in the *later* stages of initial infections, whereas in instances of the second to the sixth infections thus far tested they occur in the *early* stages, either alone or associated with normal cysts.

In some instances, guinea pigs which were fed mature oocysts after recovering from a previous infection died within 2 to 10 days thereafter with symptoms and lesions differing in all respects from those found in coccidiosis as observed in this host. Death was usually sudden and preceded by symptoms typical of those described for delayed anaphylaxis in guinea pigs. At autopsy severe hemorrhage was found to have occurred in the lungs, and the intestines were noticeably hyperemic. Cultures of the various organs were in most cases sterile, and in those cases in which growth was obtained a miscellaneous group of the commoner non-pathogenic bacteria was found. Similar symptoms have been produced in animals sensitized by subcutaneous injections of oocysts and subsequent intraperitoneal inoculations of the shock dose.

Intradermal injections of oocysts of *E. caviae* into guinea pigs which had recovered from infection with this coccidium have clearly demonstrated a cutaneous hypersensitivity. This was manifested by the appearance in approximately 48 hours of an inflamed area surrounding the point of injection, swelling, induration, and somewhat later, by central necrosis. In the only animal which received an intradermal injection while suffering from an active infection, the response occurred within 2 hours after injection. An area 3 cm. in diameter surrounding the point of injection became bright red at the end of 18 hours. Twenty-four hours after the injection the animal died. Six normal animals injected at the same time failed to show any reaction other than a slight irritation at the point of inoculation, which disappeared in 24 to 48 hours.

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Effects of Carbon-Dioxide Inhalations on Intrapleural Pressure in Dogs.*

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In our studies on the effects of broncho-constricting drugs on in-

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trapleural pressure,[1] we noted that whereas a more positive intrapleural pressure on expiration developed following the administration of such drugs, it was by no means as great proportionally as the development of a more negative intrapleural pressure on inspiration. This suggested that mere broncho-constriction was not the only factor operating to produce the effects. Since resistance to the passage of air in and out of alveoli may be expected to increase gradually the CO_2 tension in the alveoli, and in the blood, we determined to study directly the effects of CO_2 inhalation on intrapleural pressure.

Dogs were lightly anesthetized with sodium amytal or with dial and urethane. The experimental technique employed has been previously described.[2] Inhalations of CO_2 concentrations of 10% in oxygen (22 experiments) are followed by a gradual development of more negative intrapleural pressure than exists normally. The effect is similar to, but more marked and rapid than that noted after the administration of such broncho-constricting drugs as pilocarpine or eserine. It is accompanied by an increase in mean thoracic girth. Respiration, in other words, proceeds with the chest in an inspiratory position. This is probably due to the initial stimulating effect of CO_2 on what Lumsden[3] postulated as the apneustic or inspiratory center in the medulla, and it probably is the cause of the more negative intrapleural pressure. Inhalations of concentrations of CO_2 higher than 10% in oxygen (16 experiments) lead to a quick change in intrapleural pressure, in which it not only becomes much more negative on inspiration but also much more positive on expiration. The latter effect is not as great proportionally as the development of more negative intrapleural pressure on inspiration. The average thoracic girth is increased as with lower concentrations of CO_2, but in addition there is a decrease in mean abdominal girth. This may be explained again on Lumsden's thesis that the expiratory center is stimulated only by relatively high concentrations of CO_2, although the chest remains in an inspiratory position. With the vagi cut (3 experiments), the inhalation of CO_2 in oxygen resulted chiefly in the development of a more positive intrapleural pressure, especially on expiration.

Our findings may explain in part the effects on intrapleural pressure we noted after the administration of broncho-constricting

[1] Brill, S., Prinzmetal, Myron, and Leake, C. D., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 617.

[2] Brill, S., and Leake, C. D., PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 518.

