

illustrated in Fig. 10 which shows records from a cell which responded to internal rotation of the shoulder with an increase in overall firing rate. The cat's forepaw was held about 30° lateral to the normal midsagittal plane; it was then slowly moved medially until, at the end of about 40 sec, it was about 30° medial to the midsagittal plane.

The most pronounced feature was an increase in the number of isolated spikes; the burst index fell from a control 93% to 40% at the time of the maximal firing rates. It was also apparent that the doublets which did occur were wider during this sequence. The characteristic doublet interval was 1.1 msec during the resting condition (externally rotated). At the maximal firing rate, the doublet interval was nearly 4 msec (averaged over a 2 sec epoch; there was considerable variation in this behavior). The lower part of Fig. 10 shows the gradual widening of the doublet during a more rapid change. Plots of the statistics are seen in Fig. 11.

Following high firing rates from either afferent drive or antidromic activation, the spontaneous activity of some neurons was notably depressed for 30–60 sec.

## DISCUSSION

Is the doublet/burst a result of the patterning in the presynaptic drive (33) or some intrinsic property of the postsynaptic cell (16)? The gradual changes in burst pattern shown in Figs. 7 and 8 as a function of microelectrode position argue for a special response of the postsynaptic cell. The ubiquity of the doublet/burst firing patterns and their occurrence in cells of both large and small extracellular spike heights also argues against these being recordings from afferent receptor axons. Galindo et al. (16) examined this issue in some detail and concluded that the doublets were caused by an "intrinsic tendency to repetitive firing and not by the properties of the synaptic input."

In main cuneate, the afferent drive comes largely from hair and touch rather than deep proprioception (16); thus, it can be difficult to grade

---

sampled in (A) was taken in the middle of this range. As the electrode is advanced, the number of bursts per second rises. Upon withdrawal of the electrode, the burst rate drops fivefold. C. The percentage of spikes found within bursts is also greatly increased by electrode pressure. D. The number of spikes per burst is typically 2, although it varies between doublets and triplets during severe electrode pressure. E. The doublet interspike interval (or first interspike interval of the triplet) shortens to 2 msec and lengthens as the electrode is withdrawn. In this cell, both the burst recurrence rate and the internal structure of the burst appear to be altered by electrode pressure; in the deteriorating neuron of Fig. 7, these features seemed disassociated until the final deterioration. Either deterioration pattern was grounds for rejection of a neuron from further study.

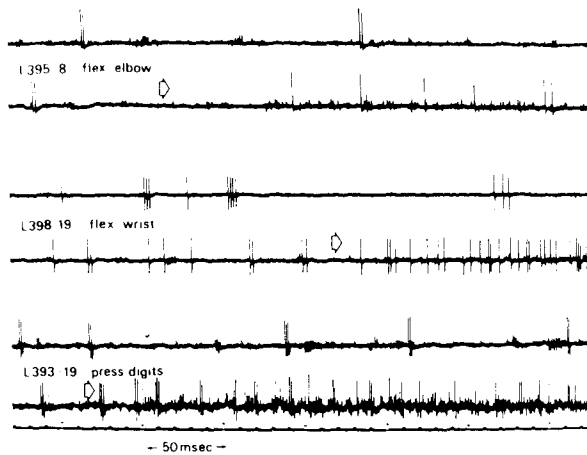


FIG. 9. Changes in firing patterns with receptive field stimulation for three ECN neurons. The upper strip of each pair is the spontaneous activity of the neuron; the evoked activity begins approximately at the open arrows in the lower strips. The cell at top (L395-8) fired in very stereotyped doublets; as the elbow was slowly flexed, the firing pattern changed to single spikes and an occasional broad doublet. In the case of cell L398-19, the spontaneous firing pattern was isolated spikes and occasional loose bursts (in contrast to the stereotyped doublets of the other cells illustrated in this paper). When the wrist was flexed, many more isolated spikes occurred, but occasional tight doublets and triplets. The stereotyped doublets and triplets in the spontaneous activity of cell L393-19 was changed by the addition of isolated spikes when pressure was applied to the digits. Increased multi-unit activity is also seen.

