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Inhibitory and Excitatory Factors Influencing the Receptive Fields of Lamina 5 Spinal Cord Cells

P. HILLMAN* and P.D. WALL

M.R.C. Cerebral Functions Research Group, Department of Anatomy, University College, London, W.C. 1

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Summary. Examination of cutaneous receptive fields (RFs) of lamina 5 cells in the lumbar spinal cord of decerebrate cats shows them to have three distinct zones with respect to mechanical and electrical stimulation. The mean response rate to both mechanical and electrical stimulation in zone 1 increases steadily up to the highest strengths used; in zone 2, surrounding zone 1 mainly proximally, mild stimuli reduce the mean rate, stronger stimuli increase it; in zone 3, mainly proximal to zone 2, all stimuli reduce the rate.

Temporally, zone 1, electric shocks near threshold produce bursts of firing followed by inhibition. With increased stimulus strength, the bursts lengthen to a second or more. In zones 2 and 3, inhibition at all strengths is preceded at higher strengths by bursts of firing.

Cold-blocking the spinal cord at lower thoracic levels reversibly increases the ongoing activity of these cells, increases the area of zones 1 and 2, and almost completely suppresses all inhibition.

Stimulation of dorsal columns and threshold stimulation of distant dorsal roots inhibits ongoing and induced activity. Barbiturate decreases ongoing activity and the duration of firing produced by cutaneous electrical stimulation but does not decrease inhibition.

These results are consistent with a model in which low-threshold fibres are excitatory only over a small central area of the RF of a lamina 5 cell (zone 1), high threshold fibres are excitatory over a larger area (zones 1 and 2), and low threshold fibres are inhibitory over the entire receptive field (zones 1, 2 and 3) with a slower time-course. This inhibition is tonically enhanced by descending influences in the decerebrate cat.

It is suggested that the high and low threshold fibres correspond approximately to the small and large diametre fibres whose balance is the basis for the coding of pain in the theory of MELZACK and WALL.

Key Words: Cutaneous receptive fields — Spinal cord — Cat — Pain

Introduction

Lamina 5 cells are particularly interesting because they respond to small myelinated afferents (WALL 1967; POMERANZ et al. 1968) and therefore might be

* Wellcome Trust Fellow, on leave of absence from the Weizmann Institute of Science, Israel.

involved in pain mechanisms triggered by such afferents (ZOTTERMAN 1939; BISHOP 1946; NOORDENBOS 1959; COLLINS 1960). WALL (1967) and POMERANZ et al. (1968) have shown that it is characteristic of these cells that they have a graded response to brush, touch and pressure in the centre of the RF but respond only to pressure applied to the edge of the RF. Electrical stimulation of afferents suggests that lamina 5 cells may be fired polysynaptically by large myelinated afferents and monosynaptically by small myelinated afferents (POMERANZ et al. 1968).

Our knowledge of lamina 5 cell responses comes partly from recordings of cell body activity in dorsal horns and partly from recordings from axons of those cells which project into the spinocervical tract. No differences have yet been observed in the discharge patterns of the cells recorded at these two sites. In this paper, cell discharges were recorded in the region of lamina 5 without reference to whether or not their axons ran in dorso-lateral white matter.

The majority of axons in the spinocervical tract (SCT), originate from cells in lamina 4 and have the response characteristics of lamina 4 cells (ECCLES et al. 1960; WALL 1960, 1965). In addition, there are certain axons which respond to a much wider range of pressure stimuli and to small myelinated afferent stimulation (WALL 1960; LUNDBERG and OSCARSSON 1961). This minority originate from cells deeper in the spinal cord in the region of lamina 5 (FETZ 1968). The literature on the spinocervical tract therefore deals with a mixed population of axons. This paper deals with cells which respond to a wide range of pressure stimuli and which show prolonged repetitive discharge following maximal stimuli to peripheral nerves. The response of these cells to natural stimuli is strongly inhibited in the decerebrate cat. Their receptive fields expand and their excitability increases if the spinal cord is blocked in a decerebrate preparation (WALL 1967). Barbiturate anaesthesia limits their response to afferent volleys, especially to impulses in small diametre afferents (WALL 1967).

In addition to the excitatory effects of afferent volleys on lamina 5 cells, four types of inhibition or habituation have been seen to be produced by peripheral stimulation. Excitation by light pressure stimulation of the receptive field was shown to be followed by inhibition (WALL and CRONLY-DILLON 1960). TAUB (1964) showed that light pressure stimulation in areas around the excitatory field might produce a labile inhibition of some cells sending their axons into the SCT. This observation has been confirmed and greatly extended by HONGO, JANKOWSKA and LUNDBERG (1968), who had previously studied postsynaptic changes produced in these cells by peripheral nerve stimulation (HONGO et al. 1966). We shall discuss below the reasons why this inhibitory surround was not reported by previous workers in the SCT (WALL 1960; LUNDBERG and OSCARSSON 1961) or in its subsequent relays (ANDERSSON 1962; GORDON and JUKES 1963; HORROBIN 1966). WALL (1967) reported that light repeated brushing of the excitatory field of lamina 5 cells led to a habituation of the initial response but that this habituation disappeared if the spinal cord was blocked in the lower thoracic segments. In the spinal rat, habituation of lamina 5 cells was observed following light repeated stimuli (WALL et al. 1967). WICKELGREN (1968), while studying the habituation of the flexor reflex, showed that repeated intense peripheral stimuli produced a progressively decreasing response in cells with lamina 5 characteristics. She attributed this habituation to the build up of an inhibition.

Faced with this evidence for a convergence on lamina 5 cells of both excitatory and inhibitory peripheral influences, we decided to investigate the spatial and temporal characteristics of this convergence. Previous speculations suggested that the excitatory-inhibitory effects were related to small-large fibre interactions (MELZACK and WALL 1965) and therefore particular attention was paid to the effects of stimulus intensity.

Methods

The methods of stimulation and recording were the same as those previously used (WALL 1967). Cats were decerebrated at the midcollicular level under ether or halothane and were maintained on artificial respiration after paralysis by gallamine triethiodide. In some animals

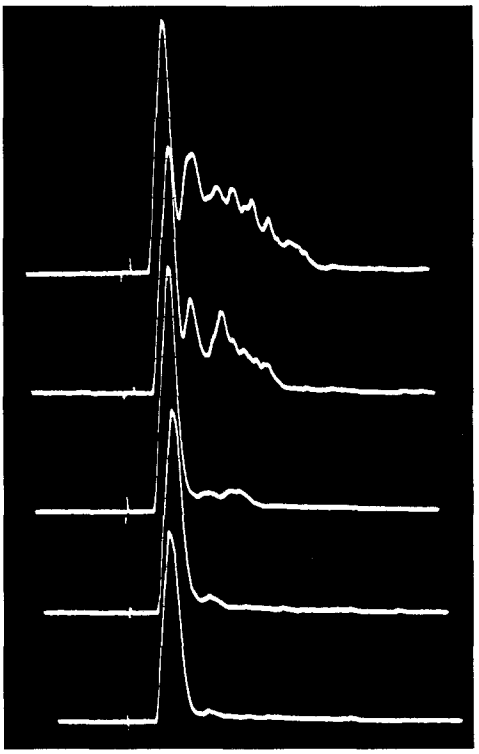

Fig. 1. *Compound action potentials in the sural nerve resulting from cutaneous stimulation* about 90 mm from the detection point. The successive traces (from bottom up) are for stimulation pulses of 0.05 msec, 2 V; 0.05 msec, 8 V; 0.05 msec, 20 V; 0.5 msec, 8 V; and 0.5 msec, 20 V. This is the range of stimulus strengths used in this experiment, and it is clear that over this range stimuli of increasing strength recruit fibres of steadily decreasing conduction velocity. Artifacts are visible at the beginning and end of the stimulus pulses. The latency of the first spike is 1.15 msec

blood volume was raised by an intravenous drip of sodium chloride 0.18% — dextrose 4.3%. Since great mechanical stability of the spinal cord was required to observe single units for several hours at a time, a pneumothorax was produced.

