known as respiratory control. *Results:* Halothane produced a dose-related decrease in *state 3* oxygen uptake when *glutamate* was the substrate. A distinct effect was seen following exposure to less than 1 per cent halothane. State 3 respiration was 25 per cent of control after treatment with 3 per cent halothane; concentrations greater than this caused no additional decrement. Changes seen following exposure to concentrations as high as 2 per cent were completely reversible; treatment with higher concentrations produced a dose-related diminution in reversibility. All concentrations of halothane studied caused *no* alterations in state 3 oxygen uptake when *succinate* was substrate. It appears that halothane affects mitochondrial electron transport at a point lying between substrate and flavin-adenine dinucleotide (FAD). Decreased mitochondrial respiratory control is characterized by lack of inhibition of oxygen uptake in the absence of ADP. Thus, *increased state 4* oxygen uptake is evidence of *decreased* mitochondrial respiratory control. When succinate served as substrate, exposure to less than 1.5 per cent halothane was accompanied by normal state respiration. Treatment with greater concentrations of the drug produced a dose-related increase in state 4 oxygen uptake. This indicates that halothane can have a profound effect on mitochondrial respiratory control. *Summary:* Halothane was shown to have two distinct effects on mitochondrial metabolism. The drug produced a dose-dependent effect on mitochondrial electron transfer, appearing to act at a point between substrate and FAD. The effect was seen when less than 1 per cent halothane was administered and was completely reversible provided concentrations less than 2 per cent were used. A significant effect on mitochondrial respiratory control (characterized by increases of as much as 400 per cent in state 4 oxygen uptake) were observed after exposure to concentrations of halothane greater than 1.5 per cent. (Supported in part by USPHS Grant GM-09070-5 and USPHS Grant 5-T1-GM-215-09 from the National Institutes of Health.)

The Influence of Anesthetics on the Variability of Myocardial Contraction with Heart Rate. N. W. Brian Craythorne, M.B., B.Ch., *West Virginia University School of Medicine, Morgantown, W. Va.* The tension created by myocardium varies with the frequency of contraction. The effects of cyclopropane, halothane, methoxyflurane and a combination of droperidol and fentanyl citrate (Innovar) on this relationship have been studied. *Methods:* Kittens and small cats (1.5 kg.) were lightly anesthetized with pentobarbital (25 mg./kg.) intraperitoneally. The heart was rapidly excised and the atria dissected. Left atrial strips (about 1 mm. wide) were attached at one end to a fixed hook and at the other to a Statham FTA-3-1 force transducer and placed in a thermostatically controlled perfusion chamber filled with Krebs solution at 37° C. A square wave stimulus from a Grass S8 Stimulator was applied across the strip using two rectangular platinum plates. A voltage just above threshold (duration 5 msec.) was used to avoid stimulation of autonomic nerves. The rate of stimulation was varied from 10 to 200 beats/minute. Ninety-five per cent oxygen and 5 per cent CO_2 was bubbled through the bathing solution which maintained a *p*H of 7.4 at a rate of 2 l./min. Halothane (0.06 per cent, 0.65 per cent, 1.4 per cent, 2.3 per cent, 2.8 per cent and 3.5 per cent) and methoxyflurane (0.25 per cent, 0.74 per cent, 1.18 per cent, 1.49 per cent, 1.74 per cent and 2.1 per cent) were vaporized in calibrated Fluotec and Pentec vaporizers, respectively. Cyclopropane was added as a mixture containing cyclopropane 7.5 per cent, oxygen 87.5 per cent and CO_2 5 per cent. The concentration of Innovar was 0.3 ml/l. or 1 ml./l. (1 ml. Innovar contains 2.5 mg. droperiodol and 0.05 mg. fentanyl). The concentration of cyclopropane was measured by the method of Linde and Price and that of methoxyflurane and halothane by gas chromatography. *Results:* When the interval between beats (I) is sufficiently long (300 sec.) the strength of the subsequent heart beat is not influenced by the previous beat. This is termed Resting State Contraction (RSC). A very short interval between beats is associated with a decrease in tension (negative inotropic effect of activation, NIEA); as the interval between beats increases, there is an increase

