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ACTIVITY PATTERNS OF CEREBELLAR CORTICAL NEURONES AND CLIMBING FIBRE AFFERENTS IN THE AWAKE CAT

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SUMMARY

1. Glass-insulated tungsten micro-electrodes were used to record from single neurones in the intermediate zone of the cerebellar cortex of cats in a state of quiet wakefulness.

2. Two hundred and seventy Purkinje (P) cells were recorded extracellularly, 95 % of which displayed an irregular tonic discharge at rates between 19 and 95/s (over-all mean 44/s), including complex spikes (c.s.) which occurred at 1·0–2·5/s (over-all mean 1·5/s). The remaining cells discharged c.s. at the usual rate but only one or two simple spikes (s.s.) per minute. C.s. of spike plus wavelet and of multi-spiked type were present in approximately equal numbers of cells.

3. Presumed climbing fibre-e.p.s.p.s were recorded from fifty-six P cells and occurred both singly and in groups of two to six e.p.s.p.s at an intra-group frequency of about 500/s. The cells giving rise to the c.f.s therefore discharge propagated impulses both singly and in short bursts as previously reported for anaesthetized animals. A single e.p.s.p. can give rise to more than one spike in the multi-spiked type of c.s., and probably to a complete c.s. event.

4. Following spontaneous c.s. the interval to the next s.s. varied from 8 to 600 ms. There was an inverse correlation between duration of the post-c.s. interval and the rate at which s.s. were discharged in the preceding 100 ms. The duration exceeded the mean s.s. interval provided s.s. rate was less than 40–50/s, and the post-c.s. interval would then constitute a real interruption of s.s. discharge.

5. When the superficial radial (s.r.) nerves were stimulated with single shocks too weak to produce a behavioural response changes in discharge pattern were detected in eighty-eight of 151 P cells tested. The initial responses were almost always excitatory and consisted in seventy-two cells of a c.s., in eleven of a c.s. preceded by a brief increase in s.s. and in two cases of a s.s. discharge alone. The spino-olivo-cerebellar paths responsible for the c.s. showed transmission characteristics similar to those reported for animals anaesthetized with barbiturates.

6. C.s. were readily evoked by tapping or squeezing the forepaws.

7. Excitatory responses to nerve stimulation were usually followed by a depression of the tonic s.s. discharge. Its duration ranged widely in different cells (from 10 to

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500 ms) and it would coincide with equally variable periods of facilitation previously seen in neurones of nucleus interpositus. It is therefore likely that such facilitations of the cerebellar nuclear cells result at least in part from reductions in the tonic inhibitory input from the P cells.

8. Thirty-six units were classed as 'probable cortical interneurones'. They discharged more regularly, at rates between 9 and 28/s. Twenty such units (56 %) responded to s.r. stimulation with a brief excitation not usually followed by any pronounced depression.

INTRODUCTION

As a result of intensive anatomical investigation and of electrophysiological studies in anaesthetized or decerebrate animals the 'wiring diagram' of the mammalian cerebellar cortex is well understood (see Eccles, Ito & Szentagothai, 1967; Palay & Chan-Palay, 1974; Armstrong, 1978, for reviews). However, there is clear evidence that the operating characteristics of the cortical circuits are considerably influenced by anaesthesia and decerebration (e.g. Bloedel & Roberts, 1969; Gordon, Rubia & Strata, 1973) and additional investigations are therefore needed in intact unanaesthetized animals. Such studies to date have had two main preoccupations. Thus in the cat, Purkinje (P) cell discharge patterns have been recorded in relation to the sleep–waking cycle (Marchesi & Strata, 1971; Hobson & McCarley, 1972) and in the monkey correlations have been sought between P cell discharge and the execution of conditioned movements of the forelimbs (Thach, 1968, 1970; Gilbert & Thach, 1977; Harvey, Porter & Rawson, 1977).

Here we have studied the tonic or background discharge of cortical neurones in cats in a state of quiet wakefulness and also their responses to weak electrical stimulation of a cutaneous nerve of the forelimb (superficial radial, s.r.). The majority of records were from P cells but some units were believed to be cortical interneurones. The recordings were made from the intermediate zone of the cortex, and mostly from the anterior lobe. This zone is a major receiving area for inputs from the limbs (Oscarsson, 1973) and its P cells project mainly to neurones of nucleus interpositus (ip.n.s).

We have paid particular attention to the complex spikes (c.s.) of the P cells because destruction of climbing fibres (c.f.) produces signs similar to those of cerebellectomy (see Armstrong, 1974, for references) suggesting that they are of crucial importance for cerebellar function. In anaesthetized animals the cells which give rise to the c.f.s commonly discharge in bursts of up to six impulses at 500/s so that each c.s. is generated by a corresponding sequence of up to six excitatory post-synaptic potentials (c.f.-e.p.s.p.s). It has been claimed that the number of e.p.s.p.s is an important determinant of the form of the c.s. (Mano, 1970) and one theory of cerebellar cortex (Gilbert, 1974) indeed assumes a one-to-one correspondence with the spikes of the c.s. We have been fortunate to obtain apparently intracellular records from substantial numbers of P cells and have therefore sought to test these points.

Responses of cerebellar cortical neurones to stimulation of forelimb cutaneous nerves have not previously been studied in intact animals but they have been intensively investigated in decerebrate or anaesthetized animals (Eccles, Faber, Murphy, Sabah & Táboříková, 1971*a*, *b*; Eccles, 1973; Armstrong, Cogdell & Harvey,

1979). The studies of Eccles *et al.* have shown that such stimulation evokes in the P cells a complex mixture of accelerations and depressions of the tonic background discharge. Short latency (5–10 ms) simple spike (s.s.) accelerations occur due to mossy fibre (m.f.) input via the direct spino-cerebellar paths and larger accelerations with slightly longer latency (10–20 ms) occur due to inputs via m.f.s of spino-reticulo-cerebellar paths and c.f.s of spino-olivo-cerebellar paths. Since transmission in both m.f. and c.f. paths is strongly influenced by anaesthesia we have tried to determine whether the various paths are open for transmission in awake animals and thus to provide a base line for further studies regarding their functions during active movements.

In anaesthetized animals the initial excitatory responses of P cells are followed by reductions in the tonic s.s. discharge which are at least in part attributable to the c.f. input and thus perhaps to disfacilitations of the P cells via c.f. excitation of the Golgi cells which inhibit m.f.-granule cell transmission (Armstrong *et al.* 1979). Such depressions should lead to disinhibition of ip.n.s and indeed in chloralose-anaesthetized animals there are bursts of ip.n. discharges which are appropriately timed and which constitute the most prominent response to nerve stimulation (Armstrong, Cogdell & Harvey, 1975). Such bursts are much reduced or absent in decerebrate or barbiturate-anaesthetized preparations (Eccles, Rosén, Scheid & Tábořiková, 1974; Cody & Richardson, 1978) in which P cell pauses may be shorter (see Armstrong, 1974, for references). Since delayed facilitations are common in ip.n.s of awake animals (Armstrong & Rawson, 1979) we have attempted to determine whether corresponding pauses are present in the P cells and thus whether changes in P cell firing can possibly account for these responses.

Some of the results have been reported in brief (Armstrong & Rawson, 1976; Rawson, 1977).

METHODS

Single cerebellar cortical neurones were recorded using tungsten-in-glass micro-electrodes in awake cats sitting quietly in a small enclosure. The animals were the same as those in which interpositus neurones were studied and a full account of the experimental techniques is given in the preceding paper (Armstrong & Rawson, 1979).

RESULTS

Stable extracellular recordings were obtained from a total of 327 single units in a total of seventeen adult cats.

Micro-electrode penetrations were made between 2 and 7 mm lateral to the cerebellar mid line so that most units lay in the intermediate zone of the cortex. Tracks began in lobule VI but because the micro-electrode was angled forward by 30° relative to the stereotaxic vertical most units from buried areas of cortex lay within the anterior lobe. Units were sought on the basis of their tonic background discharge.

