13. Medications

Overview and Purpose

As a general rule, we assume that restoring circulation in a cryonics case will not be sufficient to maintain cellular viability, even in conjunction with hypothermia. (For information on the limits of CPS, consult the chapter on cardiopulmonary support.) We advocate administering medications to cryonics patients, after death has been pronounced, in pursuit of two primary goals:

1. To **promote circulation** by

a) improving blood flow

b) restoring volume.

2. To **inhibit processes which tend to cause cellular injury** in

a) the brain and

b) cells in general.

Note that *the first objective must be satisfied in order to achieve the second objective*. The circulatory system must remain open and unobstructed (in particular, free from blood clotting or sludging) to allow other medications to reach the brain. Even more important, the circulatory system must remain unobstructed to enable subsequent cryoprotective perfusion. If perfusion is not possible, all our efforts to avoid cellular injury may be nullified by massive ice damage when the patient is cryopreserved.

Medications therefore are not an "optional extra" to augment rapid cooling and cardiopulmonary support if the team can find time for them.

Whenever team members have access to the patient these two medications (as an absolute minimum) should be regarded as essential:

1. **Citrate**, an anticoagulant that prevents formation of blood clots.

2. **Heparin**, an anticoagulant that prevents formation of blood clots.

Administering medications is a greater challenge than inducing hypothermia or applying cardiopulmonary support. Training is required, and judgment must be exercised. Logistical issues and problems associated with preparation of medications will add to the challenge when the team attempts to administer the full recommended range.

Source and Validation

Dr. Peter Safar, whose book *ABC of Resuscitation* popularized the concept of CPR in 1957, established the International Resuscitation Research Center (now the University of Pittsburgh Safar Center for Resuscitation Research) in 1979. In a series of experiments he demonstrated the effectiveness of high perfusion pressures and hemodilution, in conjunction with mild hypothermia, to restore cerebral circulation and revive animals after periods of ischemia following cardiac arrest.

In 1992, researchers Mike Darwin and Steven B. Harris MD ran a series of groundbreaking medications experiments to inhibit the toxic cascade of biochemical reactions that normally follows cardiac arrest. In some of their work they coupled this approach with the induction of mild hypothermia which Safar had pioneered. They were able to resuscitate dogs without measurable cognitive deficit after more than 14 minutes of arrest, with one animal recovering after more than 15 minutes.

The medications which we recommend for cryonics patients are those which were used in all three series of trials by Darwin and Harris. While the efficacy of each of these medications has not been individually established, we believe there is reasonable evidence that the full set of drugs enabled resuscitation without measurable cognitive deficit after a longer period of

arrest than has been achieved in any other known resuscitation research, using a canine model.

Prior History

Additional medications have been used in cryonics cases in the past, but have been dropped from cryonics protocol. These include neuromuscular blocking/anti-shivering agents, calcium channel blockers, iron chelators, and cell membrane stabilizers. In 2002 cryonics researcher Mike Darwin proposed the protocol which we reproduce below for historical purposes and future research.

Proposed 2002 Alcor Stabilization Medications Protocol

1. Vasopressin
2. Epinephrine
3. K-PEP Phosphoenol Pyruvate(PEP)
4. Propofol
5. Heparin,
6. Vital-Oxy
7. 4-Hydroxy TEMPO (TEMPOL)
8. Cyclotrol (Acetylsalicylic Acid and Ketorolac)
9. SMT (S-Methyl Isothiourea)
10. Dilazep
11. Acetyl-L-carnitine (ALCAR)
12. MIA (5 (N-Methyl-N-Isobutyl)-Amiloride
13. Lidocaine & Magnesium Chloride
14. Tacrolimus (Prograf)
15. Ethyl Pyruvate
16. FBP & DB-CAMP (d-Fructose 1.6-diphosphate & Dibutyryl Cyclic AMP)
17. Streptokinase
18. Trifluoperazine
19. Minocycline Hydrochloride
20. PARP-X (3-amino benzamide)
21. Vercuronium
22. Maalox

23. Tromethamine (THAM) OR Dextran-40 & THAM (Tromethamine)
24. Mannitol-Dextran-40 Injection
25. MicroThrx (Pluronic F-68)

Current Full Stabilization Medications Protocol

We list the following medications in the sequence which we believe would be optimal during a cryonics case. The rationale for this sequence, and circumstances which may cause the team to deviate from it, are described below.

Small Volume Medications

1. Propofol (200 mg - fixed dosage). Propofol is a general anesthetic and is used for two reasons. The first reason is to reduce metabolism of the brain to reduce oxygen and glucose requirements, and the second reason is to prevent the theoretical possibility of recovery of awareness due to aggressive cardiopulmonary support.

2. Sodium Citrate (10 grams for patients < 40 kg, 20 grams for patients > 40 kg). Citrate is an anticoagulant that prevents the formation of blood clots that can interfere with blood circulation and cryoprotective perfusion. By chelating calcium, it also prevents autoresuscitation of the heart. It is administered as a custom formulation of 20% w/v sodium citrate in water, packaged in 50 mL sterile vials.

3. Heparin (50,000 IU – fixed dosage). Heparin is an anticoagulant that prevents the formation of blood clots that can interfere with blood circulation and cryoprotective perfusion. Heparin loses effectiveness at low pH (pH < 6.7), so control of pH is important during a cryonics stabilization. This is why other anticoagulants are also important.

4. Vasopressin (40 IU – fixed dosage, second 40 IU dose concurrent with Vital-Oxy). Vasopressin is *a vasopressor* that is used to increase blood pressure during cardiopulmonary support. There is no need to

administer vasopressin if the patient's temperature is near or below +20 degrees C at time of administration as it is ineffective at cold temperatures.

5. **Minocycline** (200 mg- fixed dosage dissolved in 10 mL saline). Minocycline is a broad spectrum bacteriostatic antibiotic and free radical scavenger with good tissue and brain penetration that possesses a broad variety of neuroprotective properties including inhibition of metalloproteinases, iNOS, PARP, mitochondrial cytochrome c release and, apoptosis.

6. **SMT (S-methyl-isothiourea)** (400 mg – fixed dosage dissolved in 10 mL saline). SMT is a neuroprotectant (iNOS inhibitor) that is used to protect the brain from ischemic injury. SMT also raises blood pressure.

