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The Use of diamox in the treatment of glaucoma

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THE USE OF DIAMOX IN THE TREATMENT OF GLAUCOMA

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I. INTRODUCTION

This thesis is presented as a review and analysis of all available medical literature on the use of Diamox (Acetazolamide or 2-acetylamino-1,3,4 thiadiazole-5-sulfonamide) in the treatment of the various forms of glaucoma.

Jonas S. Friedenwald (1), in his Proctor Award Lecture before the Association for Research in Ophthalmology, called attention to the use of such a drug in the treatment of glaucoma. He stated that the results of his experiments on the formation of intraocular fluid raise the question as to whether more effort might not profitably be directed toward a reduction in the formation of aqueous in glaucoma cases as well as toward increasing the outflow of fluid from the eye which represented the major approach at that time.

Within the past two years much laboratory and clinical investigation has been directed toward such a goal. The subject of this thesis represents the most concerted effort made to reduce intraocular tension by inhibiting the formation of the aqueous humor, which in essence is the theory advanced by Friedenwald.

Diamox was discovered by Roblin and his colleagues (2,3) in the laboratories of the Chemotherapy Division of the American Cyanamid Company at Stanford, Connecticut. It was developed in the search for powerful inhibitors of carbonic anhydrase related to sulfanilamide, which had been identified by Mann

and Keilin (4) as a specific carbonic anhydrase inhibitor.

Kinsey (5) reported finding high concentrations of bicarbonate in the interior chamber of the rabbit eye which was added confirmation to Friedenwald's hypothesis (1) that bicarbonate secretion is an important factor in the formation of the aqueous humor. On this basis it was assumed that inhibition of the responsible enzyme, carbonic anhydrase, might lower intraocular pressure by decreasing the rate of secretion. The recent availability of extremely potent carbonic anhydrase inhibitors suggested an exploration of the effects of such agents on the intraocular pressure and dynamics.

II. CHEMISTRY OF DIAMOX

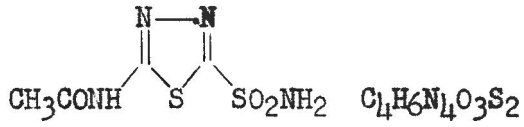
The history of the development of Diamox dates back to 1940 when Mann and Keilin (4) reported that sulfonamides unsubstituted on the sulfonamide nitrogen were highly active as carbonic anhydrase inhibitors. Additional information regarding the specific inhibition of this enzyme system was provided by Schwartz (6) in 1949 when he reported on sulfanilamide in the control of edema associated with congestive heart failure.

Roblin and colleagues (2,3) stated in 1950 that the idea regarding the high degree of inhibitory action on carbonic anhydrase which the heterocyclic sulfonamides might possess was based on the assumption that a competition between carbon dioxide and the bicarbonate ion and the sulfonamide group might account

for the known inhibitory action of sulfanilamide and other unsubstituted sulfonamides on this enzyme. They found by experiments that practically all of the heterocyclic sulfonamides investigated were very effective inhibitors, with some having 100-2000 times the activity of sulfanilamide. They prepared heterocyclic sulfonamides by synthesis from thioheterocycles by low temperature chlorination followed by amidation of the sulfonyl chlorides.

One such compound is Diamox which has an unsubstituted sulfonamide group, a heterocyclic ring, and an acetylated amino group. The compound is a weak acid, slightly soluble in water (2,3).

Structure of Diamox:



$C_4H_6N_4O_3S_2$

III. PHYSIOLOGY OF AQUEOUS FORMATION

As a basis for understanding the mode of action of Diamox and its place in glaucoma therapy it is helpful to review the physiology of aqueous formation.

Almost all authors now agree that a constant though small amount of aqueous humor is being constantly formed and eliminated from the eye (7,8,9).

Experimental and clinical evidence (8,9) indicates that normally fluid is constantly coming into the eye and leaving it by flow. This fluid arises in large part behind the iris,

presumably from the ciliary body, fills the posterior chamber, flows between the iris and the lens into the anterior chamber, and leaves the eye at the iris angle. Thermal circulation plays some part in the movement of the aqueous and is the result of difference in temperature between various regions of the anterior chamber (9).

