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THE RECOVERY OF RESPONSIVENESS OF THE SENSORY SYNAPSES IN THE LATERAL GENICULATE NUCLEUS

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The normal ganglion-cell discharge from the retina consists of a brief high-frequency burst of impulses. The short refractory period and prolonged phase of supernormality in the recovery cycle of the optic nerve and tract fibres are properties well suited to handle such a discharge (Bishop, Jeremy & Lance, 1953). The ganglion-cell discharge may, however, undergo important modification in the lateral geniculate nucleus before relay to the cerebral cortex. One of the most important factors determining such a modification is the nature of the recovery cycle of the synapses and neurones in the nucleus. A detailed account of the recovery of the geniculate synapse from the refractory state has already been published (Bishop & Evans, 1956). Recovery from refractoriness in this nucleus is principally determined by the rate at which normal conduction ability returns in the presynaptic fibres. Slowed conduction in relatively refractory axons means that the absolutely refractory period of the synapse is greater the longer the effective presynaptic pathway. An upper value of 0·85 msec was set for the absolutely refractory period, with conditioning and testing stimuli applied to the presynaptic pathway (optic tract) about 10 mm from the lateral geniculate nucleus. The geniculate neurones were always capable of responding as soon as conduction became possible in optic tract fibres. By stimulation of the optic nerve and with spike height as an index, the relatively refractory periods of the presynaptic and post-synaptic spikes recorded in the lateral geniculate nucleus were 1·7 and 1·6 msec, respectively. Supernormal excitability on the part of the geniculate neurones commences while the optic nerve fibres are still relatively refractory.

It is the aim of the present paper to describe the stages of the recovery cycle from refractoriness up till 5 sec after the discharge of the geniculate neurones. A re-examination of the results of Bishop & Evans (1956) shows that the early phase of supernormality referred to above extends from about

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0·95 to 1·65 msec. The results given below show that the recovery cycle which follows this early stage then shows alternating periods of subnormal and supernormal responsiveness, each of increasing duration. These phases are examined in detail. Recovery after brief repetitive stimulation will be described in a subsequent paper together with an analysis of the relationship between recovery and the after-potentials of the geniculate neurones. The earlier work of G. H. Bishop & O'Leary (1940), Marshall & Talbot (1940, 1941, 1942), Talbot & Marshall (1941) and Marshall (1949) on the recovery of responsiveness of the geniculate neurones will be discussed in relation to our findings.

Understanding of the fundamental properties of the spinal motoneurones and of the synapses associated with them is now much more complete than that of any other neurone type in the central nervous system. It is clear, however, that other neurone types and synaptic centres in the central nervous system have properties some of which diverge widely from those characteristic of the spinal motoneurone. For this reason it is important that attention should be directed towards the study of a variety of synaptic centres. The earlier paper of Bishop & Evans (1956) and the present study provide information relating to the recovery properties of sensory neurones and their associated synapses.

METHODS

Adult cats were used in all experiments, and were anaesthetized with intraperitoneal allobarbitone (Dial, Ciba, 0·5 ml./kg.). If necessary small amounts (totalling 0·3 ml.) of sodium pentobarbitone (Sagatal, May and Baker) were added intravenously. The cat's body temperature, read with a rectal thermometer, was controlled within normal limits (38–39° C) with the aid of an electric heating blanket. The general methods used have been adequately described in previous communications from this laboratory (cf. particularly Bishop, Jeremy & Lance, 1953). The eyeball was resected and the optic nerve prepared for electrical stimulation by being suspended clear of orbital tissue. The response of the opposite lateral geniculate body was recorded by means of a stereotaxically directed steel micro-electrode introduced down through the intact cerebral cortex. The recording position was determined by electrolytically depositing iron from the tip of the micro-electrode by means of a current of 30–40 μA flowing for 15 sec; the brain was subsequently perfused, first with normal saline and then with 10% formalin saline containing 1 g/100 ml. of potassium ferrocyanide. The blue spot at the recording site was found in serial histological sections after paraffin embedding.

RESULTS

The notation used for referring to the principal structures contributing to the wave form of the geniculate response following optic nerve stimulation is standard for this laboratory (cf. particularly Bishop & McLeod, 1954; Bishop & Evans, 1956). Ordinarily we use the term 'contralateral t_1' to designate the group of tract fibres of larger diameter that have come from the contralateral optic nerve. Since only crossed fibres have been used in this investigation the term 't_1' will be sufficient, and also with respect to the term 'r_1' which

refers to the corresponding post-synaptic propagated discharge of the geniculate neurones. Similarly the terms 't_2' and 'r_2' will be used to refer respectively to the presynaptic and post-synaptic responses in the lateral geniculate nucleus associated with activity in the group of optic tract fibres of smaller diameter (Fig. 1, C.R.). The analysis of the wave form of the geniculate response and the method used for measuring it have been given in earlier publications (cf. particularly Bishop & Evans, 1956).

The curve of recovery of responsiveness of the geniculate synapses following transmission was determined by applying a test volley to the synapses and progressively increasing the interval between conditioning and testing shocks

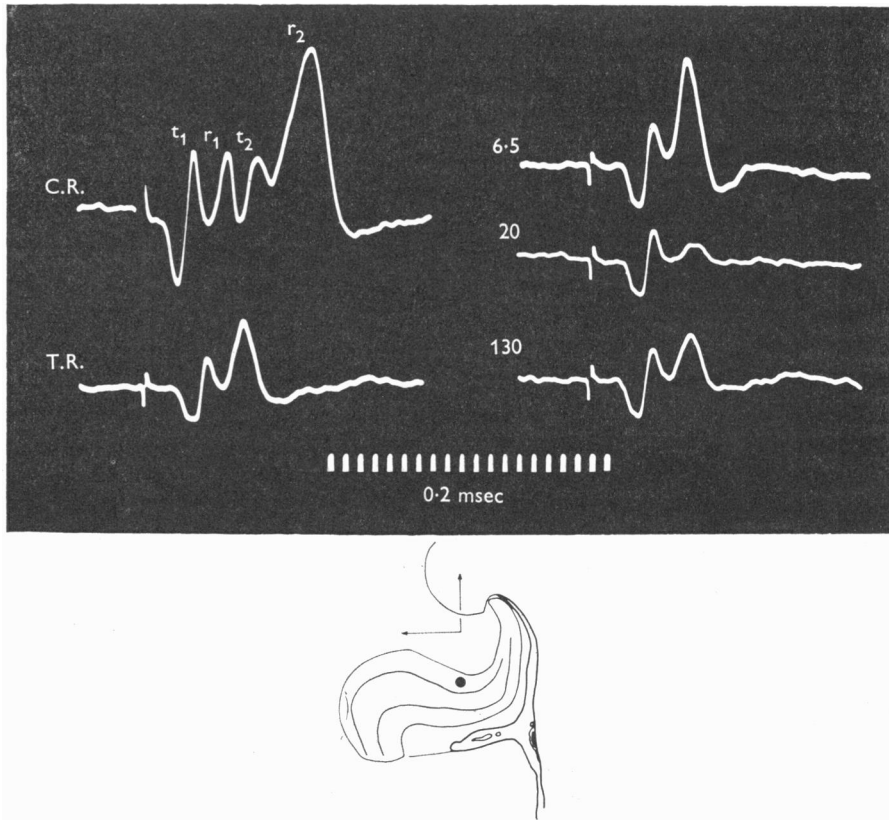

Fig 1. Recovery of responsiveness of geniculate synapses following a maximal conditioning shock applied to the contralateral optic nerve. C.R., conditioning response; t_1, t_2, presynaptic spikes; r_1, r_2, corresponding post-synaptic spikes. T.R., unconditioned test response, 47% maximal for t_1. Remaining traces show conditioned test responses at shock intervals indicated in msec. Recording site was close to filled circle in outline drawing of parasagittal section of lateral geniculate nucleus; arrows indicate horizontal and vertical Horsley–Clarke planes. For details see text.

in the usual way. In carrying out this procedure and in assessing the results obtained a variety of factors had to be taken into consideration. It will be convenient to discuss these factors first, before presenting the curve of recovery of responsiveness. While all these factors are of importance in this context, some are of technical interest only, whereas others also merit consideration because of the clues they provide to the organization of the lateral geniculate nucleus. The detailed description of our results from the latter point of view will be reserved for a later publication.

