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The Presence of Ineffective Synapses and the Circumstances which Unmask Them [and Discussion]

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The presence of ineffective synapses and the circumstances which unmask them

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In this paper, we shall show that there are substantial numbers of nerve terminals which are normally ineffective. In the intact animal, occasional signs of the postsynaptic effectiveness of these fibres can be seen under conditions of optimal spatial summation or increased excitability or decreased inhibition. If the normally functioning afferent nerve fibres are blocked or cut, some of the previously ineffective fibres immediately establish an effective drive of cells. If the normal afferents are cut and allowed to degenerate, large numbers of cells begin to respond to new inputs. The presence of ineffective synapses in the adult offers an alternative to sprouting or the opening up of polysynaptic pathways as a possible mechanism to explain plasticity of connections in adult brains.

When searching for signs of plasticity, it is convenient to examine those regions of sensory afferent systems in which the receptor surface is mapped. The spatial separation of information on the receptor surface is preserved at various stages of the central pathways of the visual, auditory and somatosensory systems. Here we shall examine three locations in the somatosensory system; the spinal cord, the dorsal column nuclei and the thalamus. In each of these relay stations, the body surface is mapped in a clear cut and predictable way which varies little from animal to animal. This predictability of the normal pattern means that deviations produced by new or unmasked connections can easily be detected. The meaning of a map on a single cell level is that afferents must run from a particular location on the body surface to excite cells at a particular location in the relay station. When a cell has a receptive field on the skin and responds monosynaptically to axons originating in that area, it is necessary that axons must stream from that skin area to terminate on the cell. First we shall ask if the terminal arborizations of arriving fibres are restricted just to the cells which they are known to excite or if they have, in addition, more widespread terminations which might be called into action under special circumstances. We shall ask this question in the spinal cord where the map of one leg is spread over several centimetres and therefore where out of place afferent terminals can be detected more easily than in the other two structures where the map is contained within millimetres.

1. What is the actual anatomical distribution of afferent fibres?

Most anatomists have concentrated their studies of terminal degeneration following dorsal root section on the segments close to the entry point of the cut root. It is here that the bulk of the degeneration occurs and, as we shall see, it is in this region that cells respond monosynaptically to impulses arriving over a particular dorsal root. However, some anatomists have reported

that there is a diffuse innervation of dorsal horn for many segments away from the entry point (Liu 1956; Sprague 1958; Szentagothai 1964; Imai & Kusama 1968). In their paper, Imai & Kusama showed that section of the L4 dorsal root results in degeneration in dorsal horn extending from T11 to S1. In view of this reported extensive distribution of roots, we decided to reinvestigate the matter using physiological methods which would allow us to discover the distribution of the terminal arborizations of single fibres (Wall & Werman 1976). In adult cats, we stimulated within the spinal cord with tungsten microelectrodes. This produced impulses in nearby afferent fibres which ran antidromically to dorsal roots where we recorded them.

