gested that this technique may be of some value in separating the two processes—percentage of cells surviving at the site of arrest or injection and growth rate of the surviving cells—in the investigation of the various factors (*6*) known to influence the incidence of tumor metastases (*7*).

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5 July 1960

Couplet Periodic Breathing Response to High Carbon Dioxide and High and Low Oxygen

Abstract. A breathing pattern is described which is characterized by a grouping of two breaths followed by a prolonged apnea and which may involve a mechanism different from at least one type of Cheyne-Stokes breathing. The pattern can be eliminated by breathing 9 percent O_2 or 10 percent CO_2. However, the pattern frequently persists during breathing of high oxygen.

Considerable time and effort have been devoted to the study of periodic breathing since the early observations of Cheyne (*1*) and later of Stokes (*2*). The respiratory pattern named after these men is characterized by a series of breathing efforts gradually increasing in magnitude to a peak followed by a gradual decrease, each series of respiratory efforts being separated by an apneic period sometimes lasting for 60 seconds or longer. Later, Biot (*3*) published a monograph on Cheyne-Stokes breathing in which he discussed another type of respiratory irregularity, sometimes seen in meningitis, calling attention to its differences from Cheyne-Stokes breathing. Conner (*4*) has made additional observations on this breathing pattern and re-emphasized the fact that Biot's breathing is marked by complete irregularity of amplitude and duration of the apneic periods. Thus Biot's breathing is visualized as an arrhythmic variation of respiration while Cheyne-Stokes breathing is considered to be a rhythmic variation. Precision in the classification of these two types of breathing has not always been evident, for there has been some tendency to identify any deviation from "normal" as Cheyne-Stokes breathing. Recently this looseness in terminology has again been called to account (*5*).

This report concerns the possibility of the existence of another type of respiratory irregularity distinct from those previously described (*6*).

Dogs anesthetized with thiopental sodium-chloralose sometimes show a regularly grouped pattern of breathing which is characterized by two (occasionally three or more) breaths separated in time by 3 to 5 seconds, followed by a more prolonged apneic period. Frequently this breathing pattern can be induced by giving additional injections of thiopental (Fig. 1). This couplet pattern is similar to Cheyne-Stokes breathing in that it is a rhythmic variation. However, its form differs from Cheyne-Stokes breathing in several respects: there are fewer breaths per group, the apneic phases are of shorter duration, the breaths are of about the same amplitude, and the breaths are apparently not as labored as are those at the peak of the breathing phase in Cheyne-Stokes respiration. The couplet pattern is not similar to Biot's breathing, which is an arrhythmic variation. In a strict sense Biot's breathing is not truly periodic but merely respiratory events appearing in a disoriented fashion.

The couplet pattern is always eliminated by breathing 9 percent oxygen. The significant stimulation of breathing occurring with this gas mixture indicates that the chemoreceptor mechanisms are functional.

In response to breathing 10 percent CO_2 (21 percent O_2) there usually appears a stimulation which eliminates the couplet pattern. Thus it is not essential that the animal be nonresponsive to CO_2 before the respiratory variation is evident, although some depression of the respiratory center is inevitable after the administration of thiopental. On occasion, however, the couplet pattern may appear spontaneously without administration of additional thiopental. In a few cases the administration of CO_2 caused a progressive increase in the number of breaths per group and a decrease in the duration of the apneic periods. In this latter situation there is presumably a more pronounced depression of the respiratory center.

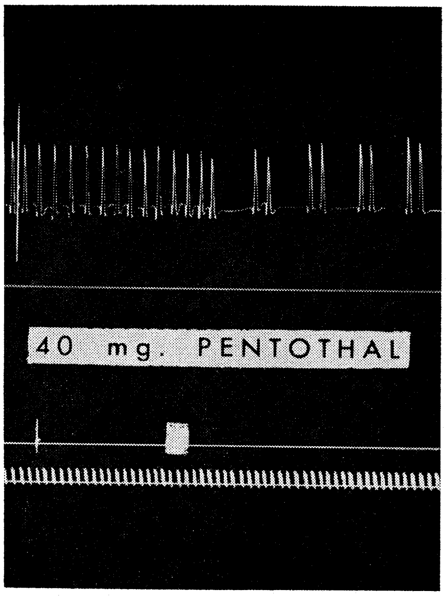

Fig. 1. Production of couplet periodic breathing by the intravenous injection of thiopental (Pentothal). The tracings (top to bottom) are as follows: pneumographic respiration, signal, and time (each tick represents 2 seconds).

