EVALUATION OF SENSIBILITY AND RE-EDUCATION OF SENSATION IN THE HAND

EVALUATION OF SENSIBILITY AND RE-EDUCATION OF SENSATION IN THE HAND

A Lee Dellon, M.D.
Professor of Plastic Surgery
Johns Hopkins University

Accurate indications, advere reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

ISBN: 978-0-692-33095-1
4th Printing
Reprinted 2015 Lightning Source
Library of Congress Cataloging in Publication

Dellon, A. Lee
Evaluation of sensibility and re-education of sensation in the hand.

Bibliography
Includes index.
1. Hand—Surgery—Complications and sequelae. 2. Nerves, Peripheral—Surgery—Complications and sequelae. 3. Hand—Innervation 4. Peripheral nerves—Surgery
WE830 D358e] RD559.D44 617’57501 80-20698

PREFACE 4TH PRINTING

EVALUATION OF SENSIBILITY AND RE-EDUCATION OF SENSATION

When I wrote *Evaluation of Sensibility and Re-Education of Sensation* in 1980, I had finished my Plastic Surgery residency at Johns Hopkins Hospital and Hand Surgery fellowship with Dr Raymond T. Curtis in Baltimore. I was beginning my private practice and writing my first book. It was an amazingly exciting academic time. It is now 35 years later, and time to look back at the impact of my first book and decide if it is time for a new printing of this material.

I remember that in preparing the first edition of this book, I would walk and think up subtitles for the chapters. I would go to the Hopkins Library, find each original reference, and actually read it. The drafts of each chapter were hand written and then typed. The finished draft was taken to Williams & Wilkins, the publishing company, with me praying they would accept to print and publish it. Today, writing is composed upon the computer, saved to the hard drive, reformatted by a graphic designer, and published on line. A huge transformation of the publication process. Today, I have published five different books, each with various iterations and subsequent printings. I have published more than 450 scientific papers in peer-reviewed journals. I have published more than 100 book chapters in other doctors' books. Most of this material is available online, especially at Dellon.com.

THE MATERIAL PUBISHED IN THIS, MY FIRST BOOK REMAINS RELEVANT, AND YET UNAVAILABLE TO MOST READERS INTERESTED IN THE SUBJECT OF SENSIBILITY EVALUATION, THE HISTORY OF NEUROSENSORY TESTING, AND SENSORY REHABILITAITON.

It is time for my early research and that of the researchers before me to be made available on the internet. The first edition has been "remastered" as they say in the music industry. Simply put, the book, which was never placed into digital media, has been retyped and reformatted, but otherwise unchanged from the original. Only this Preface has been added. Towards that point, great thanks go to Elaine Lanmon (justsk8@gmail.com), the graphic designer, Scott Eagle (scott@highlevelstudios.com), my webmaster for Dellon.com, and Lightning Source (http://www.lightningsource.com), the online publisher. Finally, to Luiann Olivia Greer, my wife, and partner since 1997, I give profound thanks and gratitude for providing the peaceful and creative environment in which I have been able to research, write, and educate.

The contents of the book can be downloaded in its entirety and obtained as a bound version from Amazon.com, or each of the three different parts of the book can downloaded separately, for free at Dellon.com.

From the perspective of 35 years, hindsight reveals that the first section of Evaluation of Sensibility and Re-Education of Sensation, Back to Basics, has material still not available in any collection anywhere else. For this section alone, historically, this book needed to be reprinted, so that

young investigators today can read and see the experience of the early workers in the field of neurosensory anatomy and morphology. The second section, Evaluation of Sensibility, introduced the concept that examination of the hand must be done with instruments and techniques that are based upon neurophysiology, standardized, and using normative data. This section introduced my Moving Two-Point Discrimination Test, which has become adopted world-wide as a measure of large fiber regeneration related to touch perception and innervation density. The pattern of sensory recovery described in this section, which I described while still a Johns Hopkins medical school student, has been confirmed and the concepts applied to neurosensory testing in the feet and the face. New equipment, such as the Pressure-Specified Sensory Device (PSSD) has been developed by myself based upon the principles in this chapter, and this device is now an accepted standard in evaluation of sensibility. The third section, Re-Education of Sensation, proved to be the starting point for a widespread international movement of techniques I developed, again while a medical student, and now used routinely for rehabilitation of the hand, and the foot, after nerve injury and repair.

I remain immensely proud of my first book and am delighted to be able to present its content afresh on the world wide web.

A Lee Dellon, MD, PhD
Professor of Plastic Surgery
Professor of Neurosurgery
Johns Hopkins University
2015

FOREWORD

RAYMOND M. CURTIS, M.D.

This book more than fulfills its author's purpose by providing a bridge that connects the Hand Surgeon to Neuroscientist, each of these to the Hand Therapist, and all to the patient with an injured peripheral nerve. The book is scholarly and authoritative, yet written in a way that easily translates the complex material. The content is comprehensive, and arranged to be of maximal educational benefit. Each statement is referenced, and the reference appears both at the end of the chapter and at the end of the book in a separate bibliography, which will ease future recall.

To place this book in historical perspective we must realize that since Sterling Bunnell's classic monograph in 1944, the vast majority of subsequent texts have dealt with either specific surgical techniques or anatomic studies related to the hand. The trend is toward published symposia or multi-authored texts. Even the emphasis on rehabilitation has excluded the sensory aspects. Thus, Lee Del-Ion's contribution is unique, and we are indeed indebted to him for this tremendous undertaking. His broad background in basic science and research, his search of the past for clues to the future, his more than a decade of meticulous evaluation of patients with impaired peripheral sensibility have culminated in this single-authored book. The book is reminiscent of Bunnell, not only in specific areas, for example, use of comparative anatomy to discuss the evolution of the sensory end organ as Bunnell did for the upper limb, but also in original contributions. Dr. Dellon demonstrated in primates the fate of sensory corpuscles after denervation and following nerve repair. Dr. Dellon is responsible for urging that our evaluation techniques for sensibility have a neurophysiologic basis. He demonstrated the pattern of sensory recovery following nerve repair, initiated the use of vibratory stimuli administered by tuning forks for peripheral nerve problems, added the terms "moving-touch" and "constant touch" to our vocabulary, and conceived the moving two-point discrimination test. Equally important he developed and refined sensory rehabilitation to be consistent with this evaluation scheme, incorporating specific sensory exercises at the appropriate time in the recovery process. These exercises emphasize finger movement and object recognition. This Sensory Re-education has produced unparalleled results.

Outstanding is the model of the sensory endings in the fingertip, which is found in Chapter 2. The Section on Evaluation of Sensibility critically reviews the relevance of every previously described clinical test. The separate existence of a vibratory sense is disproved. Finally, the author's own evaluation scheme is described in detail for each potential clinical setting. The Section on Reeducation of Sensation begins with the most comprehensive review of end-results of nerve repairs, in which essentially every published report is collated and reduced to a common reporting format. The historical and technical aspects of

Sensory Re-education will be welcomed by a world in which this concept increasingly is being accepted, and already producing improved results.

The volume clearly has been a labor of love of many years for Lee. He has recognized that knowledge develops from the thousands who precede, and to these he shows his gratitude. We are under a heavy debt to him. His volume takes its place as one of the outstanding contributions to medicine and biology.

Baltimore 1980

FOREWORD

ERIK MOBERG

Once the world knew only two centers of culture, one in Europe and the other in China. Only distorted rumors connected the two, arriving over endless camel trails. Neither center influenced the other. In order for Marco Polo to see in person these two different worlds and initiate communication, he needed a young unbiased brain together with an ability for fearless traveling.

In important parts of basic neuroscience and clinical nerve work the situation has been similar. On the one hand, neurophysiology is developing a micro-"electrology" capable of tracing even single nerve impulses. In animal experiments computerized studies are revealing much of great interest. On the other hand, the clinical observations of modern hand surgery have added a wealth of new knowledge concerning hand function, impossible to obtain in the animal laboratory. Patients provide the examples to distinguish the different qualities of sensory function and between afferents to the conscious and unconscious level. This is the basis for all rehabilitation. Yet between these two fields the contacts are almost missing. There is even a barrier in their terminology.

The young author of this book is the first one to connect these two antipodes, each so important to the other. Dr. Dellon's enormous enterprise, to travel through and scrutinize modern physiology and other basic sciences and to summarize and combine these with modern hand surgery reminds one of the ancient explorer.

Sterling Bunnell in his "Surgery of the Hand.," in spite of the language barriers, reviewed almost all of the important literature. Similarly, as should be the rule in scientific work, Dr. Dellon has included important work from different times and languages. The references are not only mentioned, they are, when necessary, translated, read, and digested. (It is a pleasure to find even the rarely quoted but important work of Stopford from the l920's included.) And so the information in this book will no doubt remain for a long time the source by which less penetrating authors will escape.

Sensory Rehabilitation, which has been neglected for so long a time from our follow-up work, has now been elevated to an established position through the intense personal efforts of Dr. Dellon. A thorough description of the when and how is given as a necessary guide for this critically needed therapy.

And so this book is unique in the flood of hand surgery literature of today. No doubt it will give rise to conflicting opinions and controversy, which is the basis of all progress. After reviewing the established facts, the author guides the reader to many remaining unsolved questions. This book will find readers from many fields.

It has been a rare privilege to follow Dr. Dellon's work from his early beginning to this outstanding presentation.

Gotteborg 1980

PREFACE

The purpose of this book is to bridge the potential, if not actual, gap between those involved with the neurosciences and those involved with the care of the peripheral nerve. The bridge is a personal one; its construction begun 12 years ago, attempting to seek a firmer basis for understanding and, hopefully, correcting problems encountered in the operating room and the surgical follow-up clinics. It's a bridge whose final span will continually be under construction.

Research into the mechanisms of sensibility, the neural process which transduces external stimuli, has lagged enormously behind research into motor function. Yet, without sensation, the central, conscious perception or appreciation of those peripherally generated neural impulses, the hand is virtually immobile. Without sensation, visual control must be added to guide hand action. Since the mid-1960's, neurophysiologists and anatomists have brought microdissection, single-unit nerve recording, and electron microscopy to bear upon the sensory component of the mixed nerve. These insights have provided a more valid basis for understanding the sensory receptor population in the fingertip, for evaluating sensibility following nerve injury and repair, and for rehabilitating the hand.

However, as the basic scientist and the clinician evolve into ever more highly specialized areas, separation and loss of communication result in failure to utilize each other's vital contributions. It is, unfortunately, rare for either the clinician to read the basic science literature or the basic scientist to examine a patient. Surely fruitful areas for further exploration would arise from the latter, and answers to perplexing problems derive from the former.

It is hoped that the correlated view presented in this book will reach the medical student's lecture halls in microanatomy and classrooms in physical diagnosis. It is hoped that this bridge aids the peripheral nerve surgeons (be they hand, orthopedic, plastic, or neurosurgeons) in evaluating the hand with a nerve injury, in understanding the meaning of that evaluation, and in choosing and completing the indicated therapy, sensory re-education. It is hoped that neuroscientists reading this book will take pride in finding application of their "basic" contributions and be challenged to enter the clinical arena. Finally, it is hoped that this book provides more than a bridge, rather, a bond between the surgeon and the hand therapist, providing rational techniques to allow the patient to fulfill the maximum potential for sensory recovery in the shortest possible time.

The origin of our present misconceptions of sensory receptor morphology and physiology is explored in Chapter 1. These misconceptions are corrected in Chapter 2 with a contemporary model of the glabrous skin and in Chapter 3 with a distillation and interpretation of contemporary neurophysiology. The usually neglected sensory end organs are focused upon in Chapter 4, after denervation and in Chapter 5 after reinnervation. Evolution of my technique for evaluating sensibility comprises Chapters 6 through 9, which present a historical review of sensory testing, critically review alternative approaches to sensory

testing, and culminate in Chapter 10, my personal approach to evaluating sensibility. Chapter 11 reviews the end result of nerve repair since 1940 and provides the data base for an historic control. The development, technique, and results of sensory re-education conclude the book in Chapter 12.

The text is designed for maximum educational benefit. Each Chapter has its own bibliography arranged numerically as the reference arises in the text. A combined bibliography, arranged alphabetically, precedes the index. The index is comprehensive, including both subjects and authors cited in the text. The referenced works have each been read, unless the reference is specifically attributed to another author's citation or quote. This required, in many cases, language translation. At the conclusion of most chapters is a section on clinical implications, transferring theory into practice. Where appropriate, new avenues for research are suggested. Where the work referred to is my own, the text is written in the first person. Some of this material, as noted in the bibliography, is "hot-off-the-press" and as such is not yet available in the published "scientific literature." In these instances, sufficient data has been included to justify the conclusions. Thus, this text represents a highly personal approach to its subject material. It is, however, an approach which I believe incorporates the basic science and clinical knowledge of today into a unified philosophy and application.

ACKNOWLEDGEMENTS

The single greatest factor permitting my dream of this book to become a reality has been the love and understanding of my boys, Evan and Glenn. The book represents an irreplaceable and precious commodity, time spent away from them. And certainly in the last 6 months of this book's preparation, even when I was with them, I was away. For their realization that the fulfillment of this dream was so important to me, and for their providing the peace of mind required for its fulfillment, I can only say, "Thank you" and "I love you."

The preparation of the book required assistance. I was truly fortunate to be able to work with two talented medical illustrators. Sue Seif did all the book's illustrations except Chapter 2. The illustrations for Chapter 2 are by Mark Lefkowitz and are an outgrowth of his thesis project. I had the privilege to be the scientific advisor to both Sue and Mark for their Master's Theses and have been delighted with the work they've produced for this text. I know their future illustrations will enhance the medical community beyond the foreseeable future.

The photographic contributions to this book are from three sources. Robert M. McCIung and Margo N. Smyrnioudis, from the Department of Audiovisual Services, the Union Memorial Hospital, did the studio staged photography for Chapters 6, 9, and 12. Raymond (Peter) E. Lund, RBP, FBPA, Director of Pathology Photography and Instructor in Pathology at the Johns Hopkins Hospital, and his staff, did the photomicroscopy for Chapters 5 and12, co-ordinated the special timing required to reproduce figures from journal texts which were kindly loaned from the Welch Library, and reproduced my patient slides into prints. Bryce Munger, M.D., Chairman of the Department of Anatomy of the Milton S. Hershey Medical Center, did the electron microscopy for the book, including the previously unpublished light micrographs of the Merkel cell-neurite complexes in Chapter 2. My deepest thanks to you all.