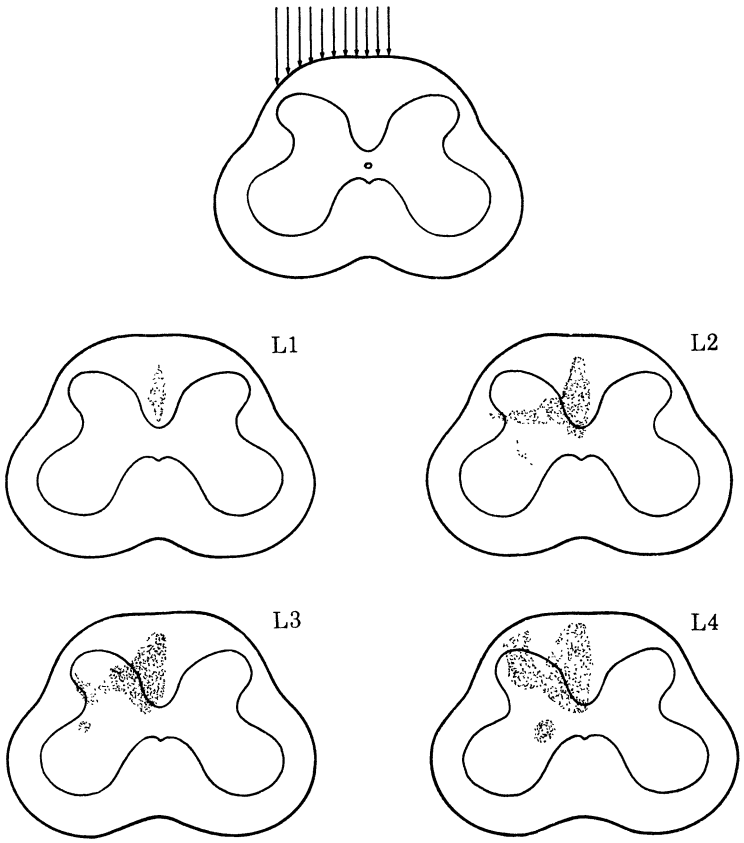

FIGURE 1. The region of termination of afferents from filaments of the L1, 2, 3 and 4 dorsal roots in dorsal horn grey matter of the junction of the L7 and S1 segments. The arrows indicate the direction of penetrating stimulating microelectrode tracks separated by 200 μm. The dotted areas indicate the region rom which the stimulating electrodes evoked antidromic spikes on the distant roots when pulses of 25 μA strength and 50 μs duration were applied. (From Wall & Werman 1976.)

In this way, it was possible to follow the entire course of bundles of fibres or single fibres all the way from their entering dorsal root to their terminations. It was found that all filaments examined in the L2, 3 and 4 dorsal roots contained axons which projected at least as far as the S1 segment. The course of single fibres was followed to their apparent terminals. Thresholds, latencies and relative refractory periods were measured for single axons. These measurements confirmed that continuous axons ran from dorsal roots to distant segments. The majority of fibres with long range central arborizations were shown to have normal receptive fields in the dermatome of their parent dorsal root. Not all entering fibres send off these long range branches but we found that 15 of 80 consecutive single axons located in the L2 dorsal root sent branches

at least 5 segments caudally to the S1 dorsal horn. In summary, all fibres arborize in the segments immediately adjacent to their entry point but collaterals are also sent in decreasing numbers to more and more distant segments up to at least 5 segments rostrally and caudally (figure 1).

2. What anatomical distribution of afferents is needed to generate the physiological receptive fields of cells in the spinal cord

(*a*) *Overall map*

Each dorsal root subserves its dermatome. Within the spinal cord, cells in a particular segment respond to the dorsal root of that segment and their receptive fields on the skin lie in the segmental dermatome (Wall 1960; Brown & Fuchs 1975). Within each segment, the distal part of the dermatome is represented medially and the proximal part laterally. There is an overlap between neighbouring dermatomes but this never extends more than two segments rostrally or caudally. If all lumbar sacral dorsal roots are cut except for one, no cells are found responding to natural stimulation in an area two to three segments rostral to the intact root (Basbaum & Wall 1976). Therefore it would seem that the physiological map is explained by the arrival of afferents over the nearest dorsal root and over the two adjacent roots.

(*b*) *Single cells*

We can ask the same question of single cells as we have just asked of the whole segment. Over what route do the afferent fibres run from the peripheral receptive field to make contact with a single cell? The most suitable cells for answering this question are cells in lamina 4 which have a receptive field responding monosynaptically only to low threshold mechanoreceptors attached to myelinated afferent fibres (Wall 1960; Fetz 1968; Pomeranz, Wall & Weber 1968; Brown 1971). This type of cell has a small receptive field (r.f.) limited to less than one toe if on the distal foot or less than 1 cm^2 on the leg. When hair movements or light pressure are used to excite the cells, the edge of the excitatory r.f. is abrupt and does not merge into an inhibitory surround. The size of the r.f. is remarkably stable when the cell's excitability is varied. If excitability is increased by post-tetanic potentiation, by strychnine, by heating of the skin or by removal of descending inhibition by reversible cold block of thoracic cord in decerebrate animals, there is no detectable change in the size of the r.f. (Wall 1960, 1967; Brown 1971). Similarly, there is no change if cell excitability is decreased by barbiturates or by asphyxia or by pyramidal tract stimulation or by brain stem stimulation (Wall 1960; Fetz 1968). High intensity pressure stimuli outside the receptive field fail to excite the cell and either fail to produce an inhibition or produce a weak inhibition with prolonged delay. If recordings are made from a single cell and dorsal roots are progressively cut, there is no change whatsoever in the receptive field until a small fraction of a particular dorsal rootlet is sectioned, whereupon, the entire receptive field disappears (Wall 1960). This last observation was repeated with reversible anodal blocking of dorsal roots (Merrill & Wall 1972). Taken together, these facts lead to the conclusion that these cells are completely dependent for their monosynaptic drive on a group of afferents running in a microbundle in a nearby dorsal root. Pressure stimuli applied to areas outside the r.f. fail to show any monosynaptic excitatory or inhibitory connections arriving over remote dorsal roots.

