tion of tumor growth in the remainder of the animals. The trauma associated with injection of saline did not lead to tumor regression. The observation period for experiment 1 is 164 days, for experiment 2 it is 97 days, and for experiment 3 it is 72 days. The tumor is uniformly fatal to guinea pigs that do not show complete tumor regression.

The only complication of BCG treatment was the occasional occurrence of infection with a Gram-negative organism at sites of BCG injection.

This is the first report of animal immunotherapy based on the principle that tumor growth is inhibited at sites of delayed hypersensitivity reactions provoked by antigens unrelated to the tumor. Our work differs from other previous work (*5*) on BCG and tumor growth in several important respects. (i) Our experiments involve treatment of established palpable tumors. Most animal experiments involve BCG-mediated prevention of tumor growth. (ii) Tumors that were 100 mg in size completely regressed as a result of local BCG therapy. The maximum tumor load that could be effectively treated with systemic BCG treatment was 10^5 cells (*6*). (iii) For optimum therapeutic effect contact between BCG and tumor cells was necessary. This critical variable has not been appreciated before. (iv) Treatment with BCG prevented the formation of clinically detectable metastases. Our model may be conveniently used for experiments designed to resolve the question of the nature of the mechanism of immunologic tumor destruction and the question of whether established tumors in sites other than the skin can be controlled by the type of immunotherapy described.

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References and Notes

1. A. C. Williams, and E. Klein, *Cancer* **25**, 450 (1970); D. Morton, F. R. Eilber, R. A. Malmgren, W. Wood, *Surgery* **68**, 158 (1970); G. Mathé, J. L. Amiel, L. Schwarzenberg, M. Schneider, A. Cattan, J. R. Schlumberger, M. Hayat, F. de Vassal, *Lancet* **1969-I**, 697 (1969); I. Hunter-Craig, K. A. Newton, G. Westburg, B. B. Wacepy, *Brit. Med. J.* **2**, 512 (1970).
2. B. Zbar, H. T. Wepsic, H. J. Rapp, T. Borsos, B. S. Kronman, W. H. Churchill, Jr., *J. Nat. Cancer Inst.* **43**, 33 (1969); B. Zbar, H. T. Wepsic, H. J. Rapp, J. Whang-Peng, T. Borsos, *J. Nat. Cancer Inst.* **43**, 821 (1969).
3. B. Zbar, I. D. Bernstein, T. Tanaka, H. J. Rapp, *Science* **170**, 1217 (1970).
4. Materials used in this study were provided by the U.S.-Japan Cooperative Medical Science Program-NIH (NIAID).
5. L. Old, B. Benacerraf, D. A. Clarke, E. A. Carswell, E. Stockert, *Cancer Res.* **21**, 1281 (1961); D. Weiss, R. S. Bonhag, D. Leslie, *J. Exp. Med.* **124**, 1039 (1966); H. O. Sjogren and J. Ankerst, *Nature* **221**, 863 (1969).
6. G. Mathé, P. Pouillart, F. Lapeyraque, *Brit. J. Cancer* **23**, 814 (1969).
7. K. A. Brownlee, *Statistical Theory and Methodology in Science and Engineering* (Wiley, New York, 1961), p. 123.

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Somatosensory System: Organizational Hierarchy from Single Units in Monkey Area 5

Abstract. *The receptive fields of single cells in area 5 of monkey parietal cortex were studied by extracellular recording. Cells were driven primarily by gentle manipulation of multiple joints residing on one or more limbs. Both excitatory and inhibitory convergence were demonstrated. It is postulated that the multijoint receptive fields of area 5 are the result of convergence from single-joint cells of the primary receiving area. An analogy is drawn between the modification of information in the visual and somatosensory systems.*

Previous studies of response characteristics to physiological stimulation of single cells in the somatosensory system (*1–6*) have not suggested an organizational hierarchy analogous to that demonstrated by Hubel and Wiesel (*7*) in the visual system. Indeed, Powell and Mountcastle (*1*) emphasize the fidelity with which response properties of peripheral somesthetic receptors are reproduced by single units in the somatosensory thalamic relay nucleus (VPL) and primary cortical receiving area, S1 (Brodmann's cytoarchitectonic areas 3, 1, and 2). This is in marked contrast to the visual system where messages undergo considerable modification, especially in the cortex.