Factors associated with the conditioning response

In order to test recovery processes it is important to ensure that the testing volley should only reach geniculate neurones that have been discharged by the conditioning volley. The conditioning shock was therefore made supramaximal for all the fibres in the optic nerve. It remained possible, however, that a maximal optic nerve volley might still have associated with it a fringe of subliminally excited geniculate neurones that could be brought to discharge only by a suitably timed second volley. Bishop & Evans (1956) have already discussed this problem. From an analysis of the random fluctuations in the amplitude of the geniculate response to a constant afferent volley, they concluded that the subliminal fringe associated with a smaller presynaptic volley is completely discharged by a larger independent volley. In other words, as the unconditioned presynaptic volley grows in amplitude with increasing shock strength the geniculate cells are progressively brought into the discharge with no 'islands' of subliminal fringe excitation remaining. Several other lines of evidence lend strong support for this view, namely:

The relationship between the amplitudes of the t_1 and r_1 spikes, normally and with conditioning. Curve (*c*) of Fig. 2 shows the normal unconditioned t_1/r_1 relationship and the other curves show the relationship at the indicated times (4·2, 10·5 and 20·5 msec) after a conditioning volley maximal for t_1 and t_2. It will be seen that, at the 4·2 msec interval, the increase in amplitude of the r_1 spike due to supernormal excitability on the part of the geniculate neurones is independent of the amplitude of the r_1 response over practically the whole range of the afferent bombardment. The increase in the r_1 spike due to supernormal excitability is a measure of the size of the available subliminal fringe, since the latter determines the maximum facilitation that can occur with a test volley whatever the means used to obtain the facilitation. The fact that the amount of the facilitation is constant and independent of the amplitude of the r_1 spike indicates not only that the size of the subliminal fringe is constant, but also that the fringe associated with a smaller presynaptic volley is completely discharged by a larger independent volley.

At an interval of 10·5 msec after the conditioning response (Fig. 2) the r_1 spike is reduced because the recovery cycle of the geniculate synapses has

now entered a prolonged phase of depression. Again, the amount of the depression is constant and independent of the amplitude of the r_1 spike. At an interval of 20·5 msec the depression of the r_1 spike has greatly increased being about maximal at this time (Fig. 3*d*). In all the curves in Fig. 2 the reduction in amplitude of the r_1 spike as the t_1 volley reaches a maximum is due to summation of the r_1 negativity with the prodromal positivity of the t_2 spike.

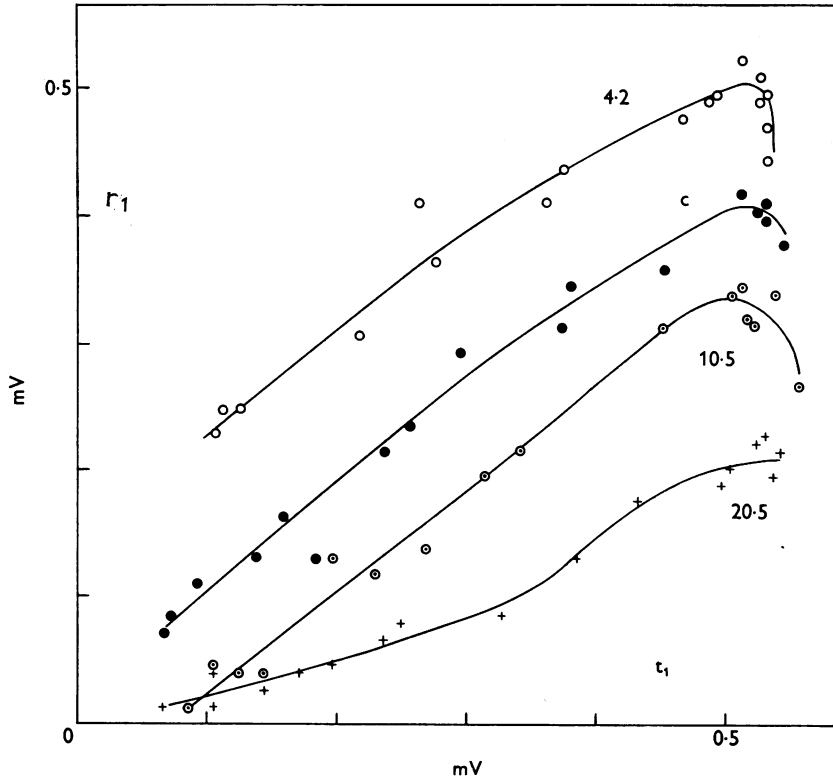

Fig. 2. Relationship between amplitude of presynaptic spike (t_1) and post-synaptic spike (r_1) in response to increasing stimulating shocks applied to the contralateral optic nerve. (C), normal control curve. Remaining curves show the relationship at times indicated in msec following a conditioning shock which was maximal for t_1 and t_2. Abscissae (t_1) and ordinates (r_1) are given in millivolts. Recording site indicated by filled circle in outline drawing in Fig. 1. For details see text.

For this reason the plotting of the curves was stopped just short of a maximal t_1 volley. The change in slope of the curve at the 20·5 msec interval, when the amplitude of the t_1 volley falls below about 50% maximal, is due to the fact that the post-synaptic propagated discharge is now failing almost completely and the amplitude of the response comes to be determined very largely by the non-propagated synaptic potential.

Maximal conditioning and testing shocks. By using maximal conditioning and testing volleys the possibility of a 'supra-maximal' geniculate response was sought at nine recording sites in five preparations. Shock intervals between 3 and 5 msec were chosen to correspond with the peak of the late phase of increased synaptic responsiveness (see below). It is difficult to study the early phase of facilitation when using a maximal conditioning shock because the later stages of the conditioning response in the lateral geniculate nucleus interferes with the recording of the testing volley. The detailed analysis of these results will be published elsewhere. For our present purposes it will be sufficient to say that there was no indication that a fringe of subliminally excited neurones was available to the t_2 test volley under these circumstances; on eight of the nine occasions the r_2 spike was substantially reduced (by 20–30%) and one one occasion it was unchanged. The behaviour of the r_1 spike was somewhat more complicated; it was usually unchanged (five occasions) once it was slightly reduced (to 85%) and on another occasion it could not be measured because of the superimposition of the r_1 and t_2 spikes. On the remaining two occasions the r_1 response was clearly increased in amplitude (125 and 142% respectively, normal = 100%), the r_2 response being then reduced by an amount about the same as that by which the r_1 response was facilitated. Our explanation for the latter finding, based on a detailed analysis of the strength–response curves and on single unit recording (to be published elsewhere) is that there are occasional cells in the nucleus that are innervated both by t_1 and t_2 afferent fibres. In the present instance these cells were normally discharged only by the t_2 fibres, being subliminally excited by t_1 fibres. During the supernormal phase of recovery from discharge, however, the cells were then fired by the t_1 volley and were refractory to the t_2 volley. The important observation for the present paper is that, although there may be occasional cells in the nucleus that lie in the subliminal fringe of a maximal t_1 volley, they are nevertheless discharged by a volley maximal for t_2.

