

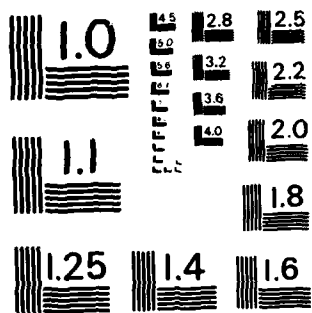
AD-A131 017 THE HEALING AND TRANSPLANTATION OF SKULL(U) INSTITUTE 1/1
FOR MEDICAL RESEARCH SAN JOSE CA NEUROSKELETAL
TRANSPLANTATION LAB D J PROLO ET AL. 25 JUN 83

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THE HEALING AND TRANSPLANTATION OF SKULL

Final Report
Office of Naval Research
Contract N00014-81-C-0354

June 25, 1983

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Principal Investigator

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Research Director

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THE HEALING AND TRANSPLANTATION OF SKULL

A. SUMMARY

Over the past several years investigators at the Neuroskeletal Transplantation Laboratory, The Institute for Medical Research, San Jose, California, have studied the transplantation of human and animal skull. Our goals have been the following: (1) to understand the healing of fresh and preserved (frozen) autogeneic human skull; (2) to investigate the mechanisms by which autogeneic and allogeneic canine skull becomes incorporated into host cranium; (3) to modify allogeneic skull implants in order that repair be augmented; (4) to develop an allogeneic malleable skull implant for universal use in human cranioplasty; (5) to further the clinical application of allogeneic human bone, dura mater and fascia lata by providing a research base for progress in the transplantation of these tissues; (6) to maintain a human tissue bank for clinical distribution of bone, dura mater and fascia lata; (7) to participate in the formation of standards for the banking of human musculoskeletal tissue; (8) to disseminate knowledge of tissue banking to neurosurgeons as primary providers and utilizers of transplantable tissue.

As a result we have published a number of papers and communicated our progress at professional meetings (see Publications). Our paper on fresh and preserved autogeneic skull reviews the cellular, roentgenographic and scintigraphic responses in 5 patients with fresh autogeneic skull and 53 patients who had delayed cranioplasty with frozen autogeneic skull. Because the availability and use of an allogeneic tissue is vastly expanded by sterilizing cadaver bone procured nonsterilely, we have investigated and reported on the effectiveness, kinetics, and safety of ethylene oxide for sterilizing human bone, dura mater and fascia lata. Forthcoming from these studies is the protocol by which we sterilize and process these tissues. Since April, 1977, our laboratory has provided over 5,000 deposits of bone and over 1,400 sections of dura mater and fascia lata for human implantation. No reports of infection have occurred among patients receiving these tissues.

We have also published the results of sterilizing allogeneic dog grafts with ethylene oxide, gamma irradiation and chloroform:methanol and on subsequent graft remodeling when implanted in the canine skull. Grafts sterilized with

chloroform:methanol remodeled best, but there was little difference between bone sterilized by other means and bone aseptically procured and frozen only. The results confirmed that sterilization did not harm grafts beyond freezing alone.

In the course of operating a tissue bank for human bone, we occasionally have observed bone that is discolored yellow. We confirmed that this discoloration was due to tetracycline and estimated the total body burden of tetracycline carried by several donors. From these estimates we concluded that the slow release of tetracycline from bone in maternal adults containing these large amounts of tetracycline would not be deleterious to fetal bone and tooth development.

The major thrust of our research over the past three years has been to study the time course of incorporation and remodeling of transplanted skull at 6 weeks, 12 weeks and 6 months, and to compare grafts/implants prepared by different methods. One of the most promising methods of bone preparation is that devised by Marshall Urist (Urist, M.R., Mikulski, A. and Boyd, S.D. A chemosterilized antigen-extracted autodigested alloimplant for bone banks. Arch. Surg. 110: 416-428, 1975.) We therefore have compared incorporation and remodeling of these decalcified, autolysed, antigen-extracted, allo- and autoimplants (AAA bone) to that of the fresh autograft (the most suitable type of bone graft). In one experiment decalcified, AAA implants were fortified with fresh cancellous bone from the recipient's iliac crest so that this composite graft might be compared to AAA bone without fresh marrow, and to the fresh autograft at 6 months. There was no difference between the composite graft and the decalcified (AAA) alloimplant without fresh marrow. In another experiment at 6 months, we compared the fresh autograft to the frozen autograft and to the decalcified (AAA) implant of autogeneic bone. 10.3