in a steady-state manner. One of the advantages of studying external cuneate is that proprioception is the major, if not only, modality represented (11, 30, 31) and input can be graded in a manner not easily attained with the more phasic hair and touch receptors. Gradation of afferent drive via intracellular injected current is most useful in differentiating the rhythmic firing mode from the extra spike mode in motoneurons (8) and in pyramidal tract neurons (9); when one cannot inject steady current into a cell due to an extracellular recording technique, it is important to be able to grade a sustained synaptic drive as in Fig. 10.

It is our hypothesis that the isolated spikes which appear during this sequence are, in fact, doublets where the extra spike has failed to occur. If this hypothesis is correct, one might expect to see other indications of this failure. The gradual widening of the doublet (Figs. 10 and 11) accords well with the model (Fig. 1) developed from intracellular recordings (7, 11, 12). In these intracellularly observed cases of doublets, a large depolarizing hump is seen following each spike. This "delayed depolarization" or "depolarizing afterpotential" appears to rise through the

falling threshold and elicit the extra spike (which may, of course, elicit another extra spike if it too has a large hump following it).

Our extracellularly obtained picture of doublet firing would be consistent with a large depolarizing hump which typically exceeds threshold by a large safety margin, the extra spike thus arising well before the peak of the hump would occur. This would suggest that the hump decreases in size as afferent drive increases or that the threshold rises relative to the hump, e.g., through Na inactivation which would accord well with the decreased spike heights. Thus, the extra spikes would arise later along the rising phase of the hump. As the doublet interval corresponding to the time-to-peak of the hump is approached, one would expect an increased incidence of failures, i.e., the extra spike would fail to occur and one would see single isolated spikes. Thus, the concomitant widening of the doublet and the decreased incidence of extra spikes accord well with this model.

The depolarizing afterpotentials which underlie the extra spike mode are seen in all neurons of Clarke's column (13, 23), which is the spinal homologue of external cuneate (1). They are also ubiquitous among "fast"

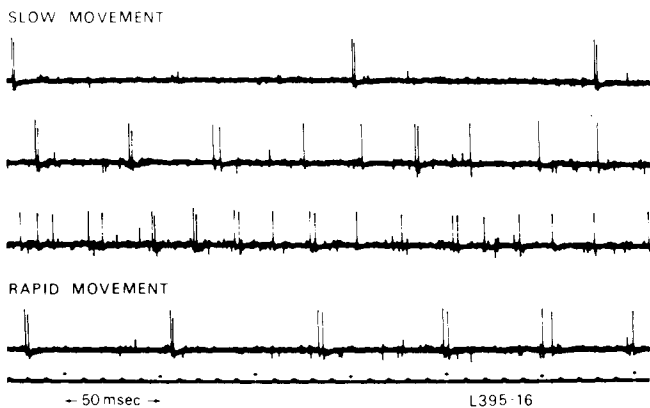


FIG. 10 Effect of receptive field stimulation upon firing pattern of cell L395-16. During resting spontaneous activity (top line), this cell characteristically fired in 1.1 msec doublets. Rapid movements of the forelimb caused many isolated spikes to appear. It was discovered that a slow internal rotation of the shoulder was capable of gradually changing firing patterns. The second and third lines show characteristic firing patterns near the beginning and near the end of this 40 sec long movement. The doublets which do occur are often wider; many isolated spikes appear. The changes in spike heights seen here are characteristic of most ECN cells as the average firing rate increases. The widening of the doublet, concomitant with the occurrence of isolated spikes, suggests that the second spike of the doublet is occasionally failing to be generated. Indeed, during other movements one can sometimes see a sequence of doublets widening and then single spikes appearing, as shown in the bottom line.