Post-tetanic potentiation. A study of the phenomenon of post-tetanic potentiation provides information regarding the size of the subliminal fringe about active geniculate neurones. With supramaximal conditioning and testing shocks the mean post-tetanic potentiation of the r_1 spike in five experiments was only 103% (normal = 100%); in only one experiment was there a significant increase (Bishop, Burke & Hayhow, 1959). It is interesting to note that with a submaximal testing shock the post-tetanic potentiation was 114%, which is about the same as the post-discharge supernormal responsiveness reported in this paper. This finding presumably indicates that both phenomena are limited in the same way by the available subliminal fringe.

All the above evidence indicates that a maximal optic nerve volley does not leave a fringe of subliminally excited neurones. A testing volley under these

circumstances must therefore only reach synapses and neurones that have been discharged by the conditioning volley; i.e. it tests post-discharge recovery processes and not subliminal excitation.

Method used for expressing results

The fact that the amount of the facilitation or depression is constant over almost the whole range of test volley size has another important consequence: it provides a way of comparing the degree of facilitation or depression from one experiment to another and so generalizing the results obtained. In this paper changes in post-synaptic responsiveness, both in the direction of facilitation and depression, are expressed as a percentage of a fixed r_1 amplitude, namely, the r_1 spike produced by an afferent volley which is 50% maximal for t_1. The latter procedure was adopted because it is easy to determine the maximal amplitude of the t_1 spike, whereas the r_1 spike is affected by the appearance of the t_2 response. The relationship between the amplitudes of the t_1 and r_1 spikes was plotted in every experiment and the amplitude of the r_1 spike produced by a 50% maximal t_1 spike could be read off from this graph (cf. Bishop & Evans, 1956).

Factors associated with the test response

Many of the factors which have to be considered in relation to the test response have already been discussed in an earlier paper (Bishop & Evans, 1956). These include the selection of the recording site, the quantitative analysis of the wave form of the geniculate response, spontaneous fluctuations in the excitability of the geniculate neurones and effects of changes in the depth of the anaesthesia. Two factors constitute a special hazard, namely, the movement of the brain with respect to the micro-electrode and changes in the threshold for stimulation of the optic nerve. With regard to the former, when a suitable recording site was found it was usual to wait about half an hour before commencing the series of recordings, to allow the geniculate tissue to adapt itself, mechanically and biologically, to the presence of the micro-electrode. Any movement is usually indicated by changes in the relative amplitudes of the t_1 and r_1 spikes. Plots of the t_1/r_1 relationship both before and after a particular recording series were usually carried out and compared (cf. Bishop & Evans, 1956). The main factor altering the stimulus threshold of the optic nerve was the shunting effect of the collection of tissue fluid. Usually the nerve can be suspended clear of orbital tissue in such a way that this is not a problem and careful swabbing every 1–2 hr, or the installation of drainage, usually ensures that the threshold remains almost constant during the recording series. A large number of unconditioned test responses recorded throughout the recovery cycles provided a check on the constancy of the recording conditions. The interval between each sequence of conditioning

and testing stimuli (5–10 sec) was chosen to avoid as far as possible any cumulative changes in excitability. The early phases of recovery, covering supernormality and early subnormality, were usually recorded twice for each cycle.

Presynaptic excitability changes

Using antidromic volleys in the optic nerve, Bishop, Jeremy & Lance (1953) have already studied the changes in the excitability of the optic tract fibres during recovery from discharge. By recording the optic tract volleys in the lateral geniculate nucleus, however, it is possible to obtain information about the properties of the fibre terminals. Details of the recovery of the fibre terminals from the refractory state have already been published (Bishop & Evans, 1956) and the later stages of the recovery process are reported here (see Table 1 and 2; Figs. 3*a* and 5*a*). The data given in Tables 1 and 2 were obtained from eleven preparations in which a total of nineteen recovery cycles were analysed. Supernormality commences about 1·7 msec after discharge,

TABLE 1

t_1 amplitude (% of maximal)	Number of cycles	Mean supernormality (%)
30–39	8	179
40–49	6	159
50–59	3	139
60–69	2	134

reaches a peak at 4·6 msec and terminates at about 34 msec. Subnormality does not normally occur following a single conditioning volley. The time course of the phase of supernormality is very similar to that reported by Bishop Jeremy & Lance (1953) using antidromic stimulation and, like the r_1 spike, we found it to be independent of the amplitude of the t_1 volley. By contrast with the antidromic results, however, the amplitude of the response on the part of the fibre terminals showed a much greater increase during supernormality, having an average maximum of 151 % for a volley which was 50 % maximal for t_1. Between 110 and 120 % was the value obtained by stimulating the optic tract and recording from the optic nerve. It is difficult, however, to make a valid comparison between these results because of the difficulty in obtaining maximal stimulation of the whole optic tract by means of buried electrodes. It is probable, however, that, as far as supernormality is concerned, the fibre terminals do not differ from the portion of the axon in the optic tract. In one experiment bipole electrodes were placed in the optic tract between the chiasma and the nucleus. The recovery cycles of the tract fibres at that site were obtained by recording the antidromic volley from the nerve and the reverse procedure gave the recovery cycle of the optic nerve fibres. The maximum supernormality in the two instances was 118 and 153 %, respectively, the orthodromic test volley in the latter instance being 49 %

maximal for t_1. Thus if different parts of the axon vary with respect to the degree of supernormality it is the optic nerve on the one hand which differs from both the optic tract and fibre terminals on the other. This may, however, be a result of the preparation and general treatment of the optic nerve rather than a true physiological difference.

It has been pointed out above that the amount of the facilitation of the r_1 spike during supernormality is constant with increasing volley size so that the percentage facilitation progressively declines. The same is true of the t_1 response (see Table 2) and this fact again enables us to compare the supernormality found in one experiment with that found in another by expressing the amount as a percentage of the amplitude of the tract spike which was 50% maximal for t_1. In order to test the validity of this method of comparison the mean supernormality found in seven recovery cycles in which the amplitude of the t_1 volley was close to 50% maximal (range 47–54, mean 50%) was compared with the mean supernormality in the remaining twelve recovery cycles, in which the amplitude of the t_1 volley fell outside this range (i.e. 32–62%). The former group has a mean actual supernormality of 149% while the latter had a mean calculated supernormality of 152%. The above details are interesting in relation to the organization of the lateral geniculate nucleus because they indicate that any given small sample of geniculate neurones is innervated by afferents having a wide and fairly smooth range of fibre diameters. Other evidence is available which points in the same direction (Bishop, 1959).

Despite the fact that test shocks of constant strength are applied to the optic nerve, it is obvious that the corresponding volleys applied to the geniculate synapses undergo marked fluctuations during the recovery cycle. Marshall (1949) attempted to obtain constant test volleys by repeated adjustment of the intensity of the conditioning shock. Unfortunately, under the experimental conditions it is very difficult to do this with any precision. In this study corrections were made after the experiment by using the graph of the unconditioned t_1/r_1 relationship to obtain the r_1 spike that would be expected for any given amplitude of t_1 volley. Regarding the amplitude of the r_1 spike obtained in this way as the unconditioned post-synaptic spike, the amount of the facilitation or depression was then found by subtraction from the conditioned spike actually recorded. Plots of the t_1/r_1 relationship were carried out before and after the recording of a particular recovery cycle and it was important to determine that, during the cycle itself, the regularly recorded unconditioned test response did fall on this t_1/r_1 line. The amounts of facilitation or depression were then expressed as a percentage of the unconditioned r_1 spike produced by a presynaptic volley which was 50% maximal for t_1.

