Cerebral dehydration action of glycerol

I. Historical aspects with emphasis on the toxicity and intravenous administration

Oral glycerol (1 Gm. per kilogram every 6 hours) has a dehydration effect on the central nervous system. Prolonged continuous administration of glycerol does not produce marked alteration of fluid and electrolytes. It is almost totally excluded from the brain, which excludes the problem of rebound overhydration. It has significant nutritional value nad none of the side effects of steroids. The major toxic effects of glycerol (hemolysis, hemoglobinuria, and renal failure) can be prevented and are a function of concentration and route of administration. Glycerol does not hemolyze red blood cells when it is prepared with isotonic saline in concentrations up to 40 per cent. Human intravenous glycerol has been used safely on a number of occasions with plasma levels reaching 10 mmoles per liter to measure turnover rates in adults and infants. The same oral glycerol dose is effective in lowering ocular tension and cerebrospinal fluid pressure. The plasma concentration response curve for normal human eyes has been previously determined. Intraocular pressure begins to fall when plasma glycerol is approximately 10 mmoles per liter. It is proposed that continuous intravenous glycerol be considered for treatment of cerebral edema in patients not able to take oral glycerol.

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Animal and human dehydration action

Virno and associates,[78] in 1961, first described the action of oral and intravenous glycerol in reducing experimentally induced cerebral edema in rabbits. Expansion and contraction of the exposed cerebral cortex was measured by a pointing device mounted on the surface of the brain.

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In a later study,[76] glycerol was given by gastric tube to rabbits with intraocular hypertension induced by means of water intoxication. The intraocular hypotensive-acting glycerol lasted for about 6 hours and the effective dose proved to be very similar to the most effective dose to produce cerebral dehydration. Mandell and associates[44] used 4 Gm. per kilogram of glycerol for the treatment of cerebral edema in rabbits induced by triethyltin sulfate. Within one hour, brain water fell by 9.5 per cent and brain sodium

by 15 per cent. At 6 hours, brain water returned to pretreatment values, whereas sodium levels were almost normal. They did not demonstrate an over-rehydration of the brain after discontinuing glycerol.

In 1963, Cantore and associates[14] reported the use of oral glycerol for the reduction of cerebral edema in animals and man. In 1965, they[15] reported its effect on a much larger series of patients: 62 patients had a space occupying lesion, 75 patients were observed during neurosurgery, 84 were postoperative patients, and a "limited number" had pseudotumor cerebri. They reported excellent results with no associated rebound overshoot or toxicity other than gastric irritability predisposing to nausea and vomiting. More important, however, was their observation that no additional electrolytes were needed with patients treated with glycerol for extended periods of time. In comatose patients, appropriate amounts of water and electrolytes were given without interfering with antiedema effect. The diuresis following administration of glycerol was not great. A single dose ranged from 0.5 to 2.0 Gm. per kilogram, and in some cases they gave 5 Gm. per kilogram per day in 8 divided doses. Bovet and associates[9] pointed out that although glycerol promoted diuresis, its action of reducing cerebral edema was not dependent on diuresis. Along this same line, it has been reported that glycerol is effective for control of intracranial hypertension even in nephrectomized animals.

Buckell and Walsh[11] described the use of oral glycerol in 2 patients with benign intracranial hypertension. Pure glycerol, 75 ml., produced about 30 to 40 per cent less diuresis than did a similar dose of urea. They also did not find rebound rehydration of the brain. Following the publications of Bovet and associates and Buckell and associates, numerous reports[3, 16-18, 20, 23, 30, 33, 40, 45, 46, 50, 58, 70, 71, 77] of oral glycerol appeared in the literature describing its action on the reduction of intraocular pressure but only a few on central nervous system (CNS) dehydration.

Plasma glycerol levels necessary for reducing intraocular pressure have been studied by McCurdy and associates.[45] Eight normal human volunteers were given a 50 per cent solution of lemon-flavored glycerol in doses of 1.0 to 1.27 Gm. per kilogram after an overnight dehydration of 12 to 14 hours. Plasma and urine glycerol levels were measured by the glycerolkinase enzymatic method of Wieland.[81] Blood glycerol determinations revealed an average fasting control value of 0.51 mmoles per liter (4.6 mg. per 100 ml.). After glycerol ingestion, blood levels rose to a maximum of 20 mmoles per liter in 60 to 90 minutes. Plasma osmolality rose an average of 19 mOsm. per kilogram of water. There was a tendency for osmolality to remain elevated even after ocular tension began to return to normal. Glycerol excretion revealed that only 7.5 to 13.9 per cent of the total glycerol appeared in urine during the 2½ hour period of study. Intraocular pressure fell in all 8 normal subjects within 7 to 12 minutes after ingestion. Accordingly, they showed that plasma glycerol and osmolality varied inversely with the ocular tension. Maximal ocular hypotension occurred at 50 to 90 minutes. Ocular pressure began to fall at plasma glycerol levels of approximately 10 mmoles per liter. Blood volume was not measured directly, but hematocrit levels fell an average of 4.8 per cent with the lowest value 80 minutes after ingestion. No hemolysis was noted, and all hematocrit values returned "toward control values by the end of the study." Serum sodium fell an average of 4.5 per cent during the same period. Blood glucose levels remained constant in the 4 subjects in whom it was measured.

Absolon[1] has reported on a patient with benign intracranial hypertension treated with oral glycerol for 22 days in the hospital and 18 weeks as an outpatient. Glycerol was effective in controlling the papilledema; the only side effect noted was nausea. When glycerol was stopped, the papilledema returned. Glycerol was not given again.