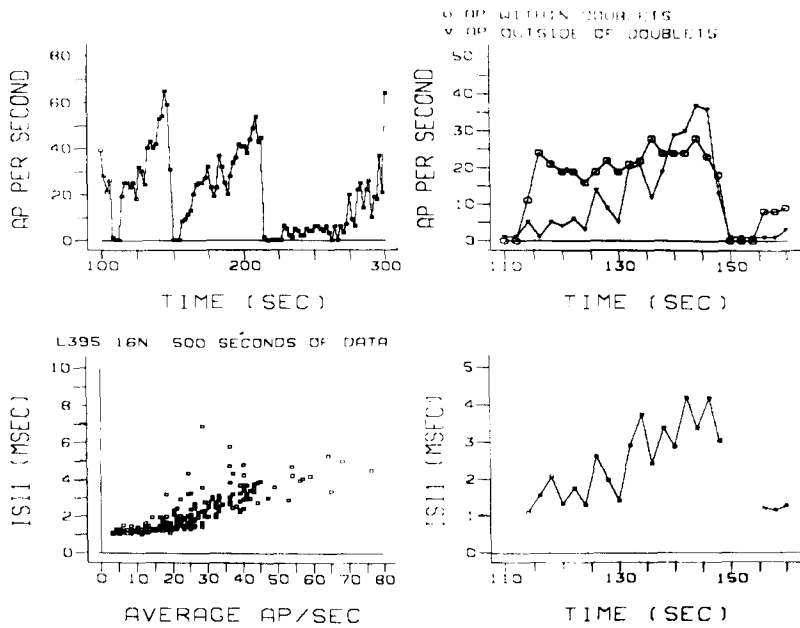


Fig. 11. Statistical parameters for the cell's responses illustrated in Fig. 10. At upper left, the average firing rate is shown increasing linearly during internal rotations of the shoulder through a  $60^\circ$  arc. The silent periods correspond to the return of the forelimb to the lateral position. The period following 230 sec corresponds to the forelimb being held in the lateral position; at 270 sec, another slow rotation is begun. The doublet rate increases initially but immediately reaches a plateau. This indicates that the further increase in total firing rate is due to spikes occurring outside of doublets; this is explicitly illustrated in the graph at the upper right for the first of the three rotation sequences shown. The number of spikes outside of doublets is initially very small, but grows linearly to eventually exceed the number of spikes found within doublets. The doublets that do occur, however, are broader (on the average), as seen in the plot at lower right. The plot at lower left is a scatter plot of the doublet interval versus the average firing rate for 500 sec of data sequence such as illustrated at upper left, again showing this gradual broadening of the doublet.

pyramidal tract neurons (9), more so than in "slow" ones or in motoneurons (8, 14).

The findings also suggest that extra spikes are more likely at low levels of neuronal activity and may diminish with increased activity, further suggesting an automatic gain control in the repetitive firing mechanism of the neuron (5). Our present data are in general agreement with this picture. The mechanisms underlying the depolarizing humps (6) are insufficiently understood, but seem to involve delayed action potentials in dendrites, e.g., the antidromic invasion of the dendrites by the action

```

C-LINF00 UW
01.01 E
01.02 L
01.15 S EL=2;S IL=20;S I1=10;S IT=10;S EX=EL*1E3
01.16 S P=1;S TI=EX;S J=-1
01.20 S EP=EP+1;S IS=0;S TI=TI-EX;S KT=0;S KS=.01;S BU=0;S SP=0
01.30 D 2
01.40 I (EX-TI)3.01;I (K-IL)1.3;D 2;I (I1-K)1.4;S K1=K;S SP=SP+1
01.80 S SP=SP+1;D 2;I (K-IT)1.8;S KT=KT+K1;S KS=KS+K1*2;S BU=BU+1
01.90 G 1.4

02.10 S J=J+1;I (J-255.5)2.5;I (FG(0)+2)2.11,2.18,2.11
02.11 Ø FP(0,-1);G 2.19
02.18 Ø FP(0,LI)
02.19 L
02.20 S P=1;S J=0
02.50 S K=FABS(FG(J))/5;S TI=TI+K;I (2047/5-K)2.1,2.1;S IS=IS+1

03.01 S RA=IS/EL;S BE=BU/EL;S EV=RA+BE-SP/EL;S BI=100*SP/IS
03.02 S SB=0;S S1=0;S CV=0
03.10 T %4,1,EP*EL,%3," ",RA," ",EV,%3.01," ",BE,%3," ",BI,"% ",
03.11 S LI=LI+1
03.12 I (BU-1)3.2,3.2;S SB=SP/BU;S S1=KT/BU
03.14 S CV=FST((KS-KT+2/BU)/(BU-1))/S1
03.20 T %4.02,SB," ",S1,CV
03.21 Ø FP(P-1,-2);Ø FP(P,EP*EL);Ø FP(P+1,RA);Ø FP(P+2,EV)
03.22 Ø FP(P+3,10*BE);Ø FP(P+4,BI);Ø FP(P+5,10*SB)
03.23 Ø FP(P+6,100*S1);Ø FP(P+7,100*CV);Ø FP(P+8,-1);S P=P+9;G 1.2

10.10 Ø FP(0,-3);L
*
```

