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Improved Outcome of Surgical Flaps Treated with Topical Dimethylsulfoxide

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Objective
The objective of this study was to analyze the effect of dimethylsulfoxide (DMSO) on skin flap viability.

Background
Dimethylsulfoxide has been shown to decrease necrosis of random skin flaps in the rat model, but no human studies have been performed. The authors performed a randomized, prospective study on the effect of DMSO on skin flap viability in patients undergoing mastectomy and inguinal lymphadenectomy.

Methods
Twenty-four patients had topical 60% DMSO applied to their flaps every 4 hours × 10 days after operation and 27 patients had operation alone. The maximum area of flap ischemia was traced by a masked observer and measured by cut and weigh technique. Significance of differences between the treatment and control group was determined by Student's t test.

Results
The mean area of ischemia for the DMSO group was 16.33 U *versus* 44.93 U for the control group. This difference was statistically significant ($p = 0.01$).

Conclusions
The authors conclude that topical application of DMSO reduces skin flap ischemia in humans and recommend its use after operation in which skin flaps are created.

Tissue flap necrosis continues to be a problem in surgical procedures such as mastectomies and, to a greater extent, ilioinguinal lymphadenectomies. The morbidity from flap loss can be substantial and can result in increased costs due to prolonged hospital stay and the need for additional surgery or increased number of out-patient visits or both.

Pharmacologic attempts at enhancing flap viability (*e.g.*, the use of vasodilators, antiadrenergic agents, anti-inflammatories, free radical scavengers, and hemorrheologic drugs) are aimed at addressing specific threats to flap survival. Although the physiology of acutely raised flaps is not understood completely, at least four insults currently are recognized as important in the development of irreversible flap necrosis: 1) ischemia, 2) nerve

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section (with the release of catecholamines), 3) activation of the inflammatory–prostaglandin cascade, and 4) free radical reperfusion injury.

Dimethylsulfoxide (DMSO) is a naturally occurring, highly polar, stable, hygroscopic organic compound whose metabolites normally are found in humans.[1] It is remarkably nontoxic[2] and can be administered topically, intraperitoneally, or intravenously.[3,4] Dimethylsulfoxide has been shown to have biochemical properties that protect against ischemic injury. Its mechanism of action may involve vasodilation of the subdermal capillary bed,[5,6] platelet deaggregation,[7,8] and free radical scavenger activity.[9,10]

Dimethylsulfoxide has been shown to reduce necrosis in skin flaps in the rat model with both its topical[6,11] and intraperitoneal[4,12] administration. Other investigators, though, have not been able to repeat these findings in a similar model.[13,14] With respect to human flap surgery, the literature contains only a favorable case report.[15] In a slightly different context, intravenous administration of DMSO was shown to allow extensive, immediate intraoperative tissue expansion.[3]

To our knowledge, no prospective randomized study of the efficacy of DMSO in preventing flap ischemia in humans has been performed. Currently, the only U.S. Food and Drug Administration-approved use for DMSO is in the treatment of interstitial cystitis. Our institution is uniquely qualified to perform such a study because in 1979, the state legislature allowed the use of DMSO for the treatment of any disease within Oregon, thus facilitating our obtaining approval from investigational review boards for human studies using DMSO.

We hypothesized that topical DMSO would promote flap viability and reduce tissue loss. To test this hypothesis, we performed a randomized, prospective, single-masked study comparing the topical application of DMSO to operation alone in patients undergoing mastectomies and ilioinguinal lymphadenectomies.