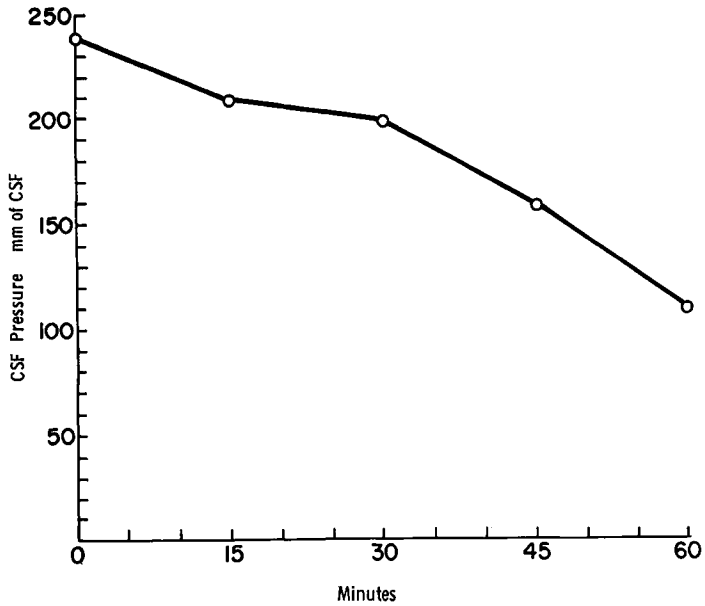

Fig. 1. Effect of a test dose of 50 per cent glycerol in 0.9 per cent sodium chloride, 1 ml. per kilogram (90 ml.), by nasogastric tube, on CSF pressure in a patient (Case 1) with benign intracranial hypertension.

The only other references we have knowledge of in regard to the CNS dehydration effect of glycerol are our own studies. Newkirk and associates* treated a patient in coma with intracranial hypertension secondary to Echo III encephalitis with oral glycerol (1 ml. per kilogram every 6 hours) for 21 days; there was a favorable outcome. Despite a fluid intake of 3,000 ml. per day, normal serum, potassium, chloride, and CO_2 values were maintained. Two additional patients (Cases 1 and 2) with benign intracranial hypertension were given oral glycerol tests.

Case 1. A 15-year-old obese boy was treated with antibiotics for otitis media. Two days later he developed diplopia, nausea, vomiting, and a headache. On the twelfth day of illness, the diplopia was much worse. On the thirty-fifth day, the CSF pressure was 370 mm. of CSF. He had a normal Tobey-Ayer test, skull roentgenogram, brain scan, and arteriogram. On the forty-fifth day, he was given a test dose of glycerol with the results shown in Fig. 1. He was then placed on glycerol, 1 ml. per kilogram, orally, every 6 hours. By the fiftieth day, he was symptom free.

Case 2. A 38-year-old woman presented with headaches and visual complaints ("wavy lines" and "black spots"). On the twenty-first day of illness, bilateral papilledema with mildly enlarged blind spots were found. Normal arteriogram and pneumonencephalogram were obtained. The CSF pressure was 400 mm. On the forty-eighth day, a glycerol test was done. The results are shown in Fig. 2. Glycerol was discontinued because of nausea and vomiting, so she was treated with dexamethasone, 1.5 mg. three times daily. With this treatment, CSF pressures ranged from 120 to 180 mm.

The plots of the cerebrospinal fluid (CSF) pressure versus time in minutes of these 2 patients are shown in Figs. 1 and 2, respectively. These graphs are virtually identical to those presented by Buckell and Walsh[11] for the CNS and are similar to those presented by McCurdy and associates[45] for the eye.

We are not aware of any specific or potential problems directly related to the anticerebral edema action of glycerol, such as increased cerebral blood flow or subdural hemorrhage extension, as have been reported with urea.[8]

*Newkirk T. A., Tourtellotte, W. W., and Reinglass, J. L.: Prolonged control of increased intracranial pressure by glycerol, Arch Neurol. In press.

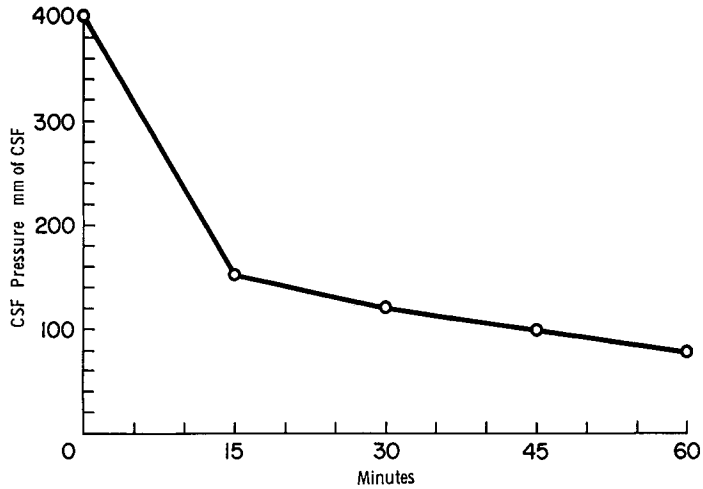

Fig. 2. Effect of a test dose of glycerol, 3 ml. per kilogram (180 ml.) by nasogastric tube on CSF in a patient (Case 2) with benign intracranial hypertension.

Toxicity

Glycerol is constantly metabolized by the body, hence it would seem safe to conclude a priori that within a certain range it is innocuous. It would seem that this is the case, since a 2½-year-old child survived without any obvious sequelae after the accidental ingestion of 23 Gm. per kilogram.[21]

Nevertheless numerous misconceptions exist about the toxicity of glycerol, most of which resulted from poorly controlled studies which did not delineate dosage, route of administration, or concentration. In 1876 Ustimowitsch[72] reported that given by the intravenous route glycerol gave rise to hemoglobinuria and albuminuria. Simon,[63] in 1915, reported hemolysis and Piras[52] in 1925, found abnormalities in the kidney, liver, and intestines. These investigators either used undiluted glycerol or did not report the concentration or dose. Contrarily, Arnschink,[2] in 1887, and Leo[41] and Niclous,[48] in 1903, did not report the occurrence of hemoglobinuria after oral glycerol.

However, it remained for Johnson and co-workers,[35] in 1933, to dispel some of the previously reported conclusions. They studied rats, dogs, and man in an effort to further understand the toxicity and pharmacologic parameters of glycerol. Rats were divided into 4 groups and fed a diet which contained 20, 40, or 60 per cent glycerol for nearly a year. Growth, weights, and number of weaned offspring did not vary from those of controls. All rats were put to death and postmortem examinations were made on kidney, liver, and intestines. No abnormalities were found. Dogs given diets which contained 35 per cent glycerol for 50 weeks showed similar growth curves to the control group. Erythrocyte counts did not change. No albuminuria was found. Three dogs given 9.0 Gm. per kilogram per day for one year showed no ill effects. Microscopic studies of lung, kidney, liver, and spleen showed no abnormalities. But 3 Gm. per kilogram given intraperitoneally produced hemoglobinuria, and a similar dose given subcutaneously also produced albuminuria and hemoglobinuria.