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Conclusion from 1 *and* 2

There is evidently a mismatch between the observed anatomy which shows a widespread distribution of long range terminal arborizations and the observed physiology which shows that cells' monosynaptic receptive fields are formed by impulses arriving over nearby roots.

3. Are there conditions under which latent connections produce a postsynaptic effect in the intact animal?

(*a*) *Spatial summation*

Cells were selected of the small area lamina 4 variety discussed above. Two nearby dorsal roots were left intact but mounted on a series of electrodes in such a way that they could be either stimulated or blocked by anodal polarization (Merrill & Wall 1972). Cells were found which responded monosynaptically to stimulation of both roots. When one of the two roots was blocked, the response to the natural receptive field completely disappeared even though the other root was still transmitting (figure 2). When dorsal roots were divided into a series of rootlets it was regularly found that electrical stimulation of many neighbouring rootlets, one by one, resulted in a monosynaptic response of the cell. However, only one of these rootlets contained the afferents responsible for the receptive field. Once this single rootlet had been cut, no natural stimulation resulted in firing of the cell even though electrical stimulation of the neighbours showed that they contained excitatory fibres capable of firing the cell. Figure 3 shows

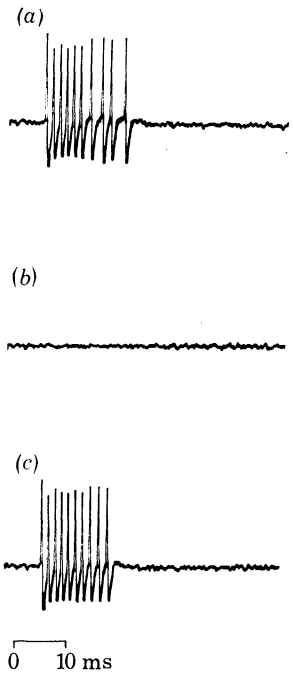

Figure 2. (*a*) Response of a lamina 4 dorsal horn cell with a small brush touch receptive field on the foot to electrical stimulation of its receptive field. (*b*) Anodal block of one dorsal root abolished the response of the cell. In spite of this disappearance of the peripheral receptive field, stimulation of the neighbouring dorsal root still evoked a monosynaptic response in the cell. (*c*) Reappearance of the cell's response following removal of the anodal block. The small differences of response between *a* and *c* are consistent with the response variations seen between succeeding responses in the normal intact animal. (From Merrill & Wall 1972.)

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this phenomenon in 4 cells. In each case, all the afferents capable of exciting the cell following pressure stimulation of the skin ran in one rootlet of the L7 dorsal root but 2–3 rootlets in the rostral and caudal direction contained fibres capable of firing the cell if they were electrically stimulated. It was concluded that there was a highly efficient group of afferents contained in one rootlet but that neighbouring rootlets contained afferents which also terminated on the cells but which were relatively ineffective and only excited the cells when electrical stimuli of the root produced a synchronous volley which would optimize spatial summation.

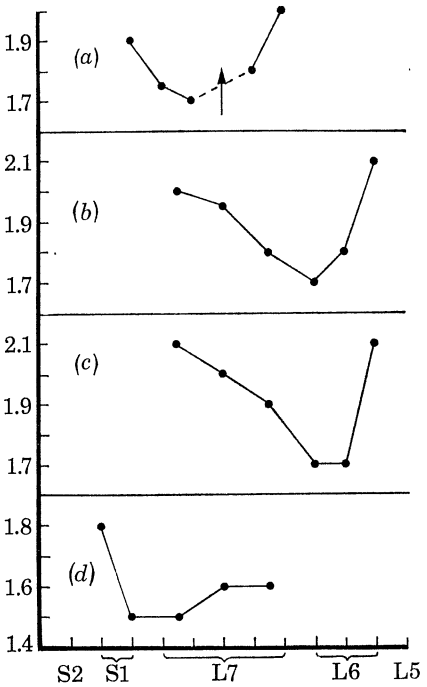

FIGURE 3. Latencies for four dorsal horn cells to stimulation of fractions of lumbar and sacral dorsal roots. The stimuli were applied to the roots as shown along the horizontal scale. The vertical scale in each case shows the corresponding latencies (in ms). The arrow in *a* indicates that stimulation of middle rootlet in L7 failed to drive the cell. (From Merrill & Wall 1972.)

