One of the authors reported (*8*) that the liver catalase has the same influence on the activity as the uricase described above in the course of carcinogenesis. Uricase is found only in the liver tissue of mice and rats. No investigation of uricase has ever been demonstrated in the research in experimental cancer production.


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## Circulatory and Autonomic Factors in Bulbar Facilitation and Inhibition of Reflexes[1]


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The close association of autonomic effects and bulbar and diencephalic facilitation and inhibition of the patellar reflex has been pointed out previously (*1–4*). It appeared desirable to determine whether bulbar facilitation bears any relation to the well-known Orbeli phenomenon, which involves enhancement of the muscular contraction evoked by direct motor nerve stimulation when the sympathetic supply to the muscle is simultaneously stimulated.

Cats were anesthetized with Nembutal (30 mg/kilo) and were prepared as illustrated in Fig. 1. In some experiments only one hind limb was used, and in other experiments both hind limbs were prepared as follows. Steel pins were drilled into the extremities of the femur so that a very rigid fixation of the limb could be arranged. The iliopsoas muscle was sectioned, and the saphenous and sartorius branches of the femoral nerve and the whole sciatic trunk and its hamstring branches were divided. In one leg the quadriceps branch of the femoral nerve was also sectioned to provide a distal stump for direct stimulation of the motor nerve to the quadriceps muscle by means of shielded electrodes. The other limb was so arranged that the knee jerk could be recurrently elicited by a rhythmically actuated solenoid.

The reticular formation of the brainstem, the posterior hypothalamus, and the mesencephalon was explored with stereotaxically oriented concentric electrodes. Stimuli consisted of 60-cps pulses of approximately 10-sec duration with a strength of 5–10 v. The femoral motor nerve-quadriceps muscle preparation was rhythmically stimulated through the distal stump of the nerve by means of 0.1-v sine wave applied at the rate of 1/sec. Blood pressure, when recorded, was taken from the carotid artery, and drug infusions were administered through in-dwelling needles in the external jugular vein. The femoral artery and adrenal veins were exposed for clamping, the lumbar sympathetic chains were loosely ligated for later avulsion, and the upper lumbar cord was exposed through the dura and a loose ligature applied for later severance at L1.

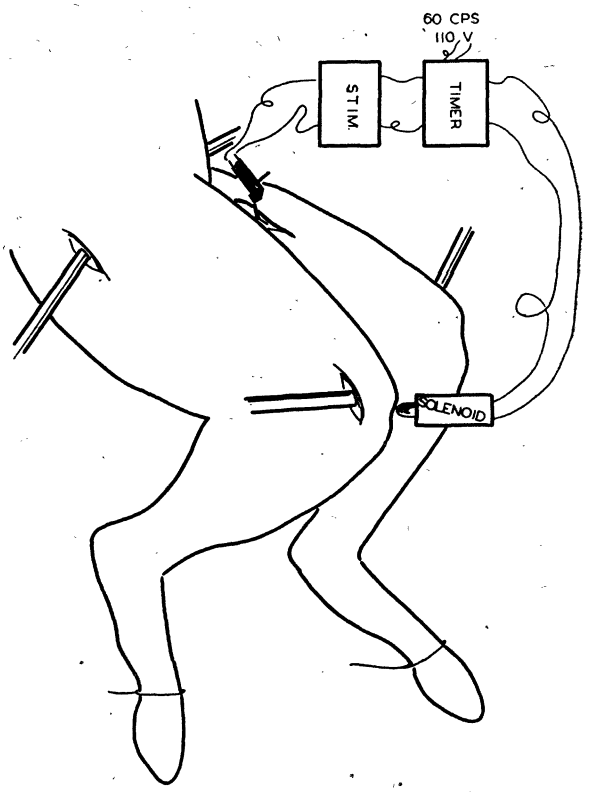


FIG. 1. Schemata of cat preparation. Both hind limbs are rigidly fixed by steel pins drilled into the extremities of the femurs. A rhythmically actuated solenoid activates the patellar reflex on one side which has been completely denervated with the exception of the quadriceps branch of the femoral nerve. The other side has been completely denervated, and the distal stump of the quadriceps branch of the femoral nerve is enclosed in shielded electrodes which recurrently stimulate the motor nerve fibers.

The first experimental procedure attempted was to determine the effect of surgical interference with the sympathetic supply to the limb on bulbar facilitation of the knee jerk. Figure 2A shows mesencephalic facilitation of the knee jerk, and Fig. 2B shows abolition of the response after bilateral resection of the lumbar sympathetic chains and clamping of both adrenal veins. The second procedure involved pharmacologic interference with sympatholytic drugs subsequent to, during, and preceding bulbar facilitation of the knee jerk. Figure 2C shows bulbar facilitation

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[2] With the technical assistance of S. M. Olivier.

of the knee jerk accompanied (in this instance) by a vasopressor response. Figure 2E shows considerable reduction of the degree of bulbar facilitation and of the vasopressor response (although not complete abolition of either) after the intravenous infusion of 1% Dibenamine.[3] Comparable effects following the infusion of 1% Tolserol (Myanesin)[4] in a different preparation are shown in Fig. 2F. It is worthy of note here that Myanesin not unexpectedly abolishes the vasopressor response as well as the bulbar facilitation of the patellar reflex because both processes undoubtedly involve multineuron activation. Figure 2D, from a different preparation, shows the abolition of an initial facilitation, following the infusion of 1% ergotoxine, comparable to that shown in Fig. 2A.