At the earlier times, 6 and 12 weeks, the fresh autograft and decalcified (AAA) alloimplant were compared. At these times we instituted a pilot study to monitor remodeling of allogeneic decalcified (AAA) bone powder and an implant of such bone powder placed over a decalcified (AAA) allogeneic implant.

For these studies the experimental animal of choice, the domestic dog, has a satisfactorily large calvaria for studying incorporation, remodeling and resorption of cranial grafts, has physiological characteristics approaching that of primates, and is relatively inexpensive to procure and maintain. Because of the comparatively large skull, four 18 to 20 mm defects can be trephined in parietal bone. One defect left unfilled controlled for the highly variable spontaneous repair, whereas the other three defects accommodated grafts. By having each animal serve as its own control, we have the option of subtracting spontaneous repair from new bone deposited in each graft for each dog or of correlating spontaneous repair of the defect with new bone formation within the grafts. For the experimental design see Figure 1.

Results from 6 months and 12 weeks are complete. Data from the 6-week study, partially complete, are still being analyzed. We have quantified the percent defect filled by the graft and the percent spontaneously filled by ingrowing new bone (Table 1); the percent porosity of the graft or implant (Table 2); the percent new bone of the graft or implant as labeled cumulatively by tetracycline (Table 3); and the area of that new bone (Table 4). Percentages were arc sine transformed for statistical analysis. The statistical results thus far obtained are summarized in Table 5.

In brief, our results are summarized:

1. Spontaneous repair of cranial defects is highly variable among dogs. Most of the ingrowth occurs before 6 weeks. Later, between 12 weeks and 6 months, the dogs with thicker skulls continue to show spontaneous repair of defects.
2. The fresh autograft is the superior matrix for reconstructing skull.
3. Both decalcified (AAA) allo- and autografts undergo greater resorption than fresh autografts, but a greater percentage of the remaining decalcified graft is new bone.
4. Decalcified (AAA) grafts placed in recipient skulls with large diploe (thick skulls) remodel better than those placed in skulls with very little diploic space (thin skulls).

5. ✓ Spatial patterns of new bone formation differ in decalcified (AAA) auto- and alloimplants from fresh and frozen autografts. Within the center of the fresh and frozen autografts, repair tends to be focal about Haversian systems, whereas repair tends to be continuous in broad fields in decalcified auto- and alloimplants. Near the graft/skull margin new bone is continuous irrespective of graft type.

6. Packing fresh cancellous bone from the recipient's iliac crest over, and around a decalcified (AAA) alloimplant provides no advantage over the decalcified (AAA) implant alone.

7. ✓ At 12 weeks decalcified (AAA) allogeneic bone powder (size undetermined) and such bone powder in conjunction with decalcified cortical bone remodeled about the same as the decalcified (AAA) implants. However, earlier at 6 weeks decalcified bone powder has undergone greater remodeling than either the decalcified (AAA) allograft or the fresh autograft. However, the number of dogs is too small for this observation to be conclusive. Results with bone powder are, however, promising and should be investigated further.

8. Fresh autografts and decalcified (AAA) alloimplants progressively acquire more new bone from 6 weeks to 6 months. Whereas the porosity of the fresh autograft decreases with time, that of the decalcified (AAA) alloimplant may even increase.

9. We observe from microradiographs that new bone is less dense (less radiopaque) than surrounding old graft or host skull at 6 and 12 weeks. By 6 months the difference is much less obvious.

