

SECTION OF PLASTIC AND RECONSTRUCTIVE SURGERY

Faculty

Professor and Chief of Section

John A. Persing, M.D. (University of Vermont)

Professor

Michael Centrella, Ph.D. (University of Rochester)

Associate Professor

Thomas L. McCarthy, Ph.D. (University of Rochester)

J. Grant Thomson, M.D. (McGill University)

Assistant Professor

Joseph Shin, M.D. (University of Alabama)

Deepak Narayan, M.D. (Madras Medical College)

Lecturer

Bruce C. Fichandler, P.A. (Yale University)

Instructor/Chief Resident

Debora Pan, M.D. (Johns Hopkins)

Chang Kim, M.D. (Yale University)

Residents

Reza Momeni (Jefferson Medical College)

Javier D'Avila (Yale University)

Stephen Williams (Yale University)

Postdoctoral Associates

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Stephan Ariyan, M.D. (New York Medical College), MBA (University of New Haven)

Marvin S. Arons, M.D. (University of Maryland), D.M.D (Harvard University)

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David Leffell, M.D. (McGill University), Professor, Dermatology

OVERVIEW

Clinical, research and educational programs of the Section of Plastic Surgery continue to advance during the past academic year.

Through the combined efforts of the faculty, residents and research fellows, substantial progress has been made in this past year in the treatment of craniofacial and extremity disorders through minimally invasive techniques; in pioneering treatments with distraction osteogenesis in the craniofacial skeleton, particularly in the treatment of congenital airway anomalies; in oncologic treatments for melanoma and other cutaneous malignancies; in microsurgery; and, in aesthetic abnormalities of the face, trunk, and extremities

Research programs were spearheaded by Drs. Michael Centrella and Thomas McCarthy in defining intracellular and molecular mechanisms of bone production. They and colleagues have isolated promoter sequences for cytokines involved in bone production, and continue to elucidate mechanisms of control of bone production by steroid hormones and other intracellular signaling molecules. All plastic surgery residents presented their work at the annual Corso Plastic Surgery Research Day at Yale. The winners of the Research Award for 2003 are Dr. Reza Momeni for his work entitled, *Fully Coupled Microvascular Free Tissue Transfer* and Dr. Javier D'Avila for his work entitled, *Familial Angiosarcoma of the Scalp, Review of Angiosarcoma* in Connecticut.

Educational programs continue to emphasize a dynamic didactic schedule with differing formats, to encourage active participation in learning. These programs are supported by six visiting professorships annually to encourage diversity of discussion.

FACULTY ACCOMPLISHMENTS

Dr. John A. Persing, a Director of the American Board of Plastic Surgery, and Chair of the Written Examination Committee was elected Vice Chair of the Board. He was elected President-Elect of the Association of Academic Chairmen in Plastic Surgery and President of the American Society of Maxillofacial Surgeons. He serves as member of the Residency Review Committee for Plastic Surgery, was elected to the Executive Council of the International Craniofacial Society, and appointed to the Board of Directors of the American Society of Plastic Surgery.

His clinical research relates to the development of new treatments for the management of complex craniofacial anomalies, vascular lesions, and aesthetic concerns. Collaborative research with Yale faculty and fellows includes study of the psychologic effects of physical deformity. He is Associate Editor of *Plastic and Reconstructive Surgery*, and co-editor of the *Journal of Craniofacial Surgery*, and is co-editing two textbooks of plastic surgery. He is in active collaboration with the international volunteer organization, Operation Smile, in organizing educational programs for surgery caring for needing children in developing countries. He was named as one of "America's Top Surgeons" for 2002-2003.

Dr. Grant Thomson served as President of the New England Hand Society. He served on the Executive Council of the New England Society of Plastic and Reconstructive Surgeons and he was elected Membership Chair for 2003-2004. He will ascend to the rank of President of the Society in 2006-2007. He ended his 3-year term on the Editorial Board of the *Annals of Plastic Surgery*. Named as one of the Best Doctors for Surgery of the Hand in New York by the Castle Connolly Guide, for the fourth time in June 2003, he was also named as a "Top Doc" in the June 2003 issue of *New York Magazine*.

His research continues in the measurement of thumb abductor strength in carpal tunnel syndrome patients, and he is working with research fellows and medical students in the development of an endoscopic method of scapholunate arthrodesis.

