A STUDY OF CEREBROSPINAL FLUID PRESSURE MEASUREMENT IN CATS

by

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ABSTRACT

Hydrocephalus, a serious condition involving accumulation of excess cerebrospinal fluid in the ventricles of the brain and elevated cerebrospinal fluid pressure, can result from any of a number of factors, especially congenital malformations. Though many forms of treatment have been tried, only shunting is in common use today. However, shunts themselves cause many problems.

Cerebrospinal fluid is produced in the choroid plexus and central nervous system ependyma and is absorbed through the arachnoid villi. Acetazolamide (Diamox), a carbonic anhydrase inhibitor, and isosorbide, an osmotic diuretic, are expected to diminish cerebrospinal fluid pressure.

The proposed experiment involved implanting piezoelectric pressure transducers into cats' ventricles, trying to obtain baseline values, and attempting to quantify the effects of Diamox and isosorbide on cerebrospinal fluid pressure. Unfortunately, it could not be performed because of unforeseeable circumstances beyond the author's control.

A detailed discussion of several types of biological pressure transducers and their drawbacks is presented. The Pi system of Lorig, Cheng, and Ko is described and recommended for future experiments of this nature.

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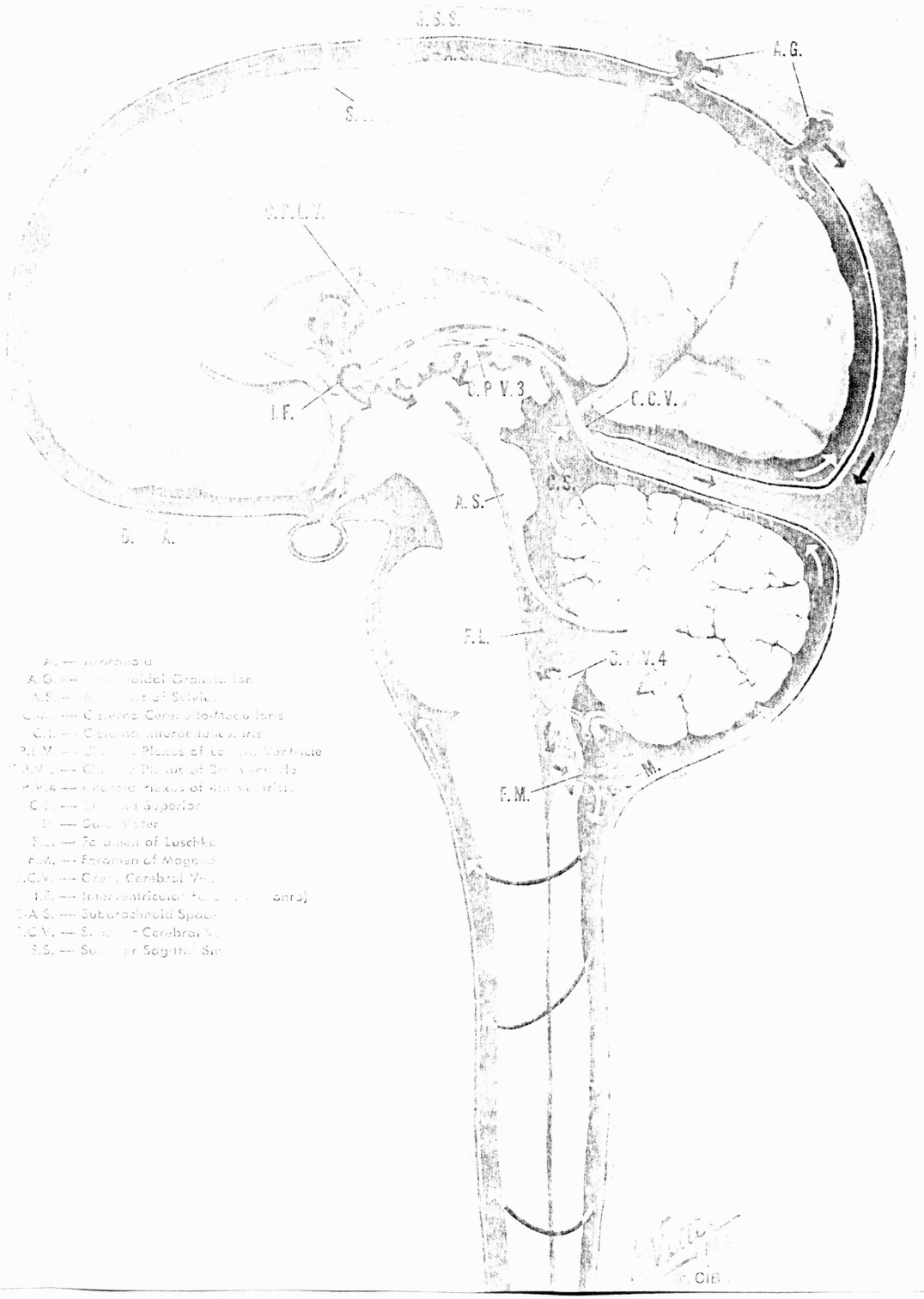
FIGURE 1: CEREBROSPINAL FLUID CIRCULATION



Netter, F. H. The Ciba Collection of Medical Illustrations, Vol. I. Rochester: The Case-Hoyt Corporation, 1972, p. 44.

