Experimental Leukemogenesis

*Abstract.* The augmenting influence of urethan on leukemogenesis by x-radiation in mice has been found to operate when the urethan treatment follows the radiation, but not when the sequence is reversed. The result is in keeping with the idea that urethan acts as a promoting factor in leukemogenesis, as defined by the two-stage mechanism hypothesis of carcinogenesis. It may also have a practical bearing on leukemia development in man.

Kawamoto, Ida, Kirschbaum, and Taylor (*1*) reported a striking augmentation of leukemogenesis in mice, whether induced by x-radiation, estrogen, or methylcholanthrene, when the animals were at the same time subjected to urethan (ethyl carbamate) administration. Since urethan alone was entirely free from leukemogenic action, its augmenting influence was described by them as "co-leukemogenic."

In line with earlier investigations on co-carcinogenesis in mouse skin (see *2*), we attempted to analyze the abovementioned co-leukemogenic action of urethan in terms of the two-stage mechanism hypothesis of carcinogenesis. If the effect were due to a summation of two similar types of action (of which one was too weak to be demonstrated by itself), one would expect the result to be the same whether the urethan preceded or followed the radiation. If, however, the urethan acts as an initiator only, or as a promoter only, then the augmentation should operate in one application sequence or the other, but not in both.

Five groups of C57bl/6 mice, each comprising 75 young adults of mixed sexes, were treated as follows: one group received x-radiation alone; one received urethan alone; one received the two concurrently (to confirm the augmentation reported by Kawamoto *et al.*); one received x-radiation followed by urethan; and one received urethan followed by radiation.

The radiation was provided by a Mühler 250-kv machine (physical factors: 200 kv, 15 ma, 0.5 mm Cu and 1.0 mm Al added filter, 50 cm target mouse distance; output 49.5 r/min). The urethan was injected intraperitoneally as a 10-percent solution in distilled water. The radiation treatment (total body) was administered in 5 doses of 90 r each, at intervals of 5 days, a total of 450 r. The urethan was also administered in 5 doses at intervals of 5 days, the mice receiving 0.2 ml per dose, a total of 100 mg. In the case where the two forms of treatment were given concurrently, the urethan was given immediately before each radiation. Where the two forms of treatment were given during separate periods, the interval between the completion of the one and the commencement of the other was 2 weeks.

The results, after 30 weeks, measured from the time of the first radiation, were as follows: x-radiation alone, leukemia in 17 of 75 survivors (23 percent); x-radiation together with urethan, 26 of 50 (52 percent); x-radiation followed by urethan, 35 of 70 (50 percent); urethan followed by x-radiation, 17 of 74 (23 percent). Urethan alone, after 30 weeks, yielded no leukemia among the 61 survivors. The results, expressed in the form of leukemia incidence curves, are shown in Fig. 1.

The fact that augmentation of leukemogenesis by urethan is obtained when urethan is made to follow the radiation, but not when the sequence is reversed, is in keeping with the idea that urethan acts as a promoting agent in leukemogenesis, as defined by the two-stage mechanism hypothesis of carcinogenesis. This is all the more surprising, since, in the case of skin carcinogenesis, urethan acts as a pure initiator (*3*), while for the lungs it is a complete carcinogen (*4*).

The present experiment is being continued until all the animals die. Meanwhile, further experiments are in progress, involving lower doses of radiation, in the hope that the effect might be observed under more critical conditions—that is, with no leukemia arising in the x-ray control series, or in the group in which the radiation follows the urethan treatment. The effect