Lorente de No'[10] found that CO_2 raised the threshold of axons of the somatic and the autonomic nervous systems. Lorente de No'[10] showed that the carbon dioxide raised the membrane potential and lengthened the refractory period of nerve. The central inhibitory effects of the carbon dioxide may well be due to the increase of membrane potential and threshold. Moreover, breathing carbon dioxide increases cerebral blood flow by dilating cerebral arterioles, increases respiratory rate and so the oxygenation of blood, shifts the hemoglobin dissociation curve so that the blood releases more oxygen to the tissues and shifts cortical pH to the acid side. In the explanation of the central inhibitory action of the carbon dioxide these factors must all be considered.

Summary. Eighteen patients were ventilated with various concentrations of carbon dioxide-oxygen for varying lengths of time and then were stimulated with super-threshold shocking current. Concentrations of carbon dioxide from 15-30% routinely prevented electrically induced seizures; with 30% carbon dioxide, 30 seconds of inhalation sufficed; with 15-20% mixtures, slightly longer periods of time were required.

[10] Lorente de No', Raphael, Studies of the Rockefeller Institute, vol. 131, 1937, New York.

16903

Central Inhibitory Effects of Carbon Dioxide. IV. Convulsive Phenomena.

K. GYARFAS, G. H. POLLOCK, AND S. N. STEIN. (Introduced by W. S. McCulloch.)

From the Department of Psychiatry, University of Illinois, College of Medicine, and Illinois Neuropsychiatric Institute.

Convulsive phenomena produced by inhalation of carbon dioxide were first mentioned by Waters.[1] Meduna and Gyarfas[2] observed 3 types of convulsive manifestations. The first type is the socalled adversive seizure which consists of conjugate deviation, extension of the arm and flexion of the leg on the side toward which the eyes turn. These fits are not accompanied by any change in the peripheral reflexes and can be explained as tonic neck reflexes due to premotor release.

The second type consists of flexion in the upper with extension in the lower extremities and is accompanied by slight rhythmical twitching. No changes in the peripheral reflexes accompany this seizure. The third type consists of sudden dilation of the pupils, absence of any reaction to light, opisthotonus, extension of all extremities, and flexion of the toes. This type of seizue was interpreted by Meduna and Gyarfas as a symptom of decortication.

Pollock,[3] Stein and Pollock,[4] Pollock *et al.*[5] demonstrated that carbon dioxide in certain concentrations inhibits the action of cortical convulsants.

Pollock and Bain[6] showed that changes in the metabolism of the brain produced by inhalation of carbon dioxide differ from those produced by cortical convulsants. In order to establish the anticonvulsant effect of carbon dioxide in man 92 experiments were carried out in 18 patients in the following way: First, the electro-shock dose of every patient was established, then carbon dioxide was adminis-

[1] Waters, R. M., *New Orleans Med. and Surg. J.*, 1937, **219**, 90.

[2] Meduna, L. J., and Gyarfas, K., Diseases of the Nervous System, in press.

[3] Pollock, G. H., Thesis, Univ. of Illinois, College of Medicine, 1948.

[4] Stein, S. N., and Pollock, G. H., PROC. SOC. EXP. BIOL. AND MED., in press.

[5] Pollock, G. H., Stein, S. N., and Gyarfas, K., PROC. SOC. EXP. BIOL. AND MED., in press.

[6] Pollock, G. H., and Bain, J. A., manuscript in preparation.

tered to the patients in sufficient concentration for a sufficient length of time to prevent the convulsant action of the current. The concentration of carbon dioxide varied from 15 to 30% and the duration of administration from 25 to 170 seconds. A description of the technic and of other details has been given by Pollock *et al.*[5]

Administration of carbon dioxide produced, in all our cases, the following convulsive phenomena: Initial periocular twitching followed by either an extensor hypertonus in all extremities or, more often, slight flexor spasm in the arms and extension in the legs, consecutive transitory plastic tonus, increasing occipital rigidity and opisthotonus, finally, a high degree of extensor rigidity appeared in all limbs, the fingers in *main d'accoucheur* position, toes in flexion. The dilated pupils reacted to light on all but 2 occasions. The tendon and skin reflexes could not be elicited on account of the muscular rigidity. Pathological reflexes were not seen during or after the convulsions though in some cases they preceded them. No tongue biting, incontinence, or postconvulsive stupor appeared. The respiratory and circulatory changes observed were those described by Meduna and Gyarfas.[2] The fits did not appear to be self-limiting. E.E.G., though obscured by muscular movements, was always clearly not of the grand mal type. The electrical activity of the cortex returned to normal shortly after discontinuing inhalation of carbon dioxide.

The clinical symptoms, the E.E.G., and the absence of postseizure stupor, correspond to decerebrate seizures. Our observations indicate, therefore, that the apparently different types of convulsive phenomena described by Meduna and Gyarfas[2] represent only different phases of one activity.

Summary. 1. Combination of E.S.T. with CO_2 inhibits the convulsion.

2. Inhalation of 30% CO_2 and 70% O_2 produced in all cases observed convulsive phenomena of decerebrate character.

16904

Mode of Action of Desoxypyridoxine.

W. W. UMBREIT AND J. G. WADDELL. (Introduced by H. Molitor.)

From the Merck Institute for Therapeutic Research, Rahway, N. J.

Antagonisms caused by metabolite analogues are generally accepted as being due to a competition between the analogue and the natural substrate for some enzyme system of the cell.[1] The inhibitor is thought to occupy a space on the surface of an enzyme which would normally be used by the metabolite. The relatively high ratios of analogue to metabolite usually required are considered as a reflection of relative affinity of the enzyme protein for the metabolite and its analogue. While these concepts have served as useful tools and have perhaps been entirely valid in many cases, it has also been apparent that they must be amplified to cover more complex situations; for example, where the substance used is a structural analogue of a vitamin which functions in the form of a coenzyme with a low dissociation constant. Such a case is offered by the action of desoxypyridoxine in competing with the vitamin B_6 group. This compound, 2,4-dimethyl-3 hydroxy-5 hydroxymethylpyridine, was reported by Ott[2] to act as a powerful antagonist of pyridoxine in the chick. Two moles of desoxypyridoxine counteracted 1 mole of pyridoxine when the latter was limiting. Emerson[3] showed that, in the rat, approximately 50 parts of desoxypyridoxine brought on the

1 Woolley, D. W., *Advances in Enzymology*, 1946, **6**, 129.

2 Ott, W. H., PROC. SOC. EXP. BIOL. AND MED., 1946, **61**, 125.

3 Emerson, G. A., *Fed. Proc.*, 1947, **6**, 406.