INTRODUCTION

Problem Statement

Hydrocephalus is a serious condition characterized by accumulation of excess cerebrospinal fluid in the ventricles of the brain and by elevated cerebrospinal fluid pressure, often resulting in skull enlargement, brain damage, dementia, disturbance, and even death. Hydrocephalus is divided into two classes: communicating hydrocephalus, in which the ventricles of the brain are connected normally, and obstructive, or non-communicating, hydrocephalus, in which a physical obstruction such as a tumor blocks cerebrospinal fluid flow in or between the ventricles. The latter type of hydrocephalus results in a somewhat more localized pressure buildup (16).

The distinction between communicating and obstructive hydrocephalus is somewhat arbitrary and misleading for several reasons. Several types of so-called non-communicating hydrocephalus are characterized by only partial blockage between the ventricles or contain patent interventricular connections but possess other deformities which interfere with cerebrospinal fluid flow. A number of types of obstructive hydrocephalus also exhibit problems related to cerebrospinal

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fluid absorption. Thus, the two classes of hydrocephalus are in some ways similar as far as symptoms and methods of management are concerned.

Hydrocephalus occurs as a congenital defect in one to two per thousand live births and as a side effect in 90 to 95 percent of babies born with spina bifida cistica, which itself occurs in two to five per thousand live births (16, 24). One suggested etiology is overdevelopment of the choroid plexus, which produces cerebrospinal fluid (8). Hydrocephalus may also develop in persons of any age as a result of neurosurgery, neoplasm, hemorrhage, or meningitis.

Stenosis of the aqueduct of Sylvius is fairly common in infants with congenital hydrocephalus. This condition can result from a highly branched aqueduct with numerous "blind alleys" and only a small, narrow connection to the fourth ventricle or from gliosis following certain types of _in utero_ infection. It has even been suggested by some researchers that mild cases of aqueductal stenosis may result from a sex-linked recessive trait. Another well-known deformity, the Dandy-Walker malformation, results from an obstructed foramen of Magendie and obstruction of one or both foramina of Luschka, leading to an enlarged fourth ventricle with a cystic roof. A third anatomical anomaly resulting in congenital hydrocephalus is the Arnold-Chiari malformation, which can be divided into three categories: Type I, in which the medulla protrudes downward into the spinal canal and is covered with peglike growths originating from cerebral and cere-

bellar tissue; Type II, which is quite similar to Type I except that the fourth ventricle also extends into the spinal canal; and Type III, which consists of a cerebellar herniation through a bony defect and is essentially an occipital meningoencephalocoele (24).

Although many forms of treatment have been suggested within modern times, none have been greatly successful. Ventriculostomy of the third and fourth ventricles has been virtually abandoned because of problems in alleviating obstruction and total ineffectiveness against coexisting absorption deficiencies. Choroid plexectomy and electrical coagulation of the choroid plexus, believed to be the major site of cerebrospinal fluid production, reduced fluid production at the price of a very high mortality rate. Another technique that has been used is ventriculocisternal shunting, which attempts to short-circuit various problems above the foramen magnum. The major drawback is the operation's 30% mortality rate, which may be a function of the numbers of neoplasm patients who undergo this treatment. Chances for survival are much better if the patient is older and has patent foramina (10).

The current concept of hydrocephalus treatment involves draining cerebrospinal fluid by means of a shunt and dates back as far as 1908 (33). Such tubes have been connected from the ventricles to the heart and venae cavae, peritoneal cavity, pleural cavity, Fallopian tubes, ureters, middle ear and Eustachian tubes, longitudinal sinus, and the gall bladder

as well as to temporary extracorporeal drainage sites (6). Many shunts are made of silicone rubber impregnated with barium sulfate to render them visible in X-rays, with valves composed of 316 stainless steel (7). Serious material and mechanical complications exist.

Traditional biocompatibility problems include an immune response to the foreign body, thrombogenic and hemolytic effects, and greatly enhanced susceptibility to bacterial infection. Material failures also result from corrosion of metallic elements in the body's extremely harsh internal milieu, abnormal calcification related to shunt components, cracks and kinking in tubes, and denaturation and degradation of rubber (5, 19). Sterilization is an important consideration since all the commonly used methods--dry heat, autoclave, chemical agents, and radiation--damage many polymers (25). Heat, chemical additives, and other aspects of manufacture may render polymers useless.