Fig. 12. See Appendix A for explanation of this FOCAL program.

potential from the trigger zone proceeds slowly, so that this process is not finished at the time the soma repolarizes, allowing current to flow centrally from the depolarized dendrites and elicit a hump in the soma. A wider dendritic action potential (24, 34) would have the same effect. D. K. Hartline and W. H. Calvin (unpublished observations) have recently found that, in the lobster stretch receptor, slowed retrograde invasion of the soma can produce doublets because the initial segment recovers its excitability during the delayed somatic spike. While only a broadened AB spike was seen intrasomatically, a doublet was simultaneously recorded from the axon. It is difficult, at present, to use inferences from such proposed mechanisms to illuminate the central question: What factors augment the extra spike mode?

*Injury* may augment the extra spike mode; certainly, the distortion of the soma-dendritic geometry might lead to extra spikes by further delaying antidromic invasion. While the injury factor is sometimes difficult to rule out in individual cases, the ubiquity of the extra spike discharges in main and external cuneate, fast pyramidal tract cells, and in spinal motoneurons under a variety of conditions argues against the extra spike mode as a mere artifact, as does its modification by afferent drive.

*Anoxia* has been shown to augment the delayed depolarization in spinal motoneurons and to give rise to a double antidromic discharge (26).

*Pharmacological means* of augmentation are best illustrated in the work of Galindo et al. (16), where iontophoretic glutamate, ATP, and gallamine were used. Gallamine at typical experimental doses increased what we would call the "burst index" and the number of spikes per burst. Clearly, it would be of considerable interest to explore the effects of other drugs, especially anticonvulsants, upon the extra spike mode.

*Disuse or deafferentation* have been hypothesized to augment the extra spike mode and related phenomena (5, 21, 35). Deafferentation of external cuneate via dorsal rhizotomies results in a profound loss of the large synaptic terminals containing round vesicles (27) yet the spontaneous activity continues (20, 21, 33) after several days pause. Mechanisms for this hypothesized augmentation may involve deafferentation-associated changes in dendritic geometry (17, 18, 32, 36) or they may merely involve the disuse which accompanies deafferentation (25, 28). Disuse as an augmenting stimulus for the extra spike mode accords well with the "automatic gain control" implications noted above.

#### APPENDIX A: INTERSPIKE INTERVAL STATISTICAL COMPUTATIONS

Figure 12 shows the FOCAL program used to compute the relevant statistics and which created the printouts illustrated in Fig. 3. A local modification of FOCAL (called LINFOC UW) for the LINC-8 computer was utilized which had a 256 word section of memory into which interspike intervals could be placed by the parent LINC program (which retrieved them from tape files); the FOCAL program could also use the section to pass parameters derived from the FOCAL computations back to the LINC program (which accumulated them on tape for later plotting). This is the explanation for the FP (put) and FG (get) commands and for the lines 3.21 to 3.23. Interspike intervals were saved in 0.2 msec units; thus the division by 5 in line 2.50. A maximum interspike interval (2047/5) is not really an interspike interval; it indicates that period had passed without a spike.