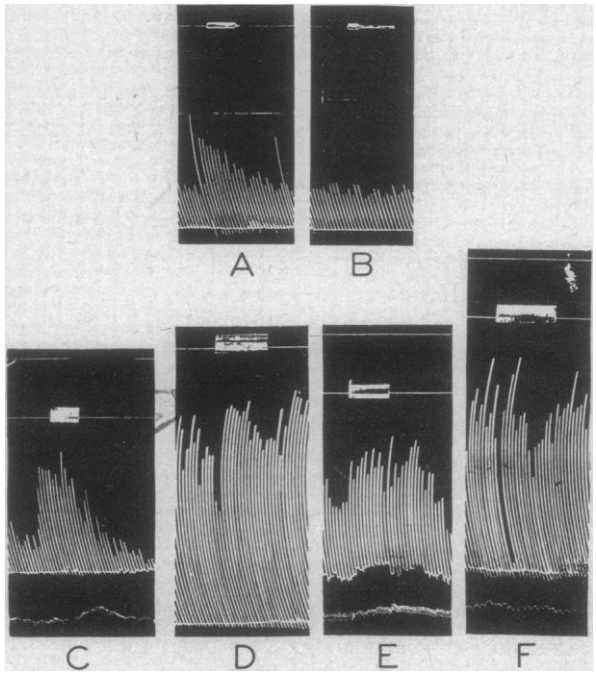


FIG. 2. A. Mesencephalic facilitation of the patellar reflex (5 v). B. Mesencephalic facilitation of the patellar reflex (5 v) after resection of both lumber sympathetic chains and occlusion of both adrenal veins. C. Bulbar facilitation of the patellar reflex (and pressor response) (2 v). D. Same as C in a different preparation without blood pressure record during infusion of 0.1 cc 1% ergotoxine. E. Same preparation as in C during infusion of 0.6 cc 1% Dibenamine. F. Same as C but different preparation during infusion of 1 cc 1% Tolserol (Myanesin).

The necessity for complete interference with the sympathetic supply to the limb in order to produce abolition of facilitation is shown by the following. Figure 3A illustrates hypothalamic facilitation of the knee jerk which is depressed but not abolished by resection of both lumbar sympathetic chains (Fig. 3B). Subsequently the adrenal veins were compressed bilaterally with the unusual result, shown in Fig. 3C,

[3] The Dibenamine was generously provided by Smith, Kline and French Laboratories.

[4] We are grateful to E. R. Squibb and Sons for making Tolserol available to us.

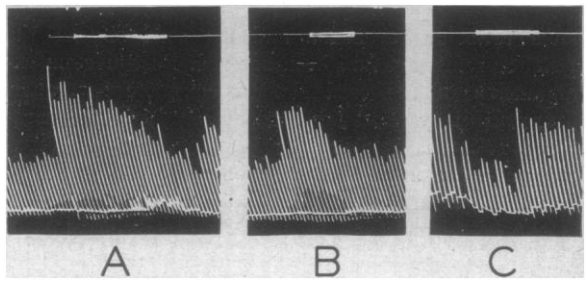


FIG. 3. A. Hypothalamic facilitation of the patellar reflex (2 v). B. Same as A except that lumbar sympathetic chains have been cut. C. Same as B except that in addition both adrenal veins have been clamped.

that the previous facilitation was converted into an inhibition. This result is not typical, the common effect simply being an absence of faciltation.

These results suggest that bulbar facilitation of the patellar reflex might well represent central activation of the Orbeli phenomenon analogous to the *piqure diabetes* first described by Claude Bernard (*5*). In order to test this hypothesis bulbar facilitation of the recurrently elicited knee jerk was obtained as shown in Fig. 4A, and then the isolated femoral motor nerve-quadriceps muscle preparation isolated *in situ* from the central nervous system was rhythmically activated at the same frequency as the knee jerk. Stimulation of the bulbar source of knee jerk facilitation apparently enhanced the contraction of the nerve-muscle preparation as shown in Fig. 4B but it is not certain that this effect is entirely free of stimulation artifacts. Intravenous administrations of adrenalin have also caused an enhancement in both knee jerk and nerve-muscle preparations to the same extent.