Shunts also carry many mechanical problems. Lack of standardization with regard to expressing surgical specifications and to maintenance, implantation, and testing procedures retards progress and promotes confusion. Valves such as the Holter and Pudenz have relatively high failure rates; for instance, too low a flow rate will not effectively reduce intraventricular pressure, yet too large a flow can conceivably result in partial to complete collapse of the ventricles. All types of shunts frequently clog with cellular debris, proteins, tissue fragments, etc. (5), although this problem

can be somewhat reduced by flaring the end of the shunt, as is the case with the Multiflanged Ventricular Portnoy Catheter (9). The risk and pain of surgery must be repeated as often as necessary to accommodate growth or replace failed components.

Two shunting systems commonly used today are the ventriculoatrial and ventriculoperitoneal shunts, in which the cerebrospinal fluid drains into the heart and peritoneal cavity, respectively. In one study, 65 of 134 recipients of these devices experienced complications, with 26.2% experiencing catheter blockage, 18.5% having postoperative convulsions, and 15.4% suffering from infections. Of all the complications, 53.8% were shunt-related, including blockage, leakage, valve malfunction, disconnection, shortening, and kinking. Of these two shunts, the ventriculoperitoneal results in slightly more complications initially but seems much better for long-term use. For example, a patient with a ventricoloperitoneal shunt is five-eighths as likely to have an infection as a patient with a ventriculoatrial shunt. Prophylactic doses of penicillin are fairly effective for combating the major pathogen, Staphylococcus epidermidis. There is less need for growth revision in ventriculoperitoneal shunts, and many ventriculoperitoneal complications are sufficiently minor that they can be remedied by surgery performed under local anesthesia. Reported ventriculoperitoneal complications include omental and peritoneal adhesions, ascites (fluid accumulation in the abdomen), intra-abdominal

cysts, volvulus (an obstructive twisting of the gut), and perforations of the vagina, scrotum, and rectum. Ventriculo-atrial shunt hazards are much more serious, including clotting and vascular occlusion of the venae cavae, accumulation of fluids in the pleural cavity, pulmonary emboli, septicemia, and a 30% infection rate (6, 10, 13, 22).

Another major type of shunt is the ureteral shunt, in which a kidney is removed and the cerebrospinal fluid drained into the corresponding ureter. Though it has the lowest death rate of any shunting procedure, it is quite unpopular for two reasons: firstly, it can result in serious problems related to renal electrolyte imbalance, including sodium depletion. There is also an ever-present risk that the other kidney may someday fail. Thus, shunting can create as many problems as it solves (10).

Because many shunt failures are associated with rejection of foreign matter, one team of researchers is experimenting with a lumbo-omental graft, in which a section of the omentum with blood vessels intact is incubated in a test tube at body temperature and later grafted to the spinal meninges during a laminectomy. By creating space in the bone, dura, and arachnoid, the laminectomy helps to relieve pressure, while excess cerebrospinal fluid is absorbed with amazing efficiency by the omental graft. Although results thus far appear promising, a good deal of work must be done before the technique can be tried on human subjects. A large graft would probably be necessary, making the procedure fairly haz-

ardous (33).

It should be emphasized that shunting is only a life-sustaining measure and that presently there is no known cure for hydrocephalus. The need for a substitute or auxiliary treatment which would be safer, more effective, and less traumatic and invasive is therefore quite obvious. For example, effective chemotherapy would reduce injuries, damages, and fatalities associated with shunt implantation and could in effect "buy time" for infants by delaying the need for life-threatening surgery.

Additional Background Information

To gain an insight into chemical control of hydrocephalus, it is necessary to have some knowledge of the cerebrospinal fluid itself. The cerebrospinal fluid supports the brain and spinal cord and helps protect them from injury by acting as a damping fluid or "shock absorber." Without this damping action, routine activities such as climbing a flight of stairs would injure the brain. Cerebrospinal fluid volume and pressure in a healthy man or woman lying down are approximately 150 ml and 10 mm Hg, respectively (34) and are maintained by fluid production and absorption.

Research strongly suggests that the cerebrospinal fluid serves as a cleansing fluid by ridding the brain of certain metabolic wastes and by-products. It is also thought to stabilize certain neurochemical factors such as pH and concentration of amino acids and of catecholamines. Histological examination of choroid plexus tissue reveals a glandular

structure with ciliated epithelium on villi consisting of stroma and vessels. Enzymes involved in secretion, particularly carbonic anhydrase, are also present (6).

The cerebrospinal fluid contains greater concentrations of magnesium, chloride, and sodium ions than does blood plasma and is lower in concentration of glucose, proteins, amino acids, uric acid, calcium, phosphate, and potassium. It is separated from the plasma by carrier-mediated transport of solutes. The solutes attach to the carrier molecules on the blood side of the interface and separate from the carrier molecules on the cerebrospinal fluid side. Choroid plexectomy does not alter cerebrospinal fluid composition and does not entirely halt cerebrospinal fluid formation. It has thus been postulated that a portion of the cerebrospinal fluid comes from the central nervous system ependyma (18). Absorption occurs in the arachnoid villi, or granulations, which in turn are connected to the venous sinuses. The fluid passes through the foramina of Monro, the third ventricle, the aqueduct of Sylvius, and the foramina of the fourth ventricle and enters the subarachnoid space in the cisterna magna (4). (See Fig. 1)

At least two classes of drugs have been observed to diminish cerebrospinal fluid pressure. Two likely choices for this experiment are isosorbide, an osmotic diuretic, and acetazolamide, a carbonic anhydrase inhibitor (27, 28). Because these two drugs function by means of different mechanisms, it is conceivable that using them in the proper com-

bination would potentiate the effects of both.