Duke-Elder in 1927 (10) advanced the theory that the composition of the aqueous humor closely resembled that of a dialysate of the blood plasma. He felt that the aqueous was in diffusional exchange with the blood plasma.

In 1944 Friedenwald (11) stated that there seemed to be general agreement regarding the fact that some exchange of constituents does occur between blood and aqueous by a group of processes termed diffusion in summation. He further states that dynamic factors are superimposed upon this equilibrating trend which prevent development of complete equilibrium between blood and plasma. These dynamic factors were summed together as secretion by Duke-Elder and Davson (12). The attempt was made by Kinsey and Grant (8) to separate them into secretion and leak.

Friedenwald (11) believes the determining factors in regard to the diffusional exchange between blood and aqueous are the size, mobility, and ionic charge of each component on one hand, and on the other the permeabilities or membrane characteristics of the several barriers across which exchange takes place.

Kinsey and Grant (8) have concluded that a secretory mechanism is required to account for the observed transfer of electrolytes, while diffusion alone may account for the transfer rates of water and non-electrolytes. They have computed co-efficients of transfer for each of the components of the intraocular fluid based on the measurement of their rate of transfer from blood to aqueous.

Work with radioactive isotopes of sodium, chlorine, etc. suggest that each constituent of the aqueous humor enters and leaves the anterior chamber at its own particular rate and that one is not justified, therefore, in speaking of a "rate of formation" of aqueous humor as such (7).

The Friedenwald theory for the production of aqueous humor seems to be the most generally accepted. This concept (11,1), as it relates to the movement of constituents of the plasma into the posterior chamber, involves the production of unbalanced hydroxyl ions and the simultaneous diffusion of all the constituents of the plasma into and out of the posterior chamber. He postulates the presence of a cytochrome system in the ciliary epithelium which reduces molecular oxygen enabling it to react with water to form hydroxyl ions. The hydroxyl ions are produced in excess and react with carbon dioxide to form bicarbonate ions which are electrically neutralized by sodium and other cations diffusing from the blood. These salts after diffusion into the posterior chamber maintain the aqueous

hypertonic to the plasma. The resulting hypertonicity causes the diffusion of more water into the posterior chamber. This excess water transfer dilutes the other substances which are diffusing to and fro between the blood and posterior chamber, so that, at steady state, they exist in lower concentration in the aqueous humor than in the plasma. The aqueous humor so formed flows between the iris and the lens into the anterior chamber, where there is further exchange of nonelectrolytes along with a major exchange of water across the iris. The electrolytes do not exchange, however, because the walls of the blood vessels of the iris are impermeable to ions under normal conditions.

All the constituents of the aqueous humor of the anterior chamber then escape from the eye at the angle at a rate of about three micro liters per minute (8,13,9,14). The influx of water as a result of hydrostatic and osmotic pressures, particularly the latter, is responsible for the intraocular pressure. The magnitude of the pressure depends on the rate of production of hydroxyl ions in the epithelium of the ciliary body, the ease of outflow at the angle, and, to a lesser extent, the porosity of the blood aqueous barriers. Under normal conditions they may vary independently and give rise to either an increase or decrease in intraocular pressure (1,9,11,14,15).

IV. ACTION OF DIAMOX

The ability of Diamox to inhibit the enzyme carbonic

anhydrase was first shown by Berliner and his colleagues (16) when they demonstrated the relation between acidification of the urine and excretion of potassium. Carbonic anhydrase mediates the process of urine acidification by accelerating the conversion of carbon dioxide and water to carbonic acid in the tubular cells (17). The ionization of carbonic acid to form hydrogen ion and bicarbonate ion is thus indirectly dependent on carbonic anhydrase activity. The hydrogen ions then replace the sodium ions of the disodium phosphate and sodium bicarbonate present as buffers in the glomerular filtrate. Sodium is thus conserved by excreting sodium acid phosphate, and it returns to the blood. The carbonic acid formed diffuses back into the blood. When Diamox is utilized to inhibit carbonic anhydrase activity, there is less hydrogen made available for the acidification process and consequently more sodium excreted. Berliner (16) has shown that increased potassium excretion also results because of the decrease in hydrogen ions with which potassium ions normally compete for tubular excretion.

