Failure of the Hering-Breuer Reflex to Account for Tachypnea in Anesthetized Man:

A Survey of Halothane, Fluroxene, Methoxyflurane, and Cyclopropane

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The pattern of respiration during anesthesia, characterized by small tidal volumes with rapid respiratory frequencies, has been attributed to increased activity of the Hering-Breuer reflex, following sensitization of pulmonary stretch receptors by the drugs. This thesis was tested by stretching the lungs with pressures chosen to increase the FRC by approximately one and two times the tidal volume. Neither the pattern of ventilatory changes after pressure loading nor the classical inhibitory ratio gave evidence of an active Hering-Breuer reflex in 30 lightly anesthetized, tachypneic, normal adult males. Rather, the change in ventilation mimicked closely that produced by an increased viscous work of breathing. It is proposed that the state of anesthesia abolishes control mechanisms rather than sensitizing reflex control of breathing.

A HUNDRED YEARS AGO Hering[1] and Breuer[2] demonstrated that when the lungs of rabbits were stretched by inflation there was reflex inhibition of subsequent inspiratory effort. Further studies of Head,[3] Adrian,[4] and Widdicombe[5] have shown that this reflex is one of several mediated via the vagus, characterized by slowly-adapting receptors with a low threshold. Whitteridge and Bülbring,[6] studying afferent activity in the vagi of spinal and decapitated cats inhaling nitrous oxide, cyclopropane, trichloroethylene, chloroform, or ether, clearly showed that these drugs sensitized the receptors in the tracheobronchial tree and parenchyma, such that any degree of stretch produced a corresponding larger amount of afferent activity. Dundee and Dripps suggested that sensitization would explain the tachypnea that develops during inhalation anesthesia.[7] This explanation for the tachypnea during anesthesia is appealing because of its simplicity, but there is considerable evidence that in man the reflex is not active.[8, 9, 10, 11]

The usual technique for demonstrating the Hering-Breuer reflex in animals during spontaneous respiration maintains inflation (usually by occlusion of the airway) preventing exhalation. After a time, an inspiration occurs from the inflated end-inspiratory position. The magnitude of the Hering-Breuer reflex is expressed as the ratio of this time to the duration of a respiratory cycle before the stretch. This quotient is called the inhibitory ratio. But, if tachypnea in man is to be explained by a reflex which limits tidal volume, the inspiratory occlusion technique would be inappropriate to demonstrate it. Since the receptors have a low threshold and adapt slowly, sensitization by anesthesia should result in a *decrease* in tidal volume. If exhalation is not prevented, it starts earlier, leading to an *increase* of respiratory frequency when the lungs are stretched.

We have designed a study to compare five anesthetic techniques. Neither the classical inhibition ratio, nor a pattern of decreased tidal volume, V_T, with increased frequency, f, gave evidence for activation of the reflex when

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the stretch receptors were stimulated by increasing the pressure within the breathing circuit. The pressure was sufficient to increase the FRC by one to two tidal volumes. These observations are controlled by two comparisons: (1) the comparison of several anesthetic techniques, which give rise to varied initial frequencies of breathing, and (2) the comparison with a similar increase in the work of breathing produced by resistance loading.

Methods

Thirty male patients, free of cardiopulmonary disease, in five groups of six patients each, were anesthetized with halothane; fluroxene; methoxyflurane; cyclopropane; or cyclopropane after 10 mg. morphine and 0.6 mg. atropine as premedication. The first four groups were premedicated with 0.4 to 0.6 mg. of atropine or scopolamine and 100 to 150 mg. pentobarbital, administered at least one hour prior to induction. Six additional healthy males were studied when awake to determine the normal response to the breathing circuit and stresses employed, using a mouthpiece mounted on the Y piece of the anesthesia apparatus described below.

Anesthesia was induced by inhalation. In the first three groups nitrous oxide was used during induction, but it was discontinued and high inflows of oxygen-anesthetic mixture were delivered for a half hour before observations were begun. Tracheal intubation of an anesthetized patient was facilitated by 60 mg. succinylcholine intravenously administered. No topical anesthetic was used.