Acetazolamide (also known as Diamox or 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide) is a potent, enzyme-specific carbonic anhydrase inhibitor with no significant observed side effects observed during experiments with hydrocephalus patients. Carbonic anhydrase catalyzes the reversible production of carbonic acid from water and carbon dioxide; the carbonic acid, in turn, is broken down reversibly into hydrogen and bicarbonate ions. Normally, the hydrogen ions thus liberated replace sodium in several compounds, including sodium phosphate, in order to conserve sodium. These cations also prevent bicarbonate loss in urine by converting bicarbonates back to carbonic acid and react with ammonia to form ammonium ions to help retain calcium, potassium, etc. However, Diamox drastically alters this equilibrium so that diuresis occurs, sodium is excreted into the urine, and osmotic pressure is lowered, causing cerebrospinal fluid to be absorbed by the bloodstream. Continuous administration of acetazolamide inhibits cerebrospinal fluid formation by inhibiting brain and spinal cord carbonic anhydrase, whereas intermittent dosage increases uptake by means of diuresis (12, 15).

Isosorbide, an osmotic diuretic, is preferred over glycerol, urea, and mannitol because it can be administered orally instead of intravenously and does not cause gastrointestinal or renal disturbance (20). Presumed to function by raising blood osmolarity, this drug has been reported to be 66-8%

effective in partially and totally communicating hydrocephalus and 32% effective in totally obstructive hydrocephalus (28).

Before any drug is used in experimentation, anticipation and measurement of side effects is desirable. Because of their diuretic properties, isosorbide and Diamox will definitely increase urine output by causing the kidneys to excrete more water in the urine. It is quite likely that there will also be some effect on venous blood pressure caused by the change in venous fluid volume. This, in turn, could affect arterial blood pressure. Clearly, it is important to quantify influence on arterial and venous blood pressure and urine formation, effectiveness in reducing cerebrospinal fluid pressure, and duration of effects for these drugs, both individually and in combination.

METHODS AND MATERIALS

One of the problems associated with testing various drugs in the treatment of hydrocephalus is that progress is quite difficult to assess and quantify. Anticipated long-term benefits of the drugs are observed (if at all) in a qualitative manner. Phrases such as this are common in the medical literature: "Child X showed no increase in head circumference in three months and seems to be growing normally." In some adults, hydrocephalus does not produce noticeable enlargement of the skull, rendering this method of measurement useless. Also, irreparable damage may already have ensued by the time the physician sees that the medications are not proving effective and decides to try other more traditional methods of treatment (6). Patients in seemingly arrested states of hydrocephalus can still be in danger from sudden increases in cerebrospinal fluid pressure; for example, a violent cough can easily raise cerebrospinal fluid pressure from seven to fifty mm Hg, five times the normal pressure (34).

One of the oldest methods of measuring cerebrospinal fluid pressure is the lumbar puncture method, in which a known amount of cerebrospinal fluid is removed from the spinal canal between the sacral vertebrae and used to calculate pressure by osmotic principles. Although the region punctured is the cauda equina, a fan-shaped configuration of spinal nerves just below the spinal cord proper, paralysis and infection can result in addition to the accompanying

severe pain. A similar method for instantaneous short-term measurement involves withdrawing fluid from the brain ventricles. This method, too, is potentially dangerous, useless for long-term continuous measurement, and quite painful (31). Because of the invasive nature of long-term measuring devices in this area, intraventricular cerebrospinal fluid pressure is most commonly monitored on a continuous basis during neurosurgery for periods of several hours, with the longest monitoring times recorded being five to seven days (17). If such a long-term pressure monitor were implanted in a laboratory animal free to move about as usual and pursue a normal, active life, the effects of common activities such as walking, breathing, sleeping, etc. on cerebrospinal fluid pressure (with and without drugs) could be measured and quantified. Such a device should not interfere with normal function of the organism by being cumbersome, painful, or damaging. In this way, it would be much easier for physicians to estimate dosages for human patients, who will want to be as active as possible.

Adult, random-bred cats were chosen as laboratory animals in this project for several reasons. First, a variety of stereotaxic atlases and equipment are readily available (29). Behavior is easy to observe, and cats are a convenient size for surgery and other experimental procedures. Cost of the animals was also considered.