Kinsey (5) demonstrated the excess of the bicarbonate ion in the aqueous over that in the plasma. In view of the Friedenwald scheme (1), regarding the importance of the bicarbonate ion in aqueous secretion, the use of Diamox seemed indicated as a means of lowering intraocular pressure. It was first necessary to determine if carbonic anhydrase was present in the ciliary epithelium, as this enzyme was necessary for Diamox to

be effective. In 1952 Maren (18) reported levels of carbonic anhydrase in the ciliary body comparable to those in the kidney. Wistrand, according to Posner (19), added confirmation with his report in 1951 that carbonic anhydrase was present in the uvea of the rabbit in the ratio of 1:14 as compared with its blood concentration.

Preliminary trials to determine the effect of Diamox on ocular physiology were performed on rabbits by Grant and Trotter (20). They reported that intravenous injection of Diamox in a dosage of 10-100 mgm. per kilogram produced definite lowering of intraocular pressure. They also reported that no effect on the intraocular pressure was produced by subconjunctival injections and repeated dropping of a saturated solution of Diamox on the cornea.

Posner (19) states that Diamox probably acts on the eye both by inhibiting aqueous secretion and by dehydrating the vitreous and the ocular tissues as is its action on accumulations of fluid elsewhere in the body.

Breinini and Görtz (21) present the generally accepted view regarding the action of Diamox on the aqueous producing mechanism in the eye. They state that production of the bicarbonate ion is partially dependent on the enzyme carbonic anhydrase. In its absence the reaction proceeds at a much slower rate. In the normal eye the excess bicarbonate ion is responsible for drawing in cations (chiefly sodium) from the stroma, which is also

present in excess in the aqueous; and because of the hypertonicity of the aqueous, due in large part to the presence of these electrolytes, there is a resultant inflow of water. They assumed the electrolyte pattern of the glaucomatous eye was similar.

They (21) assume that the inhibition of carbonic anhydrase by Diamox causes the above reaction to proceed as follows: the bicarbonate ion enters the aqueous at a reduced rate, and its lower concentration causes a reduction in the sodium ions present; the osmotic pressure of the aqueous falls which results in a reduction in the influx of water; and as a result the intraocular pressure should decrease. For proof of this hypothesis electrolyte determinations would be necessary.

Clinical evidence that such a process is occurring within the ciliary epithelium is provided by the water provocative test (21). Such a test given to a patient with chronic simple glaucoma will cause the development of ocular hypertension. This is based on the difference in osmotic pressure that exists between the diluted plasma and the aqueous, which causes a greater influx of water. The intraocular pressure again falls when the aqueous becomes so diluted that the disparity in pressure no longer exists. With depression of the electrolytes in the aqueous as a result of the administration of Diamox, a more nearly normal pressure curve results during the provocative test as the osmotic pressure differential between the plasma

and the aqueous is reduced.

Becker (22) in 1954 reported that while one of the major effects of Diamox is on the kidney producing a marked diuresis of sodium, potassium, bicarbonate and water, such is not the cause for its effect on the aqueous producing mechanism of the eye. He states that a reduction in intraocular tension can be demonstrated in nephrectomized rabbits. Also, dogs made refractory to the diuretic effect of Diamox by ammonium chloride acidosis, or repeated doses of the drug itself still show ocular hypotension following its administration. He concludes that the ocular action is independent of the renal effect.

Thus the attractive hypothesis can be formulated that action of Diamox inhibiting the enzyme carbonic anhydrase causes a suppression of inflow of aqueous humor into the eye (19,20, 21,22,23). Added confirmation for this hypothesis comes from repeated tonography on the same eye which shows that Diamox lowers intraocular pressure without significant change in the facility of outflow (24).

V. DOSAGE AND ADMINISTRATION OF DIAMOX

Breinini and Görtz (21) state that the goal of glaucoma therapy is to provide constant normalization of intraocular pressure.