In this same study observations were made on 14 college students given 30 ml. of glycerol (1.3 to 2.2 Gm. per kilogram) in orange juice with each meal for 50 days. The subjects were observed for changes in weight, erythrocyte and leucocyte counts, and hemoglobinuria. No pathologic findings were noted. Because Rosenfeld[57] and Lewis and Corley[42] reported elevated urinary excretion of uric acid, Johnson and associates also studied this aspect. Using a dietary control, they were able to confirm that basal metabolic rates and temperatures

in these students were not changed significantly. Therefore, Johnson and associates concluded that oral glycerol was exceedingly safe in man.

A number of reports of the toxic effects of glycerol appeared in the literature following the comprehensive study of Johnson and associates. Sugimoto[68] noted anemia in rabbits treated subcutaneously with 3 ml. per kilogram of glycerol. Maignon and Grandclaude[43] reported venous sclerosis in dogs following injection of 3.5 ml. of glycerol. Pfeiffer and Arnove[51] noted that 0.75 ml. per kilogram of glycerol was the lowest subcutaneous dose capable of producing hemoglobinuria in rats. They also reported that ascorbic acid provided protection. In a review of glycerol in 1940, Deichmann[21] concluded that the quantity necessary to produce toxicity varied with the mode of administration—the dose needed with the intraperitoneal route was the lowest, that with the subcutaneous, intermediate. The oral route was nontoxic. Furthermore, Miner and Dalton[47] noted that albuminuria, hemoglobinuria, and anemia had never been reported as a result of taking glycerol orally.

In 1956, Cameron and Finckh[12] finally settled the question of hemolysis and hemoglobinuria as a function of concentration and route of administration. In the rat, subcutaneous concentration of 5 to 50 per cent glycerol resulted in hemoglobinuria, the severity of which varied with the total dose. The smallest amount capable of producing hemoglobinuria was 0.2 ml. of undiluted glycerol per kilogram. Experiments with the intravenous injection of glycerol in rats revealed that 50 per cent solutions always produced hemolysis and in large doses led to convulsions. However, injection of 20 per cent glycerol could be given rapidly intravenously in amounts up to 20 ml. per kilogram without producing hemoglobinuria or hemolysis. Such a dose represents 20 times that shown to produce these effects by the subcutaneous route.

These results were confirmed by Zilversmit and associates.[87] They gave 10 per cent glycerol intravenously in a dose of 4.8 Gm. per kilogram as a daily dose and found no ill effects in dogs. They stated that there are no reports of hemoglobinuria, hemolysis, or renal damage from intravenous infusion of 20 per cent glycerol or less when the diluent was isotonic sodium chloride. The reason why the subcutaneous and intraperitoneal routes are 20 times more toxic than the intravenous route is not known.

Finckh[24] found that intraperitoneal glycerol was as capable as subcutaneous glycerol in producing renal damage, and both did so in the absence of hemolysis. Finckh also showed that glycerol itself was not directly toxic to the tubular epithelium. To deepen the mystery, Finckh observed that excision of the subcutaneous tissue with its surrounding zone of edema prevented the renal damage, provided that it was done within 2 hours after injection. These findings suggest that either subcutaneous or intraperitoneal injections of glycerol are capable of producing or releasing a compound which damages the kidneys. Such a compound has not been isolated.

Along this same line, Wilson and associates[84] and Oken and co-workers[49] performed micropuncture studies of individual rat nephrons damaged by glycerol administered subcutaneously. Renal failure was manifested by a greatly decreased proximal tubular fluid flow rate that persisted long after peritubular circulation seemingly returned to normal. Also, combined mannitol and isotonic sodium chloride were capable of preventing renal damage induced by 10 ml. per kilogram of 50 per cent glycerol injected subcutaneously.

Finally, the histopathologic changes in the kidneys resemble acute tubular necrosis and have been described by Bondi and associates[6] and Della Rocca and co-workers.[22] The latter studied histologic preparations of the kidneys of rabbits following the intravenous administration of 2.0 Gm. per kilogram of 30 per cent glycerol. They described vasoconstriction of the afferent glomerular arterioles. This change, they felt,

was responsible for the hematuria and could be prevented by the addition of sodium ascorbate to the glycerol.

The fact that glycerol does not have a direct toxic effect on erythrocytes was shown by Smith[67] who described the first use of glycerol for the prevention of hemolysis during freezing and thawing. Noting that glycerol had previously been used to preserve the viability of sperm, viruses, and sarcoma cells, she diluted samples of blood, 1:1, with equal volumes of 30 per cent glycerol in Ringer's solution. The samples were then frozen at –79° C. No hemolysis appeared up to 8 weeks. Further studies showed that essentially the same results could be obtained with glycerol concentrations between 10 and 20 per cent and with isotonic saline as the diluent. These findings appear to contradict earlier reports[32] in which in vitro hemolysis could be produced by low concentrations, such as 3 per cent.

Simon[63] recognized that a 1.0 per cent solution of sodium chloride protected erythrocytes against hemolysis by glycerol. Along this same line, Johnson and associates[35] pointed out that aqueous solutions of glycerol cause hemolysis, probably on the same basis as distilled water does, but that a solution of glycerol in isotonic saline was not hemolytic. Schübel[59] studied isotonic saline–washed erythrocytes to which various concentrations of glycerol were added. He found no hemolysis in saline solutions containing up to 40 per cent glycerol, while in 50 per cent solutions, 20 to 50 per cent glycerol caused hemolysis after several minutes. Similar results were obtained with urea. Urea in water is hemolytic, but when the diluent was isotonic saline very high concentrations of urea were found not to be hemolytic. They explained hemolysis by glycerol as follows: An excess of water enters the cell to such an extent that the cell membrane is disrupted by stretching; it does not disintegrate the cell membrane per se, as does saponin. It would appear that glycerol (or urea) which diffuses freely into the cell is the driving force, hence, the osmolality of the intracellular space is increased. Accordingly, a greater amount of water enters the cell by osmosis which can result in hemolysis if the swelling is excessive. It is an expected result that the addition of a solute to the extracellular space which does not readily pass the membrane, such as sodium chloride, would decrease the osmotic movement of water into a glycerolized erythrocyte. It turns out that hemolysis can be prevented or decreased by a salineous solute over a large range of concentrations even if the concentration of glycerol is 50 per cent.