The proposed implantations were to be performed using aseptic surgical procedure, with sodium pentothal used as a

general anesthetic. Burr holes were to be drilled into the skull at appropriate points. Using stereotaxic equipment to hold the animal's head in the proper position, a Kulite Semiconductor piezoelectric pressure transducer was to be inserted into the third ventricle as follows: a thin-walled stainless steel tube of approximately 2.8 mm internal diameter was to be inserted through the burr hole and a sharp stainless steel wire threaded through the tube to act as a stylus. The wire then was to be removed and the catheter-pressure transducer assembly threaded through the tube. For an application such as this, biocompatibility of stainless steel is considered adequate (14). Stainless steel screws were to be inserted into the cat's skull for use as electroencephalogram electrodes, with a stainless steel wire implanted just over the shoulder joint to serve as an EKG electrode. The screws and cannula were to be attached to the skull by means of dental acrylic, polymethyl methacrylate. Recovery time was estimated at one week.

The entire measurement system envisioned consists of a piezoelectric pressure transducer connected to a stainless steel cannula, which is in turn connected to an amplifier and chart recorder. The piezoelectric transducer was chosen over other types of pressure transducers for its accuracy and precision, with cost and availability being secondary in consideration. It consists of a specially manufactured crystal lattice whose internal positive and negative charges rearrange in the presence of an imbalanced applied force. These

rearranged internal charges induce surface charges of opposite polarity on opposite sides of the crystal. Surface charge can be determined by measuring the difference in voltage between electrodes attached to the surfaces. Induced charge q is directly proportional to the applied force f:

$$q = kf$$

where k is the piezoelectric constant and equals 2.3 pcoul/newton for quartz and 140 pcoul/newton for barium titanate. The piezoelectric crystal behaves as a small parallel-plate capacitor, so voltage is easily measured and can be used to calculate pressure. Thus,

$$v = \frac{q}{C} = \frac{kf}{C} = \frac{k}{\epsilon_o \epsilon_r} \frac{ft}{A} = \frac{k}{\epsilon_o \epsilon_r} pt$$

where ϵ_o is the dielectric constant of free space, ϵ_r is the relative dielectric constant of the crystal, A is the area of the crystal face, t is the thickness of the crystal, and p is the pressure. As an example, for a quartz crystal 1 mm thick and a cerebrospinal fluid pressure of ten mm Hg,

$$v = \frac{2.3 \text{ pcoul/newton}}{8.8 \text{ pF/m (1114)}} \times 1 \text{ mm} \times 10 \text{ mm Hg} \times \frac{133 \text{ Pa}}{\text{mm Hg}} = 0.3 \text{ mV};$$

with proper amplification, such a value could easily be "picked up" and recorded (26).

Although the experimentation had to be canceled before many final decisions could be made, the amplifier and pen recorder would definitely need a wide bandwidth; that is, the signal should not be attenuated over a wide range of frequencies. Adequate gain would be necessary for the amplifier

in order to be able to visualize the output more easily. Other characteristics desirable are high linearity, low hysteresis, and a range in which saturation is not likely to occur (32). Output noise would need to be identified and filtered out of the system (23).

After the cats had had ample time to recover from surgery, baseline measurements were to be collected over a period of approximately two weeks. Attempts then were to have been made to correlate cerebrospinal fluid pressure with observed behavior, EEG's, and EKG's. Dosages of isosorbide and acetazolamide were to be determined empirically, with the drugs administered by injection. Cerebrospinal fluid pressure would have again been correlated with observed behavior, EEG's, and EKG's. Approximate data analysis techniques were to have been used for the data gathered. One such method is Fourier series, in which any periodic function can be analyzed in terms of sinusoidal components. Numerical and statistical methods would have been used where possible in order to conserve valuable research time.

DISCUSSION

Unforeseeable transducer-related difficulties prevented the experiment from being performed at all. Since the transducer is a crucial but inherently weak part of the apparatus and planned procedure, it is appropriate to consider the problem in greater detail at this point.

Implantable pressure transducers for biological research are relatively scarce, with only four companies (Honeywell, Konigsberg, Kulite, and Millar) manufacturing them. These devices are generally so non-uniform and inconsistent that each transducer must be individually calibrated rather frequently. Some implantable pressure transducers possess long-term stability as low as 4 mm Hg/hr (30). Virtually all commercially available pressure transducers designed for other applications are too large for implantation and possess too high a range of operation for cerebrospinal fluid pressure measurement (11).

Piezoelectric pressure transducers, normally used for high frequency pressure or sound-pressure measurements (21), carry some problems of design and measurement. The piezoelectric transducer is normally modeled as a parallel RC circuit (representing the transducer itself) connected in parallel RC combination to account for the resistance and capacitance of the amplifier. Though proper amplification is absolutely necessary because of the small transducer output, amplification tends to worsen the frequency response. The corner frequency f_c, at which amplifier gain is equal to 0.707

times the gain for the flat portion of the frequency response plot, is defined as follows:

$$f_c = (2\pi RC)^{-1}$$

For a typical voltage amplifier, the reduction in resistance accomplished by combining the two resistances in parallel is greatly overshadowed by the increased total capacitance resulting from connecting the amplifier in parallel with the transducer. As a result, transducer outputs for low frequency pressure components are seriously attenuated. Using a charge amplifier with a feedback capacitor to offset the capacitance increase improves the situation to some extent. For example, an overall capacitance of 1 nF with an overall resistance of 10 Mohm would result in a corner frequency of 17 Hz. To reduce the corner frequency to a more desirable value of 0.17 Hz would require an overall resistance of 1000 Mohm, which would cause serious noise artifacts because of precision difficulties in manufacturing resistors over 10 Mohm (2, 26).