10. The most obvious way that cranial grafts remodel is by new bone growing in from the margins toward the center. The percent of new bone near the skull/graft margin is always greater than further within the graft. With time more of the central cortical bone is replaced so that by 6 months the percent new bone in the center of both fresh autografts and decalcified (AAA) alloimplants is greater than at the margins at 6 and 12 weeks (Table 6).

FIGURE 1
EXPERIMENTAL DESIGN

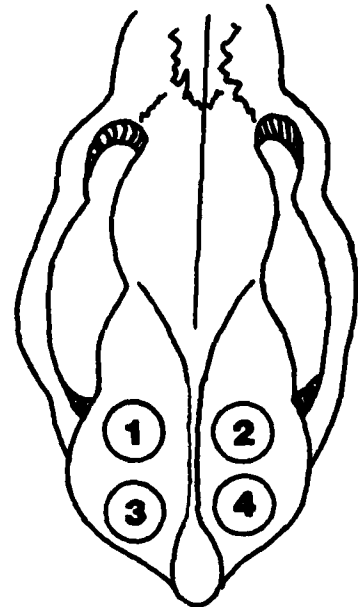
Cranial Disks: Fresh, Frozen, Decalcified (AAA)



Decalcified (AAA) Bone Powder



Decalcified (AAA) Bone Powder over Decalcified (AAA) 1/2 Skull Disk



General Design

1. Defect unfilled -- worst case situation
2. Fresh Autograft -- best case situation
3. Experimental Bone Implant
4. Experimental Bone Implant

Experiment 1. 6 Months, Allogeneic Implants

1. Defect
2. Fresh Autograft
3. Decalcified (AAA) Alloimplant
4. Composite Graft of Decalcified (AAA) Alloimplant

Experiment 3. 12 Weeks

1. Defect
2. Fresh Autograft
3. Decalcified (AAA) Alloimplant
- 4a. Decalcified (AAA) Bone Powder
- 4b. Decalcified (AAA) Bone Powder over Decalcified (AAA) 1/2 Skull Disk

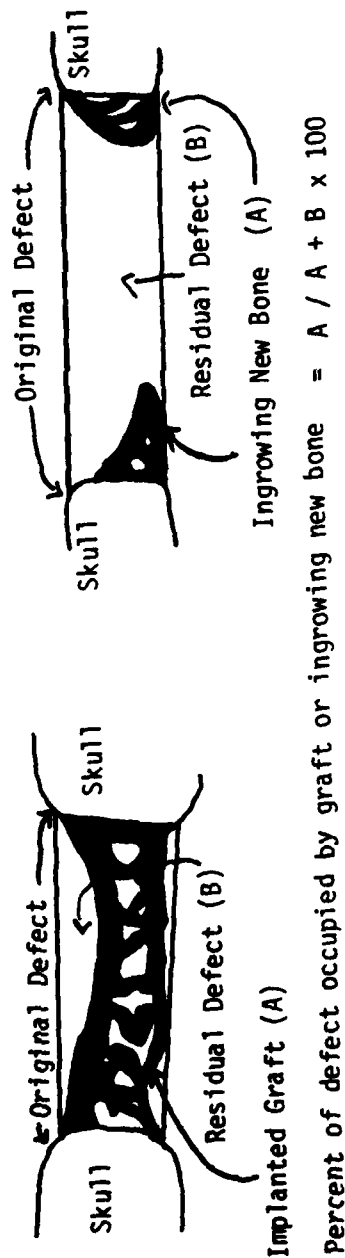
Experiment 2. 6 Months, Autogeneic Bone

1. Defect
2. Fresh Autograft
3. Frozen Autograft
4. Decalcified (AAA) Autograft

Experiment 4. 6 Weeks

1. Defect
2. Fresh Autograft
3. Decalcified (AAA) Alloimplant
- 4a. Decalcified (AAA) Bone Powder
- 4b. Decalcified (AAA) Bone Powder over Decalcified (AAA) 1/2 Skull Disk