Spontaneous activity

Purkinje cells. Two hundred and seventy units were identified as P cells by the presence of both s.s. and c.s. in their discharges. The s.s. were usually biphasic

positive-negative potentials ranging in amplitude from 1 to 6 mV. In four units the spikes were almost 20 mV peak to peak (the giant spikes of Granit & Phillips (1956)) suggesting that the micro-electrode was very close to the cell body. Owing to the

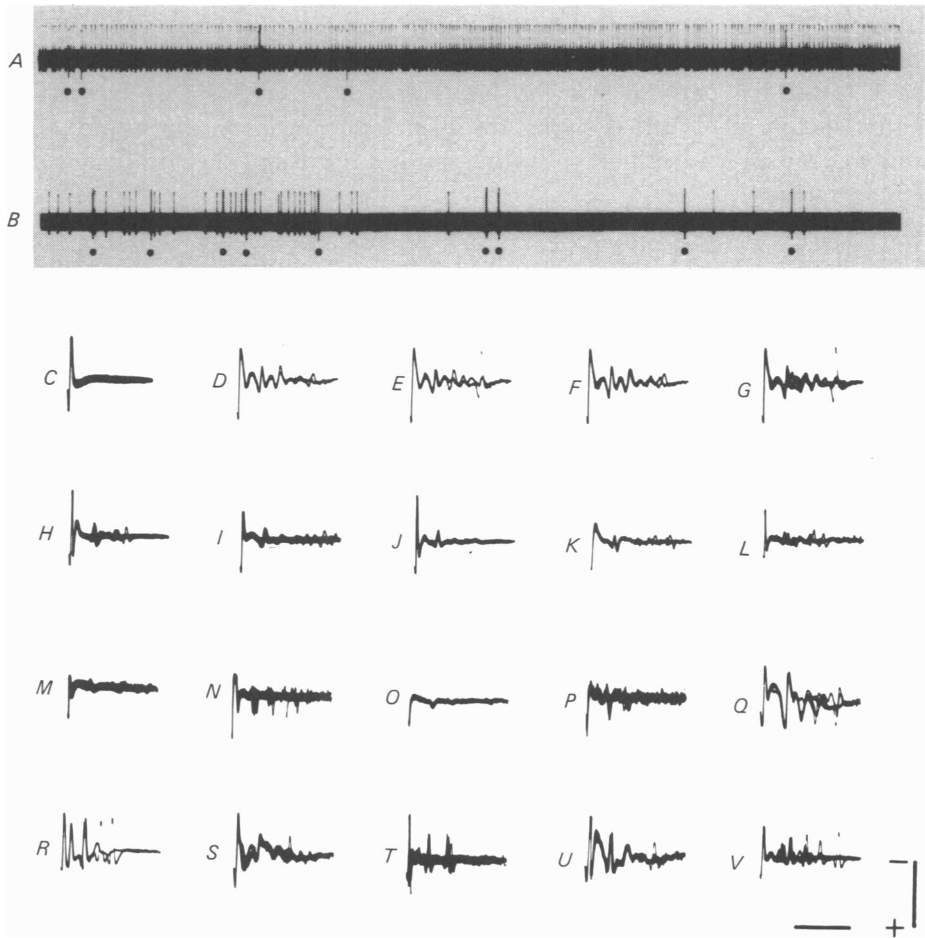

Fig. 1. Extracellular recordings from Purkinje cells. *A* and *B*, discharges of one unit at different times during its recorded lifetime. Complex spikes are marked by dots. *C*, superimposed traces of simple spikes of another unit. Sweep triggered by the rising phase of the action potential in this and all subsequent traces in Fig. 1. *D–G*, each two or three superimposed traces of c.s. from the same unit as in *C*. *H–V*, each shows several superimposed traces of c.s. from fifteen different P cells recorded in one animal. Voltage calibration, 2 mV; Time, 500 ms for *A* and *B*, 5 ms for *C–V*.

risk of mechanical injury to the cell under these conditions, such large potentials were not deliberately sought. Recordings were obtained for periods ranging from a few minutes to 2 h.

Approximately 95 % of the P cells discharged s.s. more or less continuously except for occasional pauses lasting up to 5 s. Interspersed among these discharges were c.s., occurring at very much slower rates (see below). Fig. 1*A* and *B* illustrate the behaviour of one typical unit which discharged briskly throughout the recording except for occasional periods when the s.s. rather abruptly slowed greatly or ceased

leaving only c.s.; brisk discharge resumed equally abruptly. These changes were not accompanied by any overt behavioural change in the animal. Eighty-four units were chosen at random for detailed analysis of the tonic discharge and during periods of s.s. activity the mean firing rates (inclusive of c.s.) of these units ranged from 18·5 to 94·9 impulses/s with an overall mean rate of 44 impulses/s. A frequency-gram of the mean rates is given in Fig. 2*A* where it is evident that the majority discharged at

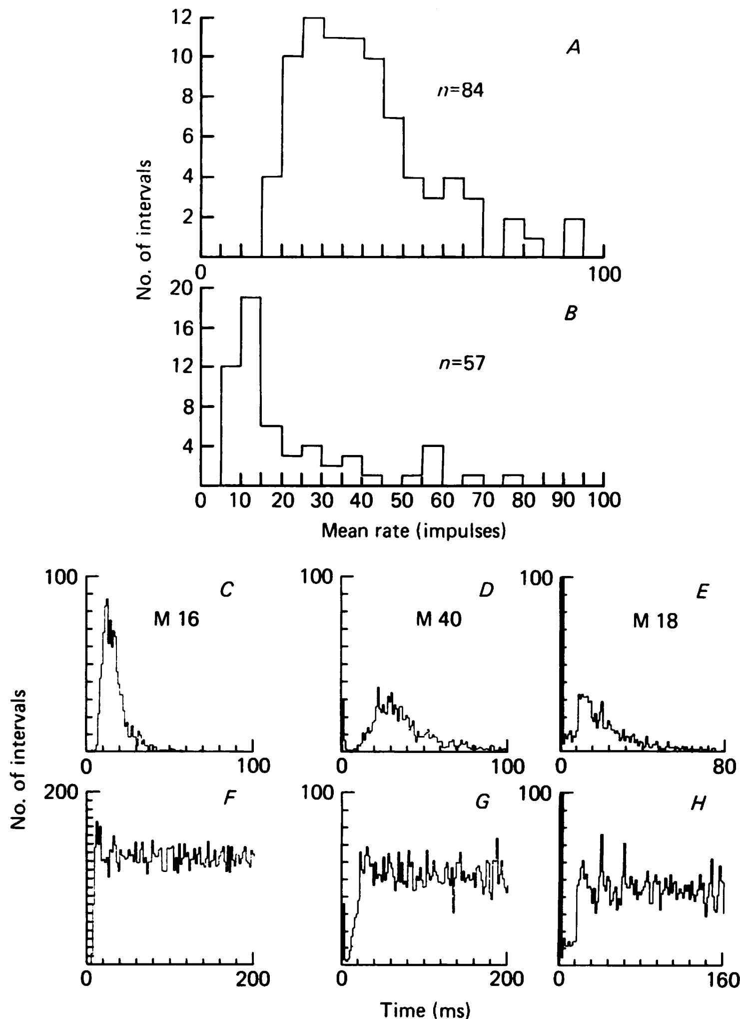

Fig. 2. Statistics of unit discharges. *A*, frequency histogram of the mean rates of discharge for eighty-four P cells. Each value computed from one or more batches of 1000 successive interspike intervals (both s.s. and c.s. are included). *B*, frequency histogram of the rates for fifty-seven units which yielded no recognizable c.s. See text for further explanation. *C*, *D* and *E*, interspike interval histograms for three P cells. Note that in *D* and *E* the intervals of 2–3 ms arose because the computer was triggered more than once from the c.s. which were of the multi-spike type (see text). Such multiple triggering was avoided when mean rates were to be computed. Mean intervals in ms are given with each histogram. Each histogram 1000 intervals and 100 bins. *F*, *G and E*, autocorrelograms prepared from the same batches of intervals as in *C*, *D* and *E*, respectively.

20–50/s; only five units displayed rates above 70/s. Interspike interval histograms revealed that the distribution of intervals was always skewed with a more or less pronounced long tail to the right, as illustrated for three cells by Fig. 2 *C–E*. The irregularity of the discharge was evident in the high coefficients of variation of the intervals (range 0·48–0·97; over-all mean 0·79) and the large standard deviations (range 8·8–55 ms; over-all mean 18 ms). The irregularity was also demonstrated by the autocorrelograms which did not usually show the pronounced recurring peaks and troughs characteristic of regular rhythmic discharge (Fig. 2 *F–H*).

Approximately 5 % of the P cells (observed for periods of 3–6 min and not included in the above analysis) discharged c.s. together with only one or two simple spikes per minute.

Form of complex spikes. In many cases these events could be isolated for study because the initial impulse in the c.s. reached a slightly greater positive level than the s.s. discharged by the same neurone. This enabled triggering of a fast oscilloscope sweep to provide a display of the c.s. alone. Records obtained from one unit using this technique are presented in Fig. 1 *D–G* in each of which two to three successive c.s. are displayed. The records show that the c.s. in this cell was almost constant in form between trials except for some variation towards the tail end of the response. In some trials the wavelets following the initial spike were followed by an almost full sized spike but more commonly the response was terminated only by a wavelet. For comparison Fig. 1 *C* displays s.s. of the same unit.

C.s. of other units are shown in Fig. 1 *H–V* which illustrate superimposed responses from each of fifteen P cells which were recorded in one animal: the form of the response ranged from a full-size spike followed by one or more small wavelets (e.g. Fig. 1 *H*) to a response type in which the wavelets were replaced by or interspersed with one to three almost full-sized spikes (e.g. Fig. 1 *R*). Generally speaking the c.s. in any particular unit was rather constant in form though there was some variation in the number of wavelets and especially in the number and size of spikes. Making a rough division of the responses into 'spike and wavelet' and 'multiple spike' types, the two forms were encountered in approximately equal numbers so that, for example, in one cat there were nineteen of the first type and fourteen of the second.