METHODS

Between 1988 and 1992, 55 consecutive patients with breast cancer, malignant melanoma, or metastatic squamous cell carcinoma who had skin flaps created during mastectomy or ilioinguinal lymphadenectomy (with or without cisplatin hindquarter isolation limb perfusions) were studied. Patients were excluded who had conditions that would predispose them to compromised circulation (*e.g.*, vasculitis, systemic lupus erythematosus, diabetes mellitus, steroid use, or collagen vascular disease). Patients with a history of radiation to, or prior operation on, the proposed operative site also were excluded. Patients were not excluded based on tobacco use. Patients were informed of the investigational nature of the study and gave written informed consent in accordance with

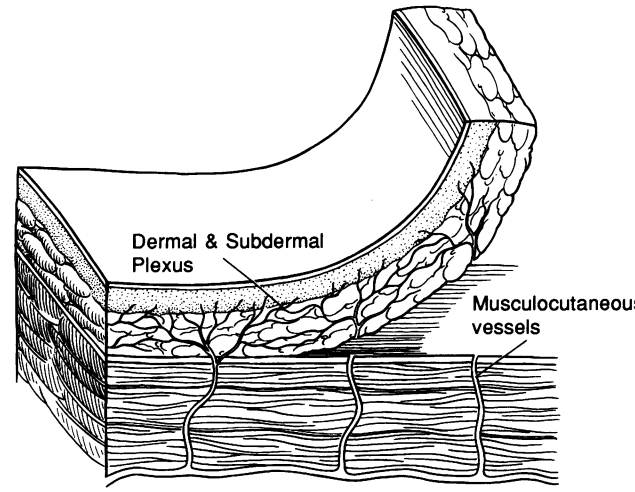

Figure 1. Example of the plane of dissection and blood supply to a random cutaneous advancement flap.

institutional and U.S. Food and Drug Administration guidelines. Randomization was performed by a computerized system. The flaps dissected during mastectomy and inguinal lymphadenectomy were cutaneous advancement flaps (Fig. 1).

Mastectomy flaps were created in the following fashion: Oblique elliptical incisions were made on the breast, including a lateral extension toward the axilla to facilitate exposure for the axillary lymph node dissection. The ellipse of skin excised with the specimen contained the entire nipple–areola complex, any incision from prior biopsy, and any skin with tumor involvement, all with the appropriate margins of tumor-free tissue. Skin flaps were dissected in the plane of Cooper's ligaments, between subcutaneous fat and underlying breast tissue, and elevated to the level of the clavicle superiorly, the lateral aspect of the sternum medially, the edge of the latissimus dorsi muscle laterally, and the origin of the rectus abdominis sheath inferiorly (Fig. 2). The superior and inferior flaps were reapproximated without tension. Two closed suction drains were inserted, one in the axilla and one on the anterior chest wall, to prevent accumulation of serous or hemorrhagic fluid beneath the flap or in the axilla. Drains were removed when the output was less than 30 ml/day, typically between days 5 and 10.

Groin flaps were created using two parallel transverse incisions, one beginning at the anterosuperior iliac spine and extending toward the pubic tubercle and the other approximately 6 cm inferior and parallel to the first, below the inguinal ligament. In this fashion, a bipedicle flap (*i.e.*, skin bridge) was created that gave access to the iliac, obturator, and inguinal nodes (Fig. 3). The ilioinguinal lymph node dissection was performed as described by Karakousis.[16,17] Concurrent hyperthermic isolation limb perfusion of the lower extremity was allowed using the technique as described by Stehlin,[18] Krementz and

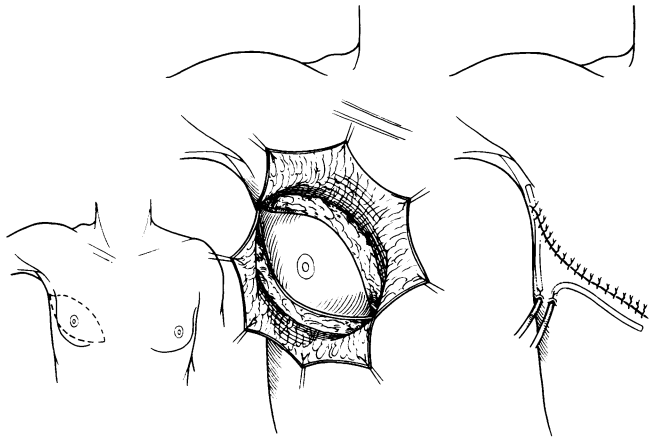

Figure 2. Incisions, random cutaneous advancement flap, and surgical drain placement for mastectomy.