Special thanks to Walter Ehrlich, M.D., Associate Professor of Environmental Physiology in the Johns Hopkins School of Hygiene and Public Health. He combines both the literary skill of a linguist and the scholarly patience of a medical scientist. He was thus able to translate for us the works of Weber, von Frey, Valentin, and others. His is a unique contribution.

Finally, a thank you to Susan Vitale, Senior Editor, to George Stamathis, Production Coordinator, and to the production staff at Williams & Wilkins, my publisher. The completed book reflects their skill and experience, and I am deeply grateful for their efforts and professionalism.

CONTENTS

SECTION 1

Back to Basics

SECTION 2

Evaluation of Sensibility

SECTION 3

Re-Education of Sensation

Section 1

Back to Basics

Chapter 1
CLASSICS

INTRODUCTION

ANATOMY

PHYSIOLOGY

At the outset do not be worried about this big question—Truth. It is a very simple matter if each one of you starts with the desire to get as much as possible. No human being is constituted to know the truth, the whole truth, and nothing but the truth and even the best of me must be content with fragments, with partial glimpses, never the full fruition…what is the student but a lover courting a fickle mistress who ever eludes his grasp? …The hardest conviction to get into the mind of a beginner is that the education upon which he is engaged is not a college course, not a medical course, but a life course.

Sir William Osler[1]

The student, new to his chosen field of endeavor, eagerly reads and memorizes the introductory material. It is in a textbook. It is taught by a Professor. It is marked right or wrong on an exam. The student assumes that what he is learning is true. Yes, the student should constantly question. But when the field of study is anatomy or physiology, human or comparative, or all of these, the totality of material to master is so huge there is no time to question its truth. There is not even time to master it all! The student usually is working to his capacity just to survive! During the late 19th century and early 20th century, a few professors of great reputation dominated scientific thinking in these areas. Many of their teachings have been handed down to us, not only unchanged but unchallenged.

An example of material transmitted to us in this matter is the following scheme of the modalities of cutaneous sensation and their corresponding receptor systems[2].

Touch and pressure	Free nerve endings, particularly those in relation to hairs, Meissner's corpuscles and Pacinian corpuscles
Warmth	End organs of Ruffini
Cold	Krause's end bulbs or corpuscles
Pain	Free nerve endings

The modalities of deep sensation and their corresponding receptor systems are:

Pressure	Pacinian corpuscles
Pain	Free nerve endings
Proprioception	Free nerve endings, Pacinian corpuscles, muscle spindles and Golgi end organs

I began studying anatomy and physiology in 1966. This scheme is from a textbook published in 1978.(2) With the exception of pain being subserved by the free nerve endings, this scheme is entirely wrong! The associations are wrong and the Merkel disc is omitted. It is the purpose of this chapter to explain the evolution of this scheme.

ANATOMY

The misconceptions began with the anatomy of cutaneous sensibility. Anatomy in the 19th century was a descriptive science. In 1836, Pacini redescribed the corpuscle Vater had described in 1741.[3] This corpuscle was the first to be discovered because it was the largest, being visible by gross dissection and without magnification. In 1853, Wagner, using a hand lens and maceration technique, described the corpuscle which Meissner, 1 year later, described in more detail.[4] As microscopes became available, gross anatomic description gave way to histology. There followed an outpouring of descriptive material on sensory endings, in many tissues and in many species. This investigative work was not standardized. Every new method of tissue preparation (dilute acid, dilute alkali), and every new histochemical stain brought new descriptions.

At the turn of the century the following techniques were in use: Merkel's osmic acid, Golgi's silver chromate, Ehrlich's methylene blue, Ranvier's gold chloride, Cajal's silver nitrate, and Bielschowsky's ammonical silver.[5] But what was truth? And what was artifact? The height of this sensory ending proliferation was reached in Botezat's classification of 1912. He listed 36 separate endings in glabrous (nonhairy) skin in addition to those in the hairy skin (Table 1.1).[6]

For me, "the way out" of this seemingly hopeless maze was provided by Winkelmann.[5] Utilizing meticulous silver staining technique, he restudied the hairy and glabrous skin of many mammals. His histology was documented photographically. His book summarized a decade of this work and reviewed thoroughly the previous literature (404 references). In brief, the only sensory end organs he confirmed in glabrous skin were the Pacinian corpuscle, the Meissner corpuscle and the Merkel cell-neurite complex. These end organs, their innervation pattern, and relationship to the organization of the skin, are illustrated in Chapter 2.

What about the Krause end bulb (for cold) and the Ruffini end organ (for heat)? These holdovers from antiquity cannot be confirmed in glabrous skin with the modern techniques.

As reviewed by Winkelmann,[6] Krause's end bulb has gone by several other names: genital corpuscle (as Kraus described it in the glans penis), endkopseln (as Krause described it in the elephant!), Dogiel's body, and the mucocutaneous end organ. Krause's end bulbs don't occur in normal glabrous skin. The mucocutaneous end organ is the configuration imposed upon the axons by the physical confines of transitional skin. Thus in areas without hair follicles or ret ridges, the mucocutaneous end organ may be found. The Ruffini Body, as reviewed by Winkelmann,[5] does not occur in glabrous skin. Most of what

Ruffini described as the most common receptors in the skin were rolled nerve trunks, i.e., artifacts. The criteria for end organ existence, outlined by Winkelmann,[5] are: (1) repetitive observation of the structure, and (2) continuity between known nerve structure and end organ. These criteria can be fulfilled by studying serial thick sections of tissue gently handled and carefully stained. My own work has confirmed these tenets.[7] Except for Krause and Ruffini, no one has seen their end organs in glabrous skin, and it is time that modern teaching and writing reflected this.

PHYSIOLOGY

As the magnifying glass and gross anatomy were the forerunners of electron microscopy and molecular biology, so may the comparative sensory studies and physiology be considered the forerunners of single unit nerve neurophysiology. Johannes Muller is often cited for "the law of specific nerve energies," 1828, which stated that "for each sensation there is a specific receptor, a specific nerve pathway, and a specific central locus of appreciation."[5] In the context of cutaneous sensibility, this sounds quite "specific," yet our review of the writings of Muller suggests a more general concept. In his book, he did propose a theory of specific energy but for senses such as sight, hearing, pressure, friction, galvanism and sensation. He did not discuss cutaneous sensory submodalities.[8]

Direct experiments followed. In 1882, Magnus Blix,[9] investigating the sensory submodalities of heat, cold, and touch, described sensory spots on the skin. In view of the proliferation of sensory end organs being described during the last quarter of the 19th century, it was only a matter of time until the structure/function correlation began.

The correlations still being taught to our generation were formulated in detail in 1896 by Max von Frey[10] (Fig. 1.1). He was a careful observer and his investigation and writings continued into the first quarter of the 20th century. But his correlations were the product of arm chair theorizing.

von Frey did punctate stimulation of the skin. For example, his 1894 publication[11] "concerned the threshold and conditions of threshold in mechanical stimulation"! He found that pressure points ("Druckpunkte") have different thresholds in different parts of the body. He found a continuum between pressure points and pain points ("Schmerzpunkte"), and described punctate sensibility as a mosaic. To von Frey, touch meant pressure and he never spoke of touch as being movement, only as pressure. In studying the hairy skin, he observed that there was a place where the angle of the hair is acute to the skin, and here pressure is felt when the hair is touched. He thus preceded Pinkus by 7 years in describing the "Haarscheibe"! He concluded his theorizing in this paper by saying that "where there is no hair, one might think of the Meissner corpuscle as the organ of pressure sense." He believed that free nerve endings were for pain.

von Frey's deductions were made on the basis of comparing "known: receptor morphology with observed sensory capacity plus intuition. For example, he knew the cornea could perceive pain, but not

cold or pressure, and that the cornea contained free nerve endings. Thus, free nerve endings subserved pain! He knew the conjunctiva had Krause's end bulbs and could perceive cold. Thus Krause's end bulbs subserved cold. He extrapolated from this to the hypothesis that the cold spots in the finger ("Kaltpunkte") contained Krause's end bulbs. Without such clear reasoning, he assigned the Rufini body to the warm spot ("Warmpunkte"). Up to this point he did not mention the Pacinian corpuscle or the Merkel disc.

Table 1.1
Mechanisms of the Naked Skin and of the Hairy Skin[a]

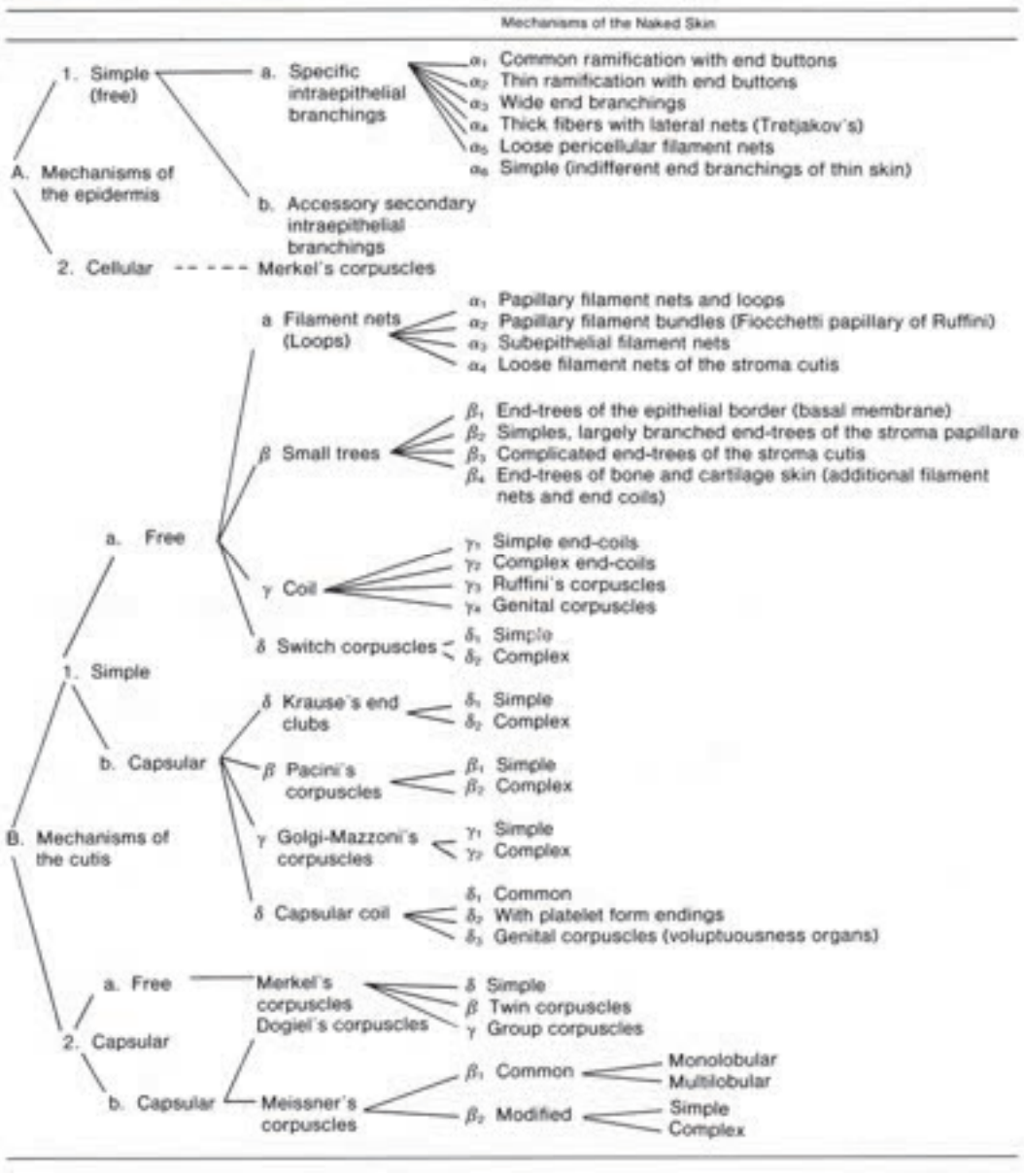

Table 1.1—continued

Mechanisms of the Hairy Skin

Mechanisms of the skin scarcely covered with hair	Mechanisms of the epidermis	Simple Exist only on specific location and is reduced to 3 forms = x_1, x_2, x_3
		Cellular—Merkel's corpuscles
	Mechanisms of the cutis	Reduced to a few forms, especially end trees
Mechanisms of the skin densely covered with hair	Mechanisms of the epidermis	Almost only α_0 exists reduced to a minimum
	Mechanisms of the cutis	Not found
HAIR AS SENSORY ORGAN		
(The hair follicles are the carriers of the mechanisms which are reduced in the surrounding skin. Specific forms are the straight terminal fibers and the circular main- and accessory mechanisms on the neck of the hair follicle)	Containing erectile bodies (Tactile hair)	With circular sinus (Sinus hair)
		Without circular sinus
	Active tactile hair = sensory hair (with voluntary muscles)	Passive tactile hair (without voluntary muscles)
	Without erectile bodies	Common hair
		Hair of transitional form (original-primordial-tactile hair)

In what truly amounted to a monograph,[10] von Frey detailed his investigational techniques, tools (Fig. 1.2), results, and theories. It is in this paper that we see the development of his "sensory hairs" (Fig. 1.3). They followed as a more ready means of testing pressure (touch to him) than his complex graphing apparatus (Fig. 1.4). von Frey discussed in more detail his assignment of pressure more in receptor (by which he meant touch/pressure) to the Meissner corpuscle. He wrote that the Vater corpuscles (he never called it the Pacinian corpuscle) were too few and too deep to be a cutaneous pressure receptors, whereas the Meissner corpuscles were numerous and superficial. He emphasized again that the Meissner corpuscle was the hair follicle of the glabrous skin. With regard to the Merkel discs, von Frey wrote that "the proposition that Merkel's discs in humans are found in skin where there are not Meisners, speaks against their function as 'sensory' organs, because the sensory function here is always covered by hair."