Unit spikes were recorded with glass microelectrodes filled with 3 M KCl and with resistances of 2—4 MΩ. The spikes were fed to a voltage discriminator to produce pulses which were

used to trigger a counter and to brighten the oscilloscope trace. Two methods of display were used: time of occurrence of impulses after stimulus on the horizontal axis versus stimulus intensity on the vertical axis (WALL 1959), and pulse interval on the vertical axis versus time on the horizontal axis (WALL 1960).

Cold blocking of segments of the spinal cord (WALL 1967) was achieved in the lower thoracic segments in order to avoid the large changes of blood pressure which follow more rostral blocking. Three segments of lower thoracic cord were exposed. Stimulating electrodes were placed on the most rostral exposed dorsal columns at about T9. Recording electrodes were placed on a small dorsal rootlet of a caudal, sacral or coccygeal segment. One centimetre cubes of mammalian Ringer ice were placed on the segments T10—11. In a few minutes, no antidromic compound action potential could be recorded on the caudal dorsal rootlet after dorsal column stimulation rostral to the iced region and no evoked response from the dorsal column stimulation could be detected on the lamina 5 cell under observation. For reasons discussed previously (WALL 1967), we can assume that, in this condition, there is a conduction block of at least the dorsal half of the spinal cord in the cooled segments. The block was reversed by removal of the ice and warming of the cord. Blocking and unblocking as repeated up to ten times in the same animal without substantial signs of irreversible changes.

Mechanical stimulation was manual and was subjectively categorized as brush, touch, pressure, or pinch.

For cutaneous electrical stimulation, two 26-gauge hypodermic needles were inserted in the skin 5 mm apart. Some recordings of the compound action potential in the sural nerve resulting from electrical stimulation of the skin are shown in Fig. 1. These show that the conduction velocities of fibres excited by electrical stimuli of strengths in the range of those used in this experiment are inversely correlated with stimulus strength. Considerable variation was however noted in the absolute thresholds for firing the various groups.

Results

The excitatory responses and method of locating these cells have been described previously (WALL 1967; POMERANZ et al. 1968) and will be discussed only briefly here except where additional observations have been made. Our primary aim was to add an analysis of inhibitory mechanisms.

Decerebrate Preparations

Ongoing Activity

Many cells were silent in the absence of intentional stimuli to the skin. Some were active with an irregular distribution of pulse intervals but with a steady mean frequency which varied from cell to cell with rates of 1—8 impulses/sec. A few cells generated periods of irregular firing interspersed with periods of high frequency bursts. The firing pattern of impulses within these bursts was fixed for each cell. The bursts contained 2—5 impulses with pulse intervals of 2—10 msec. This ongoing activity is not produced by local damage to the cell by the microelectrode because similar activity has been recorded in SCT axons many segments away from the cells of origin.

Excitation and Inhibition Produced by Mechanical Stimuli

As previously described, when a microelectrode penetrates the grey matter of lumbar dorsal horn, cells are recorded in the region of Rexed lamina 4 which have relatively small cutaneous excitatory receptive fields and which respond to brush, touch and light pressure but which do not increase their firing rates if heavy pressure or pinch is applied. Ventral to these cells, in the region of Rexed lamina 5, there are cells with larger receptive fields which can be divided into three zones as shown in

Fig. 2. Three other examples of the excitatory parts of receptive fields of such cells were illustrated in WALL 1967 (Fig. 6). The same general organisation of RFs was found in all cells examined in lamina 5 in segments L4-S2. For convenience of cutaneous stimulation, we concentrated on the lateral part of segments L7 and S1 because in this region the cells' RFs are contained within a band running from the lateral two toes along the side of the foot to the lateral ankle.

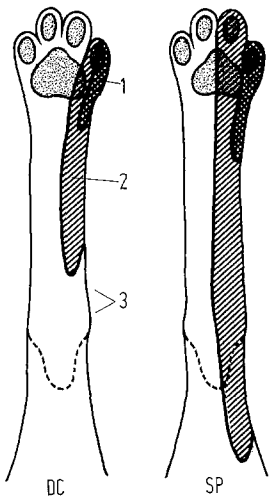

Fig. 2. *Receptive fields of a single cell in the lateral part of lamina 5 in L 7.* On the left, DC, the receptive field is shown in the decerebrate cat. Zone 1, the cell responded to brush, touch and crushing of the skin. Zone 2, brushing inhibited the cell while pressure and pinch excited it. Zone 3, (outer boundaries too vague to be shown), brush, touch and pressure inhibited the cell but did not excite it. The location of the numbers 1, 2 and 3 also shows the points of electrical excitation whose effects are described in the text and shown in Figs. 5 and 7. On the right, SP, the receptive field of the same cell is shown after the lower thoracic spinal cord had been blocked by cooling. Zones 1 and 2 had expanded as shown. Zone 3 has disappeared

Zone 1: within this zone, brushing of hair caused the cell to fire. The mean frequency of firing increased as the intensity of pressure was increased from light touch to heavy pinch. Figs. 3 and 4 show the effect of placing an "alligator" clip on the skin in the centre of zone 1. The cell shown in Fig. 3 was silent before the clip was applied. Immediately after the stimulus started, the cell began to fire at a high frequency which adapted over a period of about 30 secs to a slightly lower firing frequency which was then maintained for the remaining 2 min while the clip was left on. As the clip was taken off, there was a brief high frequency burst of impulses produced by movement of hair. During the subsequent 90 secs, the cell fired 12 times and then returned to silence. The cell illustrated in Fig. 4 was active at a rate of 1 impulse every 2 secs before stimulation. After the clip was applied there was intense firing followed by adaptation to a sustained level of high frequency response. On removal of the stimulus, the firing frequency initially dropped for a period of about 30 secs followed by the appearance of a new pattern of firing. The lower band was produced by high frequency bursts of 2—4 impulses. The bursts occured at irregular intervals. Between the bursts, the cell fired with irregular lower pulse intervals. The two cells shown represent the extremes of those observed. Some returned rapidly, after the removal of the clip, to their resting state while others continued to fire in a new pattern for long periods after the removal of the stimulus. Some of this variation between the cells could be attributed to their different levels of excitability as judged by their resting discharge rates before the stimulus. Some of the variations must be attributed to the variable amount of damage produced in the skin by the rapid manual application of a clip.

