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:

\[
\begin{align*}
\text{N} & \text{N} \\
\text{CH}_3\text{CONH}^\cdot\text{C} & \text{C}\cdot\text{SO}_2\text{NH}_2 \\
\text{S} & 
\end{align*}
\]

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 1954 Becker reported the reduction of intraocular pressure in man following oral administration of Diamox. Since that time many papers have

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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 $H^+\text{HCO}_3^-$. The $H^+$ ion is quickly lost to the blood stream by diffusion and $Na^+$ enters the eye to form a solution of $NaHCO_3$ 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 $HCO_3^-$ 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 Ballentine 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 $HCO_3^-$ 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 $HCO_3^-$ 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
oxygen to pass through the aqueduct of Sylvius. The ventricular fluid was slightly xanthochromic and the protein was 100 mg. per cent.

A diagnosis of noncommunicating, internal hydrocephalus was made and a right ventriculoperitoneal shunt was performed on the 33rd day of life. He was discharged, improved, on the 12th postoperative day (Fig. 1). A revision of the ventriculoperitoneal shunt was necessary on Aug. 11, 1951. The inferior end of the tube had escaped from the peritoneal cavity and symptoms of increased intracranial pressure had developed.

For 3½ years, from August 1951 to April 1955, there was no sign of increased intracranial pressure. He had a left-sided focal cerebral seizure in July 1954, but cerebrospinal fluid pressure was normal.

Fig. 1. Patient at age of 6 weeks (June 11, 1951) after right ventriculoperitoneal shunt.

On May 17, 1955, the patient was readmitted with signs of increased intracranial pressure. These consisted of drowsiness, irritability, vomiting and generalized weakness. There was bulging of the scalp around the tube, and he had papilledema and bilateral Babinski sign. On June 7, 1955, a revision of the ventriculoperitoneal shunt was performed. His condition improved but 2 weeks later a cerebrospinal fluid cyst in the abdomen necessitated an exploratory laparotomy, on June 28, 1955. He was discharged a month later as greatly improved.

Except for one cerebral seizure he did well until Sept. 30, 1955, when, again, symptoms of increased intracranial pressure developed. The circumference of his head was 50.5 cm. and he was noticeably lethargic. There was a nontender mass in the abdomen and subcutaneous fluid was present along the tract of the tube. After 100 cc. of spinal fluid were withdrawn via percutaneous puncture of the tube, the child was much brighter and the cystic abdominal mass disappeared.

Between Oct. 2, 1955 and Nov. 4, 1955, it was necessary to aspirate the tube about once every 4 days. An average of 117 cc. of cerebrospinal fluid were withdrawn each time. Aspirations were performed only after development of signs of increased intracranial pressure, which were lethargy, weakness, anorexia, vomiting, and a tense scalp over the bony defect. With reduction of intracranial pressure there was always dramatic improvement in the patient’s clinical picture.

On Nov. 4, 1955, the 4th ventricle was explored and observed to be small. The
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aqueduct of Sylvius was not patent and could not be intubated. A right Torkildsen's procedure was performed and the tube was proven to be patent. During a stormy postoperative course, over a period of 52 days, aspiration of the ventriculoperitoneal tube was still necessary, approximately every 2nd day, with an average of 89 cc. of cerebrospinal fluid being withdrawn on each occasion.

On Dec. 27, 1955, a lumbar pneumoencephalogram failed to fill the ventricular system. On the same day 200 cc. of oxygen were injected into the ventriculoperitoneal tube. The lateral ventricles filled, but no gas could be passed into the posterior part of the 3rd ventricle or aqueduct of Sylvius. A radiological diagnosis of a lesion in the posterior part of the 3rd ventricle or aqueduct of Sylvius was made. Subsequently the patient was maintained by a series of ventriculoperitoneal tube aspirations, every 2nd or 3rd day, as before.

At this point it was felt that the patient provided an unusual opportunity to study the influence of certain drugs on the rate of formation of the cerebrospinal fluid. The required frequency of aspirations (every 2nd or 3rd day) and the average amount of fluid withdrawn at each aspiration were used as base-line data. Trials were made with Pitressin and Diamox. The effect of the Diamox was so striking that we confined the remainder of the study to this drug.

