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THE MANRISE TECHNICAL REVIEW (MTR)

is a bimonthly publication devoted to knowledge about sustaining human life. Its primary concern is with means offering increased probability of surviving clinical death. Other related topics will be included at a later time, such as the elimination of aging processes, avoidance of heart disease, prevention of accidents, etc.

The most widely recognized means of increasing probabilities of clinical death survival involves lowering of body temperatures to a point where all constituents are solidified. This state is properly an extreme form of profound hypothermia* and may be termed "solid state hypothermia" (SSH). The early issues of MTR will be concerned exclusively with this topic.

In this first issue of MTR you will find a brief history and overview of methods used for inducing SSH, and basic technical information of concern to persons who are currently working with these methods.

The second and third issues of MTR will be a combined document, including both a protocol for the induction of SSH and detailed procedures for the implementation of the protocol. This two-part document will be hole-punched for insertion in a loose leaf notebook.

Later MTR issues, in 1972 and following years, will include revised pages to be inserted in the protocol-procedure notebook. MTR subscribers will thereby have an up-to-date set of instructions for induction of SSH, as well as current technical information in this area.

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* hypothermia is the medical term for a physiological state characterized by low body temperatures.

BRIEF HISTORY AND OVERVIEW OF METHODS USED FOR INDUCTION OF SOLID STATE HYPOTHERMIA (SSH)

by Linda L. Chamberlain

and Fred R. Chamberlain

Solid State Hypothermia is induced by performance of the operations called for by a SSH "protocol", or formal procedure statement. Protocols for induction of SSH have been changing rapidly during the last year, and this article is intended to provide a point of reference concerning SSH protocols, and perspective with regard to the complexity which is involved with implementation.

The reader is cautioned that this article is *not* a complete guide to the subject. MTR intends to publish an integrated document which will serve this function.

In 1966, at the request of R.C.W. Ettinger, Dr. Peter Gouras formulated a protocol for inducing SSH, based on a review of Dr. Dante Brunol's method later published in We Froze the First Man, by Robert F. Nelson. Dr. Gouras' initial protocol received little revision during a period of almost four years. Since then, many changes have occurred.

In mid 1970 Mr. Art Quaife, a mathematical logician at Berkeley, California, wrote to Mr. Saul Kent of the Cryonics Society of New York concerning a "medically best method for cryonic suspension". He continued corresponding concerning this issue with other persons, including Dr. Gouras. Dr. Gouras sent Mr. Quaife a revised protocol which Mr. Quaife distributed for comment and review to many individuals interested in the subject.

Dr. Armand Karow suggested that the base of the cryoprotective solution be an intracellular, or "Collin's" solution, rather than an extracellular or "Ringer's" solution. Art Quaife and Dr. Gouras exchanged extensive correspondence concerning the cooling of patients and the diffusion of cryoprotective agents into their tissues. Mr. Quaife performed mathematical analyses which guided critical decisions in formulating a more effective protocol.

In June, 1971, following Dr. Karow's suggestions and the results of Art Quaife's analyses, Dr. Gouras presented a second revision to his protocol, at the Fourth Annual Cryonics Conference and Scientific Congress at San Francisco. The following discussion of methods for induction of SSH is based on the ideas of Gouras, Quaife and others who have been responsible for the development of the existing level of understanding in this area.

Although many circumstances may be assumed to provide the context for recommended courses of action, a usually valid assumption is that the patient is in a hospital and reaches a critical stage where clinical death is imminent. References to hospitals and other special equipment are based on this assumption as to circumstances.

First, an outline of general objectives:

1) Cool the patient as rapidly as possible to the freezing point of water, preserving a stable chemical state with respect to the interiors of all cells;

2) Introduce a cryophylactic substance so as to permit preservation of the liquid state with minimum toxicity as temperatures are lowered as far as possible below the freezing point of water;

3) Continuation of cooling until all cells are solidified at liquid nitrogen temperatures.

These objectives correspond to Dr. Gouras' three phases of cryonic suspension (induction of SSH) as presented in June, 1971.