Most authors (19,20,21,25) felt that since Diamox inhibits secretion of the aqueous, the most effective use of the drug is

by a method which gives continuous action and thereby provides prolonged suppression of aqueous.

Becker (25) reported on a series of 169 patients with glaucoma and stated that 75 to 90% responded with over 40% inhibition of flow on the following dosage schedule. Adults received 250 to 500 mgm. orally every four to six hours. Children received 50 to 100 mgm. every six to eight hours. In patients that were vomiting or who were resistant to oral therapy 250 mgm. of the sodium salt of Diamox was given intravenously in 3 cc. of distilled water and repeated in two hours. Thereafter, oral administration was possible as the vomiting ceased with fall in intraocular pressure.

Posner (19) stated that the drug should be administered in 250 mgm. doses two to four times daily. He further states that in cases of acute narrow angle glaucoma larger initial doses of 750 to 1000 mgm. may be required, especially to reduce the tension preoperatively.

Grant and Trotter (20) adopted a dosage schedule ranging from 125 to 500 mgm. orally every twelve hours and in a few cases used single intravenous injections of 250 to 500 mgm. They based the dosage on the clinical effect attempting to obtain and maintain lowered intraocular pressure with the lowest dose possible. It was their opinion that it was usually necessary to employ Diamox almost to the level that the patient could

tolerate the side effects. They also found that oral administration every twelve hours usually controlled the pressure while a longer time interval reduced the effectiveness.

Breinini and Gortz (21), in their report of 32 cases, found the optimal dose to be 500 mgm. in the morning and 250 mgm. in the evening. They followed this dosage schedule until they obtained a normal intraocular pressure and then changed to 500 mgm. in the morning or 125 mgm. four times daily. Their goal was also to obtain the desired pressure reduction with the smallest possible dose.

The oral route of Diamox administration was generally accepted as being most desirable unless the patient was vomiting (19,20,21,22,23). Becker (25) stated, however, that in several cases of acute congestive narrow angle glaucoma intravenous administration was required to obtain a reduction in pressure.

VI. SIDE EFFECTS OF DIAMOX THERAPY

Following the clinical application of Diamox to glaucoma therapy, certain side effects have appeared which differ from those seen in the laboratory.

On an experimental basis Diamox has been shown to be relatively non-toxic for dogs (26). Eighteen experiments were performed in which dogs were given intravenous doses ranging from 2-2000 mgm. per kilogram with a 100 percent survival rate. No serious or irreversible side effects were found in five

dogs who received 100 mgm. per kilogram per day over a sixteen month period. However, with continuous high dosage in the form of 1000 mgm. per kilogram intravenously daily for three days potassium depletion and death resulted in adult dogs.

Grant and Trotter (20) state that while in most cases some side effects have been noted, no toxic manifestations or ocular side effects have appeared. They further state, however, that some limitations on the usefulness of the drug are imposed by systemic side effects especially following prolonged administration. They reported no unpleasant reactions following oral administration of an initial dose of 500 mgm. However, practically all patients given 250 mgm. two to four times daily for several days developed some side effects. These were "pins and needles" and paresthesias more marked in face, hands, and feet. They felt that such frequent administration did not allow recovery of the acid base balance, and was possibly the cause of the toxic symptoms.

Belsky (27) reported on side effects in patients with heart failure receiving Diamox therapy. He stated that the toxic effects noted were a sense of numbness and pins and needles in the face and extremities, and drowsiness of moderate to extreme degree. These symptoms appeared in all patients receiving a daily dose of one gram or more. The symptoms encountered on a dosage schedule of 0.5 gram were minimal.

He reported no skin manifestations, and no hematopoietic or renal toxicity.

Becker (25) states that the administration of Diamox must be considered a systemic form of therapy as it acts on an enzyme in many parts of the body. Therefore, the effect of chronic inhibition of the enzyme on functions of the red blood cell, the kidney, the lens, the pancreas, the gastric mucosa, etc, must be considered (25,28,29,30). He confirms the presence of paresthesias of the face, hands, and feet in 75 to 80% of all cases treated, and also found excessive fatigue in 4 to 5%, and anorexia in 10 to 15%. He reported no toxic effects of dermatitis, agranulocytosis, or renal damage.