Large Volume Medications

7 & 10. **Decaglycerol/THAM** (2 x 200 ml- fixed dose). Decaglycerol is a glycerol polymer used to osmotically inhibit cerebral edema similar to mannitol. THAM is a buffer that is used to mitigate acidosis. Decaglycerol/THAM is administered as a custom formulation of 20% w/v decaglycerol and 4.5% w/v THAM (tromethamine) in water, packaged in 2x 200 ml sterile vials. The first 200 ml dose should be administered (I.V. push) after completion of small volume medications administration, and the second 200 ml dose is to be administered upon completion of administration of all other medications.

8. **Vital-Oxy (formerly known as Oxynil)** (0.7 ml/kg up to 70 mL, dissolved in 150 mL saline). Vital-Oxy is a proprietary mixture of antioxidants and an anti-inflammatory agent developed by Critical Care Research, Inc., each mL of which contains 3.23 mg PBN (alpha Phenyl t-Butyl Nitrone), 1.55 mg melatonin, 195 IU d-alphatocopherol (vitamin E), and 1.55 mg carprofen in an emulsion of Cremophor EL and 155 mg ethanol in water.

Fluids That Require Gastric Administration

> **9. Maalox** (250 ml – fixed dosage). Maalox is an antacid that is used to stabilize the pH of stomach contents to prevent erosion of the stomach wall by hydrochloric acid at low temperatures. Failure to prevent this can lead to contamination of the circulatory system with stomach contents and abdominal swelling during later perfusion.

Optional Medication

> **11. Hetastarch** (250 ml – fixed dosage). Hetastarch is a volume expander used to restore volume in dehydrated patients and increase cerebral perfusion during CPS.

Washout Medication

> **12. Streptokinase** (250,000 IU – fixed dosage dissolved in 5 to 10 mL normal saline). It's added to washout solution prior to remote blood washout or first cryoprotection flush in the OR).

The Importance of Patient Assessment

Cryonics protocols should not be applied on a one-size-fits-all basis. Medications that are contraindicated for some patients can be a high priority for others. For example, rapid volume restoration with large volume medications is a high priority for patients who have become severely dehydrated. The choice of stabilization medications ideally requires some medical training or experience (see chapter on patient assessment).

Abbreviated Stabilization Medications Protocol

In some cases it may not be possible or practical to administer the full set of medications. A full medication kit may not be available, or non-cryonics personnel may be administering medications. Medications may have to be obtained from a hospital pharmacy on an emergency basis.

Inability to administer the full medication protocol is usually due to absence of a cryonics standby team. It therefore usually coexists with inability to initiate prompt and sustained cardiopulmonary support (CPS) after cardiac arrest. In these cases personnel should focus on prompt cooling and rapid transport, but should still make every effort to administer the following medications in an effort to keep the circulatory system open, protect against free radical damage, prevent cerebral edema and abdominal swelling.

The minimal set of medications to be administered if stabilization procedures cannot begin promptly after cardiac arrest is called the Abbreviated Protocol or Abbreviated Set of Medications. It consists of:

1. **Sodium Citrate (if available)** (10 grams for patients < 40 kg, 20 grams for patients > 40 kg).

2. **Streptokinase** (250,000 IU – fixed dosage).

3. **Heparin** (50,000 IU – fixed dosage).

4. **Tempol** (if available) (5 g – fixed dosage - dissolved in 20 ml normal saline). Tempol is a low molecular weight superoxide scavenger used to mitigate ischemia-induced free radical damage. It is used only in the Abbreviated protocol.

5. **Minocycline** (200 mg dose- fixed dosage).

6. **Decaglycerol** (200 ml- fixed dosage).

7. **Maalox** (250 ml –fixed dosage for gastric administration).

8. **Streptokinase** (250,000 IU - fixed dosage - add to blood washout solution prior to remote blood washout or first cryoprotection flush in the OR).

Administration of these medications should be followed by at least ten minutes of chest compressions to distribute the medications, accompanied by surface cooling.

There is no firm time limit of clinical death beyond which the abbreviated set of medications should be administered instead of the full set.

However, as a general guide, the abbreviated set is indicated for patients who've suffered more than one hour of cardiac arrest.

Emergency Instructions for Stabilization

For cases in which a cryonics standby team is not available, but local medical personnel are available to initiate basic stabilization procedures promptly after cardiac arrest, Alcor maintains a set of instructions called *Emergency Instructions for the Stabilization of Alcor Cryopreservation Patients*. The medications in those instructions are:

> **1. Propofol** (2 mg/kg). Reduces metabolic demand.
>
> **2. Streptokinase** (250,000 IU). Dissolves existing blood clots.
>
> **3. Heparin** (420 IU/kg). To prevent the formation of new clots.
>
> **4. Epinephrine** (0.2 mg/kg). A vasopressor.
>
> **5. Gentamicin Sulfate** (1 mg/kg). Antibiotic.
>
> Chest compressions and surface cooling are also to be performed as described above for the Abbreviated Stabilization Medications Protocol

Evolution of Dosages

For most of cryonics history transport teams were trained to adjust dosages for medications based on patient body weight. These calculations were difficult for team members who lacked mathematical aptitude, and errors occurred even in training sessions where participants were not under the kind of time pressure that is typical during case work. Also, many team members had difficulty drawing volumes that were specified to a high degree of precision— less than 0.1 ml in some instances. The medication worksheet is reproduced in Figure 13-1 for historical reference.

Medication Calculation Worksheet

(*Less than 30 minutes ischemic time*)

(For more than 30 minutes, the order of the medications may change)
(Check with CryoTransport Manager for protocol)

Patient: _____

Alcor #: _____ Date: _____

Scribe: _____

Alcor
Life Extension Foundation

* First Medications to Administer *

Medication	Bag	Notes:	Package Contents	Package Concentration/mL	Dose (per kg)	A Calculated Dose / 1 kg (cc)	B Calculated Dose (cc)	Date: Time (Military) Meds Drawn:	Date: Time (Military) Meds Administered:
! = Administer within 15 minutes of Promit									
Dextran 1 (Promit)	1	[1]	30 mL	150mg	Give All	0.75	30		
! Sodium Heparin	1	[2]	4 mL	10,000 units	420 Units	0.042			
! Potassium Chloride	1	[2]	20 mL	2 mEq	1 mEq.	0.5			
! THAM	IV-1	[2]	500 mL of 0.3M	.036 gm	Give All	12.5	500		
! Diprivan (Propofol)	1	[3]	20 mL	10 mg	2 mg	0.2			
! Streptokinase (Streptase)	1	[4]	5 mL	50,000U	Give All	0.13	5		
! Vecuronium (or Norcuron)	1	[5]	10 mL	1 mg	0.1 mg	0.1			
! Deferoxamine (Desferol)	1	[6]	500 mg/vial	500 mg/vial	Give All	0.2	8		
! Vasopressin	2	[7]	1 mL	20 units	0.5 units	0.025			
! Dextran 40 (Rheomacrodex) (I.V.)	IV-2	[2],[12]	500 mL	.1 gm	Give All	12.5	500		
Mannitol	IV-3	[2]	500 mL	.2 gm	2 gm.	12.5	500		
Chlorpromazine (Thorazine)	2		10 mL	25 mg	3 mg	0.12			
Methylprednisolone (Solumedrol)	2	[8]	8 mL	8 mL/vial (1 gm)	Give All	0.2	8		
Bactrim [AND]	2	[9]	10 mL/vial			Give All	0.25	10		
Gentamicin Sulfate [OR]	2		2 mL	40 mg	1 mg.	0.025			
Erythromycin	2	[10]	1 gm	50 mg	Give All	0.5	20		
Maalox	oral	[11]	250 mL	250	Give All	6.25	250		

