intracellular potential. The favourable geometric situation is provided in the hippocampus by the arrangement of the somas of the pyramidal cells practically in a single layer parallel to the ventricular surface and with their apical dendrites perpendicular thereto. Dr. Gloor states that the extracellular 'laminar profile' of our Fig. 1*E* with a sharp peak of positivity at the soma could be due to an active synaptic depolarization generating EPSP's in the apical dendrites. We need not discuss in detail the merits of this alternative explanation of the 'laminar profile'; it is sufficient to recognize that from it arises the prediction that intracellular recording from the soma would discover a depolarization, the electrotonically transmitted EPSP; whereas, in fact, we reported that a large hyperpolarization was found in 76 of the 79 cells recorded from successfully. We submit that the laminar profile in conjunction with this intracellularly recorded hyperpolarization admits of no interpretation other than an active synaptic hyperpolarization of the somatic region of the pyramidal cells, that is, of inhibitory synaptic action concentrated on the soma. Such a location would give a source for current flowing extracellularly into two sinks, one in the region of the apical dendrites, the other in the opposite direction in the region of the basal dendrites, as was actually shown diagrammatically in our Fig. 1*F*. Dr. Gloor denies the existence of the latter sink on the irrelevant grounds that it is not negative to the indifferent earth electrode. Its existence is of course indubitably established by the slope of the extracellular laminar profile from the positive peak at the soma layer (about +2 mV) to a relatively negative level in the stratum oriens (about +0·5 mV).

It is strange that Dr. Gloor maintains that the extracellular positive wave at the pyramidal layer cannot be safely equated with the intracellularly recorded IPSP's unless it can be shown to be associated with inhibition of unit discharge. This was frequently observed, but not reported. Surely it is sufficient that the extracellular positivity is concurrent with the large hyperpolarization of the IPSP, or is Dr. Gloor doubting whether IPSP's are inhibitory? There is a precise correlation (within 1 msec) between the onsets of the IPSP's and of the positive potential recorded outside the soma in response to all three inputs. However, as we stated, the development of a later negative potential in the apical dendrites obscures the prolonged low hyperpolarizing current that would be expected for inhibitory synapses generating an IPSP with a half decay time of 50–80 msec in a membrane that has a time constant of about 10 msec[1].

It is irrelevant for criticism of our paper that Dr. Gloor cites his own evidence from extracellular observations that a source on apical dendrites with a sink on the soma is "an inhibitory potential" and that in the stratum oriens there are various neurones having axons projecting up to the apical dendrites. We made no statements for or against other inhibitory sites on the pyramidal cells. Our exclusive statement referred to the synapses responsible for the large IPSP's generated in the somas of pyramidal cells by the inputs used in our experiments. However, it will be appreciated from the foregoing discussion that intracellular recording is desirable before positive extracellular potentials are attributed to inhibitory synaptic action. It is a minor point that, in criticizing our claim to have used three separate inputs, Dr. Gloor states that the: "Local stimulation must have activated the terminals of the commissural pathways". This statement is incorrect. The commissural pathway projects to the hippocampal region under examination from a direction opposite to the site of the locally stimulating electrodes[2].

Having disposed of Dr. Gloor's criticisms we reassert that the amazing concentration of basket cell synapses on the pyramidal cell somas provides the only structures that could produce the powerful inhibitory synaptic action that is specifically exerted on these somas. In a parallel investigation on the cerebellum, it has likewise been shown that the concentration of basket cell synapses on Purkinje cell somas gives the structural basis of the powerful inhibitory action on Purkinje cells[3].

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Medullary Vagal Effects of *d*-Lysergic Acid Diethylamide in the Decerebrate Cat

Despite the fact that 2-brom-*d*-lysergic acid (BOL-148) and *d*-lysergic acid diethylamide (LSD-25) are both potent anti-metabolites of serotonin *in vitro*[1,2], they do not exhibit similar behavioural or pharmacological effects *in vivo*. LSD-25 has been shown to produce bradycardia, a decrease in respiratory rate and hypotension in the pento-barbitalized, intact cat[3]. This is in contrast to the hypertension and tachycardia produced in spinal animals. The explanation advanced for these effects has been that in the intact animal the hypertension and tachycardia, due to peripheral vasoconstriction, are masked by more potent effects of LSD-25 on higher centres. BOL-148 was also shown to have no effect on heart rate and a weak non-specific effect on blood pressure in the intact anæsthetized cat in doses up to 1 mg/kg (ref. 3). In the decerebrate cat, ergot alkaloids cause hypotension and bradycardia via medullary vagal centres[4,5]. Therefore, we attempted to study possible vagal effects of LSD-25 and BOL-148 in the decerebrate cat.