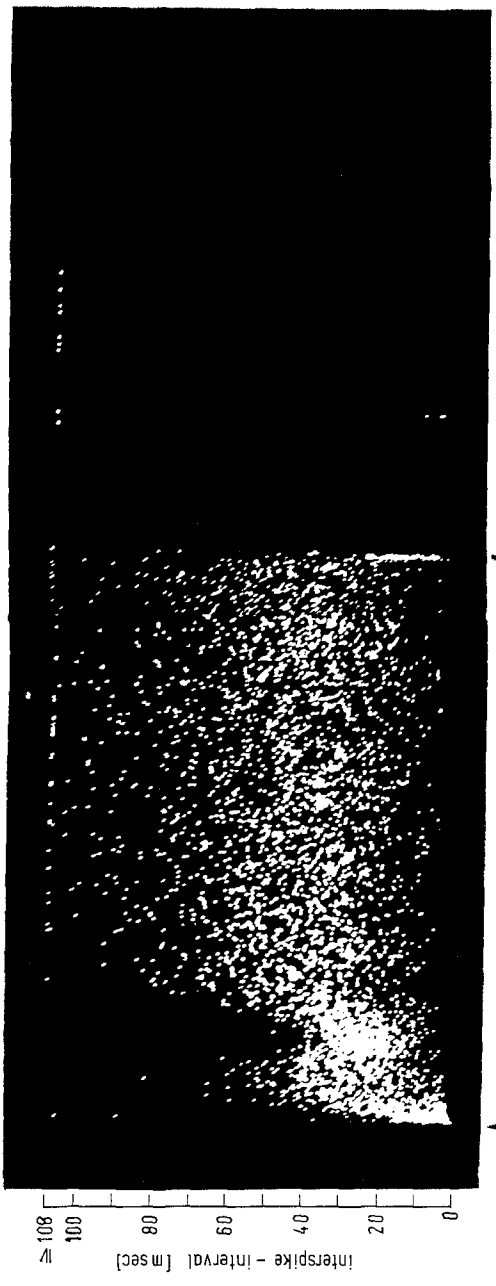

Fig. 3. *Firing pattern of a lamina 5 cell before, during and after the application of a clip to zone 1*, the most sensitive part of its cutaneous receptive field. The duration of the record is 5 min running from left to right. Each dot is produced by a single nerve impulse. The vertical position of the dot indicates the pulse interval between the recorded impulse and the preceding one. The cell was silent before the application of the clip. When the clip was applied, the cell began to fire at a high frequency which adapted (non-monotonically) to a lower sustained frequency. When the clip was removed after 2.5 min there was a brief burst produced by hair movement. The cell responded with 12 impulses during the next minute and then became silent again. Arrows indicate the time of application and removal of the clip

Zone 2: this area surrounded zone 1. It extended over a greater area proximal to zone 1 than distal. It formed a relatively narrow band lateral and medial to zone 1. The general direction of the whole field extended proximo-distally along the dermatomal pattern. Light brushing or hair movement never produced excitation but produced inhibition of ongoing activity. If the ongoing activity of the cell

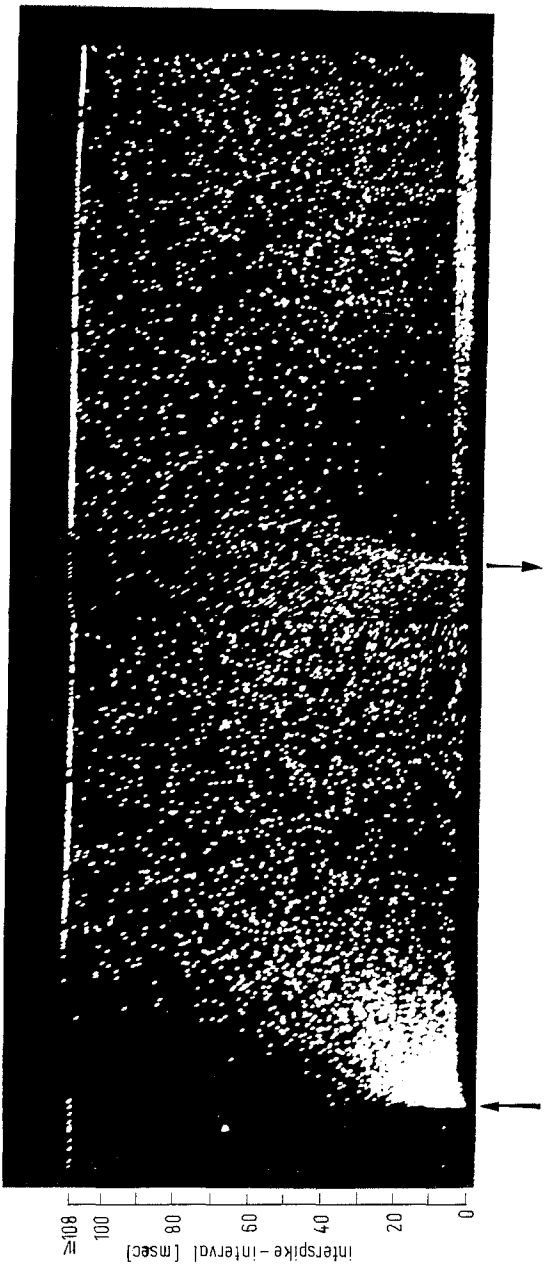

Fig. 4. *Same as Fig. 3 but another lamina 5 cell.* This cell was active at a low frequency in the absence of intentional stimulation. When the clip was applied, high frequency firing commenced which adapted (again non-monotonically) to a steady lower frequency. When the clip was removed the frequency of firing dropped but after 30 secs rose again to a new pattern of sustained firing in which intermittent bursts of high frequency firing occurred

was increased by steady pressure in zone 1, light brushing in zone 2 usually decreased the rate of firing. If the cell was made to fire by electrical stimulation applied through hypodermic needles in zone 1, brushing in zone 2 did not inhibit the repetitive burst evoked by the electrical stimuli. In contrast to the inhibitory effect of brushing, pressure or pinching in zone 2 excited the cell. There was a gradient of threshold so that mild pressure close to the edge of zone 1 would pro-

duce firing while pinching was required on the outer edge of zone 2. The excitatory response was not produced by mechanical spread of the stimulus from zone 2 to zone 1 because intentional lateral movement of the skin in zone 2 did not evoke firing.

Zone 3: extended mainly proximally from zone 2 along the dermatome but was also present medially, laterally, and distally. No mechanical stimuli ever produced excitation. Light brushing, touching and light mechanical vibration produced inhibition of ongoing activity. The exact boundary of this region was difficult to determine with natural stimuli because the inhibition weakened at the outer edge and because the inhibitory effect of repeated light stimuli habituated.

Effect of Repetitive Electrical Stimulation on Ongoing Activity

Pairs of 26 gauge hypodermic needles separated by 5 mm were placed in the skin in various parts of the receptive field of lamina 5 cells. The ongoing level of firing of the cell was raised if necessary by applying steady pressure in zone 1 until the mean frequency was above 5/sec. An example of the results obtained is shown in Fig. 5. The cell under observation had the receptive field shown in Fig. 2 and

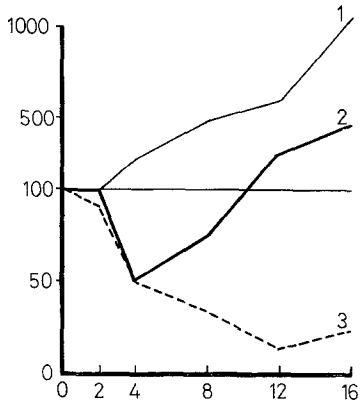

Fig. 5. *The effect of repetitive electrical cutaneous stimulation* on the ongoing activity recorded in the decerebrate state from the lamina 5 cell whose receptive field is shown in Fig. 2. DC. Pairs of hypodermic needle stimulating electrodes were placed in the skin at the points 1, 2 and 3 shown on Fig. 2. Stimuli were square waves with 0.05 msec duration at 5/sec with the voltages shown on the lower scale. Line 1 shows the effect of stimulation at point 1 in zone 1. All effective voltages produced an increase of the firing rate. Line 2 shows the effect of stimulation in zone 2 where low voltages produced an inhibition and higher voltages increased the firing rate. Line 3 shows the repetitive stimulation in zone 3 produced inhibition at all the applied voltages. The firing rate is shown as a percentage of the resting level on the vertical scale. Note that different linear scales are used above and below 100%

the three pairs of stimulating electrodes were located at the positions shown by the numbers 1, 2 and 3. The total number of impulses produced by the cell in 20 sec periods was counted before, during and after application at a particular intensity of 0.05 msec electrical square waves at 5/sec through one of the pairs of electrodes. The firing rate of the cell during the stimulation was recorded as a percentage of the average firing rate during the two control periods. The intensity was varied from 0—16 volts. Electrodes of the type used on the cats were inserted into the

volar distal forearm skin of one of us (PDW) and it was found that the stimulus could just be detected at 2 volts and was mildly painful at 16 volts. At the highest intensity, the sensation seemed to the subject to remain localised around the region of the stimulating electrodes.

