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PERSPECTIVES IN BASIC SCIENCE

Mannitol therapy revisited (1940–1997)

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Intravenous (i.v.) hypertonic mannitol, the first pharmacologic agent to be used for prophylaxis against acute renal failure (ARF) [1], was introduced by Homer Smith in 1940 to estimate glomerular filtration rate (GFR) in humans and dogs [2]. Smith noted the osmotic diuretic effect of mannitol. This was followed by Selkurt in 1945 who showed that mannitol ameliorated ischemic ARF in the dog [3]. In the half century that elapsed since then, mannitol prophylaxis against ARF in humans was used widely but not universally by the nephrology community.

The purpose of the present communication is to review the effect of mannitol on normal kidney function as well as its clinical therapeutic potential in the prevention of ARF and protection of skeletal muscle function following crush injury.

Osmotic diuretics are freely filterable, low molecular weight substances that due to their limited reabsorption and small size create an osmotic force in the tubular fluid sufficient to retard the reabsorption of fluids and solutes (notably NaCl) along the nephron. Thus, osmotic diuresis results in urinary loss of water, sodium, potassium and divalent cations.

Mannitol, a six-carbon nonmetabolizable polyacohol with a molecular weight of 182, is perhaps the oldest and most widely employed osmotic diuretic agent [2]. Numerous studies in experimental animals and humans, under both physiologic and pathophysiologic conditions, have contributed significantly to our understanding of its renal and extrarenal actions. A compound with similar effects is sorbitol. Glucose may likewise act as an "endogenous" osmotic diuretic agent when present at sufficiently high concentrations in the glomerular filtrate, to exceed the reabsorption capacity of the proximal nephron. Other partially or poorly reabsorbable agents, such as urea and sulfates, were included in the past in the category of osmotic diuretics, because, when present in high concentrations in plasma, they may increase urine flow rate, in part by a mechanism similar to that of mannitol [4].

Beyond its action as a diuretic agent, mannitol has been used by many renal physiologists, over the past five decades, as an important tool in the study of the mechanisms of salt and water transport at the tubular and cellular level. As a physiologic probe, mannitol has contributed to our understanding of these transport processes.

Key words: mannitol, crush injury, acute renal failure, diuretics.

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The introduction of mannitol for prophylaxis against postoperative ARF following cardiovascular surgery [5, 6] was associated with a dramatic decline in the occurrence of such ARF. Furthermore, mannitol clearly protects renal graft function during cadaver kidney transplantation [7, 8]. In addition, mannitol as an adjunct is useful for the prevention of myoglobinuric ARF in humans [9]. Our experience in the salvage of lives and limbs in victims of crush injury following mass disasters suggests that mannitol has also beneficial extrarenal effects [9].

Finally, in addition to being a hyperosmotic agent, mannitol has been shown also to be an effective scavenger of free hydroxyl radicals in many biologic systems at least extracellularly [10, 11] since mannitol is an impermeant solute.

RENAL EFFECTS OF MANNITOL

Intravenous administration of mannitol results in a brisk diuretic/natriuretic response. Depending on the dose adminstered, urine flow in humans may reach 20% to 30% of the filtered load of water, and up to 10% to 15% of the filtered Na^+ may be excreted during the height of the diuresis [4]. In the dog, even larger inhibition of water and salt reabsorption has been reported, with massive doses of mannitol injected [12].

Concomitant with the diuresis and natriuresis produced by mannitol, the excretion of other ions such as Ca^{2+}, Mg^{2+}, phosphate and bicarbonate is also increased. Urinary concerntration and dilution ability is severely impaired, and urine osmolality tends to approach isotonicity during peak diuresis [13]. Many studies in the past have focused on the tubular effects of mannitol as the dominant mechanism by which the diuretic effect of the drug is achieved. However, in addition to its actions on salt and water reabsorption along the nephron, mannitol has important glomerular, systemic and renal hemodyanmic effects, which, in turn, may influence and modulate its tubular actions. Furthermore, since injeced mannitol is confined primarily to the extracellular fluid compartment, the increase in osmotic pressure induced by mannitol results in water shifts from the intracellular compartment. Such redistribution of fluid may lead to extracellular volume expansion, as well as a decrease in plasma oncotic pressure, and blood viscosity and hematocrit values, which will further increase renal perfusion. Finally, the increase in extracellular fluid volume may activate endogenous natriuretic agents, and suppress antinatriuretic hormone systems, thereby contributing to the diuretic/natriuretic effect of mannitol. The major renal actions of mannitol are as follows:

(*1.*) Increase in cortical and medullary blood flow due to a decrease in RVR

(2.) Increase in GFR during renal hypoperfusion. Variable effects on GFR in kidneys with normal function.

(3.) Prominent diuretic/natriuretic action due to inhibition of tubular reabsorption of water and salt.

(4.) Increase in urinary excretion of K^+, Ca^{2+}, Mg^{2+}, phosphate and bicarbonate.

(5.) Dissipation of medullary hypertonicity. Impairment of urinary concentration and dilution capacity.

(6.) Increase in renal interstitial pressure and in intratubular pressure.

(7.) Indirect actions on the kidney through an increase in ECF volume, dilution of plasma proteins and decrease in blood viscosity, release of prostaglandins and ANF, and inhibition of renin angiotensin system

Effects of mannitol on renal hemodynamics

In most experimental settings, infusion of hypertonic mannitol increases renal blood flow (RBF), apparently by reducing renal vascular resistance (RVR) [14–16]. The increase in total RBF is reflected by a concomitant increase in both cortical blood flow and medullary perfusion [17, 18]. Moreover, the effect of mannitol on RBF is observed under normotensive conditions [15], as well as in animals made hypotensive by bleeding, and in the hypoperfused rat kidney, an experimental model of "prerenal failure" [19]. The restoration of RBF and GFR following mannitol infusion in the hypoperfused kidney [3, 19, 20] is the rationale for its use in the treatment and prophylaxis against impending ARF.

On the other hand, massive doses of mannitol may cause a paradoxical constriction of the main renal artery [21] with an increase in RVR, and decrease renal perfusion [22]. This phenomenon may be due to constriction of the efferent arteriole in response to the high concerntration of mannitol. The mechanism by which mannitol exerts its effects on RBF is not thoroughly understood. In the *in situ* perfused dog kidney, Goldberg and Lilienfield [23] demonstrated that systemic infusion of hypertonic mannitol resulted in a marked decrease in RVR. A similar decrease was produced by direct infusion of mannitol into the renal artery, and also by dextran and saline infusion, but not during infusion of whole blood. These decreases in vascular resistance correlated with diminshed hematocrits of the perfusion fluids, suggesting that the diminished viscosity of blood following mannitol infusion could contribute to the increase in RBF [23]. Earlier observations [14] have also suggested a similar linkage between the decrease in the hematocrit and RVR. However, assuming that blood at physiologic rates of flow has a stable viscosity, the observed changes in hematocrit were not sufficient to explain the effects of mannitol on RVR. Therefore, additional mechanisms, unrelated to changes in blood viscosity, must be invoked. It is of interest that renal denervation and autonomic ganglioplegia did not influence the effects of hyperosmotic mannitol on RVR [23]. This suggests that suppression of enhanced sympathetic activity is probably not involved in the mechanism of action of mannitol on RVR.