Frequency of occurrence of c.s. Complex spikes occurred irregularly at mean rates between 1·0 and 2·5/s (each rate calculated from observations of at least 100 events) with an over-all mean of 1·5/s. The shortest interval observed was 40 ms and the longest was 5 s. Occasionally some units discharged as many as eight c.s. in 1 s, but such high rates persisted for only 1–2 sec. By triggering the computer from the large initial spike it was possible to compile inter-c.s. interval histograms and typical results for three units are shown in Fig. 3 *A*, *C* and *E*. Joint interval density scattergrams revealed no tendency for long or short intervals to be followed by any particular intervals and autocorrelograms revealed no longer-term regularity or rhythmicity (Fig. 3 *B*, *D* and *F*).

Mechanism of generation of the c.s. Fifty-six of the P cells which were studied extracellularly were subsequently penetrated by the micro-electrode. These cells gave a short-lived injury discharge which was accompanied by a DC shift though the AC recording system precluded measurement of its magnitude. Cessation of the injury discharge was followed by the appearance of large (up to 20 mV) unitary

depolarizations occurring both singly and in groups of two to six. These events could be recorded for periods ranging between a few seconds and 8 min, though they usually decreased in amplitude with time after penetration. The depolarizations were distorted by the characteristics of the recording system but it was clear that succes-

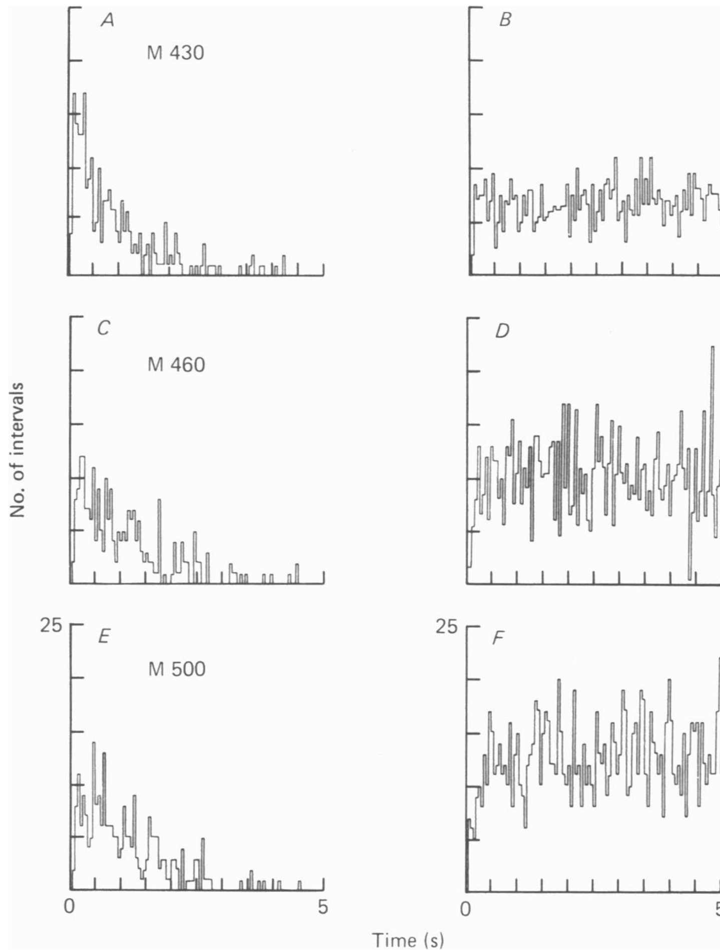

Fig. 3. Statistics of complex spike discharges. *A*, *C* and *E*, inter-c.s. interval histograms for three P cells. Each histogram constructed from 250 successive intervals. Uniform scaling of vertical axes. Mean interval in ms given with each display. Bin width, 50 ms. *B*, *D* and *F*, autocorrelograms prepared from the same batches of intervals as in *A*, *C* and *E*, respectively. Uniform scaling of vertical axes. Bin width, 50 ms.

sive events in a group occurred at approximately 2 ms intervals and declined progressively in amplitude. Examples from two cells are shown in Fig. 4*A* and *B*.

These responses appeared to be identical with responses identified by Eccles, Llinas & Sasaki (1966*a*) as the c.f.-e.p.s.p.s which are believed to generate the c.s. and this identification was confirmed by the finding that the distribution of intervals between the depolarizations (considering each group as a single event) was identical with that for the c.s. recorded extracellularly in the same cell (see Fig. 4*C*). In addition, when s.r. stimulation generated a c.s. in a P cell, this response was replaced

after penetration by a c.f.-e.p.s.p. (or group of e.p.s.p.s) evoked at the same latency and threshold.

Since each c.f.-e.p.s.p. is believed to be produced by a single impulse in the c.f., our recordings of these events give an indication of the firing pattern of the cells

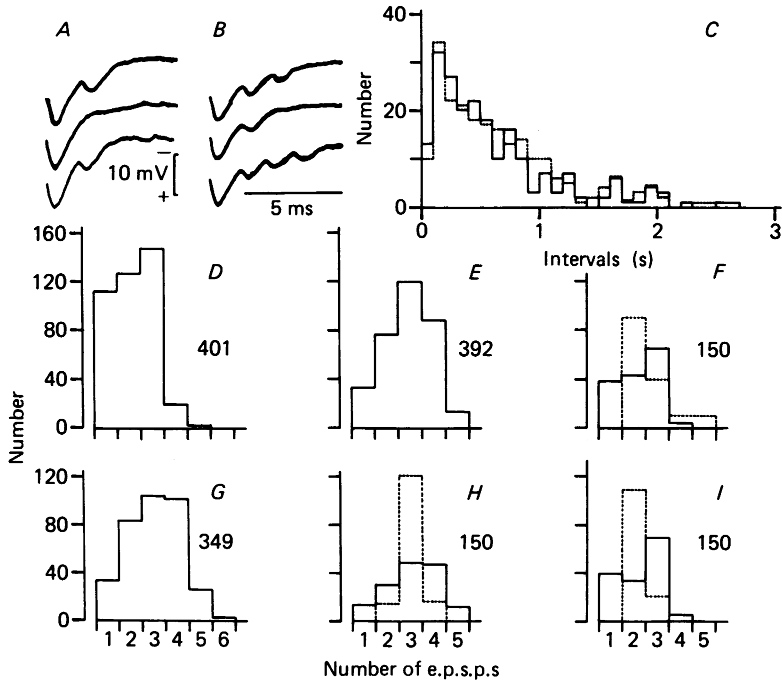

Fig. 4. Climbing fibre e.p.s.p.s recorded from P cells. *A* and *B*, three successive spontaneous bursts of e.p.s.p.s recorded from each of two P cells. *C*, comparison of the c.f.-e.p.s.p.s with the c.s. recorded before penetration in one unit. Continuous lines show the frequency of occurrence of different intervals between spontaneous bursts of e.p.s.p.s. Interrupted lines show the frequency of occurrence of different intervals between c.s. Each histogram includes 200 consecutive observations. Mean interval between e.p.s.p. groups was 604 ms; mean interval between c.s. was 624 ms. *D–I*, histograms showing the frequency of occurrence of different numbers of e.p.s.p.s in each of many spontaneously occurring bursts in six different units. Number of observations shown beside each display. Note that the broken lines in *F*, *H* and *I* show the number of spikes in each of a similar number of c.s. recorded before penetration of the unit.

which give rise to the c.f.s (presumably olivary neurones; see Armstrong, 1974 for references and discussion). Whenever possible, therefore, we have determined the number of e.p.s.p.s in a succession of spontaneously occurring groups. In each of thirty-six units in which a minimum of forty groups were recorded the modal number of e.p.s.p.s per group was 3, but the mean number varied from 1·9 to 3·1. Frequency distributions of e.p.s.p.s/group for six typical units are shown in Fig. 4*D–I*. The largest number of e.p.s.p.s found in any group was six (vide Fig. 4*G*) but single e.p.s.p.s were not uncommon, indicating that the olivary neurones sometimes discharge single impulses. There appeared to be no correlation between the number of e.p.s.p.s in successive groups, the number varying in an apparently random

manner. Neither was there any obvious relationship between the number of e.p.s.p.s in successive groups and the intervals between the groups: the correlation coefficients for a long series of groups (100–125) in each of two units were not significantly different from zero (0·03 and 0·09).