in tension (positive inotropic effect of activation, PIEA). RSC, NIEA and PIEA can be measured. With the exception of fentanyl, all the agents depressed RSC. Cyclopropane had no effect on PIEA but increased the half-life of NIEA. Halothane and methoxyflurane decreased PIEA but halothane increased NIEA whereas methoxyflurane decreased NIEA. Innovar increased PIEA and also increased NIEA. With all the anesthetics studied, tension decreased as rate of stimulation decreased from 150 to 30 impulses per minute. However, if the tension at a given rate is presented as a percentage of the control at the same rate, the variance is less marked. The higher the concentration of anesthetic used, the smaller the variation of tension with rate.

Control of Sensory Input at Spinal-cord Level: A Possible Mechanism of Anesthesia. RUDOLPH H. DE JONG, M.D., and IRVING H. WAGMAN, PH.D., *Department of Anesthesiology, University of Washington, Seattle, and National Center for Primate Biology, University of California, Davis, Calif.* Melzack and Wall (Science *150:* 971, 1965) recently proposed a "gating" system in the dorsal horn of the spinal cord which modulates afferent impulses arriving from the skin. Balance between impulses in large and small fibers determines setting of this gate by presynaptic mechanisms arising from cells in the substantia gelatinosa. Input into the CNS of impulses related to noxious cutaneous stimuli may thus be controlled physiologically in the dorsal horn of the spinal cord. *Method:* We are reporting the effect of halothane on dorsal horn neurons in 18 anemically decerebrated rhesus monkeys. Temperature, arterial pressure and end-expired CO_2 were maintained within physiologic norms. Unit activity from single neurons in lamina IV was recorded with extracellular microelectrodes at L7-S1. Characteristics of these cells in the unanesthetized immobilized monkey were: (1) spontaneous firing at irregular rate; (2) large ipsilateral receptive field, responding to several modalities of cutaneous stimulation (touch, pressure, pinch, cooling); (3) brief burst, followed by an inhibitory pause, elicited by A-fiber volleys in sural nerve; (4) prolonged bursting, increasing in frequency and duration, with repetitive stimulation, elicited by C-fiber volleys; (5) diffuse inhibitory fields. The effect of 1 or 2 per cent halothane in oxygen on these responses was then studied. (Earlier observations had shown that 1.5 to 2 per cent halothane produced surgical anesthesia in the monkey.) Electrode position was histologically verified. *Results:* 1. Halothane transiently increased spontaneous firing, followed within one to two minutes by a gradual decrease in spontaneous activity as anesthesia progressed. Usually, spontaneous activity ceased after 15 to 20 minutes. 2. Threshold to cutaneous stimulation rose and the size of the receptive field shrank during anesthesia. Light touch, pressure or pinching failed to elicit a response, but a stronger cutaneous stimulus still evoked a response when 1 per cent halothane was given. A central patch of cutaneous excitability persisted when 1 per cent halothane was given. Increasing the anesthetic concentration abolished all responses to natural stimulation of the skin. 3. The burst of responses to C-fiber stimulation disappeared before the response to A-fiber stimulation. During induction, the late neuronal response to nerve stimulation increased in latency, then fell out. With deepening anesthesia, the burst gradually shortened. Finally, only one or two responses to A-fiber stimulation could be obtained. 4. In contrast to the profound depression of cells in lamina 4, units lying some 100–200 μ deeper which were excited by rotation of joints were little depressed by 2 per cent halothane. 5. Recovery of function of the cells in lamina 4, and expansion of the borders of the cutaneous receptive field to their original limits, were usually complete 15 to 20 minutes after halothane was replaced with oxygen. *Conclusions:* We conclude that halothane profoundly depresses the transmission of sensory impulses at the first central synapse in the monkey. This effect, as also indicated by Wall (ANESTHESIOLOGY *28:* 46, 1967), may be an important mechanism of general anesthesia. Additional studies with other anesthetics and analgesics, as well as quantitation of anesthetic depression, are in progress. (Work done during Dr. de Jong's tenure as a Guest Investigator at the National Primate Center. Supported by Career Devel-