B = A x Patient kg

The precalculated dosages in column A (and the tables) can only be used if the Package Concentrations are the same as those shown above. If not, then dosages *must* be re-calculated using the below formula:

Dosage (per kilogram) times Patient's Weight (in kilograms) divided by Package Concentration equals the volume to administer.

[1]	Must be administered between 2 and 15 minutes before Dextran-40.
[2]	Push total Volume
[3]	Shake emulsion well before use. Use strict aseptic procedures - contains no preservatives.
[4]	Reconstitute with 5 cc sodium chloride.
[5]	Dry powder with diluent in package. Diluent is 10 cc of bacteriostatic water for injection. Use it all.
[6]	Reconstitute with 2cc sterile water per / 500 mg vial. (4 vials needed)
[7]	Vasopressin replaces Epinephrine as a far superior pressor.
[8]	8 cc Actovial (use all)
[9]	Packaging concentration in each 10 cc vial should be 800 mg Sulfamethoxysole and 160 mg Trimethoprim
[10]	Reconstitute with 20 cc sterile water / 1 gm vial.
[11]	Administer through gastric tube, using 60 cc catheter tip syringe.
[12]	Of them all, this absolutely MUST be administered within 15 minutes of Dextran 1.

Alternate Method To Calculate Dosage [B]

Multiply Patient Weight in kg by the calculated dose for a 1 gram kilogram patient (the number in [A], (enter cc to administer in [B], unless that column is already filled in with a predetermined dosage that fits all patients.

1 ml = 1 cc
1 kg = 2.2 lbs
1 lb = .45 kg

Figure 13-1. A medications dosage calculation worksheet formerly used by Alcor. The complexity of the calculations made it unpopular with standby personnel.

In March, 2003, while working for Alcor, Charles Platt initiated a dialogue with Harris that led to a simplification of dosages, using a lookup table instead of calculations. This lookup table is now obsolete but may still be found in some medication kits that were distributed regionally at that time.

Harris also eliminated the following medications, either because the need for them was debatable or because they had not been used in all three series of the Darwin/Harris animal trials: Deferoxamine, Chlorpromazine, methylprednisolone (Solu-medrol), Sulfamethoxazole (Bactrim), and erythromycin. Any team members discovering these medications should mark them DO NOT USE and set them aside.

After further consultation, first with Platt and then with de Wolf, Harris recommended that dosage calculations could be eliminated entirely for almost all the remaining drugs. Most of them are not toxic in large doses, and since a rigorous and proven rationale for converting dosages from the canine experiments to dosages for human patients had never been developed, Harris

felt that it was unnecessary and potentially misleading to pretend that a precise dose existed.

During the years since 2003, other smaller, incremental changes have been made to the medication protocol recommended by Harris and used at Alcor and at Suspended Animation. In particular, the method for preparing Vital-Oxy has changed significantly resulting in better emulsions. (Note that in old training documents, it was referred to as Oxynil. Its name was changed when another drug was marketed under that name, for use in conventional medicine. Any vials containing "Oxynil" should be marked DO NOT USE and should be set aside.)

The medication protocol may continue to evolve, especially in response to practical experience gained during cases.

Packing of Medications

The large number of medications used in cryonics requires a well thought out organization of the many vials, bottles, IV bags, and supplies to facilitate methodical preparation and execution of the medications protocol. In 2003 Alcor introduced the use of Thomas Packs to organize and transport the medications. The reasoning was that medical professionals would feel more familiar and therefore more comfortable with the use of these packs. Figure 13-2 shows a Thomas pack opened for access, and figure 13-3 shows its separate small-meds pouch.

Figure 13-2. A Thomas Pack of the type commonly used by emergency medical personnel. Equipment is in the main pack while medications are in the separate yellow pouch shown at top-right.

Figure 13-3. Medications in the separate pouch that is part of a Thomas Pack. High-volume medications in cryonics cases cannot fit in the pack, and the syringes for administering the meds must be packed separately. For these and other reasons, the Thomas Pack system was eventually discontinued in cryonics cases.

A major perceived problem associated with Thomas Packs is that the system offers few visual clues as to where medications are located, and their sequence of administration is unclear. Another limitation is that the medications are separated from the supplies to draw and administer them.

To remedy these issues Suspended Animation adopted a medium-sized Pelican case to store its medications and supplies. It is shown in Figure 13-4.

Figure 13-4. The system developed by Suspended Animation to store medications and supplies. Each transparent tube packed in the lid could be pulled out, and the caps were easily removed. Appropriate syringes were included in each tube. High-volume medications were packed in foam dividers beneath the white tray, which was intended to rest across the rails of a portable ice bath.

The guiding principles of the Suspended Animation system were:

1. All medications and supplies should be easily visible after opening the case.

2. The small-volume medications were placed in plastic numbered tubes in chronological order of administration.

3. The large volume medications were likewise numbered, while being located in the bottom of the container.

4. Medications and the supplies to prepare and to administer them were combined.

Suspended Animation also introduced a simplified dosage chart, on two laminated pages (shown in Figure 13-5 and Figure 13-6).