Piezoelectric materials possess a high but finite resistivity; thus, surface charges will eventually dwindle to zero, thereby preventing a dc response. Since nightly variations in cerebrospinal fluid pressure patterns have been reported (31), such a lack of dc response would cause incomplete and potentially misleading data to be collected. Because of high transducer source impedance, the slightest current between the two transducer terminals can result in a deceptively large voltage value unless connected to an ampli-

fier with impedance of, for example, 100 Mohm. Availability appears to be a particularly important limitation since the desired transducer is no longer being manufactured and a lesser quality piezoelectric transducer arrived too late to be of use for this endeavor.

Another common type of pressure transducer, the strain gauge-diaphragm variety, appears to have its share of disadvantages for this particular application. Such devices operate on the principle of a membrane deflected by pressure. The strain gauges, arranged in either two or four arms of a Wheatstone bridge circuit, exhibit resistance proportional to their length according to the formula $R = \rho L/A$ where ρ = resistivity, L = length, and A = cross-sectional area of a strain gauge. Thus, when the diaphragm deflects and the gauges stretch, the circuit exhibits a change in voltage output with either ac or dc excitation. Unfortunately, this type of transducer is too large and possesses too high a range to be of much value in measuring cerebrospinal fluid pressure. Frequency response problems are highly likely since the device requires a catheter for connection to circuitry outside the animal's body. Finally, behavior of a circular diaphragm is described by a formidable equation:

$$z(r) = \frac{3(1-\mu^2)(R^2-r^2)^2\Delta P}{16Et^3(1+(z(r)/t)^2/2)}$$

where z = deflection, r = distance from the center, R = radius of the diaphragm, E = Young's modulus, t = diaphragm thickness, and μ = Poisson's ratio. Large radius and small

thickness, the optimal requirements for high sensitivity, are exactly the opposite of parameters required for high natural frequency and thus good frequency response.

The capacitive pressure transducer appears promising in some ways but also presents some problems. Two metal plates separated by a vacuum (or preferably a dielectric) store charge and generate a potential difference across the space according to the capacitance equation,

$$C = \epsilon_o \epsilon_r A/d$$

where C is the capacitance, ϵ_o is the dielectric constant of free space, ϵ_r is the relative dielectric constant of the material between the plates, A is the area of overlap between the plates, and d is the distance between them. Thus, capacitance can be changed by varying distance between plates, area of overlap, or the nature of the dielectric material, with the first method being most commonly used in pressure transducers. Pressure moves the plates and changes the distance between them, with the resulting change in capacitance sensed by appropriate impedance bridges (1). Most capacitive pressure transducers consist of one or two stators (stationary electrodes) attached to the transducer case or to a ceramic base of some type. In the more common dual stator configuration, the electrodes serve as two arms of an ac bridge circuit. In the single stator transducer, the stator is present in the form of a diaphragm attached to a transformer and LC circuit. The major problem with this type of capacitive transducer is the need for equipment to provide excita-

tion (21). However, capacitive transducers require a change of only ten angstroms or so in distance between plates. Similarly, force requirements are extremely small; for example, for two capacitor plates with an area of 2 cm^2, one mm apart, to produce an output of 100 V, a force of approximately one dyne is required. Because the mechanism is not a function of plate material, high stability is typical. Unfortunately, large output impedance requires careful consideration to electrical shielding in order to avoid overloading the amplifier. As with most other pressure transducers, large size and high range are limiting factors.

The Bourdon tube transducer, another well-known device for measuring pressure, was also considered. The transducer itself consists of a curved or twisted tube having an oval or elliptical cross-sectional area and sealed at one end. The difference in pressures inside and outside the tube tends to make the tube more circular in cross-section (2). Deflection varies with ratio of major to minor cross-sectional axes, tube length, difference between internal and external pressure, time rate of twisting (for twisted Bourdon tubes), and tip-to-port angle and radius of curvature for curved tube varieties. It is also inversely related to wall thickness and modulus of elasticity. Unfortunately, it is quite difficult to manufacture Bourdon tubes of sufficiently small size for implantation in the ventricles, and the devices are quite vulnerable to mechanical shock and vibration damage (21).