To study cutaneous pressure thresholds, von Frey developed a graded series of sensory hairs. These were 40 to 100 μm. in diameter and made from human straight hair. When these hairs were bent upon application, the force required was taken as the threshold. von Frey recommended a series of hairs, first a child's, the a woman's, the a man's, and finally a horse hair. Pig's bristle was too strong, he found, and caused the sensation of pain. In time von Frey came to call the thickest sensory hairs "pain hairs." He sent a set of these to Henry Head for use in Head's classic studies.[13] An example of von Frey's use of his sensory hairs to map sensory spots is shown in Figure 1.5. Later, von Frey was to attach his sensory hairs to a tuning fork, electromagnetically driven, to evaluate punctate vibratory sensibility.[14]

MAX VON FREY,

UNTERSUCHUNGEN

ÜBER DIE

SINNESFUNCTIONEN

DER

MENSCHLICHEN HAUT.

ERSTE ABHANDLUNG:

DRUCKEMPFINDUNG UND SCHMERZ.

Aus den XXIII. Bande der Abhandlungen der mathematisch-physischen Classe der Königl. Sächsischen Gesellschaft der Wissenschaften

N° III.

MIT 16 TEXTFIGUREN.

LEIPZIG

BEI S. HIRZEL

1896.

Einzelpreis: 5 Mark.

Figure 1.1. Frontpiece from von Frey's 1896 paper in which he correlates sensory perception with sensory end organs.(10)

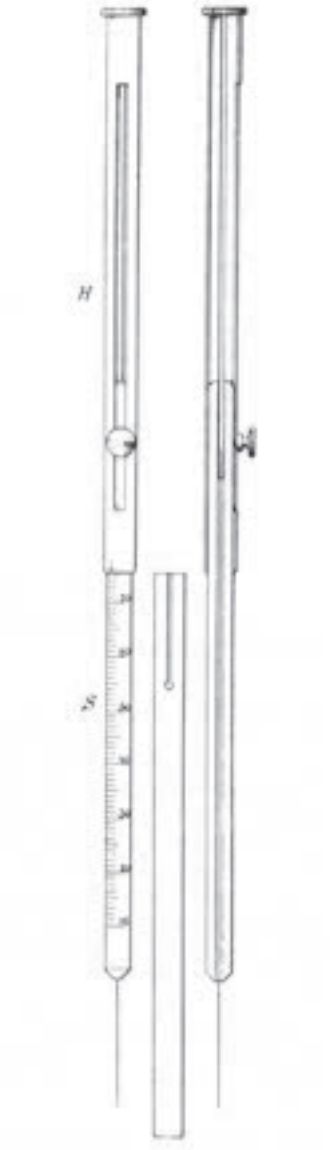

Figure 1.2. von Frey's aesthesiometer for testing pain.(10)

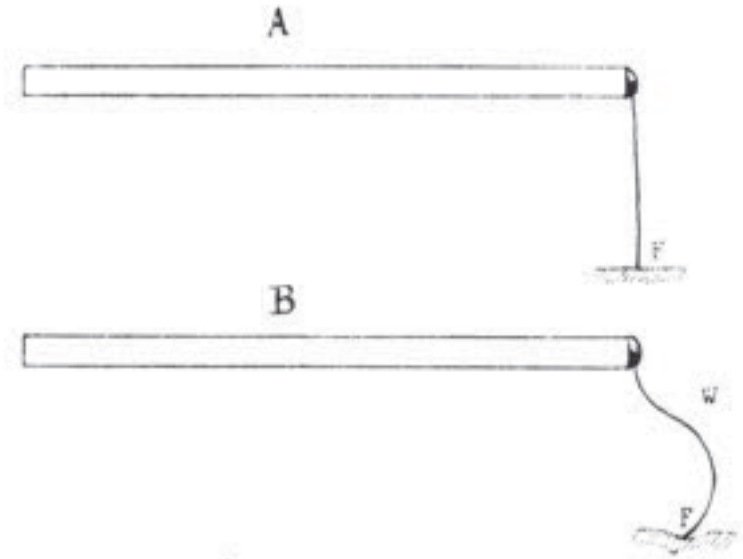

Figure 1.3. von Frey's sensory hairs.[10] These were made by fixing a hair to a candlestick. The cutaneous pressure threshold was the force required to bend the thinnest hair that produced a perception.

The next approach of physiologists foreshadowed the psychophysical studies of today. Head,[15] Trotter and Davies,[16] and Boring,[17] each reported elective division of one of their own cutaneous nerves. They then carefully recorded the observations on their own loss and sensory recovery. The most notable controversy to come from this approach was Head's concept of protopathic and epicritic sensation. In essence, he viewed these as representing two physiologically distinct sets of nerve fibers, receptors, and central mechanisms. The first dealt with early returning, unpleasant sensations and the second, with later returning, discriminative functions. Head did not attempt detailed structure/function correlations. His theory, however, conflicted with von Frey's and a spirited debate in the "letters to the editors" columns enlivened the journals of that day.[18]

Two diverse trends now entered the picture: Neurohistology, as evidenced by the Woorland-Weddel school, and Neurophysiology, as evidenced by the Adrian school. Woolard, and later his pupil, Weddel, correlated sensory and histologic findings, primarily by using methylene blue staining techniques. By employing thick sensations and photographic documentation, they were able to record the histologic findings in a way the rest of the world could also examine. They found that a touch spot actually contained many overlapping fibers, that the measure of discriminating two points was related to the extent of this overlap, that pains sensibility was related to free nerve endings[19] and that "a stimulus at the periphery is presented to the spinal cord as a complex spatial and temporal pattern of impulses."[20] Ultimately, they were to reject the concept of punctate sensibility in favor of a more Unitarian hypothesis. They proposed two categories of endings. In hairy skin, these were the dermal nerve network and hair follicles. In glabrous skin, these were the dermal nerve networks and the nonspecific encapsulated end organs.[21]

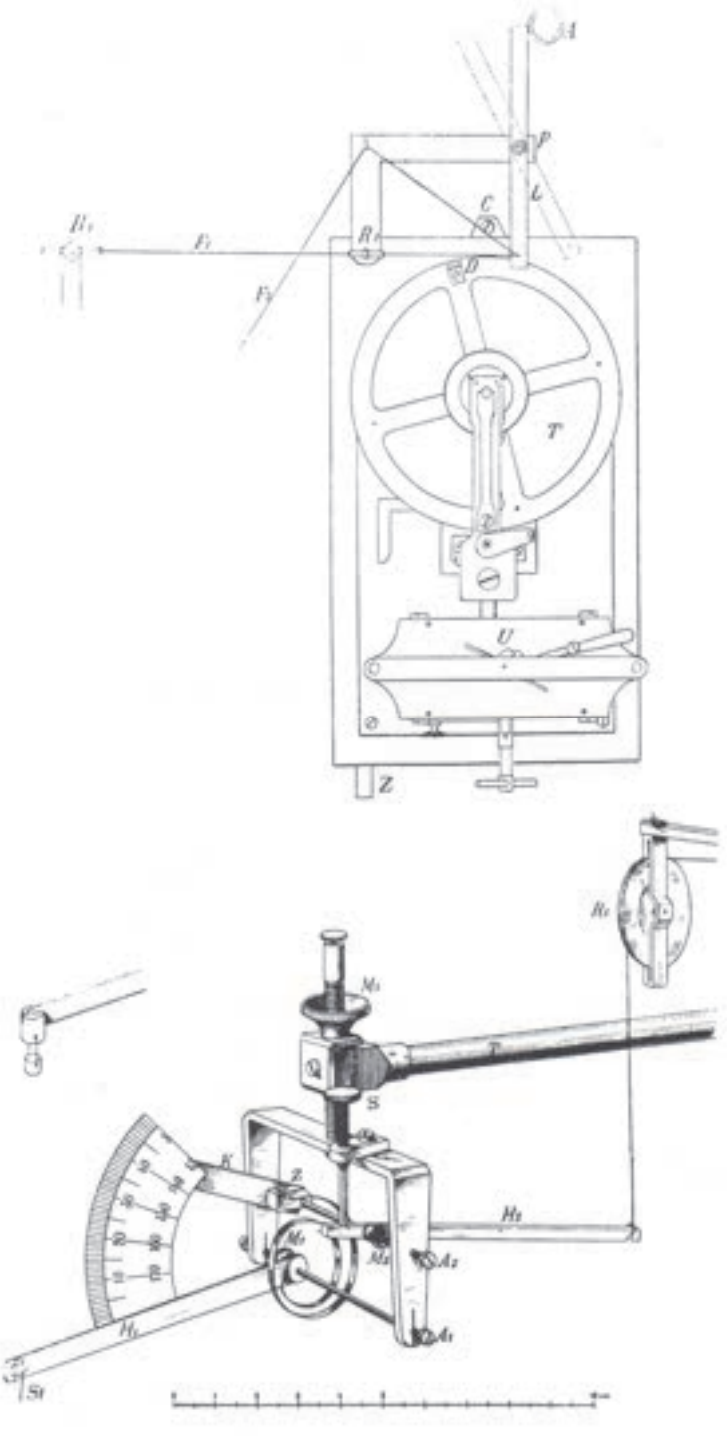

Figure 1.4. von Frey's diagram of his pressure recording apparatus.[10]

Figure 1.5. Example of the sensory maps of von Frey.[10] This map, of the volar wrist skin, demonstrated the punctate pattern of the pressure spots.

Other reviewers of the field at that time arrived at different conclusions, however. In particular, Walsche[22] concluded that each sensory submodality was served by a fiber/receptor system that was complete from periphery to the central nervous system. Walsche based his reasoning on the pioneering electrophysiological recording of Lord Adrian in the Physiological Laboratory, Cambridge, England.

Adrian[23] developed a technique for "single unit" fiber recording while stimulating the fiber's peripheral receptor field. He began with a nerve-muscle model in the frog, progressed to a Pacinian corpuscle-cat mesentery model, and then settled on the Pacinian corpuscles in the plantar aspect of the hind second toe of the cat. In this final model, Adrian recorded from the internal plantar nerve.[23] In his 1926 paper, he wrote: "The end organs sensitive to pressure are not known with certainty, but they are generally supposed to be the touch corpuscles in the skin and the Pacinian and other types." Adrian applied pressure by a glass rod to the footpad by increasing the weight from 5 to 100gm upon the pad. Continuous nerve impulses were recorded which adapted slowly to the stimulus intensity. In 1929, a report of further studies with this model[24] indicated that "pressure gives an immediate discharge of impulses from the (Pacinian corpuscle)." This work is the basis for the correlation "pressure-Pacinian corpuscle" which appeared in texts for the next half century.

The neurophysiology of the Pacinian corpuscle was re-examined with a more sophisticated electrophysical technique by Lowenstein and Rothkamp,[25] Lowenstein,[26, 27] and Lowenstein and Mendelson[28] at Columbia during the late 1950's and early 1960's. Lowenstein used the cat mesentery model and stimulated the corpuscle directly by "compressing it with fine rods and piezo-electric crystals."

Although he clearly wrote "in a rapidly adapting receptor, such as the Pacinian corpuscle …," the fact that his stimulus was one of pressure, that he did not suggest a clinical correlation in terms of sensation for the corpuscle, and that he emphasized generator potentials rather than conducted action potentials, I believe combined to perpetuate the pressure-Pacinian myth.

How can we understand the conflict between Adrian's slowly adapting Pacinian and Lowenstein's rapidly adapting one? In reply to my question, Michael Merzenich, who trained with Vernon B. Mountcastle at Johns Hopkins and is now in the Department of Physiology, School of Medicine, University of California, San Francisco, wrote:[29]

(Adrian) "erroneously described Pacinian corpuscle as pressure receptors, on the basis of what they regarded as direct evidence derived from isolated corpuscles. Vibrations introduced inadvertently with their stimulation led to continuous responses in isolated corpuscles; they then believed the receptor responded to continuous pressure, when in fact they were responding to their accidental continuous stimulation. This fact is hard to believe until you see a Pacinian corpuscle in operation! Then you believe how such a mistake could be made. Surprisingly (this) mistake was repeated shortly thereafter by Gammon and Bronk."[30]

As Winkelmann's work with morphology had led me out of the sensory receptor swamp, so too did the work of Mountcastle with neurophysiology lead me out of the sensory fiber swamp. Mountcastle had tabulated (see Table 1.2) the relationship of mechanoreceptor properties, as defined by single-unit recordings in monkey hands, with human perceptions. He correlated Merkel discs with slowly-adapting fibers, Meissner corpuscles with superficial, low-frequency vibration (flutter), and Pacinian corpuscles with deep, high-frequency vibration. The language of that table is pure neurophysiology and not intended for clinical application. The concept of the chart, relating sensation of a fiber/receptor system based on the fiber's property of adaption, is the foundation of my approach to evaluating sensibility (see Chapter 10). (The specific neurophysiologic aspects of adaption are described in Chapter 3.) However, Mountcastle still included proprioception as being related primarily to joint receptor (see discussion in Chapter 9). Although Mountcastle's table (Table 1.2) did not contain reference to dermal Krause's end bulbs and Ruffini endings, these endings are still included in his drawing of the skin and on a table on sensory ending.[32] For the first time, though, free nerve endings are correlated with reception of temperature,[33] and no sensory submodality is attributed to the supposed dermal endings of Krause and Ruffini.