When the patients reached a clinically stable state of light anesthesia and were breathing spontaneously, the reservoir bag of a standard Foregger anesthesia circle breathing system was replaced by a 13 liter Collins respirometer with Reichert ventigraph. The spirometer Sadd valves and canister had been removed (fig. 1). After a regular respiratory pattern had been recorded for one minute, a five-pound weight was added to the bell of the spirometer. One minute later a second five-pound weight was added. After another minute both weights were removed. Several minutes later, the procedure was repeated except that ten pounds were added at a time. The addition of five- and ten-pound weights to the spirometer bell corresponded to an increase in airway pressure of 4.5 and 9 torr, respectively.

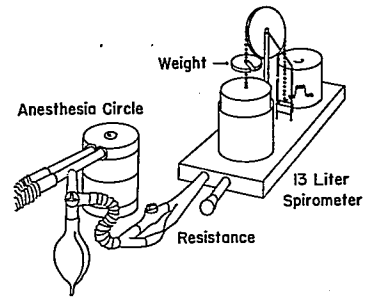

FIG. 1. Apparatus used in the experiments. Weights hung from the spirometer bell bead chain increase the total pressure within the breathing circuit. A narrow tube bypassed by a large-bore valve increased resistance during both inspiration and expiration when the valve was closed.

After these observations had been completed the response to a fixed non-elastic resistance to respiration was recorded for one minute. The resistance (10 cm. $H_2O \times L.^{-1} \times sec.^{-1}$ during laminar flow) was chosen to approximate the order of magnitude of increased work of breathing during pressure-loading (0.15 kg. $\times$ m. $\times$ $min.^{-1}$). (Resistance breathing was studied in only two patients of the halothane group.)

V_E, V_T, and f were tabulated from the spirometer records after correction to BTPS. Changes with the addition of the weights, and with the addition of the fixed non-elastic resistance, were taken as the difference between the loaded measurements and the average of the measurements before and after loading. The changes were analyzed by Student's *t* test.

The inhibitory ratio was calculated after measurement of the respiratory cycle length from the spirometer record, using a microscope with a micrometer eyepiece (10× magnification). The change in FRC resulting from pressure loadings was measured by the shift in spirometer baseline after correction for the compliant volume of the circuit and of an assumed FRC of 2.5 liters.

Results and Interpretation

The average respiratory frequencies, tidal volumes, and minute volumes for the five groups of six patients each are given in table 1, together with the changes that resulted from two different pressure loads and one viscous load. The control pattern of tachypnea with small V_T was especially marked in the three halogenated hydrocarbon groups. Resting minute volumes were normal to slightly-depressed except during fluroxene anesthesia, when several patients had slightly elevated minute volumes.

Response to Pressure Loading

Significant ventilatory reduction usually resulted from increased airway pressure, but f did not increase further; on the contrary, more often it decreased. This decrease was highly significant after pressure loading during halothane and during cyclopropane-with-morphine anesthesia. In the other three groups the lesser response was significant. On the average, V_T was reduced after both the five-pound load and the ten-pound load in all groups except that of cyclopropane-with-morphine anesthesia. The reduction in tidal volume was not significant during methoxyflurane anesthesia at either of the pressures studied, but was significant for halothane, fluroxene, and cyclopropane at one or both of the pressure levels. The ratio of inspiratory to expiratory time was not grossly altered (but these times were not measured accurately). It is interesting to note that the patients with the lowest control ventilatory measurements showed the least decrease during pressure loading. The response of awake man was a decrease in V_T and V_E of borderline significance with little or no change in respiratory frequency.

Response to Viscous Loading

Increasing the work of breathing by the imposition of a resistance within the breathing circuit produced little or no change in the f in any of the four anesthetic groups studied. The average V_T and V_E during resistance breathing decreased in all four groups, but the decrease was significant only for the two halogenated hydrocarbons. The largest response occurred in the cases with largest initial values. In no patient did we see a sustained increase in FRC of as much as the concurrent V_T.

The Pattern of Response to Loading

Figure 2 shows the pattern resulting from two pressure loads and one viscous load. Panel *A* shows the response of normal awake man to the circuit and loads. Panels *B* through *F* represent the five anesthetics studied. The average change in f was quite small in every case, tending to decrease during both pressure and viscous loading. V_T decreased with loading during halogenated hydrocarbon anesthesia (panels *B* through *D*). The decrease was less for five-pound loads than for ten-pound loads, nearly the same whether ten pounds was achieved in two steps or one, and approximately the magnitude of response of a similar increase in the viscous work of breathing.