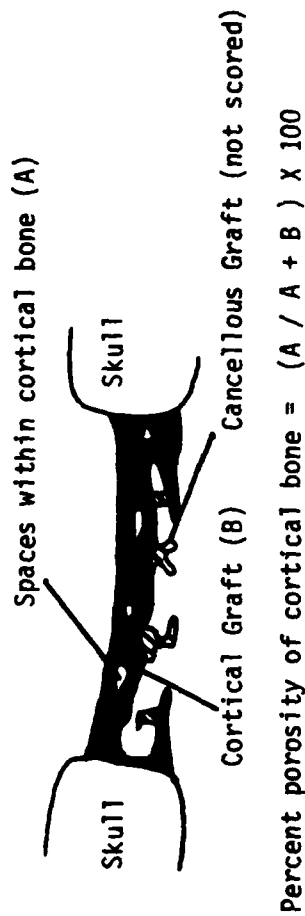
TABLE 1. PERCENT OF DEFECT FILLED



Defect	6 weeks	12 weeks	6 months
Fresh autograft	10.9 (7) (2.1 - 25.4)*	10.8 (8) (1.8 - 27.9)	19.7 (16) (4.0 - 66.5)
Frozen autograft	93.5 (6) (89.1 - 95.5)	94.1 (8) (86.6 - 98.9)	98.0 (16) (87.5 - 100)
Decalcified (AAA) autograft			75.8 (8) (59.8 - 88.3)
Decalcified (AAA) allograft	71.4 (6) (53.0 - 91.1)	58.0 (8) (40.2 - 91.9)	51.9 (7) (36.4 - 100)
Decalcified (AAA) bone powder	77.5 (3) (54.1 - 90.0)	69.1 (4) (55.3 - 83.3)	78.2 (16) (39.7 - 100)
Decalcified (AAA) bone powder + decalcified 1/2 disk	88.9 (3) (66.7 - 100)	63.2 (3) (50.6 - 85.6)	

* Mean, number of grafts, range of values

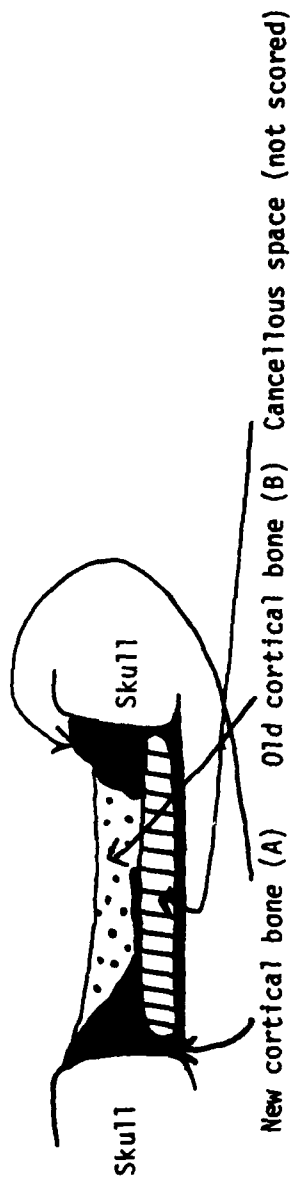
TABLE 2. PERCENT POROSITY



	6 weeks	12 weeks	6 months
Defect	31.3 (7) (26.2 - 47.6)*	18.9 (8) (6.0 - 39.0)	19.5 (16) (4.0 - 37.5)
Fresh autograft	17.5 (6) (12.8 - 27.9)	14.4 (8) (9.7 - 23.7)	11.8 (16) (6.0 - 17.8)
Frozen autograft			15.9 (8) (7.8 - 28.2)
Decalcified (AAA) autograft			23.1 (7) (13.1 - 34.1)
Decalcified (AAA) allograft	20.2 (6) (12.9 - 34.3)	19.7 (8) (9.4 - 28.3)	30.8 (16) (17.3 - 52.9)
Decalcified (AAA) bone powder	NA	NA	NA
Decalcified (AAA) bone powder + decalcified 1/2 disk	NA	NA	NA