Pitressin failed to have a prolonged effect. On Jan. 15, 1956, 2 units of Pitressin were given by subcutaneous injection every 6 hours. This regimen was continued for 15 days. A transitory effect was obtained and 4 days elapsed without the necessity of aspiration. The base-line conditions were then spontaneously reestablished and aspiration was necessary every 2nd or 3rd day, as before (Fig. 2). Unfortunately efforts to collect 24-hour specimens of urine were unsuccessful. However, he continued to void regularly and catheterization did not seem justifiable.

After a brief drug-free interval a trial of Diamox* was begun Feb. 5, 1956. Diamox, 1000 mg. a day, was given for a period of 2 months. It was administered in 4 oral doses of 250 mg. in order to maintain a continuous high level of activity. Dur-

* This drug was suggested to us by Dr. John Beck of the Royal Victoria Hospital.
ing this period aspirations were noticeably less frequent and became necessary only at 6- to 9-day intervals (Fig. 2). The patient's general condition improved in that he appeared stronger and had a better appetite.

In order to determine whether the favourable change was ascribable to the drug or to some uncontrolled variable, the Diamox was discontinued abruptly. From April 5 to May 2, the patient had no Diamox and the frequency of aspirations increased as before.

On May 2, the Diamox therapy was resumed and continued without interruption for 6 weeks. During this period aspirations never became necessary. A daily dose of 1000 mg. was reduced to 500 mg. at the end of the first 3 weeks. The patient gained strength and improved generally.

The question again arose as to whether the effect was produced by Diamox. The drug was discontinued abruptly for the 2nd time, on June 15. Three days later signs of increased intracranial pressure were evidenced by bulging of the suboccipital craniectomy, drowsiness, irritability, and vomiting. Immediately following aspiration of 100 cc. of cerebrospinal fluid dramatic improvement in the patient's clinical condition occurred. Aspirations were required again on the 11th and 14th days after the drug had been stopped. On each occasion 125 cc. were removed (Fig. 2). The patient's general condition began to deteriorate. It was felt that he had had an adequate trial without the drug, so that Diamox therapy was resumed on June 29, 1956.

As can be seen in Fig. 2, the favourable effects observed during May with 1000 mg. of Diamox continued when the dosage was reduced to 500 mg. daily. Therefore, an attempt was made to establish a minimal daily dose. The daily dose recommended ranges from 5 mg./kg. for a diuretic effect, to a total daily dose of 1000 mg. for the treatment of severe epilepsy or acute glaucoma.

Between June 29 and July 29 a graded series of increasing daily dosages, ranging from 62.5 mg. to 1000 mg., were administered in step-like fashion. Aspirations were required every few days until after the 1000 mg. per day level had been reestablished. This dose represents 80 mg./kg. in our patient and was the maximum daily dose used in this study. From July 29, 1956 to the end of this study in April 1957, the patient remained on 1000 mg. of Diamox daily except for 1 week in November.

![Fig. 3. Patient at age of 5 years during present study (July 14, 1956).](image-url)
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Fig. 4. Pneumoencephalogram via shunt tube during present study (Aug. 23, 1956). Demonstration of degree of hydrocephalus caused by obstruction of aqueduct of Sylvius and posterior part of 3rd ventricle.

Two days after the reestablishment of the maximal dose (July 31) it was necessary to aspirate from the tube. The patient then remained free of increased intracranial pressure for a period of 16 days. During this period of improvement he suffered an attack of measles. Three days after the rash, signs of increased intracranial pressure appeared. Four small (30 and 50 cc.) aspirations were made. On August 23, 100 cc. of spinal fluid and oxygen were exchanged via the ventriculoperitoneal tube. The lateral ventricles were enlarged and the 3rd ventricle was almost completely obliterated (Fig. 4). During this procedure a roentgenogram of the chest, taken in the upright position, revealed no gas in the peritoneal cavity. Following the pneumogram the patient’s condition improved and intracranial pressure remained normal. He was discharged home September 15, and continued well. From Aug. 23, 1956 until the end of March 1957 intracranial pressure, as judged clinically, remained normal and aspirations were not required except during 1 week in November 1956, when the dosage of the drug was reduced, as hereafter described.

