References and Notes

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3. The determinations of cellular antigens were made by the Ohio State University Blood Testing Laboratory as cooperators under Regional Project NC-2.
4. This report is published, with the approval of the director, as paper No. 921, Journal Series, Nebraska Agricultural Experiment Station. This is a contribution from Regional Project NC-2 (Improvement of Dairy Cattle Through Breeding).

3 October 1958

Use of an Organic Carbon Dioxide Buffer in vivo

Abstract. The compound 2-amino-2(hydroxymethyl)1,3-propane diol was administered intravenously to apneically oxygenated dogs over a 1-hour period. Arterial blood *p*H remained normal, and an estimated 18 to 28 percent of the CO_2 produced during apnea was recovered in the urine.

Pardee (*1*) and Krebs (*2*) have shown that in vitro "CO_2 organic buffers" can maintain pCO_2 constant in the gas phase according to the equation:

$$R\text{-NH} + H_2O + CO_2 \rightleftharpoons HCO_3^- + R\overset{+}{N}H_2$$

One of these compounds, $(CH_2OH)_3C—NH_2$, was utilized in the apneically oxygenated dog to combat the increase in pCO_2 and the concomitant rise in H^+ concentration.

"Apneic oxygenation" (*3*) is a condition of ventilatory arrest, induced with succinylcholine chloride, following a 1-hour period of ventilation with 100-percent oxygen (denitrogenation), and during which the trachea is connected to a reservoir containing 100-percent oxygen. In this condition oxygenation of the blood is maintained but CO_2 accumulates. After 1 hour of apnea one typically observes (*4*): (i) a 50-percent fall in arterial oxygen saturation and a fall in oxygen uptake to 60 percent of the control value; (ii) a rise in arterial pCO_2, (for example, to 376 mm-Hg), in total plasma CO_2 (to 41.4 mmole/lit.), and in plasma HCO_3 (to 31.0 mmole/lit.); (iii) a fall in arterial blood *p*H (for example, to 6.56) and a drop of the plasma HCO_3^-/H_2CO_3 ratio to 3. Signs of severe hypercapnia are present: wide fluctuations in systemic blood pressure, bradycardia, cardiac arrhythmia, a 200-percent increase in intracranial pressure, a rise in serum potassium level, and anuria. It has been established (*4*) that 40 percent of all dogs maintained under such conditions die within the hour of apnea. Reestablishment of spontaneous ventilation in the survivors required at least 1 hour of mechanical ventilation with pure oxygen.

Six mongrel female dogs were subjected to "apneic oxygenation" for periods of 1 hour to 1 hour and 20 minutes. At the onset of apnea an intravenous 0.33*M* infusion of 2-amino-2(hydroxymethyl)1,3-propane diol (*5*) in 0.2-percent NaCl was administered at the rate of 1 ml/kg min—a quantity deemed sufficient to bind the estimated amount of CO_2 produced by the animal (approximately 0.33 mmole/kg min). After 1 hour of apnea, (i) arterial oxygen saturation was 100 percent and oxygen uptake was at preapneic levels; (ii) average arterial pCO_2 was 89 mm-Hg, total plasma CO_2 was 52.9 mmole/lit., and plasma bicarbonate was 50.1 mmole/lit.; (iii) arterial blood *p*H was maintained within 0.2 *p*H unit of the control preapneic level and after 1 hour of apnea averaged 7.37; the HCO_3^-/H_2CO_3 ratio was 19. Mean blood pressure remained close to that of the preapneic control period and heart rate decreased, but no arrhythmia occurred, and cerebrospinal fluid pressure did not change significantly from normal (Fig. 1). Serum potassium levels remained constant, and instead of renal shutdown there was profuse diuresis.

The urinary *p*H averaged 7.54, the HCO_3^- concentration was 89 mmole/lit., and 26 percent of the estimated total CO_2 produced by the animal during apnea (*6*) was recovered in the urine. The dogs resumed spontaneous breathing between 15 and 20 minutes after the end of the procedure, and all of them survived, without any apparent ill effect. Two animals in this series underwent successfully a second period of 80 minutes of apnea, 16 and 23 days, respectively, after the first one.

This organic buffer base appears to combat the deleterious effects of CO_2 retention in two ways. The compound's CO_2 buffering capacity maintained *p*H within the normal range and limited the rise in pCO_2, even though the total amount of CO_2 produced and retained by the body was considerably greater than it was in the control group of apneically oxygenated animals. (The lesser production of CO_2 by the control animals, as compared with that of the experimental group, probably reflects a depression of metabolic function.) In addition, 18 to 28 percent of the estimated total amount of CO_2 produced during apnea was excreted by way of the kidney.