[3] Lumsden, T., *J. Physiol.*, 1923, **58**, 111.

drugs. There is direct evidence that resistance to breathing increases alveolar CO_2 concentration.[4] While it is often stated that CO_2 itself causes broncho-constriction, direct bronchoscopic observation has shown that CO_2 inhalations in man seem always to dilate the bronchi.[5] Our observations confirm and extend Lumsden's thesis that CO_2 first stimulates an inspiratory medullary center, and later, or with higher concentrations, an expiratory medullary center. We believe that any significant effect on intrapleural pressure in an intact body is mediated by central respiratory control in determining whether respiration shall continue with the chest in a relative inspiratory or in a relative expiratory position. The effects on intrapleural pressure of broncho-dilatation or broncho-constriction,

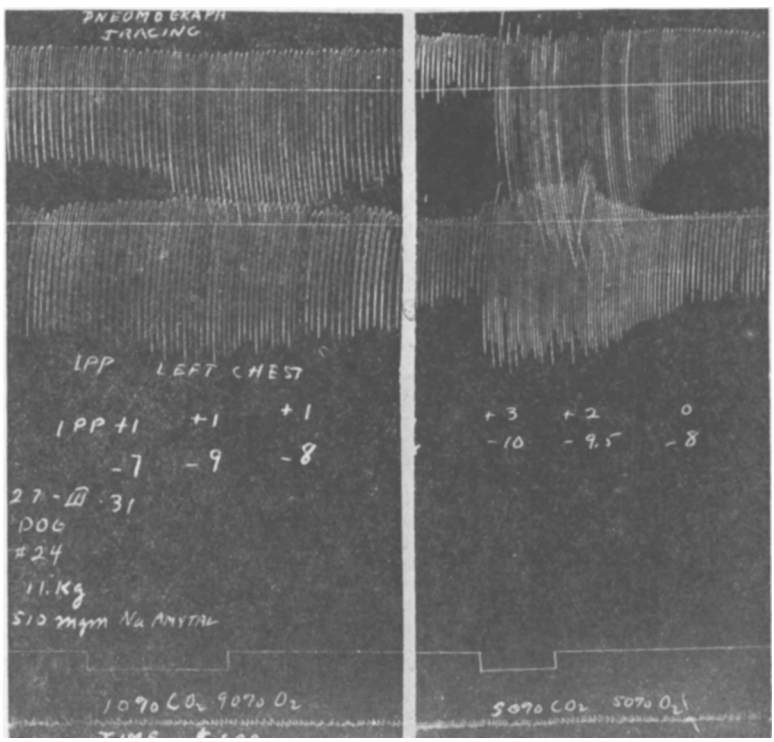

FIG. 1.

Kymographic record of effects of inhaling concentrations of 10% CO_2 and 50% CO_2 in oxygen respectively on intrapleural pressure and chest size as indicated by pneumograph in an 11 kilo dog lightly anesthetized with sodium amytal. Downstroke in pneumograph tracing records inspiration. Intrapleural pressure figures given in centimeters of water.

[4] Davies, H. W., Haldane, J. S., and Priestley, J. G., *J. Physiol.*, 1919, **53**, 60.

[5] Brunn, H., and Brill, S., *Ann. Surg.*, 1930, **92**, 801.

whether caused by drugs or otherwise, are probably governed by this factor. An explanation may thus be afforded for the emphysema noted in chronic asthmatics or after prolonged exposures to rarefied atmospheres. In the former case, the slight increase in alveolar and blood CO_2 tension due to broncho-constriction may act as the ever present stimulant to the inspiratory medullary center tending to fix the chest more and more in an inspiratory position. In the latter instance chronic oxygen want may be the continued stimulant.

TABLE I.

Effects of the inhalation of 10% CO_2 in oxygen on intrapleural pressure and thoracic girth in a 17 kilo dog lightly anesthetized with sodium amytal.

	Intrapleural Pressure in Cm. H_2O		Thoracic Girth	
	Inspiration	Expiration	Inspiration	Expiration
			cm.	cm.
Normal	—4.5	+0.5	54.6	54.2
CO_2 inhaled	—8.0	+0.5	55.3	54.2
CO_2 off	—6.5	+0.5	55.0	54.2

These considerations give further support to the use of CO_2 inhalations in the prophylaxis or treatment of post-operative atelectasis. Stimulation of an inspiratory medullary center by increasing the relative size of the thorax, and thus by making intrapleural pressure generally more negative, would tend to pull out a collapsed area of the lung. Since certain operative procedures, or the pre-operative use of atropine, may make intrapleural pressure more positive, and thus favor atelectasis,[6] CO_2 inhalations during or after operation are indicated to combat this tendency, in addition to its use as an adjunct or synergist to anesthesia.

[6] Brill, S., and Leake, C. D., *Am. J. Physiol.*, 1930, **93**, 636.