My own work attempted to base the evaluation of sensibility on a firm, neurophysiologic basis. In1968, I began the use of 30 and 256 cps tuning fork testing to evaluate the low and high frequency, quickly-adapting fiber group. Movement detection was attributed to these fibers, although a vibratory stimulus was used to test them and the perception they mediated was termed moving-touch. Direct pressure of the examiner's fingertip, or the classic Weber two-point discrimination test was used to

evaluate the slowly-adapting fiber group. Constant-touch and pressure were attributed to these fibers and their receptor presumed to be the Merkel disc. It was emphasized that the Pacinian corpuscle was not a pressure receptor.[34] Although there was no direct evidence to assign the Meissner's corpuscle and Merkel disc to these fiber groups, I felt, as Mountcastle[31] had, that by morphologic analogy these were the best assignments. This approach broke the touch-pressure categorization of all touch submodalities into moving and constant-touch, with moving-touch being further subdivided based on the turning curves of the quickly-adapting fibers.[35]

Table 1.2
First-Order Afferents Feeding Lemniscal System Via Dorsal Columns[a]

Source	Type	Mechanoreceptor Submode
Hairy skin	Quickly-adapting fibers sensitive to hair movement (movement detectors)	Touch-pressure (and flutter)
	Slowly-adapting fibers innervating touch pads (Iggo)	Touch-pressure
Glabrous skin	Quickly-adapting fibers innervating dermal ridges (probably Meissner's corpuscles) (movement detectors)	Touch-pressure (and flutter)
	Slowly-adapting fibers innervating dermal ridges (probably Merkel's discs)	Touch-pressure
Dermis and deep tissues	Fibers ending in Pacinian corpuscles (detectors of high frequency transients)	Vibratory sensibility
	Slowly-adapting fibers ending in fascia and periosteium (Ruffini-like)	Touch-pressure
	Fibers ending in joint capsules and joint ligaments (Ruffini-like)	Position-sense kinesthesia

[a] Adapted from V. B. Mountcastle and I. Darian-Smith[31]

This approach, and these correlations, were presented to the Johns Hopkins Medical Society on February 3, 1969. The tests were conducted on a series of patients in whom the pattern of sensory recovery following nerve injury had been mapped. On July 20, 1969, the manuscript was rejected by the Johns Hopkins Medical Journal with the comment: "There are no data which might support the opinion of the authors and there for no real contribution is made in terms of proving or disproving any concepts."[36]

Whenever possible, thereafter, I took the opportunity to point out the correlation between Meissner's, Pacinian's and Merkel discs, fiber adaption properties, and the sensory submodalities attributed to them[37-42] (see table 1.3). It is gratifying, therefore, to note that in the most recent tabulation of "sensibility and receptor organs" to appear in clinical text, George Omer has correctly correlated pressure perception with Merkel disc, vibration with the Pacinian corpuscle, and temperature perception with free nerve endings.[43]

Table 1.3
Correlation between Merkel, Meissner's, and Pacinian Endings, Fiber Adaptation Properties, and Sensory Submodalities[a]

Fiber Property	Sensory Perception	Sensory Receptor
Slowly-adapting	Constant-touch pressure	Merkel cell—neurite complex
Quickly-adapting	Moving-touch flutter	Meissner corpuscle
Quickly-adapting	Moving-touch vibration	Pacinian corpuscle

[a]See expansion of this schema in Table 3.4 and 10.1

A recent trend is worth noting. At the beginning of the 20th century, increasing numbers of neurohistologists described increasing numbers of sensory receptors. Today we believe that there are three that can be demonstrated reproducibly. Today, near the beginning of the 21st century, increasing neuroscientists are describing increasing neurophysiologic classes (if not numbers) of nerve fiber populations. One recent categorization is based on Mountcastle's properties of adaption, but subdivides the quickly-adapting fibers into two major groups (SA I and SA II).[44] The current leader in "hair splitting is the classification of cutaneous mechanoreceptors into 11 groups.[45] While this last report provides a useful algorithm for the neurophysiologist in the experimental setting, I believe that my approach, based upon Mountcastle's work, still provides the basis of a meaningful clinical examination, and the best current synthesis from antiquity and artifact.

References:

1. Osler W: The student life, in Franklin AW (ed): *A Way of Life and Selected Writing of Sir WIlliam Osler*. New York: Dover, 1958, pp 172 - 173.
2. Sunderland S: *Nerves and Nerve Injuries*, ed 2. Edinburgh: Churchill-Livingstone, 1978, p344.
3. Pacini F: Nuovo Giralle Letherali, 1836, p 109. Cited by Winkelmann RK: Nerve Endings in Normal and Pathological Skin. Springfield: Chrles C Thomas, 1960.
4. Meissner G: Beiträge sur Kenntnis der Anatomie and Physiologie der Haut. Leipzig: Leopold Voss, 1853, p 47, and Untersuchungen uber den Tostsuin. Z Rat Med 7:92 - 119, 1859. Cited by Winklemann RK: Nerve Endings in Normal and Pathological Skin. Springfield: Charles C Thomas, 1960.
5. Winkleman RK: Nerve Endings in Normal and Pathologic Skin. Springfield,: Charles C Thomas, 1960.
6. Botezat E: Die Apparrate des Gefühlssinnes der nackten und behaarten Saügetieshaut, mit Berucksechtegung des Menschen. Anat Anz 42:278 - 318, 1912.
7. Jabaley ME, Dellon AL: Evaluation of sensibility by microhistological studies, in Omer G, Spinner M (eds): Management of Peripheral Nerve Problems. Philadelphia: WB Saunders, 1980, Ch23, 62.
8. Muller J: Uber die phantastischen Gesichtsercheiningen. Koblenz: J Holscher, 1826.
9. Bliz M: Experimenteia bidrag till Lösning of fragan om hudnervernas specifiko energi. Ups Lakarefor Forhandlingar 43:427 - 441, 1882.

10. von Frey M: Untersuchungen über die sinnesfunktionen der menschlichen Haut. Abh Sächs Ges (Akad) Wiss 40:175 - 266, 1896.
11. von Frey M: Beitrage zur Physiologie des Schmerzsinns, II. Ber Sachs Ges Wiss 46:283 - 296, 1894.
12. von Frey M: Beitrage zur Physokogie zur Sinnesphysiologie der Haut, III. Ber Sachs Ges Wiss 5:166 - 184, 1895.
13. Rivers WHR, Head H: A human experiment in nerve division. Brain 31:323 - 450. 1905.
14. von Frey M: Physiologische Verusche über das Vibrationsgefuhl. Z Biol 65:417-427, 1915.
15. Head H: The afferent nervous system from a new aspect. Brain 28:99 - 115, 1905.
16. Trotter WB, Davies HM: The peculiarities of sensibility found in cutaneous area supplied by regenerating nerves. *J Psychol Neurol* 20:102 - 131, 1913.
17. Boring EG: Cutaneous sensation after nerve division Q *J Exp Physiol* 10:1-95, 1916.
18. Munger B: Personal communication, March 22, 1980.
19. Wollard HH, Weddel G, Harpman JAL Observations on the neurohistologic basis of cutaneous pain. J Anat 74:413 - 419, 1940.
20. Weddel G, Sinclair DC, Feindel WH: Anatomical basis for alterations in quality of pain sensibility. *J Neurophysiol* 11:99-109, 1948.
21. Weddel G, Palmer E, Palli W: Nerve endings in mammalian skin. Buil Rev 39:159 - 195, 1955.
22. Walsche FMR: The anatomy and physiology of cutaneous sensibility: A critical review. Brain 65:45 - 112, 1942.
23. Adrian ED, Zotterman Y: The impulses produced by sensory nerve endings. Part 3. Impulses set up by touch and pressure. *J Neurophysiol* 61:464 - 483, 1926.
24. Adrian ED, Umrath K: The impulse discharge from Pacinian corpuscle. *J Physiol* 78:139 - 154, 1929.
25. Lowenstein WR, Rothkamp R: The sites for mechano-electrical conversion in a Pacinian corpuscle. *J Gen Physiol* 41:1245 - 1265, 1958.
26. Lowenstein WR: Biological transducers. Sci Am 203:99 - 108, 1960.
27. Lowenstein WR: On the "specificity" of a sensory receptor. *J Neurophysiol* 24:150 - 148, 1961.
28. Lowenstein WR, Mendelson M: Components of receptor adaption in a Pacinian corpuscle. J Physiol 177:377 - 397, 1965.
29. Merzinich MM: Personal communication, October 6, 1976.
30. Gammon GM, Bronk DW: The discharge of impulses from Pacinian corpuscles in the mesentery and its relation to vascular change. *Am J Physiol* 114:77 – 84, 1935.
31. Mountcastle VB, Darian-Smith I: Neural mechanisms in somesthesic, in Mountcaslte VB (ed): *Medical Physiology*, ed 12. Saint Louis: CV Mosby, 1968, Ch 62.
32. Mountcastle VB, Physiology of sensory receptors: Introduction to sensory process, in Mountcastle VB (ed): *Medical Physiology*, ed 12. Saint Louis: CV Mosby, 1968, Ch 61.
33. Mountcastle VB: Pain and temperature sensibilities, in Mountcastle VB (ed*): Medical Physiology*, ed 12. Saint Louis: CV Mosby, 1968, Ch 63.
34. Dellon AL, Curtis RM, Edgerton MT: Evaluating recovery of sensation in the hand following nerve injury. *Johns Hopkins Med J* 130:235 – 243, 1972.
35. Mountcastle VB, Talbout WH Darian-Smith I, et al: A neural base for the flutter vibration. Science 155:597 – 600, 1967.
36. Personal communication, Editor, *Johns Hopkins Med J*. July 30, 1969.
37. Dellon AL, Curtis RM, Edgerton MT: Re-education of sensation in the hand following nerve injury. *Plast Reconstr Surg* 53:297 – 305, 1974.
38. Dellon AL: Changes in primate Pacinian corpuscles after volar pad excision and skin grafting (Letter to Editor). *Plast Reconstr Surg* 58:614 – 617, 1976.
39. Dellon AL: Two-point discrimination and the Meissner corpuscle (Letter to Editor). *Plast Reconstr Surge* 60:270 – 271, 1977.

40. Dellon AL: The moving two point discrimination test: Clinical evaluation of the quickly adapting fiber-receptor system. *J Hand Surg* 3:474 – 481, 1978.
41. Dellon AL: The paper clip: Light hardware for the evaluation of hand sensibility. Contemp Orthop 1:39 – 44, 1979.
42. Dellon AL: The plastic ridge device and moving two-point discrimination (Letter to the Editor). *J Hand Surg* 5:91 – 93, 1980.
43. Omner GE: Sensibility testing, in Omer GE, Spinner M (eds): Management of Peripheral Nerve Problems. Philidelphia: WB Saunders, 1980, Ch 1.
44. Iggo A: Cutaneous and subcutaneous sense organs. Br Med Bull 22: 97 – 102, 1977.
45. Horch KWM, Tucket RP, Burgess PR: A key to the classification of cutaneous mechanoreceptors. *J Invest Dermatol* 69:75 – 92, 1977.

Chapter 2

CLASSICS

NEW MORPHOLOGY

While it is as yet uncertain whether the sensitive fibers end externally in loopes or in absolutely free ends, it is generally held that a vast number are externally related in some way to the little bodies know as the corpusles of Meissner, of Vater or Pacini … the structure of these corpuscles does not differ so essentially as to induce the belief that they must have different philological functions, were it not for their varying anatomical relations to tissues.

S. Weir Mitchell, 1872[1]

It seems likely that further human experiments, in which attention is particularly directed to the end-organs, may extend our knowledge of sensation considerably, and shed light upon the problems related to the receptors themselves.

J. S. B. Stopford, 1930[2]

INTRODUCTION

The purpose of this chapter is to presents of glabrous skin in their primate environment. This is done in a medical illustration that encompasses the most contemporary light and electron microscopic observations on the nature of these sensory "corpuscles," their relationship to the dermal nerves, and the basic organization of the cutis.

Aware in 1978 that all extant text illustrations of the glabrous skin were deficient in some critical aspect, and aware that the monograph I was planning must contain the most accurate and detailed illustrations of the apparatus of peripheral sensibility. I approached Ranice W. Crosby. She is the Director of the Department of Art as Applied to Medicine and Associate Professor at the Johns Hopkins-School of Medicine. I proposed a thesis project for one of her students that would culminate in the production of a three-dimensional model of the glabrous skin, a synthesis of current histological and neurophysiological

thought. Mark Lefkowitz accepted this challenge and prepared the color plates in this chapter from the model that was prepared as his Master's thesis in 1979.[3] The original model, itself, has been doated to the Raymond M. Curtis Hand Center at the Union Memorial Hospital in Baltimore, Maryland, and has been displayed there since August 2, 1980.

It is consistent with the theme of this monograph that as recently as 1967 a review on the "comparative anatomy and physiology of the skin" excluded the area of mechanoreceptors in glabrous skin.[4] However, within a decade, reviews of light and electron microscopy of these previously ignored sensory receptors had appeared.[5-8] Accordingly, only sufficient reference will be included in the following text to support the inclusion or exclusion of material encompassed in the medical illustrations.

The sensory end organs do not stand alone! Our understanding of their supporting structure comes primarily from the work of Cauna,[9] who worked with silver unpregnation techniques and later Weddel,[10] with methylene blue vital dyes. The patter that emerges consistently is of subcutaneous digital nerves branching beneath the glabrous skin, rising to form a subdermal plexus of fascicule, and branching again to form the subpapillary plexus or nerve network. These networks contain both myelinated and non-myelinated nerves. From the subpapillary plexus, myelinated (group A, beta) fibers emerge to innervate specific sensory end organs. The Pacinian corpuscle is innervated at the subdermal level. The Meissner corpuscle and Merkel "corpuscle" are in specific relationship to the dermal-epidermal junction. Beneath the papillary ridge, or fingerprint, is an elongated epidermal peg, the intermediate ridge. This is bordered by a dermal papillae on each side, each of which, in turn, is bordered by a shorter epidermal peg, the limiting ridge. Within a dermal papilla, between a limiting ridge and a intermediate ridge, is a Meissner corpuscle. At intervals along the longitudinal length or undersurface of the intermediate ridge, a sweat duct pierces the basal layer of germinal epidermis. At these junctures along the intermediate ridge lie the Merkel cell-neurite complex, the so-called Merkel corpuscle. The limiting ridges, bound down to the periosteum by collagen bundles, thus describe a mechanical transducer that transmits a touch stimuli efficiently to the sensory end organs. Along the length of the papillary ridge, these functional units are separated by septae which effectively divide the glabrous skin into small segments, each of which is maximally innervated by a single myelinated nerve for each type of sensory end organ within that segment. Yet overlap of nerve fibers below the septae provide the mechanism for the partially shifted peripheral receptive fields that permit tactile gnosis (see Chapter 3 and Figs 2.2 and 2.3).