The linear variable differential transformer is a re-

luctive device, converting pressure into an ac voltage change by changing the reluctance path between two or more coils with ac excitation. The LVDT contains one primary and two secondary coils with a mobile core and experiences a change in mutual inductance when pressure moves the core. The Biotronex BL-9630 is one such transducer. In the BL-9630, the primary coil is excited by an ac voltage of 5-20 V (peak-to-peak) having a frequency between 1.5 and 15 kHz. As with other LVDT's, somewhat sophisticated equipment is required for excitation. Phase angle distortion is also present, approaching 90° at low frequencies. For a cerebrospinal fluid pressure waveform of extremely large period, such a lag could lead to drastically misleading results. Catheter frequency response is another likely source of error (3).

Other reluctive methods exist for pressure transduction. In one such method, pressure causes deflection of a diaphragm between two iron core coils, thereby changing mutual inductance. In an alternate design, rotation of a twisted Bourdon tube turns an attached armature (magnetically permeable strip), increasing the flux gap of one coil as it decreases the gap of the other coil. Both of these reluctive transducers are useless for the proposed experiment, with minimum ranges of 0-5 psid and 0-5 psi, respectively.

Perhaps the best solution to the problem at hand is the so-called Pi system developed by Lorig, Cheng, and Ko. A pressure-sensitive transistor of appropriate range manufactured by Pitran-Stow Labs is mounted in the kovar portion of

a kovar-Pyrex tube 10 mm overall diameter. A kovar cap and port are attached to the tube in order to seal off the transducer end. The cerebrospinal fluid contacts the pressure-sensitive diaphragm through a standard silicone rubber catheter inserted through the port and positioned so as to extend into the ventricles. The Pyrex end of the kovar-Pyrex tube is also sealed and contains the necessary electronic components. The device itself is fastened to subcutaneous muscle just external to the skull.

Power for the Pi system is provided by two sources in parallel, a 1.3 V AgO battery and a radio-frequency inductive power source with a nominal frequency of 3.5 MHz. The battery is capable of supplying 50μA to the circuitry and permits either intermittent long-term operation or continuous short-term operation. The system is designed such that the RF is available any time and is particularly useful during battery failure. Also contained in the Pi system are signal processing systems, built-in temperature compensation modules, and both analog and digital readout of the cerebrospinal fluid pressure and transducer temperature.

The pressure transducer current is modulated by the cerebrospinal fluid pressure as follows: a pulsatile waveform whose period is proportional to pressure gates the transmitter carrier on and off. Thus, the nominal carrier frequency of approximately 100 MHz contains bursts of RF energy related to pressure. Subcarrier repetition rate ranges from 1 to 10 kHz. By including a temperature trans-

mitter operating at a slightly different frequency, transducer temperature is readily displayed. In this way, appropriate temperature correction calculations can be made with relative ease. The package has been tested in dogs for periods of seven months with no leakage to the electronic components, minimal inflammatory response and corrosion effects, and long-term stability high enough for drug experimentation and physiological investigations (17).

This author feels that the proposed project, quantifying the effects of pharmaceutical agents on the production and absorption of cerebrospinal fluid, has a good deal of merit. However, the investigation is essentially futile without proper transduction to assure the experimenter of reasonably accurate results. Although the Pi system is definitely more complicated and expensive than many commercially available systems, it appears to show promise for use as a key to better understanding of drug therapy in hydrocephalus.

REFERENCES

1. Busser, J. H. and B. N. Feinberg. Measurements. In: CRC Handbook of Engineering in Medicine and Biology, Vol. I, edited by D. G. Fleming and B. N. Feinberg. Cleveland: CRC Press, 1976, pp. 373-404.

2. Cobbold, R. S. C. Transducers for Biomedical Measurements: Principles and Applications. New York: John Wiley & Sons, 1974.

3. Cromwell, L., F. J. Weibell, and E. A. Pfeiffer. Biomedical Instrumentation and Measurements, 2nd edition. Englewood Cliffs: Prentice-Hall, Inc., 1980, pp. 140-145.

4. Cutler, R. W., L. Page, J. Galicich, and G. V. Watters. Formation and absorption of cerebrospinal fluid in man. Brain 91:707-720, 1968.

5. Dawson, B. H., E. Dervin, and O. B. Heywood. The problems of design and implantation of shunt systems for the treatment of hydrocephalus. Developmental Medicine & Child Neurology 17:78-84, 1975.

6. Fisher, R. G. The cerebrospinal fluid. Mayo Clinic Proc. 50:482-486, 1975.

7. Gibbons, D. F. Biomedical materials. In: CRC Handbook of Engineering in Medicine and Biology, Vol. I, edited by D. G. Fleming and B. N. Feinberg. Cleveland: CRC Press, 1976, pp. 253-290.

8. Guyton, A. C. Basic Human Physiology: Normal Function and Mechanisms of Disease, 2nd edition. Philadelphia: The W. B. Saunders Co., 1977, p. 325.

9. Haase, J. and R. Weeth. Multiflanged Ventricular Portnoy Catheter for hydrocephalus shunts. Acta Neurochirurgica 33:213-218, 1976.