Zone 1: Fig. 5, line 1. The stimulus was applied at point 1, Fig. 2. As the stimulus intensity was raised, a threshold point was reached at which each shock evoked a discharge from the cell. Further increases of stimulus intensity increased the number of impulses in each synchronous burst so that the total number of impulses produced by the cell rose steadily. If the discharge pattern produced by each shock was examined as will be discussed in detail below, it was seen that the synchronous repetitive discharge of the cell was followed by a period of silence during which the normal ongoing activity of the cell did not occur. The synchronous activity was not added on top of the ongoing activity, rather it substituted for it. If the impulses contained in the synchronous burst were subtracted from the total firing of the cell, it could be seen that the ongoing activity was inhibited by the stimulus. We see therefore that while the graph shows a steadily rising excitation of the cell, this increased firing is taking place on an increasing background of inhibition. On one occasion the lowest effective stimulus at a point in zone 1 produced inhibition although increased strength of stimulation produced a curve similar to that shown in Fig. 5.

Zone 2: Fig. 5, line 2. The stimulus was applied at point 2, Fig. 2. When electrical stimuli were applied in this region, low level stimuli which had been sufficient to produce synchronous firing when applied to zone 1, always reduced the average level of ongoing activity. As the stimulus intensity was raised, a point was eventually reached where synchronous responses were evoked. Further increases of stimulus intensity produced an increase in the numbers of these synchronous responses to each stimulus. Eventually an intensity of stimulus was reached where the frequency of response during stimulation was higher than during the control periods.

Zone 3: Fig. 5 line 3. The stimulus was applied at point 3 Fig. 2. When skin was stimulated in this region, low voltages which were just threshold for excitation in zone 1 produced inhibition. As the voltage was raised, the inhibition increased and reached a maximum. Further increases of stimulus voltage failed to produce any additional decrease of the average firing rate of the cell.

The intensity of inhibition produced by low voltage stimulation in zones 2 and 3 varied with frequency of stimulation. The optimal frequency was about 10/sec and the inhibition fell off if the frequency was either increased or decreased. To give a typical example, the maximal inhibition at a fixed stimulus voltage and duration for one stimulus point was 57% at 10/sec, 37% at 100/sec and 20% at 2/sec.

Temporal Pattern of Responses to Single Electrical Shocks

Pairs of hypodermic needles separated by 5 mm were again placed in various parts of the receptive fields of lamina 5 cells. Square-wave stimuli were applied once a second. The stimulus intensity was increased in steps from 1 V or 2 V to 20 V with a duration of 0.05 msec, and then 2—20 V at 0.5 msec, with five responses being recorded at each step. The lowest stimuli were slightly above threshold for firing the cells when applied to zone 1 and they were slightly above threshold for

stimulating the largest myelinated afferent fibres as judged by sural nerve recordings (Fig. 1). They were at threshold for producing detectable sensation when applied through the skin of the human forearm. The highest voltages were sufficient to stimulate the full range of myelinated afferents (Fig. 1). It must be assumed that there was some current spread to deep subcutaneous structures at the highest voltages, because, if the electrodes were in skin over the gastrocnemius muscle, small local twitches could be observed at each stimulus.

Zone 1: Fig. 6: left picture. The lowest voltage stimulus produced a short repetitive burst of response followed by a silent period. The latency of the first response was 5—7 msec after a stimulus on the foot. As the intensity of the stimulus was raised, the duration of firing became more and more prolonged so that firing extended into the silent period. In some of the most excitable cells, the increased firing lasted for more than 1 sec so that the response to subsequent stimuli overlay the tail of the response from preceding stimuli. This very prolonged firing gives rise to the "wind-up" phenomenon (MENDELL 1965). Each cell began its response by firing at a high frequency followed by a gradual decline of frequency. However within this overall pattern, there were fixed periods of high and low frequency response. This "banding" phenomenon has been described previously (MENDELL 1965; POMERANZ et al. 1968). The latency of and number of these bands of high frequency response varied from cell to cell. At the highest intensities of stimulation, certain bands of high frequency response appeared with latencies of hundreds of milliseconds. In Fig. 6, left, a particularly strong and delayed band appears as the maximal intensity is approached. It will be noticed that as the intensity of stimulus is further increased the latency of this band also increases. We have no explanation of this curious phenomenon of increasing latency which might be produced either by some very long lasting inhibition which accumulated from stimulus to stimulus or by some new inhibition introduced by the highest strength stimuli.

Zone 2: Two examples are shown in Fig. 6 middle and right. The response patterns were recorded from the same cell as that shown on the left. In the middle picture, the stimulus point was in zone 2 proximal to zone 1 and, in the right picture, the stimulus point was distal. The lowest stimulus intensities which were adequate to fire the cell if applied to zone 1 failed to make the cell respond in zone 2. However, there was a period of 50—150 msec of silence or decreased firing of the cell following these low voltage stimuli. As the stimulus intensity was raised, a point was eventually reached at which the cell responded either with a single impulse or with a repetitive burst. After this response, there was a silent period. As the intensity was further increased, there was an extension of the repetitive burst but it was never as prolonged as those observed when zone 1 was stimulated. If the stimulus point was moved in zone 2 from the edge of zone 1 to the outer edge of zone 2, the threshold rose and the duration of repetitive firing fell. The thresholds in the region of zone 2 distal to zone 1 were higher than in the proximal part of the zone as can be seen by comparing Fig. 6 middle with that on the right. Similarly the duration of repetitive firing evoked from the distal part was less than that which could be produced from the proximal region.

The latency of the first response to stimulation in the more excitable parts of zone 2 on the foot was 7—9 msec but this rose to as long as 20 msec for the less