Suspended Animation

LOW VOLUME MEDICATIONS

	Medication	Dosage	Details
1	**Propofol** Liquid (Diprivan)	**200 mg** Fixed dosage	1 vial (20 ml at 10 mg/ml). Draw the full amount into a 30 ml syringe. Administer the full amount.
2	**Streptase** Powder (streptokinase)	**250,000 units** Fixed dosage	1 vial (250,000 units). Add 5 ml saline or sterile water immediately before use. Shake to dissolve. Draw all of solution into syringe, administer entire amount through filter.
3	**Heparin** Liquid (sodium heparin)	**100,000 units** Fixed dosage	3 vials (4 ml at 10,000 units/ml each). Draw all of the first two vials and half of the third vial into a 10 ml syringe. Administer this amount. Discard the remainder.
4	**Aspegic** Powder (Injectable aspirin)	**200 mg (1 ml)** Fixed dosage	1 vial (1 g). Add 5 ml sterile water immediately before use. Shake until dissolved. Draw only 1 ml into 5 ml syringe, using a filter. Administer only 1 ml. Discard the rest.
5	**Vasopressin** Liquid	**200 units total** Fixed dosage	10 vials (1 ml at 20 units/ml each). Draw all vials into a 10 ml syringe. Administer only 5 ml. Wait 15 minutes, then use remaining 5 ml (until patient temperature is below 25 Celsius.)
6	**Epinephrine** Liquid	**30 mg total** Fixed dosage	1 vial (30 ml at 1 mg/ml). Draw entire vial into 30 ml syringe. Administer 1 ml every 3 minutes until none left, or until patient temperature falls to 25 Celsius.
7	**SMT** Powder	**400 mg** Fixed dosage Backup dose supplied	1 vial (400 mg) +1 backup. Add 9 ml saline 2 days (max) before use. Shake to dissolve. Administer entire amount using filter. If solution is unused after 2 days, discard it and use backup.
8	**Citrate-Dextrose** Liquid	**100 ml** Fixed dosage Backup dose supplied	2 vials (50 ml) +2 backup. Use 100 ml to dissolve NiKy powder 2 days (max) before use. Shake to dissolve. See below.
9	**NiKy** Powder Keep frozen	**1.5 grams** Fixed dosage Backup dose supplied	1 vial (1.5 grams) +1 backup. After dissolving with 100 ml Citrate-Dextrose, administer entire amount using filter. If solution is unused after 2 days, discard it and use backup.
10	**Ketorolac** Liquid	**7.5 to 15 mg** Dosage must be adjusted for patient weight	1 vial (2 ml at 30 mg/ml). For patients 100 kg or more: draw 0.5 ml into 3 ml syringe and use this amount. For patients 50 kg or more: draw and use only 0.25 ml.
11	**Gentamicin** Liquid	**80 mg** Fixed dosage	1 vial (2 ml at 40 mg/ml). Draw the full amount into a 3 ml syringe. Administer the full amount.

Administer low-volume medications in numerical order.
Start high-volume medications simultaneously if possible (see other side of this sheet).
After using each medication, mark it with an X and put it back in the meds container for verification.
Save used syringe filters in a ZipLoc bag
For meds that require filter sterilization, use a new needle for administration.

Figure 13-5. A laminated page developed at Suspended Animation to guide personnel in administering medications.

Suspended Animation

HIGH VOLUME MEDICATIONS

	Medication	Dosage	Details
H1	**Vital-Oxy** Liquid Concentrate (proprietary emulsion)	**80 ml or less** Dosage must be adjusted for patient weight	1 bottle (80 ml). Inject 150 ml warmed saline into bottle. Mix. Use heating pad to warm if necessary. Administer via IV line. For patients under 100 kg, reduce dosage in ratio to weight.

The following three fluids should be piggybacked on to 1 liter of saline solution.

	Medication	Dosage	Details
H2	**Dextran 40** Liquid	**250 ml** Fixed dosage	1 bottle (500 ml of 10% solution). Use only HALF of the supplied amount. Administer 250 ml via IV line.
H3	**THAM** Liquid	**250 ml** Fixed dosage	1 bottle (250 ml of 0.6M solution). Administer the whole quantity via IV line.
H4	**Mannitol** Liquid	**100 grams** Fixed dosage Backup dose supplied	1 IV bag (500 ml of 20% solution/100 grams) +1 backup. Administer the whole quantity via IV line. Mannitol crystallizes readily; to liquify use a warming pad or immerse in hot water.

The following medication is to be administered orally.

	Medication	Dosage	Details
H5	**Maalox** Liquid	**250 ml** Fixed dosage	1 bottle (355 ml). Use about two-thirds of the bottle. Administer to stomach via gastric tube or Combitube (white #2 tube) in esophagus, NOT the trachea.

Start low-volume medications first (see other side of this sheet).
However, Vital-Oxy is a very high-priority medication.

Try to administer high-volume meds at the same time as low-volume meds if possible.
Also try to administer high-volume meds simultaneously with each other.

After using each medication, mark it with an X
and put it back in the meds container for verification.

Maintain the IV during transport to blood washout and setup for washout.

This card was revised July 6, 2006

Figure 13-6. Continuation of the medications instructions developed at Suspended Animation. The high-volume meds were labeled H1, H2, etc. to match the instruction page.

In 2008 Alcor introduced its own new packaging system, combining the medications and supplies in vacuum sealed bags with identifying cards.

Preparation of Medications

Medications in cryonics are mostly supplied in (sterile) vials, while fluids come in either bottles or bags. Bottles are often in used for drugs that have been prepared by the cryonics organization itself or an associated research company.

Team members are likely to encounter drugs that come from three different sources:

1. Medical supply houses

2. Chemical supply houses

3. Compounded in-house

The last two kinds of medications can present formidable challenges in the field because they require additional steps before administration. What follows is a brief treatment of medications that are currently used in cryonics and require special attention.

Medications Requiring Reconstitution

Some medications cannot be stored as a liquid without degradation or decomposition occurring. These medications are stored in powder form and must be dissolved in a liquid prior to use. This process is known as reconstitution.

In the current recommended protocol, the following medications require reconstitution:

Streptokinase

SMT

TEMPOL

A reference sheet or laminated card will be provided by the cryonics organization, specifying the solvent that should be used to reconstitute each drug. Sterile water or normal saline (sodium chloride solution) may be used.

The most important thing to remember about medications that need reconstitution is that they often need to be used within hours of preparing them. They cannot be returned to the inventory of the cryonics organization if they are unused after reconstitution. For this reason it is important to acquire some knowledge and experience in predicting when cardiac arrest is likely. If medications are drawn and the patient lives for a number of days, these medications usually have to be discarded and replaced with fresh ones. For this reason some cryonics organizations include duplicate vials of the same medication.

Reconstitution Procedure. First draw the right volume of the appropriate solvent into a syringe. Then insert the needle through the rubber insert in the cap of the vial containing the powdered medication, and inject the solvent into the vial. Remove the syringe and gently shake the vial until the power dissolves completely. It is very important to visually check whether the resulting solution is clear, because undissolved particles will present problems when the medication will be administered and may also clog small vessels of the patient.