Forty cats, 2–4 kg, were used. Tracheal, arterial and venous cannulations and placement of subcutaneous electrodes were carried out under ether anæsthesia. Decerebration was accomplished by suction through the superior colliculi following ligation of the common carotid arteries and compression of the vertebral arteries. Adequacy of decerebration and intactness of the lower brain stem were judged by the presence of decerebrate rigidity and rhythmic spontaneous breathing. Following decerebration, at least 1 h elapsed before recording in order to eliminate the influence of the anæsthetic. Blood pressure was measured by means of a strain gauge. Respiration was recorded by a transducer attached to the side-arm of the tracheal cannula. Lead II of the standard electrocardiogram was routinely recorded with the animal supine. These parameters were recorded simultaneously on a Sanborn Poly-Viso. Drugs were dissolved in saline (1–2 mg/ml.) and administered intravenously within 30 sec.

Table 1. Summary of Pulse Rate, Blood Pressure and Electrocardiographic Findings in the Decerebrate Cat following LSD-25

No. of animals	Dose (mg/kg)	Pulse rate (heart rate/min) Control	Pulse rate (heart rate/min) Maximum	Blood pressure (mm/Hg) Control	Blood pressure (mm/Hg) Maximum	Abnormal rhythm No.	Abnormal rhythm Aver. duration
4	0·2	160 ± 12	108 ± 20	$\frac{160 \pm 20}{90 \pm 30}$	$\frac{120 \pm 22}{50 \pm 20}$	0/4	—
4	0·3	153 ± 45	110 ± 46	$\frac{140 \pm 40}{90 \pm 32}$	$\frac{103 \pm 10}{60 \pm 30}$	1/4	2 min
12	0·4	175 ± 40	93 ± 42	$\frac{135 \pm 30}{80 \pm 20}$	$\frac{90 \pm 15}{40 \pm 15}$	10/12	20 min

Table 1 summarizes the results obtained with LSD-25 (0·2, 0·3 and 0·4 mg/kg): bradycardia, hypotension and a decrease in respiratory rate were observed. In one of the 4 cats administered 0·3 mg/kg, transient auriculo-ventricular (A.V.) nodal rhythm was produced lasting 2 min. At 0·4 mg/kg dose level, 10 of the 12 animals developed

conduction disturbances. *P–R* prolongation followed by complete heart block or A.V. nodal rhythm with retrograde auricular conduction was observed, although the latter disturbance was seen more frequently. Fig. 1*A* is an electrocardiographic tracing illustrating this effect. The change in conduction lasted 6–28 min, averaging 20 min in duration. Artificial respiration was maintained prior to and following drug administration in 4 animals to rule out possible secondary effects due to anoxia. These cats all developed similar conduction abnormalities following the administration of LSD-25. An immediate return to regular sinus rhythm, and improvement in blood pressure and respiration were noted following either bilateral vagotomy or atropinization (1 mg/kg). (Fig. 1*B*).

In 4 cats the vagii were sectioned in the neck, and in 4 other animals atropine (4 mg/kg) was given 15 min prior to administration of LSD-25. In these animals, no conduction disturbances were observed. The changes in blood pressure and cardiac rate were not so marked as in those preparations without pre-treatment.

To rule out the carotid sinus mechanism as the mediator of the effects observed, 4 cats were subjected to bilateral excision of the carotid bifurcation. LSD-25 (0·4 mg/kg) produced effects similar to those observed in animals with carotid sinuses intact.

BOL-148 (0·4 mg/kg) produced mild, transient slowing of heart and mild hypotension lasting not more than 60 sec. The effects seen with 1·0 and 2·0 mg/kg were more pronounced and lasted 3–5 min. At the higher dose-levels QRS changes and *T* wave inversion were observed in the electrocardiogram (Fig. 1*C*). No A.V. nodal rhythm or second degree heart block with A.V. dissociation was produced even with the larger doses of BOL-148. Bilateral vagotomy resulted in an increase in heart rate if done at the height of these changes, but pre-vagotomized animals were not protected as they were with LSD-25.