Breinini and Görtz (21) are of the opinion that the inhib-ition of carbonic anhydrase by Diamox is on a quantitative basis whereby structures containing small amounts of the enzyme are inhibited by doses small enough to have no effect on vital processes. Westbrand, according to Breinini and Görtz (21), has shown, for example, that the activity of the enzyme in the red blood cell is seven times that in the ciliary process. This experimental evidence, they feel, shows that there is little danger of inhibiting respiratory exchange in the red blood cell by the therapeutic level of Diamox.

Breinini and Görtz (21) reported symptoms of paresthesias and tingling in the extremities of patients receiving 500 mgm. of Diamox orally, but did not find the complaints severe

enough to merit dosage reduction. Drowsiness was an occasional complaint as was anorexia and nausea. Polyuria was reported as excessive in some cases and a sulfonamide rash was a rare complaint. They found no evidence of ocular toxicity.

Becker (25) introduced another consideration in regard to prolonged Diamox therapy when he mentioned the theoretical possibility that the outflow channel from the anterior chamber might suffer disuse atrophy following the prolonged inhibition of aqueous inflow. He reported, however, on fifty patients who received "round the clock" Diamox for periods ranging from six months to one year without evidence of toxicity to ocular structures, or of further compromise in the facility of the aqueous outflow. Several authors (19,21,23,25) expressed the opinion that more evidence is needed regarding the effect of continuous suppression of aqueous inflow on the lens, cornea, and other ocular tissues. Becker (22) also states that there is a possibility that long term Diamox therapy may have an effect on ocular tissue by interfering with the carrying of nutrients and waste products, both of which are functions of the aqueous.

Grant and Trotter (20) suggested that the side effects of Diamox therapy may represent functional, rather than organic, disturbance since they disappeared within one day following cessation of therapy.

VII. RESULTS IN TREATMENT OF GLAUCOMA WITH DIAMOX

The first report on the effect of Diamox in glaucoma was made by Becker in January of 1954 (23). He reported on a series of nineteen patients among which there were twenty five eyes of fifteen patients with various types of glaucoma not controlled by conventional methods. These patients were treated with single doses of 500 to 1000 mgm. of Diamox orally. In every case a reduction in the intraocular pressure resulted. He reported that within sixty to ninety minutes the pressure began to fall, reached a maximum in three to five hours, and returned to the initial levels in eight to twelve hours. A prompt pressure reduction followed a second dose of the drug. He found that in general the higher the intraocular pressure, and the lower the facility of outflow the longer the time required for pressure to fall to normal limits. He found a similar response in the ten normal eyes in the series, though with much smaller decreases in pressure.

On the basis of tonographic tracings taken in each of the nineteen patients Becker (23) found that the fall in the intraocular pressure occurred without measurable change in the facility of outflow.

In June of 1954 Grant and Trotter (20) reported on the effect of oral Diamox administration in forty patients, of whom eight were normal and thirty two with various types of glaucoma involving fifty eyes. The patients were followed with frequent

tonometric and occasional tonographic measurements, and all eyes were examined gonioscopically. They stated that Diamox was more effective the higher the initial pressure, and that commonly the pressure was lowered by about one third. They reported Diamox had little effect in normal eyes.

They (20) found that a greater effect was produced in treat-ment of two cases of narrow angle glaucoma than in other condit-ions, and noted that subsequent experiences have been similar.

A lowering of intraocular pressure to normal range was produced in eighteen cases of open angle glaucoma which were uncontrolled on standard topical medication. These patients were doing well after four weeks of therapy though they had not established duration of effectiveness.

They reported good results in the treatment of two patients with acute glaucoma secondary to iridocyclitis when standard therapy had proved inadequate. However, poor results followed attempted treatment of glaucoma due to extensive peripheral anterior synechias (20).

In September of 1954 Breinini and Görtz (21) reported on thirty two glaucoma patients treated with Diamox. They stated seventeen of the patients were successfully treated and fifteen were failures. More than one half of the patients with secondary glaucoma were successfully treated while less than half of the chronic simple glaucomas were successful. Those patients with uveitic hypertension showed a greater response than any

other

type of glaucoma. They point to the tendency of patients with chronic glaucoma to become refractory to Diamox therapy.