The first objective is to "cool the patient as rapidly as possible to the freezing point of water, preserving a stable chemical state with respect to the interiors of all cells". Cooling may be accomplished by external application of cold gases or fluids.

If fluids are flowing in the patient's circulatory system (heart still beating, cardiac massage or compression, heart-lung-resuscitator (HLR) in use), fluids cooled at the skin will be carried to the body core and cooling will be effectively accomplished. If no fluids are circulating through the patient's veins and arteries, external cooling alone will be insufficient.

Fluids may be caused to flow in the patient's circulatory system by pumping them into the arteries and removing them from

the veins. This constitutes "perfusion". If the "perfusate" (fluid used in perfusion) is chilled, and if external cooling is also applied, then cooling will be effectively accomplished. Cold liquids should be applied externally, rather than cold gases, for more rapid cooling.

"Preserving a stable chemical state with respect to the interiors of all cells" poses numerous alternatives. Experimental animals are given chemicals such as acetazoleamide which prevents heart failure as their body temperatures are lowered to approximately the freezing point of water. They are successfully resuscitated -- therefore the chemical environment (animal's own blood) is "stable" at freezing temperatures.

Dr. Gouras' early protocols called for the use of saline "ringer's" solutions as a perfusate; brain surgery has been performed on humans with blood replaced by chilled Ringer's solutions in operations lasting the better part of an hour. These people recovered with no sign of neurological damage, so (within limits) it seems that the saline Ringer's solution provides a chemically stable environment.

Evidence has accumulated that a perfusate with the same chemicals (non-saline) as those inside the cell better sustains kidneys stored for periods of a day or longer at low temperatures. These intracellular (or "Collin's") solutions are very different from the saline "Ringer's" solutions -- it appears that these also are a stable chemical environment for the cell.

"Artificial bloods" using types of substances commonly found in air conditioners have been used in experimental animals at normal body temperatures for months.

Among all these alternatives, the current substance preferred for "preserving a stable chemical state with respect to the interiors of all cells" is the intracellular "Collin's" solution. Logically, it is best, since it minimizes all osmotic pressures across cell walls as protective enzyme-actuated cell functions relax with decreasing temperature.

"Preserving a stable chemical state with respect to the interiors of all cells" also relates to sustaining a cell's normal processes necessary for life. The cell consumes oxygen and food (glucose), and releases wastes. What happens if oxygen content drops? Do the cells die? How fast? Many of the answers to these questions are not available.

Almost all authorities advising on the induction of SSH have stated that rapid cooling is preferable to attempts to sustain tissue oxygenation, in terms of maximizing probability of cell survival. Several have indicated that once deprived of oxygen for

periods of ten minutes or more, cells' probabilities of survival may be reduced by immediate reoxygenation. Therefore, unless continuity of tissue oxygenation can be maintained throughout the clinical death episode and on into the cooling operation, use of a heart-lung-resuscitator or other heart-lung machine is not recommended for the purpose of oxygenation, particularly if it slows down the cooling procedures.

The current recommendations of Dr. Gouras are for total replacement of blood with intracellular "Collin's" solution immediately following clinical death. Heparin should be administered by injection immediately before clinical death, if possible. Otherwise, it should be added to the perfusate when Collin's solution is introduced to replace the blood.

Perfusion with Collin's solution, chilled to 0°C, should be accompanied by external cooling. When 0°C body core temperature is reached, a waiting period of 24-30 hours is possible, if required, before lowering of temperature is continued.

Perfusion into a femoral artery is recommended, with a "T" shaped cannula so that perfusate flows both toward the heart and down the circulatory system of the leg. Fluid is removed from the adjacent femoral vein, again using a "T" shaped cannula. If "T" shaped cannulae are not available, the ordinary cannulae used instead should be directed toward the heart. Perfusion pressure should not exceed 200 mm. Hg.

To move directly into the area of practical procedures, suppose that the patient is being externally cooled, and that cannulae are in place. A supply of chilled Collin's solution is on hand, and the time is reached when perfusion must begin. What fundamental steps are necessary?