Marked differences in the *in vivo* action of LSD-25 and BOL-148 are illustrated in this study. LSD-25 appears to have a medullary stimulating action, as contrasted with BOL-148 which probably has direct cardiac toxicity when administered in large doses. BOL-148 has little or no effect on medullary vagal centres. Both LSD-25 and BOL-148 appear to penetrate the brain with little difficulty[6], although selective uptake by specific brain sites cannot be ruled out from these studies. Serotonin antagonism cannot explain the differences observed since BOL-148 is as potent an antagonist to serotonin as LSD-25 (ref. 7). Cholinesterase inhibition does not appear to be the mechanism involved since LSD-25 and BOL-148 are only weak inhibitors of true cholinesterase, although they exhibit marked pseudo-cholinesterase inhibition[8]. It is interesting to note that the dose of LSD-25 required in this study to produce cardiac conduction disturbances in the decerebrate cat approximates the amount of LSD-25 needed to produce clear-cut behavioural effects in the unanæsthetized cat[9].

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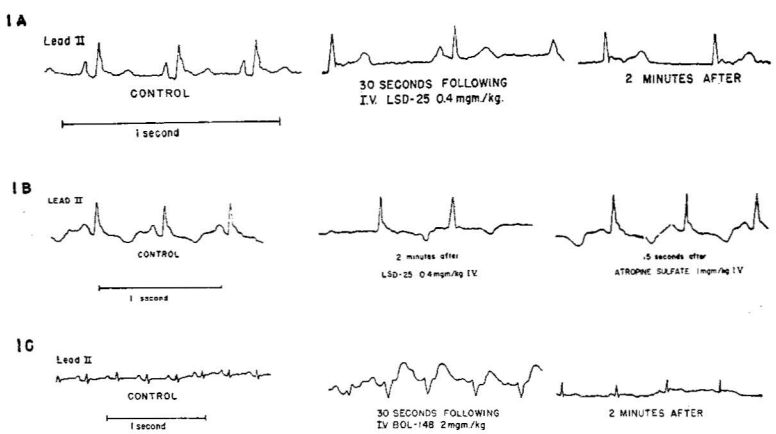

Fig. 1. *A*, Effects of LSD-25 on the electrocardiogram of the cat; *B*, effects of atropine sulphate on reversing the effects of LSD-25; note reappearance of *P* waves following atropinization; *C*, effect of BOL-148 on the electrocardiogram of the cat

Crab Axons showing a Prolonged Repolarization Phase

A FURTHER type of response from isolated crab axons has been recorded by a new technique. The method is to thread an isolated axon through two holes in a fine polythene tube. The axon outside the tube is treated with isotonic sucrose solution and then raised into paraffin oil. Inside the tube test solutions can be flowed over the axon membrane. The effect is to produce an isolated 'node' of excitable membrane. Non-polarizable potassium chloride wick electrodes provide stimulating and recording connexions on each side of the 'node'. This method gives the normal variety of responses from different fibres[1]. In one type of fibre, when bathed by normal sea-water, the action potential shows a very prolonged repolarization phase of 25 msec with two discrete segments of 1 msec and of 24 msec, and during the later segment a supernormality develops, that is, during the falling phase of the first action potential a second action potential can be elicited by a weaker stimulus. The absolute refractory period extends for a period of 2 msec, up to the end of the first phase of the repolarization. Following this for 3–5 msec a period of typical subnormality leads to the period of supernormality which can last as long as 30 msec (Figs. 1 and 2 *a* and *b*).

When the 'node' is stimulated by direct current there is a repetitive response. Before the first action potential a normal local potential develops, but the following action potentials arise at a level of depolarization greater than the amplitude of the first local potential. Therefore no pacemaker potentials can be seen, that is, the later action potentials grow out of the falling phase of the preceding action potential (Fig. 2 *c*). With strong direct currents the amplitude of subsequent action potentials is greatly influenced and oscillatory processes become noticeable.

If a second current pulse is applied during the second segment of the repolarization its shape and time relations can be altered, cathodal current lengthening and anodal current shortening the repolarization. During the repolarization phase and the refractory period the ratio of the 'inward' to 'outward' resistance, as measured by small current pulses, is smaller than in normal fibres. All the evidence at present available suggests that the later prolonged segment of the repolarization is due to a low level of increase of potassium permeability. If then the level of rectifica-