* mean, number of grafts, range of values

TABLE 3. PERCENT NEW BONE



$$\text{Percent new cortical bone} = A / (A + B) \times 100$$

	6 weeks			12 weeks			6 months		
Defect	96.0	(7)	(94.5 - 100) *	97.3	(8)	(90.2 - 100)	89.4	(16)	(73.3 - 100)**
Fresh autograft	27.6	(6)	(17.7 - 38.3)	51.1	(8)	(23.9 - 86.4)	67.1	(16)	(55.5 - 88.1)
Frozen autograft							53.5	(8)	(27.2 - 84.3)
Decalcified (AAA) autograft							78.1	(7)	(68.2 - 88.5)
Decalcified (AAA) allograft	22.9	(6)	(7.1 - 57.3)	42.1	(8)	(24.8 - 56.5)	85.4	(7)	(63.3 - 96.1)
Decalcified (AAA) bone powder	43.9	(3)	(32.7 - 53.7)	42.4	(4)	(12.6 - 74.8)			
Decalcified (AAA) bone powder + decalcified 1/2 skull disc	20.3	(3)	(9.3 - 40.0)	48.6	(3)	(32.7 - 59.8)			

* mean, number of grafts, range of values

** Some material in front of the tetracycline-labelled new bone recorded blue and was radiolucent.

TABLE 4 mm^2 NEW BONE

	6 weeks	12 weeks	6 months
Defect	5.4 (7) (0.8 - 12.3)	5.9 (8) (0.7 - 17.9)	9.5 (16) (2.1 - 26.1)
Fresh autograft	11.9 (6) (6.6 - 16.7)	18.7 (8) (7.1 - 25.9)	27.1 (16) (16.7 - 37.3)
Frozen autograft			17.3 (8) (4.7 - 32.0)
Decalcified (AAA) autograft			16.3 (7) (4.1 - 23.4)
Decalcified (AAA) allograft	9.1 (6) (3.1 - 24.7)	13.1 (8) (5.0 - 28.3)	22.4 (16) (10.4 - 42.2)
Decalcified (AAA) bone powder	17.6 (3) (10.7 - 23.8)	13.9 (4) (3.5 - 30.2)	
Decalcified (AAA) bone powder + decalcified 1/2 skull disk	13.5 (3) (3.5 - 32.3)	11.7 (3) (7.2 - 17.4)	

TABLE 5

STATISTICALLY SIGNIFICANT DIFFERENCES BETWEEN TREATMENTS

	Experiment 1: 6 Months Allogeneic Series	Experiment 2: 6 Months Autogeneic Series	Experiment 3: 3 Months
% Defect Filled	Fresh autografts > decalcified and composite allografts, $p < 0.025$.	Fresh autografts > decalcified or frozen autografts, $p < 0.005$.	Fresh autografts > decalcified allografts, $p < 0.001$
% New Bone	No difference between decalcified and composite allografts.	Frozen autografts < fresh and decalcified autografts, $p < 0.05$.	No difference between fresh autografts and decalcified allografts.
% Porosity	Decalcified and composite allografts > fresh autografts, $p < 0.001$.	Decalcified autografts > fresh autografts, $p < 0.005$, and frozen autografts, $p < 0.05$.	No difference between fresh autografts and decalcified allografts
mm ³ New Bone	No difference between decalcified and composite allografts.	Fresh autografts > frozen and decalcified autografts, $p < 0.005$.	No difference between fresh autografts and decalcified allografts.

TABLE 6 PERCENT NEW BONE NEAR THE GRAFT/SKULL MARGIN VS THAT WELL WITHIN THE GRAFT

	6 weeks		12 weeks		6 months	
	margin	center	margin	center	margin	center
Fresh autograft	45.8	27.6	77.8	51.3	84.5	67.1
Frozen autograft					82.1	53.5
Decalcified (AAA) autograft					94.8	78.1
Decalcified (AAA) allograft	61.8	22.6	89.3	42.1		
Decalcified (AAA) bone powder	83.5	43.9	82.2	42.4		
Decalcified (AAA) bone powder + decalcified 1/2 skull disk	54.2	20.3	85.5	48.6		