Both methods of correction mentioned above assume that the changes in

amplitude of the t_1 volley are due solely to fibres entering or leaving the response, the single spike in the response remaining unchanged. It is possible, however, that general and regional fluctuations, both of the membrane potential and of the time relations of the impulse, could lead to alterations in the amplitude of the t_1 spike without involving an increase or decrease of the number of fibres activated. That the latter effects can be neglected for the present purpose is indicated by the fact that, on nine occasions, the conditioned t_1 response was never increased and was not reduced by more than a few per cent when maximal conditioning and testing shocks were used. Any change in amplitude that occurs when submaximal shocks are used is, therefore, due almost entirely to fibres entering or leaving the response. As was pointed out above, the results can be expressed in a way that is independent of changes in the amplitude of the unconditioned r_1 response.

The early supernormal phases

The results of a typical experiment are shown in Figs. 1, 2 and 3; these were all obtained from the same preparation. The tip of the micro-electrode was located in layer A (Thuma, 1928) at approximately the anteroposterior and mediolateral mid point of the lateral geniculate nucleus (1·5 mm from the medial edge and 2·8 mm from the anterior pole; Fig. 1). The traces shown in Fig. 1 were selected from those used in the preparation of Fig. 3*a*, *c* and *d*. The conditioning response (C.R. Fig. 1) was maximal for t_1 and t_2 while the test response (T.R.) was 47 % maximal for t_1. The t_1/r_1 graph shown in Fig. 3*b* was obtained immediately before the recording of the recovery cycle (Fig. 3*a*, *c* and *d*). The t_1, r_1 values of the mean unconditioned test response obtained during the recovery cycle are indicated by the arrow (Fig. 3*b*). Some hours later the traces used in the preparation of Fig. 2 were recorded but, in the interval, a very slight movement of the micro-electrode had occurred so that graph *C* of Fig. 2 is not comparable to Fig. 3*b*. The recording site was then labelled by deposition of iron from the micro-electrode (Fig. 1).

With a maximal conditioning volley (C.R. Fig. 1) the presence of the r_2 spike made about 2·5 msec the least shock interval at which a measurement of the test response could be made. Graph (*a*) of Fig. 3 shows the time course of the supernormality of the presynaptic fibres. Graph (*c*) shows the time course of the recovery cycle of the post-synaptic spike, uncorrected for changes in t_1, from about 2·5 msec until recovery is complete. Unconditioned test responses were recorded before every conditioning–testing sequence and the changes in the conditioned r_1 spike have been expressed in graph (*c*) simply as a percentage of the corresponding unconditioned spike. In graph (*d*) the measurements of the conditioned r_1 spike have been corrected for changes in the t_1 volley and then plotted as a percentage of the r_1 spike produced by a presynaptic volley that was 50 % maximal for t_1. When plotting commenced,

supernormality was already present and persisted for a shock interval of 8·6 msec.

Of the total of eighteen recovery cycles recorded from ten cats, fourteen clearly showed this late phase of supernormality, one returned only to normal and the remaining three approached normality before the onset of the phase of deep subnormality. Taking all these experiments into account the peak of

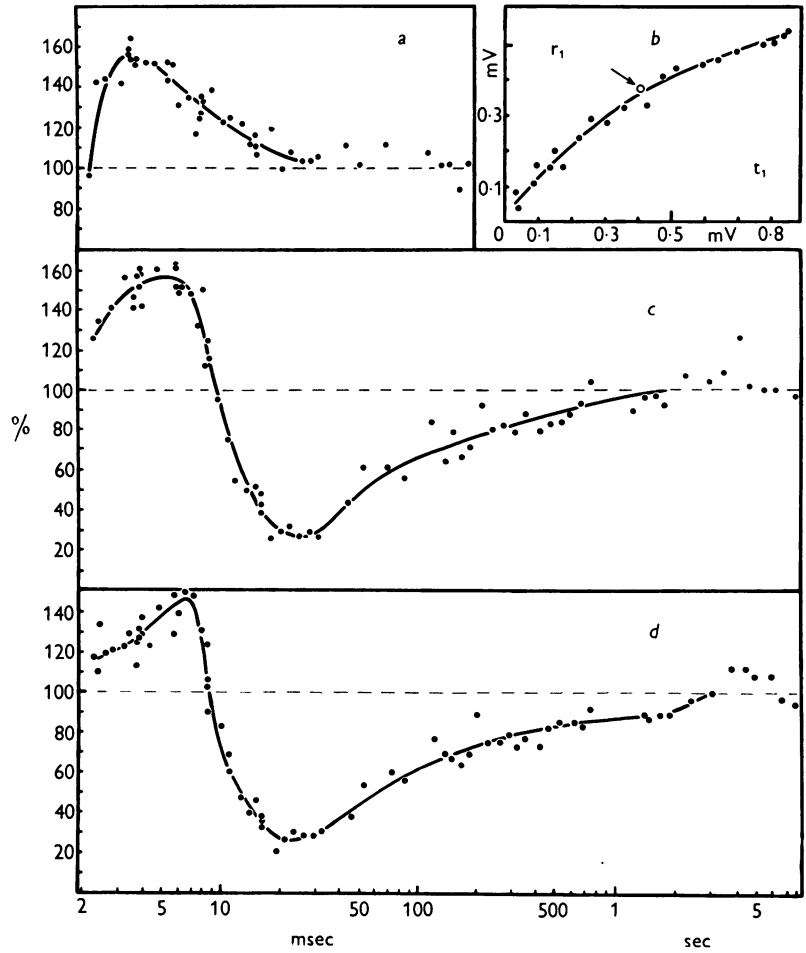

Fig. 3. Curves of recovery of responsiveness of geniculate synapses following a maximal conditioning shock applied to the contralateral optic nerve. Responses in Fig. 1 were selected from those used for above curves. Curve (*a*), recovery of presynaptic spike (t_1). Curve (*b*), relationship between amplitudes of presynaptic and post-synaptic spikes in response to increasing afferent stimulation; open circle indicated by arrow shows mean unconditioned test response obtained during recovery cycle. Curves (*c*) and (*d*), recovery of post-synaptic spike, uncorrected (*c*) and corrected (*d*) for presynaptic excitability changes. Abscissae (log-scale) are common to graphs *a*, *c* and *d*. For details see text.

supernormality had a mean corrected value of 113% at a shock interval of 4·7 msec. Details of both the corrected and uncorrected recovery cycles are given in Table 2. The fact that conduction velocity recovered to normal at a shock interval of about 1 msec (cf. Graham & Lorente de Nó, 1938) means that the shock intervals given in the table can be translated directly into response intervals without significant error. It will be seen that, owing to the prolonged increase in the t_1 volley, the supernormality in the uncorrected recovery cycles had a mean value of 181% and persisted for a shock interval of 9·9 msec.

Shock intervals between recovery from absolute refractoriness (about 0·8 msec) up till 2·5 msec cannot be studied by using a maximal conditioning volley (see above). Bishop & Evans (1956) have, however, studied this interval by using a conditioning volley that was usually just submaximal for t_1. They pointed out that supernormality on the part of the r_1 spike began before the return to normal of the t_1 spike at about 1·7 msec. There was clearly an early phase of supernormality that could not be accounted for by changes in the size of the t_1 volley. Using Bishop & Evans's data we have now defined this phase of supernormality by means of a systematic correction for changes in the t_1 volley (Fig. 4). Six preparations provided data which were suitable for this detailed analysis and the results are set out in Table 2. Supernormality commenced at 0·95 msec (mean shock interval), reached a peak of 114% at 1·14 msec, and terminated at 1·66 msec. An early peak of supernormality round about 1 msec was present in all the six preparations examined. Unfortunately, with the smaller conditioning volley the longest shock intervals used by Bishop & Evans were generally less than 3 msec, so that there was only a relatively small overlap between their recovery cycles and those reported in this paper.