The device used for perfusion will have some kind of tank or reservoir, and it will be filled with chilled Collin's solution. The device will have a tube of some kind to be connected to the patient's arterial cannula, and some means of regulating perfusion pressure. All air should be purged from the perfusate tube, and it is connected to the patient. The level of perfusate in the reservoir is measured, and pressure is raised to a safe level (150 mm. Hg., perhaps). Perfusion has begun.

The level of the perfusate reservoir must be repeatedly measured, and the time of measurement recorded. This, coupled with a knowledge of the reservoir's dimensions, will provide a record of total input and input flow rate.

The cannula from which fluid is draining should be connected to a tube leading to a second reservoir *lower than* the patient (to prevent back pressure). The level in this reservoir should

also be measured repeatedly, and the time of measurement recorded, providing a record of total output and output flow.

By these two measurements, it is not only possible to measure flow through the patient's circulatory system, but it is also possible to determine if the patient is gradually losing or accumulating fluid.

Since the patient is being cooled, temperatures at a number of points will be measured. A check of the perfusate reservoir will assure that the perfusate is properly chilled, and a check of perfusate leaving the patient will show how much the fluid is warmed up while passing through the patient's circulatory system. Also, by means of probes inserted through natural body openings of the digestive tract, body core temperature can be measured.

Other temperatures can be measured, such as temperatures outside the coils in a heat exchanger, temperatures in specific gravity measuring cylinders, and temperatures at multiple points on a patient's skin.

As implied by the last paragraph, many aspects of perfusion remain to be discussed. The perfusion device may have a heat exchanger to keep the perfusate chilled, specific gravity measurements of perfusate may be necessary and may be temperature dependent. Also, the pH (acidity/alkalinity) of the perfusate must be measured and controlled within certain limits (pH 7.4 is ideal). The subject of the second objective involving cryophylactic agents remains to be discussed, and the problems of perfusion pertinent to this phase are very complex. For all these questions separate articles are appropriate, and will appear in subsequent issues of MTR.

Even a logically organized series of articles might leave a great number of questions unanswered. Such as "What goes into Collin's solution?" "What equipment do you use for perfusion?" "How much heparin should be injected?" Other questions of a very practical nature exist, such as "Shouldn't you have a blank death certificate sith you, to facilitate immediate certification of clinical death?" or "Where is the cooling and perfusion accomplished if the hospital doesn't assist?" (and none have, to date.)

An adequate treatment of *all* applicable questions can be provided only by a document uniting a protocol with all of the detailed procedures necessary to make it practical and workable under the many different circumstances that may arise. MTR subscribers will receive their copy of this document in late 1971.

SPECIFIC GRAVITY AND pH OF DMSO-COLLINS' AS A FUNCTION OF TEMPERATURE AND CONCENTRATION

by F. R. Chamberlain

In the second or "cryophylactic" phase of SSH induction, the concentration of dimethyl sulfoxide (DMSO) must be increased so as to maintain the perfusate in a liquid phase with decreasing temperature (below 0°C).

Starting from any point of equilibrium, if the concentration of DMSO in the perfusate is increased, the freezing point of the perfusate is decreased, but the freezing point in the tissues drops more slowly, since the DMSO must diffuse out into the tissues, displacing water. As the DMSO displaces water in the tissues, water displaces DMSO in the perfusate, lessening its concentration, and the perfusate's freezing point rises toward original values.

Obviously, DMSO must be added continuously, and water removed continuously, to maintain a gradually increasing concentration of DMSO in both perfusate and tissues. This process must be guided by a measurement of DMSO concentration in the perfusate.

The specific gravity of the perfusate may be measured as a means of determining DMSO concentration. Since specific gravity rises slightly with decreasing temperature, a family of curves for specific gravity vs. temperature were plotted from measurements (figure 1) for Collins' solution with DMSO.

The Collins' solution used was C-4 without Mg SO_4, phenoxybenzamine, albumin or heparin. Half the prescribed amount of glucose was included. Specific gravity was measured with calibrated hydrometers. Temperature measurements were taken simultaneously by insertion of a thermister into the hydrometer cylinder.