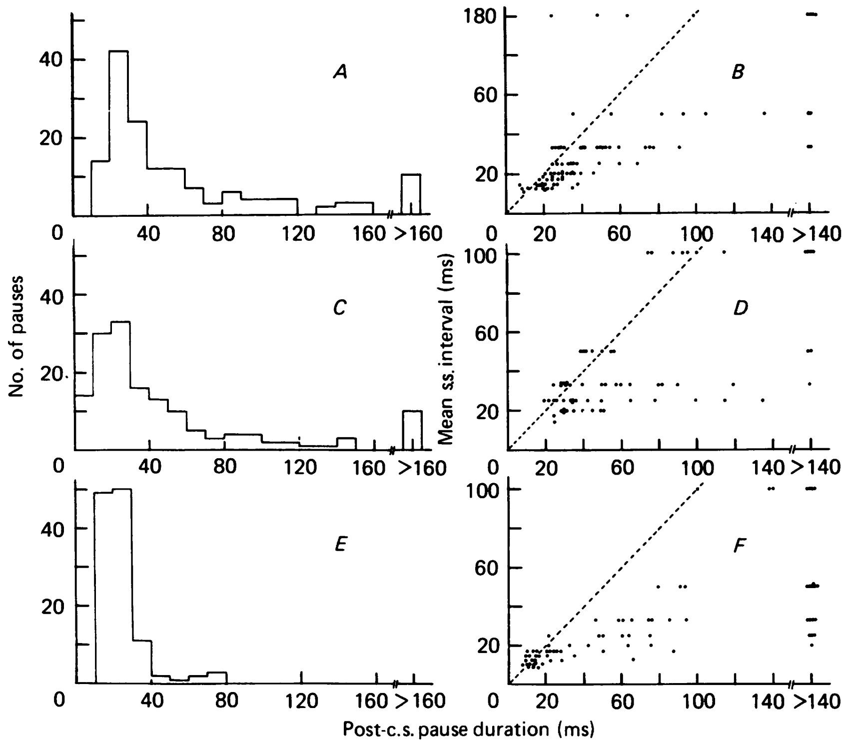

Fig. 5. Pauses in P cell discharge of simple spikes following complex spikes. *A*, *C* and *E*, frequency histograms for the intervals between spontaneous c.s. and the next s.s. in three units. *A* and *C* include 150 observations; *E* includes 108 observations. *B*, *D* and *F*, pause duration plotted against the level of s.s. discharge immediately preceding the c.s. in three different units. Mean s.s. interval derived from counts of the number of s.s. in the 100 ms preceding each c.s. Broken lines indicate the relationship expected if the interval following each c.s. was equal to the mean s.s. interval. Number of observations, 84 in *B*, 65 in *D*, 74 in *F*.

Where possible the number of spikes in a large number of extracellularly recorded c.s. and the number of e.p.s.p.s in each of a similar number of intracellularly recorded depolarizations was compared. Such comparison was attempted only in cells in which the c.s. displayed several well-developed spikes because in units with 'spike plus wavelet' c.s. the wavelets were often difficult to count and their nature is uncertain. Sufficient observations were obtained in only three units and Fig. 4 *F*, *H* and *I* compare for each of these the number of spikes in 150 successive extracellularly recorded c.s. (interrupted lines) with the number of e.p.s.p.s in the same number of intracellularly recorded groups (continuous lines). In each cell the number of e.p.s.p.s was more variable than the number of spikes and furthermore although in each cell the minimum number of spikes was two, single e.p.s.p.s were quite common, indicating that a single e.p.s.p. can give rise to more than one spike.

Post-c.s. pauses. In anaesthetized animals, it is well established that a spontaneously occurring c.s. is often followed by a variable pause in the tonic discharge of s.s. (see Armstrong, 1974 for references). In our experiments the durations of the intervals between a c.s. and the next s.s. were highly variable both in any one cell and between cells. The over-all range was from 8 to 600 ms and in twenty-five units in each of which a minimum of seventy-five c.s. were measured, the mean duration ranged from 28 to 72 ms with an over-all mean of 49 ms. Frequency distributions of the intervals duration for three typical cells are shown in Fig. 5*A*, *C* and *E*. Afterwards s.s. resumed at approximately their pre-c.s. frequency.

It was observed that when background s.s. rate was high, intervals following the c.s. tended to be short. Thus for the unit of Fig. 5*E*, the s.s. rate was high (about 80/s) and post-c.s. interval duration was limited to between 14 and 74 ms (mean 28 ms). By contrast the units in Fig. 5*A* and *C* were firing at lower rates (about 25–40/s) and the intervals were both longer (means of 65 and 55 ms, respectively) and more variable (10–530 ms in *A*, 8–450 ms in *C*).

In view of these observations, and a previous claim that post-c.s. interval duration is inversely related to s.s. rate (see Discussion), a measure of the ambient s.s. activity was obtained in fourteen cells, including those of Fig. 5, by determining the s.s. rate in the 100 ms before each of a large number of c.s. This was plotted (as s.s. interval) against the duration of the corresponding post-c.s. pause. The results for three cells are shown in Fig. 5*B*, *D* and *F* where the interrupted lines indicate the duration predicted if the post-c.s. intervals were no longer than the mean interval between s.s. It is clear that a rough inverse relation exists with s.s. rate and a similar relationship was in fact found for all fourteen units studied. Furthermore, it is clear in Fig. 5*B*, *D* and *F* that many post-c.s. intervals exceeded the prevailing s.s. interval and that the difference tended to increase markedly with increasing s.s. interval. In general, post-c.s. intervals were longer than the s.s. interval provided the prevailing s.s. rate was less than 40–50/s and they could then properly be termed pauses.

Activity of other cortical neurones

A further fifty-seven units were recorded which discharged only ordinary action potentials. These were subdivided tentatively into two groups on the basis of their discharge patterns.

Possible P cells. Twenty-one neurones were classed as possible P cells on the grounds that their discharge rates (range 17–76/s; over-all mean 40/s) and interspike interval distributions, (positively skewed) were very similar to those of identified P cells. Furthermore their autocorrelograms indicated an irregular discharge similar to that of P cells and contact with the units was maintained over quite long distances of micro-electrode travel.

The absence of c.s. in these units might well be due to inactivity of the c.f. afferents. However, four were penetrated by the micro-electrode and typical c.f.-e.p.s.p.s were then recorded even though c.s. were not detectable in the extracellular record. This observation would seem to confirm that at least these units were in fact P cells and it shows in addition that a c.s. is not always detectable from outside the cell, presumably because it consists of only one spike not distinguishable from a s.s.

Possible interneurones. A further thirty-six units were classified as possible inter-

neurones. The majority of these neurones discharged at low rates (5–28/s; over-all mean 28/s) so that in Fig. 2 *B* which is a frequency histogram of the mean rates of all fifty-seven unidentified units, the two left hand columns are made up entirely of

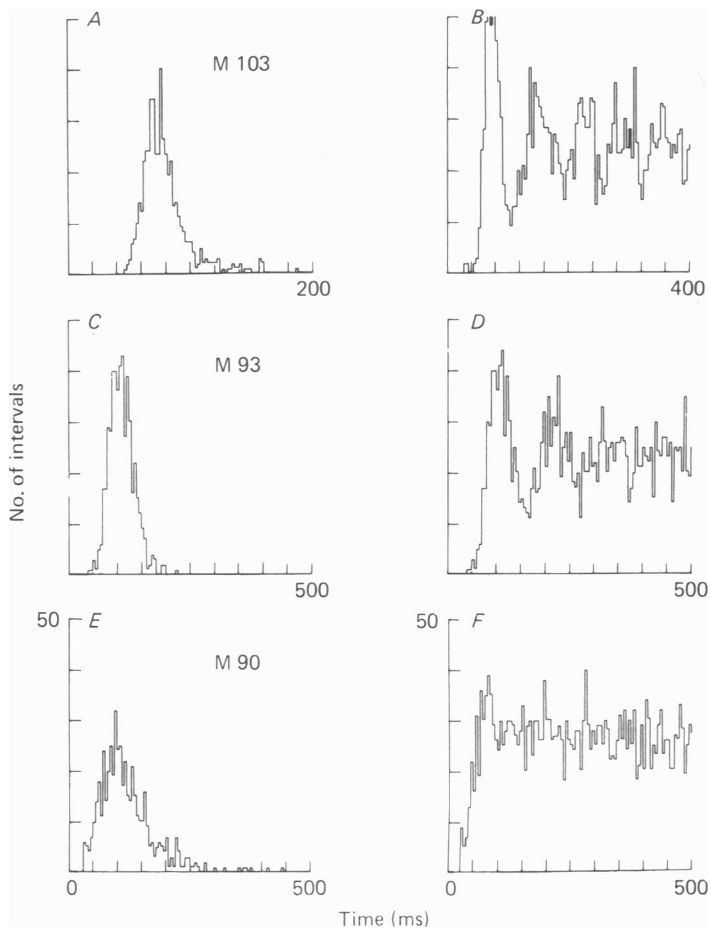

Fig. 6. Discharges of presumed cerebellar cortical interneurones. *A*, *C* and *E*, interspike interval histograms for three different units. Each histogram constructed from a batch of 500 successive intervals. Uniform scaling of vertical axes. Bin width, 2 ms in *A*, 5 ms in *C* and *E*. Mean interval in ms shown beside each display. *B*, *D* and *F*, autocorrelograms constructed from the same intervals as in *A*, *C* and *E*, respectively. Bin width, 4 ms in *B*, 5 ms in *D* and *F*. Uniform scaling of vertical axes.

thirty-one 'interneurones'. Only five 'interneurones' displayed rates over-lapping with the confirmed or possible P cells and these discharged much more regularly than P cells. In consequency of the more regular discharge, the interspike interval histograms for interneurones (e.g. Fig. 6 *A*, *C* and *E*) were often more symmetrical than those for P cells and the autocorrelograms usually displayed peaks and troughs (e.g. Fig. 6 *B* and *D*, and cf. Fig. 2).