Figure 5*A* and *B* shows the corresponding presynaptic and post-synaptic recovery cycles, respectively, with shock intervals up to 10 msec, the phases being recorded successively at the same site in the nucleus. The two phases of supernormality of the r_1 spike are seen to be separated by a phase of relative subnormality at about 2 msec. In recording this cycle the conditioning shock was just submaximal for t_1 with shock intervals up to 2 msec, and thereafter it was made maximal for t_1 and t_2. The early phase of supernormality ends at about the same time as the conditioned t_1 and r_1 spikes regain their unconditioned amplitude (cf. Bishop & Evans, 1956). That the two phases of supernormality can be distinguished may, therefore, be due to the fact that the conditioned test volley is increasing rapidly in amplitude during the first 2–3 msec, whereas it remains relatively constant during the subsequent 5 msec (Fig. 5*A*). The early phase is, therefore, one of relative supernormality only, whereas the later phase is one of true supernormality because both the conditioned t_1 and r_1 spikes are actually larger than normal.

TABLE 2

		Absolutely refractory period (msec)	Supernormality: Phase	Onset (msec)	Peak time (msec)	Peak supernormality (%)	Termination (msec)
t_1	Antidromic*	0·47	—	(2–3)	(4–6)	(110–120)	33 (20–45)
	Orthodromic	0·81 (0·7–0·92)†	—	1·7 (1·4–2·0)†	4·6 (3·3–6·5)	151 (132–180)§	34 (22–70)
r_1 (corrected)	—	< 0·85†	Early phase‖	0·95 (0·94–0·96)	1·14 (0·83–1·42)	114 (102–126)§	1·66 (1·05–2·2)
			Late phase	−(< 2·0–4·3)	4·7 (2·4–7·0)	113 (77–146)§	6·7 (3·6–11·3)

		Absolutely refractory period (msec)	Onset, early phase	Peak time, late phase	Peak supernormality late phase (%)	Termination late phase
r_1 (uncorrected)	—	0·81 (0·70–0·92)†	1·6 (1·35–1·85)†	4·8 (2·7–6·0)	181 (128–292)	9·9 (6·7–13·8)

The values given are mean values, the range of variation being given in brackets.

* Bishop, Jeremy & Lance (1953). † Bishop & Evans (1956). § Expressed as % of amplitude (t_1 or r_1) when t_1 was 50% maximal.

‖ Based on data from Bishop & Evans (1956).

TABLE 3

	Subnormal phase: Uncorrected maximum subnormality	Corrected: Maximum subnormality	60	80	Change of slope: 87	90	100	Terminal supernormality: Corrected: Peak	Termination
r_1 (% recovery)	44 (31–68)	32 (20–44)			(75–100)			114 (8–30)	100
Shock interval (msec)	24 (16–30)	19 (15–26)	83 (70–90)	170 (130–230)	220 (170–250)	1050 (500–1800)	2 sec* (1·4–3·0)	3·8 sec* (2–5·5)	5 sec* (4·5–6)

The values given are mean values, the range of variation being given in brackets. Shock intervals are in milliseconds except where indicated.*

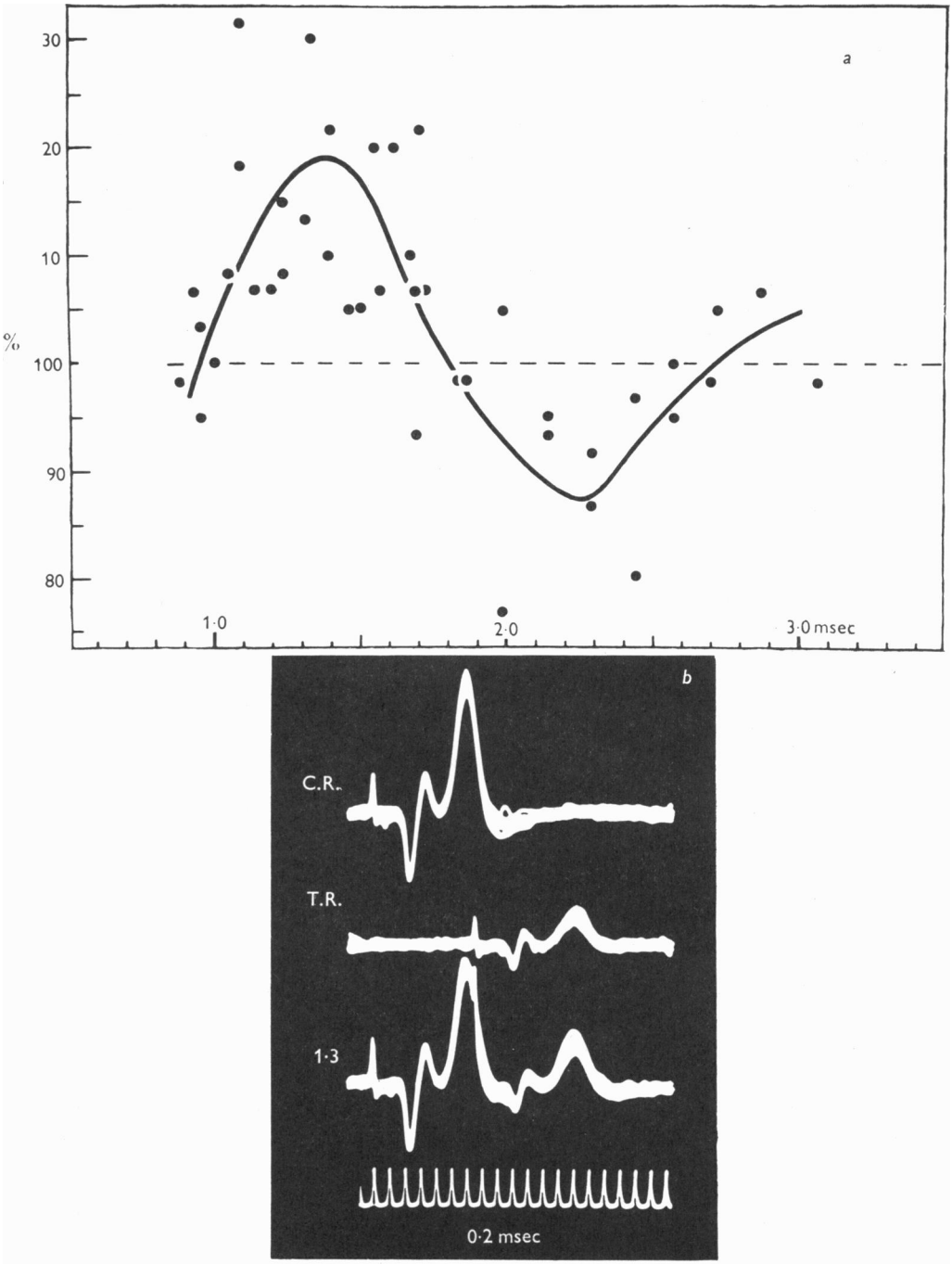

Fig. 4. Recovery of responsiveness of geniculate synapses during first 3 msec after a conditioning shock, 90% maximal for t_1, applied to contralateral optic nerve. Test stimulus 31% maximal for t_1. (*a*) Post-synaptic spike recovery curve corrected for changes in the t_1 spike due to relative refractoriness and subsequent supernormality. (*b*) Superimposed geniculate responses (10 traces each). C.R., conditioning response, T.R., test response, unconditioned and conditioned at a shock interval of 1·3 msec.