I believe that Miller et al.[11] are correct in concluding that peripheral cutaneous sensory receptors can be divided into three groups: free nerve endings with unexpanded tips, endings with expanded tips, like the Merkel cell-neurite complex, and encapsulated endings, like the Pacinian and Meissner corpuscle. In glabrous skin, extensive modern staining of primate material has failed to demonstrate Krause's end bulbs or Ruffini endings.[12, 13] The end bulbs seen by Krause in mucous membranes have been

confirmed,[12] and these, probably with Winkelman's mucocutaneous end organ, represent an attempt by quickly-adapting fibers to form end organs in skin which is devoid of hair follicles or dermal papillae. That is, the mucocutaneous end organ is the transitional ending of the quickly-adapting fiber between Meissner corpuscles in glabrous skin and the innervated hair follicle in hairy skin. As the Merkel cell-neurite complex represent the expanded tip ending in glabrous skin, so the Ruffini spray endings represent the end organ of the slowly-adapting fibers in nonglabrous skin. These Ruffini soray endings have been observed on hair follicles in hairy skin[14] and primate hairy facial skin.[15] This scheme is carried out in tissues other than skin, too. In joints, for example, the slowly-adappting fibers are represented by Ruffini spray endings (expanded bulb endings), and the quickly-adapting fibers are represented by Pacinian corpuscles (encapsulated endings)[16] (See Table 2.1).

Evolution of Corpuscles

In the evolution of the species homo sapiens, the development of the cerebral cortex is a dominant feature. A significant portion of the cerebral cortex is the parietal lobe, which contains a broad area, critical to sensation. It would appear logical that the peripheral mechanisms of cutaneous sensibility that are the input to this central computing area also should be highly evolved. I am unaware of any treatise on the evolution of the cutaneous sensory end organs, but I believe insight can be gained from correlating previous comparative anatomy reports, the previous comparative anatomy reports, the classification of the animal kingdom, geologic time, and observations on patients following nerve repair.

In Table 2.2, a greatly shortened classification of the animal kingdom is correlated with geologic time periods for a few critical animal species, using standard reference works.[17,18] The geologic periods are listed in Table 2.3 for chronologic comparison.[19]

The earliest peripheral cutaneous sensory mechanisms were simple nerve networks as in the invertebrates. These evolved into nerve networks plus free nerve endings in the earliest vertebrates.[20] Such early vertebrates, like the lamprey eel, developed in the Jurassic Period, about 150 million years ago. The Cretaceous Period was at the end of the Mesozoic Era, and was the time of the dying out of the great retiles, and the origin og the smaller mammals and birds. Deciduous trees and grass were developing, and in this setting ducks and geese, opossum and moles appeared. For these animals, a sensitive nose was essential. In the case of the birds, the forelimbs were wings, and their hard beak, for example, had to serve to detect seeds or larvae in marshland. The beak developed, therefore, as an organ of touch.[21] In the mole, the limbs were digging tools, the eyes were blind, and so, again, the snout developed into a touch organ.

As the need for tactile discrimination was added to the need for simple protective sensibility, peripheral sensory structures differentiated. The best studied birds are ducks and geese,[12, 20-25] and they

have two well-defined sensory end organs in their bills. The Herbst (1848) corpuscle is a Pacinian-like corpuscle, and the Grandry (1869) corpuscle is a Merkel cell-neurite-like corpuscle. The contrasts and similarities are best described by Munger,[22, 23] and these represent in evolutionary terms the development of a specific encapsulated end organ for the quickly-adapting fibers (Herbst) and an expanded tip ending associated with an epithelial cell for the slowly-adapting fibers (Grandry). An end organ analogous to the Meissner corpuscle is not present in these species. Among mammals from this Cretaceous Period, the mole, and especially the opossum, have been studied. The mole's snout has a sensory apparatus described by Eimer (1871) and elaborated upon by Boecke[12] and Munger.[26] This organ of Eimer has small encapsulated nerve terminals at its base as well as expanded nerve endings in relation to epithelial celss at its base. The opossum snout has both Pacinian corpuscles and Merkel cell-neurite complexes.[22] Thus, the mammals of this period that were requiring increasingly finer tactile discrimination also developed sensory receptors along the pattern described for the bird's bill. But no sensory end organ analogous to the Meissner corpuscle has been observed in the mammals that developed more than 70 million years ago.

Table 2.1
General Pattern of Nerve Endings

Nerve Ending	Skin			Joint
	Glabrous	Transitional	Hairy	
Free nerve	Present	Present	Present	Present
Expanded tip	Merkel cell-neurite complex	None known	Pilo-Ruffini complex Haarscheibe	Ruffini spray endings
Encapsulated	Pacinian corpuscle Meissner corpuscle	Krause end-bulb Mucocutaneous end organ	Hair follicle	Pacinian corpuscle

As evolution implies transition, I believe we should not be surprised to find a transitional form of sensory corpuscle develop prior to the Meissner corpuscle. The transitional corpuscle has been named variously over the last century. It is Krause's end bulb, Krause's genital corpuscle, Winklemann's mammalian end organ or mucocutaneous end organ, etc.[12] In essence, in response to a need for finer discrimination of moving stimuli, small corpuscles composed of a few lamellar cells around a nerve terminal developed in the deep to superficial dermis, such as have been noted in the opossum, beneath the hairless snout skin,[27] and in many mammalian species in the glans penis and clitoris,[12] and by Krause in the conjunctiva and lip.[12] The opossum, although evolving in the Cretaceous Period, did not evolve until the Eocene Period or later in many parts of the world, and thus represents a good species for this transitional end organ.[28] The raccoon, developing more recently in the Eocene, was first noted to have

these small encapsulated corpuscles by Zollmann and Winkelmann[29] in 1962. Munger and Pubols[27] documented these simple corpuscles extensively and demonstrated them to be quickly-adapting receptors. The raccoon has five flexible toes on each foot, no clavicles, and generally diminished vision and hearing.[28] They are excellent tree climbers and are extremely dextrous with their forepaws. The simple corpuscles in the raccon lie just at the base of the dermal papillae adjacent to the Merkel-Rete papillae.

Table 2.2
Animal Kingdom

Classification			Geologic Period
Phylum	Protozoa		
	Mollusca		
	Arthropoda		
	Chordata		
Subphylum		Vertebrata	
Class		Marsipobranchii (lampreys)	Jurassic
		Pisces	
		Amphibia	
		Reptilia	
		Aves	
Subclass		Anseres (duck, goose)	Cretaceous
		Passeres (songbirds)	Eocene
		Mammalia	
		Theria	
Order		Marsupialica (opossum)	Cretaceous
		Eutheria	
		Insectivora (mole)	Cretaceous
		Rodentia (mouse)	Eocene
		Carnivora (raccoon)	Eocene
		Primates	Eocene
Suborder		Prosimiae (lemur)	
		Simiae (monkey)	
		(baboon)	
		(gorilla)	
		(man)	

The Meissner corpuscle represents, I believe, the most recent sensory corpuscle to evolve. The earliest species in which I am aware that a Meissner corpuscle has been described is the mouse.[30] In the mouse, small lamellated corpuscle, some with multiple innervations, are located within the dermal papillae. Meissner corpuscles, to be described in greater detail below, have been identified in every primate studied.[12]

Thus, in the most recently evolved mammals, the primates, there are three sensory end organs that serve as the mechanoreceptors to the transducer touch stimuli. The organizations of these receptors with respect to the skin and their nerve fibers is the subject of the rest of this chapter. But, for emphasis here with respect to evolution, I believe the Meissner fiber/receptor system not only provides the basis for the highest degree of tactile discrimination, tactile gnosis, but also provides a high degree of "overkill." By overkill, I mean a high ratio of nerve fibers to receptor. The degree of peripheral receptive field overlap possible in this fiber/receptor system has great survival value. Following a nerve repair when a significant

number of axons fail to regenerate to the fingertip, the Pacinian system with few fiber to start and a 1:1 fiber to receptor ratio has a small chance to recover, while the Merkel cell-neurite system, with more fiber to start with but with less than a 1:1 fiber to receptor ratio, has the least chance to recover. The Meissner system, with the greatest number of fibers to start with and a greater than 1:1 fiber to receptor ratio, has the best chance to reinnervate the necessary peripheral innervations density to permit recovery of functional sensation (see Fig 7.5). Recognition of the Meissner corpuscle as the most recent corpuscle to evolve gives further emphasis to the use of the moving two-point discrimination test (Chapter 8) to evaluate sensibility and the object recognition tasks involved in sensory re-education (Chapter 12).

Table 2.3
Geologic Time

Era	Period	Epoch	Years Ago
Cenozoic	Quaternary	Recent	Present
	Tertiary	Pleistocene	
		Pliocene	
		Miocene	
		Oligocene	
		Eocene	55,000,000–35,000,000
		Paleocene	70,000,000–55,000,000
Mesozoic	Cretaceous		135,000,000–70,000,000
	Jurassic		180,000,000–135,000,000
	Triassic		225,000,000–180,000,000

Vater-Pacinian Corpuscle

The facts regarding the historical priority for naming this end organ are best outlined by Lee.[31] Vater was the first to describe the presence of this structure, which he termed “papillae nervae.” Almost a century later, Pacini redescribed these structures, adding the description of the concentric lamellae separated by fluid. He believed these were part of the lymphatic system. In 1844, Henle and Kolliker were the first to relate the corpuscle to nerve fiber, thereby describing the first nerve ending.

The entire subject of the Pacinian corpuscle is reviewed by Winkelmann[12] (but is inaccurate regarding its role as a pressure detector, see Chapter 3). Cauna and Mannan[32] have reported its embryologic development, and ultrastrucural reports are numerous.[33-35]

To be emphasized here is that the Pacinian corpuscle is a deep dermal and subcutaneous sensory receptor, 1 to 4 mm long and 0.5 to 1 mm wide, innervated by a single myelinated nerve. Estimates of the number of corpuscles present vary from 200 per thumb, 600 per hand, 120 p34 centimeter of a volar pulp. The corpuscle develops between the 3rd and 5th months of fetal life, which is earlier than Meissner corpuscle. The axon enters the corpuscle, loses its myelin sheath, and enters the inner core. The inner core

contains a granular material that stains for nonspecific cholinesterase. The axon terminal tip contains numerous mitochondria. The axon is surrounded by 49 to 60 concentric lamellae. The inner few lamellae are split by a fissure, while the outer lamellar cells are contiguous with the epineurium of the nerve fiber.

The Pacinian corpuscle may be found in clusters, but in such cases each is usually innervated by its own nerve fiber. The Pacinian corpuscle may be occasionally bilobed, and in such a situation, a cross-section would give a picture similar to the so-called Golgi-Mazzoni body. (1878)[12] The arteriovenous glomerular apparatus is found often near a Pacinian corpuscle.

In this book, light microscopy of the Pacinian corpuscle is illustrated with the Masson trichrome stain (Fig. 5.19), hematoxylin and eosin (Fig 12.25), and with silver stain (Fig. 5.19).

MEISSNER CORPUSCLE

The Meissner corpuscle was described originally in a paper co-authored by Wagner and Meissner in 1852, with the description of the corpuscle further elaborated by Meissner in two subsequent papers in 1852 and 1856.[36] This corpuscle has been identified repeatedly by many current investigators, and descriptions are available in excellent light microscopic studies by Cauna[36, 37] with frozen section and silver staining techniques, by Weddell[38] with methylene blue, by Ridley[39] in human normal and pathologic states, and ultrastructural studies.[40-42]

Under light microscopy, the Meissner corpuscle appears as an encapsulated, oval end organ within the dermal papilla. There may be bilobed corpuscles, but most commonly a single lobed corpuscle is present. The lobulations may be two to four, each appearing full and plump. Within each lobulation, there appears to be a stacked series of flattened discs which, in fact, represent the lamellar cells. The nuclei which appear usually at the endge or side of the “capsule” are lamellar cell nuclei. With Masson trichrome stain, the pink-staining tissue within the corpuscle is axoplasm and the blue-staining fibers are the connective tissue that comprises structureal framework for the lobular architecture.[43] With silver and methylene blue techniques, each corpuscle is demonstrated to have multiple innervations, ranging from two to nine separate nerve fibers. Two to three fibers enter at the base of the corpuscle, other rising in the dermal papilla to enter the corpuscle from its sides or top. The fibers lose their myelin sheath as they enter the corpuscle, and the lamellar cells may represent either perineurial (Schwann) cells or modified epithelial cells, or both.

The Meissner corpuscles are related to the papillary ridge and more specifically to the intermediary ridge. They vary in frequency from one every other or every third ridge at the digital pulp, to a frequency of every fifth or sixth in the palm. Ruimentary Meissner-like corpuscles are located in the distal dorsal (still glabrous) finger skin. Meissner corpuscles arise about the 7th month of fetal life and diminish in frequency with advanced age.[36, 39, 44]

Within the Meissner corpuscle, the terminal nerve filaments end as either multiple fine enlargements, bulbs, or loops, or as fine networks by light microscopy. By electron microscopy, each terminal nerve filament contains numerous mitochondina and is ensheathed by a lamellar cell process. No desmosomes have been noted. Between lamellar cell process is a fine, interlamellar ground substance. There is no true capsule and this interlamellar substance is in communication or is contiguous with the extracellular space of the dermal papilla.

The multiple fiber innervations of the Meissner corpuscle allows for overlap of the peripheral receptive fields of individual fibers in a manner not possible with the Pacinian corpuscle or the Merkel cell-neurite complex.

The innervated hair follicle of hairy skin is most certainly the morphologic and neurophysiologic analog of the Meissner corpuscle in glabrous skin.

In this book Meissner corpuscles are illustrated in trichrome (Figs, 4.3 and 5.3), silver (Figs 4.4, 5.4, 5.16, 5.17, and 12.25), and nonspecific cholinesterase (Fig 4.2) stains from light microscopy and from electron micrographs (Figs. 4.5, 5.5, 5.6, and 10.5).

MERKEL CORPUSCLE

In 1875, Merkel[45] wrote a very thorough paper, in which he described Tastzekken (touch cells) and Tastkorperchen (touch corpuscles) in geese, ducks, pigs, cows, sheep, and man. That Merkel was thorough is evident, not only from his exhaustive comparative anatomy studies, but also from his referral to the Pacinian corpuscle as the Vater corpuscle, and to the Meissner corpuscle as the Wagner corpuscle.[45] Merkel described nerve terminals ending in relationship to clear cells in the basal layer of epidermis of rete pegs in human fingertips. He called the clear cells “touch cells” and the combination of epithelial cell and nerve terminal a “corpuscle.” He never implied an encapsulated end organ for his corpuscle. He believed it to be an end organ of touch.