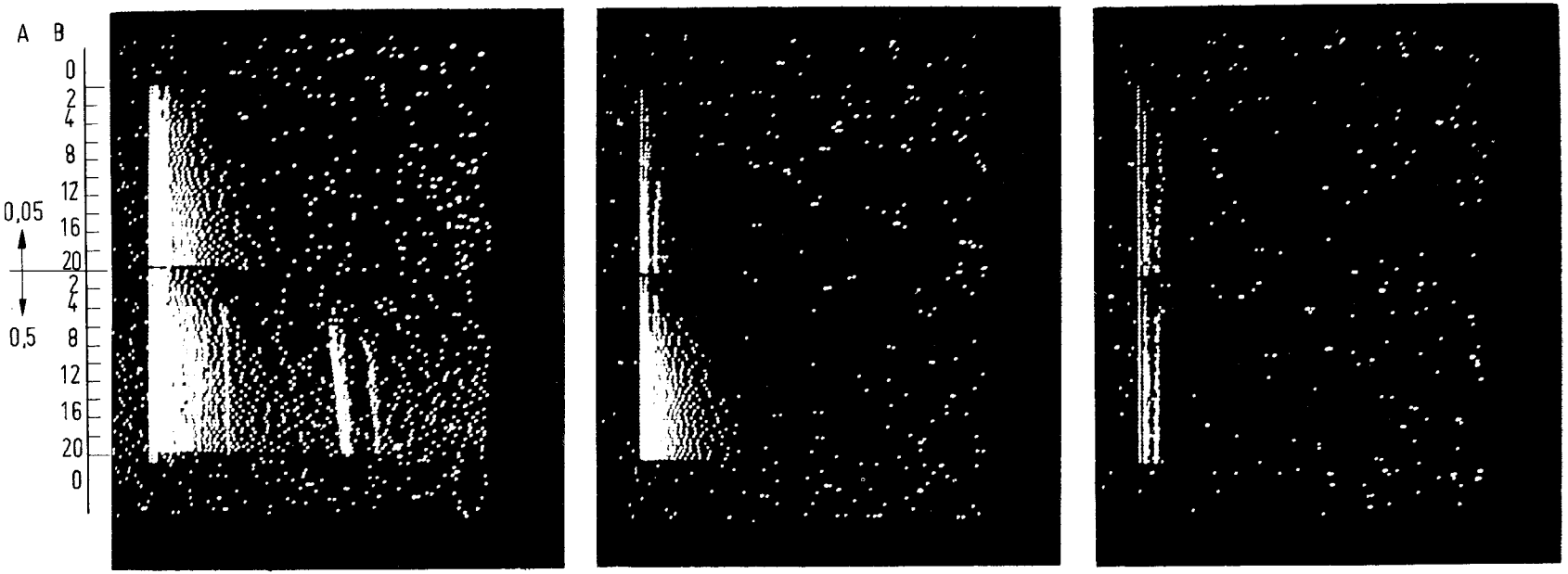

Fig. 6. *The temporal pattern of discharge evoked from a lamina 5 cell* by application of electrical stimuli to three regions of its receptive field: Left picture = zone 1; centre = zone 2 proximal to zone 1; right = zone 2 distal to zone 1. Each nerve impulse produced a single dot. Time runs from left to right in the pictures, the total sweep of each line in each picture being 800 msec. The stimuli were repeated at 1/sec, and given in sets of 5 of equal strength, preceded and followed by "stimulus-off" periods at the top and bottom of the pictures. Scales A and B give the stimulus length in milliseconds and strength in volts. The first vertical line of dots on the left of each picture is the stimulus artifact

excitable regions. It seems likely from conduction distance and threshold measurements that such long delays as 20 msec as compared with 7 msec could not be explained by a delay of afferent impulse conduction time but must have been produced by a multisynaptic connection between stimulated afferents and the observed cell.

Zone 3: Zone 3 had been differentiated from zone 2 by the failure of mechanical stimuli to excite the cell. The two zones could not be differentiated by the responses produced by single electrical stimuli, since there was simply a steady rise of electrical threshold as the stimulus point moved from one zone to the other. It was necessary to use higher intensity electrical stimuli to excite by zone 3 stimuli. It is not possible to say at this time if the response to electrical but not to mechanical stimuli was produced by the synchronous stimulation of afferent fibres from the skin of this zone or if the stimulus had spread to deeper structures. It does not seem likely that the stimulus had spread to zone 2 because the cells would often respond to stimuli applied to zone 3 skin at an intensity which failed to produce contractions in muscle immediately below the stimulus point.

Effects of Blocking Impulses Descending from the Head in the Decerebrate Cat

These were produced by cold blocking the spinal cord in lower thoracic segments by the method described. Since the block is easily reversible, it was possible to observe the properties of cells in both the decerebrate and low spinal state. The changes observed can be attributed to blocking impulses descending from the head rather than from the cervical enlargement or rostral cord because similar changes have been seen after cord section at C1 (WALL 1967). The changes observed in spinal cord cells after block are unlikely to be caused by cardiovascular effects. No alteration of blood flow or colour could be seen in surface vessels on the lumbar cord observed during the onset of the block. We report here only those cells from which we were able to record throughout the period of blocking and unblocking. No detectable movements occurred during blocking.

Ongoing Activity: the rate of ongoing activity in almost all cells increased when the cord was blocked. This increase was as reliable a sign of block as the failure of transmission of impulses along the dorsal columns. Many cells which were silent in the decerebrate animal became active after cold block. The lowest range of increase recorded was a cell which was silent in the decerebrate animal and fired at 6 impulses per second after cord block; the highest range was a cell whose firing rate rose from 5—52 impulses per second.

Excitation and Inhibition Produced by Mechanical Stimuli

An example of the expansion of excitatory RFs produced by blocking the spinal cord is shown in Fig. 2.

Zone 1: The area of this zone increased. In the example shown, the proximodistal length of the RF in the decerebrate was 20 mm which expanded to 30 mm in the spinal state. In some cells, this increase was much less, often only 1—2 mm. The direction of the expansion was always most marked proximally with very much smaller extensions laterally, medially and distally. It was not possible to tell if there was a change of threshold to brushing in the centre of zone 1 because it was so sensitive even in the decerebrate state that movement of a few hairs ex-

cited the cell. On pinching the skin in zone 1, the cell responded at a higher frequency in the spinal than in the decerebrate state. When habituation of the excitatory response to light repeated brushing was observed in the decerebrate animal, this habituation disappeared after cord block.

Zone 2: There was always a very much more marked expansion of the size of zone 2 than of zone 1. In the cell illustrated in Fig. 2, the proximal border of zone 2 was about 4 cm proximal to zone 1 in the decerebrate state. It expanded to 7 cm proximal to zone 1. Distally, zone 2 involved only the most lateral toe in the decerebrate state and extended onto the next more medial toe after cord block. The expansion of RFs was always along the dermatome with a preferential proximal extension. The pressure threshold for excitation decreased and the frequency of response increased in the spinal state. Where inhibition had been evoked by brushing in the decerebrate state, the inhibition disappeared or became very weak after cord block.

Zone 3: disappeared or became very difficult to detect.

Effects of Repetitive Electrical Stimulation on Ongoing Activity

Zone 1: Repetitive stimulation of the skin in this zone always produced a greater increase of the number of impulses from lamina 5 cells in the spinal animal than in the decerebrate. To give an example from the cell shown in Fig. 2 and Fig. 5, in the decerebrate state, a 12 V, 0.05 msec stimulus repeated at 5/sec raised the rate of firing from 4.9/sec to 27.5/sec. Each stimulus produced a repetitive burst of 5—6 impulses. When the spinal cord was blocked, the ongoing rate of activity without stimulation rose from 4.9/sec to 22.2/sec. When the skin was stimulated at the same location and intensity as before, the rate of firing now rose from 22.2/sec to 63.3/sec and each stimulus produced a repetitive burst of more than 10 impulses.

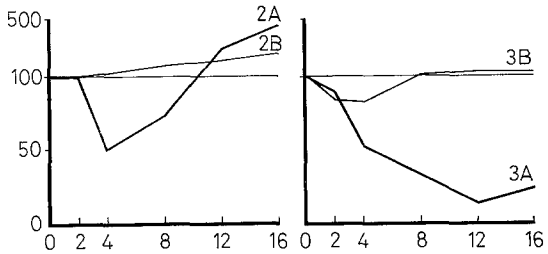

Fig. 7. *As in Fig. 5 but showing the effect of blocking the spinal cord* in the lower thoracic region. Line 2A is the same as line 2 in Fig. 5 and shows the increase and decrease of activity produced in the decerebrate preparation by repetitive stimulation in zone 2. Line 2B shows the results of exactly the same stimulation after the cord had been cold-blocked at T10. It will be seen that the inhibition produced by low voltage stimuli no longer appeared. On the right, line 3A is the same as line 3 in Fig. 5 and was produced in the decerebrate cat. It shows that low voltage stimuli produced a strong inhibition. When the cord was blocked and the same stimuli were applied line 3B was produced showing a marked decrease of the inhibition

Zone 2: The decrease of activity produced by low voltage stimulation in the decerebrate state disappeared or was greatly decreased when the spinal cord was blocked. Comparisons are shown in Fig. 7. Line 2A is the same as line 2 in Fig. 5. It shows the activity during 5/sec stimulation at various voltages as a percentage

of the spontaneous rate. Line 2A shows that in the decerebrate state, low voltage stimulation of 2—4 V produced a marked decrease of activity. The effect decreased as the voltage was raised to 8 V and at 12 V there was an increase of activity. When the same procedure was repeated with the spinal cord blocked, line 2B was generated in which there was no sign of decrease produced by the lower voltages but an increased activity as the voltage was increased. The highest voltage used, 16 V, produced a smaller percentage increase in the spinal state than in the decerebrate but it must be remembered that these figures were calculated from the change of firing rate during stimulation compared to the base line rate of firing before and after the stimulation period. The base line rate was considerably higher in the spinal state and the actual rate of evoked firing was higher in the spinal state though the percentage increase was smaller. To give an example, stimulation at 16 V produced a rise in the decerebrate state from 4.5—19.8 imp./sec and in the spinal from 19.5—41.4 imp./sec.