The receptive fields of VPL neurons are modality specific and entirely contralateral (*2*). Kinesthetic cells respond to movement of one joint in one direction only, and touch cells respond to small areas of stimulation. In S1, cells show similar properties (*3*). Intramodality convergence, that is, convergence of more than one joint, is not reported. Intermodality convergence is extremely rare. In general, within S1, the modalities of touch and kinesthesis are segregated into separate cellular columns. In a later study of S1, Werner and Whitsel (*4*) found no evidence for convergence of either type. In view of the recently demonstrated bilateral projection of S1 to Brodmann's area 5 of parietal cortex (*8*), we investigated receptive field properties in this region to determine whether higher order interaction may exist within the somatosensory system.

Short-term experiments were carried out in six *Macaca mulatta*, weighing 2 to 3.5 kg. Animals were prepared under a short-acting barbiturate (sodium methohexital) and later were studied in the awake, unanesthetized state (paralyzed with gallamine triethiodide and artificially respired). Wound margins and pressure points were infiltrated with a long-lasting local anesthetic preparation (procaine in peanut oil). Adequate fluid and electrolyte intake was given intravenously, and temperature and blood pressure were monitored. Single unit extracellular recording was undertaken with tungsten microelectrodes, insulated except for a 2- to 10-μm tip exposure. Unit activity was led through a field effect transistor source follower to a Tektronix 1A7A amplifier and recorded on magnetic tape with a concurrent voice channel. Joints were manually rotated. Skin was stimulated with blunt probes, brushes, and air blasts. For every cell excited by joint manipulation, care was taken to rule out effects of concurrent touch or tissue deformation. A unit was con-

Table 1. Receptive field properties of cells in area 5.

Properties			Cells (No.)
Modality			
Position sense only			47
S1 properties		5	
Involvement of more than one joint		42	
One limb	6	(+5 from T-P)	
Two limbs	24	(+4 from T-P)	
Three limbs	7		
Four limbs	5		
Touch only			9
S1 properties		2	
S2 properties		7	
Touch-position sense convergence (T-P)			9
Unable to characterize			10
Total			75
Laterality			
Contralateral only			23
Ipsilateral only			3
Bilateral			39
Unable to characterize			10
Total			75

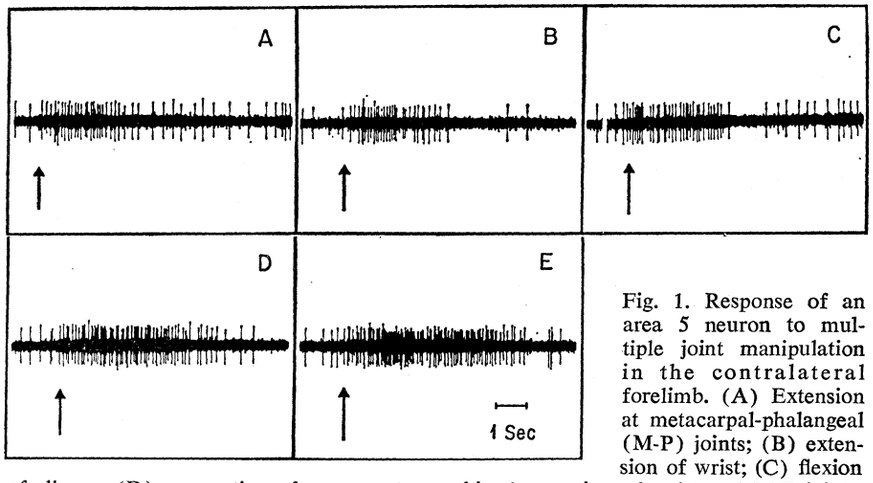

Fig. 1. Response of an area 5 neuron to multiple joint manipulation in the contralateral forelimb. (A) Extension at metacarpal-phalangeal (M-P) joints; (B) extension of wrist; (C) flexion of elbows; (D) summation of response to combined extension of wrist and M-P joints; and (E) maximum response from simultaneous M-P joint extension, wrist extension, and elbow flexion. Arrows indicate onset of stimulus.

sidered sensitive to joint rotation only if (i) the response pattern to movement was independent of the way in which the limb was held, and (ii) no response was obtained from stimulation of the areas of skin, hair, or deep tissues that were deformed by manipulation or movement. The latter was checked with the limb held stationary in both extremes of joint position.