On November 20, electrolyte studies were made on the blood. A CO₂ combining power of 13.1 mEq./l. was reported; however, Na, K, and Cl were within normal limits. Four days later, November 24, the daily dosage of Diamox was reduced to 500 mg. The following day, November 25, the patient was readmitted because of drowsiness, irritability, and vomiting, although he appeared well hydrated. His vital signs were normal. The suboccipital bony defect was not bulging. However, there seemed to be a small amount of fluid along the subcutaneous tract of the ventriculoperitoneal tube. An emergency CO₂ combining power was reported as 11.6 mEq./l. It was difficult to be certain about the cause of his symptoms. First, we elected to correct the acidosis without further alteration in the Diamox regimen.
In spite of vigorous sodium lactate therapy, the patient’s symptoms gradually became worse. Three days after admission his CO₂ combining power had risen to 19.2 mEq./l., yet his clinical condition was deteriorating. On that day the skin over the bony defect was tense and it was agreed that the symptoms were most likely caused by elevated intracranial pressure. The tube was aspirated, November 28, and 200 cc. of cerebrospinal fluid were removed. This fluid was under considerable pressure. Oxygen was injected into the tube and radiographs revealed essentially the same picture as seen in the previous encephalogram. The child improved remarkably and almost immediately. He was talkative and active. Diamox was discontinued on that day, November 28, and oral sodium bicarbonate was begun in order to complete the correction of the metabolic acidosis. Six days later aspiration was again necessary and was followed by immediate improvement. Nine days after admission, December 4, the CO₂ combining power was within normal limits, and Diamox, 1000 mg. daily, was restarted the following day, December 5. During the few days that he was not receiving Diamox he had one episode of status epilepticus which began as a left-sided focal cerebral seizure. This had occurred previously in April 1956, during another interval without Diamox.

No further aspirations were required and he remained cheerful and active. He was discharged home on Dec. 22, 1956. Just prior to discharge the CO₂ combining power was reported as 13.4 mEq./l. The daily sodium bicarbonate was increased from 300 to 600 mg. 4 times a day, in a trial to determine its effect on the CO₂ combining power of the blood during Diamox therapy. At the end of 2 months of oral NaHCO₃ therapy the CO₂ combining power was 13.5 mEq./l. The administration of the NaHCO₃ had not changed, appreciably, the degree of metabolic acidosis induced by Diamox therapy. Since discharge he has been followed in the Outpatient Department, and has remained symptom free, except for the necessity of a single aspiration on April 13, 1957.

DISCUSSION

The patient presented has been shown to be suffering from a noncommunicating type of internal hydrocephalus. The clinical course at the time of this study strongly suggests that the lower end of the ventriculoperitoneal tube was obstructed. In none of the radiological studies was there evidence of communication between the ventricular and subarachnoid spaces. The ventricular spaces required frequent removal of fluid via the shunt tube in order to prevent death from elevated intracranial pressure. These conditions
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persisted throughout the 1-year study. The frequency of aspiration and the average amount of cerebrospinal fluid removed was altered markedly during Diamox therapy.

It is our opinion that this drug alters, appreciably, the amount of spinal fluid formed in the ventricles. This view is in keeping with the experimental evidence reported by Tschirgi et al.\(^\text{23}\) and confirmed by Kister\(^\text{14}\) who found a significant decrease in the flow of cerebrospinal fluid in cats after Diamox was given intravenously. This inhibitor of carbonic anhydrase has been shown to decrease the production of aqueous humor in the eye by 60 per cent.\(^\text{5}\) Carbonic anhydrase is present in high concentrations in the ciliary bodies and in the substance of the brain. It is worth inquiring, experimentally, whether or not this enzyme plays an important role in the formation of cerebrospinal fluid. Tschirgi et al.\(^\text{23}\) have suggested that carbonic anhydrase functions at the blood-brain barrier and that it is important in the formation of interstitial fluid as well. If this hypothesis is true, Diamox may be effective not only in altering the production of cerebrospinal fluid but also as a measure in the control of cerebral edema.

The evidence cited in the introduction of this paper supports the hypothesis that the effect of Diamox in epilepsy, glaucoma, and hydrocephalus is a direct one and not secondary to the renal effect. In spite of this preferred mechanism, one cannot rule out the possibility that this patient's response to Diamox is secondary to the drug's renal effect. Indeed the renal excretion of Na\(^+\), K\(^+\), and HCO\(_3^-\) must be kept in mind when one considers the electrolytic changes that accompany Diamox therapy.