It is likewise possible that mannitol may exert its renal vasodilatory action indirectly, that is, by releasing other vasoactive agents. Thus, in the hypoperfused rat kidney, prior treatment with cyclooxygenase inhibitors markedly attenuated the renal vasodilatory effect of mannitol [20]. During hypoperfusion, the intrarenal infusion of prostacyclin (PGI_2), but not of prostaglendin E_2 (PGE_2), resulted in an increase in RBF, and restored the renal vasodilatory response to mannitol. Interestingly, the renal vascular response to mannitol was not altered by pretreatment with an angiotensin-converting enzyme inhibitor, inhibitors of the kinin-kallikrein system or inhibitors of thromboxane synthesis. These findings suggest that in the ischemic hypoperfused rat kidney the vasodilatory response to mannitol administration is mediated largely by increased PGI_2 synthesis [20]. An additional indirect mechanism by which mannitol may exert its action on renal hemodynamics is by augmenting atrial natriuretic factor (ANF) release. It has been recently demonstrated that mannitol infusion may increase plasma levels of this vasodilatory natriuretic hormone, apparently due to the intravascular volume expansion induced by mannitol or directly by the effect of hyperosmotic perfusion [24]. It remains to be established if, and to what extent, ANF may mediate the natriuretic and vasodilatory response to mannitol.

The increased renal perfusion following mannitol is associated with a proportional increase in both cortical and medullary blood flow [16–18]. The fact that medullary blood flow is significantly increased by hypertonic mannitol may contribute to the medullary "washout phenomenon," and is consistent with the marked dissipation of medullary hypertonicity observed during osmotic diuresis [23, 25]. This, in turn, could contribute to the mechanism by which mannitol inhibits salt and water reabsorption in the loop of Henle, and also explains, in part, the obliteration of urinary concentration and dilution capacities induced by osmotic diuresis.

Influence of mannitol on glomerular filtration rate

In contrast to the increase in RBF observed during mannitol diuresis, reports of the changes in GFR are conflicting. In the dog kidney, micropuncture studies have indicated a significant decrease in single nephron glomerular filtration rate (SNGFR) associated with a similar fall in whole kidney GFR [26].

In contrast, in the human and in the rat, whole kidney GFR is either unchanged or slightly increased during mannitol infusion [23, 27, 28]. In addition to species variations, the change in GFR in response to mannitol depends largely on the baseline condition. Thus, in the hypoperfused kidney, including the dog kidney, infusion of mannitol tends to restore GFR towards normal levels [3, 19]. It appears, therefore, that several factors may influence the GFR response to mannitol administration.

The influence of mannitol on glomerular determinants in the rat kidney was evaluated by micropuncture methodology [27]. Mannitol had a consistent and profound effect upon the SNGFR in the hydropenic rat, increasing the filtration rate by 31%. This increment was due to both increase in single nephron plasma flow and a decrease in afferent arterial oncotic pressure secondary to dilution of plasma protein. More than half of the alteration in SNGFR was due to a decrease in afferent oncotic pressure, suggesting that dilution of plasma protein has a major effect on SNGFR [27].

In a more recent study [18] it was demonstrated that superficial and deep nephron filtration rates may be influenced differentially during mannitol infusion. In the latter study, whole kidney GFR remained unchanged during mannitol diuresis. However, SNGFR of superficial nephrons increased by 31% in response to mannitol infusion, whereas deep nephron SNGFR fell by approximately 40% [18]. The redistribution of GFR from juxtamedullary to superficial nephrons may be related to a decline in efferent

resistance of deep nephrons secondary to the decrease in viscosity of the blood in the vasa recta as well as in diminution of glomerular membrane permeability [18].

The effects of mannitol on GFR under circumstances of reduced renal perfusion are of major interest, both in pathophysiologic and clinical implications. Since its introduction by Selkurt in 1945 [3], mannitol has been widely used to prevent and treat experimental and clinical ARF because of its ability to maintain glomerular filtration during renal hypoperfusion. Morris et al [19] reported that in the hypoperfused rat kidney, an experimental model of prerenal failure, prior infusion of mannitol maintained glomerular filtration, which otherwise would stop when renal arterial pressure was reduced to 40 mm Hg. Moreover, when given after hypoperfusion has been induced, mannitol will re-establish glomerular filtration that has already stopped [19]. Under the same conditions, infusion of equal or greater volumes of isotonic saline did not maintain or re-establish GFR, suggesting that the effect of mannitol is probably independent of the influence of volume expansion *per se*, or the dilution of plasma protein. The authors proposed that mannitol exerted this effect by dilating the afferent arteriole, probably due to suppression of renin release and the intrarenal formation of angiotensin II [28, 29].

A possible role for mannitol in maintaining GFR during renal ischemia, by reducing endothelial cell swelling, was originally suggested by Flores et al [30]. These authors proposed that the failure of the blood flow to return to the kidney following transient ischemia, the so-called no reflow phenomenon, was due to swollen endothelial cells limiting the available vascular space. They further demonstrated that the "no reflow" and subsequent renal dysfunction were corrected by hypertonic mannitol, but not by equivalent expansion with isotonic saline or isotonic mannitol, indicating that the osmotic effects were primary [30]. More recently, Mason et [31] demonstrated by morphometric analysis that renal ischemia resulted in swelling of proximal tubular cells and thick ascending limb cells. This altered geometry led to depletion of the interstitial and vascular space in the cortex, resulting in vascular congestion, which, in turn, was responsible for the poor perfusion and impaired renal function. The injection of mannitol into the renal artery prior to ischemia reduced cell swelling and vascular congestion, and eliminated the occlusion of the thick ascending limb, thereby preventing the impairment in renal function [31].

The finding that mannitol might maintain glomerular filtration in the hypoperfused kidney is consistent with earlier observations indicating that mannitol prevented the decrease in GFR after hypotensive episodes [15, 32]. Similarly, in patients undergoing abdominal aortic aneurysmectomy [5] and open heart surgery [33], and in severely injured patients [34], mannitol has been shown to increase GFR.

It is of interest that, despite the striking protective effects of mannitol on GFR under circumstances of low renal perfusion pressure, GFR remains unchanged or even decreased in intact animals and normal volunteers infused with mannitol [15, 16, 35, 36]. These findings may imply that the beneficial actions of mannitol observed during renal hypoperfusion are probably mediated by antagonizing systems that are activated when renal perfusion is severely compromised.

Influence of mannitol on tubular salt and water reabsorption

The entire tubular length from the proximal tubule [28, 36] to the loop of Hence [18, 26, 37] to the collecting duct [18, 38] participate in the natriuretic and diuretic action of mannitol. The following are the current views on the action of mannitol along the various tubular segments.

Action of mannitol in the proximal nephron. Mannitol has no direct inhibitory effect on Na^+ transport in the proximal nephron. Rather, mannitol indirectly influences Na^+ transport by virtue of its effect on water reabsoption. The obligatory presence of mannitol in the tubular fluid retards water reabsorption along this nephron segment. As a result, the concentration of Na^+ in the tubular fluid decreases, and because cellular water content falls the concentration gradient against which Na^+ must be transported increases [4]. This in turn would diminish outward Na^+ transport, and at the same time increase the passive backflux of Na^+ into the tubule, leading consequently to a progressive reduction in net Na^+ reabsorption. When tubular Na^+ concentration reaches 30 to 40 mmol/liter below that in peritubular fluid. A limiting gradient for Na^+ transport is reached, and net Na^+ reabsorption stops [18, 26, 36, 37].