(*b*) *Decerebrate-low spinal animals*

In work to be published by Devor, Merrill & Wall, we have repeatedly checked in the S1 segment to see if we can discover cells responding to electrical stimulation of upper lumbar dorsal roots since we know that these roots project into this segment (Wall & Werman 1976). We chose the decerebrate-low spinal animal for this study since we know that the cells of lamina 4 and 5 exhibit their highest excitability in this preparation (Wall 1967). Except for a special group of cells in the extreme lateral edge of the grey matter, in the great majority of animals we found no cells responding to the distant root in less than 10 ms and very few with longer latency response. We can conclude that we can find no signs of monosynaptic post-synaptic excitation or inhibition in the great majority of cells in a segment where we know long range afferents terminate.

However, in some animals, small numbers of cells were recorded, mainly in lamina 5 but some in lamina 4, which did respond in less than 8 ms after stimulation of upper lumbar dorsal roots. The response of these rare cells was of great interest because they give a clue as to why

more such cells are not observed in most animals. The cells had normal r.f.s in their own segmental dermatome. Lamina 4 cells had small receptive fields on the foot or toes which responded to brush and touch and did not increase their discharge if the area was pinched. Lamina 5 cells had larger brush-touch fields on the same area of skin and a somewhat larger pressure field. When a filament of the L3 dorsal root was stimulated, these cells responded with one or two spikes 2–8 ms after the stimulus. The latency of the first spike varied by less than 1 ms on repeated stimulation and would follow at more than 10 Hz. All roots were intact except for one rootlet of L3. There were no signs of any excitatory field outside the distal part of the S1 dermatome. We were examining cells which were extreme examples of those which we had previously seen (Merrill & Wall 1972). Cells responded to electrical stimulation of a distant dorsal root but natural stimulation in the dermatome of that dorsal root completely failed to evoke a response. The interest here was the additional fact that in certain rare cells light brushing or touch anywhere on the leg, foot or toes outside the excitatory receptive field completely abolished the response to the distant root. While this gentle stimulus completely inhibited the effects of distant dorsal root stimulation, it produced no effect on the response from the cells natural receptive field or on the cells ongoing activity. Evidently the postsynaptic excitation from the long range afferents was specifically susceptible to inhibition produced by minor peripheral stimuli which did not influence the normal segmental input and its postsynaptic effect. If in these rare cells a minor increase of the afferent barrage was sufficient to turn off the effect of distant roots, it is reasonable to speculate that the ordinary ongoing afferent barrage or tonic cord activity might be sufficient to suppress the activity of most of the long range afferents so that their postsynaptic effect is normally not observed.

If we wish to propose that excitation by long distance afferents is normally held inhibited by an active process which is itself dependant on the segmental afferent barrage, then there are two types of experiment which are suggested. Cutting the afferents which normally excite the cell and inhibit the excitation produced by long range afferents should abolish the normal r.f. and unmask the effect of long range afferents. We shall discuss this below. A second approach is to search for a pharmacological method to abolish the inhibition while leaving the excitation intact. We believe that we have achieved this by adrenaline at relatively high doses. In decerebrate-low spinal animals, adrenaline is infused in dextrose saline at the rate of 0.25 mg kg^{-1} h^{-1}. This produces an animal with a blood pressure 120–180 mmHg (16–24 kPa) approximately twice that found in long term decerebrate preparations. We do not believe that the results to be reported are the simple consequence of the high blood pressure since such pressures are frequently recorded soon after decerebration without the aid of a vasoconstrictor and yet, as we have said, the L3 dorsal root does not excite cells in the S1 segment. When the cat has received 1–2 mg of adrenaline and more than 3 h have passed since the decerebration, the S1 segment is searched for cells responding to the distant dorsal root. In these circumstances, every electrode penetration encounters one or more cells usually in lamina 5 but occasionally in lamina 4 which are responding at a latency of less than 8 ms to the distant root stimulation. In this state of extreme excitability, we do not observe the highly specific inhibition by which the long range afferent effect is turned off. Here the inhibitions, which remain, affect both the input from the cells' natural receptive field and its response to the distant afferents and its ongoing activity.