The electrolyte and urinary studies are summarized in Table 1. After prolonged high daily doses of Diamox (June 14, 1956 and Nov. 20, 1956) the serum Na\(^+\), K\(^+\), and Cl\(^-\) are observed to be at border-line low normal levels. The CO\(_2\) combining power is altered considerably and is reported at a level approximately 50 per cent of the lower limit of normal. On both occasions the patient was active, cheerful and asymptomatic. The CO\(_2\) combining power was observed to rise to a normal level quickly following the withdrawal of Diamox (Dec. 4, 1956). It was also observed to fall to the 50 per cent level soon after restarting Diamox in spite of oral administration of 300 mg. sodium bicarbonate daily (Dec. 21, 1956). It is worth noting that the CO\(_2\) combining power on this date (16 days after Diamox was resumed) is almost exactly the same as that found on Nov. 20, 1956, after 4\(\frac{1}{2}\) months of Diamox daily. Apparently the renal excretory rate of bicarbonate is very high in the period soon after the initiation of Diamox therapy, but levels off at a lower rate which maintains a metabolic acidosis but does not completely deplete the body stores of bicarbonate. The amount of bicarbonate secreted is probably dependent upon the level of acidosis and the amount of bicarbonate present in the plasma. It was observed that after the initiation of the combined therapy of Diamox and sodium bicarbonate the urinary reaction changed from acid to alkaline. This is interpreted as reflecting increased secretion of bicarbonate. It is also observed that the degree of metabolic acidosis was approximately the same as when the
Laboratory studies of blood, ventricular fluid, and urine during present study

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Urine Specific Gravity and Reaction

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Haematology

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<td>Dec. 20, 1956</td>
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Normal Values

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<th>Cerebrospinal fluid electrolytes</th>
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<tr>
<td>Na 139–148 mEq./l.</td>
<td>CO₂ 24–34 mEq./l.</td>
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<td>K 4.3–5.4 mEq./l.</td>
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<td>Cl 99–107 mEq./l.</td>
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* Patient receiving Na lactate or Na bicarbonate.

patient was on Diamox alone. These assumptions are compatible with the experimental studies of Maren.16 He found that in dogs the renal effect of Diamox was greatly diminished by the induction of metabolic acidosis either by loss of base or gain of acid. Thus far this mechanism acts as a safety check for our patient and prevents frank toxicity that probably would be observed if the rate of renal excretion of bicarbonate remained high. In
our patient this degree of acidosis does not appear to be incompatible with a good clinical state.

Toxic manifestations such as paresthesias, drowsiness, cutaneous rash, and agranulocytosis have been reported in isolated cases. None of these has been observed in this patient.

During the above study our patient suffered attacks of chickenpox and measles. The onset of each of these acute febrile illnesses was accompanied by an increase in the frequency of the aspirations of cerebrospinal fluid required in spite of the fact that Diamox therapy was continued. One might wonder if the efficacy of this enzyme inhibitor is decreased in the body during such acute febrile illnesses. Further observations in children might clarify this point.

The patient is known to have infrequent left-sided focal cerebral seizures. He suffered two episodes of status epilepticus during our study and both after sudden withdrawal of Diamox. This is in keeping with the drug's known anticonvulsant property.

In 1953, Sweet and Locksley reported a study of the formation, flow, and reabsorption of cerebrospinal fluid in man. They hypothesized that the protein in the ventricular fluid must move out of the ventricular system and be reabsorbed through the arachnoid villi, whereas the electrolytes diffuse across the brain-fluid membrane in the ventricles and subarachnoid spaces. In our patient the ventricular fluid protein remained elevated throughout. The concentration decreased with the frequency of aspiration, but it was never observed to be less than 400 mg. per cent (Table 1). The electrolytes (Na+, K+, and Cl−) in this fluid remained at relatively normal levels. The elevated protein may be caused by the obstructing lesion or by the presence of the tube. If these possible causes could be ruled out, the persistently elevated protein might be considered as evidence in support of the hypothesis proposed by these authors.

Sweet and Locksley estimated the net production of cerebrospinal fluid which must move out of one lateral ventricle in 24 hours as 15 cc. In our patient the lateral ventricles communicated with each other although the 3rd appeared to be almost completely obliterated. At base-line conditions without Diamox we estimate the 24-hour production in both lateral ventricles to be between 30 and 50 cc.