Becker (25) has reported the use of Diamox in the short-term treatment of glaucomatous eyes in a series of two hundred consecutive patients. All of the 169 patients with glaucoma in the series had not responded to conventional medical therapy. Their therapeutic regime was continued without change except for the addition of Diamox. In normal as well as glaucomatous eyes 75 to 90% responded with over 40% inhibition of flow and only 2 to 6% failed to obtain 20% suppression of flow.

In the Becker series (25) there were forty one eyes with acute congestive narrow angle glaucoma and only one eye failed to obtain at least 20% inhibition. Of twenty two eyes with chronic narrow angle glaucoma three failed to obtain 20% inhibition. He found that in twelve eyes with hemorrhagic glaucoma a decrease in aqueous inflow (over 40%) was obtained in seven while four failed to respond with 20% inhibition. This represents a failure incidence of 33% as compared to other secondary glaucomas with only 3%.

VIII. EVALUATION OF DIAMOX IN GLAUCOMA THERAPY

Most authors expressed the opinion that a conbination form of therapy employing both standard miotic treatment and Diamox gave the most satisfactory results in the treatment of glaucoma (19,20,21,22,23,25). They also emphasized that individualization

of treatment for each patient was also very important. Miotics, although affecting ocular vasculature, are thought to have their main effect on drainage of aqueous from the anterior chamber at the iris angle (21).

Becker (22) is of the opinion that Diamox is especially valuable in the short-term treatment of glaucomatous states. He feels that if intraocular pressure can be maintained at near normal levels during such self-limited diseases as iritis, hyphema, glaucomato-cyclitic crisis serious sequelae can be reduced. Institution of this therapy, he states, makes possible more adequate gonioscopic, ophthalmoscopic, tonographic, visual, and perimeter evaluation of the eye. It has made possible more accurate diagnosis and evaluation of prognosis in acute glaucoma.

Breinini and Görtz (21) feel that success is usually determined by the duration of treatment required as in chronic glaucoma there is a great tendency for the development of a refractory state. This frequently follows a remarkable initial pressure response. They also state, however, that some glaucomas seem to be controlled indefinitely on small doses of Diamox.

Surgical therapy is still advocated as being the treatment of choice in most glaucoma cases, particularly in the acute phase. This is the only method by which the primary pathology, blockage of drainage by occlusion of the angle, can be relieved. Becker stated that even in cases of acute glaucoma that failed to respond to miotics gonioscopic examination could be performed

after Diamox administration in many instances (25). In this manner the mechanism blocking the angle could be visualized and evaluated. It has also made possible more adequate evaluation of the location and extent of synechiae in eyes suffering from narrow-angle glaucoma or aphakic glaucoma (20,21,25).

The preoperative use of Diamox was advocated by Becker (25). He feels this has reduced the incidence of vitreous loss, expulsive hemorrhage, and other complications which sometimes follow sudden decompression of eyes with high intraocular pressure. He states that the administration of Diamox in acute glaucoma cases, both primary and secondary, caused rapid clearing of the corneal edema following reduction of intraocular pressure. Thereby the ophthalmologist could better evaluate the patient's vision and fields. Findings of vein occlusion, diabetic retinopathy, neoplasms, and retinal detachments have altered the surgeon's approach on occasion. Also the repeated administration of Diamox in cases of self-limited glaucomas has avoided the necessity of surgery in many eyes in Becker's series.

Grant and Trotter (20) are of the opinion that in reversible angle closure glaucoma Diamox administration causes a pressure reduction by controlling iris sphincter paralysis. The iris sphincter is thought to be paralyzed at the high initial pressure but regains responsiveness with a lowering of the pressure. By contraction it then withdraws the iris from contact with the filtration meshwork in the angle.

Posner (19) reports that Diamox has been found useful in restoring a flat anterior chamber after cataract extraction. He also states it will be valuable as a means of relieving or preventing malignant glaucoma which is a dreaded complication of filtering operations.