In about half the cases the couplet pattern persisted during breathing of 50 to 100 percent O_2 although the apneic periods were prolonged without significant alteration of the time between the grouped breaths (Fig. 2). The various reports that high O_2 is effective in eliminating one type of Cheyne-Stokes breathing suggest that the grouped breathing here described may involve a different mechanism.

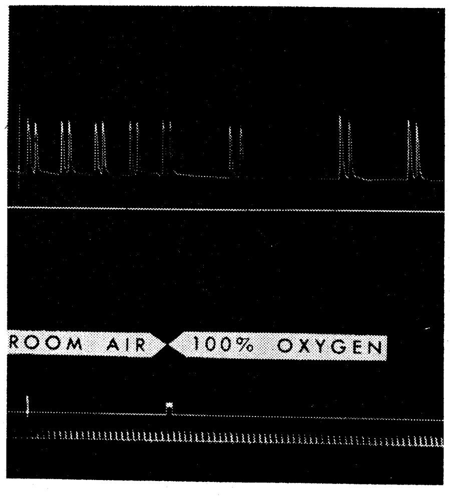

Fig. 2. Effect of 100 percent oxygen on couplet periodic breathing. Tracings are as in Fig. 1.

It also appears that these two respiratory patterns are not merely different stages in a progressive disruption of respiration, but rather distinct entities involving at least some differences in method of operation. This hypothesis is supported by the observation that as the animal is progressively depressed with thiopental the respiratory pattern changes from normal, frequently through a stage of couplet breathing, to respiratory arrest. Cheyne-Stokes breathing was not seen during this transition.

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26 May 1960

Impairment of Muscle Stretch Reflexes in Tick Paralysis

Abstract. Experiments with tick-paralyzed dogs and woodchucks have shown impairment of stretch reflexes in addition to partial paralysis at the neuromuscular junction. Stretch reflexes disappear very early during paralysis, whereas nociceptive reflexes do not appear to be directly affected. The early incoordination and the ascending nature of the paralysis may be related to impairment of stretch reflex pathways.

Paralysis caused by ticks, commonly *Dermacentor andersoni* in the western United States and Canada (*1*) and *D. variabilis* in the eastern United States (*2*), is of considerable medical and veterinary importance. Paralysis is apparently caused by a toxin secreted by engorging female ticks. The progression of symptoms (see *3*) includes incoordination, muscular weakness, and flaccid paralysis. The paralysis is ascending (Landry's type); the lower limbs, the forelimbs, the cranial motor nerve functions, and the respiratory apparatus are affected sequentially. Complete recovery is rapid if the ticks are removed prior to respiratory paralysis of the victim.

Previous workers have shown failure of neuromuscular transmission during severe paralysis (*4*), and this failure has been shown to be due to a deficiency in the release of transmitter substance (*5–7*). Emmons and McLennan (*8*) have presented preliminary data which indicate that there is a central action of the toxin in addition to the peripheral action.

In the experiments herein reported (*9*), stretch reflexes were studied in three dogs and nine woodchucks *(Marmota flaviventris)* (*10, 11*) paralyzed with *D. andersoni.* Metal shields containing the ticks were taped over a shaved area of the animals' bodies (*11*). Animals were studied either at the stage of partial paralysis (incoordination of hindlimbs, little involvement of forelimbs) or of full paralysis (flaccid paralysis; slow, gasping respiration). In all cases records obtained during paralysis were compared with those obtained under identical conditions when the animal had recovered, subsequent to removal of the ticks. In some experiments pentobarbital anesthesia was used for tests during paralysis and after recovery. In two woodchucks, to avoid use of the anesthetic, the spinal cord was sectioned at the atlanto-occipital junction while the animal was under ether anesthesia. Tests were made on the paralyzed animals after elimination of the ether and were continued over an 18-hour period after removal of the ticks. Respiration and body temperature of these animals were maintained artificially.