#### REFERENCES

1. BRODAL, A. 1969. "Neurological Anatomy in Relation to Clinical Medicine." Oxford University Press, New York.
2. BUCHWALD, J. S., S. B. HOLSTEIN, and D. S. WEBER. 1973. Multiple unit recording: technique, interpretation, and experimental applications, pp. 201-242. In "Bioelectric Recording Techniques Part A, Cellular Processes and Brain Potentials, Methods in Physiological Psychology." Vol. 1-A. R. F. Thompson and M. D. Patterson [Eds.], Academic Press, New York.
3. CALVIN, W. H. 1968. Evaluating membrane potential and spike patterns by experimenter-controlled computer displays. *Exp. Neurol.* **21**: 512-534.

4. CALVIN, W. H. 1973. Some simple spike separation techniques for simultaneously recorded neurons. *Electroenceph. Clin. Neurophysiol.* **34**: 94-96.
5. CALVIN, W. H. 1974. Three modes of repetitive firing and the role of threshold time course between spikes. *Brain Res.* **69**: 341-346.
6. CALVIN, W. H. 1975. Generation of spike trains in CNS neurons (Review Article). *Brain Res.* **84**: 1-22.
7. CALVIN, W. H., G. A. OJEMANN, and A. A. WARD, JR. 1973. Human cortical neurons in epileptogenic foci: Comparison of interictal firing patterns to those of 'epileptic' neurons in animals. *Electroenceph. Clin. Neurophysiol.* **34**: 337-351.
8. CALVIN, W. H., and P. C. SCHWINDT. 1972. Steps in production of motoneuron spikes during rhythmic firing. *J. Neurophysiol.* **35**: 297-310.
9. CALVIN, W. H., and G. W. SYPERT. 1975. Cerebral cortex neurons with extra spikes: a normal substrate for epileptic discharges? *Brain Res.* **83**: 498-503.
10. CALVIN, W. H., G. W. SYPERT, and A. A. WARD, JR. 1968. Structured timing patterns within bursts from epileptic neurons in undrugged monkey cortex. *Exp. Neurol.* **21**: 535-549.
11. CAMPBELL, S. K., T. D. PARKER, and W. WELKER. 1974. Somatotopic organization of the external cuneate nucleus in albino rats. *Brain Res.* **77**: 1-23.
12. COOKE, J. D., B. LARSON, O. OSCARSSON, and B. SJÖLUND. 1971. Organization of afferent connections to cuneocerebellar tract. *Exp. Brain Res.* **13**: 359-377.
13. EIDE, E., L. FEDINA, L. JANSEN, A. LUNDBERG, and L. VYKLYCKY. 1969. Properties of Clarke's column neurones. *Acta Physiol. Scand.* **77**: 125-144.
14. EYZAGUIRRE, C., and S. W. KUFFLER. 1955. Further study of soma, dendrite, and axon: Excitation in single neurons. *J. Gen. Physiol.* **39**: 121-153.
15. FETZ, E. E., and A. R. WYLER. 1973. Operantly conditioned firing patterns of epileptic neurons in the monkey motor cortex. *Exp. Neurol.* **40**: 586-607.
16. GALINDO, A., K. KRNJEVIC, and S. SCHWARTZ. 1968. Patterns of firing in cuneate neurons and some effects of flaxedil. *Exp. Brain Res.* **5**: 87-101.
17. GELFAN, S., T. H. FIELD, and G. D. PAPPAS. 1974. The receptive surface and axonal terminals in severely denervated neurons within the lumbosacral cord of the dog. *Exp. Neurol.* **43**: 162-191.
18. GELFAN, S., G. KAO, and H. LING. 1972. The dendrite tree of spinal neurons in dogs with experimental hind-limb rigidity. *J. Comp. Neurol.* **146**: 143-174.
19. HOSOBUCHI, Y., and B. RUTKIN. 1971. Descending trigeminal tractotomy-neurophysiological approach. *Arch. Neurol.* **25**: 115-125.
20. KJERULF, T. D., and J. D. LOESER. 1973. Neuronal hyperactivity following deafferentation of the lateral cuneate nucleus. *Exp. Neurol.* **39**: 70-85.
21. KJERULF, T. D., J. T. O'NEAL, W. H. CALVIN, J. D. LOESER, and L. E. WESTRUM. 1973. Deafferentation effects in lateral cuneate nucleus of the cat: Correlation of structural alterations with firing pattern changes. *Exp. Neurol.* **39**: 86-102.
22. KUNC, Z. 1965. Treatment of essential neuralgia of the 9th nerve by selective tractotomy. *J. Neurosurg.* **23**: 494-500.
23. KUNO, M., E. J. MUNOZ-MARTINEZ, and M. RANDIC. 1973. Sensory inputs to neurones in Clarke's column from muscle, cutaneous and joint receptors. *J. Physiol. (London)* **228**: 327.
24. LLINAS, R., and C. NICHOLSON. 1971. Electrophysiological properties of dendrites and somata in alligator purkinje cells. *J. Neurophysiol.* **34**: 532-551.
25. LAMO, T., and J. ROSENTHAL. 1972. Control of ACh sensitivity by muscle activity in the rat. *J. Physiol. (London)* **221**: 493-513.