Although the amount of CO_2 retained within the organism is high, it would appear that the living organism can tolerate it well when its two fractions, bicarbonate and free carbonic acid, are in suitable proportion to maintain the acid-base balance of the blood within normal limits.

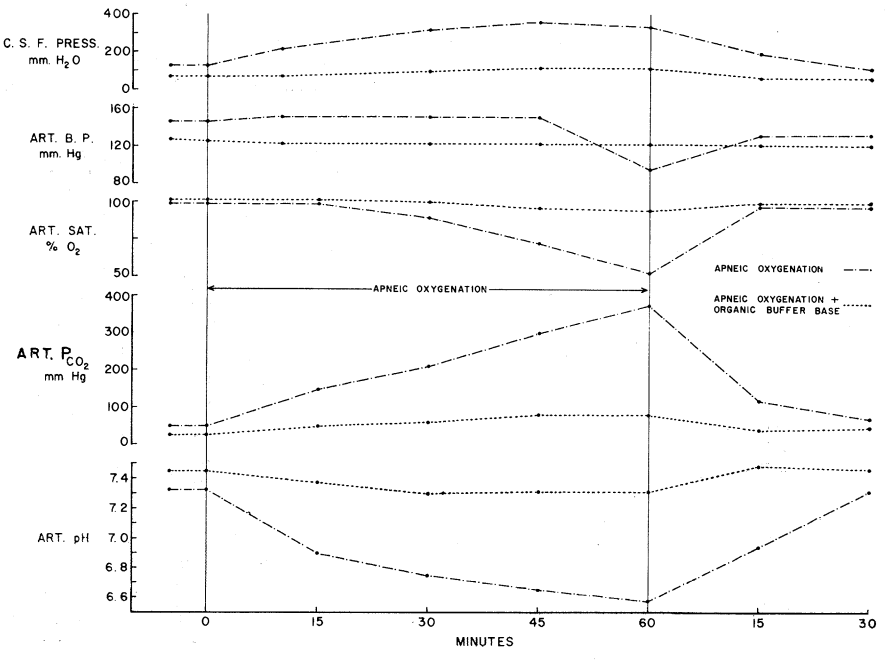

Fig. 1. Effects of intravenous administration of organic buffer base [$(HOCH_2)_3—C—NH_2$] in a dog during a 1-hour period of "apneic oxygenation." While extreme changes are observed during a similar period of apnea in a control animal (dot-dashed line), in the test animal (broken line) there is little or no change in cerebrospinal fluid pressure (CSF), in percentage of oxygen saturation of arterial blood, or in arterial blood *p*H, and there is a 45 mm-Hg rise in arterial pCO_2.

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References and Notes

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5. This compound is commonly known as "tris-hydroxymethylaminomethane" or "tris buffer."
6. The CO_2 produced was calculated on the basis of oxygen uptake when $R = 0.8$.

26 September 1958

Synchronization of Unit Activity in the Cerebral Cortex

Abstract. Simultaneous recording with micropipette electrodes from different units in the cerebral cortex revealed that units seldom fired synchronously. However, there was a temporal relationship in unit firing even when the cortex was "aroused." This relationship was most apparent when strychnine and stimulation were applied to a sensory nerve of an animal asleep or under deep anesthesia.

In a discussion on the electrical activity of the cerebral cortex, Adrian (*1*) stated that "groups of nerve cells very often tend to act in unison when there is nothing to prevent them." Random afferent messages received at the cortex resulted in a breaking down of the synchronous activity of the nerve cells. If the afferent messages were simultaneously received, or if strychnine or some other chemical agent was applied, groups of nerve cells would again respond in unison. This notion was derived from, and subsequently supported by, observations on the waves of potential recorded from isolated structures or fragments of nervous tissue (*2*) and from the cortex of experimental subjects (*3, 4*).

Recently, microelectrodes were used to record unit spike discharges which presumably originated from single nerve cells. Under certain conditions the waves of potential occurred independently of the unit spike discharges (*5, 6*), indicating that they do not necessarily represent envelopes of spikes (*5*). Although observations from these experiments with microelectrodes sometimes suggest the presence of synchronization of unit discharges, especially subsequent to the application of strychnine (*7*), the activity of different cortical units was not simultaneously investigated.

This report concerns the activity of cortical neurons simultaneously recorded with two micropipette electrodes inserted into the somatosensory cortex of cats. The tips of the microelectrodes were estimated to be less than 0.5 mm apart. When a microelectrode picked up spike activity, it was left undisturbed while the other microelectrode was used to study similar activity of other nerve cells within a sphere approximately 1 mm in diameter. Cats were prepared either with a transection between the superior and inferior colliculi (*4*) or with intraperitoneal injection of thiopentone sodium. Stimulating electrodes were placed on a peripheral sensory nerve contralateral to the exposed somatosensory cortex. Toward the end of each experiment, strychnine solution was applied to the area of the cortex where the electrodes were inserted.