The patterns of response in the two cyclopropane groups were somewhat different. The frequency of breathing was slower to start with and showed less decrease with both pressure and viscous loading. The V_T during cyclopropane without morphine showed the same changes as did V_T during halogenated hydrocarbon anesthesia. When morphine premedication preceded cyclopropane anesthesia, the decrease during pressure loading was abolished. The decrease in V_T with viscous loading was of the same magnitude as in the other groups.

The Inhibitory Ratio

The classical expression of the Hering-Breuer reflex is a period of inspiratory inhibition by lung inflation, usually measured by the ratio of the duration of the first respiratory cycle after loading to the last respiratory cycle before loading. Table 2 shows the average ratios and the corresponding increase in functional residual capacity produced by pressure loading. In no group was a significant increase in the ratio produced by inflation of the order of one or two tidal volumes.

The individual results are plotted in figure 3. The period of the first breath after stimulation divided by the period of respiration before stimulation is plotted against the degree of stimulus, *i.e.*, the increase in functional re-

TABLE 1. Effects of Pressure and Viscous Loading on Breathing During Anesthesia

Anesthetic	Resting Value		Change with 5 lb. Load		P	Resting Value		Change with 10 lb. Load		P	Resting Value		Change with Viscous Loading		P
	Mean	S.D.	Mean Change	S.D.		Mean	S.D.	Mean Change	S.D.		Mean	S.D.	Mean Change	S.D.	
Halothane															
f	30.4	2.0	−0.8	1.5	N.S.	30.2	5.8	−3.1	1.4	<0.01	31	*	−1.0	*	
V_T	0.184	0.041	−0.038	0.021	<0.05.	247	0.070	−0.127	0.001	<0.01	0.200	*	−0.014	*	
V_E	5.68	127	−1.20	0.07	<0.05	7.35	2.04	−4.24	1.90	<0.01	6.23	*	−0.60	*	
Fluroxene															
f	32.5	5.7	−1.5	1.3	<0.05	33.3	5.7	−1.0	2.8	N.S.	33.0	8.0	−1.2	0.4	N.S.
V_T	0.304	0.057	−0.045	0.073	N.S.	0.332	0.070	−0.100	0.088	<0.01	0.292	0.075	−0.100	0.045	<0.05
V_E	9.92	2.63	−185	191	N.S.	11.00	2.80	−4.12	2.32	<0.01	9.29	132	−5.15	0.14	<0.01
Methoxyflurane															
f	34.8	5.7	−0.2	1.2	N.S.	31.5	4.9	−1.4	2.2	N.S.	30.3	2.8	+0.4	1.0	N.S.
V_T	0.236	0.071	−0.040	0.005	N.S.	0.275	0.002	0.075	0.007	N.S.	0.270	0.051	−0.137	0.006	<0.01
V_E	7.96	141	−127	1.09	N.S.	8.60	1.44	−2.50	2.01	<0.05	8.15	1.77	−3.07	0.78	<0.01
Cyclopropane															
f	20.2	3.0	−0.6	1.2	N.S.	21.8	4.9	−0.7	0.9	N.S.	23.3	0.1	−0.7	0.6	N.S.
V_T	0.301	0.003	−0.078	0.053	<0.05	0.324	0.072	−0.178	120	<0.05	0.307	0.087	−0.126	0.103	N.S.
V_E	6.00	1.20	−1.74	0.95	<0.05	6.88	1.15	−4.20	1.44	N.S.	7.1	24	−2.89	1.39	N.S.
Cyclopropane after morphine															
f	18.3	5.6	−1.4	0.9	<0.05	19.1	4.4	−1.9	0.8	<0.01	20.5	3.0	+0.1	1.1	N.S.
V_T	0.329	0.102	+0.023	0.115	N.S.	0.320	0.063	+0.030	130	N.S.	0.331	0.122	−0.130	0.007	N.S.
V_E	5.01	0.83	−0.19	1.05	N.S.	6.14	0.85	−0.37	2.58	N.S.	6.50	1.80	−2.56	149	N.S.
Awake man															
f	11.7	4.2	+0.8	1.4	N.S.	12.8	4.4	+0.5	2.9	N.S.	12.2	3.3	−4.5	0.1	N.S.
V_T	0.980	0.240	−0.150	0.44	N.S.	0.832	0.710	−0.240	−0.201	<0.05	0.913	0.104	+0.114	0.348	N.S.
V_E	11.12	3.5	−1.50	4.42	N.S.	10.43	3.31	−3.46	5.42	N.S.	10.02	2.08	−3.18	4.14	N.S.

f = respiratory rate per minute; V_T = tidal volume in liters; V_E = minute volume in liters per minute; P = probability of occuring by change; N.S. = not significant.