To use figure 1 in determination of DMSO concentration in perfusate, measure both specific gravity and temperature and interpolate for DMSO concentration. An example is indicated at a specific gravity of 1.06 and a temperature of -6°C. The concentration of DMSO in the perfusate would appear to be about 27 per cent.

In addition to specific gravity, values of pH were measured. The Collins' solution alone had a pH of approximately 7.0, but addition of DMSO in low percentages (3-5%) increased pH into the 7.4 to 7.6 range. At 50 percent DMSO, pH ranged from 8.0 to 8.4 depending on temperature. Precise measurements were not possible, and these data are only valuable as a preliminary indication that pH balance problems may exist when high percentages of DMSO are used.

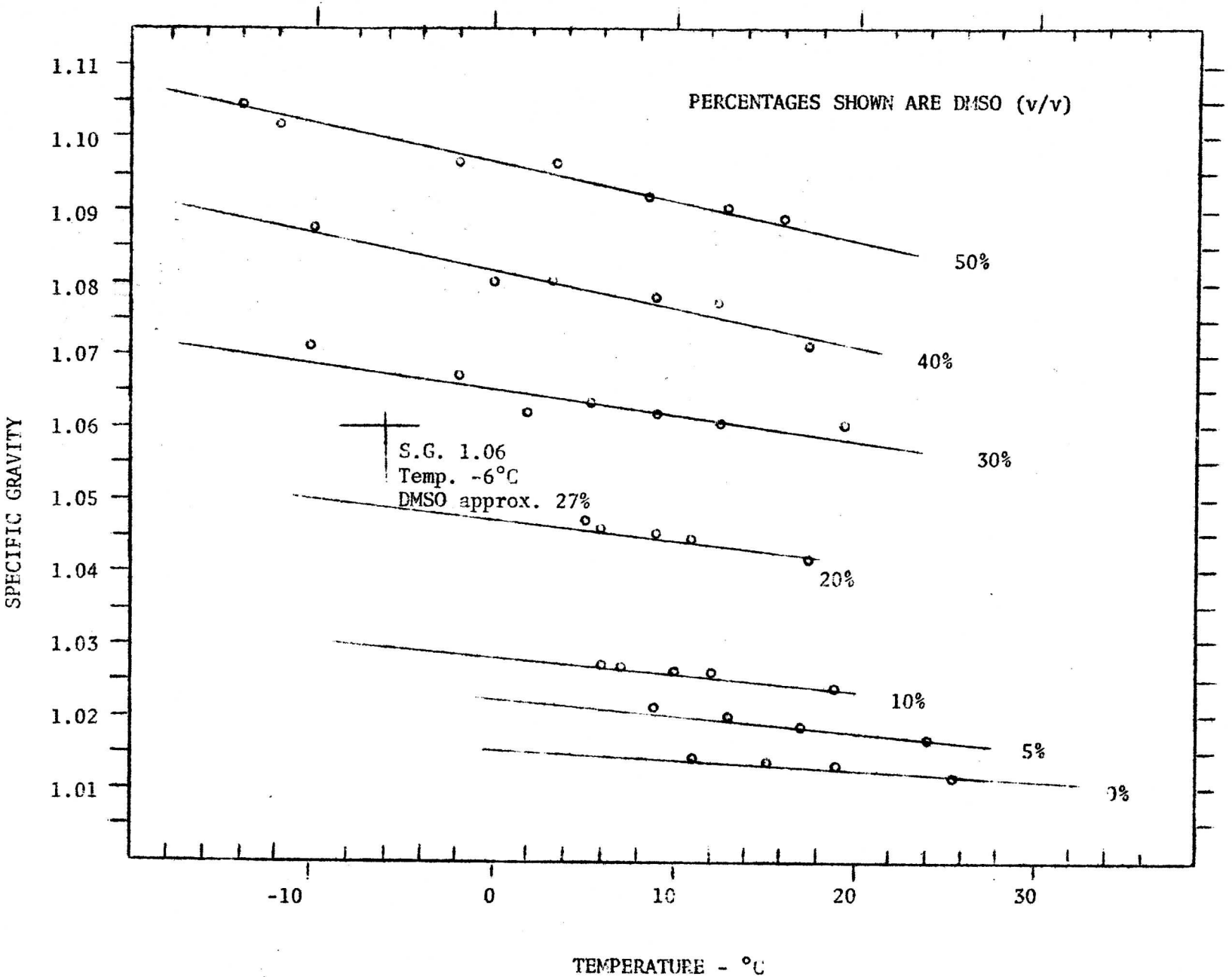


Figure 1. Specific Gravity vs Temperature for Collin's Solution with DMSO

ELEMENTS OF THE RECOMMENDED PERFUSATE AND OTHER CHEMICALS OF POSSIBLE VALUE

by L. L. Chamberlain

In considering the induction of SSH, the proper perfusate is of central importance. At the time of this writing the recommended base perfusate is a solution (C-4) used by Collins' et al in recent kidney preservation experiments. (Dimethyl sulfoxide (DMSO) is added for temperatures below 0°C).

Figure 1 below gives instructions for making up Collins' C-4 [1] perfusate; this solution is not known to be commercially available.

BALANCED ELECTROLYTIC FLUID (SOLUTION C) USED TO PERFUSE CANINE KIDNEYS

C_1	C_2	C_3	C_4	Components	gm/liter
X	X	X	X	1. KH_2PO_4	2.05
X	X	X	X	2. $K_2HPO_4 \cdot 3H_2O$	9.70
X	X	X	X	3, KCl	1.12
X	X	X	X	4. $NaCHO_3$	0.84
		X	X	5. Procaine HCl	0.10
X	X	X	X	6. Heparin (500 u/l)	
			X	7. Phenoxybenzamine	0.025
	X	X	X	8. Glucose	25.0
X	X	X	X	9. $MgSO_4 \cdot 7H_2O$	7.40

a. Components 1-6 sterilised by autoclaving.
b. A faint turbidity appeared immediately after adding phenoxybenzamine but disappeared on standing within 24 hours.