The "spontaneous" discharges of the cortical units recorded from Bremer cats and from cats under deep general anesthesia were remarkably similar. They occurred in bursts, each consisting of five to ten short trains of spikes; the intervals between the trains measured from 100 to 400 msec (Fig. 1, *A*). The spike trains recorded from any given pair of units appeared almost simultaneously, with discrepancies varying from 2 to 40 msec. Recordings from cats under light general anesthesia showed many units discharging also in bursts, but the temporal relationship between the bursts from different units was less clear. At times, rythmic bursting activity was recorded from one unit while random discharges were obtained from the other unit. While the animal was waking, bursting activity became less frequent, and when the tail of the cat was pinched, continuous discharges of spikes were recorded. However, a close examination of the records, such as that shown in Fig. 1, *B*, revealed that although synchronous discharges of the two units were scarcely present, there was a tendency for the discharges of the units to pause at about the same time and for the periods to be of similar length (as indicated by the dots in the record).

Stimulation of the peripheral nerve elicited responses with initial spike latencies at intervals either between 5 and 10 msec or between 20 and 30 msec (Fig. 1, *C* and *D*). Those occurred at intervals of 5 to 10 msec and sometimes recurred at intervals of 20 to 30 msec (Fig. 1, *E*). Application of strychnine caused, in most instances (52/60), repetitive discharges in nearly synchronous trains, with discrepancies of 1 to 8 msec in the initiation of the first spike discharge in the trains (Fig. 1, *F*). On some occasions (8/60) the repetitive discharges of one unit were not accompanied by repetitive discharges of the other (Fig. 1, *G*).

The observations cited above, therefore, provide direct evidence to support the notion originally proposed by Adrian (*1*). There are, however, some limiting considerations. (i) Units within a sphere of 1-mm diameter seldom fire at precisely the same instant. (ii) When the cortex is "aroused," the unit activity is said to be "desynchronized," but a relationship between the discharges of the units still exists. (iii) Evoked spike re-

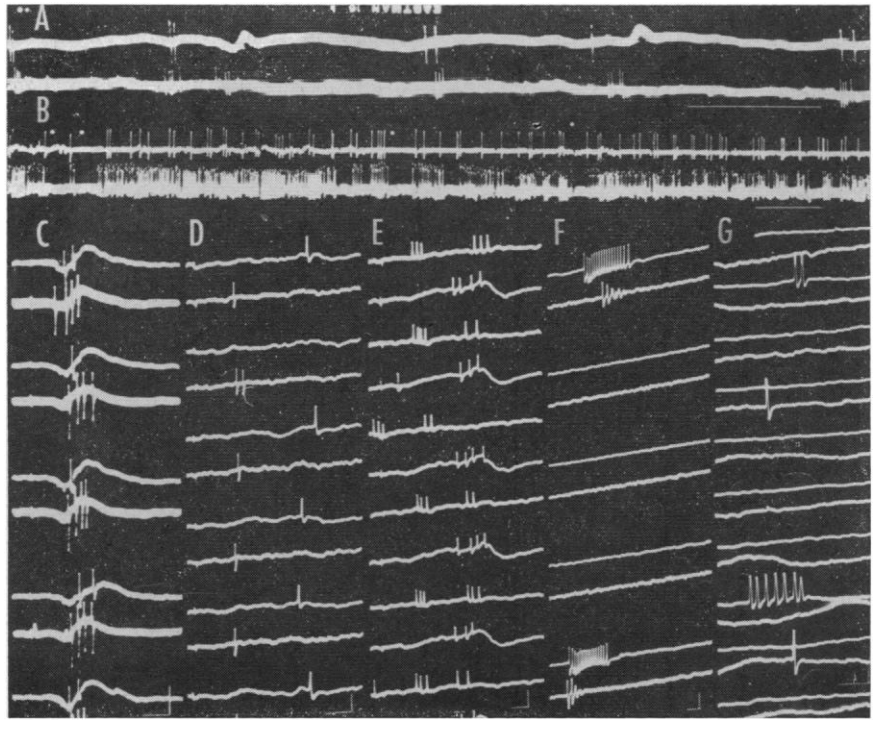

Fig. 1. Synchronous discharges of nerve cells in cerebral cortex: *A*, Discharges subsequent to Bremer section between superior and inferior colliculi; *B*, discharges in response to tail-pinching when cat was waking up from general anesthesia; *C, D, E*, responses to peripheral sensory nerve stimulation; *F, G*, trains of spike discharges following local application of strychnine. Upward deflection represents positivity. Horizontal bars represent 200 msec in *A* and *B*, 5 msec in *C* through *G*. Vertical bars represent 2 mv.