Seventy-five cells were isolated in area 5. In general, area 5 cells were difficult to isolate and study. The cells had low, spontaneous firing rates, and their receptive fields appeared to change with time. This differs from reported observations (*1–6*) and our own data of cells in VPL, S1, and the second somatosensory cortical area (S2) where receptive field properties remain constant. The receptive field properties of 65 cells were characterized (Table 1). The majority (84 percent) responded to gentle joint rotation. In marked contrast to receptive fields of cells in VPL and S1, receptive fields of area 5 kinesthetic cells were not restricted to a single joint, nor were they strictly contralateral. Fifty-one cells (68 percent) displayed convergence from two or more joints. Forty cells (53 percent) involved more than one limb, and five cells involved all four limbs. Three cells displayed only ipsilateral representation, and 39 cells (52 percent) had bilateral input.

Both summation and antagonism were observed among kinesthetic inputs converging on area 5 cells. Figure 1 illustrates summation involving several joints. This cell responded to the following isolated movements in the contralateral upper extremity: (i) extension of the metacarpal-phalangeal joints as a unit (Fig. 1A), (ii) extension of the wrist (Fig. 1B), and (iii) flexion of the elbow (Fig. 1C). Summation could be demonstrated between any of these motions (Fig. 1D), and the response was maximum for simultaneous movement at all three of these locations (Fig. 1E).

Figure 2 demonstrates antagonism as well as summation. First, there was excitatory interaction between hip and knee in the contralateral hind limb. The cell responded to flexion at the hip only when the knee was maintained in the extended position during movement (Fig. 2B). There was no response to knee manipulation alone (not illustrated), and a minimum response

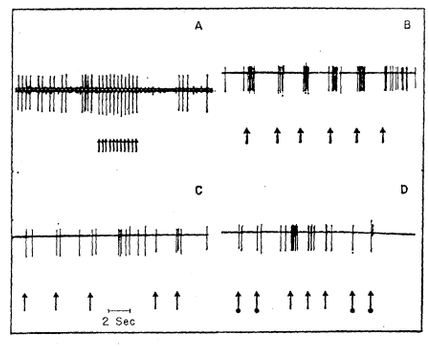

Fig. 2. Intermodality and intramodality convergence on a single area 5 neuron. Arrows indicate onset of stimulus. (A) Repetitive pressure stimulation to ulnar surface of contralateral hand; (B) flexion of hip with knee extended in contralateral hind limb; (C) flexion of hip with knee flexed in contralateral hind limb; (D) arrows with ball indicate simultaneous flexion of both hips with knees extended. Plain arrows indicate flexion of contralateral hip alone with knee extended. There was no observable response to flexion of ipsilateral hip alone (not illustrated).

to hip flexion with the knee flexed (Fig. 2C). Second, antagonism was shown between the two hind limbs. Movements of the ipsilateral hind limb had no effect on the cell (not illustrated). However, when both hips were simultaneously flexed with knees extended (Fig. 2D), the response of the cell was much less than that for flexion of the contralateral hip alone, with knee extended (Fig. 2B). Thus, concurrent flexion of the ipsilateral hip antagonized the excitatory response to flexion of the contralateral hip.

Convergence of various joints on a single area 5 neuron did not appear to be random. For cells with single-limb receptive fields (13 percent), maximum activation was usually obtained by limb movement into positions of physiological flexion or extension (*9*), sometimes associated with rotation or abduction-adduction at the proximal joints. Proximal joints were more frequently involved than distal.