Dr. Joseph Shin continues in his position as Director of the Yale Craniofacial Center. In addition to management of cleft lip and palate disorders, Dr. Shin continues his work in the field of distraction osteogenesis of the craniofacial skeleton. This work centers on the element of both intraoral as well as both the development and innovation in the area of internal distraction of osteogenesis. This work has been ongoing and is supplemented by additional investigations in the laboratory along with Drs. Michael Centrella and Thomas McCarthy into the molecular pathways for osteo response to mechanical strain. Drs. Centrella, McCarthy and Shin have studied the effect of mechanical osteoblast cultures in an attempt to design an in vitro system to replicate mechanical forces simulating forces in distraction osteogenesis.

Dr. Deepak Narayan, a graduate of the Yale Plastic Surgery Residency Program, recently joined the faculty. His main interests are oncologic reconstruction, melanomas, and pediatric plastic surgery. Dr. Narayan was awarded the OHSE Research Grant and the Plastic Surgery Educational Foundation Research Grant to study the pathogenesis of Dupuytren's disease. He as recently listed in *the Guide to America's Top Surgeons* by the Consumer Research Council, Washington, D.C.

Dr. Michael Centrella: During the last year Dr. Centrella continued studies funded by the National Institute of Arthritis, Musculoskeletal, Skin Diseases and the Arthritis Foundation. The goal of this research effort is to understand molecular mechanisms that control gene expression by osteoblasts in situations associated with normal development, trauma, or inflammation, or in response to agents used to manage skeletal tissue disease associated with joint inflammation. Specifically, it is hoped to determine how steroid hormones regulate growth factor and growth factor receptor expression by osteoblasts to identify meaningful points for focused intervention. We propose that it is essential to define and to dissect complex molecular interactions that occur between osteoblast transcription factors and steroid hormone receptors in order to target these molecules in appropriate ways. His laboratory includes post-doctoral fellows, visiting scholars and medical students.

Dr. Thomas McCarthy: His laboratory was the first to identify mechanisms that control IGF-I gene expression by osteoblasts. He and his colleague, Dr. Centrella, showed that hormones such as PTH and PGE₂, which increase the accumulation of intracellular cAMP, activate a transcription factor termed C/EBPdelta that then translocates from the cytoplasm to the nucleus. In the nucleus, activated C/EBPdelta then associates with response elements in exon I of the IGF-I gene and thereby increase gene promoter activity. Surprisingly, C/EBPdelta is expressed in a constitutive manner in differentiated osteoblasts, in contrast to other tissues where it appears to be a component of the acute phase response. This laboratory also was the first to demonstrate that the steroids estrogen and glucocorticoid both control IGF-I expression by osteoblasts through changes in C/EBPdelta expression, or through the ability of C/EBPdelta to bind DNA. This work provided the first evidence to show how high levels of estrogen limit osteogenesis, perhaps accounting for the lower bone mass found in women vs. men, and for the increase in bone remodeling that occurs post menopause. Subsequently, this laboratory found that constitutive C/EBPdelta gene expression by osteoblasts is controlled by a transcription factor termed Runx2, which is an essential component of osteoblast differentiation and bone formation. When Runx2 levels and Runx2 activity increase, C/EBPdelta levels follow, and then secondarily high levels of C/EBPdelta eventually counteract this increase and suppress Runx2 activity. Therefore, this laboratory defined novel intracellular loops of positive and negative feedback control between these several important transcription factor systems that regulate osteoblast growth factor expression. This laboratory is now extending these observations to identify domains on C/EBPdelta and on Runx2, which interact with specific domains on the intracellular protein receptors that bind estrogen and glucocorticoid.

EDUCATIONAL PROGRAM

The faculty in Plastic Surgery have developed a comprehensive, defined curriculum for resident and student education. This structure affords the Resident the opportunity to acquire a broad base of knowledge

and the core information necessary for Board certification in Plastic Surgery. Research and special clinical interest opportunities are afforded. In addition, continuing education lectures and seminars are provided for physicians in practice.

During the first 3 years of postgraduate education, the clinical experience in General Surgery is coordinated to support a career in Plastic Surgery. In the second segment of the educational program (PGY4-6), there is a broad clinical experience in plastic surgery supported by multiple conferences offered to enhance an understanding of the principals of plastic surgery.