Merkel’s osmium preparation may well have been demonstrating melanocytes, but other investigators of his era made similar observations, such as Ranvier, using gold chloride (1877) and Retzius using silver (1894).[12] Nevertheless, the Merkel “corpuscle” never seemed to make it inot the orthodoxy of anatomy. von Frey never included it in his scheme of sensory-histology correlation (see Chapter 1). He didn’t need another “touch corpuscle.” For von Frey, touch was pressure and he already had Pacinian and Meissner corpuscles for his correlations! Subsequent (and present day) text books simply excluded the Merkel corpuscle. As recently as 1955, the Merkel corpuscle was said to be an artifact.[46] Winkelmann[12] states that Cauna “did not find the,” referring to Merkel’s corpuscle; however, Figure 18 in Cauna’s 1954 paper[9] is clearly a Merkel corpuscle, although Cauna identified it only as a nerve network beneath the intermediate ridge. In 1960, Winkelmann consistently demonstrated what he

termed “hederiform,” or ivy-like nerve terminals ending along the intermediate epidermal ridge in relation to clear cells in the basal layer of glabrous skin. However, Winkelmann believed the Merkel corpuscle was similar to a Meissner corpuscle, listed it as a subclass under the Meissner corpuscle, suggested it should stain for cholinesterase activity since the Meissner does (but in fact the Merkel doesn’t), suggested it subserved touch and, in particular, motion.

Thus, although after a generation of neglect the Merkel corpuscle was rediscovered, there was still a long way to go. There have been few published photomicrographs of the Merkel corpuscle in man, and to this end I have included Figure 2.1, kindly contributed by Bryce L. Munger, M.D., Chairman of the Department and Professor of Anatomy at the Milton D. Hershey Medical School. It is appropriated that these illustrations come from him since in 1965 he published the first electron micrographs of the Merkel cell and its secretory granules, and coined the term that is most appropriate, and which I have adpted in this book, the Merkel cell-neurite complex.[26]

Munger described the Merkel cell-neurite complex in glabrous opossum snout in 1965. That same year Mann and Straille described a structure in the cat with clear cells and nerve terminals associated with a tylotrick (thickened, nonpellage body) hair and a n intimately associated epidermal pad.[47] This complex was slowly-adapting. Previously, Iggo and Muir[48] had demonstrated the cat touch dome to be a receptor related to a slowly-adapting fiber. This touch dome, although unassociated with a hair, is located on the hairy, is located on the hairy cat paw and was morphologically analogous to the Haarscheibe (hair disc) described by Pinkus in 1904 on the hairy skin of man.[49] The Haarscheibe of man and the tylotrich follicle and touch pad of cats, although in hairy skin, had in common with Munger’s glabrous opossum snout receptor the association of a clear epithelial cell and an expanded bulb nerve termination.

There can no longer be any question of the existence of a Merkel cell-neurite complex that is the receptor part of the slowly-adapting fiber/receptor system. It has been described on the human trunk (1966),[55] the rat back as well as hairy skin of rabbits, mice, and guinea pigs (1967),[55] hairy skin of monkey forearm and hand (1969),[52] and the glabrous fingertips of the raccoon (1971).[53] The have been many confirmatory reports.[54-60] The description to follow is based upon these studies.

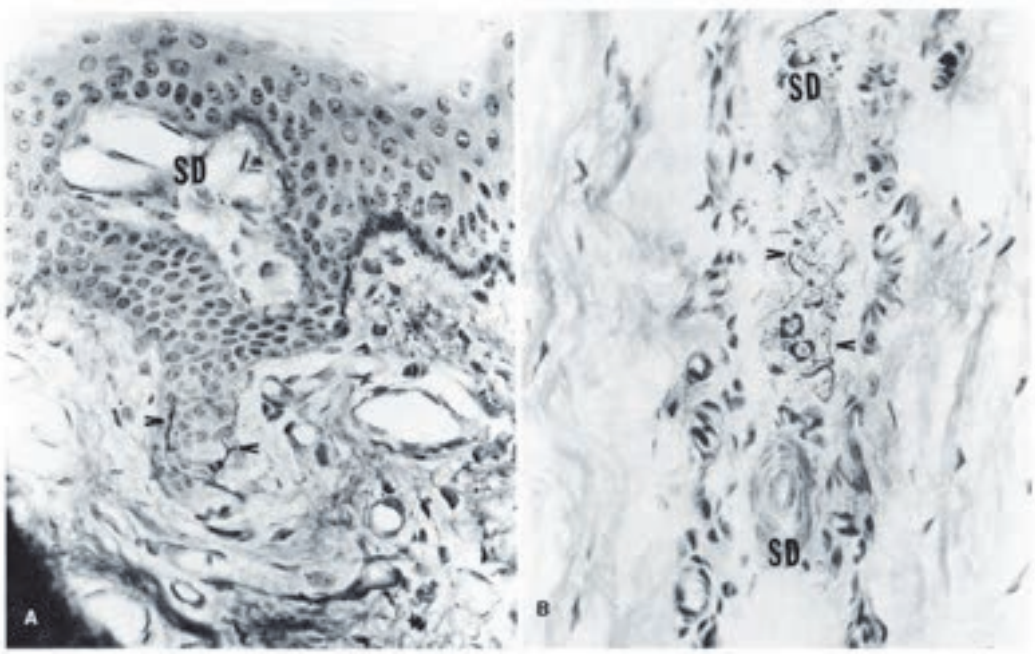

Figure 2.1 Merkel cell-neurite complex, human glabrous skin, silver stain (SevierpMunger). ***A*** Vertical section through intermediate epidermal ridge at level of seat duct (SD), demonstrating neurites (arrowhead) in relation to Merkel cells (x 512). ***B*** Horizontal section through base of intermediate ridge to demonstrate relationship of neurites (arrowhead) to sweat ducts (SD) (x 380).

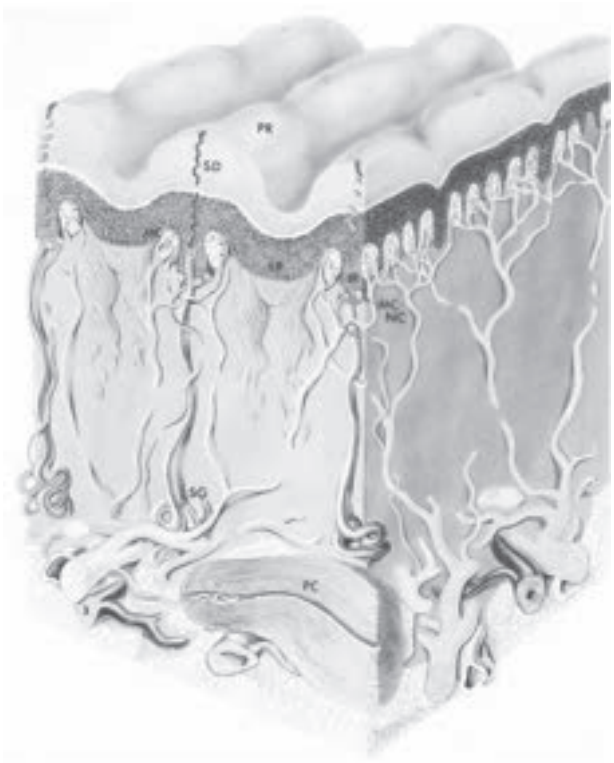

Figure 2.2 Model of distal glabrous human skin: **MC**, Meissner corpuscle; **MD**, Merkel cell-neurite complex; **PC**, Pacinian corpuscle; **LR**, limiting ridge; **IR,** intermediate ridge; **PR**, papillary ridge; **SG**, sweat gland; **SD**, sweat duct. Note multiple innervation for Meissner corpuscles, single innervation for Pacinian corpuscle and Merkel cell-neurite complex. Note overlapping peripheral receptive fields.

Figure 2.3 Model of distal glabrous human skin. Abbreviations are same as in Figure 2.2.

The Merkel cell is a large cell located in the basal layer of the epidermis. In hairy skin, it is either in groups below an elevated pad (Haarscheibe) or associated with a hair (tylotrich) or vibrissae), while in the glabrous digital skin it lies in groups of four about the entrance of the sweat duct into the intermediate ridge (Fig. 2.1). A single myelinated nerve innervates a Haarscheibe in humans, a tylotrich hair in cats, and a group of Merkel cells about the sweat duct in the glabrous skin, In cats, a single nerve fiber may innervate four to seven touch domes on the hindleg. The Merkel cells of the Haarscheiben and tylotrich are associated intimately with hairs, those of the touch dome and glabrous skin are not. The Merkel cell has a nucleus with irregular borders and contains electron-dense cytoplasmic granules polarized toward the side adjacent to the nerve terminal. The granule's histochemical content remains unknown. In man, desmosome-like communication have been identified, between the Merkel cell and neurite. The origin of the Merkel cell, neural crest versus non-neural epithelium, remains debated. The Merkel cell is intimately associated with the neurite, which has lost its myelin and ends in expanded bulbs in a disc-like array around or about the Merkel cell.

Although Adrian and Zottermann[61] suggested that the Pacinian corpuscle was the pressure receptor, the work of Werner and Mountcastle[62] demonstrated that only a slowly-adapting fiber/receptor system was responsive to vertical skin displacement in a linear fashion. The Merkel cell-neurite complex, the, must be the pressure receptor (see Chapter 3).

In this book, in addition to Figure 2.1, the Merkel cell-neurite complex is illustrated in hematoxylin and eosin (Figs. 4.7 and 5.7) and in silver (Figs 5.16 and 12.25) stain for light microscopy and for electron microscopy (Figs. 10.6 and 10.7).

MODEL OF THE DISTAL GLABROUS SKIN

Figures 2.2 and 2.3 are medical illustrations prepared to illustrate the histology of the distal glabrous skin of the primate, based upon the references and material developed above, and Lefkowitz's thesis.[3]

References:

1. Mitchell SW: *Injuries of Nerves and Their Consequences*, 1872. American Academy of Neurology Reprint Series, p 19, New York: Dover, 1965.
2. Stopford JSB: *Sensation and the Sensory Pathway*. London: Longsmans, Green, 1930, Ch XI.
3. Lefkowitz M: *A Model of the Glabrous Skin of the Fingertip*, Master's thesis. Johns Hopkins University, Baltimore, 1979.
4. Montagna W: Comparative anatomy and physiology of the ski. Arch Dermatol 96:357 – 363, 1967.
5. Iggo A: Cutaneous receptors, in Hubbard JF (ed): *The Peripheral Nervous System*. New York: Plenum Press, 1974, Ch12, pp 374 – 404.
6. Breathnach AS: Electrom microscopy of cutaneous nerves and receptors. J Invest Dermatol 69:8 –26, 1977.
7. Horch KW, Tuckett RP, Burgess PR: A key to the classification of cutaneous mechanoreceptors. J Invest Dermatol 69:75 – 82, 1977.
8. Iggo A: Cutaneous and subcutaneous sense organs. Br Med Bull 33:97 – 102, 1977.
9. Cauna N: Nature and functions of the papillary ridges of the digital skin. Anat Rec 119:449 – 468, 1954.
10. Weddell G: Nerve endings in mammalian skin. Biol Rev 30:159 – 195, 1955.
11. Miller MR, Ralston HJ, Kasahara M: The patter of cutaneous innervation of the human hand. Am J Anat 102: 183 – 201, 1958.
12. Winkelmann RK: *Nerve Endings in Normal and Pathologic Skin*. Springfield, III: Charles C Thomas, 1960.
13. Dellon AL: Personal observations, unpublished.
14. Halata, Z: Spezifische innervation, Ch. 6, in Orfanos CE (ed): *Haar and Haarkrankheiten*. Stuttgart: Gustav Fischer Verlag, 1979.
15. Biemesderfer D, Munger BL, Binck J, et al: The Pilo-Ruffini complex: A non-sinus hair and associated slowly-adapting mechanoreceptor in primate facial skin. Brain Res 142:197 – 222, 1978.
16. Halata Z: The ultrastructure of the sensory nerve endings in the articular capsule of the knee joint of the domestic cat (Ruffini corpuscle and Pacinian corpuscles). J Anat 124:717 – 729, 1977.
17. Blackwelder RD: Classification of the Animal Kingdom. Carbondale, III: Southern Illinois Univ Press, 1963.
18. Rothschild NMV: A Classification of Living Animals. New York: John Wiley & Sons, 1961.
19. Webster N: *The Living Webster Encyclopedic Dictionary*. Chicago: English Language Inst of America, 1975.
20. Kappers CVA, Huber GC, Crosby EC: *The Comparative Anatomy of the Nervous System of Vertebrates, including Man*. New York: Hafner, 1960.