Ryan,[19] and Janoff et al.[20] Cisplatin was the perfusion agent at temperatures lower than 40 C for 1 hour. At the completion of the procedure, two closed suction drains were placed in the iliac and inguinal regions and brought through the skin lateral to the incisions. Drains were removed when their output was less than 30 ml/day, typically on postoperative days 10 to 14.

The control group received no treatment to their flaps. The treatment group received topical DMSO according to the following protocol: 60 ml of a 60% DMSO solution (60% DMSO, 10% urea, and 30% water) was sprayed on the entire flap area, intraoperatively, and then every 2 hours for the first 48 hours and finally, every 4 hours during postoperative days 3 through 10. Patients were instructed on the correct method of application by the surgical oncology nurses, and all patients demonstrated proficiency.

The Surgical Oncology Research Fellows evaluated the skin flaps. They were not directly involved in the clinical care of the patient and were not the operating surgeon. The observer was unbiased. Observers wore face masks impregnated with DMSO while evaluating flaps so they could not detect its scent from patients in the treatment group, and all evidence of DMSO and its application was removed from the examination room. Patients were instructed that the observers must not know whether they were in the treatment or control group.

Skin flaps were evaluated on each postoperative day that the patient was in the hospital (range, 2–5 days). Thereafter, patients were seen in clinics weekly for three to five visits. Infrequently, if patients lived at a great distance from our institution, they were seen every 2 weeks for their last two to four outpatient visits.

The criterion for nonischemic areas was normal skin color. The criteria for ischemic areas were purple mottling, or black, nonvital skin, requiring debridement.

Ischemic areas were traced onto clear plastic sheets at each examination. The largest area recorded during the follow-up period for each patient was traced onto analytical paper, cut out, and weighed. The weight obtained, in micrograms, was the value used as the value for statistical analysis. Student's t test was used to determine the statistical significance of differences in the data.

RESULTS

Patients

Fifty-five patients were randomized. Four patients were lost to observation, leaving 51 evaluable patients; DMSO was discontinued in 2 patients because of wound infections, in 1 patient due to the development of vesicles along the inferior aspect of her incision and in the last patient secondary to postoperative nausea and vomiting, following cisplatin therapy.

Of the 51 evaluable patients, 24 were randomized to treatment with DMSO and 27 were randomized to the control group. Thirty-three patients were admitted for mastectomy (16 treatment and 17 control) and 18 patients for ilioinguinal lymphadenectomy (8 treatment and 10 control). There were no significant differences between the treatment and control groups with respect to age ($p = 0.01$) or incidence of smoking ($p = 0.30$). Patient characteristics are listed in Table 1.

Three patients in the lymphadenectomy group did not undergo simultaneous cisplatin hyperthermic isolation limb perfusion: two of these patients were in the control group, one with penile squamous cell carcinoma and another with malignant melanoma, and one was in the treatment group, a patient with squamous cell carcinoma metastatic from the perianal region to the inguinal nodes.

Areas of Ischemia

The areas of flap ischemia for the treatment and control subjects are plotted in Figure 4. The mean area of

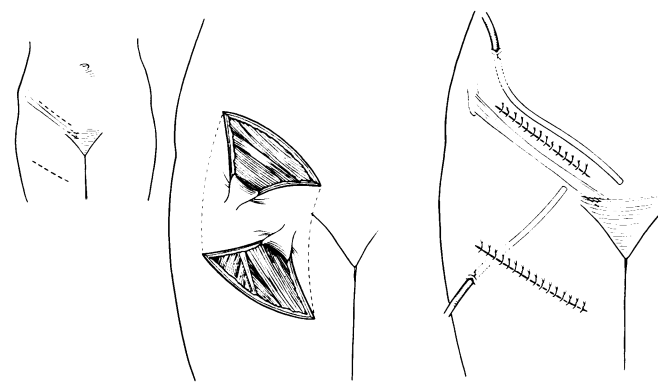

Figure 3. Incisions, random cutaneous bipedicle flap, and surgical drain placement for ilioguinal lymphadenectomy.