Some medications must be filtered before or during administration. A syringe filter is used for this purpose. A medication that has not completely dissolved can present problems during filtration, sometimes requiring "brute force" to get the solution through the filter. Team members should inspect medications that have been reconstituted a number of times prior to administration to ensure that the chemical has not come out of the solution and collects at the bottom of the vial.

Filtration

Chemicals prepared and packed at cryonics facilities under non-sterile conditions must be filtered with a 0.2 micron filter prior to or during administration. A syringe filter will remove foreign particles. The most important point that needs to be stressed is that the needle that was used to draw the reconstituted solution into the syringe must be discarded and

replaced with a fresh needle before filtration, to insure that the medication will not be pushed through the filter into the same (contaminated) needle again.

In a number of cryonics cases, team members have experienced difficulty forcing solutions through syringe filters, and have had to exert extreme pressure. This problem may indicate that reconstitution of the medication was not successful and the solution still contained particles that did not dissolve. In general, if extreme plunger pressures are required to achieve flow, team members should discard the filter because such pressures can expose them and the patient to risk. The integrity of the filter may also suffer at such pressures.

Viscosity

Some medications that come in glass bottles are so "thick" that rapid administration using a drip is not practical. Vital-Oxy and Decaglycerol/THAM are examples. In such cases team members can draw the contents into a number of large syringes and give them as a bolus.

Multiple Doses

Ideally, multiple smaller doses of vasopressin should be administered on as-needed basis to maintain blood pressure during CPS to achieve target metrics, such as 5% end tidal CO_2. However, for simplicity in the current protocol, the doses of vasopressin have been reduced to two large doses. The last vasopressin dose is to be administered immediately before or during Vital-Oxy administration because the cremaphor emulsifier of Vital-Oxy is known to reduce blood pressure.

Although multiple doses can be given from the same syringe, a persistent mistake in training sessions and actual cases has been to administer the complete amount in a syringe in the "heat of the moment". Therefore, each dose should be prepared separately in its own individual syringe.

Storage

All medications can be refrigerated. Because medications should be administered as rapidly as possible, they should be prepared, reconstituted, and drawn into syringes before they are needed. As indicated above, this will require good judgment in predicting the time when the patient will go into cardiac arrest. Team members should seek advice on this topic from palliative care givers (hospice nurses) and medical professionals such as critical care doctors and nurses.

As a quality control measure, all syringes must be labeled and numbered so that information about which medications have been administered (or not administered) will be available to team members and writers of case reports. In addition, each label should be marked with a permanent marker after the medication has been administered.

Intravenous Access in Cryonics Patients

Although medications can be administered directly through the skin or even through the nose, most medications benefit from being injected into a vein of the patient. Medications can also be injected into an artery, but this entails some risk and should be attempted only by skilled medical professionals.

Two fundamental points are especially important:

1. Administration of multiple medications requires the placement of a secure catheter.

2. Prompt restoration of blood flow and keeping the circulatory system open is necessary for effective administration of drugs.

If only one drug will be administered to the patient (usually heparin), it may be injected into a vein. Raising the vein will be challenging unless cardiopulmonary support is being applied concurrently, to create some blood pressure.

Where more than one drug will be used, an intravenous catheter must be placed to secure patent access to the vein, eliminating the need to find a new

injection site for each successive medication. The catheter can also be connected to an intravenous line to deliver fluids to the patient.

As for the need for blood circulation, this may seem obvious, yet cases in cryonics have been reported where a series of medications were injected into a vein without any attempt to induce circulation. Administration of medications without circulation will not confer benefits on the patient and may even be detrimental when many different medications are administered without flow. Restarting blood circulation by manual or mechanical chest compressions will not only facilitate timely distribution of the medications through the circulatory system, it may also help in locating and placing a catheter in a patient.

One of the biggest challenges in cryonics cases has been to obtain venous access to place a catheter. Case histories provide ample evidence that even people with medical qualifications and extensive experience may have difficulty achieving intravenous access in a cryonics patient. In some cases this has resulted in no administration of medications at all. In others, some surgical access to the patient's vessels (a "cut-down") was required.

The three most important reasons why obtaining venous access in cryonics patients is difficult are:

1. **Dehydration.** Most patients that present for cryonics procedures have become severely dehydrated during the terminal phase of their illness. A cryonics organization may encourage care givers to keep the patient hydrated up until the point of clinical death, but re-hydrating the patient after pronouncement will require venous access in itself.

2. **No cardiopulmonary support.** Until blood circulation has been restored, the lack of blood flow in vessels will make it harder to locate, palpate and access them. Manual or mechanical chest compressions should be administered.

3. **Fragile Vessels.** Most cryonics patient are very old and suffer from advanced fragility of the vessels. In such cases, medical professionals with extensive experience will have the best chance of placing a catheter successfully and securely.

Prioritizing Stabilization Interventions

Unless a secure catheter or port is already in place at the time of legal death, the stabilization team will need to make a decision whether to place a catheter prior to moving the patient to the icebath or after the patient has been moved to the icebath. Because even short delays between cardiac arrest and restoring circulation can contribute to the so called "no-reflow" phenomenon (see the chapter on cardiopulmonary support), it is extremely important to start mechanical CPS in the icebath as fast as possible. Another reason to delay placing the catheter until the patient has been placed in the icebath is to avoid dislodging the catheter upon moving the patient.

Often rapid interventions such as placing a catheter or starting a drip produce unexpected challenges and complications. If this happens, even longer delays before vigorous mechanical cardiopulmonary support can be started are guaranteed. To avoid this scenario, priority must be given to cardiopulmonary support.

Sequence of Medications

Administering a full set of cryonics medications can take more than one hour, if we include the time required for fluids. This raises issues about the priority in which the medications are administered and the advantages of simultaneous administration.

The recommended sequence of medications represents a compromise between importance and practicality. On a practical basis we suggest using the low-volume medications first, to maximize the chance of administering as many as possible. Within the low-volume group, we place the most essential drugs at the top of the list: Propofol, to remove any chance that vigorous resuscitation will restore awareness in the patient, and citrate and heparin, to reduce the risk of blood clots obstructing the vascular system.
A strong case can be made to broaden these three essential medications to include one drug that increases the patient's blood pressure to improve blood flow to the brain immediately after pronouncement of legal death (when the patient is not cold yet). Rapid administration of drugs to increase blood flow

to the brain during chest compressions not only confers direct protection to the brain but also enhances cooling of the brain by improving circulation. Such drugs are called vasopressors. Epinephrine and vasopressin are examples.