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Conclusion from 3

There are special circumstances in the intact animal when ineffective afferents may produce postsynaptic excitation but in the usual physiological preparations, these effects are not observed.

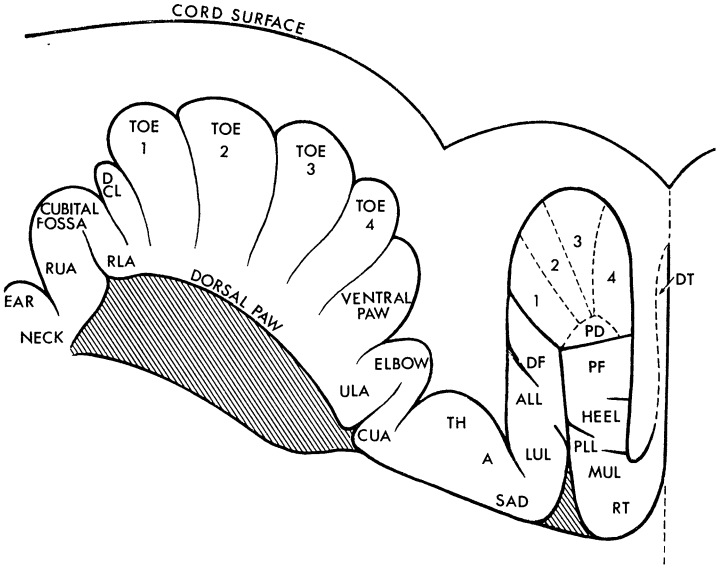

FIGURE 4. A 'felinculus' of the body surface representation within the gracile and cuneate nuclei. Abbreviations from left to right: RUA, rostral upper arm; RLA, rostral lower arm; DCL, dew claw; ULA, ulnar lower arm; CUA, caudal upper arm; TH, thorax; A, abdomen; SAD, saddle and lumbar back; LUL, lateral upper leg; ALL, anterior lower leg; DF, dorsal foot; PD, foot pad; PF, plantar foot; PLL, posterior lower leg; MUL, medial upper leg; RT, root of tail; DT, distal tail. Cross hatching indicates areas where deep pressure is necessary to fire the cells. (From Millar & Basbaum 1976.)

4. Does abolition of a cell's normal input produce immediate unmasking of ineffective afferents?

To answer this question, we shall turn to the dorsal column nuclei. In the cluster region of these nuclei, the cells are excited by primary afferents originating in the skin. Cells respond to brushing of the hair or touching the skin in a small restricted r.f. The cells are arranged in an exact and repeatable somatotopic map. To use these maps for quantitative purposes it was first necessary to remap the normal intact nuclei (Millar & Basbaum 1975). Figure 4 shows the overall map. These maps were produced in intact adult cats in which the nuclei were mapped with tungsten microelectrodes, under barbiturate anaesthesia. A single transverse plane was mapped with a grid of recording points separated by 100 μm in each direction. At each grid point, the body surface was brushed and the point was assigned a body location depending on the response of the cells in that area. Figure 5 shows a distribution for the normal animal, of these points, for the hind quarters which were divided into 5 areas: toes 42 %, foot 17 %, anterolateral leg 18 %, postero-medial leg 8 % and finally trunk (abdomen and lumbar back) 19 %. These figures are based on 15 normal intact nuclei with a total of 672 recording points.

Next a partial deafferentation of one hind leg was carried out by cutting all dorsal roots on one side caudal to L3 with the exception of the S1 dorsal root (Millar, Basbaum & Wall 1976). The dorsal column nuclei were then mapped over a period of 12 h following the root section.

The results are shown in figure 5. As is to be expected, a substantial number of the recording grid points within the nucleus gracilis failed to respond to peripheral stimulation. At these points, cells with ongoing activity were recorded and this activity often occurred in bursts. This non-responding area made up a total of 33 % of the nucleus. Much more surprising is the fact that the trunk area has expanded from its normal area of 19 % up to 28 %. An increase of the foot area also occurred. Some of the remaining responding cells had the usual responses but there were also cells detected with a series of abnormal responses. About one third of the cells required rapid hair movement rather than the usual slow movement before they would fire.