Action of mannitol in the loop of Henle. Seely and Dirks [26] were the first to indicate the importance of the loop of Henle as a predominant site of the diminished salt and water reabsorption during osmotic diuresis. Their findings were verified by others [18, 37].

It is likely that the inhibition of Na^+ reabsorption in the loop of Henle is restricted mainly to the thin ascending limb [4]. In contrast, salt reabsorption in the thick ascending limb occurs mainly by a secondary active mechanism mediated by an Na^+ $2Cl^-$ K^+ carrier [39]. Since salt reabsorption in this segment is load dependent, the increased delivery of salt and water during osmotic diuresis may actually enhance Na^+ reabsorption. This is supported by the observation that free water reabsorption is progressively increased in man during osmotic diuresis [40]. Additionally, in the rat [18] but not in the dog [26] there is a significant reabsorption of salt and water between late proximal and early distal tubular sites of superficial nephrons.

In summary, the effects of mannitol diuresis on loop function involve a marked reduction in water and salt reabsorption in the descending and thin ascending limbs, respectively, followed by incomplete recapture of the increased Na^+ tubular load in the thick ascending limb [4]. The magnitude of these effects may depend on the fitered load of mannitol as well as on species differences.

Action of mannitol on the distal tubule and collecting duct. During osmotic diuresis the delivery of salt and water to the distal tubule and collecting duct is markedly increased. However, the final segments of the nephron fail to recapture the increased delivered loads of salt and water. Apparently, the high distal flow rate overwhelms the capacity for Na^+ reabsorption in the collecting duct [4].

The function of the collecting duct during osmotic diuresis was studied by the microcatheterization and micropuncture techniques [18, 38]. Both studies demonstrated that the reabsorption of delivered salt and water was diminished in the collecting duct during mannitol diuresis. Moreover, at the medullary collecting duct mannitol had direct inhibitory influence on sodium reabsorption above and beyond its osmotic natriuretic properties [38].

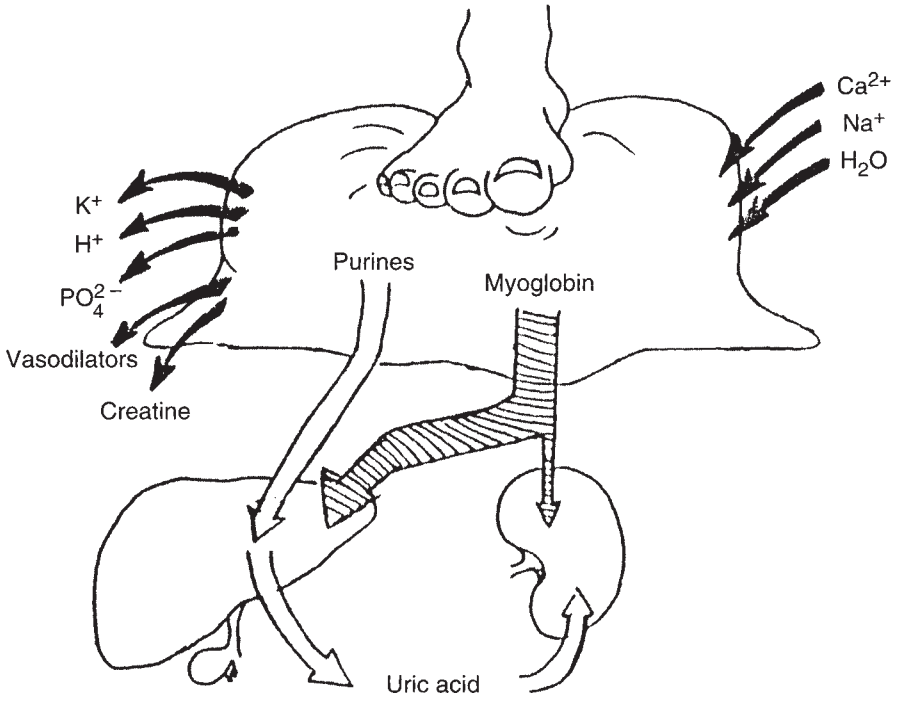

Fig. 1. Mechanism of myoglobinuric ARF following crush injury to skeletal muscle. Mechanical pressure and the resulting membrane stretch cause sarcolemmal leak. As a result extracellular water, sodium and calcium flood the myocytic cytosol leading to muscular swelling, hypovolemia and hypocalcemia. The stretched sarcolemma leaks into the extracellular fluid potassium and the nephrotoxic metabolites myoglobin, purines (precursors for urate) and phosphate [83]. Mannitol treatment (not shown in the figure) may decompress the swollen muscle, thus conceivably relieving sarcolemmal stretch and restoring its impermeability. By such muscular action and by increasing urinary elimination of nephrotoxic muscular metabolites, mannitol could reduce their pool in the extra cellular fluid and their burden on the kidney.

Action of mannitol on the transport of ions other than sodium. Mannitol may increase the urinary excretion of K^+, Ca^{2+}, Mg^{2+} and of phosphate [4, 28, 37, 41–44] parallel to its natriuretic effects.

Urinary concentration and dilution during mannitol infusion. Osmotic diuresis as in the case of hypertonic mannitol tends to abolish the ability to concentrate or to dilate the urine [4, 46, 47]. This osmotic interference with urinary concentration is due in part to medullary washout and loss of medullary hypertonicity [13, 15].

Miscellaneous effects of mannitol. In addition to the direct renal tubular, glomerular and hemodynamic effects of mannitol, this agent may influence renal function indirectly by an effect on other endocrine or local systems. As pointed out in earlier sections, the effects of hypertonic mannitol on the release of ANF [24] and vasodilatory prostaglandins [20] on the one hand, combined with the suppression of the renin-angiotensin system [48, 49], may be important factors in determining the diuretic/natriuretic actions of mannitol. Moreover, infusion of hypertonic mannitol may significantly affect local pressures within the kidney, which may secondarily influence tubular reabsorption of salt and water. Thus, direct measurements of renal interstitial pressure by chronically implanted capsules in dog kidney have clearly demonstrated a marked increase during mannitol infusion [49]. Evidently, the tubular lumen is not compressed by the increased interstitial pressure, since intratubular hydrostatic pressure is also markedly increased during mannitol infusion [50]. In fact, direct recordings of hydrostatic pressures have demonstrated a widening of the pressure gradients between the intratubular pressure in the proximal nephron and the adjacent peritubular capillaries [50]. The increased luminal hydrostatic pressure following mannitol infusion may assist in keeping the patency of the tubular lumen, and prevent its occlusion during ischemic and toxic insults to the kidney.

Beneficial extrarenal effects of hypertonic mannitol

Due to its hyperosmotic properties, mannitol may affect other systems in addition to the kidney. Some of these extrarenal effects, such as the actions on the central nervous system, the muscles and the cardiovascular system, are of major clinical importance. The following section will briefly summarize a few aspects of these extrarenal effects, some of which are based on our personal experience.