Table 1. PATIENT CHARACTERISTICS

Patient Characteristics	Treatment Group		
	Treatment	Control	p Value*
Mean age (yrs)	53.7	61.5	0.10
No. of smokers	4	9	0.30
Mastectomy (N)	16	17	—
Lymphadenectomy (N)	8	10	—

* Student's t test.

ischemia was reduced from 44.93 μg in the control group to 16.33 μg in the group treated with DMSO. This difference was highly statistically significant (p = 0.01).

The areas of flap ischemia for the treatment and control patients, analyzed according to operation, are plotted in Figure 5 (lymphadenectomy patients) and Figure 6 (mastectomy patients). In these analyses, there was still less flap ischemia in the treatment groups, but these differences only approached statistical significance (p = 0.06, lymphadenectomy patients; p = 0.08, mastectomy patients). The mean areas of ischemia for the treatment and control groups, analyzed according to type of operation, are listed in Table 2.

Performance of cisplatin hyperthermic isolation limb perfusion did not significantly affect the area of flap ischemia (p = 0.81). The area of flap ischemia was not significantly greater in smokers than in nonsmokers (p = 0.58).

Side Effects

Many patients experienced erythema and warmth at the application site and the garlic-like breath odor characteristic of DMSO. Neither of these side effects was bothersome enough to cause noncompliance. Vesicles developed at the site of application in one patient. No other toxicities were observed or reported.

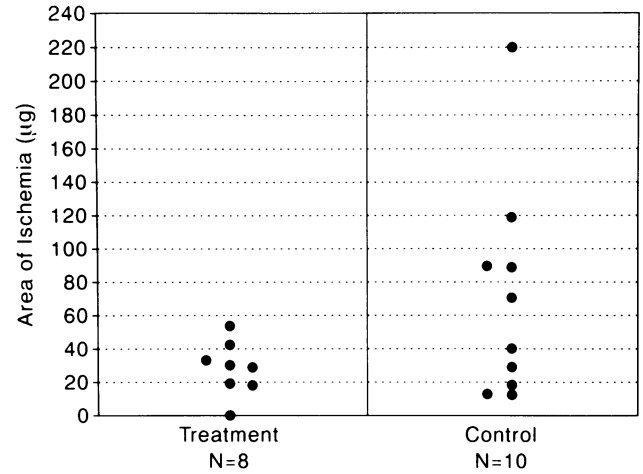

Figure 5. Areas of flap ischemia (measured in micrograms by cut and weigh technique) for treatment (topical DMSO) and control subjects in the ilioinguinal lymphadenectomy group (p +0.06).

DISCUSSION

A better understanding of skin physiology and blood supply has allowed surgeons to design flaps with greater viability. The advent of microvascular anastomotic techniques has permitted the transfer of tissues from distant parts of the body (*i.e.*, free flaps). Yet despite these advancements, flap necrosis and ischemia still limit the ability of surgeons to adequately span tissue gaps left by disease processes, surgical resection, or trauma. Flap loss

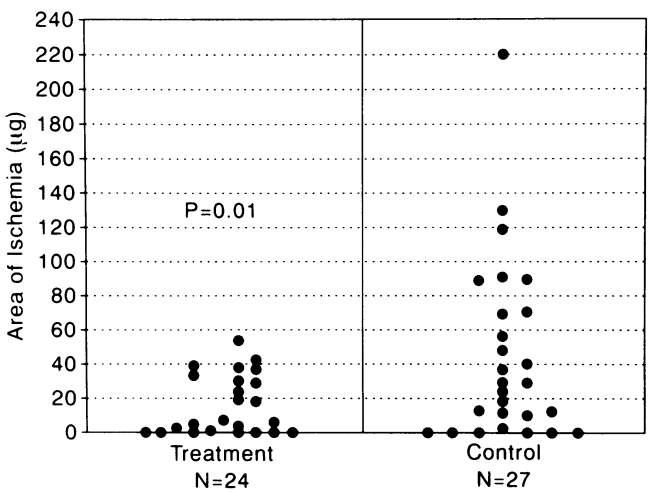

Figure 4. Areas of flap ischemia (measured in micrograms by cut and weigh technique) for all study patients. The difference between the treatment group (topical dimethylsulfoxide) and the control group was highly significant (p = 0.01).