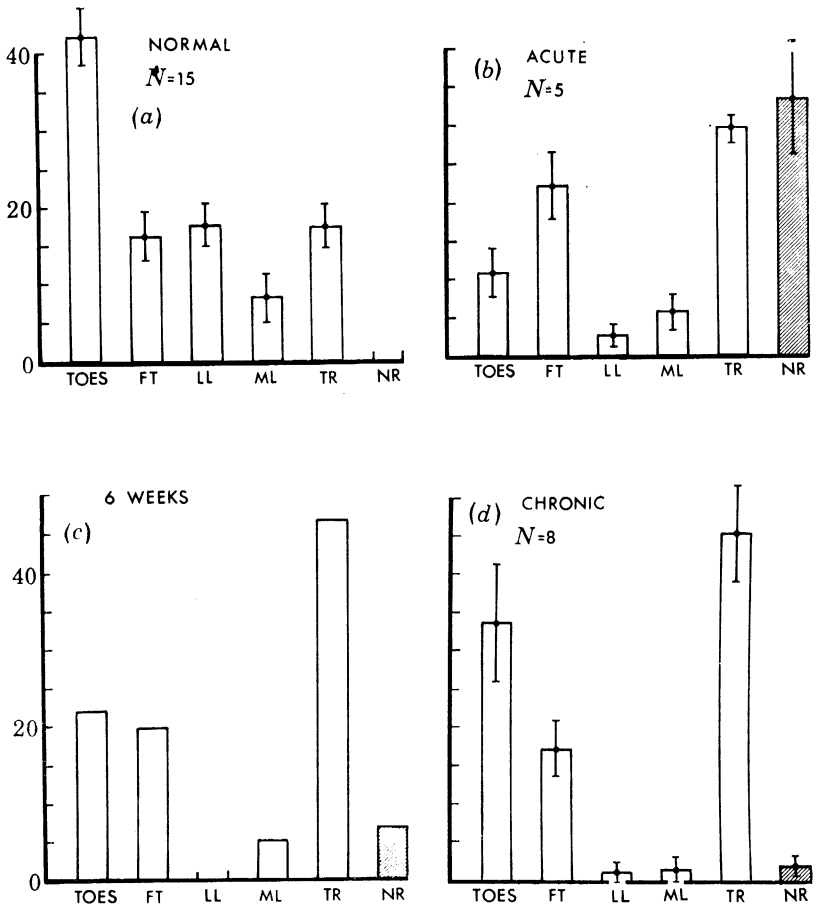

FIGURE 5. Graphs of the percentage distribution of the different body regions in a transverse 'map' across the caudal gracile nucleus. For each map, the size of a particular region was calculated from the number of grid points where cells had receptive fields within the region. These grid point totals were then converted to percentages and then averages were calculated from a series of maps in different animals. For *a*, *b* and *d* the number of maps from which the graphs have been calculated is indicated as *N*. *c* is taken from a single map.

In each graph the height of the bar representing a particular region indicates the mean percentage size of this region in the nucleus (in the plane of the map). The standard deviation of the size of each region is shown. The regions are indicated on the ordinate: TOES includes all grid points where cells with receptive fields on individual toes or the foot pad were found. FT includes grid points with field on the foot and heel. LL represents the whole antero-lateral leg. ML the postero-medial leg, perineum and groin. TR represents the trunk as far as the caudal borders of the rib cage, TH the thorax rostral to this level. NR represents spontaneously active but non-driveable cells. *a* shows the distribution of the normal, intact gracile. *b* shows the distribution in the nucleus immediately after all dorsal roots caudal to L4 except S1 had been cut. *c* shows the distribution in a single animal with S1 intact 6 weeks after rhizotomy. *d* shows the distribution in cats with S1 or L7 intact which survived at least 8 months between operation and mapping. (From Millar, Basbaum & Wall 1976.)

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Some of the receptive fields were abnormally small. Habituation of response to stimuli repeated at 1 s intervals was seen in some cells whereas this was never seen in a normal nucleus. The most striking abnormality was the appearance of cells with two clearly separated receptive fields. Five of these cells were encountered in a total of 217 recording points. One receptive field was on the foot and one on the abdomen. Such cells have never been reported in intact preparations. We concluded that certain cells had acquired new connections which were unmasked by cutting the afferents which normally drive them.