Following the reports by Smith, pre–quick freeze glycerol treatment of erythrocytes to prevent ice artifacts became a common practice. In the method of Huggins,[31] for example, a final concentration of glycerol of 5.6M (52 per cent) is used. Although reports of hemolysis have been found with this method, they have been shown to be caused by slow freezing and thawing technique with the subsequent formation of ice crystals[53] or to suspension of the erythrocytes in a "artificial" protein solution.[73] It is estimated that as much as 5 Gm. of glycerol per 100 ml. is given at the time of transfusion, even though the erythrocytes have been washed in the accepted fashion.[64]

To our knowledge, no adverse side effects which are permanently disabling have been produced by oral glycerol.

Nausea and vomiting induced by the sweet taste of glycerol can be a problem severe enough to require discontinuation of the therapy. Johnson and associates,[35] after some experimentation on their graduate students, disguised the sweet taste of glycerol with orange juice. A layer of orange juice was floated on about 35 ml. of glycerol. Immediately following the rapid drinking of this, leaving about 5 ml. of the viscous material clinging to the sides of the tumbler, a swallow of orange juice from another glass was taken. Thus, they gave orange juice immediately preceding and following the glycerol and there was little to be tasted except the orange juice. Jaffe and Light[33] had patients sip, through a

soda straw, 150 ml. of a 50 per cent v/v solution of glycerin in a pleasant lime-flavored aqueous vehicle in cracked ice. Approximately 5 per cent of them still vomited. Cantore and associates[15] attenuated the sweetish taste of glycerol by diluting it 50 per cent in 0.9 per cent saline. Lemon juice was added and the mixture was chilled. They also noted that ingestion of a small amount of food helped. Parenteral injection of an antiemetic substance 15 to 30 minutes prior to ingestion of glycerol was carried out in patients predisposed to vomiting.

We have used all of the above procedures, as well as iced tomato juice. Trimethobenzamide hydrochloride (Tigan) administered by suppository or by mouth taken approximately 30 minutes earlier gives near-perfect relief, as does intramuscular prochlorperazine (Compazine) 5 to 10 mg., 30 minutes before glycerol administration.

Minor neurologic complaints such as headache and dizziness have been mentioned in some reports.[11, 45] D'Alena and Ferguson[20] reported 2 patients as having more serious side effects. An 82-year-old woman with hypertension was given one oral dose of 2 Gm. per kilogram, about twice the usual dose. Within several hours she developed a headache, nausea, and shaking of one arm. The patient was asymptomatic in several days. A second patient with diabetes mellitus developed moderate diabetic acidosis 2 days after initiation of glycerol therapy. Within 24 hours after stopping glycerol and starting insulin, he was under control. It was unlikely that glycerol contributed directly to the problem in this patient.

Human intravascular studies

Bowesman[10] is believed to have reported the first intravascular use of glycerol. He injected 2 to 3 ml. of 10 per cent glycerol into the femoral artery at weekly intervals for the control of leg edema secondary to elephantiasis. Patients were followed up to 40 days with measurements of limb circumference. Results were satisfactory and no ill effects were noted.

Sloviter[65] showed that a considerable quantity of glycerol in relatively dilute form could be given intravenously to human subjects with no ill effects. His study was undertaken because of concern about the amount of glycerol which remained in the erythrocyte-glycerol mixture of stored red blood cells at the time of transfusion. Five per cent glycerol in isotonic saline was given intravenously for 3 to 6 hours to hospitalized patients. The largest amount given was 1.2 Gm. per kilogram. Monitoring heart rhythm and rate showed no change. No headache, visual symptoms, pain at the injection site, or venous thromboses occurred. Plasma hemoglobin concentrations obtained up to 7 hours after infusion were not significantly different from preinfusion values. No hemoglobinuria was found, but there was a moderate diuresis.

Intravenous infusion of sterile 30 per cent glycerol solutions in 10 per cent sugar or in 6 per cent dextran diluted in 0.9 per cent sodium chloride was used by Cantore and associates.[15] When the solution was injected at a rate of 60 drops per minute (0.8 to 1 Gm. per kilogram total dose), a marked reduction of increased intracranial pressure resulted, even in the most serious cases. However, intravenous administration was used only in a "limited" number of patients because of the "frequent" occurrence of "transient" hemoglobinuria. No data were presented.

Wolf and associates[85] studied elimination rates of glycerol in term and premature infants by intravenous infusion of 0.1 Gm. of glycerol per kilogram in 5 minutes and found the highest elimination rate in premature newborn infants. Four-week-old infants had rates nearly as high as did adults. Birth weights ranged from 3,000 to 4,190 grams. No ill effects were reported. Havel[27] infused glycerol-2-H^3 intravenously to young men before, during, and after exercise to measure turnover rates. The dose of glycerol was not great. The highest plasma concentration attained was 0.154 μmoles

per milliliter (1.4 mg./100 ml.), and no ill effects were noted. Faster turnover occurred during exercise. Senior and Loridan,[60] using much higher doses of intravenous glycerol, studied 22 control subjects, 4 patients with glucose-6-phosphate dehydrogenase (G-6-P-DH) deficiency, one patient deficient in amylo-1,6-glucosidase, and 2 patients deficient in phosphorylase. They infused 10 per cent glycerol in isotonic sodium chloride in a dose of 120 mmoles per square meter of body surface over a 4 minute period. This is about 19 Gm. for a 70 Kg. man. The disposal rate was most rapid in the G-6-P-DH–deficient patients and faster than that of the control subjects for the other groups. Half life for glycerol in the control subjects was about 30 minutes. The highest blood level obtained was 10 mmoles per liter. No toxic effects were reported.

Several authors[13, 56, 74, 75, 79] have described the intravenous use of 30 per cent glycerol in 20 per cent sodium ascorbate for use in ocular and cerebral hypertension. The sodium ascorbate was added because in animal experiments it was shown to prevent the hemoglobinuria and renal changes that result with intravenous glycerol. These authors used 0.6 Gm. per kilogram of glycerol and 0.28 Gm. per kilogram of sodium ascorbate in a total volume of 140 ml. given over a 15 to 20 minute period. No hemolysis or hemoglobinuria was noted.

