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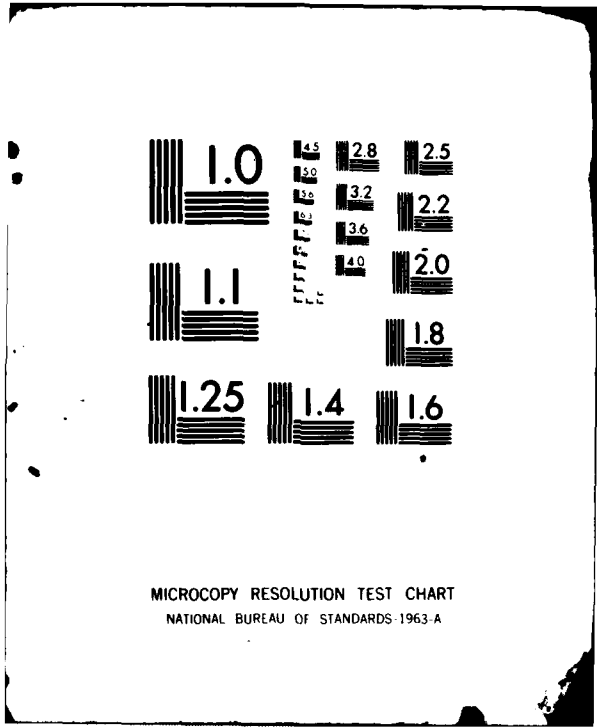
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TRANSPLANTATION OF HUMAN SKULL AND DURA MATER

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TRANSPLANTATION OF HUMAN SKULL AND DURA MATER

A. Summary

Over the past five years investigators at the Neuroskeletal Transplantation Laboratory, The Institute for Medical Research, San Jose, California, have studied the transplantation of human and animal skull and dura mater. Our goals have been the following: (1) to understand the healing of fresh and preserved (frozen) autogenous human skull; (2) to investigate the mechanisms by which autogenous 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.

Our paper on fresh and preserved autogenous skull reviews the cellular, roentgenographic and scintigraphic responses in 5 patients with fresh autogenous skull and 53 patients who had delayed cranioplasty with frozen autogenous skull. Because the availability and use of an allogeneic tissue is vastly expanded by a means of sterilization, a very major focus has been the development of a safe sterilant. Therefore, the effectiveness, kinetics, and safety of ethylene oxide has been comprehensively investigated and the results published for sterilization of human bone, dura mater and fascia lata. A protocol has been established. Since April, 1977, our laboratory has provided over 3000 deposits of

bone and over 1000 sections of dura mater or fascia lata after sterilization by ethylene oxide prior to lyophilization for human implantation. No reports of infection have occurred among patients receiving these tissues.

Our work already completed in 28 dogs compares the healing of allogeneic skull sterilized by ethylene oxide, gamma irradiation, and lipid extraction/enzyme inhibition with methanol-chloroform-iodoacetic acid. Presently in progress are studies in dog to assess healing in partially decalcified, chemically-treated implants of allogeneic skull.

Through our numerous presentations and publications we have informed neurosurgeons across the United States about the biology, proper use, and technical procedures involving the transplantation of human bone, dura mater and fascia lata.

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, Maryland, 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., Pedrotti, P.W., White, D.H.: Ethylene oxide sterilization of bone, dura mater, and fascia lata for human transplantation. Neurosurgery 6: 529-539, 1980.
4. Prolo, D.J.: The neurosurgeon in transplantation: provision and use of cadaver tissue and organs. Neurosurgery 6: 342-343, 1980.

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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, 1982. (in press)
9. Prolo, D.J., Pedrotti, P.W., Burrell, K.P. and Oklund, S.: Superior osteogenesis following chemical sterilization of transplanted allogeneic canine skull. Clin. Orthop. (accepted for publication).

C. Presentation (listed in chronological order)

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.T. and Rodrigo, J.J.: Viability of replaced frozen autograft skull. Presented at the 23rd Annual Meeting of the Western Neurosurgical Society, Sept. 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, Boston, Massachusetts, May 15-18, 1978.
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, Boston, Massachusetts, May 15-18, 1978.

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, Oct. 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 Third Annual Meeting, American Association of Tissue Banks, May 28-30, 1979, New Orleans, Louisiana.
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, Oct. 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.

D. Conclusions

1. Repair of autogenous fresh and preserved human skull of membranous derivation is identical with endochondral bone of the skeleton. Autogenous skull separated from its blood supply is metabolically intensely active after delayed implantation with resorption usually predominating over appositional new bone formation in the human. (See Section B, Publication 2).
2. Ethylene oxide is a safe, effective surface and interstitial sterilant of bone, dura mater and fascia lata provided it and its reaction products (ethylene glycol and ethylene chlorohydrin) are removed from tissues by lengthy lyophilization. (See Section B, Publication 3).
3. These tissues when sterilized by ethylene oxide may be implanted into human recipients with a strong likelihood of incorporation and revitalization.
4. Brilliantly yellow adult allogeneic human bone may be safely transplanted. This yellow fluorescence implies the donor's antemortem use of the chromophore tetracycline over long periods. Such bone may be safely implanted in patients not allergic to tetracycline. (See Section B, Publication 7).

5. Allogeneic canine cranium sterilized with gamma irradiation demonstrates impaired radiodensity at 6 months after implantation in an unrelated dog, and inferentially is less protective. (See Section B, Publication 9).
6. Allogeneic canine cranium sterilized with ethylene oxide serves an osteoconductive (trellis) function only. (See Section B, Publication 9).
7. Canine cranium chemically sterilized with methanol-chloroform-iodoacetic acid is a superior allogeneic implant for cranioplasty and provides an osteoinductive as well as an osteoconductive template for revitalization. (See Section B, Publication 9).

E. Major Accomplishments

1. We have reported the first comprehensive description of the biological events following transplantation of fresh and deep frozen autogenous 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 3000 deposits of human bone and over 1000 sections of dura mater and fascia 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 apositional new bone formation. Using these techniques, we have operated on 56 dogs.

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 75 small bur hole defects in 34 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 disseminated knowledge concerning the harvesting, processing and sterilization of bone, dura mater and fascia lata within the neurosurgical community. Based on our work and that of others, use of these tissues is commonplace now among neurosurgeons across the United States.

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