Inhibition of the patellar reflex has also been investigated in the same fashion. After bulbar inhibition of the knee jerk was obtained, the cord was sectioned at L1 by tying a thread through the cord and removing the knotted ligature. The bulbar inhibitory effect was again sought. The effect persisted in spite of the fact that all nervous connections between the brain-

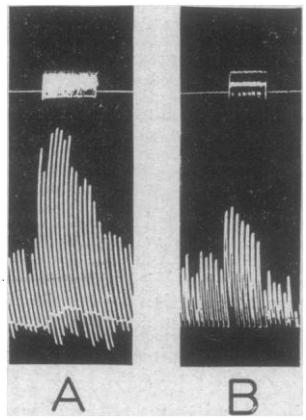


FIG. 4. A. Bulbar facilitation of patellar reflex (5 v). B. Same preparation as A; bulbar facilitation of opposite femoral motor nerve-quadriceps muscle preparation recurrently activated by 0.1 v.

stem reticular formation and the cord site of the patellar reflex arc had been severed. Post-mortem examination of the cord showed complete severance. This inhibitory effect has been obtained in 3 preparations. It is characterized by inconsistency of elicitation; and it is at no time so strong, so complete, or so rapid in appearance as when the cord is intact. Occlusion of the femoral artery may depress bulbar inhibition of the patellar reflex, decrease the degree of inhibitory after-discharge, and increase the extent of "escape" from prolonged bulbar inhibitory stimulation.

It appears obvious from these results that bulbar facilitation of somatic reflex activity involves the production of adrenalin and the activation of the sympathetic supply to the limb. It is not yet clear that such facilitation precludes any additional or substitutive facilitatory mechanisms in the orthodox sense at the site of the patellar reflex arc within the cord. It is apparent that the sympathetic system and adrenalin liberation may be activated by stimulation of the bulbar reticular facilitatory system in such a fashion as to resemble a *piqure d'Orbeli* in the Bernardian sense (*5*). The presence of some circulatory factor in the bulbar inhibitory phenomenon also seems apparent, but the nature of this effect is as yet obscure.

Ever since Orbeli's first report on the effects of adrenalin on neuromuscular fatigue (*6*), various investigators have reaffirmed and extended his original findings. Thus Corkill and Tiegs (*7*) showed that both adrenalin and sympathetic stimulation would enhance the height of muscular contraction, and Gruber (*8–10*) has shown that adrenalin enhances muscular contraction, delays the onset of fatigue, and introduces significant variations in the time relations of various phases of muscular contractions. Tuttle (*11*) claimed that adrenalin increased the tonus of the quadriceps and of the patellar reflex. Recently Bülbring and Burn and collaborators have carried out intensive and significant investigations concerning the mode of action of adrenalin on neuromuscular and central nervous system activity (*12–16*). Their results indicate that the phrenic nerve-diaphragm preparations show an increased tension duration to maximal stimulus volleys due to the direct action of adrenalin on the muscle fiber. They also find that flexor and extensor movements induced by descending motor tract stimulations can be depressed or enhanced under different circumstances by adrenalin, and that nerve action potentials may be enhanced by a non-circulatory effect of intra-arterially injected adrenalin. From additional evidence that adrenalin may enhance transmission at the neuromuscular junction in the phrenic nerve-diaphragm preparation, they conclude that adrenalin may increase the nerve-muscle response in three ways: (1) to a minor extent by augmenting the contraction of the muscle fiber itself; (2) by improving neuromuscular transmission; and (3) by improving excitability and conduction in the motor nerve fiber. It is tempting to draw the conclusion that the effects described here constitute a central nervous system activation of the effects described by Bülbring and Burn, but much work remains before this point can be confirmed.

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## On the Use of Calomel Half Cells to Measure Donnan Potentials


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Since their use by Loeb (*1*), calomel half cells have been widely employed in measuring interface potentials that arise between suspensions of charged colloids and solutions of electrolytes with which they may be in equilibrium (i.e., Donnan potentials). In making these measurements it has been commonly assumed that no junction potential exists at the KCl saturated bridge which is inserted in the suspension. Recently, this assumption has been questioned by Jenny *et al.* (*2*) who interpret their data to mean that the junction potential may be appreciable. This has led the present writers to re-examine the assumption that two calomel half cells can measure a Donnan potential even if one explicitly assumes that the transference numbers of $K^+$ and $Cl^-$ are equal.

In order to predict the emf which will result from the insertion of electrodes into any system, the proper procedure is to write down each individual process that occurs when $n$ faradays pass through the circuit in question, to add these processes and to obtain the net cell reaction. The emf for the cell is then given by,

$$\Delta F = -nF_y E_{\text{cell}}$$

where $F_y$ is the faraday. This procedure is applied below to the classical model of a Donnan system.

Assume that a suspension of potassium colloid, KR, (phase I) is in equilibrium with a solution of KCl (phase II) across a membrane permeable to KCl but not to colloid. The equilibrium condition is:

$$a_{(KCl)}{}^{(I)} = a_{(KCl)}{}^{(II)}$$