Turnover and excretion

Free glycerol is present in the plasma of rabbits, sheep, guinea pigs, rats, and man. In man, the concentration of plasma glycerol is increased by norepinephrine and decreased by insulin.[61] During states of mobilization such as starvation and hyperthyroidism, the plasma glycerol concentration may rise to 3 to 4 mg. per 100 ml.[5] Glycerol given to diabetic patients during partial insulin withdrawal leads to a decrease in ketones and in glycosuria, suggesting that glycerol may be metabolized without the aid of insulin.[25]

Glycerol is removed from the body by the liver (80 to 90 per cent) and the kidney (10 to 20 per cent).[7] This would appear to be consistent with the observation of Wieland and Suyter[82] of the distribution of glycerokinase. The distribution of glycerol is generally felt to correspond to the extracellular space, 50 to 65 per cent of the body weight.[29] Exactly how quickly intravascular glycerol equilibrates with the tissue water is not precisely known, but it is probably within minutes during continuous intravenous infusion at a constant rate.[83]

Renal excretion has been observed by Zilversmit and McCandless,[86] who reported that, when the plasma levels of glycerol reach 1 mg. per milliliter (1.1 mmoles per liter) or below, the amount of urinary glycerol is "negligible." Kruhøffer and Nissen[37] have shown that essentially complete reabsorption of glycerol occurs in cats at low filtered loads, but that more and more glycerol appears in the urine as the plasma concentration increases. The reason for this is based on the assumption that "reabsorption" at low filtered loads is predominantly accounted for by metabolic conversion of glycerol by the tubular lumen cells to CO_2, glucose, and lactate. At higher plasma concentrations, the glycerol converting enzymes become saturated and glycerol spills into the urine. Swanson and Thompson,[69] using stop-flow methods, found that glycerol was completely reabsorbed when the plasma concentration was less than 15 mg. per 100 ml. (1.6 mmoles per liter) in the dog. For concentrations between 30 and 200 mg. per 100 ml. (3.2 and 21.3 mmoles per liter), the fractional reabsorption tends to approach a roughly constant value depending on the state of diuresis.

The nonrenal (essentially hepatic) contribution to glycerol turnover has been studied by Winkler and associates[83] in the dog. They found that, over the physiologic range of glycerol concentrations (up to 0.5 mmoles per liter), the relationship of the uptake to plasma concentration is described by a simple regression line. At higher concentrations uptake departs from

linearity and simulates a saturation-type kinetic curve. Over a seventyfold range of plasma glycerol concentrations conformed to a specific equation describing a segment of a hyperbola. They also showed that, during constant intravenous infusion of glycerol, a steady state of plasma glycerol and tissue specific activity is achieved, so that glycerol uptake and input is simply the infusion rate divided by the plasma glycerol specific activity. It was found in this study that asymptomatic values of plasma glycerol activity are reached in 20 to 30 minutes with or without a priming dose.

Also of interest is that glycerolkinase has been found in intestinal mucosa,[26] lymphatic tissue,[36] lung,[38] and pancreas.[28] Whether glycerol is metabolized by all of these tissues is not known.

Advantages of glycerol as an intracranial hypotensive agent

For a long time we have needed a cerebral dehydration agent that can be used on a continuous basis. Steroids, although effective in cerebral edema, have a limitation by the nature of their well-known side effects, such as duodenal ulcer, psychoses, fluid retention, and predisposition of patient to infection. These effects would be particularly undesirable in patients with encephalitis or meningitis or in postoperative patients. Furthermore, steroids are most effective in cerebral edema due to neoplasm and pseudotumor cerebri.

Urea[34, 54, 55] and mannitol[4] cannot be used on a long-term basis because of the marked water and electrolyte washout associated with their use. Mannitol is not reabsorbed from the tubular lumen to any appreciable degree, therefore, a high percentage of the administered dose undergoes renal excretion, causing very marked osmotic diuresis.

Glycerol does not produce much water or electrolyte loss and does not depend solely on the kidney to reduce brain water,[15] although it gains access to renal tissue easily.[19, 80] Glycerol has been reported effective in the nephrectomized animal,[15] which suggests it removes water from the brain by an extrarenal mechanism. Only 100 ml. of brain water is necessary to increase intracranial pressure profoundly.[62]

Reed and Woodbury[54, 55] measured the amount of water removed from the CNS of rats by the administration of urea. If their findings are applicable to man, then adequate reduction of CSF pressure requires removal of about 100 ml. of water. This volume of water could easily be accommodated by expansion of the systemic vascular compartment, without a need for diuresis. Urea regularly produces a rebound overshoot of intracranial pressure. The second or slow ascent phase is felt to be due to urea entering or remaining in the brain cells after the extracellular urea level falls, and thereby water moves by osmosis into the brain producing an increase of intracranial pressure.

Waterhouse and Coxon,[80] in a well-presented study, demonstrated the existence of an efficient CSF-brain barrier to glycerol by simultaneous perfusion of intravascular and ventricular systems with radioactive glycerol. Because glycerol does not enter the CNS, these results would indicate that rebound overshoot of CSF pressure would not be expected with glycerol. Whether or not glycerol is metabolized by brain tissue is currently disputed,[66, 80] but the point remains that in the intact animal the intracellular concentration has not been found to exceed the extracellular concentration.[80] In cases in which the blood-brain barrier is not intact, it is conceivable that the reverse may be true.

Crone[19] measured the arteriovenous difference of glycerol and found that glycerol disappeared no more readily than did Evans blue dye which does not pass the blood-brain barrier. On the other hand, Sloviter and associates[66] found normalization of ipsilateral hemispheric electroencephalogram changes due to hypoglycemia (rabbits) when intracarotid glycerol was given; he suggested that glycerol passed the barrier and acted as a substrate for brain metabolism.

The nutrient value of glycerol (4.32 calories per gram) is of some importance, as it can supply a caloric yield greater than that supplied by an equal amount of glucose. One gram per kilogram given orally every 6 hours to a 70 Kg. man would supply 1,210 calories per 24 hours.

Proposed use of intravenous glycerol for cerebral edema

Based on this review of the world literature, it is our opinion that the intravenous administration of glycerol on a continuous basis has not been systematically studied as a means of controlling cerebral edema or CNS rehydration. We believe that on the basis of the evidence, serious consideration should be given to such therapy. It is apparent that, when given in low concentrations in the proper vehicle, glycerol does not produce hemolysis or renal lesions as was previously believed. It is anticipated that intravenous administration should eliminate nausea and vomiting; hence, it becomes a more suitable agent for use in coma with increased intracranial pressure and preoperative dehydration of the CNS.