One limitation of vasopressors is that they are rapidly eliminated by the body (even after pronouncement of the patient) and therefore require intermittent administration. As the patient gets colder, the need for intermittent administration diminishes.

Intermittent administration of medications requires anticipation and methodical planning. Multiple doses should not be given from the same syringe as this raises the risk of someone inadvertently giving the whole dose at once. A series of syringes should be prepared, each containing one dose to be delivered at pre-determined intervals.

Although we believe that the patient will benefit from intermittent administration of vasopressors, the intervals at which dosages should be repeated are not based on exact science. It is therefore important for the team leader (or scribe) to ensure that team members will not become too distracted by watching the stopwatch. One could indicator of the decreasing efficiency of the vasoactive medications is to monitor end tidal CO_2 values (see the chapter on monitoring).

If team members are sufficiently well trained and well organized, we recommend that they should try to save time by giving large-volume fluids at the same time as the small-volume medications.

 This conveys two benefits:

1. Simultaneous administration increases the chance that important large-volume fluids will be given to the patient. This is especially important in the case of Vital-Oxy, which should be given the highest priority.

2. Small-volume medications will benefit from being "followed" by fluids in the line.

Skilled medical professionals may even be able to deliver multiple fluids at the same time, but case simulations and actual cases have demonstrated that the procedure to "piggy back" different fluids can cause confusion and error.

Unless someone is skilled in this technique, we do not recommend it for cryonics stabilization procedures.

Correct administration of medications is treated in mainstream nursing and emergency medicine texts, but we have to emphasize, here, that when small-volume medications are given through the IV line, the line above the point of administration needs to be clamped off (by squeezing or an actual clamp) to prevent the medication going up the line instead of down the line.

Intraosseous Infusion

An important alternative to conventional intravenous administration of medications is to introduce them into the marrow of the bone, which is in continuity with venous circulation. This procedure is known as "intraosseous infusion," and eliminates the need to locate, palpate and puncture a vein by injecting a needle. It has become increasingly popular in emergency medicine (in the armed forces, in particular).

Since the mid-2000s intraosseous infusion has also been used in cryonics. There are a number of technologies to place a catheter into the bone marrow ranging from using a simple intraosseous needle to equipment that can "drill" or "shoot" the needle into the bone.

Although intraosseous access to the circulatory system can be obtained in numerous places in the body, the most common locations are the breastbone (sternum) and the tibia (the large bone below the knee). The procedure requires some skill and training, but is not plagued with as many challenges as conventional intravenous access, and can be established within one minute by experienced team members.

The most basic method of intraosseous infusion is the use of an intraosseous needle (Jamshidi bone marrow needle). Needle size can range from 14G to 18G. Unless the small size of a patient mandates a smaller bore needle, the larger bore needles are recommended in cryonics because they allow for faster administration of the large volume medications. The preferred location for intraosseous access is the proximal tibia. After identifying and disinfecting the landmark, the needle is pushed through the periosteum into the bone using a screwing motion. This is illustrated in Figure 13-7.
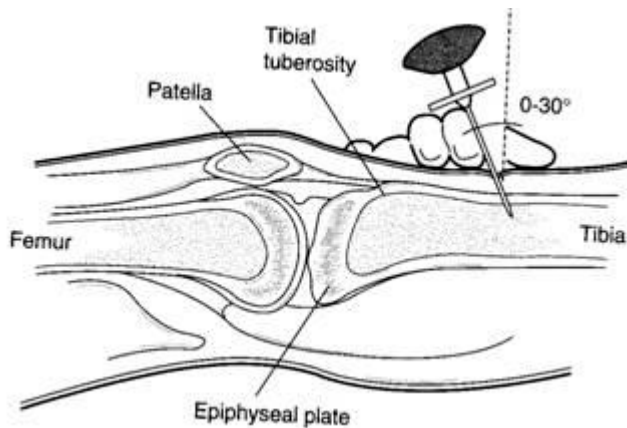
Figure 13-7. Inserting an intraosseus needle.

The indicator that one is into the bone is when resistance disappears and the needle "gives." At that point the needle stylet can be withdrawn and the needle is connected to the IV line to administer fluids and medications. Manual intraosseous needles are (relatively) small, inexpensive, and allow for repeated attempts when initial attempts fail. One disadvantage is the manual strength that is required to insert the needle. To address this challenge, and to make this technology more feasible for emergency settings, specific intraosseous infusion devices have been developed by medical equipment makers.

The first of these devices is called the BIG (Bone Injection Gun), which uses a spring loaded needle to obtain access to the bone marrow. The second of these devices is called the EZ-IO. The EZ-IO uses a lithium battery driven power driver to insert the needle into the bone marrow. Both devices eliminate the need to manually insert the needle with a lot of pressure. This enables the user to focus exclusively on accurate placement of the needle without the risk of causing trauma to the patient or himself.

A third option is the F.A.S.T. 1. Unlike the other two devices, the F.A.S.T. 1 is designed to be used on the sternum of the patient and still requires manual force to insert the intraosseous needle.

In cryonics both the FAST and EZ-IO have been chosen for case work, but the EZ-IO seems likely to become the method of choice because it

eliminates the challenges of using blunt force to place a needle and eliminates scenarios where placement of the F.A.S.T. 1 competes with chest compressions and ice placement.

Intraosseous infusion can be used at multiple locations simultaneously. This creates an opportunity to give small- and large-volume medications at the same time or can be used when two large volume medications compete for priority.

The only serious contra-indications for the use of intraosseous infusion in cryonics patients would be the presence of bone fractures, and any disease that increases the risk of a fracture during placement of the needle. If intraosseous infusion is attempted under these circumstances, fluids can collect in a confined space without entering the patient's circulatory system. When placement is contra-indicated in a certain area (the left tibia), another location can be chosen (the right tibia or the sternum).

Endotracheal Drug Administration

Some drugs can also be administered via the lungs of the patient. The typical scenario where endotracheal drug administration can be advantageous is when a patient already has a patent airway in place prior to pronouncement, and gaining access to the circulatory system is not possible or desirable. The drawback of this method is that only a small number of medications can be administered in this fashion. Be careful to follow these guidelines for endotracheal drug administration:

1. It can be used only for the vasoactive agents epinephrine and vasopressin.

2. The recommended dose is 2.5 times the intravenous or intraosseous dose.

3. The medication must be diluted in 10 ml of saline or sterile water. Sterile water is preferred because it increases drug absorption.