Since the receptive field of the cell in Fig. 2 expanded, the stimulus point 3, which had been in zone 3 in the decerebrate state was now in zone 2 of the spinal state since pinching of the skin produced excitation of the cell. Lines 3A and 3B Fig. 7 show a comparison for this stimulus point of the effect of various voltages of repetitive stimulation in the two states. In the decerebrate state, 3A, stimulation had produced only a decreased activity. In the spinal animal, low voltages produced a comparatively small decrease and the highest voltages used in this series were beginning to produce a small increase.

Zone 3: most or all of zone 3 in the decerebrate state developed zone 2 type responses. Beyond the edges of the expanded zone 2, small and weak inhibitions could sometimes be detected.

Temporal Patterns of Response to Single Electrical Shocks

Spinal blocking produced an increase of the periods of excitation and a decrease or complete disappearance of the inhibitory periods.

Zone 1: For each voltage, the duration of repetitive firing and the number of impulses in the burst increased. This repetitive firing extended out into the period during which the cell had been silenced in the decerebrate state. Inhibition was often still visible following the repetitive burst but was reduced in both intensity and duration.

Zone 2: An example of the change of response pattern is shown in Fig. 8. The pattern of firing on the left is that shown by the cell in the decerebrate and on the right in the spinal state. The stimulus point was in zone 2, but in the spinal state, the border of zone 1 had approached close to the stimulus point. The lowest stimulus used failed to produce firing in either condition but in the decerebrate state it produced a prolonged reduction of ongoing activity which is visible for only a brief period in the spinal animal. As the stimulus intensity is raised step by step the frequency within the burst and the duration of the burst are increased in the spinal animal. The obvious silent period which follows the response in the decerebrate state is only just apparent in the spinal animal for the middle range of stimulus intensities. For the highest stimulus intensities, the prolonged repetitive firing swamps the silent period, and delayed bands of high frequency response can be seen on the right which do not appear at all in the decerebrate condition. During

this most intense stimulation, there are no signs of the inhibition which was so obviously present when the same stimulus was given while the spinal cord was not blocked. There was usually a small decrease of both the latency and threshold for

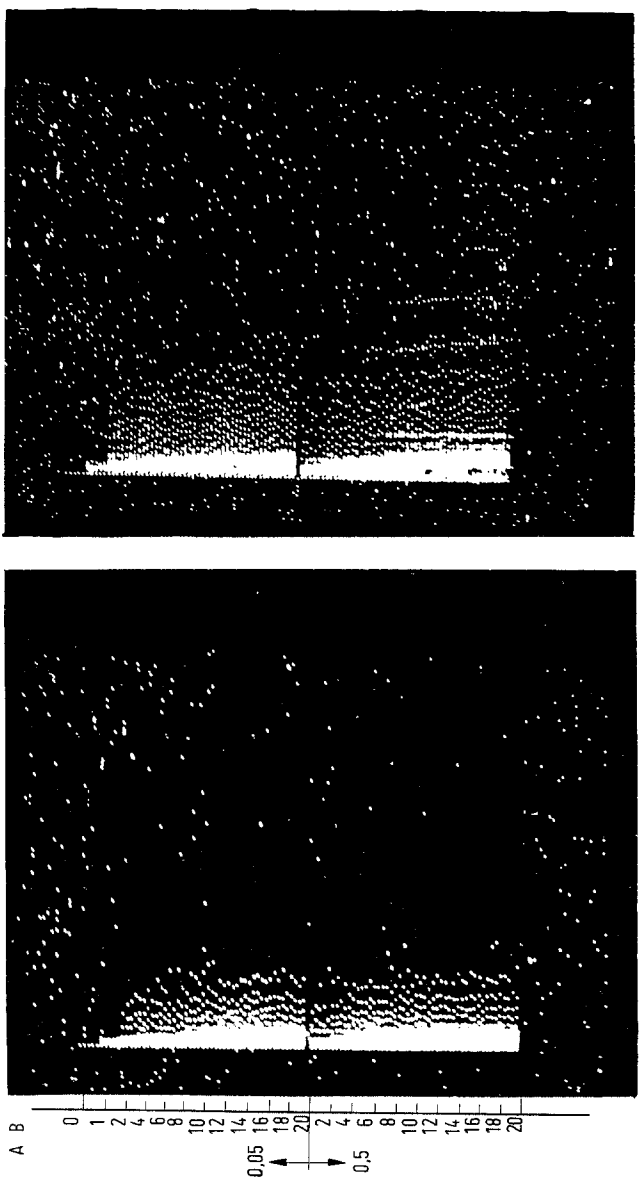

Fig. 8. *The effect of spinalizing on the temporal pattern of discharge evoked from a lamina 5 cell* by application of electrical stimuli to zone 2 of its receptive field. Left picture: decerebrate state; right picture: spinal state. Display and axes as in Fig. 6

the first response of the cell. As in the decerebrate state, there was a marked gradient of threshold and duration of firing. This gradient extended from the most excitable region of zone 2 where it joined zone 1 to its outer edges.

Zone 3: since this region was either submerged under the expanded zone 2 or became weak and indefinite, no response patterns could be produced.

Dorsal Column Stimulation

We have shown that cutaneous afferents with low mechanical or electrical thresholds have strong inhibitory as well as excitatory effects on lamina 5 cells. It is known that low threshold and not high threshold cutaneous afferents send axons up the dorsal columns (WALL 1961). It is also known that these dorsal column axons originate from dorsal root axons which send collaterals into the dorsal horn (TAUB and BISHOP 1965). It was therefore interesting to stimulate the dorsal columns to compare their effect with that of peripheral axons because this stimulation would bombard dorsal horns with very large volleys limited to axons originating from low threshold peripheral axons.

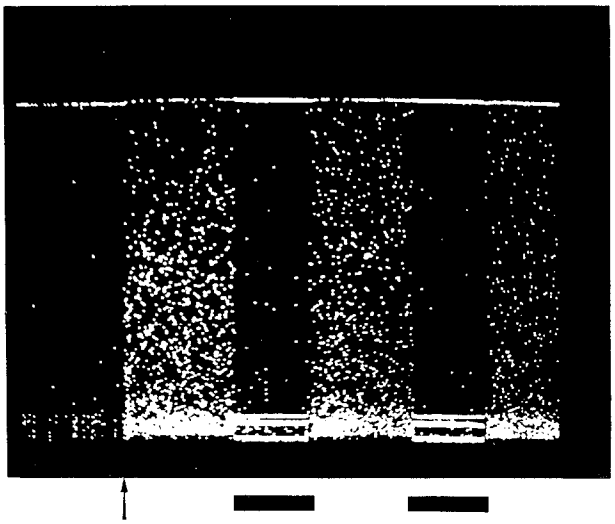

Fig. 9. *The effect of dorsal column stimulation on the response of a lamina 5 cell to mechanical stimulation.* As in Figs. 3 and 4, but bars showing time during which the thoracic dorsal columns were stimulated at 10/sec. Vertical scale about as in Figs. 3 and 4, duration of record 2.5 min