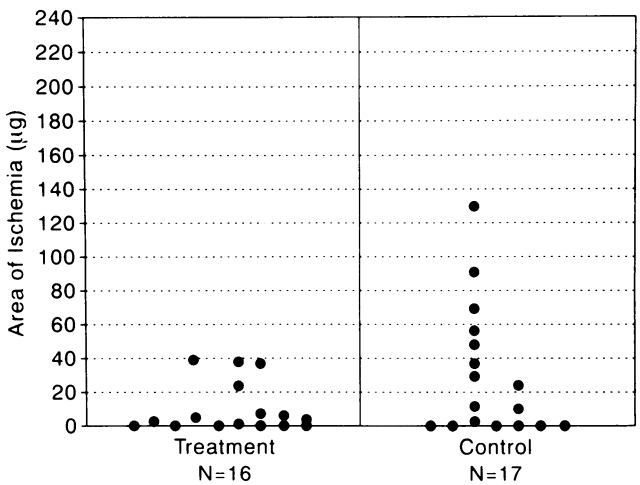

Figure 6. Areas of flap ischemia (measured in micrograms by cut and weigh technique) for treatment (topical DMSO) and control subjects in the mastectomy group (p = 0.08).

Table 2. AREA OF FLAP ISCHEMIA FOR TREATMENT AND CONTROL GROUP BY OPERATION

Operation Performed (N)	Area of Ischemia (μg)		
	Treatment Group	Control Group	p Value*
Mastectomy (33)	10.38	30.00	0.08
Lymphadenectomy (18)	28.25	70.30	0.06
All patients (51)	16.33	44.93	0.01

* Student's t test.

contributes to patient morbidity and increased health care costs.

Our study showed that the topical administration of 60% DMSO significantly reduced flap ischemia in humans undergoing mastectomy and ilioinguinal lymphadenectomy. Furthermore, these differences were not attributable to differences in tobacco use, age, or cisplatin perfusion therapy. Therefore, we attribute the differences to the use of topical DMSO. When the two surgical groups were analyzed separately, though, the benefit only approached significance, most likely due to the smaller numbers of patients included in these independent analyses.

Our results concur with those of Adamson et al.,[6,15] who observed a beneficial effect of DMSO on skin flap survival in the rat model. They applied 70% DMSO topically to rat dorsal pedicle flaps and observed a reduction in tissue sloughing from severe in all control rats to minimal sloughing in two thirds of the experimental group and moderate tissue loss in the remaining one third. He also showed dilatation of small- and intermediate-sized vessels in rabbits' ears treated with DMSO. Roth,[11] with the same experimental model as Adamson et al., found increased flap survival with the topical application of both 10% and 70% DMSO. Carpenter et al.[4] and Grossman et al.[12] showed significant improvement in flap survival with intraperitoneal administration of DMSO. The former study used a venous occlusion model in studying rat epigastric skin flaps and gave DMSO with reperfusion and after operation. The latter study showed near-total survival of rat dorsal skin flaps with intraperitoneal DMSO. Conversely, other investigators have found only marginal or even detrimental effects of dimethylsulfoxide in the rat model.[13,14] Our study is the first to show the beneficial effect of DMSO on flap viability in humans.

The mechanisms by which DMSO increases flap viability are not fully understood. The flaps created during the mastectomy and lymphadenectomy procedures were cutaneous advancement flaps. The blood supply to this type of flap is derived from the musculocutaneous arteries at the flap's base. The distal aspects of the flap, the area most vulnerable to ischemia, relies on collateral blood flow from the subdermal arterial plexus. The beneficial effects of DMSO on flap survival may be secondary to DSMO's vasodilatory action at the subdermal arterial plexus, its ability to prevent platelet aggregation within these vessels, or its free radical scavenger activity in the distal aspects of the flap or both.