It is probable that the dosage of glycerol required to produce ocular dehydration is the same as that for cerebral dehydration.[76] It has been shown[45] that a fall in intraocular pressure begins at plasma glycerol levels of approximately 10 mmoles per liter. Therefore, it is reasonable to devise an intravenous infusion scheme for cerebral dehydration which results in blood levels of 10 mmoles per liter.

To convert the oral dosage used by McCurdy and associates[45] to an intravenous one is complex. For example, the intestines contain glycerolkinase, and the blood from the gut is carried to the liver which metabolizes about 80 per cent of the body's glycerol. Therefore, the total oral dose is not distributed to the systemic extracellular water space (CNS is not included) to which glycerol equilibrates. Since the half-life of glycerol in man is about 30 minutes and the oral dose of glycerol lowers the CSF pressure for 6 hours, it is again obvious that the effective plasma concentration of glycerol is much less than the amount based on calculated total oral dose after a correction for metabolism and its solution in the total body water space.

We have been able to make only speculations based on the conversion of animal data to man. When glycerol was given intravenously to dogs, data have been reported to be similar to those in man[83] at the rate of 0.05 mmoles per minute per kilogram, for one to 2 hours—a plasma concentration of 2 mmoles per liter was obtained and sustained. This turns out to be 6.5 Gm. of glycerol per day per kilogram, similar to the oral dosage needed to produce cerebral dehydration.

Is it possible that an intravenous route is less effective in maintaining a blood level of glycerol than is the oral one? Or is it possible that blood levels of glycerol increased to 10 mmoles per liter, the minimum value given for intraocular dehydration, will produce cerebral dehydration?

Along this same line, Cantore and associates[15] infused intravenously 0.3 Gm. (3.3 mmoles) of glycerol per minute, 1 Gm. (19 mmoles) total dose. They said, "It always produced a marked antiedematous effect, even in the most serious cases." They gave no CSF pressure data in relationship to the initiation of glycerol therapy or glycerol blood levels. It is possible that plasma levels in the area of 10 mmoles per liter were reached. Of great importance is the report by Senior and Loridan.[60] They gave 19 Gm. of glycerol intravenously to a 70 Kg. man (0.27 Gm. per kilogram) as a 10 per cent solution in isotonic saline in 4 minutes and obtained a maximum blood level of 10 mmoles per liter, the minimum concentration reported by McCurdy and associates[45] necessary to produce ocular dehydration.

With the information at hand, we think it is possible to explore the possibilities of the safe administration of glycerol via the intravenous route on a continuous or semicontinuous basis in man.

References

1. Absolon, M. J.: Unusual presentation of benign intracranial hypertension, early treatment with oral glycerol, Br. J. Ophthalmol. **50**:683-688, 1966.
2. Arnschink, L.: Ueber den einfluss des glyzerins auf die zersetzungen im thierkörper und über den nährwerth desselben, Z. Biol. **23**:413-432, 1887.
3. Awasthi, P., and Srivastova, S. W.: Role of oral glycerol in glaucoma, Br. J. Ophthalmol. **49**:660-666, 1965.
4. Barry, K. G., and Berman, A. R.: Mannitol infusion. III. The acute effect of the intravenous infusion of mannitol on blood and plasma volumes, N. Engl. J. Med. **264**:1085-1088, 1961.
5. Bergman, E. N.: Glycerol turnover in the nonpregnant and ketotic pregnant sheep, Am. J. Physiol. **215**:865-873, 1968.
6. Bondi, R., Marchi, F., Tosi, P., and Susini, A.: Ricerca compazativa sulla nefrosi emoglobinurica di glicerolo nel coniglio di giovane nel coniglio adulto, Arch. De Vecchi Anat. Patol. **50**:257-288, 1967.
7. Borchgrevink, C. F., and Havel, R. J.: Transport of glycerol in human blood, Proc. Soc. Exp. Biol. Med. **113**:946-949, 1963.
8. Bouzarth, W. F., and Tucker, A. C.: Factors influencing subdural hematoma formation in the dog, Surg. Forum **17**:407-409, 1966.
9. Bovet, D., Cantore, G. P., and Guidetti, B.: Il glicerolo in neurochirugia. Nova therapia dell ipertensione endocranica, Gazz. Int. Med. Chir. **66**:3021-3034, 1961.
10. Bowesman, C.: Intra-arterial glycerin treatment of elephantiasis, Br. J. Surg. **26**:86-89, 1938.
11. Buckell, M., and Walsh, L.: Effect of glycerol by mouth on raised intracranial pressure in man, Lancet **2**:1151-1152, 1964.
12. Cameron, G. R., and Finckh, E. S.: The production of an acute haemolytic crisis by the subcutaneous injection of glycerol, J. Pathol. **71**:165-171, 1956.
13. Cantore, G. P., Guidetti, B., Pecori-Giraldi, J., and Virno, M.: Glicerolo endovenoso nel trattamento dell' ipertensione endocranica, Policlinico (Prat.) **73**:553-561, 1966.
14. Cantore, G. P., Guidetti, B., and Virno, M.: Oral glycerol for the reduction of intracranial pressure, Excerpta Medica International Congress Series 60, p. 128, 1963.
15. Cantore, G. P., Guidetti, B., and Virno, M.: Oral glycerol for the reduction of intracranial pressure, J. Neurosurg. **21**:278-283, 1965.
16. Casey, T. A., and Trevor-Roper, P. D.: Oral glycerol in glaucoma, Br. Med. J. **2**: 851-852, 1963.
17. Charan, H., and Sarda, R. P.: Glycerol in cataract surgery, Am. J. Ophthalmol. **63**:88-89, 1967.
18. Consul, B. N., and Kulshrestha, O. P.: Oral glycerol in glaucoma, Am. J. Ophthalmol. **60**: 900-907, 1965.
19. Crone, C.: The permeability of brain capillaries to non-electrolytes, Acta Physiol. Scand. **64**: 407-417, 1965.
20. D'Alena, P., and Ferguson, W.: Adverse effects after glycerol orally and mannitol parenterally, Arch. Ophthalmol. **75**:201-203, 1966.
21. Deichmann, W.: Glycerol, behavior in the animal organism (a review of the literature), Ind. Med. (Ind. Hyg. Sect.) **9**:60-67, 1940.
22. Della Rocca, L., Pecori-Giraldi, J., Cantore, G. P., and Virno, M.: Studio funzionale ed isotologico dell' apparato renale dopo somministrazionne di glicerolo per via endovenosa nel coniglio, Gazz. Int. Med. Chir. **71**:944-951, 1966.
23. Drance, S. M.: Effect of oral glycerol on intraocular pressure on normal and glaucomatous eyes, Arch. Ophthalmol. **72**:491-493, 1964.
24. Finckh, E. S.: The indirect action of subcutaneous injections of glycerol on the renal tubules in the rat, J. Pathol. **78**:197-202, 1959.
25. Freund, G.: The metabolic effects of glycerol administered to diabetic patients, Arch. Intern. Med. **121**:123-129, 1968.
26. Haessler, H. A., and Isselbacher, K. J.: The metabolism of glycerol by intestinal mucosa, Biochim. Biophys. Acta **73**:427-436, 1963.
27. Havel, R. J.: Some influences of the sympathetic nervous system and insulin on mobilization of fat from adipose tissue: Studies of the turnover rates of free fatty acids and glycerol, Ann. N. Y. Acad. Sci. **131**:91-101, 1965.
28. Hokin, L. E., and Hokin, M. R.: Phosphoinositides and protein secretion in pancreatic slices, J. Biol. Chem. **233**:805-810, 1958.
29. Holst, E. J.: Glycerol oxidation in the animal organism, Acta Physiol. Scand. **7**:69-79, 1944.
30. Holzhauer, A., and Pilger, I. S.: Oral glycerol, a clinical confirmation, Trans. Pac. Coast Otoophthalmol. Soc. **45**:399-404, 1964.
31. Huggins, C. E.: Frozen blood: Principles of practical preservation, Monogr. Surg. Sci. **3**: 133-173, 1966.
32. Jacobs, M. H., Glassman, H. N., and Parpart, A. K.: Hemolysis and zoological relationship: Comparative studies with four penetrating nonelectrolytes, J. Exp. Zool. **113**:277-300, 1950.
33. Jaffe, N. S., and Light, D. S.: Oral glycerin