By mobilizing and redistributing fluid from edematous organs and tissues, mannitol may improve their function while at the same time expand the depleted intravascular space in human trauma casualties [9]. Studies in our laboratory have shown that mannitol may facilitate decompression of experimental compartment syndrome in the dog [51]. The decompressive effect of mannitol was presumbly due to its osmotic activity, which tended to augment fluid removal from the interstitium of the injured muscle. More recently, we have shown that hypertonic mannitol enhances recovery of injured muscle in rats with experimental crush injury induced by applying mechanical pressure on the hind limb [52]. Hypertonic mannitol caused a significant increase in twitch amplitude following direct electrical stimulation of the crushed muscle. Moreover, the effects of mannitol on the recovery from crush injury was augmented by hyperbaric oxygen treatment. Others have shown that hyperbaric oxygen is useful in the management of experimental compartment syndrome in the dog [53]. Taken together, these studies in experimental crush syndrome suggest that the combination of intravenous hypertonic mannitol and hyperbaric oxygen may, in the future, be an important adjunct in the treatment of some forms of crush injury in humans. Since mannitol decompressed post-traumatic turgid edematous muscles, it is reasonable to assume that such decrease in sarcolemmal stretch reduces the leak of muscule myoglobin

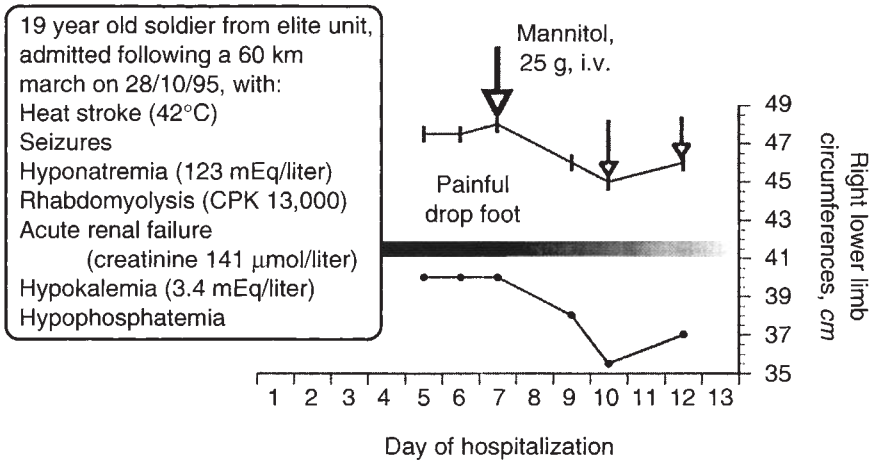

Fig. 2. Compartmental decompression with mannitol in a patient with post-exertional rhabdomyolysis. A 19-year-old army recruit from an elite unit was hospitalized with exertional rhabdomyolysis and heat stroke following a 60 km strenuous march in which he carried heavy equipment. His initial treatment did not include mannitol. On the seventh day after his admission to the hospital, his entire right lower limb became extremely painful, swollen, and hard to palpation. He also developed right sided drop foot. Intravenous mannitol therapy resulted in the disappearance of the pain within hours. The limb became softer to palpation and its circumference was reduced. The late clinical course was uneventful, and normal motor function of the right foot returned within weeks. Several months after the event, the solider recuperated completely and returned to his unit and full physical activity. Thus, the use of mannitol in this patient preempted the necessity to perform fasciotomy, which is the "standard" treatment for this complication. Had fasciotomy been performed it is doubtful whether he could have been able to return to his demanding elite unit. In our experience, fasciotomy for compartment syndrome associated with post-traumatic rhabdomyolysis carries great risk to life and limb [9]. Symbols are: (-|-) thigh; (-●-) calf. **(NOTE ADDED IN PROOF).**

urate and phosphate (Fig. 1). Thus, mannitol would reduce the load on the kidney of these nephrotoxic agents and therefore protect the kidney during rhabdomyolysis. Mannitol appears to be useful in exertional compartment syndrome in humans (Fig. 2) **(NOTE ADDED IN PROOF).**

Fasciotomy for the treatment of the compartment syndrome following crush injury carries a definite risk to life or limb [9]. A trial of i.v. mannitol may afford means of non-surgical decompression in the compartment syndrome and at least buy precious time in the setting of mass disaster where operating theaters are busy and scarce. When mannitol is not effective within an hour, then fasciotomy is indicated as a last resort to decompress intracompartmental "hypertension."

Finally, when applied in a dosage of less than 200 g/day mannitol has been used safely and widely for several decades to relieve cerebral edema and to treat increased intracranial pressure in humans. Intravenous hypertonic mannitol reduces intracranial presure and is also known to cause a definite increase in cerebral blood flow [54, 55]. An attempt was made in our hospital to correlate the decompressive effect of mannitol with central nervous system function in human victims of head trauma (Fig. 3) (M. Feinsod, unpublished observations). Thus, within 30 minutes the decompressive action of mannitol was followed by correction of the pathologic prolongation of trigeminal evoked potentials. It is likely that this normalization of evoked potentials was due to amelioration of brain edema and the decrease in intracranial pressure. However, an incidental improvement in cerebral circulation could also have contributed to the observed normalization of measured brain electrical activity.

Effects of mannitol on the cardiovascular system

The influence of mannitol in expanding extracellular and intravascular volume and improving circulatory function was alluded to in previous sections. The beneficial effect of mannitol on the circulation is due to its ability to increase venous return and cardiac preload, thus stabilizing arterial pressure and organ perfusion. However, in addition, mannitol has a direct positive inotropic effect on the heart as shown in the isolated working heart model [56, 57]. Such an effect of hypertonic solution in improving myocardial contractility may be due to the increase in intracellular calcium concentration in the myocytes exposed to hyperosmolarity [57].

Finally, mannitol has been shown to exert favorable effects on myocardial edema and infarct size in experimental models of myocardial infarction and reperfusion. Thus, intracoronary perfusion with hyperosmotic mannitol significantly reduced the early myocardial edema and infarct size following coronary occlusion and reperfusion [58]. In another study, mannitol-treated hearts demonstrated improved postischemic left ventricular function, greater coronary blood flow and improved structural preservation compared with hearts reperfused with isoosmotic solutions [59]. It was postulated that early treatment with mannitol during postischemic reflow prevented cell swelling, therby maintaining cell voulume and enhancing myocardial viability. However, other mechnisms, not related directly to the osmotic properties of mannitol, such as its action as a potent hydroxyl free radical, scavengers may also be involved in protecting the ischemic myocardium [11]. However, mannitol does not enter cells and