Gastrocnemius muscle was activated by maximal electrical stimulation of the sciatic nerve. Stretch reflexes were elicited by tap of the patellar tendon or by pull of the severed Achilles tendon; controlled mechanical stimuli were delivered by appropriate solenoid devices. In some cases muscle tension was recorded on a Grass polygraph by means of a strain gauge attached to the Achilles tendon. In other experiments gross electromyograms were obtained from the muscle by means of two recording electrodes spaced 2 cm apart in the belly of the muscle (*12*).

Table 1 gives the experimental conditions and the degree of neuromuscular impairment in seven paralysis-recovery experiments. In addition, stretch reflexes alone were studied in one partially paralyzed dog and one fully paralyzed woodchuck. Muscle stretch reflexes could not be elicited in any of the paralyzed animals. Figure 1 gives representative mechanical records obtained from a fully paralyzed woodchuck and typical electromyograms from a partially paralyzed dog. It is significant that stretch reflexes were invariably absent even though neuromuscular transmission in partially paralyzed animals was only slightly reduced. Partially paralyzed animals, examined grossly, exhibited considerable muscular power. They were able to stand briefly but lacked sufficient hindlimb coordination to walk.

Transmission from dorsal root to ventral root was studied in three fully paralyzed woodchucks by electrical recording techniques described previously (*13*). Two normal woodchucks were studied for comparison. The reflex discharge in normal animals consisted of a short-latency spike followed by a prolonged irregular discharge, tentatively identified as monosynaptic (*2N*) and polysynaptic responses, respectively. In one of the paralyzed animals bleeding was excessive and no transmission was observed. The ventral root discharges from the other two paralyzed animals differed from those of normal woodchucks in that the *2N* spike was not elicited by isolated dorsal root stimuli but did appear during and following tetanic stimulation. While close comparison of such responses in normal and paralyzed animals is difficult, the results are consistent with the other evidence for impairment of stretch reflexes. In addition, since mus-

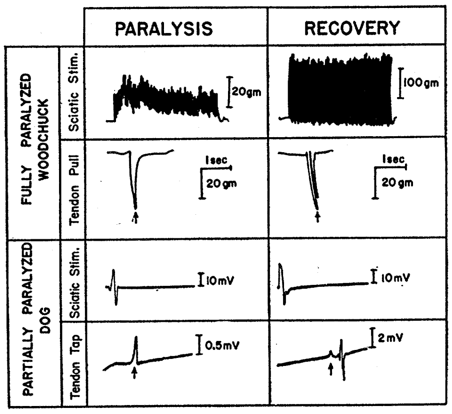

Fig. 1. Impairment of neuromuscular transmission and muscle stretch reflexes in paralysis-recovery experiments. The animals were anesthetized with pentobarbital. Arrows identify stimulus (mechanical) artifacts in records. Woodchuck: mechanical recording of muscle tension from Achilles tendon; frequency of sciatic stimulation was five pulses per second. Dog: Electromyogram recording from gastrocnemius muscle; oscilloscope traces are 50 msec in the upper row and 100 msec in the lower row.

Table 1. Degree of neuromuscular impairment in paralysis-recovery experiments. EMG, electromyogram.

Animal and experimental procedure	Degree of paralysis*	Neuromuscular impairment† (%)
Dog, pentobarbital, EMG	Partial	14
Woodchuck, pentobarbital, EMG	Partial	10
Woodchuck, spinal, tension	Partial	30
Dog, pentobarbital, EMG	Full	88
Woodchuck, pentobarbital, tension	Full	92
Woodchuck, spinal, EMG	Full	77
Woodchuck, pentobarbital, EMG	Full‡	40

* Assessed from symptoms of the animal before anesthetization or section of the spinal cord. See text for criteria. † Estimated from measurements made during paralysis and again in the same animal after recovery. ‡ A 4-hour delay between the removal of ticks and the recording of the EMG allowed some recovery to occur.