c. Components 8 and 9 added as 50% solutions immediately before use.
d. pH 7.0 (25°C)

It was by use of this modified intracellular fluid that results superior to surface cooling could be obtained without continuous perfusion during storage.

In earlier experiments using simple surface cooling, mannitol and phenoxybenzamine were injected prior to removal and prior to reimplantation of the kidneys. For some reason, although phenoxybenzamine is included in C-4, mannitol is omitted.

A problem precipitate occurs when DMSO is used with Collins' C-4 solution. It is suspected that magnesium (in $MgSO_4 \cdot 7H_2O$; 14.8 gm/liter) is the cause of this precipitate. Although it is undesirable to entirely eliminate the magnesium from the solution, one source advises that no more than 0.2 gm/liter be used.

Human albumin could be added (10 gm/liter) to minimize swelling during perfusion. At the cost of $10.00 per gram, however, it may not be feasible to use human albumin. Dr. Peter Gouras suggests Dextran (M.W. 40,000) might be added as an albumin substitute.

It is adviseable to maintain the solution pH at the normal physiological range of 7.4. For this purpose Hepes Buffer is currently recommended. Tris-buffer is acceptable as a substitute in an emergency.

The straight Collins' solution as described above is used in the Immediate Phase of induction of hypothermia (ambient to 0°C). During the Cryophylactic Phase (0°C to -79°C) DMSO is added to the Collins' solution in gradually increasing percentages. Determination of percentage of DMSO can be figured using specific gravity and temperature measurements (see "Specific Gravity and pH of DMSO-Collins' as a Function of Temperature and Concentration", page 12, this issue).

For any percentage of DMSO, equilibrated in the patient's tissues, there is a minimum temperature below which crystalization will occur. This can be determined by use of a eutectic diagram[2] (figure 2) for water-DMSO.