in cataract surgery, Arch. Ophthalmol. **73**: 516-518, 1965.
34. Javid, M.: New use of old agent, Surg. Clin. North Am. **38**:907-927, 1958.
35. Johnson, V., Carlson, A. J., and Johnson, A.: Studies on the physiological action of glycerol on the animal organism, Am. J. Physiol. **103**: 517-534, 1933.
36. Kit, S., and Granham, O. L.: Glycerol metabolism of normal and malignant lymphatic tissues. The preferential labeling of tumor serine and glycine, Cancer Res. 16: 937-942, 1956.
37. Kruhøffer, P., and Nissen, O. I.: Handling of glycerol in the kidney, Acta Physiol. Scand. **59**:283-294, 1963.
38. Lands, W. E.: Metabolism of glycerolipides: A comparison of lecithin and triglyceride synthesis, J. Biol. Chem. **231**:883-888, 1958.
39. Larsen, J.: Elimination of glycerol as a measure of the hepatic blood flow in the cat, Acta Physiol. Scand. **57**:224-234, 1963.
40. Lebensohn, J. E.: Oral glycerin: Simplified calculation of the dose, Am. J. Ophthalmol. **56**:315-316, 1963.
41. Leo, H.: Ueber die ausnutzung des glycerins im Körper und seine Bestimmung im Harn, Pfluegers Arch. **93**:269-276, 1902.
42. Lewis, H. B., and Corley, R. C.: Studies in uric acid metabolism. III. The influences of fats and carbohydrates on the endogenous uric acid elimination, J. Biol. Chem. **55**:373-384, 1923.
43. Maignon, F., and Grandclaude, C.: Action sclérosante des injections intraveineuses de glycérine. Effets sensibilisants d'une premiére injection, C. R. Acad. Sci. **190**:890-892, 1930.
44. Mandell, S., Taylor, J. M., and Kotsilimbas, D. G.: The effect of glycerol on cerebral edema induced by tri-ethyltin sulphate in rabbits, J. Neurosurg. **24**:984-986, 1966.
45. McCurdy, D. K., Schneider, B., and Scheie, H. G.: Oral glycerol: the mechanism of intraocular hypotension, Am. J. Ophthalmol. **61**: 1244-1249, 1966.
46. Mikuni, M.: Iwafa, K., and Iwata, R.: Oral glycerol in glaucoma. On the effects of oral administration of glycerin on glaucoma, Jap. J. Clin. Ophthalmol. **18**:957-962, 1964.
47. Miner, C. S., and Dalton, N. N., editors: Glycerol, New York, 1953, Reinhold Publishing Company, p. 402.
48. Niclous, M.: Contribution a l'étude physiologique de la glycérine. H. Glycérine normale du sang, ses variations dans quelques conditions physiologiques et expérimentales. Injection intraveineuse et ingestion de glycérine; dosage dans le sang, élimination par l'urine, J. Physiol. Path. Gen. **5**:827-842, 1903.
49. Oken, D. E., Arce, M. L., and Wilson, D. R.: Glycerol-induced hemoglobinuric acute renal failure in the rat. I Micropuncture study of the development of oliguria, J. Clin. Invest. **45**:724-735, 1966.
50. Palmieri, L., Graziano, F. M.: Azione del glicerolo per via orale nel glaucoma acuto, Ann. Ottalmol. Clin. Ocul. **89**:749-753, 1963.
51. Pfeiffer, C., and Arnove, I.: Glycerol toxicity and hemoglobinuria in relation to vitamin C, Proc. Soc. Exp. Biol. Med. **37**:467-469, 1937.
52. Piras, A.: Ricerche istologiche su organi di conigli trattati a lungo con iniezioni sottocutanee di piccole dosi di glicerina, Arch. Di Farmacol. Sper. **40**:251-256, 1925.
53. Rapatz, G., and Luyet, B.: Electron microscope study of erythrocytes in rapidly cooled suspensions containing various concentrations of glycerol, Giodynamica **10**:193-210, 1968.
54. Reed, D. J., and Woodbury, D. M.: Effect of urea and acetazolamide on brain volume and cerebrospinal fluid pressure, J. Physiol. **164**: 265-273, 1962.
55. Reed, D. J., and Woodbury, D. M.: Effects of hypertonic urea on cerebrospinal fluid pressure and brain volume, J. Physiol. **164**:252-264, 1962.
56. Restive-Manfridi, M. L., and Pecori-Giraldi, J.: Il glicerolo endovenoso quale fattore ipotensivo nella chirurgia oculare, Ann. Ottalmol Clin. Ocul. **93**:1195-1202, 1967.
57. Rosenfeld, G.: Harnsäurestudien, nach Versuchen von Dr. v. Lebinski u. Dr. Johannes Hoffmann, Klin. Wochenschr. **3**:1908-1909, 1924.
58. Rubichi, E.: Glicerolo ed ipertono oculare, Romagna Med. **15**:651-657, 1963.
59. Schübel, K.: Zur Pharmakologie des Glycerins, Sitzungsb d Phys.-Med. Soz zu Erlangen, pp. 67-68, 1935-1963; pp. 263-266, 1937.
60. Senior, B., and Loridan, L.: Studies of liver glycogenoses with particular reference to the metabolism of intravenously administered glycerol, N. Engl. J. Med. **279**:958-965, 1968.
61. Shaftir, E., and Gorin, E.: Release of glycerol in conditions of fat mobilization and deposition, Metabolism **12**:580-587, 1963.
62. Shenkin, H. A., and Bouzarth, W. F.: Medical progress: Clinical methods of reducing intracranial pressure; role of the cerebral circulation, N. Engl. J. Med. **282**:1465-1471, 1970.
63. Simon, I.: Studi sull' azione della glicerina. I. Intorno all' azione emolitica della glicerina in vitro ed in vivo, Arch Di Farmacol. Sper. **20**:120-145, 1915.
64. Sloviter, H. A.: A method for preparing thawed erythrocyte-glycerol mixtures for transfusion, Am. J. Med. Sci. **231**:437-440, 1956.
65. Sloviter, H. A.: Effects of intravenous administration of glycerol solutions to animals and man, J. Clin. Invest. **37**:619-626, 1958.
66. Sloviter, H. A., Shimkin, P., and Suhara, K.:

Glycerol as a substrate for brain metabolism, Nature **210**:1334-1336, 1966.

67. Smith, A. U.: Prevention of haemolysis during freezing and thawing of red blood cells, Lancet **2**:910-911, 1950.
68. Sugimoto, K.: Der Restkohlenstoff der lymphe und des blutserums unter verschiedenen Bedingungen, Arb. Dritten Abt. Anat. Inst. Kaiserlich Univ. Kyoto Ser. D **5**:154-160, 1935.
69. Swanson, R. E., and Thompson, R. B.: Renal tubular handling of glycerol and ethylene glycol in the dog, Am. J. Physiol. **217**:553-562, 1969.
70. Trevor-Roper, P. D.: Experience with the use of glycerol and other hypotensive agents in glaucoma, Eye Nose Throat Mon. **44**:74, 1965.
71. Trevor-Roper, P. D.: The use of oral glycerol in glaucoma (summary), Proc. R. Soc. Med. **57**:37-38, 1964.
72. Ustimowitsch, C.: Ueber die angebliche zuckerzersetzende eigenschaft des glycerins, Pfluegers Arch. **13**:453-460, 1876.
73. Valeri, R., and Henderson, M. E.: Recent difficulties with frozen glycerolized blood, J. A. M. A. **188**:1125-1131, 1964.
74. Virno, M., Bucci, M. G., Giraldi, J., and Cantore, G. P.: Azione ipotonizzante oculare del glicerolo somministrato per via endovenoso, Boll. Ocul. **55**:225-236, 1965.
75. Virno, M., Bucci, M. G., and Pecori-Giraldi, J., et al.: Intravenous glycerol-vitamin C (sodium salt), as osmotic agents to reduce intraocular pressure, Am. J. Ophthalmol. **62**: 824-833, 1966.
76. Virno, M., Cantore, G. P., Bietti, C., and Bucci, M. G.: Azione del glicerolo sulla pressione endoculare dei conigli, Boll. Ocul. **41**:815-821, 1962.
77. Virno, M., Cantore, G. P., Bietti, C., and Bucci, M. G.: Oral glycerol in ophthalmology. A valuable new method for the reduction of intraocular pressure, Am. J. Ophthalmol. **55**: 1133-1142, 1963.
78. Virno, M., Chiavarelli, S., and Cantore, G. P.: Azione del glicerolo sull' edema cerebrale nel coniglio dopo craniectomia, Gazz. Int. Med. Chir. **66**:3509-3515, 1961.
79. Virno, M., Della Rocca, L., Pecori-Giraldi, J., and Cantore, G. P.: Scomparsa dell ematuria provocata dal glicerolo endovenoso nel coniglio mediante associazeare glicerolo-ascorbato di sodio, Gazz. Int. Med. Chir. **71**:1160, 1966.
80. Waterhouse, J. M., and Coxon, R. V.: The entry of glycerol into brain tissue, J. Neurol. Sci. **10**:305-311, 1970.
81. Wieland, O.: Eine enzymatische methode zur bestimmurg von glycerin, Biochem. Z. **329**: 313-319, 1957.
82. Wieland, O., and Suyter, M.: Glycerokinase: Isolierung und Eigenschafter den Enzyms, Biochem. Z. **329**:320-331, 1957.
83. Winkler, B., Steel, R., and Altszuler, N.: Relationship of glycerol uptake to plasma glycerol concentration in the normal dog, Am. J. Physiol. **216**:191-196, 1969.
84. Wilson, D. R., Thiel, G., Arce, M. L., and Oken, D. E.: Glycerol induced hemoglobinuric acute renal failure in the rat, Nephron **4**:337-355, 1967.
85. Wolf, H., Melichar, V., and Michaelis, R.: Elimination of intravenously administered glycerol from the blood of newborns, Biol. Neonate **12**:162-169, 1968.
86. Zilversmit, D. B., and McCandless, E. L.: Fate of intravenously administered glycerol, Proc. Soc. Exp. Biol. Med. **95**:755-757, 1957.
87. Zilversmit, D. B., Salky, N. K., Trumbull, M. L., and McCandless, E. L.: The preparation and use of anhydrous fat emulsions for intravenous feeding and metabolic experiments, J. Lab. Clin. Med. **48**:386-391, 1956.