An additional point of difference was the scarcity of short interspike intervals: even in those few cells which over-lapped in mean rate with the P cell population

there were few intervals shorter than 20 ms whilst such intervals were common amongst P cells with comparable mean rates.

Whilst the above observations provide reasonable grounds for distinguishing these units from the P cells they do not of course provide a full identification. However,

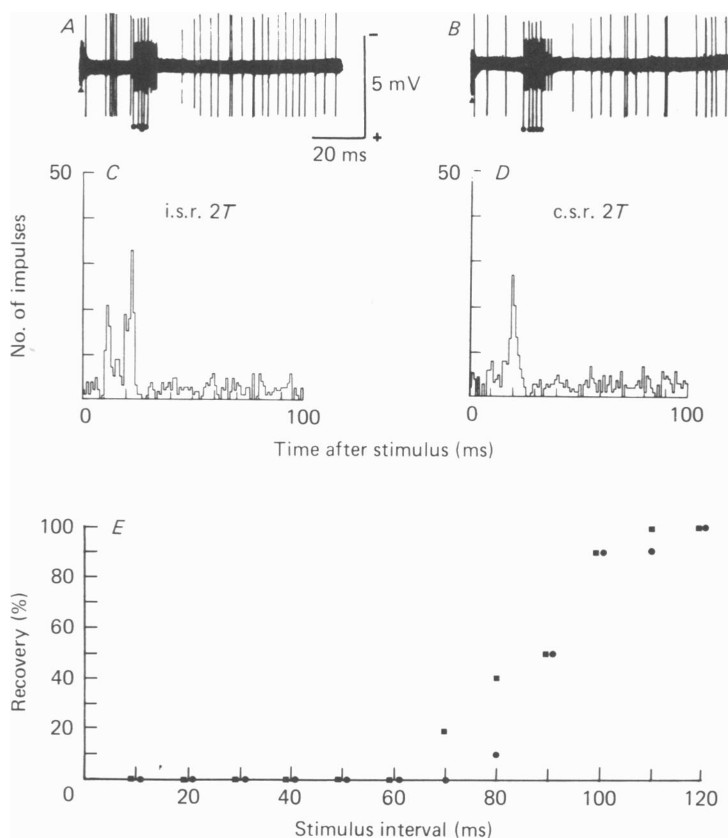

Fig. 7. Purkinje cell responses to cutaneous afferent volleys. *A*, five superimposed sweeps of the response of a P cell to stimulation of i.s.r. nerve at intensity $2T$. Filled triangle indicates time of application of stimulus. Dots indicate the first spike in a c.s. *B*, as *A* but stimulation of c.s.r. at $2T$. *C*, post-stimulus histogram corresponding to *A* but based on fifty consecutive responses evoked at 2 s intervals. Bin width, 1 ms. *D*, histogram corresponding to *B*; prepared as in *C*. *E*, recovery cycles for c.s. evoked in two P cells by stimulation of i.s.r. at $2T$. Two stimuli presented with different interstimulus intervals. The first invariably evoked a c.s. Each point derived by counting the number of responses to each of ten trial presentations of the second stimulus and expressing this number as a percentage of full recovery.

the action potentials were large (1–5 mV) and although the units were not 'seen' by the micro-electrode over such long distances as P cells, stable recordings were usually obtained for periods in excess of 5 min and sometimes for as long as 95 min suggesting that the records were from quite large structures. Since in addition the units were usually encountered close to the P cell layer it seems reasonable to assume that they were basket or Golgi neurones. It must however be emphasized that such identification is very tentative.

Responses to stimulation of s.r. nerve

P cell responses. The effect of single shocks to the ipsilateral s.r. nerve (i.s.r.) was tested in 151 P cells of which 88 (58 %) gave responses detectable from inspection of superimposed responses displayed on a storage oscilloscope. Stimulus intensities were restricted to the range 1–4T where T is the threshold for the most excitable fibres in the nerve, as determined in a terminal experiment (see Armstrong & Rawson, 1979). A few responses were purely excitatory or inhibitory but the majority included both excitatory and inhibitory components.

Accelerations of s.s. In three units the earliest detectable change was always a brief depression of the ongoing s.s. activity (see Fig. 9) but the large majority of initial responses were excitatory, consisting of a c.s. and/or an acceleration of the s.s. However, excitatory s.s. responses were not frequent within the range of stimulus strengths employed: seventy-two units responded with a c.s., eleven with both s.s. and c.s. and only two with s.s. alone. In forty-four of the eighty-eight responsive neurones post-stimulus time histograms were compiled from fifty successive responses in order to facilitate more detailed study. One example is shown in Fig. 7*C* beneath a specimen record of five superimposed responses (Fig. 7*A*). Comparison of the two types of display shows that the first excitatory peak (latency 10–19 ms) in the histogram is made up entirely of s.s. whilst the second peak (latency 20–27 ms) is due primarily to the c.s. evoked consistently in each trial. However, in addition a second s.s. was sometimes discharged immediately preceding the c.s.

As indicated above, initial s.s. accelerations were less common than c.s. responses and in addition they were not large; the most powerful responses observed were in fact those preceding the c.s. in Fig. 7*A* and *C* and amounting to around two spikes per stimulus. When the contralateral nerve (c.s.r.) was stimulated at similar intensities s.s. responses were generally much weaker so that although a c.s. response is clearly evident in Fig. 7*B* and *D* it is preceded by an only barely perceptible elevation in the histogram. However, the component was unequivocally recognizable when c.s.r. was stimulated at higher intensities. Considering all thirteen cells which gave excitatory s.s. responses, those to i.s.r. began with latencies ranging from 7 to 18 ms whilst for c.s.r. the range was 15–19 ms with the exception of the cell in Fig. 7*B* and *D* which had latency 8 ms and one cell responding at 10 ms.

Complex spikes. The threshold for evoking c.s. was usually low and at intensities of 2–3T a c.s. was often present in response to every presentation of the stimulus. However, even with stimuli which were apparently well supramaximal the latency often fluctuated by between 1 and 6 ms and occasionally the response would fail.

Amongst the eighty-three units yielding a c.s., twenty-seven responded with least latency between 11 and 16 ms (population mean 12·5 ms) following stimulation of i.s.r. This latency range, and the fact that none of these units responded to stimulation of the contralateral nerve, indicates that the responses were mediated via the dorsal funiculus spino-olivocerebellar path (d.f.-s.o.c.p.; Oscarsson, 1969; Armstrong, Harvey & Schild, 1973). A further fifty-one units responded to i.s.r. with latency 17–30 ms (mean 19·5) and all forty of these units which were tested also responded with similar latency (17–30 ms; mean 20 ms) to stimulation of c.s.r. A c.s. was often evoked by simultaneous stimulation of both nerves at intensities which failed to

evoke a response when either nerve was stimulated alone indicating spatial summation between the two inputs. These characteristics are compatible with transmission via the lateral funiculus spino-olivo-cerebellar path (l.f.-s.o.c.p.; Larson, Miller & Oscarsson, 1969; Armstrong *et al.* 1973). So far as we could judge the narrow termination zones which the d.f.- and l.f.-s.c.o.p.s exhibit in the cerebellar cortex of anaesthetized animals, persisted in our unanaesthetized preparations. Thus successive neurones contacted in a single penetration usually displayed similar response characteristics. Furthermore, slight medio-lateral shifts of the microelectrode entry point often led to a transition in the response characteristics or indeed to encounters with cells which gave no evoked c.s. and thus presumably lay outside the termination zones.

In the remaining five units i.s.r. stimulation evoked c.s. with latencies of 25–40 ms but the cells did not respond to c.s.r. These responses were probably mediated by less direct pathways. In some cells of both the d.f.-s.o.c.p. and l.f.-s.o.c.p. categories the initial c.s. was sometimes followed by a second with latency about 120 ms, a finding which has previously been reported in anaesthetized animals (e.g. Eccles *et al.* 1971*b*).