* These values are the mean of only two studies, so statistical assessment is not warranted. All other values are means of six subjects.

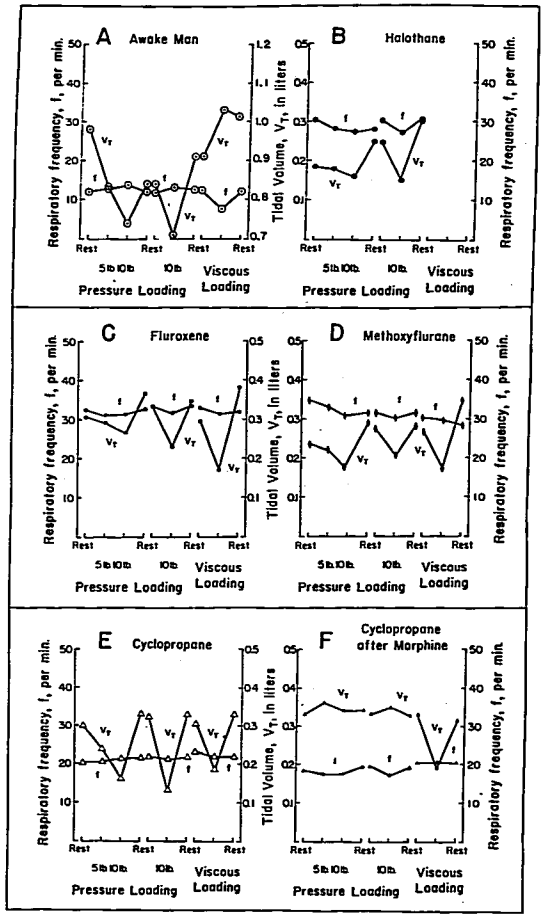

FIG. 2. Respiratory frequency and tidal volume during pressure breathing and viscous loading. Panel *A* represents the pattern of awake healthy man. Panels *B* through *F* show the respiratory frequencies and tidal volumes observed during light anesthesia in groups of six patients.

sidual volume. Panel *B* shows representative data from the study of Widdicombe of various species under barbiturate anesthesia.[8] He measured transpulmonary transpressure as an index of pulmonary stretch. A 10 cm. H_2O transpulmonary pressure in anesthetized man is approximately equal to an increase of one liter in functional residual capacity.

Our observations in the five anesthetic techniques are shown in the remaining five panels. Lines connecting pairs of points with the base line at a ratio of 1.0 represent individual pa-

tients. None of the halogenated hydrocarbons nor cyclopropane without morphine can be considered as sensitizers of the reflex. Four of the six patients receiving cyclopropane after morphine premedication might be considered to have shown some evidence of sensitization (two of these four had episodes of apnea), but the V_T of three of these patients increased, contrary to the predicted pattern.

Production of Apnea

In more than 100 observations of pressure loading involving 30 patients, we found only two apneic responses. Both occurred during cyclopropane anesthesia with morphine, but in different patients. One occurred with ten pounds of weight added to the spirometer at once, and the other when the ten-pound load was applied stepwise; the durations were 25 seconds and 18 seconds. In neither patient was the apnea reproducible several minutes later. The inhibitory ratio was calculated from observations of repeated loadings which did not elicit apnea.

Discussion

The presence of the Hering-Breuer reflex as an important part of central nervous control in lower animals, and sensitization of peripheral receptors by inhalation anesthetics, has been demonstrated beyond question. However, it is weak and not regularly demonstable in awake man or in man anesthetized with thiopental.[8] During anesthesia with nitrous oxide-halothane, Guz and co-workers could demonstrate little or no classical Hering-Breuer reflex, although the respiratory rate was rapid and the tidal volume shallow.[9] Further, local anesthetic blockade of surgically-exposed vagi did not change the pattern of ventilation in any fashion. In extending these observations they found nine patients in whom demonstrable inspiratory inhibition was abolished by vagal blockade.[10] However, this inhibitory effect was demonstrable only with large inflation volumes, of the order of 1,000 ml., and was associated with an active expiratory effort. This confirmed observations of Ritzel,[11] who found that active expiratory efforts followed large inflations and tracheal occlusion. The response to large-volume inflation is a reflex distinct from the slowly-accommodating one originally described by Hering and Breuer,[5] and would not account for tachypnea during anesthesia.