4. Endotracheal drug administration must never be used for large volume medications.

Important: If a Combitube is used for placing an airway, endotracheal drug administration cannot be used unless in the rare event where the Combitube has been placed in the trachea with the patient being ventilated through the white tube.

Pressure Infusion

This procedure should not be attempted by inexperienced team members!

Pressure infusion allows a large volume to be administered in a shorter period of time by applying pressure to the bag in which the fluid is maintained. Pressure infusion should be used in cases where the patient is so dehydrated that a rapid inflow of fluids is required to restore blood pressure. It can also be used to reduce the total amount of administration time of all the large volume medications. Two methods are possible:

1. Use an appropriate pressure infusion cuff (similar to a blood pressure cuff) or a designated pressure infusion pump.

2. Under desperate circumstances, squeeze the bag containing the fluid. This is generally undesirable, since it raises the risk of applying too much pressure or admitting air into the IV line.

When a pressure infusion cuff is used, the IV bag should be placed in the pocket and secured on the IV pole. After the IV bag is secured in the pressure cuff the bulb is squeezed to increase the pressure and thus the rate of the drip. This procedure should only be attempted if someone is designated to monitor the remaining volume in the bag and maintenance of a secure IV line and catheter.

Pressure infusion is also possible in unvented bottles by removing the filter covering the vent port and using a 20 or 50 mL syringe to inject air into the bottle to speed up the pace of the drip. This procedure should not be used by inexperienced team members and without consultation of the person overseeing the case. Failure to closely monitor and stop an infusion accelerated by pressurized air can cause venous air embolism.

Maalox Administration

Administration of Maalox should be discussed, prepared and planned by the team in advance and should not be treated as a last minute decision!

Although administration of the antacid Maalox (which is a suspension of aluminum hydroxide and magnesium hydroxide) has been a core component of cryonics stabilization protocol for many years, this fluid has routinely been omitted in recent cryonics cases for a number of reasons. Unlike the other medications and fluids, Maalox needs to be infused directly into the stomach. The challenge this presents often leads to omission of Maalox administration altogether. Another reason for routine omission of Maalox administration is limited knowledge about its objective and importance. Audrey U. Smith reviewed the importance of neutralizing hydrochloric acid in the stomach during circulatory arrest and hypothermia in her work on reviving mammals from subzero temperatures. These, and similar, observations guided the decision to use cimetidine to inhibit gastric hydrochloric acid production, and Maalox to neutralize acidic stomach contents in cryonics and the Cryovita/Alcor canine washout experiments.

   Although Maalox is the last item on the medications list, it can be administered promptly after pronouncement because IV access is not necessary. Maalox can be given either using the Combitube or using a gastric tube. A major advantage of the Combitube is that administration of Maalox can be combined with giving ventilations through the same device.

   If no ET tube is in place after pronouncement of death, a Combitube can be placed to ventilate the patient and administer Maalox. It's of crucial importance to understand the way the Combitube works to avoid ventilating the stomach or administering Maalox down the trachea of the patient.

   The Combitube works on the principle that the "natural" angle to intubate a patient is to insert the tube in the esophagus. The blue (number #1) tube is closed at the end but perforated to allow flow into the trachea. If the Combitube is placed in the esophagus, the patient needs to be ventilated using this tube and Maalox can be administered through the open ended white (number #2) tube. Placement and ventilation of the Combitube can be

validated by observing bilateral chest rise or end tidal CO2 measurements. Correct placement of a Combitube is shown in Figure 13-8.
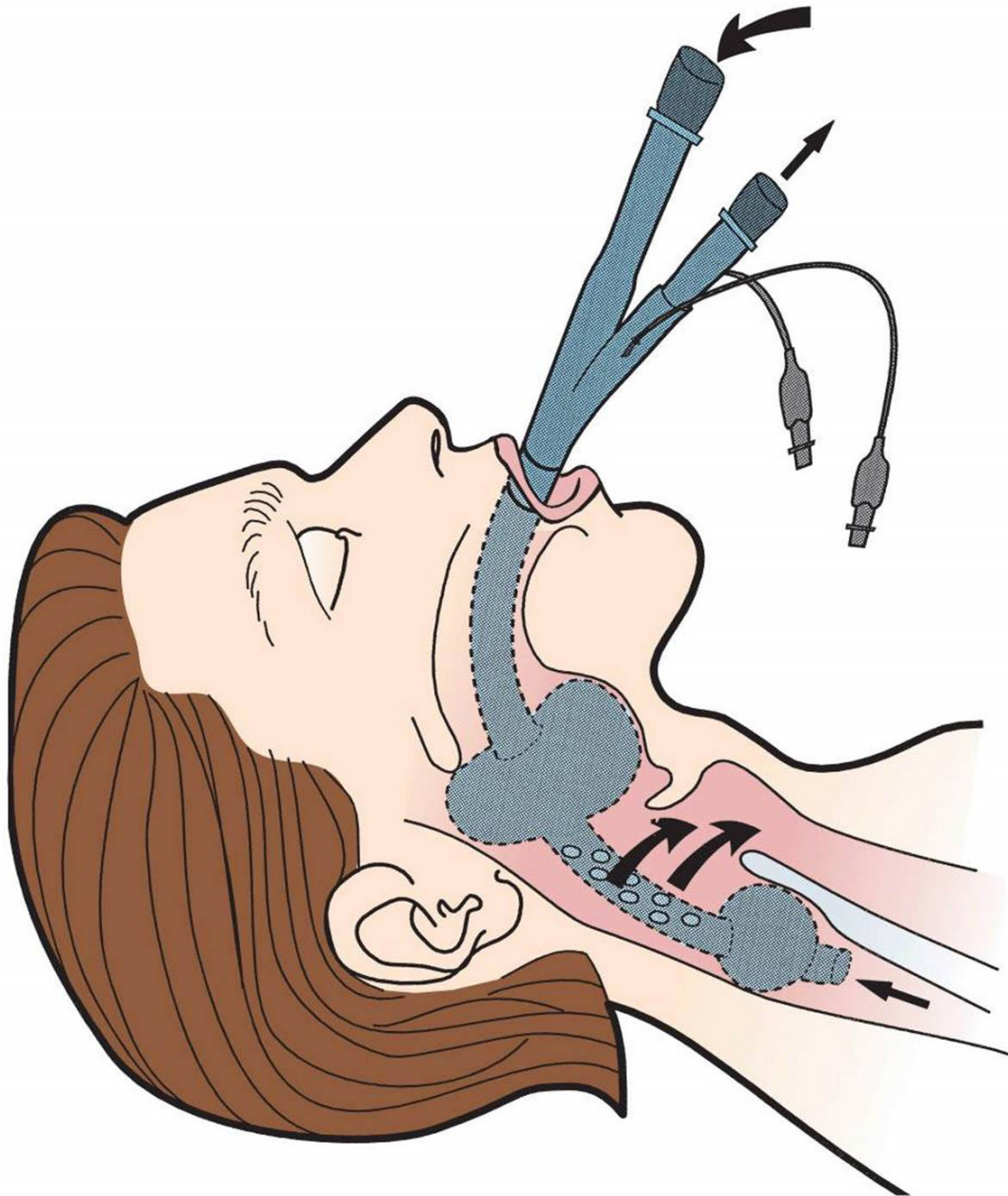