Again as in anaesthetized animals, transmission in the s.o.c.p.s usually failed at stimulus frequencies greater than 10/sec. For several units paired shocks were delivered and the influence of stimulus interval on the probability of obtaining a second response was investigated. In a few units a second response occasionally appeared at an interval of 40 ms but more usually it could not be evoked at intervals less than 50–60 ms. As the interval was lengthened the responses progressed to full recovery at around 100–120 ms. Typical conditioning curves for two cells are presented in Fig. 7*E*.

Occasionally it was possible to deliver adequate stimuli to cutaneous mechanoreceptors without provoking movements of the animal. In such cases, P cells in c.f. projection zones usually responded with a c.s. when the forepaws were gently squeezed or tapped.

On occasion, units responding to s.r. stimulation were penetrated and c.f.-e.p.s.p.s were then seen which displayed the same latency, threshold and frequency-following characteristics as the extracellular c.s. Detailed analyses of the number of e.p.s.p.s per burst were not made but the number varied in a manner similar to that found for the spontaneously occurring responses.

Depressions of s.s. activity. In a few cells the initial excitation was the only response to nerve stimulation but in the great majority it was followed in many trials by a pause in the tonic background discharge of s.s. In any one unit the duration of this depression was very variable as can be seen in the successive single sweeps of Fig. 8*A* where a silent period following the c.s. varies in duration between 30 and 130 ms. These traces also demonstrate that silent periods were sometimes present even in trials in which a c.s. failed to appear. In addition to this variation the average duration of depression as estimated from histograms also varied considerably amongst the different units, ranging from as little as 10 ms to as long as 500 ms. The complete time course of the responses in those forty-four units for which post-stimulus time histograms (p.s.t.h.s) were constructed is diagrammed above the base line in Fig. 9. Specimen p.s.t.h.s for three different P cells are presented in Fig. 8*B*, *C* and *D*. *B* and *C* show excitatory responses followed by prolonged though mild depressions lasting

around 200 ms in *B* and around 450 ms in *C*. Fig. 8*E* shows a depression lasting around 70 ms in another unit. At the stimulus intensity used for construction of this p.s.t.h. the depression was preceded by a c.s. in only three of the fifty trials. A further increase to 3·5*T* led to a marked increase in the probability of obtaining a

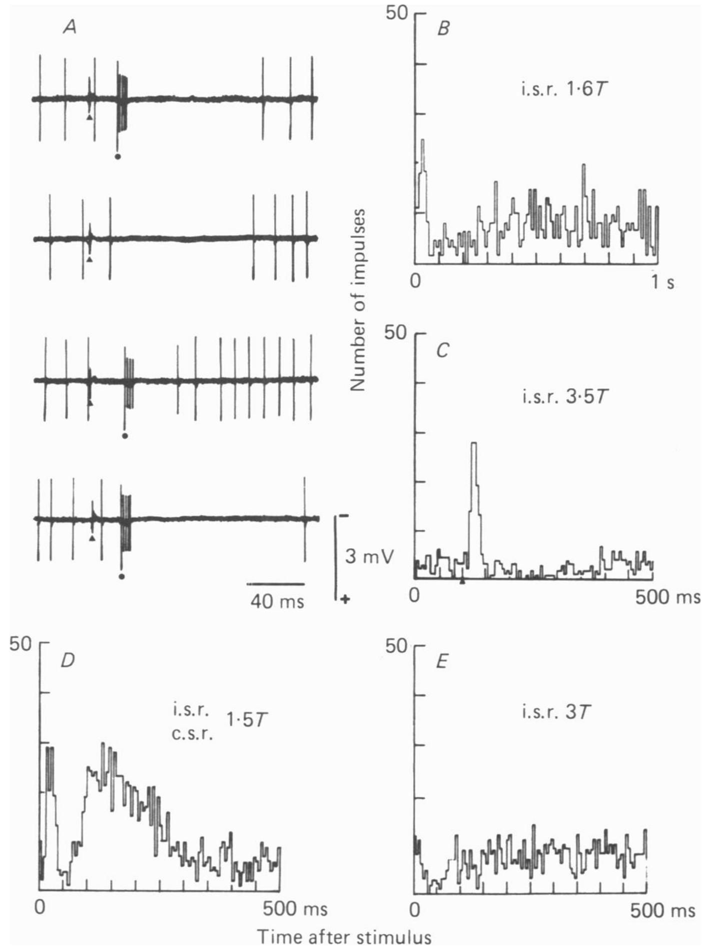

Fig. 8. Purkinje cell responses to cutaneous afferent volleys. *A*, four successive responses to stimulation of i.s.r. at 2·5*T*. Stimulus presentation marked by a filled triangle. C.s. evoked in three trials are marked by dots. *B–E*, post-stimulus histograms of fifty successive responses of four different units to stimulation at the indicated intensities. Stimulus delivered at 0 ms except in *C* where stimulus delivered at filled triangle. Note in *D* both i.s.r. and c.s.r. stimulated simultaneously. Response to either nerve alone was similar but smaller in amplitude. Short latency peaks in *A*, *C* and *D* were composed primarily of c.s. Bin widths, 10 ms in *B* and *C*; 5 ms in *D* and *E*.

c.s. but below 3*T* no c.s. were generated, this cell being one of the small number (4) in which a depression was the only response observable at intensity 2*T* (see Fig. 9).

In a few units the effects of changes in stimulus intensity were investigated and it was found that the depth and duration of the depression were graded with stimulus intensity. In some cases an increase in intensity beyond the level which evoked a c.s. in every trial produced an additional increase in duration.

Three units for which p.s.t.h.s were constructed responded with a c.s. followed by an acceleration of s.s. activity. A p.s.t.h. for one of these units is shown in Fig. 8 *D*. Interestingly enough, spontaneous c.s. in these units were followed by similar though smaller accelerations, rather than by the more usual post c.s. pauses.

Only ten of the twenty-one 'possible' P cells were tested to nerve stimulation. Six responded only to i.s.r., three with weak s.s. responses with latency 10–15 ms and three with a depression of s.s. activity similar to the P cell response in Fig. 8*E*. One unit was powerfully excited (four spikes per stimulus, averaged over fifty trials) from both s.r. nerves with latency 20–30 ms. The three remaining units were uninfluenced by nerve stimulation at intensities up to 3*T*.

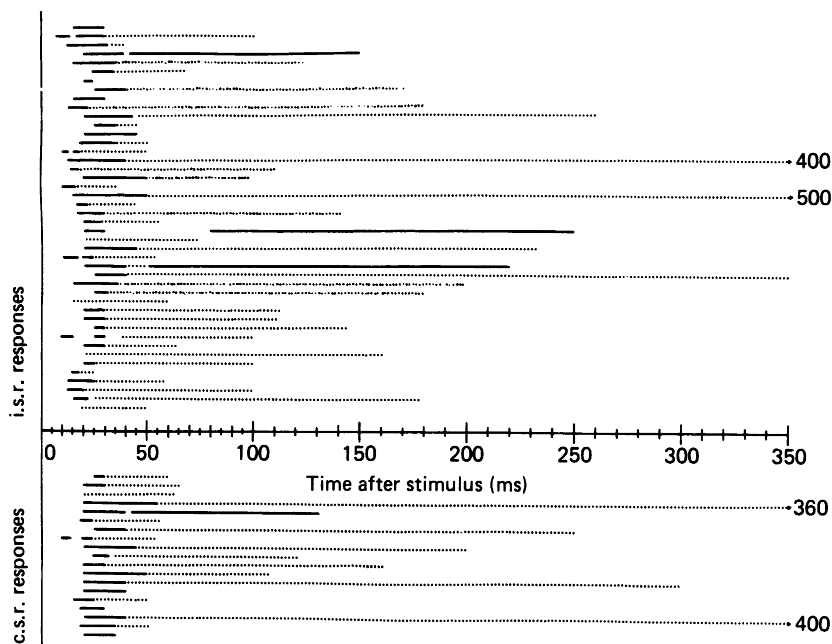

Fig. 9. Time course of Purkinje cell responses to nerve stimulation. Responses to i.s.r. plotted above base line, responses to c.s.r. below. The measures for each unit were taken from post-stimulus histograms of fifty successive responses after smoothing by eye. Excitations (—) are defined as periods when activity was above pre-stimulus levels, inhibitions (....) as periods of depression below pre-stimulus rate. All responses obtained with stimulus strength close to 2*T* (i.e. in range 1·7–2·2*T*). Responses of forty-four units to i.s.r., nineteen units to c.s.r.

Responses of presumed interneurones

All thirty-six units were tested to one or both nerves and twenty gave a detectable excitatory response. At intensities up to 3*T* response amplitudes ranged in the different units from less than one spike per stimulus to around three spikes per stimulus. Amplitudes were graded with stimulus intensity as shown for one unit by the p.s.t.h.s of Fig. 10*A* and *B*.

As judged from p.s.t.h.s responses to i.s.r. ranged in latency from 13 to 30 ms with two exceptions in which the response began at 7 ms in one case and 9 ms in the other. Those units responding at shortest latency (up to 15 ms) were not usually influenced bilaterally but units responding at longer latency (19–30 ms) were usually excited with similar latency from c.s.r.

