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**A Late Period of Subnormal Irritability Following Nerve Response.**

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The described effects of the passage of an impulse through isolated frog nerve on the irritability of the nerve are (1) the appearance of refractoriness immediately following the response and (2) under certain circumstances the appearance of supernormality, succeeding the refractoriness, and of much longer duration. By means of certain pharmacological agents, a third, still later effect may be made to appear, a depression of irritability differing from refractoriness not only in its time relations but in other respects as well. Yohimbine is the most effective agent as yet found for producing this effect, which will be referred to as "late subnormality".

About an hour after 1/20,000 yohimbine hydrochloride has been applied to the isolated sciatic nerve of *Rana pipiens*, cathode ray oscillograph observations very clearly reveal the 3 successive phases of irritability modification—refractory period, supernormal period, late subnormal period. The relatively refractory period is somewhat (0.5-1.0σ) longer than in the untreated nerve displaying supernormality; the supernormal period thus begins later than in the untreated nerve, while it ends considerably earlier. The maximum degree of supernormality is reduced. In one typical case, the maximum supernormality fell from 104.5% to 103%, and the duration of the supernormal period decreased from 138σ to 47σ. The supernormal period is immediately succeeded by the late subnormal period which lasts 5-10 seconds after the conditioning shock in the nerve yohimbinized as described. The minimum irritability during this period occurs 1-2 seconds after the shock, and after a single conditioning shock is usually 97-99% of the resting level in these lightly poisoned nerves. The subnormality may be both prolonged and intensified by stronger yohimbinization. When the drug action is strong enough to reduce the irritability during the subnormal period to about 95% of the resting level, the supernormality has ordinarily been largely or entirely removed, but there remains in the curve of recovery of irritability a crest of irritability in the region of former supernormality, and this crest tends to persist in less marked form even in deeply poisoned nerves. In these nerves the late subnormality has been observed to last 16-32 seconds.

A series of shocks, each one timed to fall in the late subnormal period of its predecessor, increases and prolongs the subnormality very markedly. Each successive shock of the series adds something to the depression left by preceding shocks, but each successive shock adds less than its predecessor. The level of minimum irritability eventually reached has been observed to be 50-96% of the resting irritability, varying with the rate of stimulation as well as with the degree of yohimbization.

This increase of subnormality with repeated stimulation distinguishes the late subnormal period from the refractory period in which the recovery of irritability is described as following the same curve after one shock or after a series of shocks each timed to fall in the relatively refractory period of its predecessor: Late subnormality also differs from refractoriness in that the ability of the nerve to respond is not decreased; the height of maximum response is undiminished during the late subnormal period, even when the depression of irritability after one conditioning shock is considerable, or when it is enormously increased by a series of shocks. Late subnormality thus resembles supernormality in being a phenomenon manifested in change of irritability but not in change of ability to respond.

Yohimbine produces certain other changes in nerve function. The absolutely refractory period is usually lengthened, particularly with the higher concentrations of yohimbine; and the height of response tends to fall. The resting irritability is not significantly affected until the poisoning is very marked, when it may fall considerably. In keeping with all earlier experience linking supernormality and after-potential, yohimbine decreases and eventually removes the after-potential.

Of the other substances whose action has been examined for the production of late subnormality, cocaine (1/20,000-1/5000), procaine (1/7500-1/5000) and quinine (1/5000-1/1000), all applied as the hydrochlorides, produce conditions similar to the one described for yohimbine, except that the subnormality is less in degree and does not last so long, usually ending in about half a second. The minimum falls correspondingly earlier than the yohimbine minimum. Further, these drugs tend to produce relatively greater removal of supernormality so that the irritability changes are less striking. The effect of repeated shocks on subnormality has not been investigated on nerves treated with these drugs.