Two-limb receptive fields were most common (37 percent, 28 cells). In all cases, optimum activation of the cell resulted from coordinated movements of the two limbs. For 18 cells, this involved opposite movements in the two limbs: flexion of one limb and extension of the other. Three of these 18 cells responded best to walking movements, that is, continuous alternation of flexion and extension. Four of the two-limb cells responded to similar motions in the two limbs. Six cells showed a combination of same and opposite movements. For example, one of these six cells responded to extension of either upper extremity, with summation upon simultaneous extension of both. In addition, one limb responded best to internal shoulder rotation, whereas the other responded best to external shoulder rotation. The optimum movement was an extension of both arms reaching to one side.

Cells with three-limb (9 percent) and four-limb (7 percent) receptive fields were activated by combinations of joint motions such that no two receptive fields were exactly alike. However, within each of these multilimb receptive fields, the optimum positions of single limbs or pairs of limbs conformed to the patterns described for one- and two-limb cells. For example, one three-limb cell was stimulated by flexion of the ipsilateral hind limb, extension of the contralateral hind limb, and flexion of the contralateral forelimb. The combination of limb positions or motions was not always addi-

tive. In one four-limb receptive field, antagonism was observed between inputs which were individually excitatory. This cell responded to extension of either forelimb with rotation to the right. Summation was noted between the two forelimbs. In addition, swinging either hind limb to the right, with knee flexed, was excitatory. Summation was noted between the hind limbs. However, when both the fore and hind limbs were simultaneously moved to the right, the cell failed to respond. Antagonism of this sort cannot be explained by simple convergence of S1 cells with single-joint receptive fields. This implies an intermediate stage of convergence within area 5.

Intermodality convergence between touch and kinesthesis was observed in nine cells in area 5. Both excitatory convergence and antagonism were noted. Excitatory convergence was demonstrated by the cell of Fig. 2. In addition to joint input, this cell responded to deep cutaneous stimulation of the dorsal, ulnar surface of the contralateral hand (Fig. 2A). Other cells showed inhibition of a kinesthetic response by touch.

Seven area 5 cells (9 percent) showed simpler properties reminiscent of those found in S1. These included contralateral, circumscribed, cutaneous receptive fields and rotation of single contralateral joints. We also encountered seven cells (9 percent) responding to tactile stimulation alone whose receptive fields resemble those commonly associated with S2 (*6*), that is, wide cutaneous receptive fields which were ipsilateral or bilateral, frequently involving a whole limb or involving symmetrical fields on the two sides of the body.

In conclusion, our survey of receptive fields of single units in area 5 suggests the presence of an organizational hierarchy within the somatosensory system. It is postulated that multijoint receptive fields of area 5 cells result from convergence of a population of S1-like cells with single-joint receptive fields. This conclusion is supported by the anatomical demonstration (*8*) of a strong, bilateral projection from S1 to area 5. The complex properties of certain area 5 cells having multilimb receptive fields suggests a further modification of somatosensory information within area 5. Therefore, it would appear that the basic organization of the somatosensory system bears some analogy to that of the visual system (*7*). In both systems, complex receptive fields are formed by summation and antagonism among inputs converging from cells with simpler receptive fields.