A further complication is introduced by reason of the fact that, during the early phase, the conditioning shock was necessarily always only maximal for t_1 (or just submaximal) whereas, with one exception, it was always made maximal for both t_1 and t_2 throughout the remainder of the recovery cycle.

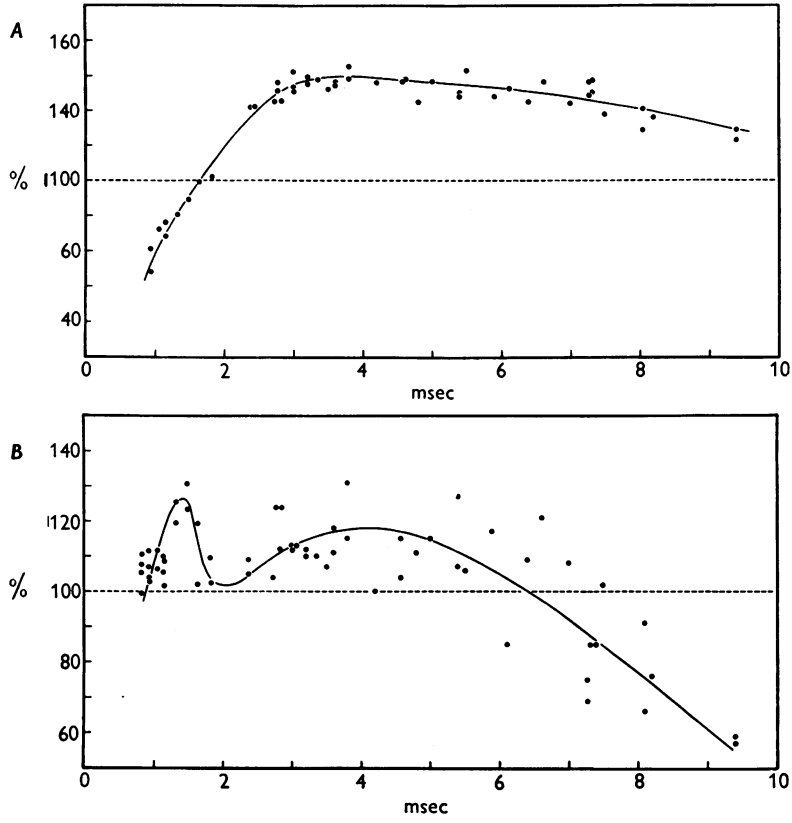

Fig. 5. Recovery of responsiveness of presynaptic (*A*) and post-synaptic (*B*) spikes. Conditioning shock applied to contralateral optic nerve just submaximal for t_1 at shock intervals up to 2 msec and thereafter maximal for both t_1 and t_2. Post-synaptic recovery curve corrected for presynaptic excitability changes. For details see text.

On the one occasion when a conditioning shock maximal for t_1 only was used throughout the whole recovery cycle there was no clear separation between the two phases. On another occasion, however, when the wave form of the conditioning response (maximal for both t_1 and t_2) allowed measurements to be made at shock intervals as early as 2 msec, there was a clear indication of an intervening phase of relative subnormality.

It is interesting to note that in the case of unit repetitive firing in the lateral geniculate nucleus the least spike interval is about 0·8 msec (unpublished

observations). The preferred intervals for repetitive firing, as indicated by the response obtained from cell populations (Bishop, Jeremy & McLeod, 1953), may also be a function of the phases of supernormality described above.

The subnormal phase

Immediately following the late phase of supernormality, at a shock interval of about 6·7 msec, the curve of recovery of responsiveness crosses sharply to a phase of deep and prolonged subnormality (Fig. 3*d*). Mean values for the various portions of the curve of recovery from depression are given in Table 3. Maximum depression (32 %) is reached at a shock interval of 19 msec, and thereafter the r_1 spike recovers, at first rapidly and then increasingly slowly. In all the curves there is evidence of a two-stage recovery process with a change of slope or 'knee' occurring at a shock interval of about 220 msec, when the response is about 87 % recovered. Though it is not very marked, this change of slope can be seen in Fig. 3*d*. The second stage of recovery takes about a further 1·8 sec to overcome the remaining 13 % of depression.

In the four recovery cycles in which shock intervals much beyond 2 sec were used there was evidence of a further phase of supernormal responsiveness having a peak at about 3·8 sec and ending at about 5 sec (Fig. 3*d*). Further work will have to be done in order to describe this late phase more adequately. The possibility of further fluctuations in responsiveness beyond about 5 sec was not examined.

Electrode position in the lateral geniculate nucleus did not seem to be an important factor in determining the form and time course of the recovery cycle. In fact recovery cycles recorded at different positions in the one preparation were closely similar. Depth of anaesthesia is probably a much more important variable. Animals were always as lightly anaesthetized as possible but in one preparation the effect of the intravenous administration of 0·5 ml. of Sagatal was studied. The drug caused a reduction in the peak supernormality of the t_1 spike and at the same time, an increase in the peak supernormality of the r_1 spike. It is unlikely that this increase in r_1 supernormality is due to a change in the available subliminal fringe because the t_1/r_1 graph remained unaltered. Further work will have to be done to elucidate the effect of the anaesthetic.

DISCUSSION

The idea that both the parts of the neurone involved in synaptic transmission, and the transmission process as a whole, would be found to have properties which would resemble, qualitatively at least, those of the axon has long been an obvious working hypothesis (cf. Gasser, 1939). It was early found that the synapses in sympathetic ganglia have a classical recovery cycle which involves an early phase of supernormality and a late phase of depression (Eccles, 1935;

Lloyd, 1939*b*) and a good correlation was obtained between the orthodromic recovery cycle and the ganglion after-potentials (Lloyd, 1939*a*).

By stimulating the posterior longitudinal bundle and adjacent tracts in the brain stem and recording the internal rectus muscle action potential Lorente de Nó (1935) estimated the absolutely refractory period of the oculomotoneurone synapses to be 0·6 msec. A maximal muscle action potential was taken as an indication that the oculomotoneurone pool was being maximally discharged by the presynaptic volley. Bishop & Evans (1956) have already pointed out that an important correction is necessary by reason of slowed conduction in the relatively refractory presynaptic fibres. Another difficulty, however, remains. Lorente de Nó's Fig. 2 shows that at a shock interval of 1·45 msec the test muscle response was approximately recovered to normal. Nevertheless, the recovery cycle of oculomotoneurones studied by Lorente de Nó & Graham (1938) with antidromic conditioning and orthodromic testing volleys showed no evidence of this early phase of rapid recovery to near normality. Instead, absolute refractoriness was followed only by a prolonged phase of gradually lessening depression. Subsequent investigations of the recovery cycle of spinal motoneurones with the same method of conditioning and testing (Brooks, Downman & Eccles, 1950*a*; Lloyd, 1951) have revealed absolute refractoriness to be succeeded directly by a brief phase of increasing depression with a minimum at 10–20 msec and thereafter gradual recovery to normal at about 100 msec. Any early phase of lessening depression or frank facilitation has been attributed to a failure of the antidromic conditioning volley to enter the motoneurone cell body (see later). In considering Lorente de Nó's early findings regarding the refractory period of oculomotoneurone synapses (Lorente de Nó, 1935), the possibility of multiple innervation of individual internal rectus muscle fibre has to be considered (Hunt & Kuffler, 1954). A maximum muscle action potential need not necessarily indicate a maximal discharge of the oculomotoneurone pool.