10. Hahn, Y. S., H. J. Kim, and H. J. Lee. Critical review of shunting procedures for hydrocephalus. Yonsei Medical Journal, 17:163-171, 1976.

11. Harvey, G. F. Instrument Society of America Transducer Compendium, 2nd edition, Part I. New York: Plenum Press, 1969, pp. 5-119.

12. Huttenlocher, P. R. Treatment of hydrocephalus with acetazolamide: results in fifteen cases. J. of Pediatrics, 66:1023-1030, 1965.

13. Ignelzi, R. J. and W. M. Kirsch. Follow-up analysis of ventriculoperitoneal and ventriculoatrial shunts for hydrocephalus. J. Neurosurg. 42:679-682, 1975.

14. Ko. W. H., M. R. Neuman, and K. Y. Lin. Body reaction of implant packaging materials. In: Biomaterials, edited by L. Stark and G. Agarwal. New York: Plenum Press, 1969, pp. 55-58.

15. Lederle Laboratories, Professional Services Division. "Diamox (Acetazolamide)." 1976.

16. Lorenzo, A. V., L. K. Page, and G. V. Watters. Relationship between cerebrospinal fluid formation, absorption, and pressure in human hydrocephalus. Brain 93:679-692, 1970.

17. Lorig, R. J., E. M. Cheng, and W. H. Ko. Systems for the long-term monitoring of intraventricular pressure in neurosurgery. In: Indwelling and Implantable Pressure Transducers, edited by D. G. Fleming, W. H. Ko, and M. R. Neuman. Cleveland: CRC Press, 1977, pp. 79-84.

18. Milhorat, T. H. The third circulation revisited. J. Neurosurg. 42:628-645, 1975.

19. Moacanin, J. and R. F. Landel. A method for measuring fatigue and aging of elastomers in physiological environments. In: Biomaterials: Bioengineering Applied to Materials for Hard and Soft Tissue Replacement, edited by A. L. Bement, Jr. Seattle: University of Washington Press, 1971, pp. 235-247.

20. Nodine, J. H., K. N. Modi, M. Rhodes, V. Paz-Martinez, L. Ibarra, and R. J. Santos. Pharmacodynamics and pharmacokinetics of isosorbide in man. Clinical Pharmacology & Therapeutics 14:196-203, 1972.

21. Norton, H. N. Handbook of Transducers for Electronic Measuring Systems. Englewood Cliffs: Prentice-Hall, Inc., 1969.

22. Nugent, R. G. Thromboembolic complications of ventriculoatrial shunts. Angiocardiographic and pathological correlations. J. Neurosurg. 24:34-42, 1966.

23. Olson, W. H. Basic concepts of instrumentation. In: Medical Instrumentation: Application and Design, edited by J. G. Webster. Boston: Houghton Mifflin Co., 1978, pp. 1-48.

24. Paine, R. S. Hydrocephalus. Pediatric Clinics of North

America 14:779-796, 1967.

25. Park, J. B. Biomaterials: An Introduction. New York: Plenum Press, 1979, pp. 88-89.

26. Peura, R. A. and J. G. Webster. Basic transducers and principles. In: Medical Instrumentation: Application and Design, edited by J. G. Webster. Boston: Houghton Mifflin Co., 1978, pp. 49-102.

27. Rubin, R. C., E. S. Henderson, A. K. Ommaya, M. D. Walker, and D. P. Rall. The production of cerebrospinal fluid in man and its modification by acetazolamide. J. Neurosurg. 25:430-436, 1966.

28. Shurtleff, D. B. and P. W. Hayden. The treatment of hydrocephalus with isosorbide, an oral hyperosmotic agent. J. of Clinical Pharmacology 12:108-114, 1972.

29. Snider, R. S. and W. T. Niemer. A Stereotaxic Atlas of the Cat Brain. Chicago: University of Chicago Press, 1961.

30. Topich, J. A. Medical telemetry. In: CRC Handbook of Engineering in Medicine and Biology, Vol. I, edited by D. G. Fleming and B. N. Feinberg. Cleveland: CRC Press, 1976, pp. 253-290.

31. Walker, A. E., L. J. Viernstein, and J. C. Chubbuck. Intracranial pressure monitoring in neurosurgery. In: Indwelling and Implantable Pressure Transducers, edited by D. G. Fleming, W. H. Ko, and M. R. Neuman. Cleveland: CRC Press, 1977, pp. 69-78.

32. Webster, J. G. Amplifiers and signal processing. In: Medical Instrumentation: Application and Design, edited by J. G. Webster. Boston: Houghton Mifflin Co., 1978, pp. 103-142.

33. Wennerstrand, J. R. and B. E. Levander. Lumbo-omental drainage of cerebrospinal fluid: a new experimental shunting procedure. Acta Chirurgica Scandinavia 140: 91-94, 1974.

34. Williams, B. Cerebrospinal fluid pressure changes in response to coughing. Brain 99:331-346, 1976.