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References and Notes

1. T. P. S. Powell and V. B. Mountcastle, *Bull. Johns Hopkins Hosp.* **105**, 173 (1959).
2. G. F. Poggio and V. B. Mountcastle, *J. Neurophysiol.* **26**, 775 (1963).
3. T. P. S. Powell and V. B. Mountcastle, *Bull. Johns Hopkins Hosp.* **105**, 133 (1959); V. B. Mountcastle and T. P. S. Powell, *ibid.*, p. 201.
4. G. Werner and B. L. Whitsel, *J. Neurophysiol.* **31**, 856 (1968).
5. Intermodality convergence has been described by P. D. Wall [in *International Symposium on the Skin Senses*, D. R. Kenshalo, Ed. (Thomas, Springfield, Ill. 1968), pp. 519–529], in Lamina Six (Rexed) of the cat dorsal horn. However, this interaction is not reflected at higher levels within the main somatosensory afferent pathway in VPL, S1, or S2. The signifiance of these spinal cord interactions with respect to organizational hierarchy within the somatosensory system is not clear at this time.
6. S. A. Andersson, *Acta Physiol. Scand.* **56** (Suppl.), 194 (1962); M. Carreras and S. A. Andersson, *J. Neurophysiol.* **26**, 100 (1963); B. L. Whitsel, L. M. Petrucelli, G. Werner, *ibid.* **32**, 170 (1969).
7. D. H. Hubel and T. N. Wiesel, *J. Physiol. (London)* **148**, 574 (1959); *ibid.* **160**, 106 (1962); D. H. Hubel, *Sci. Amer.* **209**, 54 (1963); ——— and T. N. Wiesel, *J. Neurophysiol.* **28**, 229 (1965); *J. Physiol. (London)* **195**, 215 (1968).
8. D. N. Pandya and L. A. Wignolo, *Brain Res.* **7**, 300 (1968); *ibid.* **15**, 49 (1969); E. G. Jones and T. P. S. Powell, *Brain* **92**, 477 (1969); *ibid.*, p. 717.
9. Physiological flexion describes the position of a limb assumed during withdrawal or avoidance and includes individual joint positions that are, strictly speaking, anatomical extension. In the lower limb, this involves ankle dorsiflexion and in the upper limb, posterior rotation of the shoulder and dorsiflexion of the fingers and wrist. Similarly, physiological extension means limb positions assumed for postural support. This includes ankle dorsiflexion, anterior shoulder rotation, and dorsiflexion of fingers and wrist.
10. We thank Drs. T. N. Wiesel, D. H. Hubel, S. Locke, and C. T. Lombroso for their advice, guidance, and review of this work. F.H.D. is supported by NINDS special fellowship 1 F11 NSO2254-01, NSRB. Supported in part by the Children's Hospital Medical Center Mental Retardation and Human Development Research Program (H.D. 03-0773).

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DDT Tissue Retention: Sudden Rise Induced by the Addition of Aldrin to a Fixed DDT Intake

Abstract. *The oral administration of aldrin to male and female beagles, whose diet already included a fixed, regular oral dosage of DDT, resulted in a dramatic rise in the concentrations of DDT, DDE, and DDD in blood and fat.*

It has been suggested that "a physiologic equilibrium has been reached with the present level of exposure to DDT and that continued exposure at this level will result in no additional tissue accumulation in humans" (*1*).

The degree of hepatic microsomal enzyme activity plays a dominant role in the metabolism and therefore in the half-life of certain drugs. Since the organochlorine pesticides are potent stimulants of this activity, any significant and unrecognized increase in hepatic microsomal enzyme activity could lead to disastrous effects. Thus it is vitally important to recognize, as early as possible, conditions or factors capable of markedly increasing hepatic microsomal enzyme activity.

This preliminary report of experiments with pure-bred beagles demonstrates that the concentration of DDT (*2*) and its metabolites ("total DDT") in blood and abdominal fat can rise sharply when aldrin (*2*) is added to an oral dosage of DDT, which has been maintained at a constant level for a period of months.

Eight beagles (four males and four females, aged 2 to 3 years), were fed a dose of recrystallized DDT (12 mg/kg by capsule, on 5 days of a week). When, after 10 months, a relatively stable plateau had been reached in the concentration of DDT and its metabolites in blood and abdominal fat, the dogs were given, in addition to the dose of DDT, a dose of aldrin (0.3 mg/kg by capsule, on 5 days of a week for 8 weeks). Samples of blood from the saphenous vein and abdominal fat (by biopsy) were taken from all dogs every 2 weeks and analyzed by gas-liquid chromatography, according to the method of Radomski and Fiserova-Bergerova (*3*).

The mean concentrations of DDT and its metabolites in the blood of the male dogs over the 7-week period immediately prior to the administration of aldrin were as follows: *p,p'*-DDT, 81 parts per billion (ppb); *p,p'*-DDE, 2 ppb; and *p,p'*-DDD, 7 ppb (*2*). In the blood of female dogs the mean concentrations were as follows: *p,p'*-DDT, 79 ppb; *p,p'*-DDE, 2 ppb; and *p,p'*-DDD, 7 ppb. The addition of aldrin to the intake of DDT induced an immediate