IX. SUMMARY

1. Diamox, a carbonic anhydrase inhibitor, is a new drug which has only recently been added to the physician's armamentarium for the treatment of glaucoma.

2. The action of Diamox apparently arises from its inhibition of the enzyme carbonic anhydrase in the ciliary epithelium, with resultant depression of bicarbonate ion formation. With reduction of the bicarbonate ion concentration in the aqueous there is a reduced influx of electrolytes and water from the stroma and intraocular pressure falls.

3. The drug can be administered either orally or intravenously. However, unless there is intolerance to oral administration because of vomiting, etc., this route is usually preferable.

4. Diamox produces only minimal side effects at the usual therapeutic dosage. Paresthesias about the face, hands, and feet and anorexia and nausea were reported. No evidence of ocular toxicity, agranulocytosis, or renal damage were reported.

5. Diamox appears to be most effective in short-term

treatment of glaucoma, such as in acute congestive glaucoma, secondary glaucoma, and especially uveitic hypertension. By its administration pressure may be normalized long enough to allow a more adequate evaluation of the glaucomatous eye, to allow for treatment of the underlying disease, and to allow for preparation of the patient for surgery.

6. Diamox is useful as preoperative medication making possible operation on a softer, less inflammed eye with less likelihood of complications.

7. The place of Diamox in the treatment of chronic open-angle glaucoma is still in question. An initial lowering of the intraocular pressure is produced, but a refractory state frequently occurs. It has been shown that depression of intraocular pressure can be maintained for periods of twelve months or more with repeated drug administration in some cases.

X. CONCLUSIONS

On the basis of the experimental and clinical evidence available to date, Diamox appears to be an important contribution to the established treatment of glaucoma.

It is evident that certain forms of glaucoma benefit far more than others following its therapeutic institution. The main criterion seems to be the length of time for which a reduction in intraocular pressure is required. Those requiring short-term reduction obtaining greatest benefit.

It is apparent that Diamox does not interfere with other forms of therapy, and indicated conventional means of therapy to improve facility of outflow (miotics or surgery) should not be discontinued or neglected.

The place of Diamox in long-term treatment of glaucoma demands much extensive investigation. The refractory state is one of the most characteristic findings in Diamox medication and constitutes one of the central problems at which research must be directed. There are many additional therapeutic and practical problems concerned with the advisability of long-term treatment.

Far more extensive investigation and study is required to fully evaluate the true scope of Diamox therapy in the treatment of glaucoma.

BIBLIOGRAPHY

1. Friedenwald, J. S.: Forrmation of Intraocular Fluid. Am. J. Ophthal. 32:9 1949.

2. Roblin, R. O., Jr. and Clapp, J. W.: Preparation of Heterocyclic Sulfonamides. J. Am. Chem. Soc. 72:4890 1950.

3. Miller, W. H., Dessert, . M., and Roblin, R. O., Jr.: Heterocyclic Sulfonamide as Carbonic Anhydrase Inhibitors. J. Am. Chem. Soc. 72:4893 1950.

4. Mann, T., and Keiki, O.: Sulfanilamide as a Specific Inhibitor of Carbonic Anhydrase. Nature 146:164 1940.

5. Kinsey, V. E.: Comparative Chemistry of Aqueous Humor in Posterior and Anterior Chambers of Rabbit Eyes. A. M. A. Arch. Ophthal. 50:401 1953.

6. Schwartz, W. B.: The Effect of Sulfanilamide on Salt and Water Excretion in Congestive Heart Failure. New Eng. J. Med. 240:173 1949.

7. Kinsey, V. E., Grant, W. M., and Cogan, D. G.: Water Movement and the Eye. Arch. Ophth. 27:242 1942.

8. Kinsey, V. E., and Grant, W. M.: Further Chemical Studies on Blood-Aqueous Humor Dynamics. J. Gen. Physiol. 26:119 1942.

9. Kinsey, V. E., and Barany, E.: The Rate of Flow of Aqueous Humor: II Derivation of Rate of Flow and Its Physiologic Significance. Am. J. Ophth. 32:189 1949.