B. PUBLICATIONS (Listed in Chronological Order)

1. Prolo, D.J.: Current thoughts on standards by a neurosurgeon. In Sell, K.W., Perry, U.P. and Vincent, M.M. (eds): American Association of Tissue Banks, Proceedings of the 1977 Annual Meeting. American Association of Tissue Banks, 12111 Parklawn Drive, Rockville, MD, 1978, pp 115-116.
2. Prolo, D.J., Burres, K.P., McLaughlin, W.T. and Christensen, A.H.: Autogenous skull cranioplasty: fresh and preserved (frozen), with consideration of the cellular response. Neurosurgery 4: 18-29, 1979.
3. Prolo, D.J.: The neurosurgeon in transplantation: provision and use of cadaver tissue and organs. Neurosurgery 6: 342-343, 1980.
4. Prolo, D.J., Pedrotti, P.W., White, D.H.: Ethylene oxide sterilization of bone, dura mater, and fascia lata for human transplantation. Neurosurgery 6: 529-539, 1980.
5. Prolo, D.J.: Use of transplantable tissue in neurosurgery, in Carmel, D.W. (ed): Clinical Neurosurgery Williams & Wilkins, Baltimore, 1981, pp 407-417.
6. Prolo, D.J.: The moral legitimacy of organ transplantation, Neurosurgery 8: 511-512, 1981.
7. Oklund, S.A., Prolo, D.J. and Gutierrez, R.V.: The significance of yellow bone, JAMA 246: 761-763, 1981.
8. Prolo, D.J. and Oklund, S.A.: Sterilization of bone by chemicals, in Friedlaender, G.E. and Mankin, H.J. (eds): Immunobiology of Osteochondral Allografts, Little, Brown and Co., Boston, 1983.
9. Prolo, D.J., Pedrotti, P.W., Burres, K.P. and Oklund, S.: Superior osteogenesis following chemical sterilization of transplanted allogeneic canine skull. Clin Orthop. 168: 230-242, 1982.

10. Prolo, D.J.: Cranial defects and cranioplasty. In Wilkins, R.H. and Rengachary, S.S. (eds): Neurosurgery. New York, McGraw-Hill, 1984, Part VIII, Chapter 194 (in press).

11. Prolo, D.J.: Transplantation of cadaver tissues and organs. In Wilkins, R.H. and Rengachary, S.S. (eds): Neurosurgery. New York, McGraw-Hill, 1984, Part XN, Chapter 338 (in press).

12. Prolo, D.J., Gutierrez, R.V., DeVine, J.S., Oklund, S.A.: The clinical utility of allogeneic skull discs in human craniotomy (in preparation).

13. Oklund, S.A., Prolo, D.J., Gutierrez, R.V., and King, S.E. Remodeling of cranial grafts in the canine skull at 6 weeks, 12 weeks and 6 months (in preparation).

C. COMMUNICATIONS

1. Prolo, D.J.: Current thoughts on standards by a neurosurgeon. Presented at the First Annual Meeting, American Association of Tissue Banks, May 1-4, 1977, Arlington, Virginia.

2. Prolo, D.J., McLaughlin, W.Y. and Rodrigo, J.J.: Viability of replaced frozen autograft skull. Presented at the 23rd Annual Meeting of the Western Neurosurgical Society, September 18-21, 1977, La Costa, California.

3. Prolo, D.J.: Autogenous skull cranioplasty: fresh and preserved (frozen) with consideration of the cellular response. Presented at the Second Annual Meeting, American Association of Tissue Banks, May 15-18, 1978, Boston, Massachusetts.

4. Pedrotti, P.W.: Ethylene oxide sterilization of bone, dura mater and fascia lata. Presented at the Second Annual Meeting, American Association of Tissue Banks, May 15-18, 1978, Boston, Massachusetts.

5. Prolo, D.J., Pedrotti, P.W. and Erickson, L.A.: Sterilization of bone and dura with ethylene oxide. Presented at the 24th Annual Meeting of the Western Neurosurgical Society, October 8-11, 1978, Pebble Beach, California.