21. Marshall AJ: *Biology and Comparative Physiology of Birds.* New York: Academic Press, 1960.
22. Munger BL: The comparative ultrastructure of slowly and rapidly adapting mechanoreceptors, in Dubner R, Kawamuro Y (eds): *Oral-Facial Sensory and Motor Mechanisms*. New York: Appelton-Century-Crofts, 1971, Ch 6.
23. Munger BL: Patterns of organization of peripheral sensory receptors, in Lowenstein WR (ed): *Handbook of Sensory Physiology*. Berlin: Springer-Verlag, 1971, Ch 17.
24. Saxod R: Developmental origin of the Herbst cutaneous sensory corpuscle. Experimental analysis using cellular markers. Dev Biol 32:167 – 178, 1973.
25. Gottschaldt KM, Lausmann D: Mechanoreceptors and their properties in the beak skin of geese (Anser anser). Brain Res 65:510 – 515, 1974.
26. Munger BL: The intraepidermal innervation of the snout skin of the opossum. J Cell Biol 26:79 – 97, 1965.
27. Munger BL, Pubols LM: The sensorineural organization of the digit skin of the raccon. Brain Behav Evol 5:367 – 393, 1972.
28. Anderson S, Jones JK: *Recent Mammals of the World: A Synopsis of Families*. New York: Ronald Press, 1967.
29. Zollmann PE, Winkelmann RK: The sensory innervation of the common North American raccoon (Procyon loto). J Compt Neurol 119:149 – 157, 1962.
30. Ide C: The fine structure of the digital corpuscle of the mouse toe pad, with special reference to nerve fibers. Am J Anat 147: 329 – 356, 1976.
31. Lee F: A study of the Pacinian corpuscle. J Comp Neurol 64:497 – 522, 1936.
32. Cauna N, Mannan G: Development and pastnatal change of digital Pacinian corpuscles (corpuscular lamellose) in the human hand. J Anat 93:271 – 286, 1959.
33. Pease DC, Quilliam TA: Electron microscopy of the Pacinian corpuscle. J Biophys Biochem Cytol 3:331 – 342, 1957.
34. Nishi K, Oura C, Paillie W: *Fine structure of Pacinian corpuscles in the mesentery of the cat*. J Cell Biol 43:539 – 552, 1969.
35. Spencer PS, Schaumberg HH: An ultrastructural study of the inner core of the Pacinian corpuscle. J Neurocytol 2:217 – 235, 1973.
36. Cauna N: Nerve supply and nerve endings in Meissner's corpuscles. Am J Anat 99:315 – 350, 1956.
37. Cauna N: Structure of digital touch corpuscles. Acta Anat (Basel) 32:1 – 23, 1958.
38. Weddell G: Multiple Innervation of sensory spots in skin. J Anat 75:441 – 446, 1941.
39. Ridley A: Silver staining of nerve endings in himan digital glabrous skin. J Anat 104:41 – 48, 1969.
40. Cauna N, Ross LL: The fine structure of Meissner's touch corpuscles of human fingers. J Cell Biol 8:467 – 482, 1960.
41. Breathnach AS: An Atlas of the Ultrastructure of Human Skin. London: JA Churchill, 1971.
42. Hashimoto K: Fine Structure of the Meissner corpuscle of human palmar skin. J Invest Dermatol 60:20 – 28, 1973.
43. Dellon AL, Witebsky FG, Terrill RE: The denervated Meissner corpuscle: A sequential histologic study after nerve division in the Rhesus monkey. Plast Reconstr Surg 56:182 – 193, 1975.
44. Dickens WN, Winkelmann RK, Mulder DW: Cholinesterase demonstration of dermal nerve endings in patients with impaired sensation. Neurology (Minneap) 13:91 – 100, 1963.
45. Merkel F: Tastzellen and Tastkorperchen bei den Hausthieren und beim Menschen. Arch Mikrosk Anat 11:636 – 652, 1875.
46. Weddell G, Palmer E, Palie W: Nerve endings in mammalian skin. Biol Rev 30:159 – 195, 1955.
47. Mann SJ, Straille WE: Tylotrich (hair) follicle: Association with a slowly adapting tactile receptor in the cat. Science 147:1043 – 1045, 1965.
48. Iggo A, Muir AR: A cutaneous sense organ in hairy skin of cats. J Anat 97:151, 1963.

49. Pinkus F: Ueber Hautsinnesorgars neben den menshlichen Haar (Haarscheiben) und ihre vergleisehend anatomische Bedentung. Arch Mikrosk Anat EntwMech 65:123 – 179, 1904.
50. Kawamura T, Nishiyama S, Ikeda S, et al: The human haarscheibe, its structure and function. J Invest Dermatol 42:87 – 90, 1966.
51. Smith KR: The structure and function of the Haarscheibe. J Comp Neurol 131:459 – 474, 1967.
52. Iggo A, Muir AR: The structure and function of a slowly-adapting touch corpuscle in hair skin. J Physiol 200:763 – 796, 1969.
53. Munger BL, Pubols LM, Pubols BH: The Merkel rete papilla – a slowly adapting sensory re3ceptor in mammalian glabrous skin. Brain Res 29:47 – 61, 1971.
54. Smith HR: The ultrastructure of the human haarscheibe and Merkel cell. J Invest Dermatol 54:150 – 159, 1970.
55. Kasprzak H, Tapper DN, Craig PH: Functional development of the tactile pad receptor system. Exp Neurol 26:439 – 446, 1970.
56. Kawamura T: Fine struture of the dendritic cells and Merkel cells in the epidermis of various mamals, Jpn J Dermatol 81:343 – 351, 1971.
57. Winkelmann RK, Breathnach AS: The Merkel cell. J Invest Dermatol 60:2 – 15, 1973.
58. English KB: Cell types in cutaneous type 1 mechanoreceptors (Haarscheiben) and their alterations with injury. Am J Anat 1:205 – 126, 1974.
59. Munger BL: Neural-epithelial interactions in sensory receptors. J Invest Dermatol 69:27 – 40, 1977.
60. English KB: Morphogenisis of Haarscheiben in rats. J Invest Dermatol 69:58 – 67, 1977.
61. Adrian ED, Zottermann Y: The impulses produced by sensory nerve endings: The response of a single nerve organ. J Physiol (Lond) 61:151 – 171, 1926.
62. Werner G, Mountcastle VB: Neural activity in mechanoreceptive cutaneous afferents: Stimulus-response relations, Weber functions, and information transmission. J Neurophysiol 28:359 – 397, 1965.

Chapter 3
NEUROPHYSIOLOGIC BASIS OF SENSATION

The study of the sense is a point of convergence, where, in the future, the science of physiology, psychology and physics will come together.

E.H. Weber, 1835[1]

There is one field of enquiry in which neither animal experiment nor access to a large number of patients is of much use; the study of disturbance of sensibility, more particularly, cutaneous sensibility. It is no accident that the renowned investigation of Head, Trotter and Davis, Boring, Woolard and Weddell were done in times of peace. It is a leisurely occupation. Animal experiments . . . have helped a little; but man alone . . . can describe the manifold sensations experienced after an injury to a nerve or during regeneration. Moreover, the injuries themselves must be deliberately inflicted , with great precision, and the subject has to be a fully informed member of the experimental team . . . It may be said that this is rather province of the physiologist and the anatomist. In methodology this is true enough, but the problem is intensely practical . . . What is so astonishing is that in spite of the devoted efforts of many workers the riddle of sensibility is still not yet solved.

H.J. Seddon, 1972[2]

INTRODUCTION

Ernst Heinrich Weber was expressing, perhaps, optimism as he looked ahead to the challenge provided by the study of peripheral sensibility. Sir Herbert Seddon, almost a century and a half later, was expressing, perhaps frustration. His monograph reviews a lifetime of work, recording his own observations on more than 2,200 nerve injuries. Sir Sidney Sunderland's massive book on the peripheral nerve[3] and Barnes Woodhall's review[4] of more than 3,600 peripheral nerve injuries already had been published. The British, Australian, and United States experiences had been carefully documented. Seddon wrote these words in his Preface about 6 years before his death. He looked back over the past 3 decades of clinical experience and realized that the surgeon still did not have statistical evidence from a controlled series to know whether nerve primary or secondary nerve repair gave better results, whether nerve grafting was superior or either or neither. He realized further that published reports on the end resilts of

nerve repair continued in the absence of a standardized scheme for evaluating functional sensation in the hand. Seddon would have had cause for optimism, however, had he been aware of the coming forth from Vernon B. Mountcastle's neurophysiology lab at Johns Hopkins. Seddon's book contains more than 450 references in its bibliography, but none to the basic mechanisms of sensibility elucidated by Mountcastle. Mountcastle's textbook of neurophysiology is a good starting place, for in just two chapters[4] are reviewed the elements that permitted me to develop a clinical approach to evaluating peripheral senibility that would have pleased Sir Herbert.

I have had the privilege of visiting Doctor Mountcastle's laboratory. There are the special plexiglass chairs, stereotactic devices, behavioral reward devices for the monkey subjects. These were arrayed before a phalanx of computers, oscilloscopes, stimulating and recording devices. But the hardware only hints at the guiding genius, of his "view from withing." On October 28, 1974, Doctor Mountcastle presented the Dean's Lecture to the Johns Hopkins University School of Medicine.[6] This provides an overview of the activities of Mountcastle's laboratory and spans almost 2 decades of work.

PERIPHERAL SENSIBILITY

The sensory part of the peripheral nervous system may be thought of as being comprised of sensory units. Each unit includes a neuron, located in the dorsal spinal ganglion, its central termination with the central nervous system, its peripheral afferent fibers, and it s most distal termination. This distal termination may be called the sensory ending and may be a "free" ending, a nerve network, or an ending in relationship to a nonneural structure. These nonneural structures may be hair follicles or a form of "encapsulated end organ." The encapsulated end organs, as described in Chapter 2, are Merkel cell-neurite complexes, Meissner corpuscles, and Pacinian corpuscles. Those receptors found in joints, fascia, and muscle spindles will not be considered here.

Each afferent nerve fiber is related to a defined peripheral receptive field. A stimulus of proper quality and intensity will evoke a neural impulse (response) from the axon from anywhere within its receptive field. The threshold (stimulus required to generate impulse) is lowest in the center of the field. Adjacent peripheral receptive field partially overlap. Thus, a stimulus to a point on the skin evokes a profile of neural impulses from number from the overlapping afferent fibers (Fig. 3.1). The number of nerve fibers present in a given area of skin is referred to as the peripheral innervation density and is related to the volume of cerebral cortex representing that area. Thus, for example, the hand, and in particular the fingertips, have among the highest innervation density of any place on the body surface and are represented by one of the largest area on the sensory cortex.[5]

The peripheral nerve is classified conveniently by its fiber size and whether or not it is myelinated.[7] For our purposes, the classification may be simplified to the group A, myelinated fibers, and

the group C, unmyelinated fibers. The C fibers are small, being just 1 to 2 µm. Group A is subdivided by fiber size into A-delta, 2 to 5 µm,; A-beta, 10 to 15 µm,; and A-alpha, 15 to 20 µm. The A-alpha are motor fibers. Erlanger and Gesser correlated the A-beta fibers with touch, the A-delta with sticking pain and temperature, and the C fibers with burning pain. The A-delta and C fiber groups will not be discussed further, but detailed account of their neurophysiology are available.[8-10]

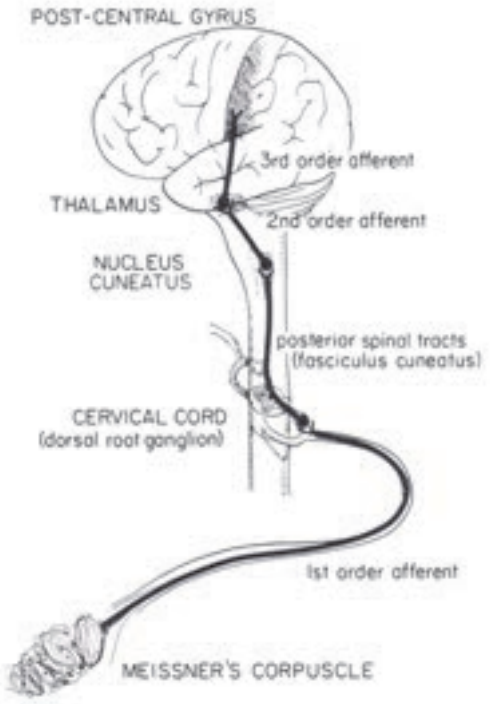

Figure 3.1. Each sensory unit consists of a neuron, located in the dorsal root ganglion, a central connection, and a peripheral termination. Peripherally, each fiber has a defined receptive field.

The group A-beta fibers, therefore, are those heavily myelinated fibers subserving the sense of touch. Mountcastle found these fibers could be subdivided based upon their adaption to a constant-touch stimulus. A fiber is termed rapidly-adapting if its impulse response drops off rapidly to zero. A fiber is termed slowly-adapting if its pulse response continues throughout the stimulus duration. Only the slowly-adapting fibers increase their rate of firing, or impulse frequency, as the stimulus intensity is increased (Fig. 3.2). Thus, only a slowly-adapting fiber can convey information regarding constant-touch (Fig. 3.3) and pressure (Fig. 3.4). The Weber test, classical two-point discrimination, in which the ends of the calipher are held in constant contact with the skin, measures the innervation density of the slowly-adapting fiber/receptor population (Fig. 3.5). The quickly-adapting fiber conveys information about transients, movement. Thus, the quickly-adapting fiber/receptor system detects moving-touch (Fig. 3.6). The “moving two-point discrimination test,” in which the two ends of the calipher (paper clip) are moved, measures the peripheral innervation density of the quickly-adapting fiber/receptor system (Fig. 3.7).[11]

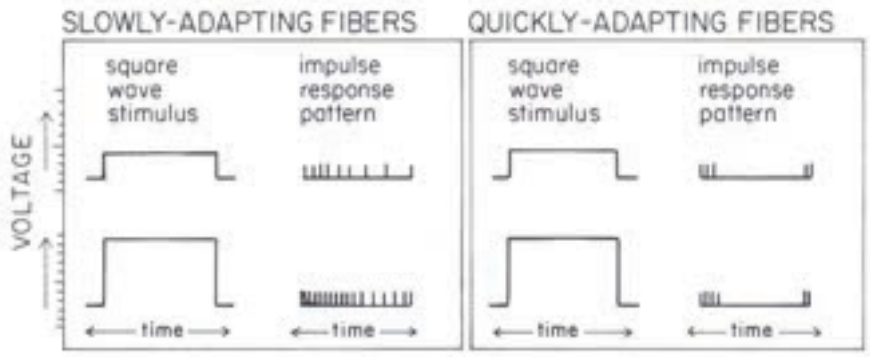

Figure 3.2. Properties of adaptation to a constant-touch stimulus. Slowly-adapting fibers continue to discharge impulses throughout duration of stimulus and increase impulse frequency in response to increased stimulus intensity. Quickly-adapting fibers fir very briefly after stimulation and then cease. There may be an "off" response. There is no changed in impulse pattern with intensity change for this stimulus.

After defining the quickly- and slowly-adapting fiber populations by their response to a constant mechanical stimulus, it remained to further test each subpopulation and attempt to relate the fiber types with their specific mechanoreceptors. The mechanoreceptor, an end organ, is actually a transducer. It transforms a mechanical stimulus into a conducted neural impulse. While the exact mechanism of this transducer process remains to be defined, much is known about the behavior of the individual types of mechanoreceptors. It will be seen that mechanoreceptors signal to the sensory cortex by a frequency code, that is, a temporal patter of impulses.