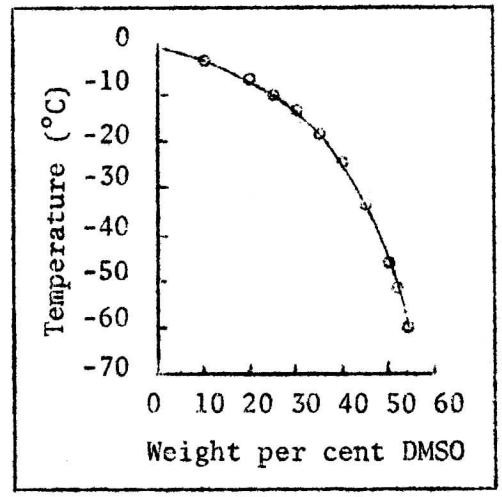
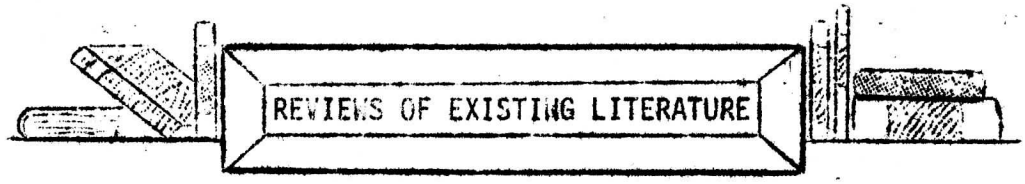


Figure 2

References

1. "Kidney Preservation for Transportation", G.M. Collins, M. Bravo-Shugarman, P.I. Terasaki, The Lancet, December 6, 1969, pp. 1219-1222.
2. "Phase Diagram for the System Water-Dimethylsulphoxide", D.H. Rasmussen, A.P. MacKenzie, Nature, Vol 220, pp. 1315-1317.



properties of DMSO

Dimethyl sulfoxide (DMSO) is a principle cryoprotective agent in current protocols for induction of SSH. A relatively complete description of its properties is provided by this reference.

["Dimethyl sulfoxide", pages 219-20 in Solvents Guide by C. Marsden and S. Mann, Interscience Publishers, New York, 1963]

Viscosity values are given (1.99 c/s at 25°C, 1.65 c/s at 35°C, and 1.39 c/s at 45°C). The viscosity of water-DMSO mixtures at 25°C reaches a maximum of 3.8 c/s at 70 percent DMSO. Heat of solution (60 cal/gm), refractive index (1.4783 at 20°C) and many other physical properties are provided.

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viscosity at low temperatures

In attempting to predict how much cryoprotective perfusate can be circulated through the body at low temperatures, one of the principle uncertainties has been the viscosity of the perfusate and its consequent resistance to flow. No published data on DMSO-water or DMSO-Collins' viscosity at temperatures below 0°C are known, but the viscosities of comparable mixtures have been documented and are published in this reference.

[Perry's Chemical Engineer's Handbook, Fourth Edition, McGraw Hill, 1963]

Page 12/18 gives the viscosities below 0°C of water mixtures of various substances, including sodium chloride, calcium chloride, methanol, ethanol, and glycerol. The values for glycerol are of interest, and are shown below.

GLYCEROL-WATER, VISCOSITY IN CENTIPOISES					
Weight %	Solution Temperature				Freezing Point
	23°F -5°C	14°F -10°C	-40°F -20°C	-22°F -30°C	
30	6.5	---	---	---	+15.0°F
40	10.3	14.4	---	---	+ 4.3°F
50	18.8	24.4	48.1	---	- 9.0°F
60	41.6	59.1	108.0	244	-30.5°F

On pages 3/199 and 3/200 is a nomogram with data for estimating the viscosities of over a hundred substances at temperatures ranging continuously from 200°C to -30°C. At 25°C, a 50 percent glycerol solution has a viscosity of 5.2 centipoises, according to this nomogram.