6. Prolo, D.J.: Techniques of preservation and sterilization of skull and dura. Presented at the Northern California Chapter of the American College of Surgeons, May 12, 1979, San Francisco, California.

7. Prolo, D.J., Pedrotti, P.W. and Burres, K.P.: Osteogenesis in lyophilized canine skull sterilized by three different methods: a preliminary report. Presented at the Third Annual Meeting, American Association of Tissue Banks, May 28-30, 1979, New Orleans, Louisiana.

8. Prolo, D.J., Pedrotti, P.W., White, D.H.: Ethylene oxide sterilization of bone and dura: effectiveness, kinetics, safety and biological response. Presented at the 25th Annual Meeting of the Western Neurological Society, September 23-26, 1979, Scottsdale, Arizona.

9. Prolo, D.J. and Rodrigo, J.J.: The neurosurgeon in transplantation. Presented at the 25th Annual Meeting of the Western Neurosurgical Society, September 23-26, 1979, Scottsdale, Arizona.

10. Prolo, D.J.: Superior osteogenesis following chemical sterilization of allogeneic canine skull. Presented at the Fourth Annual Meeting, American Association of Tissue Banks, May 11-15, 1980, Washington, D.C.

11. Oklund, S.A.: Significance of yellow bone. Presented at the Fourth Annual Meeting, American Association of Tissue Banks, May 11-15, 1980, Washington, D.C.

12. Prolo, D.J.: Use of transplantable tissue in neurosurgery. Presented at the Congress of Neurological Surgeons, October 5-10, 1980, Houston, Texas.

13. Prolo, D.J. and Oklund, S.A.: Sterilization of bone by chemicals. Presented at the Invitational Symposium, "Immunobiology of Osteochondral Allografts," NIH, April 12-15, 1981, Bethesda, Maryland.

14. Oklund, S.A., Prolo, D.J. and Gutierrez, R.V.: Healing of canine skull defects filled with chemically treated allogeneic bone, Presented at the Fifth Annual Meeting, American Association of Tissue Banks, June 14-18, 1981, St. Louis, Missouri.

15. Oklund, S.A., Prolo, D.J., Devine, J.S., King, S.E.: Operating a small bone bank: procurement, processing and packaging. Presented at the Seventh Annual Meeting, American Association of Tissue Banks, May 8-11, Inisbrook-Tarpon Springs, Florida.

D. MAJOR ACCOMPLISHMENTS

1. We have reported the first comprehensive description of the biological events following transplantation of fresh and deep frozen autogeneic human skull.

2. We have provided the first scientific evaluation of ethylene oxide as an effective and safe sterilant of bone for human implantation and established a protocol for its use.

3. We have distributed over 5,000 deposits of human bone and over 1,400 sections of dura mater and facia lata for implantation among thousands of patients without reported infection.

4. We have documented the antibiotic tetracycline as the cause of the yellow color of adult donor bone in a tissue banking laboratory and specified its safety in adults not allergic to tetracycline.

5. We have developed an experimental model to study healing of cranial bone in the dog. In each animal, repair of variously processed allogeneic skull has been compared with spontaneous regeneration of bone within a defect and

also within an optimal fresh autograft. Quantitative comparison of healing rate has been accomplished by random-point analysis of coronal microradiographs for radiodensity and of tetracycline fluorescence for appositional new bone formation.

6. By these methods we have established lipid extracted, autodigested, allogeneic canine skull as an osteoinductive implant and the superiority of this processing method over ethylene oxide and gamma irradiation for sterilization of bone.

7. We have successfully closed 115 small bur hole defects in 45 patients with allogeneic human skull sterilized with ethylene oxide prior to lyophilization. This work anticipates our plans to use malleable (partially decalcified) allografts to close larger defects.

8. We have studied the time course of cranial healing in the dog at 6 weeks, 12 weeks and 6 months investigating several methods of preparing cranial grafts.

9. The processed allograft has been found potentially suitable, but heretofore achieving about 80% of the optimal characteristics found in the fresh autograft.