The experiment was carried out as follows: cells were located in the dorsal horn of decerebrate animals with the characteristics already described. Stimulating electrodes were placed on the ipsilateral dorsal column at T10. Single shocks were given to the dorsal columns with a gradually rising intensity. For every cell examined, a voltage was reached at which the cell responded. The latency of response at threshold was variable showing that the excitation was orthodromic and transynaptic. As the intensity of the voltage increased further, the cell responded with brief bursts of repetitive firing followed by prolonged periods of silence. The repetitive burst was shorter than that evoked by electrical stimulation of zone 2 and the inhibition was more intense and prolonged. The inhibition was extremely powerful and was sufficient to turn off the high frequency firing produced by damage to zone 1. An example of this is shown in Fig. 9. The cell was in L7 at a depth of 1.45 mm below the surface with its RF on the lateral sole of the foot. In the decerebrate state, there was low-level ongoing activity with intermittent bursting. A clip was attached to the skin in zone 1 and the cell began a

period of high frequency firing similar to those illustrated in Figs. 3 and 4. During this intense firing the thoracic dorsal columns were stimulated at 10/sec. Each stimulus evoked three impulses in the cell but after this almost all of those produced by the peripheral damage were abolished, The effect was due to descending impulses because the spinal cord could be blocked rostral of the stimulus point without abolishing the inhibition. The effect was not due to antidromic invasion of the cell because no signs of fixed early latency responses of the antidromic type were recorded from the cells. The descending axons were almost certainly located in the dorsal columns and were not in neighbouring white matter which might have been stimulated by spread of current from the electrodes on the surface of dorsal columns. For the one cell tested, the effect was abolished by a relatively superficial section of the dorsal columns with a cut which did not involve other white matter. For a few cells it was possible to find stimulus points and intensities on the dorsal columns which would inhibit without exciting the cells. The optimal frequency of stimulation was about 10/sec as with peripheral stimulation. The inhibition was sufficiently powerful and long lasting that, for some cells, dorsal column stimulation at 2/sec was sufficient to abolish firing produced by a clip damaging zone 1.

Dorsal Root Stimulation

Since it had been shown that low threshold fibres from skin at a distance from zone 1 would inhibit the cell, it was interesting to stimulate low threshold fibres in dorsal roots entering segments at varying distances from the segment containing the cell under observation. It had been shown previously that dorsal root stimulation was particularly effective in exciting dorsal horn cells (WALL 1960); here we wished to find if the excitatory dorsal roots were flanked by inhibitory roots. Cells were located with lamina 5 characteristics: their ongoing activity was measured. A stimulating electrode was placed on the surface of an exposed intact dorsal root as far as possible from the cord to avoid stimulus spread to other structures. A stimulus was applied at 2 V, 0.01 msec, 5/sec and the effect of the repetitive stimulation on the ongoing activity measured. The stimulating electrode was moved from root to root and same stimulus repeated. There was a wide band of at least 5 segments where this low level of stimulation produced an increase of activity in the cell. This effect was similar to that produced from zone 1 of the skin. Rostral and caudal to these excitatory roots, there were roots which produced a decrease of activity in the cell. The excitatory roots included the one supplying the segment containing the cell under observation and the root supplying the segment immediately caudal and several roots entering the adjacent more rostral segments. Thus, while the excitatory roots straddled the segment containing the cell, they had a rostral bias.

Discussion

We conclude from these results that low threshold cutaneous afferents influence lamina 5 cells to produce a receptive field with an excitatory centre and inhibitory surround. Excitation of the cells by low threshold afferents from the centre of their receptive fields is followed by inhibition. The excitatory receptive field attributed to the action of high threshold fibres is larger in area than that produced by low threshold afferents but smaller than the inhibitory field. Finally we

conclude that impulses descending from the brain stem of the decerebrate cat greatly enhance the activity of the inhibitory mechanism which is excited by the low threshold afferents.

Inhibitory components of receptive fields of dorsal horn cells have been described by TAUB (1964) and by HONGO et al. (1968). One can conclude on the basis of receptive field size and failure to respond to flexor reflex afferents that the majority of their cells were lamina 4 cells, which are not discussed in this paper. Many have not reported inhibitory areas either for dorsal horn cells or SCT pathways (WALL 1960; LUNDBERG and OSCARSSON 1961; ANDERSON 1962; GORDON and JUKES 1963; HORROBIN 1966). The reasons for not noticing the inhibition were probably either (1) the weakness of the inhibition in spinal preparations (2) that silent cells were often driven to activity by synchronous afferent volleys and these responses are difficult to inhibit or (3) that stimulation of peripheral nerves evoked impulses of geographically separate origins so that excitation preceded inhibition.

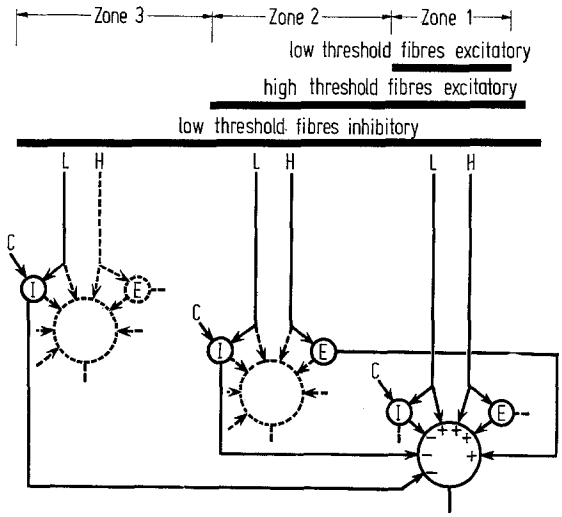

Fig. 10. *Diagram summarising a consistent model for the main results of this study.* The lines represent pathways, not axons; the arrows influences, not synapses; and the small circles systems, not cells. The large circle of the right represents the lamina 5 cell with respect to which the zones of receptive fields are defined. The other two large circles represent lamina 5 cells whose zone 1 RFs lie respectively in zones 2 and 3 of the cell on the right. Only those pathways influencing the cell on the right are fully drawn. E and I indicate excitatory and inhibitory systems and + and — excitatory and inhibitory influences on the cell in question. C indicates the descending influence on the inhibitory system. H and L indicate afferent fibres with high and low thresholds for electrical and mechanical cutaneous stimulation. The black bars represent superimposed skin areas, defined with respect to the type of fibre excitable in that area as labelled, which are the basis of the model interpretation of the zone observations

A model to summarise the results and to suggest one possible class of mechanisms is shown in Fig. 10. It is a flow diagram to show the direction of influences and is not to be read as an anatomical diagram. The lines do not represent axons. The low threshold afferents may end first on lamina 4 cells which in turn excite

lamina 5 cells (WALL 1967). Some high threshold afferents may terminate directly on lamina 5 cells (POMERANZ et al. 1968). The arrows do not represent synapses since we wish to avoid any implication of pre- or post-synaptic mechanisms. In previous speculations, the inhibition had been discussed in terms of presynaptic mechanisms which undoubtedly exist (ECCLES 1961; WALL 1964; MELZACK and WALL 1965), but it is now clear from the work of HONGO et al. (1968), that post-synaptic inhibition may also be involved. The two circles, I and E, do not represent single cells but rather inhibitory or excitatory systems.