COMMENT: These data indicate a 50 percent glycerol solution at -20°C flows under a given pressure at approximately 1/8 the rate it flows at 25°C. If perfusion of one gallon per minute were possible at 25°C, this would be reduced to about one pint per minute at -20°C. If the concentration is raised to 60 percent and the temperature is lowered to -30°C, flow decreases to 1/3 cup per minute.

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recovery from low blood oxygen levels

In the induction of SSH, blood oxygen may fall to relatively low levels, depending on the circumstances. This reference offers evidence that such conditions do not necessarily indicate permanent damage has occurred, even by today's standards.

["Survival Following Extreme Hypoxemia", by Gray and Horner, Journal of the American Medical Association, 211:1815, 16 March 1970]

"A fall of arterial blood oxygen pressure (Pao_2) to 20 mm Hg or less has generally been held incompatible with survival, but there are exceptions." This sentence introduces a study of certain exceptional patients who sustained low blood oxygen (less than 21 mm Hg) and survived without apparent neurologic damage. Two of the article's concluding statements are: "Twelve of the twenty two patients made a long term recovery, proving that even an extremely low level of Pao_2 is compatible with survival." and "Our present concept of how well a patient can tolerate the hypoxemia of respiratory or cardiac arrest without suffering irreversible damage ought to be reconsidered, especially because of current ethical problems arising in the use of heroic resuscitation and the selection of donors for organ transplant."

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mechanics of blood flow and perfusion

["Principles of Hemodynamics", by William R. Milnor, from Medical Physiology, 12 Ed., 1968, Mosby, pp. 101-117]

Dr. Milnor notes that the viscous behavior of blood approximates that of a newtonian fluid in vessels larger than 0.5 mm in diameter. In man and dog, this viscosity at 37°C is in the range of 0.03 to 0.04 poises, viscosity rising with increasing hemocrit.

In explanation, hemocrit is a measure of the proportion of red blood cells to other blood constituents. Viscosity is a

measure of a liquid's "thickness" or more precisely, its resistance to flow. "Newtonian" fluids behave in accordance with rather simple algebraic laws. In cylinders, flow is described

$$Q = \frac{\pi (P_1 - P_2) R^4}{8 N L}$$

where:

Q = *mass flow in* cm^3/sec
π = *3.14159*
P_1 = *input pressure in* $dynes/cm^2$
P_2 = *output pressure in* $dynes/cm^2$
R = *cylinder radius in cm*
L = *tube length in cm*
N = *viscosity in poises*

All of these quantities are relatively simple to use, excepting that pressure is usually not expressed in $dynes/cm^2$. Conversion factors are:

(a) 1 $pound/in^2$ = 68,947 $dynes/cm^2$

(b) 1 mm Hg = 1,333 $dynes/cm^2$

The viscosity of water is .0069 poises at 37°C, so blood (0.03-0.04) is from four to seven times more resistant to flow than water at that temperature. Water near 0°C has a viscosity of 0.0175 so it would flow about twice as easily at that temperature as blood at body temperature.

Dr. Milnor defines "vascular resistance" as "K" in the expression $K = (P_1 - P_2)/Q$, so that it is the ratio of pressure drop to mass flow (units are $dyne\text{-}sec/cm^5$). He takes a typical example of the human circulation assuming cardiac output of 6 liters per minute and shows the difference of the pulmonary vascular resistance (120) vs. the rest of the system (1,133) using typical mean values of blood pressure.

Dr. Milnor goes on to discuss errors in pressure measurement, a more elaborate form of the pressure-flow equation taking into account the kinetic energy of the blood and differences of height within the system. He treats turbulent vs. laminar flow, providing an expression for calculating the Reynold's number:

$$R = \frac{\bar{V} D P}{N}$$

Q = mass flow in cm^3/sec
R = Reynold's Number
$\bar{V}$ = average velocity in cm/sec
D = vessel diameter in cm
P = Blood density (1.05 gm/cm^3)
N = viscosity in poises (dyne-sec/cm^2)

Average velocity = $Q/A = 4Q/\pi D^2$ (cm/sec), so

$$R = \frac{\bar{V} D P}{N} = \frac{4 Q P}{\pi D N}$$

He states: "Turbulence usually develops when the Reynolds Number exceeds 2000, but the critical value varies with the experimental conditions. The transition is not abrupt, and flow that is neither perfectly laminar nor fully turbulent may be seen at Reynolds Numbers of 1000 or even less."