10. We observed that decalcified segmental grafts tend to resorb. The cancellous space and the inner lower table of cortical bone (much thinner than the outer cortical layer in the dog) are resorbed as early as 6 weeks. It appears that by 6 months the only remnant of the original graft is the center of the outer cortical table that had not decalcified during processing. This bone is undergoing remodeling at 6 months. It may be necessary for some mineral to be present to impede resorption.

11. Cancellous fresh autografts tend also to resorb by 6 months. However, the cancellous bone which remains is mostly replaced with new bone. Even at 6 weeks cancellous bone is almost 100% tetracycline labelled.

12. We observed in several sections that portions of the frozen autograft appear to lose mineral. That is, there are areas of the old graft that record blue (old, nontetracycline labelled bone) under UV illumination that are radio-lucent on microradiographs. It is probable that nonviable bone does lose mineral before being resorbed.

13. At six months fresh, frozen and decalcified (AAA) autografts were tested for their ability to withstand a steady force generated by a mechanical press. For each specimen, a force vs. displacement curve was obtained. From these curves flexural rigidity, yield stress, and ultimate stress were calculated. Although variation is great, it appears that decalcified autografts are more prone to failure than fresh or frozen autografts. Further, by comparing x-rays taken before and after testing, decalcified and frozen grafts tend to multiple fractures which may be related to defects within the graft present before testing. Also, fractures tended to originate at the graft/skull margin suggesting that the new bone binding graft to skull is weaker than older graft material.

14. We have participated in the formation of guidelines for the banking of musculoskeletal tissues as active members of the American Association of Tissue Banks.

15. We have disseminated knowledge concerning the harvesting, processing and sterilization of bone, dura mater and fascia lata within the neuro-surgical community. Based on our work and that of others, use of these tissues is commonplace now among neurosurgeons across the United States.

REPORT OF INVENTIONS AND SUBCONTRACTS (Pursuant to "Patent Rights" Contract Clause) (See Instructions on Reverse Side)		FORM APPROVED OMB NO. 22-R160
1. NAME AND ADDRESS OF CONTRACTOR (Include Zip Code) Neuroskeletal Transplantation Laboratory Institute for Medical Research 751 South Bascom Avenue San Jose, CA 95128		2. CONTRACT NUMBER N00014-81-C-0354
3. TYPE OF REPORT (Check One) ☐ a. INTERIM ☒ b. FINAL		

SECTION I - INVENTIONS ("Subject Inventions")				
INVENTION DATA (Listed below are all inventions required to be reported) (If "None," so state)				
(i) NAME OF INVENTOR(S)	(ii) TITLE OF INVENTION	(iii) CONTRACTOR DISCLOSURE IDENTIFICATION NUMBER OR PATENT APPLICATION SERIAL NUMBER	(iv) CONTRACTOR ELECTS TO FILE U.S. PATENT APPLICATION	(v) CONFIRMATORY ASSIGNMENT FORWARDED TO CONTRACTING OFFICER
not applicable	no inventions		YES NO	YES NO

SECTION II - SUBCONTRACTS (Containing a "Patent Rights" Clause)			
SUBCONTRACT DATA (Listed is information required but not previously reported for Subcontract(s) (If "None," so state)			
(i) NAME AND ADDRESS OF SUBCONTRACTOR (Include Zip Code)	(ii) SUBCONTRACT NUMBER	(iii) SUBCONTRACT PATENT RIGHTS CLAUSE	(iv) WORK TO BE PERFORMED UNDER SUBCONTRACT

SECTION III - CERTIFICATION	
CONTRACTOR CERTIFIES THAT PROMPT IDENTIFICATION AND TIMELY DISCLOSURE OF SUBJECT INVENTIONS PROCEDURES HAVE BEEN FOLLOWED	SIGNATURE <i>Donald J. Prolo</i>
DATE 12/25/83	TITLE OF AUTHORIZED OFFICIAL (Print or Type) Donald J. Prolo, M.D. Principle Investigator