Finally, though the initial excitatory responses were followed in a few units by depression, in the majority of interneurones there was no such depression (Fig. 10*A*, *B* and *C*).

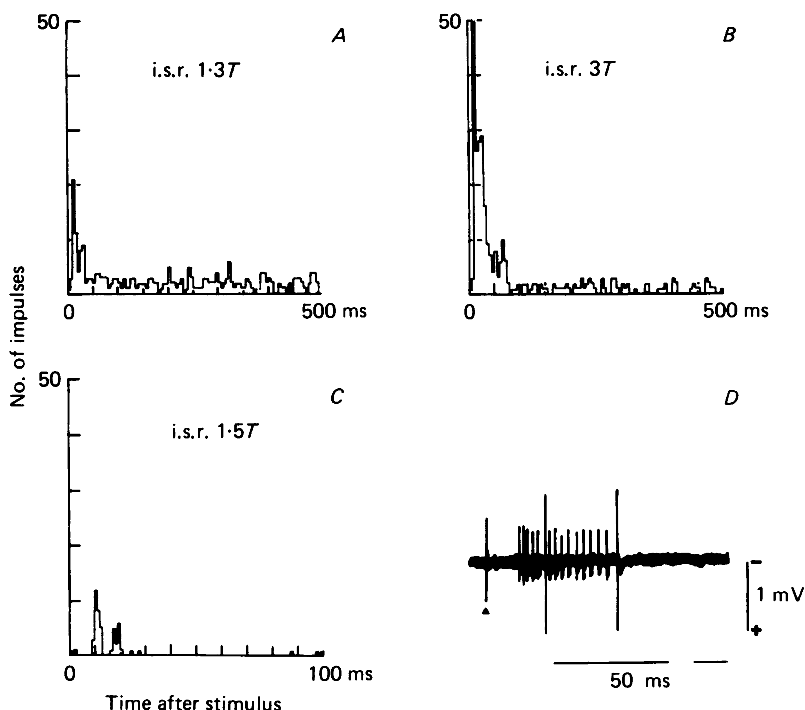

Fig. 10. Responses of presumed interneurones to cutaneous afferent volleys. Post-stimulus histograms of fifty successive responses. *A* and *B* are from the same unit, showing the effect of increasing stimulus strength. Bin width, 5 ms. *C*, a different unit; bin width, 1 ms. *D*, single sweep showing responses of a typical 'interneurone' (the large spike) and an atypical unit to stimulation of i.s.r. at 2·5*T*. Filled triangle indicates stimulus artifact.

One atypical unit was recorded for part of the time during which a typical interneurone was under study. Responses of both units to stimulation of i.s.r. at 2·5*T* are shown in the specimen sweep of Fig. 10*D*. The large spike is the presumed interneurone which usually responded with two spikes, the first with latency 16–20 ms. By contrast, the smaller unit responded with a high frequency (600/s) burst of eleven to fourteen spikes. The latency of the first spike in the burst was 8·5–9 ms. Contact with this unit was maintained only briefly and it was the only one of its type encountered. A detailed study of its spontaneous discharge was not possible but it discharged infrequently (1–3/s) in small bursts of three to six impulses. The two units were recorded just beyond a layer of P cell bodies which were encountered after traversing a layer in which the only activity was unitary c.f. responses presumably recorded from P cell dendrites (cf. Fujita, 1968). We conclude therefore that both units were located in the granular layer.

DISCUSSION

Background discharges

Discharge rates have not previously been reported for such a large population of P cells in the unanaesthetized cat but in a sample of thirteen cells from cats in a state of quiet wakefulness, Marchesi & Strata (1971) reported a range from 0 to

100/s whilst Hobson & McCarley (1972) encountered s.s. rates ranging from 3 to 100/s with an over-all mean rate of 48/s (thirty-nine cells). In our experiments around 95 % of the 270 P cells discharged more or less continuously and in eighty-five cells chosen at random from this population the rates ranged from 18·5 to 95/s with an over-all mean of 44/s. These values include both c.s. and s.s. but c.s. were discharged so infrequently (see below) that they made little contribution to the over-all rate. By contrast around 5 % of cells discharged at very slow rates producing only c.s. and a few s.s. per minute. Unfortunately none of these cells could be studied for more than a few minutes so it is not known whether this behaviour was a permenant feature. However, none of those cells which were studied for long periods (i.e. in excess of 30 min) ever slowed to such rates for longer than a few seconds so it is possible that these cells constitute a specialized fraction of the P cell population.

Comparison with studies in immobilized cats is difficult because of partial reporting but the work of Murphy & Sabah (1970) shows that whilst similar background s.s. rates obtain under light thiopentone anaesthesia, rates are slightly lower with pentobarbitone anaesthesia or after decerebration.

In awake monkeys Mano (1970) reported rates ranging from 5 to 67/s with an over-all mean rate of 29/s. However, in a sample of seventeen cells from monkeys in a state of behavioural arousal Thach (1968) has encountered an over-all rate similar to ours (48/s) although some cells fired at significantly higher rates than ours (up to 125/s).

It should be noted that in this as in most previous studies (but see Eccles *et al.* 1966*a*) P cells have been identified primarily on the basis that both c.s. and s.s. were discharged by a single cell. This criterion has never been seriously questioned although Van Gilder & O'Leary (1971) stated that in unanaesthetized paralysed cats the extracellular c.s. consisted only of one spike which was often indistinguishable from the s.s. although in some cases it might be followed by a wavelet. These authors claimed that the characteristic multiple-spike c.s. developed only after administration of barbiturate. Our results like those of Hobson & McCarley (1972), Marchesi & Strata (1971), Thach (1968) and others show clearly that such is not the case in unanaesthetized unrestrained animals. However, in around half the P cells the c.s. were of the spike plus wavelet type – presumably due to inactivation of the spike generating mechanism as a result of the large depolarization during the c.f.-e.p.s.p. (cf. Eccles *et al.* 1966*a*).

Clearly our results cannot throw much light on the adequacy of c.s. as an identifying criterion for P cells except to show that it may not invariably be reliable. Thus twenty-one cells were classed as 'possible P cells' because their s.s. discharge resembled that of identified P cells although they never yielded recognisable c.s. However, after micro-electrode penetration typical c.f.-e.p.s.p.s were recorded from four of these cells suggesting that at least in these cases extracellular recordings did not permit c.s. to be distinguished from s.s. It is possible that the same was true of the remaining seventeen possible P cells or alternatively the c.f. afferents to these neurones displayed no spontaneous activity. Less plausibly it might be suggested that these were P cells which were not in receipt of a c.f. afferent.

Since each c.s. is generated by an input to the P cells via the cell which gives rise to the c.f. it follows that recording of c.s. provides an opportunity to study the discharge patterns of these neurones (without the usual hazard that the microelectrode itself may influence the excitability of the cell). In our experiments c.s.

occurred at rates very similar to those reported by numerous other workers in anaesthetized, unanaesthetized and decerebrate preparations, suggesting that the rate is not strongly influenced by anaesthesia. Furthermore, the inter-c.s. interval histograms previously compiled by Bell & Grimm (1969) who worked with pentobarbitone-anaesthetized animals, were very similar in form to the examples presented in Fig. 3 which were typical of thirty cells studied.

Records of events which seemed to be c.f.-e.p.s.p.s have not previously been made in unrestrained animals and they are therefore of some interest despite the fact that our cells were invariably badly damaged by impalement. They established first, that although such e.p.s.p.s often occur singly, they nevertheless commonly occur in bursts of up to six at a frequency of 500/s. Thus the tendency for burst firing in the c.f.s, often noted in anaesthetized and decerebrate animals (e.g. Eccles *et al.* 1966*a*) is present also in intact cats. Secondly it is noteworthy that whilst the number of e.p.s.p.s per burst fluctuated unpredictably between one and six in all fifty-six cells recorded intracellularly, the form of the c.s. was rather constant in most cells. In addition, records made before and after impalement from a few cells capable of multi-spiked c.s. demonstrated not only that the number of e.p.s.p.s was more variable than the number of spikes in the c.s. but also that a single c.f.-e.p.s.p. could certainly generate more than one spike. Our findings do not exclude the possibility that c.s. evoked by a burst of e.p.s.p.s may be more prolonged than those evoked by a single e.p.s.p., as suggested by Eccles *et al.* (1966*a*). However, they do not support the claim by Mano (1970) that the form of the c.s. is heavily dependent on the number of e.p.s.p.s which generate it and neither can they be reconciled with the assumption of a one to one correspondence between c.f.-e.p.s.p.s and spikes in the c.s. (Gilbert, 1974). Indeed our findings raise a question as to why, if a complete c.s. can be evoked by one or two e.p.s.p.s, the c.f.s so often transmit a burst of three or more impulses. It is of course possible that such burst firing may be of no particular significance, but equally, it is possible that its significance is in relation not to the synapses with P cells but to those with intracerebellar nuclear neurones and with Golgi neurones (Palay & Chan-Palay, 1974). It is conceivable that the firing of (variable) bursts may represent a device to ensure efficient (or variable) transmission at these junctions.