Figure 13-8. Placement of the dual-lumen Combitube. Note the perforations through which ventilation takes place while the tube is anchored in the esophagus. From Trauma*, seventh edition, by Toschlog, Sagraves, and Rotondo.*

Although the Combitube is routinely placed in the esophagus, sometimes it is placed directly in the trachea. If this is the case, the patient needs to be ventilated through the white tube. If the Combitube is placed in the trachea, the Combitube cannot be used to administer Maalox because the tube with the open end has direct access to the lungs!

Warning: If you start ventilating through the blue tube this does not necessarily mean that Maalox administration is safe. What you really need to know is whether the Combitube is in the esophagus or in the trachea. Do not administer Maalox before validating tube placement and validating ventilations. If the Combitube is in the trachea, Maalox administration is not possible using the Combitube.

If a team member has validated placement of the Combitube in the esophagus, the team leader can authorize administration of Maalox through the white (number #2) lumen. The correct volume (250 ml) can be administered by pulling out the plunger of the furnished irrigation syringe, inserting the tip of the syringe in the white (number #2) tube, carefully pouring down the volume in the syringe, and pushing the plunger to "inject" it down the esophagus. This procedure needs to be repeated a number of times to deliver the complete 250 ml. An alternative for the irrigation syringe is to use the large 140 ml syringe that comes with the gastric tube discussed below.

If the patient has already an endotracheal tube in place, or endotracheal intubation has already been established by the team, Maalox needs to be administered using a gastric tube. A gastric tube enables direct access to the stomach to deliver fluids to a patient. A tube and appropriate syringe are shown in Figure 13-9.

Figure 13-9. Syringe and gastric tube suitable for infusing Maalox.

Placement of a gastric tube in a cryonics patient is not routine and may present a significant challenge. A few basic guidelines must be followed:

Do not attempt to place a gastric tube before other means of administering Maalox (such as the Combitube) have been ruled out.

Do not attempt to place a gastric tube without authorization of the team leader.

Do not risk dislodging the endotracheal tube by placing the gastric tube. If the gastric tube needs to be placed, delay administration of Maalox until all the other medications and fluids have been administered and personnel is available to monitor the airway and ventilations during gastric tube placement.

The gastric tube is a stiff large-bore tube that should be manipulated through the esophagus into the stomach. It is important to lubricate the complete tube prior to inserting it. If gastric tube placement is successful, the

Maalox can be administered by connecting the adapter on the proximal end of the gastric tube to the top of the syringe.

> Note: Normal gastric intubation requires a gag reflex for ease of placement, so it's not known whether this technique will work in the cryonics patient. If there are indications that placement doesn't work, do not force it. Discuss the issue with the team leader and consultants.

> Note: If there is an endotracheal tube in place (or the Combitube is in the trachea) another alternative would be to quickly extubate the patient and place the Combitube in the esophagus. This method requires careful coordination between team leader and team members to minimize interruption of ventilations. Do not pull out the existing tube without deflating the cuff (or cuffs in case of the Combitube)!

> REMEMBER: Administration of Maalox should be discussed, prepared and planned by the team in advance and should not be treated as a last minute decision.

It is important to remember that Maalox is not just important during CPS. The existing evidence for the benefits of Maalox use is to prevent cold-induced gastrointestinal complications. Even at low temperatures, cells still require energy and prolonged patient transport times (~ 24 hours) will produce (cold) ischemia. To counter the effects of ischemia on the stomach, administration of Maalox is recommended regardless of the quality of stabilization prior to transport.

Legal, Ethical, and Practical Issues

In Chapter 4 we dealt extensively with general legal and ethical issues relating to cryonics. In this section we will mention only those issues relating to medication of a patient.

The success of a case often hinges on a good relationship between standby/stabilization team members and medically qualified caregivers. In some instances, helpful nursing staff have allowed or enabled team members to begin giving medications immediately after pronouncement. In other

instances, hostile caregivers or administrators have prohibited any such intervention.

The relationship between team members and medical staff can be damaged permanently and irrevocably if medically qualified people have any reason to suspect that cryonicists may violate these absolute prohibitions:

Never violate instructions from the primary care physician or others who are under his authority.

Never administer any medications (or medical treatment of any other kind) prior to pronouncement of the patient.

Never give any cause for the misconception that cryonicists may attempt to hasten the death of the patient.

Since secrecy can erode trust, the Team Leader should initiate an explanation of the purpose of all the medications used to stabilize a patient after pronouncement. Without such an explanation, hospice or hospital personnel may automatically assume that the medications brought in by the cryonicists are for use while the patient is still alive. The idea of using medications after death may not occur to them, and may seem irrational.

Team members should emphasize that no DEA-Scheduled drugs are used. After the reorganization of stabilization medications that occurred in 2003, scheduled drugs have been strictly eliminated from stabilization kits. In particular, propofol has been substituted for sodium pentobarbital. If anyone asks questions about drugs in the kit which the team members are unable to answer, they should put the person in contact with the medical advisor who is advising the cryonics organization that is managing the case.

If hospital or hospice staff still refuse to allow administration of medications, team members should pursue other concessions, such as a guarantee of very prompt pronouncement that will enable rapid removal of the patient from the facility. The team can also request permission to commence cooling and cardiopulmonary support on-site, even if medications have been prohibited.

Since hospitals and hospices generally try to respect the wishes of a patient, the Team Leader should emphasize that this is his objective too. He

should be able to present documents showing that the patient had a sincere desire for rapid intervention after cardiac arrest (assuming the patient is unable to make this claim himself, and no one with medical power of attorney is available to speak on his behalf).

The threat of legal action to force an institution to recognize the desire of the patient for post-arrest medication should be used only as an absolute last resort, and only after consultation with the president or CEO of the cryonics organization that is managing the case.

In almost all instances that we know of, openness, politeness, and a respectful attitude have achieved good results, while confrontation has tended to make a difficult situation worse.