OBSERVATIONS IN A CASE OF HYDROCEPHALUS TREATED WITH DIAMOX*

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ETAZOLAMIDE (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide; Diamox) is a sulfonamide derivative with a potent inhibitory effect on carbonic anhydrase, first synthesized by Roblin and Clapp in 1950. The formula of this drug is as follows:

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\text{CH}_3\text{CONH} \quad \text{C} \quad \text{SO}_2\text{NH}_2
\]

In 1935 Roughton reported the presence of carbonic anhydrase in the red blood cells. This enzyme was shown to act as a catalyst for the reversible reaction \(\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3\). He provided an explanation of the mechanism by which catabolic \(\text{CO}_2\) is picked up from the tissues and transported in the blood stream and later released for pulmonary excretion. Since that time carbonic anhydrase has been found to be present in renal cortex, gastric mucosa, pancreas, ciliary body, and brain.

Studies of the pharmacology of Diamox were reported by Maren in 1954, and by Maren et al. in 1954. They demonstrated that Diamox lowers the rate of urinary acidification and promotes the excretion of \(\text{HCO}_3^-\), \(\text{Na}^+\) and \(\text{K}^+\) ions which carry excess water with them. The net renal effect of this drug is a diuresis and a mild acidosis. For this reason it has been used in the treatment of cardiac edema, premenstrual tension, and edema of pregnancy. In 1956 Maren reported that in dogs either loss of base or gain of acid in the range of 5–12 mEq./kg. diminished or abolished the typical renal effects of Diamox on excretion of \(\text{HCO}_3^-\).

In addition to its renal effect Diamox exerts an influence on the function of other organs in which carbonic anhydrase is found in high concentrations. It has anticonvulsant properties and has been employed with some success in the treatment of epilepsy. The mechanism of its anticonvulsant effect is, as yet, not completely understood.

In 1954 Becker reported the reduction of intraocular pressure in man following oral administration of Diamox. Since that time many papers have...
appeared in the literature reporting the efficacy of Diamox as a therapeutic agent in the treatment of glaucoma. In 1955 Friedenwald, Kinsey et al., and Becker were in agreement on the most likely mechanism by which Diamox decreases the formation of aqueous humor. There is a large amount of carbonic anhydrase in the ciliary body and this enzyme acts as a catalyst for the reaction that results in the formation of H+ HCO3-. The H+ ion is quickly lost to the blood stream by diffusion and Na+ enters the eye to form a solution of NaHCO3 which is hypertonic in comparison with its concentration in the plasma. Water then diffuses into the posterior chamber under the influence of osmotic pressure. These conclusions rest heavily upon the findings of Kinsey and others that there is a high concentration of HCO3- in the aqueous humor of the rabbit eye. In 1955 Becker reported a reduction of 60 to 65 per cent in rate of flow or production of aqueous humor in rabbit eyes after systemic administration of Diamox. In 1955 Ballantine and Maren found large amounts of Diamox present in iris and ciliary processes of the rabbit after intravenous administration of Diamox (10 to 20 mg./kg.). In 1956 Davson and Luck reported that in man the concentration of HCO3- is lower in the aqueous humor than in plasma. Their findings challenge the proposed mechanism of action of Diamox in glaucoma.

In 1954 Tschirgi et al. investigated the effect of Diamox on the pressure and rate of flow of spinal fluid in rabbits and cats. They reported that the intravenous administration of 150 mg./kg. of body weight of soluble Diamox was followed by at least a threefold reduction in rate of cerebrospinal fluid flow, or a decline of approximately 30 per cent in intracranial pressure. They believed that the inhibiting effect of Diamox on the rate of formation of H+ and HCO3- within the blood-brain barrier is responsible for a diminished rate of formation of cerebrospinal fluid and interstitial fluid within the brain.

In 1956 Kister studied the effect of Diamox and two allied compounds on the rate of flow of cerebrospinal fluid in cats. He found the rate of flow was diminished 30 per cent after intravenous injection of 0.5 to 150 mg./kg. of Diamox. His studies confirmed those of Tschirgi et al. The two other compounds (CL 8490 and CL 13850), closely resembling Diamox chemically but without the inhibitory action of carbonic anhydrase, had no effect on the flow of cerebrospinal fluid. Kister pointed out that no effect of Diamox apart from its action on carbonic anhydrase has been reported. He concluded that the decline in flow of cerebrospinal fluid following Diamox appears to be caused by its inhibitory effect on carbonic anhydrase.

**CASE HISTORY**

The patient (R.C.) is the eighth in a family of nine children. He was born on April 29, 1951, following a 3-hour labour and normal, noninstrumental delivery. There was a large occipital cephalohematoma but no fracture or unusual separation of the sutures were seen by roentgen ray. The circumference of the head increased from 38.12 cm. on the 9th day of life, to 44.5 cm. on the 27th day. Ventriculography on the 13th day revealed dilated lateral and 3rd ventricles, and failure of