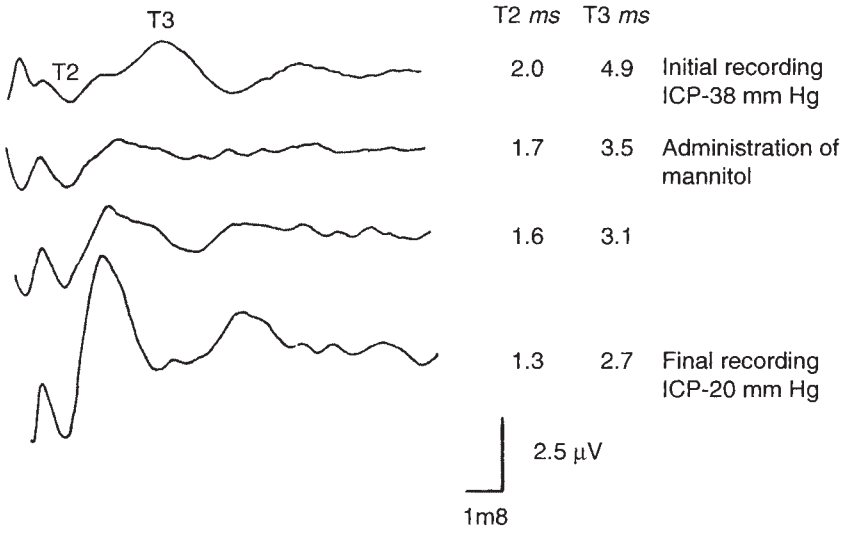

Fig. 3. Decompression of cerebral edema with mannitol. In a patient with post-traumatic cerebral edema, the effect of i.v. hypertonic mannitol infusion on intracranial pressure was measured by direct manometry (intra-cerbral pressure, ICP). Trigeminal evoked potentials (TEP) were also monitored. The upper curve taken during increased intracranial pressure shows decreased amplitude and slowing of the TEP wave pattern. The lower panels show progressive normalization of TEP following cerebral decompression induced by mannitol (Prof. M. Feinsod, Chief of Neurosurgery, Rambam Hospital, Haifa, personal communication, 1994) [85].

it is therefore not clear how it exerts intracellular scavenging activity.

Clinical use of mannitol

Extrarenal applications of mannitol. Mannitol is used in the prophylaxis and treatment of acute renal failure, for the reduction of pressure and volume of the cerebrospinal fluid and in ophthalmology for short-term reduction of intraocular pressure and vitreous volume. Some authors consider mannitol to be the most effective drug for reducing intracranial pressure associated with Reye's syndrome [60]. It is also indicated as an urinary bladder irrigant during transurethral prostate resection or bladder surgery to prevent hemolysis. In hemodialysis, mannitol infusion can be helpful in correcting cramps and hypotension associated with ultrafiltration. Cerebral edema and ophthalmoplegia due to diabetic ketoacidosis may be reversed by prompt therapy with mannitol [61]. Furthermore, mannitol can be used to enhance the excretion of drugs in intoxications (such as with barbiturate, bromide, or aspirin) [62]. The combination of mannitol and normal saline infusion has been used safely and effectively to treat the cerebral edema and hyponatremia associated with water intoxications in infants and children [63].

Pharmacokinetics. After oral administration approximately 20% of mannitol is absorbed [64]. Following intravenous administration mannitol is rapidly distributed primarily in the extracellular space [65, 66] and excreted unchanged in the urine, undergoing no metabolism [60]. The onset of diuresis or decrease in intracranial pressure occurs within 15 to 30 minutes after i.v. administration [64, 67]. The drug does not cross the blood brain barrier, its volume of distribution is 0.471/kg [68], and its half-life 70 to 100 minutes [60].

Dosage. To treat oliguria 50 to 200 g mannitol may be used intravenously as a 15% to 20% solution over 24 hours. To reduce intracranial or intraocular pressure the usual dose is 1.5 to 2 g/kg intravenously over 30 to 60 minutes as a 20% solution. When used to enhance the excretion of toxins the total dose should not exceed 200 g/day. In pediatric patients (17 years of age and younger) the maximum recommended dose is 2 g/kg [69]. Anuric patients should not routinely receive mannitol. However, a small single test dose of 12.5 g of mannitol may be given in the hope of starting diuresis.

USE OF MANNITOL FOR THE PREVENTION OF ACUTE RENAL FAILURE

One of the most common forms of ischemic ARF, and certainly the best monitored in clinical practice, is associated with kidney transplantation, particularly from cadaver donors. Well controlled prospective studies have clearly shown that mannitol has a distinct value in protecting graft function [7, 8, 70]. Furthermore, 20 years of experience in the improvement of *ex-vivo* kidney preservation solutions indicate that the addition of mannitol, or otherwise insuring hypertonicity of the perfusate (320 to 350 mOsm/kg) is critical to the efficacy of prevention of post-transplant ARF [70, 71]. One group considered mannitol in the perfusate as "indispensable" [7] for the prevention of ischemic ARF in the graft.

Mannitol also protects the kidney against radiocontrast nephropathy during heart catheterization in nondiabetic nonuremic subjects [72]. However, under the same procedure mannitol may aggravate radiocontrast nephrotoxicity in diabetic and in uremic subjects [72, 73].

In an authoritative, exhaustive review on prophylactic interventions in ARF, Conger [1] concedes that mannitol is of proven usefulness in the management of post-transplant ARF. He could not, however, document clear cut benefits of mannitol in the prevention of clinical ARF outside the sphere of organ transplantation.

Since mannitol ameliorates experimental myoglobinuric ARF as well as ischemic ARF [74, 75] and since there has been partial success with in the mannitol prevention of myoglobinuric ARF in man [76], we decided to use this agent to supplement volume replacement in casualties with the crush syndrome who were referred to us from the Southern Lebanon front (1982-1983). That front is less than 50 miles from our hospital in Haifa, so that we could see casualties and start treatment early, following extrication from accidental burial under collapsed buildings.

During the search for survivors, when a limb was excavated an i.v. line was immediately secured, and lactated Ringer's solution

Table 1. Actions of mannitol in the prophylaxis of post-traumatic acute renal failure

Extrarenal
- Extracellular volume expansion with attendant increase in cardiac output and stabilization of mean arterial pressure.
- Increased cardiac contractility [56, 57].
- Stimulation of atrial natriuretic factor release [24].
- Reduction of skeletal muscle cell edema and decompression of muscle tamponade in the compartment syndrome [51, 52]. Possible reduction of leakage of myoglobin and purine and phosphate from injured muscles. Reduced filtered load of myoglobin urate, and phosphate [83], all of which are nephrotoxic, indirectly protects the kidneys.
- Restoration of normal tonus of the dilated blood vessels in crushed muscles [80] and tilting the capillary Starling forces to favor of extracellular fluid reabsorption.

Renal
- Decrease in blood viscosity and in oncotic pressure across the glomerulus, causing an increase in glomerular filtration rate [16].
- Dilation of glomerular capillaries and stimulation of prostaglandin E and I release [20].
- Increase in proximal intratubular urine flow and prevention of obstruction [26, 74].
- Possible reduction of tubular cell swelling and injury [30, 31].
- Accelerated clearance of myoglobin, phosphate and urate from the body [74].
- Scavenging of oxygen-free radicals [10, 11].
- Massive i.v. dose of mannitol >200 g/day have been reported to cause acute renal [78, 79, 81] failure in rare cases. This type of ARF is promptly reversible following hemodialysis [78, 84].

was infused at a rate of 1.5 liters/hr. It usually took between 4 to 8 hours to complete the extrication before the casualty was made transportable to the hospital. Once urine flow started, further i.v. volume replacement was instituted at a rate of about 15 liters/day, supplemented by mannitol (200 g/day 20% solution), and alkalinization with bicarbonate.

With this regimen we were able to prevent myoglobinuric ARF in casualties suffering from the crush syndrome who were trapped under debris for 6 to 32 hours. Other casualties with the crush syndrome of similar severity, to whom i.v. fluids could not be given after more than six hours following release, all developed myoglobinuric ARF [9].