Dimethylsulfoxide has been shown to release histamine, causing vasodilation.[21] The use of an antihistamine has prevented the beneficial effect of DMSO on skin flaps.[6] Dimethylsulfoxide also increases prostaglandin E_1, a vasodilator,[22] increases cyclic adenosine monophosphate (by inhibiting phosphodiesterase), which exerts strong platelet deaggregation,[7,8] and blocks prostaglandin $F_{2\alpha}$ receptors and synthesis; prostaglandin $F_{2\alpha}$ causes platelet aggregation and vasoconstriction.[23] However, using Rubidium-86 labeling in a modification of Sapirstein's method, Roth[11] was unable to show differences in estimated blood flow between the control and treatment flaps. He concluded that some mechanism other than vasodilatation was responsible for the benefits seen with DMSO.

Several species of free radicals are formed in ischemic and reperfused tissues and are being increasingly recognized as important mediators of cellular injury.[9,24,25] The DMSO's unique structure allows it to act as an oxidizing or reducing agent and, therefore, as a free radical scavenger.[10] Free radical scavengers have been shown to improve survival of island and free skin flaps in the rat model.[26,27]

Administration of DMSO is safe and well tolerated. The two main toxicities that have caused concern over DMSO's widespread clinical use are 1) hemolysis after intravenous administration of high concentrations (> 2 mg/kg, in > 10% solution, intravenously over < 30 minutes) and 2) the potential for ophthalmologic toxicity. In toxicologic studies, the former was found to be transient and without renal or other sequelae,[2,3,28] and refractive index changes in the dog, rabbit, and pig lenses were observed at 50 to 100 times the human therapeutic dose.[2] Furthermore, human studies, including one involving the direct instillation of DMSO into the eye, have not been able to elicit ophthalmologic toxicity.[2,29,30] The local side effects of transient erythema and burning at the site of topical application (secondary to histamine release) and the garlic-like breath odor that results from DMSO's small amount (3%) of pulmonary excretion have been well described,[1,21] and were apparent in our study but did not affect compliance. Aside from the one patient in whom vesicles developed at the site of application, no toxicities were noted. The safety of DMSO use was demonstrated in our study. This is in agreement with the experience reported in the literature.[2]

Dimethylsulfoxide currently is used as an industrial

solvent and as a cryoprotective agent. In the clinical setting, there is current U.S. Food and Drug Administration approval only for the use of 50% DMSO for bladder instillation for treatment of interstitial cystitis. In Oregon, though, the state legislature has allowed DMSO to be used for the treatment and study of any disease, facilitating the performance of our study. Despite the federal restrictions, DMSO has been used in the treatment of various clinical conditions such as musculoskeletal injuries, connective tissue disorders, inflammatory conditions, and head and spinal cord injuries, mostly outside of the clinical trial setting. Its antineoplastic properties have been demonstrated *in vitro* against breast, colon, ovarian, and other cancers.[31–35] Dimethylsulfoxide is very effective in penetrating the stratum corneum and enhances transport of many substances through the skin and across cellular membranes; therefore, interest has been shown in its development as a carrier agent.[36–38] Dimethylsulfoxide has many potential medicinal applications, but controlled clinical trials demonstrating its efficacy are lacking.

CONCLUSIONS

We have shown that DMSO can limit tissue damage secondary to impaired vascular supply and surgical trauma after cutaneous flap construction. Such use could substantially reduce patient morbidity, hospital stay, number of outpatient visits, and need for subsequent operations, thereby reducing overall cost. Additionally, our findings may have applicability to other disease states where the mechanisms of tissue damage are similar, such as reimplantation, peripheral vascular disease, and ischemic injury of the myocardium or central nervous system. As more is learned about the cellular and metabolic changes that occur with tissue injury, it may be possible to develop and apply specific pharmacologic agents that protect against these changes. Dimethylsulfoxide has potential as such an agent.