G. H. Bishop & O'Leary (1940), Marshall & Talbot (1940, 1941) and Talbot & Marshall (1941) made early observations on the recovery cycle of lateral geniculate neurones. Under the conditions in which these early experiments were done no account was taken of presynaptic excitability change and post-discharge supernormality was not distinguished from facilitation by summation of subliminal excitation. Later Marshall & Talbot (1942) and Marshall (1949) attempted to offset presynaptic excitability changes by adjusting the strength of the testing shock. Marshall (1949) concluded that, for shock intervals up to 10–12 msec, refractoriness and supernormality occur and that the succeeding phase of depression lasted up to 5 sec. Marshall's supernormal phase lasted rather longer than we have found, presumably because it includes the summation of subliminal excitation as well as true post-discharge supernormality. The main (late) phase of supernormality reported in this paper

lasted for shock intervals up to 11·3 msec (mean 6·7) with a peak at a mean shock interval of 4·7 msec. The succeeding depression was maximal at a shock interval of 19 msec and thereafter recovery proceeded relatively rapidly up to 87 % of normal at 220 msec and then very much more slowly until normality was achieved at 2 sec. Recently Vastola (1959) studied the recovery cycle of geniculate neurones, using both antidromic conditioning and testing volleys. The antidromic cell body spike recovers nearly to its control height by 6 msec and then enters a prolonged phase of depression. Vastola's Fig. 7 shows the latter to be maximal at 20–30 msec and recovery to be complete between 100 and 150 msec.

The recovery of transmission in a synaptic system will depend, in a complex way, upon the diverse recovery processes in its individual parts, only one of which is the cell body of the post-synaptic neurone. One of the difficulties in determining the pattern of recovery in the individual parts of the neurone is that of assigning electrical activity to histological structure. Unfortunately, we still know relatively little about the properties of dendrites. The many factors which determine the nature of the recovery cycle of the synaptic system may be briefly reviewed.

The recovery cycle of the cell body will depend upon the way in which excitability is tested, i.e. whether by an orthodromic or antidromic volley or by direct stimulation with implanted electrodes. The recovery of the synapse as a functional whole, on the other hand, can only be tested by conditioning and testing volleys both of which are orthodromic and which also traverse the same presynaptic pathway (homosynaptic testing). The use of an orthodromic volley in this way is limited by the recovery processes in the presynaptic pathway and tests excitability changes in the post-synaptic neurone only within the limits fixed by the number and arrangement of the active presynaptic endings. By making the conditioning volley subliminal for a post-synaptic discharge it is possible to study subliminal fringe facilitation without the complication of post-discharge recovery processes (Lloyd, 1946). It is practically impossible to do this in the lateral geniculate nucleus under normal circumstances (Bishop & Evans, 1956; Bishop, Burke & Davis, 1958). In order to study post-discharge recovery processes to the exclusion of subliminal fringe facilitation it is necessary to make the conditioning volley supramaximal for all the neurones within the subliminal fringe of the test volley. While this situation can probably be achieved in the lateral geniculate preparation it is apparently not possible in the case of the motoneurone pools in the spinal cord. In the latter situation also the use of a large conditioning shock introduces the additional complication of interneurone activity. Interneurone activity leading to prolonged synaptic bombardment also makes the flexor reflex pathways much less satisfactory for studying the recovery cycle of motoneurone synapses than the monosynaptic

pathway. For these reasons few systematic studies have been made of the recovery of excitability of motoneurones following orthodromic activation (Lorente de Nó, 1935; Bernhard, 1947; Brooks, Downman & Eccles, 1950*b*; Eccles & Rall, 1951) and in particular relatively little information is available about the early part of the recovery cycle of motoneurone synapses in the first few milliseconds, when refractoriness is subsiding and the later stages of recovery are commencing. In so far as it is possible to exclude subliminal fringe facilitation, the orthodromic recovery cycle of motoneurones resembles the antidromic recovery cycle described above fairly closely except in two respects, namely (1) almost complete suppression of reflex discharge during the first 30–60 msec (Brooks *et al.* 1950*b*; Eccles & Rall, 1951), and (2) a greatly prolonged depression that may not approach normality for several seconds (Eccles & Rall, 1951; Jefferson & Schlapp, 1953; Lloyd & Wilson, 1957). The prolonged depression at intervals beyond 100–200 msec is, therefore, probably presynaptic in origin. A comparison of the antidromic recovery cycle of lateral geniculate neurones (Vastola, 1959) with the orthodromic cycle that we have reported here shows that the late prolonged phase of depression is presynaptic in origin.

The recovery of transmission at the synapse may also be tested by applying the testing orthodromic volley in different afferent fibres from the conditioning volley (heterosynaptic testing). This method, which is not practicable in the geniculate preparation, tests recovery of excitability in the post-synaptic neurone without the limitation imposed by recovery in the afferent pathway, but unfortunately subliminal fringe facilitation effects again obscure post-discharge recovery processes. Even with test intervals longer than the survival time of the synaptic facilitation process the recovery cycle may still be complicated by the prolonged depression that may occur, even when the conditioning orthodromic volley is reflexly subliminal (Brooks *et al.* 1950*b*).

Changes in the quantity of transmitter substance released during recovery may be a factor, though relatively little information is available in this regard. Apparently there is little change following a single orthodromic volley and post-activation potentiation of release such as occurs at the frog neuromuscular junction (Hutter, 1952) does not occur at either the motoneurone synapses (Brooks *et al.* 1950*b*; Brock, Coombs & Eccles, 1952) or geniculate synapses (Bishop *et al.* 1958). Marked changes probably occur, however, following repetitive stimulation (cf. Bishop *et al.* 1959). Another factor is the possible persistence of the excitatory action of the transmitter substance either because of the persistence of the transmitter substance itself (cf. Eccles, Fatt & Koketsu, 1954), or, despite the removal of the transmitter substance, the continued presence of a synaptic depolarization (i.e. synaptic potential) on parts of the post-synaptic membrane (e.g. dendrites) not invaded by a conducted impulse. This possibility will be briefly discussed below.

As far as the recovery of the post-synaptic neurone is concerned the use of an antidromic volley for conditioning avoids some of the difficulties associated with an orthodromic volley, but unfortunately introduces additional complications (Eccles, 1955). Antidromic impulses may not invade the cell body, the block being presumed to occur at either of two sites, namely, at the junction of the axon with the initial segment, or at that of the latter with the cell body itself (Brock, Coombs & Eccles, 1953; Frank & Fuortes, 1955; Fuortes, Frank & Becker, 1957). By antidromic testing the absolutely refractory period of the initial segment of the motoneurone is found to be 1·25–1·45 msec or 0·9–1·2 msec, depending upon whether or not the conditioning impulse invaded the cell body. If the cell body discharges it lengthens the refractory period of the initial segment (Brock *et al.* 1953; Fuortes *et al.* 1957). The absolutely refractory period of the motoneurone cell body ranges from 2·5 to 50 msec.

Studies involving the antidromic activation of motor axons have also brought to light the importance of the axon collateral-Renshaw cell mechanism in determining the excitability of the cell and hence the nature of the recovery cycle following activation whether by antidromic or orthodromic volleys. Both antidromic (and therefore orthodromic) inhibition and facilitation may occur (Renshaw, 1941). By recording intracellularly from the motoneurone Eccles *et al.* (1954) have related antidromic inhibition to the discharge of interneurones (Renshaw cells), activated by motor-axon collaterals and, in turn, discharging on to motoneurones. The latency of the inhibitory effect at the motoneurone, judged by the onset of hyperpolarization, is about 1·2 msec after the arrival of the impulses at the region of branching of the collateral from the main motor axon. After orthodromic activation it would follow the initial segment discharge with very little added latency. Antidromic inhibition reaches a maximum 3–10 msec later and has a total duration of about 40–50 msec. Brooks & Wilson (1959) have shown the marked contribution that recurrent inhibition makes to the depression in the motoneurone recovery cycle.