Since we suspected that there was an immediate change in the representation of the abdomen, we proceeded to study the acute effect of cutting all dorsal roots to the hind leg by sectioning all roots caudal to L3 (Dostrovsky, Millar & Wall 1976). We mapped 7 such animals with a total of 326 recording points. The abdomen and web of the upper leg were represented in 27 % of the area of the intact nucleus. On deafferentation, this expanded to occupy 56 % of the nucleus so that cells which had been in the leg area began to respond to abdominal stimulation. Again some of these newly connected units required flicking of the hair rather than slow brushing and some habituated. The latency of response following electrical stimulation of the abdominal receptive field was measured for 122 cells in the intact animal and in the deafferented animals. The distribution of these latencies was the same in the two groups of animals. We can conclude that there are large numbers of cells in the leg area of the nucleus which begin to respond to abdominal stimulation after the afferents have been cut. Furthermore it is apparent that at least some of these newly responding cells are monosynaptically connected to the afferents as are the normal cells.

Obviously it was necessary to be quite certain that individual cells had switched their receptive fields and that the apparent switch was not produced by recording techniques in which the response of some cells was buried in the noise of the ongoing activity of the intact nucleus. Furthermore, it was possible that the cells responding to the abdomen in the deafferented nucleus were silent in the intact state and were turned on by the deafferentation. If these two possibilities were the case, there would be no switching of connections but simply an unmasking of previously unnoticed or silent cells. We resolved these questions by studying single units before, during and after reversible cold blocking of the lumbar enlargement using the technique developed to study descending connections (Wall 1967). Single cells were isolated and their receptive fields were studied for a period of 30 min to be quite certain that response stability was present. Then small Ringer–Locke ice cubes were placed on the exposed L4 segment of the spinal cord and maintained until cold block of at least the dorsal columns was completed. During the block, the cord is in contact with cold saline formed by the melting of the cubes. A total of 40 units were studied; 19 with receptive fields on the foot failed to respond to any peripheral stimuli during blockade of the lumbar dorsal columns. Two units had receptive fields on the abdomen and these remained during the block. Eight units had receptive fields on abdomen and upper leg and lost the leg part of their receptive field. However, 11 units were studied which in the intact animal had brush receptive fields on the foot. When the cord was blocked at the L4 segment, the receptive fields moved from the foot onto the abdomen. For these 11 cells there was no doubt that individual cells switched their input as soon as the block was established. We can conclude that certain cells reveal their connection to alternative afferents as soon as their normal afferent drive is blocked.

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5. Are there chronic changes which increase the effectiveness of alternative afferents?

We have now four series of experiments completed which suggest that the answer to this question is yes.

(*a*) *Thalamus*

Wall & Egger (1971) removed the nucleus gracilis on one side in adult rats. Subsequent mapping showed that the hand-arm area of the VPL nucleus in the thalamus extended into the area previously supplied from the hind leg. This spread was first observed 3 days after the nucleus had been removed. If VPL was mapped 1 or 2 days after nucleus gracilis was taken out, no expansion of the arm area was seen. The change seemed to be complete by 10 days.

(*b*) *Partial deafferentation of spinal cord*

In 23 adult cats Basbaum & Wall (1976) cut all dorsal roots caudal to L3 with the exception of S1. When such a preparation was examined immediately or one day after the roots had been cut, there were no cells in the L4–5 region of the dorsal horn which responded to natural stimulation of the leg. Beginning at 1 week and complete by 1 month, cells began to appear in this segment which responded either to the dermatome of the one remaining root or to skin supplied by the more rostral roots. The properties of these newly connected cells were abnormal in six ways. (1) The location of the receptive field of the cells was characteristic of either the S1 dermatome or of segments rostral to L4. (2) Twenty-six cells were located with double receptive fields, one on the leg and one on the abdomen. (3) The size of the r.f. was sometimes very small. (4) There was less convergence from high threshold afferents than is normally observed. (5) Associated inhibitory fields were rare. (6) Habituation occurred. In addition to these single unit features, it was shown that slow waves evoked from the distant dorsal root in the chronically deafferented animal were very much increased over the acutely deafferented animal.