The favorable effects of mannitol in casualties with the crush syndrome may be due to its effect on the muscle as well as direct renal effect. Thus, mannitol can decompress swollen muscles and restore muscular contractility in experimental muscle crush injury (Fig. 1, Table 1) [51, 52]. Such protective action of mannitol on crushed skeletal muscles could conceivably reduce the sarcolemmal stretch and leak of myoglobin, purines and phosphate and thus lower the burden of these nephrotoxic muscle metabolites on the kidney. By increasing urinary clearance of myoglobin urate and phosphate, mannitol may further accelerate the elimination of extracellular pool of these metabolites. At the kidney level mannitol is thought to decrease tubular cell swelling [30, 31], thus increasing tubular flow and the dislodgment and flushing of obstructive nephortoxic myoglobin casts. Hence the use of manniol in the management of the crush syndrome appears theoretically justified.

The relative importance of each component of our regimen for the prevention of myoglobinuric ARF in humans (timing, rate of infusion, solute and alkali content of i.v. fluids), cannot be determined at present. In view of the favorable outcome of our i.v. strategy, however, we will continue to use it in the foreseeable future, with the knowledge that some of its ingredients may be redundant. Our regimen for the prevention of myoglobinuric ARF has also been adopted by the ARF Task Force of the International Society of Nephrology (Co-Chaired by N. Lemeire, Ghent, Belgium and Kim Solez, Edmonton, Alberta, Canada. The proceedings of the International Meeting on "Renal Aspects of Disaster Relief," held May 1996 in Macedonia, is in *Renal Failure*, in press).

Table 2. Mannitol nephrotoxicity

1. Occurs only following high dose of mannitol (> 200 g/day)
2. Resembles vasomotor ARF
3. Prompt recovery following hemodialysis
4. Apparently associated with decompression of increased intracerebral or intraocular pressure

Data are from Gadallah et al, *Am J Med Sci* 309:219–222, 1995 (case report and review; $N = 10$). Used with permission.

ADVERSE REACTIONS TO MANNITOL

Rapid administration of mannitol causes expansion of the extracellular fluid (ECF) and may in extreme cases precipitate congestive heart failure or pulmonary edema particulary when renal failure is established.

Administration of mannitol in dosage far in excess of 200 g/day has on rare occasions produced ARF (Table 2) [77–79].

Most of these patients received mannitol to decompress increased intra-cerebral or ocular pressures. Mannitol induced ARF in humans appear to be of the vasomotor (renal constrictor) type and responds promptly to removal of mannitol by hemodialysis treatment [78, 79]. It thus appears that whereas low doses of mannitol have renal vasodilator effects, high doses of mannitol are renal vasoconstrictor [21] to the point of precipitating ARF. Furthermore, mannitol diuresis can increase renal energy demands for Na reabsorption and so conceivably deplete ATP stores, thus rendering the kidney susceptible to ARF.

It should be re-emphasized that severe clinical complications following mannitol treatment occur rarely and only following massive doses of mannitol 400 to 900 g/day [78, 80, 81].

In the late sixties there was some concern that the hypertonicity of mannitol could damage erythrocytes. There is no clinical evidence that such damage occurs *in vivo,* particularly if mannitol solution is given i.v. directly and not added to transfused blood. Similarly, hyperkalemic effects of i.v. mannitol infusion have not been reported to our best of knowledge.

Mannitol administration may aggravate radiocontrast nephropathy in diabetic patients undergoing cardiac catheterization [72, 73].

Furthermore, 0.45% saline provided better protection against radiocontrast nephropathy than mannitol in patients with chronic renal failure [72, 73]. Thus, the use of mannitol for prephylaxis against radiocontrast nephropathy is not recommended in patients with diabetes or chronic renal failure. Mannitol, however, does offer protection against radiocontrast nephropathy in nondiabetic nonuremic patients [72].

It should be noted that 11 of 20 patients with myoglobinuric ARF of various etiologies were refractory to mannitol bicarbonate infusion started from 24 to 28 hours after admission [76].

Hyperkalemia caused by hypertonicity

An increase in plasma osmolarity, such as that caused by the presence of mannitol in the plasma or hyperglycemia, may cause a shift of water and potassium by solvent drag from the intracellular to the extracellular space. We have observed such a shift in humans when performing tests to assess the maximal tubular capacity to reabsorb water, which was done by infusion of hypertonic mannitol and antidiuretic hormone. The resulting hyperkalemia was usually mild, and rarely exceeded 1.0 mEq/liter. In clinical practice, one rarely encounters hyperkalemia during hypertonic mannitol infusion, because the kaluretic properties of mannitol apparently override the hyperkalemia caused by solvent drag [82].

The paradox of "osmotic nephrosis" (reviewed by Gadallch and Lynn, [78])

A large dose (2 to 4 g/kg body wt) of mannitol given to rabbits causes swelling and vacuolization of proximal tubular cells. Similar tubular changes were occasionally seen in renal biopsies from patients undergoing mannitol diuresis. These structural tubular changes were not apparently associated with impairment of renal function. If mannitol is capable of causing tubular swelling in normal kidneys, how does it protect against tubular epithelial swelling in impending ARF [31]? There is no explanation at present to reconcile this paradox. Furthermore, ARF following excessive dosage of mannitol resembles vasomotor nephropathy rather than toxic nephropathy.