10. Duke-Elder, W. S.: The Ocular Circulation: Its Normal Pressure Relationships and Their Physicolgical Significance. Brit. J. Ophthal. :513 1927.

11. Friedenwald, J. S.: Dynamic Factors in Formation and Reabsorption of Aqueous Humor. Brit. J. Ophthal. 28:503 1944.

12. Davson, H., and Duke-Elder, W. S.: Distribution of Reducing Substances Between Intraocular Fluids and Blood Plasma, and Kinetics of Penetration of Various Sugars into these Fluids. J. Physiol. 107:141 1948.

13. Barany, E.: Influence of Intraocular Pressure on the Rate of Drainage of Aqueous Humor. Stabilization of Intraocular Pressure or of Aqueous Flow. Brit. J. Ophth. 31:160 1947.

14. Becker, B. and Friedenwald, J. S.: Clinical Aqueous Outflow. A. M. A. Arch. Ophth. 50:557 1953.

15. Kinsey, V. E.: A Unified Concept of Aqueous Humor Dynamics and the Maintenance of Intraocular Pressure. A. M. A. Arch. Ophthal. 44:215 1950.

16. Berliner, R. W., Kennedy, T. J., Jr. and Orloff, J.: Relationship Between Acidification of the Urine and Potassium etabolism. Am. J. Med. 11:274 1951.

17. Pitts, R. F., and Alexander, R. S.: Nature of the Renal Tubular Mechanism for Acidifying Urine. Am. J. Physiol. 144:239 1945.

18. Maren, T. H.: Pharmacology and Renal Effects of Diamox (6063) a New Carbonic Anhydrase Inhibitor. Tr. New York Acad. Sc. 15:53 1952.

19. Posner, A.: Action of Diamox in Narrow Angle Glaucoma and Related Con itions. Eye, Ear, Nose, and Throat Monthly. 33:366 1954.

20. Grant, W. M., and Trotter, R. R.: Diamox (Acetazoleamide) in Treatment of Glaucoma. A. M. A. Arch. Ophthal. 51:735 1954.

21. Breinini, G. M., and Görtz, H.: Carbonic Anhydrase Inhibitor Acetazoleamide (Diamox); A New Approach to the Therapy of Glaucoma. A. M. A. Arch. of Ophthal. 52:333 1954.

22. Becker, B.: Diamox and the Therapy of Glaucoma. Amer. J. Ophthal. 38:11 1954.

23. Becker, B.: Decrease in Intraocular Pressure in Man by a Carbonic Anhydrase Inhibitor, Diamox. A Preliminary Report. Am. J. Ophthal. 37:13 1954.

24. Mansheim, B. J.: Aqueous Outflow Measurements by Continuous Tonometry in Some Unusual Forms of Glaucoma. A. M. A. Arch. Ophthal. 50:580 1953.

25. Becker, B.: The Short-Term Administration of Diamox in the Therapy of the Glaucomas. (not yet published).

26. Maren, T. H., and Wadsworth, B. C.: Relation Between the Pharmacology, Disposition, and Renal Effects of Diamox. J. Pharmacol. and Exper. Therapy. 109: 1953.

27. Belsky, H.: Use of New Oral Diuretic, Diamox, in Congestive Heart Disease. New Eng. J. Med. 249:140 1953.

28. Friedberg, C. K., Halpern, M., and Taymor, R.: The Effect of Intravenous Administration of 6063, a Carbonic Anhydrase Inhibitor, on Fluid and Electrolytes in Normal Subjects and Patients with Congestive Heart Failure. J. Clin. Invest. 31:1074 1952.

29. Birnbaum, D., and Hollander, F.: Inhibition of Pancreatic Secretion by Cabonic Anhydrase Inhibitor 2-Acetyl-amino-1,3,4-Thiadiazole-5-Sulfonamide, Diamox (6063). Am. J. Physiol. 174:191 1953

30. Janowitz, H. D., Colcher, H., and Hollander, F.: Inhibition of Gastric Secfetion of Acid in Dogs by Carbonic Anhydrase Inhibition by 2-Acetylamino-1,3,4-Thiadia-zole-5-Sulfonamide. Am. J. Physiol. 171:325 1952.