Observe that Reynolds Number can increase for either an increase in velocity or size of the vessel. In the body, flow is usually fastest in the largest vessels, and it is here if anywhere that turbulence is most likely to develop.

Dr. Milnor discusses flow in distensible tubes, noting that blood vessels expand with increased pressure, permitting more increase in flow than would be possible with rigid tubes. As pressure is applied, essentially no flow occurs until the "critical closing pressure" is reached. With normal vascular muscle tone, this ranges from 10 to 25 mm Hg. Above this, the vessel expands elastically, coming to a fixed maximum diameter about 43 mm Hg. Above this "pressure and flow are linearly proportional, as in a rigid tube."

Dr. Milnor discusses pulsatile flow, a most complex phenomonon, and provides a demonstration of how a flow pulse measured in vivo can be represented by a fourier series of four terms, providing the necessary basis for mechanical replication of a beating heart.

Fifty six references are provided, thoroughly documenting recent work relative to the subject.

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circulatory system resistance to pressure

["High Pressures Fail to Break Cerebral Arteries", Journal of the American Medical Association, (210:1844) 8 December 1969]

In dogs, pressures in cerebral arteries were raised to the point of failure. There were "no perceptible physiological changes up to 5800 mm Hg except for bulging eyes and separation of the retina." Cardiovascular collapse and death occurred in the range of 5800 - 6000 mm Hg. The investigator noted that "chronic hypertension may produce cellular changes possibly making the cerebral vessels more likely to rupture".

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surface cooling

One of the primary steps in the induction of SSH is surface cooling. This reference covers and compares various aspects of hypothermia such as methods, influencing factors, rates of cooling and rewarming.

[Temperature; Its Measurement and Control in Science and Industry, Vol. 3 (C.M. Herzfeld, editor); Part 3, "Biology and Medicine" (J. D. Hardy, editor); Section 6, "Hypothermia"; pp. 495-510, Reinhold Publishing Company, 1963.]

Distinction is made between Moderate Hypothermia (down to 15°C) and Profound Hypothermia (below 15°C). Methods of surface cooling are discussed and evaluated. Submerging patient in an ice water bath is the prefered technique. Drugs are being employed to combat the body's two principle defenses against reduction in temperature, namely vasoconstriction and shivering. Of those discussed, chloropromazine and mecamylamine have a central effect and reduce the induction time.

Rate of temperature reduction is also influenced by the size and insulation of the body cooled. A comparative chart is given for cooling rates in animals immersed in 0°C water and of men in 10°C water. pH control and influence of body weight (obese vs. slim vs. children) are also discussed. The advantages of internal cooling through vascular and body cavity cooling are also explored.

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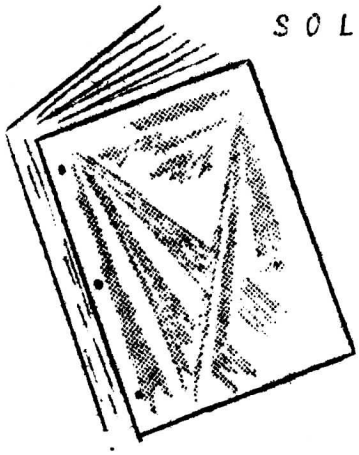

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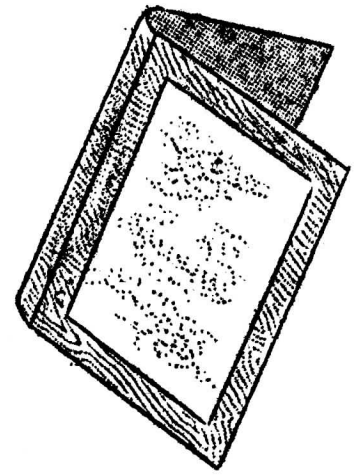

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