NOTE ADDED IN PROOF

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REFERENCES

1. CONGER JD: Interventions in clinical acute renal failure: What are the data? *Am J Kid Dis* 26:565–576, 1995
2. SMITH H: Renal excretion of hevitols and their derivatives and of endogenous creatinine like chromogen in dog and man. *J Biol Chem* 135:231–250, 1940
3. SELKURT EE: Changes in renal clerance following complete ischemia of kidney. *Am J Physiol* 144:395–403, 1945
4. GENNARI FJ, KASSIRER JP: Osmotic diuresis. *N Engl J Med* 291:714–720, 1974
5. BARRY KC, COHEN A, KNOCHEL JP, WHELAN TJ, BEISEL WR, VARGAS CA, LEBLANC PC: Mannitol infusion II. The prevention of acute functional renal failure during resection of an aneurysm of the abdominal aorta. *N Engl J Med* 264:967–971, 1961
6. MYERS BD: Nature of postischaemic renal injury following aortic or cardiac surgery, in *Acute Renal Failure in the Intensive Therapy Unit*, edited by BIHARI D, NIELD G, London, Springer Verlag, 1990, pp 167–180
7. VAN VALENBERG PLJ, HOITSMA AJ, TIGGELER RGWL: Mannitol as an indispensible constituent of intraoperative hydration protocol for the prevention of acute renal failure after renal cadaueric transplantation. *Transplantation* 44:784–788, 1987
8. COLLINS GM, WICOMB WN: New organ preservation solutions. *Kidney Int* 42(Suppl 38):S197–S202, 1992
9. BETTER OS, STEIN JH: Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med* 322:825–829, 1990
10. DELMAESTRO RF, THAW HH, BJORK J, PLANKER M, ARFORS KE: Free radicals as mediators of tissue injury. *Acta Physiol Scand* 492(Suppl I):43–46, 1980
11. MAGOVERN GJ JR, BOLLING SF, CASALE AS, BULKLEY BH, GARDNER TJ: The mechanism of mannitol in reducing ischemic injury: Hyperosmolarity or hydroxyl scavenger? *Circulation* 70(Suppl I):91–95, 1984
12. WESSON LG JR, ANSLOW WP JR: Excretion of sodium and water during osmotic diuresis in the dog. *Am J Physiol* 153:465–474, 1948
13. GOLDBERG M, RAMIREZ MA: Effects of saline and mannitol diuresis on the renal concentrating mechanism in dogs: Alterations in renal tissue solutes and water. *Clin Sci* 32:475–493, 1967
14. LILLIEN OM, JONES SG, MUELLER CB: The mechanism of mannitol diuresis. *Surg Gynecol Obstet* 117:221–228, 1963
15. BRAUN WE, LILIENFIELD LS: Renal hemodynamic effects of hypertonic mannitol infusions. *Proc Soc Exp Biol Med* 114:1–6, 1963
16. STAHL WM: Effect of mannitol on the kidney. Changes in intrarenal hemodynamics. *N Engl J Med* 272:381–386, 1965
17. VELASQUEZ MT, NOTARGIACOMO AV, COHN JN: Comparative effects of saline and mannitol on renal cortical blood flow and volume in the dog. *Am J Physiol* 224:322–327, 1973
18. BUERKERT J, MARTIN D, PRASAD J, TRIGG D: Role of deep nephrons and the terminal collecting duct in a mannitol-induced diuresis. *Am J Physiol* 240(Renal Fluid Electrol Physiol 9):F411–F422, 1981
19. MORRIS CR, ALEXANDER EA, BRUNS FJ, LEVINSKY NG: Restoration and maintenance of glomerular filtration by mannitol during hypoperfusion of the kidney. *J Clin Invest* 51:1555–1564, 1972
20. JOHNSTON PA, BERNARD DB, PERRIN NS, LEVINSKY NG: Prostaglandins mediate the vasodilatory effect of mannitol in the hypoperfused rat kidney. *J Clin Invest* 68:127–133, 1981
21. TEMES SP, LILIEN OM, CHAMBERLION WA: direct vasoconstrictor of mannitol on the renal artery. *Surg Gynecol Obst* 141:223–226, 1975
22. LILIEN OM: The paradoxical reaction of renal vasculature to mannitol. *Invest Urol* 10:346–353, 1973
23. GOLDBERG AH, LILIENFIELD LS: Effects of hypertonic mannitol on renal vascular resistance. *Proc Soc Exp Biol Med* 119:635–642, 1965
24. YAMASAKI Y, NISHIUCHI T, KOJIMA A, SAITO H, SAITO S: Effects of an oral water load and intravenous administration of isotonic glucose, hypertonic saline, mannitol and furosemide on the release of atrial natriuretic peptide in men. *Acta Endocrinol (Copenh)* 119:269–278, 1988
25. MALVIN RL, WILDE WS: Washout of renal countercurrent Na gradient by osmotic diuresis. *Am J Physiol* 197:177–180, 1959
26. SEELY JF, DIRKS JH: Micropuncture study of hypertonic mannitol diuresis in the proximal and distal tubule of the dog kidney. *J Clin Invest* 48:2330–2340, 1969
27. BLANTZ RC: Effect of mannitol on glomerular ultrafiltration in the hydropenic rat. *J Clin Invest* 54:1135–1143, 1974
28. MALNIC G, KLOSE R, GIEBISH G: Micropuncture study of the distal tubular potassium and sodium transport in the rat nephron. *Am J Physiol* 211:529–547, 1966
29. FOJAS E, SCHMID HE: Renin release, renal autoregulation and sodium excretion in the dog. *Am J Physiol* 219:464–468, 1970
30. FLORES J, DIBONA DR, BECK CH, LEAF A: The role of cell swelling in ischemic renal damage and the protective effect of hypertonic solute. *J Clin Invest* 51:118–126, 1972
31. MASON J, LOERIS B, WELSCH J, KRIZ W: Vascular congestion in ischemic renal failure: The role of cell swelling. *Miner Electrol Metab* 15:114–124, 1989
32. PETERS G, BRUNNER H: Mannitol diuresis in hemorrhagic hypotension. *Am J Physiol* 204:555–562, 1963
33. ETHEREDGE EE, LEVITIN HL, NAKAMURA K, GLENN WWL: Effect of mannitol on renal function during open heart surgery. *Ann Surg* 161:53–62, 1965
34. VALDES ME, LANDAU SE, SHAH DM, NEWELL JC, SCOVILL WA, STRATTON H, RHODES GR, POWERS SR JR: Increased glomerular filtration rate following mannitol administration in man. *J Surg Res* 26:473–477, 1979
35. WILLIAMS TF, HOLLANDER W JR, STRAUSS MB, ROSSMEISL EC, MCLEAN R: Mechanism of increased renal sodium excretion following mannitol infusion in man. *J Clin Invest* 34:595–601, 1955
36. WINDHAGER EE, GIEBISCH G: Micropuncture study of renal tubular transfer of sodium chloride in the rat. *Am J Physiol* 200:581–590, 1961
37. WONG NLM, QUAMME GA, SUTTON RAL: Effects of mannitol on water and electrolyte transport in the dog kidney. *J Lab Clin Med* 94:683–692, 1979
38. SONNENBERG H: Effects of furosemide, acetazolamide, and mannitol