SUMMARY

1. The effect of Diamox on the formation of cerebrospinal fluid has been studied in a patient with noncommunicating internal hydrocephalus over a period of 1 year.

2. During the administration of Diamox the frequency of aspiration was markedly reduced with long periods when no aspirations were necessary. Percutaneous aspiration of the shunt tube was performed only after signs of increased intracranial pressure developed. Each time the drug was discontinued signs of increased intracranial pressure, again, soon became evident.
3. Proposals concerning the possible mechanism of action of this drug have been made.
4. A brief review of the literature concerning the history and mechanism of this drug is given.

REFERENCES

10. FRIEDENWALD, J. S. Current studies on acetazolamide (Diamox) and aqueous humor flow. Amer. J. Ophthal., 1953, s.3 40: Nov., pt. 2, 139-147.

DISCUSSION

Dr. Leo M. Davidoff: I don’t know whether the audience any more than I could be convinced that the medical treatment of hydrocephalus will displace the shunt treatment
presented a few minutes before, but it certainly is interesting to see how these roles parallel each other.

**Dr. A. Earl Walker:** I wondered in Dr. Branch's presentation how much the acidosis per se had to do with the decreased production of spinal fluid. Supposing these patients were put on a ketogenic diet, would one then see a decrease in the amount of spinal fluid produced? I also would like to ask as to the amount of urine that was put out during the period when the patient was on Diamox.

**Dr. José L. Garcia Oller:** I will just mention we have had two years' experience with Diamox. We have had 7 cases. The first one was a brilliant, dramatic result, and most of the others failed.

**Dr. M. Javid:** This is a very interesting observation. Even though Diamox might have some effect, such as in the case that was described, I think that in situations that neurosurgeons have to deal with urea is much more effective.

The late Doctor Settlage of the Department of Anatomy at the University of Wisconsin and I used this agent for the last 3 years. Effectiveness of urea was compared with other hypertonic solutions and urea was found to be far superior. On this basis I feel the whole question of the use of hypertonic solutions in neurosurgery should be re-evaluated.

As far as Diamox is concerned, in one patient with a "pseudomeningocele," on comparing the effect of urea, Diamox, 50 per cent sucrose, 50 per cent glucose and mercury, I found the result with urea much more impressive. With the aid of our ophthalmological colleagues the intracocular pressure was measured on several patients with acute glaucoma and normal subjects. Comparing urea and Diamox, urea was found to be more effective. The late Doctor Settlage had similar experience with monkeys.

Personal observation with urea extends to about 150 patients. It is a very effective agent in reducing intracranial pressure. We have given it preoperatively, postoperatively, and during surgery. Urea has facilitated operative exposures. It has been life-saving in some of our cases in which postoperative cerebral edema developed. Urea has been quite helpful in some of the patients who were in a critical condition because of increased intracranial pressure preoperatively when temporary control of cerebral edema is most desirable. Also, we have used it, occasionally, during the weekend or at night as a temporary measure until such time that optimum conditions were available for diagnostic studies and surgery.

To sum it up I have found urea so effective that I would hate to be without it.

**Dr. C. L. Branch:** Thank you, Dr. Walker for these questions.

Very quickly, we have not tried the ketogenic diet. If you recall the large slide with the many entries, we did produce definitely consistent alkaline urine after large doses of sodium bicarbonate. This was given over a 2-month period from December to February. The amount given daily was 2400 mg., and the child showed no evidence of development of pressure. I don't know whether this is a worth while note or not. But it may possibly be that we probably had a more alkaline condition, that is, we reversed the acidosis and still did not get evidence of increased intracranial pressure.

As far as collecting the amount of urine is concerned, we tried that. However, we had technical difficulties on the pediatric ward and we didn't feel catheterization was justified. So we settled for frequent recordings of the specific gravity.

I am sure you don't recall that slide but there were several entries throughout the study and we had specific gravities of random specimens as high as 1.026 and as low as 1.006. So that we considered that specific gravity stayed within normal limits.

Also in the treatment of cardiac edema, the internists have found that there is a diuresis during the first day of continuous therapy but if the therapy is continued, they are disappointed in the lack of water loss, and so they recommend intermittent treatment with Diamox, and Maren has shown that the effect of Diamox on the renal tubules is greatly diminished in the presence of an acidosis, either by gain of acid or by loss of base in his chronic dogs.