If sensitization of a weak Hering-Breuer reflex were responsible for the characteristic tachypnea and small tidal volumes of halogenated hydrocarbon anesthesia, it would be important to distinguish it from other causes leading to inadequacy of spontaneous respiration during general anesthesia. We therefore designed this study not only to look for the Hering-Breuer reflex in the traditional manner by measuring the inhibitory ratio, but to test whether stretching the lungs by one or two times the tidal volume would produce a predictable pattern of response. Since pressure loading increases the work of breathing, the observations can be controlled by showing

Table 2. The Immediate Effect of Pressure Breathing on the Inhibitory Ratio and FRC

Anesthetic	Five-pound Load				Ten-pound Load			
	Mean Ratio	S.D.	Mean Increase in FRC	S.D.	Mean Ratio	S.D.	Mean Increase in FRC	S.D.
Halothane	1.09	0.07	0.265	0.146	1.16	0.11	0.512	0.167
Fluroxene	1.11	0.18	0.261	0.122	0.96	0.17	0.583	0.170
Methoxyflurane	0.97	0.18	0.228	0.061	1.14	0.32	0.545	0.178
Cyclopropane	1.18	0.68	0.306	0.111	1.00	0.12	0.713	0.276
Cyclopropane after Morphine	1.13	0.13	0.244	0.092	1.33	0.54	0.508	0.217
Awake Man	1.02	0.19	0.525	0.129	0.99	0.10	1.14	0.327

The inhibitory ratio is the ratio of respiratory frequency before loading to that after loading. The increase in FRC is in liters, BTPS. No values for the ratio are statistically different from 1.0.

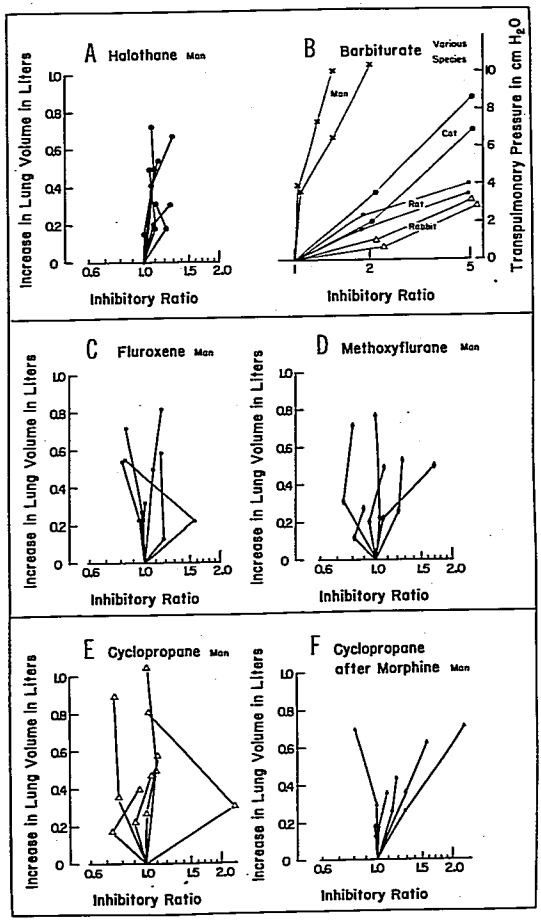

FIG. 3. The relationship between inhibitory ratio and the degree of pulmonary stretching. Panel *B* is redrawn from the data of Widdicombe. The other panels are taken from this study, using the first breath after pressure loading.

that the pattern of response during stimulation of the reflex is different from the pattern of response to increased work of breathing in the same patients, at approximately the same time.

Measurements in the awake group are included only to describe the awake response to our circuit and stresses. The response of awake man to both elastic and viscous loading is well documented.[12, 13, 14] The f, V_T, and FRC vary after loading so as to maintain an alveolar ventilation with a minimized work of breathing. Factors tending to increase the viscous resistance to breathing, such as con-

stricted or obstructed airways, are overcome by increasing the tidal volume and slowing the respiratory frequency or increasing the FRC. Factors which increase the elastic work of breathing, such as chest strapping or pressure loading, elicit a response of increased frequency with decreased tidal volume.