On an alternating weekly basis, "Indications" and Craniofacial /Aesthetic Conferences are connected with Hand and "Core" conferences. Plastic Surgery Grand Rounds are held weekly, wherein local faculty, staff, and visiting professors are invited to deliver presentations on topics of clinical interest. The Journal Club Review/Resident Conference is held monthly. There is quarterly Research Conference wherein developments from our own laboratories in bone and skin growth and wound healing are discussed, with participation by visiting lecturers from within and outside the Yale Medical Center

The Yale Craniofacial Program represents a multi-specialty programmatic effort dealing with congenital, traumatic, tumor, and vascular anomaly involvement in the craniofacial region. The Program is directed by Joseph Shin, M.D. and co-directed by John A. Persing, M.D. It has specialty representation from 18 clinical services within the medical center. There is a coordinator within the Section who is responsible for enhancing patient care delivery and research in the treatment of craniofacial disorders.

The Yale Skin Bank is under the direction of Bruce C. Fichandler, P.A. The Bank provides the needed skin for burn patients and other patients with open wounds. The Bank has been in existence since 1983.

The Microsurgery Program is directed by J. Grant Thomson, M.D. and is coordinated to concentrate expertise in replantation, microvascular reconstruction, and free flap surgical techniques. The educational program is under the director of Bruce C. Fichandler, P.A., who conducts regularly scheduled "hands on" teaching sessions for the residents with the assistance of the clinical faculty. A fully equipped microsurgery laboratory provides a supportive environment for faculty, residents, and students to develop and refine microsurgical skills and conduct experimental investigations.

The upper extremity program is directed by Grant Thomson, M.D. Traumatic, congenital, and degenerative conditions involving the hand, wrist, and the nervous system of the upper extremity are treated in this program. Repetitive work trauma and recalcitrant pain conditions are treated in a multidisciplinary program of special emphasis. One hand fellow is accepted into a one-year program each year.

The Cosmetic Surgery Team was organized to provide excellence and comprehensive services to those seeking facial and body aesthetic enhancement. John A. Persing, M.D., Joseph Shin, M.D., and Deepak Narayan are involved with this Program.

The Section's Oncologic Reconstruction Program for breast cancer, head and neck cancer, and melanoma treatment is being directed by Dr. Deepak Narayan.

The Section has continued to promote the concept of the mid-level health practitioner, participating in the education program of the Yale/Norwalk Physician Assistant Surgical Residency Program. This latter program, started in 1976, was the first surgical residency for Physician Assistants in the United States and now has more than 200 graduates. The teaching program is directed by Bruce C. Fichandler, P.A.

RESEARCH IN PROGRESS

The following areas are under active investigation in the Plastic Surgery laboratories.

Connective Tissue Regeneration

Research in this area concentrates on hard and soft tissue growth and repair, and emphasizes the control of bone and skin cell function by local (tissue-derived) and systemic regulators. Our research efforts were among the first to identify specific growth-promoting proteins produced by bone cells. We have continued to examine how hormone- and stress-induced changes in the tissue microenvironment influence growth factor and growth factor receptor expression. Current efforts focus primarily on insulin-like growth factors (IGF's) and transforming growth factor β (TGF- β) gene family members.

Bone: We have recently identified unusual features about the location and the nucleotide sequence of elements that control of IGF-1 mRNA expression in osteoblasts. These events occur under the influence of normal (parathyroid hormone) and stress-activated (prostaglandin) inducers of cyclic AMP synthesis. We will continue to examine the genomic and nuclear aspects of this process by transcriptional (promoter-reporter constructs) and transcription factor (gel shift and genomic foot-print) studies. Similarly, we have determined instances in which separate intracellular pathways control IGF binding proteins and IGF receptors in undifferentiated and in differentiating osteoblasts. We have also demonstrated that the complex profile of TGF- β receptor activation can be driven forwards and backwards by local and systemic growth regulators, providing further evidence for a plastic, multipotential bone cell phenotype. We recently cloned the TGF- β type I and type III receptor promoters and characterized DNA sequences that determine their expression in most tissues, and also specific sequences that regulate their expression by osteoblasts. We are now examining the biochemical and molecular events that determine TGF- β receptor levels in bone, skin, endothelial and cardiac cells.

Skin: After initially demonstrating that IGF-I expression was regulated by cyclic AMP-inducing factors in bone, we began to evaluate the possibility that similar events occurred in other tissues. We chose first to examine this in dermal cells, realizing that the keratinocyte-derived parathyroid hormone like protein (PTH-rp) was a potent stimulator of cyclic AMP synthesis by dermal fibroblasts. Our interest in this process was spurred by the observation that IGF-I will induce keratinocytes to synthesize new matrix components associated with skin growth and repair, but that these cells appear to require an exogenous source of IGF-I for this to occur. Therefore, we have begun to demonstrate how keratinocytes and fibroblasts intercommunicate in skin by these two proteins in order to enhance skin formation.