Since the first recordings were made from mammalian P cells (e.g. Granit & Phillips, 1956) it has been recognized that c.s. are often followed by a variable pause in the background discharge of s.s. Because antidromic impulses can be evoked soon after the onset of the pause it is clear that only its initial 10–20 ms can be ascribed to inactivation of the spike generating mechanism of the P cells (Martinez, Crill & Kennedy, 1971) and it is therefore generally agreed that at least the later part of the pause is ascribable to inhibitory actions exerted on the P cell by interneurones within the cerebellar cortex. In view of the large scale contacts which exist between c.f. collaterals and Golgi neurones it is probable that c.f. excitation of these neurones leads to inhibition of mossy fibre-granule cell transmission and thus to disfacilitation of the P cells. Further evidence pertaining to pause production is discussed at length by Armstrong (1974).

Post c.s. pauses have not previously been systematically studied in awake animals although values ranging from 15 to 30 ms are mentioned by Hobson & McCarley

(1972). In the present study pause duration was highly variable both between cells and in individual cells. The shortest values (about 8 ms) are consistent with spike inactivation as the sole cause but the majority of pauses were longer than this, with some as long as 500 ms. Duration was found to correlate inversely with the number of s.s. discharged in the 100 ms immediately preceding the c.s., thus confirming a finding made for one cell in a barbiturate anaesthetized cat by Latham & Paul (1971). This presumably indicates that one factor which determines pause duration is the ambient level of input to the P cell via the m.f. (granule cell) parallel fibre path.

The duration in fact exceeded the prevailing interval between s.s. only when the s.s. discharge proceeded at rates less than 40–50/s. Only then will there be a pause in the s.s. discharge and any disinhibitory effect on the intracerebellar nuclear neurones.

Whilst the observed variability in pause duration is certainly consistent with production via an interneuronal mechanism, it nevertheless requires some comment. One causative factor is presumably the relationship with s.s. rate discussed above but a second factor may be the transmission characteristics of the inferior olive which gives rise to the c.f.s. Thus, in anaesthetized animals Murphy & Sabah (1971) and Armstrong *et al.* (1979) have shown that when c.s. are evoked by electrical stimulation of the olive, pause duration increases with stimulus intensity, presumably due to recruitment of additional c.f.s to the volley. Since neighbouring olivary neurones show a marked tendency towards synchronous discharge due at least partly to a degree of electrical coupling (Llinas, Baker & Sotelo, 1974) and since transmission through the olive shows marked spontaneous variation (Miller & Oscarsson, 1970) it is likely that spontaneous discharges of one olivary neurone (leading to a c.s. in the P cell) will each be accompanied by the simultaneous discharge of a variable number of neughbouring neurones. In addition, there is a marked topographical localization in the olivo-cerebellar projection so that neighbouring P cells and cortical interneurones receive their c.f. innervation from neighbouring olive cells. Thus it is likely that each successive spontaneous c.s. in one P cell will be accompanied by near-synchronous c.f. input to a varying number of cortical interneurones in the immediate vicinity. Under these conditions the duration of successive pauses is likely to show just that marked variation which was observed.

Background discharges of cortical interneurones have previously been studied only in barbiturate anaesthetized animals in which Eccles, Llinas & Sasaki (1966*b*) found slow rates ranging from 7 to 30/s. Rates in the present study ranged from 9 to 28/s and although the cells were not positively identified it is likely that the majority were basket and Golgi cells since the stellate cells are significantly smaller.

Responses evoked by nerve stimulation

Stimulation of the s.r. nerves evoked both s.s. and c.s. discharges of the P cells, but the latter predominated heavily. A few cells responded with s.s. at latencies sufficiently short to suggest that volleys in the cuneo-cerebellar and rostral-spino-cerebellar tracts were responsible but the paucity of such responses recalls the similar infrequency of short latency excitations detected in interpositus neurones in the preceding paper (Armstrong & Rawson, 1979). The majority of cells were discharged with latency 12–30 ms via spino-olivo-cerebellar paths and it is presumably these responses which generated the inhibitory responses with latency 20–30 ms which were common amongst ip.n.s.

Since transmission through the spino-olivo-cerebellar paths is subject to powerful descending influences it is worth noting that at least d.f.-s.o.c.p. and l.f.-s.o.c.p. are open for transmission during quiet wakefulness. In addition the findings that c.s.

latency and probability are subject to marked fluctuation and that the frequency following capability of the paths is limited to frequencies around 10/s indicate that the transmission characteristics of the paths are very similar in awake animals and in the anaesthetized animals previously studied (see Oscarsson, 1973; Armstrong, 1974, for references).

Inhibitory responses to nerve stimulation were prominent in the majority of P cells and the onset of these responses coincided with the excitatory responses of the 'presumed interneurones'. In view of the fact that these pauses were usually preceded by a c.s. it seems likely that they were a consequence of the c.f. input to the cortex and therefore that they were generated by mechanisms similar to those producing the pauses which following spontaneous c.s. This suggestion is perhaps supported by the observation that the two types of response showed similar variations in their duration. It may be noted in passing that s.s. inhibition was present in some cells in which no c.s. were evoked whilst in others an inhibition was still present in trials when a c.s. failed to appear. These findings do not necessarily conflict with the argument above since a whole network of cortical inhibitory interneurones will influence each P cell and the input to this network is certainly not restricted to the c.f. supplying the P cell under study.

Although it is likely that input via the c.f.s played a major part in producing the depressions there is no doubt (see above) that some m.f.s were excited by nerve stimulation and it cannot be excluded that these fibres made some contribution. Indeed, since the m.f.s excite granule cells which in turn excite stellate, basket and Golgi neurones such a contribution is to be expected.

In a few P cells both spontaneous and evoked c.s. were followed by a burst of s.s. rather than a pause. A similar finding has been made occasionally in anaesthetized animals (e.g. Bell & Grimm, 1969) and whilst a precise explanation is not available, the phenomenon is of interest in so far as it provides an additional demonstration that a c.f. input may influence the s.s. rate in the period after the c.s. One possible mechanism might be provided by synaptic contacts observed between c.f. collaterals and granule cells (Palay & Chan-Palay, 1974) but alternatively it might be a disinhibitory response: it is possible that when c.s. discharges occur nearly synchronously in a group of neighbouring P cells, some cortical interneurones may be temporarily inhibited via the P cell axon collaterals.

Although we have not shown whether any of our P cells projected to those interpositus neurones which were studied in the same animals and reported in the preceding paper (Armstrong & Rawson, 1979) this is likely in view of the localization which exists in the cerebellar cortico-nuclear projection. It is interesting, therefore, to note that the P cell depressions evoked by nerve stimulation were approximately coincident with the equally variable delayed accelerations which were elicited in many ip.n.s by the same stimuli (cf. Fig. 9 and Fig. 5 of Armstrong & Rawson, 1979). Our results are therefore fully consistent with the suggestion (Armstrong & Rawson, 1979) that the delayed accelerations are explicable (in part at least) as disinhibitory responses due to a withdrawal of the tonic inhibition normally exerted by the P cells on the cerebellar nuclear neurones.

The situation in the intact cat would seem to resemble closely that reported for cats anaesthetized with α-chloralose by Armstrong *et al.* (1975, 1979) though in the absence of anaesthesia both the P cell and ip.n. responses are less strongly developed.

That the proposed disinhibitory mechanism is feasible is shown by a study by Montigny & Lamarre (1973) which demonstrates that input mediated exclusively via the c.f. system can give rise to reciprocal patterns of activity in P cells and nuclear cells. These workers showed that following administration of harmaline, which acts directly on some olivary regions to synchronize the olive cell discharges (Biscoe, Duggan, Headley & Lodge, 1973), c.s. occur synchronously in many vermal P cells at a frequency of around 10/s and in most of these cells the s.s. are completely suppressed. Fastigial neurones on the other hand respond with silent periods (immediately after the c.s.) alternating with bursts of impulses (during the silent periods in the P cells).

Thus, whilst we do not wish to minimize the importance of the c.s. itself as a remarkable and discrete event in the P cells it seems clear that the present results (and those of Armstrong & Rawson, 1979) do demonstrate that in the intact cat a cerebellar input mediated primarily via the c.f.s may produce significant acceleration of some cerebellar output neurones in addition to the brief inhibitions which are due to c.s. discharges in the P cells. Although the majority of our results were obtained using artificial nerve volleys it should be noted that c.s. were readily produced in the P cells by natural stimuli to the paws. Thus the kinds of response we have observed may play a role in normal motor control as discussed in the preceding paper (Armstrong & Rawson, 1979).

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