Based on the results of this study, we recommend the topical application of DMSO following operations in which skin flaps are created, and call for further investigation into DMSO's efficacy in ameliorating tissue injury in other disease states.

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Discussion

DR. WILLIAM P. GRAHAM III (Carlisle, Pennsylvania): It really was rather exciting to see that this subject was going to be discussed, because this goes back a long way with interest that Dr. Herndon Lehr had at the University of Pennsylvania in the 1960s using dimethylsulfoxide (DMSO) as a cryopreservative. Unfortunately, at that time, the Food and Drug Administration (FDA) stepped in and indicated that it was not something that they wished in any way to come in contact with a human patient. The rats were fine, the monkeys were fine. In addition to that, at that time, working with DMSO was a bit like being an alchemist, because it had a long history of use in veterinary medicine and yet we had very little idea of its action. It is nice to see today the sophistication that now has been attributed to the various actions of DMSO.

I certainly agree with the conclusions of the paper, based on our experimental work, that it does help. It is not going to save an irreversibly dead flap, but it is certainly going to make some of the flap that might also have gone by the boards more viable.

The one question I would raise: Given the level of complications in the control patients, have you given any thought to modifying your surgical approach and addressing the issues that we all are concerned about in surgical trauma and the things that we might be doing mechanically that are leading to our problem and therefore being able to avoid a bail-out with something like DMSO? I would also like you to comment on your selection of the particular concentration and the addition of the urea.

I certainly enjoyed the paper and I think that it does have an applicability that hopefully will lead to enlightenment such that the FDA will allow us to use.

DR. M. J. JURKIEWICZ (Atlanta, Georgia): I rise to compliment the authors on a very nice presentation. I do have several questions, some of which Dr. Graham already has raised. You alluded to toxicity. Because there are no toxicity studies in humans, did you notice anything in these patients that might relate to that?

The second thing is the practicality of the application of dimethylsulfoxide (DMSO) every 4 hours in today's practice environment where patients leave the hospital sooner. This is going to create either sleep-deprived family or lack of compliance. It is another issue.

In the abstract, you allude to the measurement of ischemia. How was the ischemia actually measured? I am not clear at all what you are measuring. There are white flaps and there are blue flaps. The white flaps and blue flaps have different kinds of lines of demarcation, and I would think that one would be a lot safer in measuring subsequent necrosis. Finally, you gave no data on subsequent necrosis at all as near as I can tell.

DR. WILLIAM S. FLETCHER (Closing Discussion): In response to Dr. Graham's question about modifying the surgical approach, I think he is probably referring to inguinal dissection. When I first came into surgery, the reported complication rate of extensive inguinal dissections was approximately 80%. Subsequently, it went down to 50%. But, it is still a big problem, especially for extensive nodal involvement in the groin and a large flap.

The bipedicle technique that we have used for many years I learned from Donald Rochlin when he was at UCLA, and it has been the most effective flap we have used. We still see some necrosis in the center of the flap if the retraction is too vigorous. But it works very well in general. And we do try to use the most appropriate flap wherever we can and trim off any marginal edges. But I do not think that a major change in the procedures would contribute much more.

The selection of concentration primarily was one of convenience. Before this study in which we wished to standardize the dose, we used everything up to 100% and it is all pretty well tolerated. One hundred percent gives you more erythema and more odor of dimethylsulfoxide (DMSO).

To answer the other question from Dr. Jurkiewicz about the concentrations; we used 60% DMSO, 10% urea, and 30% water.

The toxicity in humans has not been addressed in this country, as you know. There is very extensive literature on the use of DMSO in humans outside of this country, and there is little or no toxicity. If you give DMSO to dogs in concentrations greater than 100 times what we describe, cataracts have been described. At very high concentrations, you can see some hemolysis. This was discovered in studies to try to prevent damage from spinal cord and brain trauma. That hemolysis did not seem to result in any permanent damage.

The question of practicality and compliance I think can be dealt with by the fact that it is the first day or two that is most important. We just provide the patient with a spray bottle, and