(*c*) *Partial deafferentation of the dorsal column nuclei*

The results of this are shown in figure 5 (Millar *et al.* 1976). It is obvious in comparing the acute and chronic animals that there has been a further increase of the number of recording points responding to the abdomen and a decrease in the area where no responses to peripheral stimulation occurred. There had of course been an anatomical shrinkage of the nucleus due to the deafferentation but this amounted to only 16%, not sufficient to explain the shifts of response. From 350 recording points, 50 cells were detected with dual receptive fields. Of the responsive cells, there was a decrease in the number of cells which required rapid flicking of hair before they would respond and a decrease in the number which habituated by comparison with the acutely deafferented animals. Evidently here was a chronic increase not only of the number of cells that responded to new inputs but the strength of the synaptic connection increased with time.

Similar results were obtained for the expanded abdominal area in animals where all dorsal roots to the lumbar enlargement had been cut.

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Discussion

There are three classes of mechanism which would produce a new response in a cell following the loss of the input which normally drives the cell. The first is sprouting of intact afferents to occupy the space left by the degeneration of some other afferents. The second is the opening up of polysynaptic pathways which have been held inhibited by the normal input. The third is the unmasking of existing contacts which were normally ineffective. We have presented a *prima facie* case for the last but, of course, this does not mean that the other two mechanisms may not also operate. The immediate and reversible appearance of new receptive fields following cold block excludes any growth processes as an explanation. The fact that the latency of response of new connections was the same as that of the previous intact connections excludes the use of polysynaptic pathways as an explanation.

While unmasking of existing monosynaptic connections must be the explanation of the immediate changes, we still have to explain the chronic changes which exaggerate the immediate effect. Over a period of days and weeks, the number of responding cells increased and the efficiency of the new connections increased since the latency of response decreased, the amount of habituation decreased, and the stimulus following frequency increased. There are three locations where chronic changes might be taking place. The terminals of afferent fibres themselves might change in response to the degeneration of their neighbouring afferents. This could vary from a simple swelling of the boutons to frank sprouting. Transynaptically there are the well known changes resulting from deafferentation. It is possible that the cell surface developes a denervation hypersensitivity. The dendrites may shrink drawing existing distant contacts into a more favourable location for firing the cell. Finally we must consider the possibility of changes in inhibitory interneurons. There is clear evidence in the cord, dorsal column nuclei and in the thalamus that inhibitory interneurones exist. The cutting of the input will remove one of the drives to these cells so that there can be an immediate disinhibition. However, such cells may have an ongoing activity which will maintain some inhibition. These cells too will undergo atrophy as a result of the loss of their afferents and so there may be a further chronic decrease of inhibition and an increase of unmasking.

We have presented evidence that existing afferents take over the drive of cells following the loss of other afferents at three locations in the somatosensory system. Recently Berman & Sterling (1976) have shown an immediate unmasking of the effects of certain optic nerve terminals in the cat superior colliculus which are held inhibited by a drive from the occipital cortex. We do not wish to imply that afferents grow into the nervous system in a diffuse scattered fashion. There is overwhelming evidence that the pattern of growth of arriving afferents is highly specified and determined. However, the evidence does suggest that the anatomical extent of the terminals of cutaneous afferents is more extensive than is required to form the observed receptive fields. The edge of a receptive field must evidently be formed by the physiology of the system and therefore the size or even the location of a receptive field can be changed by shifts of ongoing activity. Nor do we wish to imply that the arrangement we have shown in 3 locations in the somatosensory systems will apply to all locations. Clearly the embryo in differentiating to the specified adult state has the alternative strategy of either withering away those branches of axons which fail to reach the correct target or of physiologically suppressing their postsynaptic effect thereby retaining a degree of plasticity.

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Discussion

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With regard to the effects of drugs, evidence exists which shows that some 'ineffective' inputs to neurones can be revealed by pharmacological techniques. Zieglgansberger & Herz (*Expl Brain Res.* **13**, 111 (1971)) showed that the application by iontophoresis of an excitant amino acid such as glutamate could increase the receptive field of dorsal horn neurons and Sillito (*J. Physiol., Lond.* **250**, 287 (1975)) has shown that by blocking inhibitory inputs to visual cortical cells with bicuculline, applied by iontophoresis, a previously ineffective excitatory input can be made to drive a neuron. Gent & I (unpublished experiments) have observed that ventrobasal thalamic neurones in the rat, which normally respond to the movement of one whisker, may respond to several whiskers following the iontophoretic application of glutamate or aspartate. The use of this type of technique might possibly reveal the presence of connections such as those Professor Wall has described.

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