Antidromic or recurrent facilitation has not received much attention, but recently Wilson (1959) has shown that the latency of the facilitatory effect seems to be longer than that of antidromic inhibition by approximately 1 msec, suggesting the presence of at least one more synaptic delay. A related phenomenon, which at present lacks a satisfactory explanation, is the recurrent efferent discharge that may occur in a few motor axons following antidromic impulses in the same axons (Renshaw, 1941). When allowance is made for conduction time, the departure of the recurrent discharge follows about 0·9 msec after the arrival of the antidromic impulse at the motoneurone. It is evident that immediately after antidromic activation some motoneurones pass through a state of increased excitability which is, however, rapidly superseded by the characteristic prolonged phase of depression. A similar

recurrent discharge has been observed in the lateral geniculate nucleus (Bishop, Burke & Davis—unpublished observations).

O'Leary (1940) has described recurrent collaterals from axons of some of the largest cells in the lateral geniculate nucleus but makes note of their relative scarcity. Recently Vastola (1959) considered that the available evidence was against the possibility that recurrent inhibition of the Renshaw-cell type by means of collaterals from the axons of principal cells occurred in the lateral geniculate nucleus. A mechanism of this kind has, however, been postulated as the basis of the repetitive firing that is a common feature of the geniculate discharge (Bishop, Jeremy & Lance, 1953).

Of the greatest importance in determining the recovery cycle of the synapse are the after-potentials of the cell body and to a minor extent the after-potentials of the initial segment and post-synaptic axon. A full discussion of the after-potentials of geniculate neurones in relation to the recovery cycle of the synapses will be reserved for a later paper (cf. Vastola, 1957, 1959). Following either orthodromic or antidromic activation of geniculate neurones the cell body spike is followed by a brief after-negativity which at about 7 msec reverses to a long-lasting deep after-positivity having a duration of 50–120 msec. There is good agreement between the time courses of these after-potentials and the phases of supernormality and the early part of the phase of subnormality described in this paper.

Both negative and positive after-potentials occur in the motoneurone cell body following the spike discharge. Very little attention has been paid to the negative after-potential but measurement of published intracellular records indicates that it only occasionally has a post-spike duration of more than about 2 msec. It rapidly decays to a large positive after-potential that reaches a maximum after 10–15 msec and has a duration of about 100 msec (Brock *et al.* 1952). The recovery cycle of motoneurones described above diverges widely from the curve that is to be expected from the after-potentials, since there is no phase of supernormality to correspond with the negative after-potential. There, is, however, a phase of relative supernormality between refractoriness and subnormality that is attributable to the negative after-potential (Brooks *et al.* 1950*a*, *b*). By intracellular recording Brock *et al.* (1953) demonstrated re-invasion of a cell body by an antidromic impulse during a brief interval (3–6 msec) following refractoriness and before the onset of depression. The negative after-potential in this instance did not reverse to positivity until about 6 msec. Fuortes *et al.* (1957) have confirmed this by direct stimulation of the motoneurone cell body with an intracellular electrode. They found that excitability approached resting threshold with a brief peak between 2–3 msec after the commencement of an antidromic cell body spike. The absence of a phase of supernormality in the recovery cycle of motoneurone synapses probably has a complex origin—prolonged relative

refractoriness, brief negative after-potential, recurrent Renshaw inhibition and weak presynaptic drive. Relative refractoriness may continue for up to 9 msec (Brock *et al.* 1953).

Supernormality in the recovery cycle of lateral geniculate synapses is probably the result of a brief relatively refractory period, a more pronounced negative after-potential, very strong presynaptic drive and possibly the absence of Renshaw-type recurrent inhibition. An additional explanation seems to be required to account for the early phase of supernormality at stimulus intervals between 0·95 and 1·7 msec, and two possibilities may be put forward. (1) There is much evidence (cf. Edwards & Ottoson, 1958) which indicates that the post-synaptic spike is generated in the initial segment. It is possible that the cell body spike may persist for a brief interval after the spike in the initial segment sufficient to provide a powerful catelectrotonic effect upon the latter. Brooks *et al.* (1950*a*) have put forward a similar explanation to account for the recurrent discharge in motor axons. (2) Freygang (1958) and similar unpublished observations from this laboratory provide evidence which suggests that, while most of the post-synaptic membrane may be excited synaptically to produce a post-synaptic potential, the dendritic membrane and possibly also part of the cell body membrane are not excited electrically and do not produce a propagating spike. The persistence of the post-synaptic potential in these regions would lower the threshold of the remainder of the cell body and of the initial segment. The absence of the earlier phase of supernormality in the antidromic recovery cycle (Vastola, 1959) is in keeping with this suggestion. One difficulty with both explanations given above is the fact that, initially at least, the catelectrotonus would have a depressive effect by lengthening the refractory period of the initial segment (Blair & Erlanger, 1933).

The emphasis in this paper has been on the lateral geniculate nucleus as providing an opportunity for studying the properties of sensory neurones and sensory synapses. The part these properties play in the visual process has been ably discussed by Marshall & Talbot (1942).

SUMMARY

1. By electrical stimulation of the optic nerve the recovery of responsiveness of the synapses in the lateral geniculate nucleus has been studied from the termination of absolute refractoriness up to shock intervals of about 5 sec. The conditioning stimulus was usually maximal for both groups of fibres in the optic nerve and the test response varied between 32 and 62% maximal for the more rapidly conducting group of fibres. Two major difficulties were (i) exclusion of summation of subliminal fringe excitation, and (ii) correction for changes in excitability in the optic nerve at the site of stimulation.

2. The organization of the subliminal fringe was studied. The relationship between the amplitudes of the presynaptic spike (t_1) and the post-synaptic spike (r_1) with increasing shocks applied to the optic nerve, both without and with prior conditioning, show that only a small fringe of subliminally excited neurones is present in the nucleus. The fact that, with conditioning, the amount of the facilitation or depression is independent of the amplitude of the r_1 spike over a wide range of afferent bombardments indicates that the subliminal fringe associated with a smaller presynaptic volley is completely discharged by a larger independent volley. From using maximal conditioning and testing shocks it was concluded that a maximal optic nerve volley does not normally have associated with it a fringe of subliminally excited neurones. Analysis of the random fluctuations in the excitability of geniculate neurones and of the phenomenon of post-tetanic potentiation provides evidence in keeping with this description of the organization of the subliminal fringe.

3. In order to provide the recovering synapses with the equivalent of a constant afferent test volley, corrections were applied to offset changes in excitability of the optic nerve at the site of stimulation by reference to the graph relating the amplitudes of the unconditioned presynaptic and post-synaptic spikes taken over a sufficiently wide range of afferent stimulation. The degree of facilitation or depression of the post-synaptic spike during recovery from discharge can be expressed in a way that is independent of the amplitude of the presynaptic spike.

4. The geniculate neurones respond normally as soon as conduction becomes possible in presynaptic fibres. At shock intervals between 0·95 and 1·65 msec, while the optic nerve axons are recovering from refractoriness the geniculate neurones pass through a brief phase of relative supernormality (114%). When the optic tract axons have regained normal responsiveness (1·7 msec) the geniculate neurones may be slightly subnormal.

5. The early phase of relative supernormality is followed by a late phase of true supernormality with a peak (113%) at a mean shock interval of 4·7 msec and ending at 6·7 msec.

6. The succeeding phase of depression was maximal at a mean shock interval of 19 msec (32%). At this time synaptic transmission through the nucleus was largely blocked. Thereafter recovery proceeded relatively rapidly up to 87% of normal at 220 msec and then very much more slowly until normality was achieved at 2 sec. This two-stage recovery from depression was always present.

7. There may be a further phase of supernormal responsiveness having a peak at about 3·8 sec and ending at about 5 sec.

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