26. NIECHAJ, A., and A. VAN HARREVELD. 1968. Effect of asphyxia on the delayed depolarization in cat spinal motoneurons. *Brain Res.* 7: 463-464.
27. O'NEAL, J. T., and L. E. WESTRUM. 1973. The fine structural synaptic organization of the cat lateral cuneate nucleus. A study of sequential alterations in degeneration. *Brain Res.* 51: 97-124.
28. PURVES, D., and B. SAKMANN. 1974. The effect of contractile activity on fibrillation and extrajunctional acetylcholine-sensitivity in rat muscle maintained in organ culture. *J. Physiol. (London)* 237: 157-182.
29. RAUSCH, J. M. 1969. Electrophysiology of the External Cuneate Nucleus in the Cat. Ph.D. Thesis, University of Washington, Seattle.
30. ROSÉN, I., and B. SJÖLUND. 1973. Organization of group I activated cells in the main and external cuneate nuclei of the cat: Identification of muscle receptors. *Exp. Brain Res.* 16: 221-237.
31. ROSÉN, I., and B. SJÖLUND. 1973. Organization of group I activated cells in the main and external cuneate nuclei of the cat: Convergence patterns demonstrated by natural stimulation. *Exp. Brain Res.* 16: 238-246.
32. RUTLEDGE, L. T., J. DUNCAN, and N. CANT. 1972. Long-term status of pyramidal cell axon collateral and apical dendritic spines in denervated cortex. *Brain Res.* 41: 249-262.
33. SCHWARTZ, S. T. 1965. Analysis of Resting Activity in the Cuneate Nucleus, Ph.D. Thesis, Yeshiva University.
34. TERZUOLO, C. A., and T. ARAKI. 1961. An analysis of intra- versus extracellular potential changes associated with activity of single spinal motoneurons. *Ann. N.Y. Acad. Sci.* 94: 547-558.
35. WARD, A. A., JR. 1969. The epileptic neuron: Chronic foci in animals and man, pp. 263-298. In "Basis Mechanisms of the Epilepsies." H. H. Jasper, A. A. Ward, Jr., and A. Pope, [Eds.], Little, Brown, Boston.
36. WESTRUM, L. E., L. E. WHITE, and A. A. WARD, JR. 1964. Morphology of the experimental epileptic focus. *J. Neurosurg.* 21: 1033-1046.