on medullary collecting-duct function in the rat kidney. *Pflügers Arch* 373:113–123, 1978
39. GREGER R: Ion transport mechanism in thick ascending limb of Henle's loop of mammalian nephrons. *Physiol Rev* 65:760–797, 1985
40. GOLDBERG M, MCCURDY D, RAMIREZ M: Differences between saline and mannitol diuresis in the hydropenic man. *J Clin Invest* 44:182–192, 1965
41. WESSON LG: Magnesium, calcium and phosphate excretion during osmotic diuresis in the dog. *J Lab Clin Med* 60:422–432, 1962
42. DUARTE CG, WATSON JF: Calcium reabsorption in proximal tubule of the dog nephron. *Am J Physiol* 212:1355–1360, 1967
43. BETTER OS JR, GONICK HC, CHAPMAN LC, VARADY PD, KLEEMAN CR: Effect of urea-saline diuresis in renal clearance of calcium, magnesium, and inorganic phosphate in man. *Proc Soc Exp Biol Med* 121:592–596, 1966
44. MAESAKA JK, BERGEN ML, BORNIA ME, ABRAMSON RB, LEVITT MF: Effect of mannitol on phosphate transport in intact and acutely thyroparathyroidectomized rats. *J Lab Clin Med* 87:680–691, 1976
45. STINEBAUGH BJ, BARTOW SA, EKNOYAN G, MARTINEZ-MALDONADO M: Renal handling of bicarbonate: Effect of mannitol diuresis. *Am J Physiol* 220:1271–1274, 1971
46. GOLDBERG M: The renal physiology of diuretics, in *Handbook of Physiology, Renal Physiology*, edited by ORLOFF J, BERLINER RW, Washington DC, American Physiological Society, 1973, pp 1003–1031
47. WESSON LG JR, ANSLOW WP: Effect of osmotic and mercurial diuresis on simultaneous water diuresis. *Am J Physiol* 170:255–269, 1952
48. VANDER AJ, MILLER R: Control of renin secretion in the anesthetized dog. *Am J Physiol* 207:537–546, 1964
49. OTT CE, NAVAR LG, GUYTON AC: Pressures in static and dynamic states from capsules implanted in the kidney. *Am J Physiol* 221:394–400, 1971
50. BRENNER BM, TROY JL, DAUGHARTY TM: Pressures in cortical structures of the rat kidney. *Am J Physiol* 222:246–251, 1972
51. BETTER OS, ZINMAN C, REIS DN, HAR-SHAI Y, RUBINSTEIN I, ABASSI Z: Hypertonic mannitol ameliorates intracompartmental tamponade in model compartment syndrome in the dog. *Nephron* 58:344–346, 1991
52. RUBINSTEIN I, KEREM D, MELAMED Y, BETTER OS: Hyperbaric O_2 and mannitol enhance recovery from muscle crush injury, in *Proceedings of the 19th Annual Meeting of the European Underwater Biomedical Society on Diving and Hyperbaric Medicine*, edited by REINERTSEN RE, BRUBAKK AO, BOLSTAD G, Trondheim, 17–20 Aug, 1993, pp 137–141
53. STRAUSS MB, HARGENS AR, GERSHUNI DH, HART GB, AKESON WH: Delayed use of hyperbaric oxygen for treatment of a model anterior of compartment syndrome. *J Orthop Res* 4:108–111, 1986
54. JOHNSTON IH, PATERSON A, HARPER AM, JENNET WB: The effect of mannitol on ICP and CBF, in *Intracranial Pressure*, edited by BROCK M, DIETZ H, Berlin, Heidelberg, New York, Springer Verlag, 1972, pp 176–180
55. MILLER JD: The effects of hyperbaric oxygen at 2 and 3 atmospheres absolute and intravenous mannitol on experimentally increased intracranial pressure. *Eur Neurol* 10:1–11, 1973
56. BEN-HAIM SA, EDOUTE Y, HAYAM G, BETTER OS: Sodium modulates inotropic response to hyperosmolarity in isolated working rat heart. *Am J Physiol* 263(Heart Circ Physiol 32):H1154–H1160, 1992
57. BEN-HAIM SA, HAYAM G, EDOUTE Y, BETTER OS: Effect of hypertonicity on contractility of isolated working rat left ventricle. *Cardiovasc Res* 26:379–382, 1992
58. GARCIA-DORADO D, THEROUX P, MUNOZ R, ALONSO J, ELIZAGA J, FERNANDEZ-AVILES F, BOTAS J, SOLARES J, SORIANO J, DURAN JM: Favorable effects of hyperosmotic reperfusion on myocardial edema and infarct size. *Am J Physiol* 262:H17–H22, 1992
59. LUCAS SK, GARDNER TJ, FLAHERTY JT, BULKLEY BH, ELMER EB, GOTT VL: Beneficial effects of mannitol administration during reperfusion after ischemic arrest. *Circulation* 62(Suppl I):34–41, 1980
60. REYNOLDS JEF (editor): *Martindale: The Extra Pharmacopoeia* (CD-ROM version). Denver, Micromedex, 1990
61. FRANKLIN B, LUI J, GINSBERG-FELLNER F: Cerebral edema and ophthalmoplegia reversed by mannitol in a new case of insulin-dependent diabetes millitus. *Pediatrics* 69:87–90, 1982
62. WERREN SE, BLANTZ RC: Mannitol. *Arch Intern Med* 141:493–497, 1981
63. NUTMAN J, HILL JH: Treatment of water intoxication with mannitol. (letter) *Am J Dis Child* 146:1130–1131, 1992
64. REILLY MJ (editor): *Pocket Consultant: Diuretics*. Washington DC, American Society of Hospital Pharmacists, 1976
65. GRABIE MT, GIPSTEIN RM, ADAMS DA, HEPNER W: Contraindications for mannitol in aphakic glaucoma. *Am J Ophthalmol* 91:265–267, 1981
66. GILMAN AG, GOODMAN LS, RALL TW, MURAD F (editors): *Goodman and Gilman's The Pharmacological Basis Of Therapeutics* (7th ed). New York, Macmillan, 1985
67. MADSEN PO, KNUTH OE, WAGENKNECHT LV, ET AL: Induction of diuresis following transurethral resection of the prostate. *J Urol* 104:735–738, 1970
68. CLOYED JC, SNYDER BD, CLEEREMANS B, BUNDLIE SR, BLOMQUIST CH, LAKATUA TJ: Mannitol pharmacokinetics and serum osmolality in dogs and humans. *J Pharmacol Exp Ther* 236:301–306, 1986
69. ANON: *Guidelines for Administration of Intravenous Medications to Pediatric Patients* (2nd ed). Bethesda, American Society of Hospital Pharmacists, 1984
70. GRINO JM, MIRAVITLLES R, CASTELAO AM: Flush solution with mannitol in the prevention of post transplant renal failure. *Transplant Proc* 19:4140–4142, 1987
71. BONVENTRE JV, WEINBERG JM: Kidney preservation ex vivo for transplantation. *Annu Rev Med* 43:523–553, 1992
72. WEISBERG LS, KURNIK PB, KURNIK BRC: Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int* 45:259–265, 1994
73. SOLOMON R, WERNER C, MANN D, D'ELIA RNJ, SILVA P: Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 331:1416–1420, 1994
74. ZAGER RA: Rhabdomyolysis and myohemoglobinuria in acute renal failure. (Perspectives in Clinical Nephrology) *Kidney Int* 49:314–326, 1996
75. BURKE TJ, ARNOLD PE, SCHRIER RW: Prevention of ischemic acute renal failure with impermeant solutes. *Am J Physiol* 244:F646–F650, 1983
76. ENEAS F, SCHOENFELD PY, HUMPHRIES MH: The effect of infusion of mannitol sodium bicarbonate on the clinical course of myoglobinuria. *Arch Int Med* 139:801–805, 1979
77. WARREN SE, BLANTZ RC: Mannitol. *Arch Intern Med* 141:493–497, 1981
78. GADALLAH MF, LYNN M: Case Report: Mannitol and nephrotoxicity syndrome. Role of hemodialysis and postulate of mechanism. *Am J Med Sci* 309:219–222, 1995
79. DORMAN HR, SONDHEIMER JH, CADNAPAPHORNCHAI P: Mannitol induced acute renal failure. *Medicine* 69:153–159, 1980
80. RUBINSTEIN I, ONN E, WINAVER J, BETTER OS: Mannitol impproves the circulatory deffect in experimental crush injury. (abstract) *J Am Soc Nephrol* 6:475, 1995
81. GOLDWASSER P, FOTINO S: Acute renal failure following massive mannitol infusion. *Arch Intern Med* 144:2214–2216, 1984
82. MORENO M, MURPHY C, GOLDSMITH C: Increase in serum potassium resulting from the administration of hypertonic mannitol and other solutions. (abstract) *J Lab Clin Med* 73:291, 1969
83. BOLES JM, DUTEL JL, BRIERE J, MIALON P, ROBASCKIEWICZ M, GARRE M, BRIERE J: Acute renal failure caused by extreme hyperphosphatemia after chemotherapy of an acute lymphoblastic leukemia. *Cancer* 53:2425–2429, 1984
84. NAKHOUL F, BETTER OS: Acute renal failure following massive mannitol infusion and enalapril treatment. *Clin Nephrol* 44:118–120, 1995
85. BETTER OS, RUBINSTEIN I, WINAVER J: Osmotic diuretics: mannitol, in *Handbook of Experimental Pharmacology* (vol 119), edited by GREGER RF, KNAUF H, MUTSCHLER E. Berlin, Springer Verlag, 1995, pp 421–441