The model is drawn to show the input-output relations of the right hand lamina 5 cell. The other two cells would have the centres of their RFs in zones 2 and 3 of the right hand cell. The low and high threshold afferents from zone 1 converge directly or indirectly onto the cell and excite it. The high threshold afferents are shown as exciting an auxiliary excitatory-facilitatory mechanism, E. This mechanism has four functions: 1) There is evidence for a very prolonged facilitation and excitation following the arrival of a volley in high threshold afferents except under barbiturate anaesthesia. 2) Within the period of repetitive discharge, there are fixed periods of higher frequency firing or "bands". These bands cannot be attributed to the arrival of groups of afferent impulses at differing conduction velocities because shortening the conduction distance does not produce a simple compression of the bands. It seems more likely that these periods are produced by some synchronised repetitive firing pattern in associated excitatory interneuronal circuits. 3) During periods of relatively high level ongoing activity, high frequency "bursts" sometimes appear among the more randomly occurring impulses. There is a fixed temporal pattern within these bursts. Since we observed trains of such bursts during the transition from the spinal to the decerebrate state and since such a transition is unlikely to change the pattern of arriving impulses, it seems reasonable to propose that the fixed pattern within the burst is formed by the repetitive activity of some excitatory interneuronal pool. 4) The excitation of a cell by stimulation of high threshold afferents within zone 2 of its RF had a longer latency than did excitation following zone 1 stimulation. Interpolated excitatory interneurons could explain this increased latency.

Next, the model proposes that the low threshold afferents trigger an associated set of inhibitory interneurons, I. This system would produce the silent period which follows the excitation generated in the right hand cell by stimulation of low threshold afferents in zone 1. Since it may be that lamina 4 cells conduct the excitatory effect from the incoming low threshold afferents to the lamina 5 cells, the inhibition might be expressed at any location from the terminals of the incoming afferents on the lamina 4 cells to post-synaptic effects on the lamina 5 cells. Such afferents do set off presynaptic changes in terminals (WALL 1958) and post-synaptic changes in lamina 4 and 5 cells (HONGO et al. 1968). It is further suggested that the I system also projects onto nearby and more distant cells in lamina 5. This projection is introduced to explain the purely inhibitory effects of low threshold afferents from zones 2 and 3. It will be seen that we are proposing a single inhibitory receptive field underlying and larger than the two excitatory receptive fields. The extension of the inhibitory RF beyond the edge of the excitatory RF creates zone 3. This is reminiscent of the analysis of goldfish retinal ganglion cell RFs by WOLBARSHT et al. (1961), who showed that the inhibitory surround of the

excitatory centre is in fact a wide area of inhibition on which is superimposed a smaller central excitatory area.

Finally the model suggests that impulses descending from the brain stem of the decerebrate cat activate the inhibitory system which is also triggered by low threshold afferents. SHERRINGTON and SOWTON (1915) showed that there was an exaggeration of cutaneous reflexes if the spinal cord was cut in a decerebrate animal. DOWNMAN (1955), DOWNMAN and HUSSAIN (1958), and LUNDBERG (1964) showed that impulses descending in the dorsolateral white matter were responsible for this tonic inhibition. In this paper we show that cord block decreases the various signs of inhibiting activity such as the silent period following zone 1 stimulation, and the inhibitions following zone 2 and 3 stimulation.

Similarly, the increase of ongoing activity, which was always observed following cord block, could be explained by disinhibition. The simplest explanation for the results of cord block is that descending impulses stimulate a local segmental inhibitory system which can also be stimulated by afferent volleys. It is not necessary to postulate that the descending impulses also influence a facilitatory system, although such a system is of course not excluded.

The functional advantage to various sensory systems of inhibitory surrounds or backgrounds has been repeatedly discussed in terms of improved resolution. Spatial and temporal resolution might be increased by the pressure of such inhibitory mechanisms associated with excitatory transmission. In addition, the dynamic range over which the system will signal the intensity of the stimulus may be extended by associating an inhibitory mechanism with the excitatory system. Where the inhibitory surround is placed asymmetrically about the excitatory centre, as in the present experiment, the receptive field may have properties which make the cell sensitive to movement in a particular direction. HONGO et al. (1968) have suggested that the marked asymmetry of the inhibitory fields for their cells might produce just such directionally sensitive cells. We have seen no signs of this in the cells reported here but the effect is difficult to test because a brush moved *against* the direction in which hairs lie is mechanically far more effective than brushing hair *in* that direction. Whatever may be the functional significance of the inhibitory mechanism, it is evident that the inhibition operates most effectively against the effects of light mechanical stimuli. Intense stimuli generate excitation which overwhelms the inhibitory effects. The firing patterns of the cells and hence the resolution of the transmission system are variable and are determined by at least two converging influences, the descending impulses and the pattern of afferent impulses in low and high threshold afferents.

We have described the results in terms of responses to increasing strengths of mechanical and electrical stimuli. There are striking similarities in the receptive fields whichever method is used. For example, low level mechanical and electrical stimulation both produce inhibition in zone 2 while higher levels produce excitation. We wish to propose that the reason for these similarities is related to fibre diametre. The extensive recent work of HUNT and MCINTYRE (1960), IGGO (1968), and BURGESS and PERL (1967) have described the many specific types of peripheral mechanoreceptor. It is true that light mechanical stimuli activate fibres of all diametres but it is also true that more and more small fibres are recruited by more intense stimuli. The ratio of active beta fibres to delta fibres drops as the stimulus increases from brush to pressure (SIMINOFF 1965). Myelinated nociceptors occupy the lowest part of the delta-gamma range (BURGESS and PERL 1967). It seems clear that, while hair movement and touch excite both A beta and A delta fibres, pressure adds mainly activity in fibres with conduction velocities below

50 m/sec (SIMINOFF 1965; BURGESS and PERL 1967). Within this group of smaller fibres, there is a further extension of the relationship of the smallest fibres having the highest mechanical thresholds (BURGESS and PERL 1967).

Similarly, for electrical stimuli applied through needles in the skin, the ratio of small to large active fibres increases with stimulus intensity. The actual intensity at which the different fibre groups are recruited depends not only on the fibre diametre but also on the proximity of the fibres to the electrodes. Thus the afferent volley produced by a low level stimulus may contain impulses in some small fibres which happen to be particularly close to the electrodes. However, as the stimulus increases the proportion of impulses in small versus large fibres will increase. This is shown in Fig. 1 and can also be implied from the fact that the low level stimuli did not produce pain in man while the higher ones did. This psychological result correlates with the report of COLLINS et al. (1960) who showed that pain was only elicited when the smaller diametre fibres were included in the afferent volley.

We propose therefore that as the spinal cord receives afferent volleys containing a larger and larger proportion of impulses in smaller fibres, the lamina 5 cells respond with increasing excitation and facilitation. In contrast, when the afferent volleys contain a high proportion of impulses in the larger low threshold afferents, inhibitory mechanisms became active in the cord. The inhibitory effects spread more widely in lamina 5 than the excitatory ones. The reformulation of the results in terms of fibre diametre rather than threshold allows a consideration of the relation of this paper to that of MELZACK and WALL (1965). They speculated that afferent impulses which triggered pain reactions passed through a "gate control" mechanism whose effectiveness was set by the relative balance of active large versus small afferent fibres and by impulses descending from the head. This paper supports some of their speculation and extends it by showing that the spatial origin of the different types of fibre is a crucial factor in determining the central effect of the afferents on any particular cell. It is important to stress that we do not propose any particular significance to fibre diametre *per se* but only that this factor appears to be correlated with some functional peripheral or central specialisation. Further, there is no evidence that lamina 5 cells do in fact trigger pain reactions but, since they are excited by high threshold afferents, they remain possible candidates as transmitters to central pain mechanisms. MELZACK and WALL (1965) suggested that the actual mechanism of the gate control might be exerted presynaptically on the terminals of afferent fibres. With the work of HONGO et al. (1968) and others it has become much less likely that this is the only mechanism. In this paper, while we can say nothing of mechanisms, we do conclude that the output of lamina 5 cells depends on the interactions set off by incoming impulses from low and high threshold fibres, that there is a relationship between these contrasting effects and fibre diametre and that the interactions depend on the spatial origin of the fibres and on impulses descending from the head.

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Prof. P.D. WALL
M.R.C. Cerebral Functions Research Group
Department of Anatomy
University College
Gower Street
London, W.C. 1