We hope to use the information from these lines of research to identify, target, and activate specific connective tissue cell populations in order to enhance the processes of skeletal and dermal growth, regeneration, and repair.

Craniofacial Growth and Development

Analysis of effectiveness of various forms of cranioplasty and orbital advancement techniques are ongoing.

The psychologic, neurodevelopmental and socioeconomic impact of congenital and traumatic facial deformity are being investigated.

Distraction Osteogenesis

The current efforts in our laboratory concentrate using molecular techniques to investigate the clinical phenomenon of distraction osteogenesis. Distraction osteogenesis has been useful in correcting congenital malformations of the lower extremity and it has been only recently applied to the craniofacial skeleton. Specific mechanisms of distraction osteogenesis over time have been utilized to elongate the facial skeleton and correct dysmorphic conditions of the mid-face and the mandible. Conditions that have been treated are hemifacial microsomia and various craniofacial syndromes such as Aperts Syndrome and Crouzon Syndrome. Our laboratory efforts are centered around developing an in-vitro model for bone cell growth and an in-vivo model to replicate the effect of bone cell growth and development utilizing distraction osteogenesis. We are investigating receptor mediated signaling events in fetal osteoblast. Specifically we are interested in looking at transforming growth factor TGF-Beta (TGF-B) and insulin like growth factor-1 (IGF-1) in bone cells.

Telemedicine

Additional investigations of our group involve the use of telemedicine technology to facilitate wound care. Using high speed dedicated T-1 lines we have established various protocols using internet/intranet systems to facilitate wound care for patients with problems of mobility i.e. patients with vascular disease and lower extremity disease and peripheral vascular disease as well as patients with spinal cord injuries. These studies are ongoing with Gaylord Rehabilitation Hospital as well as the Section of Vascular Surgery.

Microvascular Surgery

The primary patency rate of clinical microvascular anastomoses is 85-93%. Revision of a thrombosed anastomosis is successful only 50% of the time. Current research is designed to investigate the factors involved with salvage of failed microvascular anastomoses. Other studies investigate the role of vessel clamping and core body temperature on the success of free tissue transfer.

Social Aspects of Public Policy

With changes in healthcare financing in recent years, the impact of these changes on the quality of resident education, research, and ultimately patient care have been studied.

Esthetic Breast Shape

This area of investigation focuses on improving our understanding of the factors influencing the shape of the female breast. Breast shape is determined by breast volume and surface area of the skin envelope. This laboratory has developed a simple photographic method to measure these two parameters. Preliminary studies are being conducted to determine the relationship between breast volume and surface area that results in an esthetically pleasing breast shape in normal female volunteers. This relationship will then be applied to a variety of clinical situations, including reduction mammoplasty, augmentation mammoplasty, and breast reconstruction, to determine whether this method can be used to predict the correct volume and surface area changes necessary to obtain a good surgical result.

Flap Physiology

Clinical and animal model studies have provided insight into the vascularity and physiology of musculocutaneous flaps. A rat TRAM flap model has been developed, and preliminary data has addressed queries concerning the optimal timing of surgical delay as well as the extent of the delay procedure required. Additional studies have quantified blood flow changes in musculocutaneous flaps. For example, computerized ultrasound in clinical cases and tissue oxygen studies in rat models have further characterized flap vascularity. Ischemic preconditioning has been shown, by our laboratory, to improve flap survival. Current investigations focus on the mechanism of this effect using a combination of blood flow measurement and microdialysis to measure intra-flap metabolite measurement.

Hand Surgery

Cadaver investigations include hand anatomical dissection, evaluation of new flaps, and investigation of tendon and pulley biomechanics.

A study involving cultured tenocytes investigates the role of cellular strain on collagen and glycosaminoglycan synthesis. This has implications for tendon healing and gliding in a synovial sheath.

In addition, several clinical investigations are in progress. One study involves measuring the strength of thumb abductor muscles in normal individuals and in patients with carpal tunnel syndrome before and after surgery. This has significance in the evaluation of the severity of carpal tunnel syndrome and the effectiveness of treatment.

Cosmetic Surgery

Anatomic studies are being done on the soft and hard tissue relationships in the face, so as to design new and more effective strategies for facial rejuvenation.

Body image studies are being conducted on patients undergoing body contouring, abdominoplasties, and breast surgery using digital imaging and psychologic analyses. The purpose of this work is to better match patient expectation and surgical result. This research has also spawned work in body image issues in reconstructive surgery, such as cleft lip, traumatic hand deformities, and skin cancer.

ACTIVE GRANTS

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