It is interesting to note that Breuer used opiate anesthesia in his original investigation of the reflex.[2] Henderson and Rice demonstrated that morphine enhanced the inflation reflex in rabbits, which they attributed to central action of the drug.[15] May and Widdicombe also found enhancement by opiates of the Hering-Breuer reflex in the cat, which they attributed to bronchoconstriction resulting in increased stretch receptor activity.[16] Widdicombe found a difference in stretch receptor activity when stimulated during inflation as compared with that during maintained inflation.[17] During phasic constant-volume inflation, a drug causing bronchoconstriction enhanced the Hering-Breuer reflex, but during maintained inflation of the lungs acetylcholine reduced the receptor response. It was proposed that during maintained inflation acetylcholine constricts the entire bronchial tree with the displacement of gas into the alveoli. This would tend to decrease the activity of the stretch receptors in the airway. In the case of phasic inflation, however, the airway resistance might result in a greater transbronchial pressure with distention of the larger bronchi. Pressure breathing (constant increase in mean airway pressure) would be more comparable to maintained inflation than the method of study of inhibition ratio in the first respiratory cycle after inflation. Conceivably, morphine and cyclopropane (both weak bronchoconstrictors) could change the mechanical stimulation of receptors by increased pressure. As seen in Panel *F* of figure 2, only during cyclopropane after morphine was there a difference in responses to the two types of increased work of breathing.

That only two instances of apnea were noted in more than 100 observations is consistent with other studies showing the reflex to be weak in man compared with the rat and rabbit. Receptors may be sensitized, but the reflex is either absent or impaired at other loci. Since increased work of breathing gives rise to similar changes in the respiratory pattern, we believe that the response is not attributable to sensitization of the Hering-Breuer reflex. Rather, we suggest that the chain of neuromuscular events accomplishing the work of breathing is depressed by the state of general anesthesia, so that increased effort does not follow an increased load. We feel that these patterns are evidence not for the sensitization of a control mechanism but rather for depression or absence of a control mechanism. Depression of other respiratory control mechanisms during anesthesia has been demonstrated.[18, 19] If this view is correct, the rational treatment of tachypnea during anesthesia is not additional depression by intravenous narcotics in an attempt to slow the rate, but mechanical augmentation of the respiratory volume by assistance or control of respiration.

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Drugs

LOCAL ANESTHETICS Cinchocaine, amethocaine, cocaine and procaine block the calcium-evoked release of catecholamines from the adrenal medulla. The block is dose-dependent and parallels the anesthetic potency of these agents. This effect on the cell membrane of the chromaffin cells is analogous to the effect of these local anesthetic agents on the cell membrane of peripheral nerves; that is, blocking the influx of potassium in one instance and calcium in the other. This block can be overcome with high concentrations of calcium. These agents also block acetylcholine-evoked release of catecholamines from the adrenal medulla. This response, however, is not dose-dependent, and cannot be reversed with high concentrations of calcium, and the dose necessary for blockade does not correlate with the anesthetic potency of the agents. These agents are structurally similar to acetylcholine and may act in this instance by competitive inhibition. (*Jaanus, S. D., Miele, E., and Rubin, R. P.: Analysis of the Inhibitory Effect of Local Anesthetics and Propranolol on Adrenomedullary Secretion Evoked by Calcium or Acetylcholine, Brit. J. Pharmacol. 31: 319 (Oct.) 1967.*)

EPINEPHRINE AND ADRENERGIC BLOCKADE Effects of a three-hour epinephrine infusion were studied in three groups of sheep which were either untreated, premedicated with an alpha-adrenergic blocking agent (phenoxybenzamine), or premedicated with both alpha- and beta-adrenergic blockers (phenoxybenzamine + propranolol). In untreated sheep, the immediate effects of epinephrine infusion were similar to those observed in other species, whereas in phenoxybenzamine-pretreated animals responses were those of beta-adrenergic stimulation. In animals pretreated with both alpha and beta blockers, immediate responses to epinephrine was virtually absent. Twenty-four hours later, untreated and phenoxybenzamine-treated animals were hypotensive, but there was no evidence of diminished blood or plasma volumes or myocardial failure. Sheep treated with both alpha and beta blocking drugs had delayed severe hypotension and died unless given adrenal cortical steroids during the night. (*Halmagyi, D. F. J., and others: Effect of Adrenergic Blockade on Consequences of Sustained Epinephrine Infusion, J. Appl. Physiol. 23: 171 (Aug.) 1967.*)