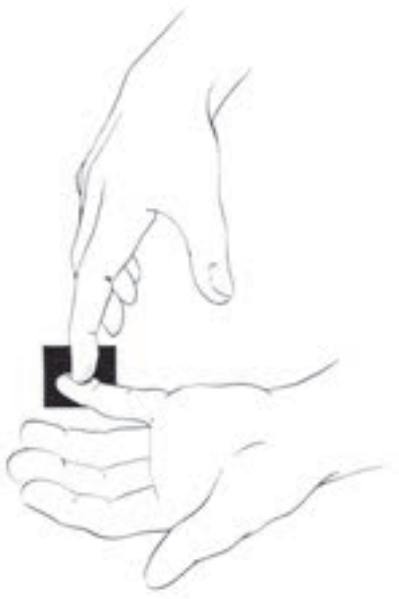

Figure 3.3. Perception of constant-touch is mediated by the slowly-adapting fiber/receptor system

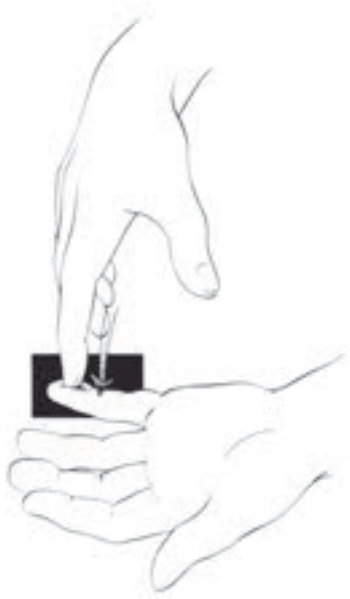

Figure 3.4 Perception of pressure is mediated by the slowly-adapting fiber/receptor system

Figure 3.5 The Weber test, classical two-point discrimination, measure the innervation density of the slowly-adapting fiber/receptor system.

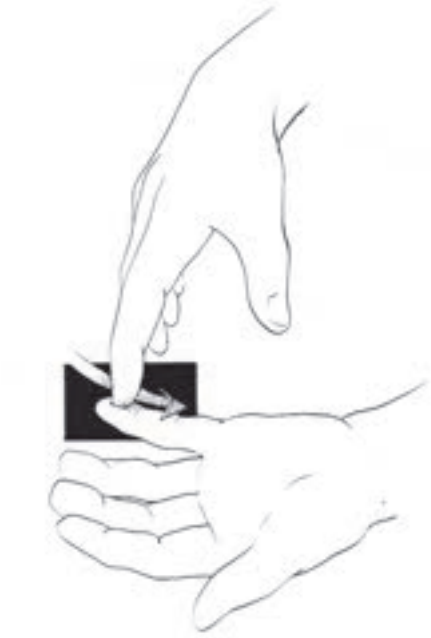

Figure 3.6 Perception of moving-touch is mediated by the quickly-adapting fiber/receptor system.

Figure 3.7. The moving two-point discrimination test measures the peripheral innervation density of the quickly-adapting fiber/receptor system.

Slowly-Adapting Fiber/Receptor System

The slowly-adapting fiber/receptor system was first directly studied in the touch-pad of the cat's hairy skin by Iggo.[12] Since then it had been well-define in the cat,[12-15, 29-30] rabbit,[12] alligator,[15]opossum,[16] raccoon,[17-23] monkey,[17, 18, 28, 47] baboon,[45] and man[24-27] both in hairy[12-15, 24-30] and glabrous[16-19, 21-23, 26, 45, 47] skin.

There are two neurophysiologic properties that define slowly-adapting fiber/receptor systems. The first is that the neural impulses continue to discharge throughout the duration of the stimulus, although the frequency diminishes with duration (Fig. 3.8). The second is that there is a change in response (frequency of impulse) with stimulus intensity change (Fig 3.9). Thus, when the mechanical

probe is pushed deeper into the skin, there are more frequent neural discharges recorded from the fiber. The slowly-adaptors are the pressure sensors.

What are the receptors for the slowly-adapting mechanoreceptors of the skin? In hairy skin they are the Merkel cell-neurite complex. Pinkus[31] described these in man in 1904. Pinkus' drawings of the Haarscheibe are morphologically analogous to the touchpad of the cat. The Merkel cell-neurite complex may be intimately associated with the base of a hair follicle as described by Straille for the "tylotrich" hair[32] and Andres for the "sinus" hair[33] in the cat. These receptors may be stimulated by direct pressur or by deflection of the associated hair. In glabrous skin, the Merkel cells are again located in the basal layer of the epidermis but in certain relationship to the epidermal rete. In monkey and man they are located only at the base of the intermediate ridge about the entrance site of the sweat duct. These are the so-called type I slowly-adapting receptor.

Neurophysiologically, the slowly-adapting response fibers can be subdivided based upon other considerations. These are summarized in Table 3.1 from the Iggo's review.[34] Essentially, the type II fiber/receptor system is uncommon, appears similar to the endings described by Ruffini [it is not associated with Merkel (epithelial) cells,[35] although it has been observed at the base of a hair follicle[36]], responds to stretching of skin adjacent to its receptive field, and has a resting (non-stimulated) discharge. a type II receptor may be thought of as a Merkel cell-neurite complex without the Merkel cell! They are almost rare. Brown and Iggo found them to comprise just 3% of the slowly-adaptors in the rabbit and 9% of those in the cat's hairy skin.[14] Knibestal and Vallbo[27] found only 7% of their slowly-adapting fibers in human glabrous skin to fit into the type II category.

Do slowly-adapting cutaneous mechanoreceptors respond to stimuli other than constant-touch and pressure? Slowly-adapting fibers have been demonstrated to alter their impulse frequency to mechanical stimulus when their environmental temperature changes, but these rate changes are very much less than those generated by changes in the mechanical stimulus.[15, 35] Thus, although they do respond to changes in temperature, they do not convey the perception of temperature. Similarly, for sinusoidal mechanical stimuli, slow-adaptors showed a frequency modulation in phase with low frequency vibration, but the stimulus amplitudes were not appropriate for human perception of movement.[25, 38] In an earlier study, human Haarschiebe were directly stimulated with a 100-cps vibratory punctate stimulus. There was no sensation elicited.[37]

One additional point is worth discussing for our purposes about the slowly-adapting fibers. What percent of peripheral cutaneous afferents are slowly-adapting? No one knows. To answer the question would require single unit analysis of every fiber in a nerve. Even at the level of the digital "nerve," there are 2500 axons. We can arrive at an estimate, however. In 1966, Mountcastle[8] estimated that just 10% were slowly-adapting. This figure may have come from the work later noted that of 505 fibers tested,

there were 53 type I SA. But what should be the denominator? Should we include C fibers and A-delta fibers? A useful comparison for the clinician, interested in functional recovery (see Chapter 6) is the percentage of slowly-adapting fibers to the total A-beta group. Several studies have recorded large numbers of single units and reported their results. Implicit in this statement is the realization of the bias in the selection of the axons that were counted. However, a brief tabulation of these (see Table 3.2) reveals that about 36% of the group of A-beta are slowly-adapting.

Quickly-Adapting Fiber/Receptor System

The quickly-adapting fiber/receptor system was the first to be investigated by microdissection. First, Lowenstein removed the onion-like capsule and demonstrated that the site of the generator potential, the unmyelinated intracorpuscular axon, was distinct from the site of the all-or-nothing potential, the first node of Ranvier.[40] It was also noted that the threshold for stimulation rose after capsulectomy. These concepts were depicted graphically in 1960 (Fig. 3.10).[41] Next, Lowenstein was one of the first to demonstrate fiber specificity by showing that:

> the mechano-receptor membrane of the nerve ending of the Pacinian corpuscles is insensitive to thermal stimuli … Although a change in temperature *per se* does not excite the receptor membrane it modities markedly the mechanically excited charge transfer through the membrane … In a rapidly-adapting receptor, such as the Pacinian corpuscle, … the exciting agent can be clearly distinguished from the modifying agent.[41]

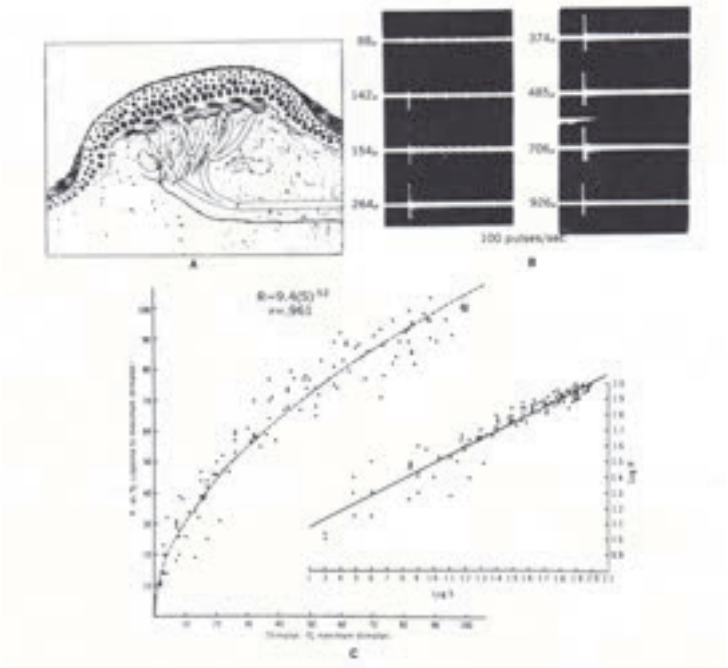

Figure 3.8. Slowly-adapting fiber/receptor system. ***A***. Drawing of touch-pad found in cat hairy skin, from light and electron microscopic studies by Iggo and Muir.[13] ***B***. Record of nerve impulses evoked in single fiber by mechanical stimulation of touch-pad it innervated. Skin indentation in micrometers shown to left of record. C. Data pooled from 10 of the studies illustrated in Bl demonstrating power-law relationship between stimylus and response. (Adapted with permission from V.B. Mountcastle(ed): *Medical Physiology*, ed 12. Saint Loui: CV Mosby, 1968, Ch 61-62.[5])

Table 3.1
Slowly-Adapting Cutaneous Mechanoreceptors[a]

	Type I	Type II
Slowly-adapting	x	x
Responds to vertical displacement	x	x
Responds to lateral skin stretch		x
Resting discharge, usual		x
Receptors per axon	1–5	1
Receptor type	Merkel	Ruffini
Usual frequency response to stimulus	High	Low
Usual discharge to maintained stimulus	Irregular	Regular

[a] Adapted from A. Iggo.[34]

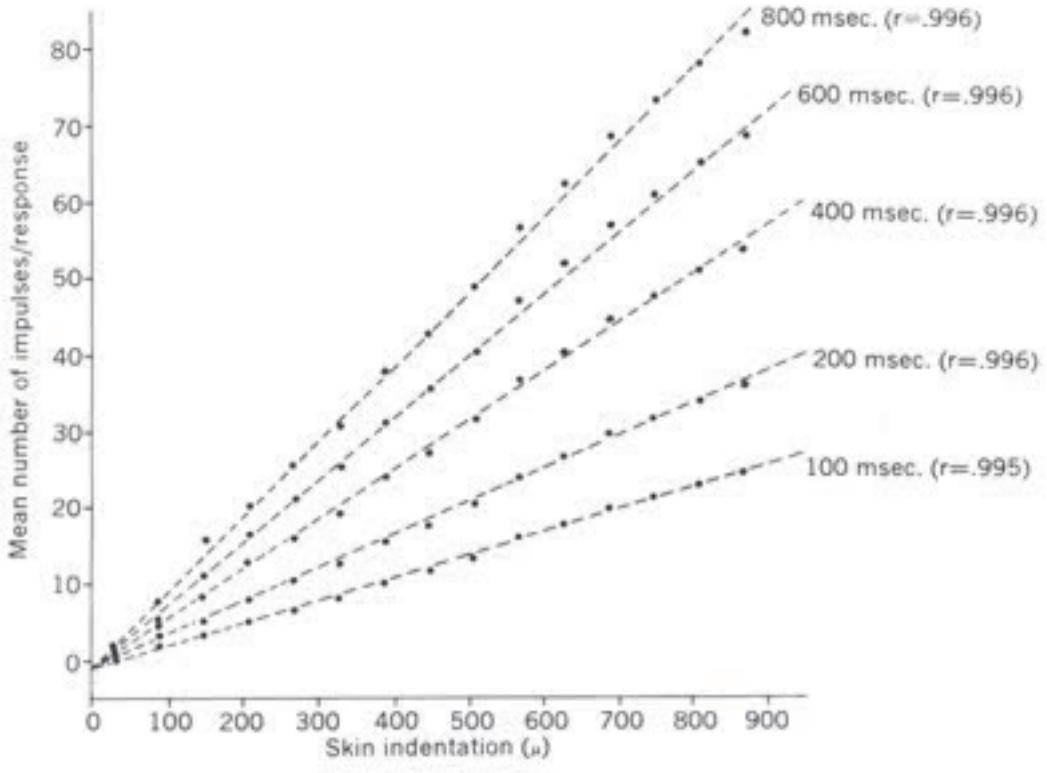

Figure 3.9. Slowly-adapting fiber/receptor system. Single unit recordings from glabrous skin of the monkey from a 1-mm receptive field on the fingertip. Each line demonstrates the relationship between stimulus intensity (skin indentation) and impulse response. The series of lines demonstrate that this relationship holds for stimuli of varying (longer) duration. (Adapted with permission from V.B. Mountcastle(ed): *Medical Physiology*, ed 12. Saint Loui: CV Mosby, 1968, Ch 61-62.[5])

Table 3.2
Estimate of Percentage of Group A-beta That Are Slowly-Adapting Fibers

Reference No.	Animal	Skin	No. of Group A-beta Fibers	Slowly-Adapting (%)
14	Cat	Hairy	501	31
14	Rabbit	Hairy	271	32
16	Monkey	Glabrous	70	21
27	Human	Glabrous	61	75
37	Monkey	Hairy	221	34
38	Monkey	Glabrous	523	40
45	Baboon	Glabrous	21	52
Total			1,672	36

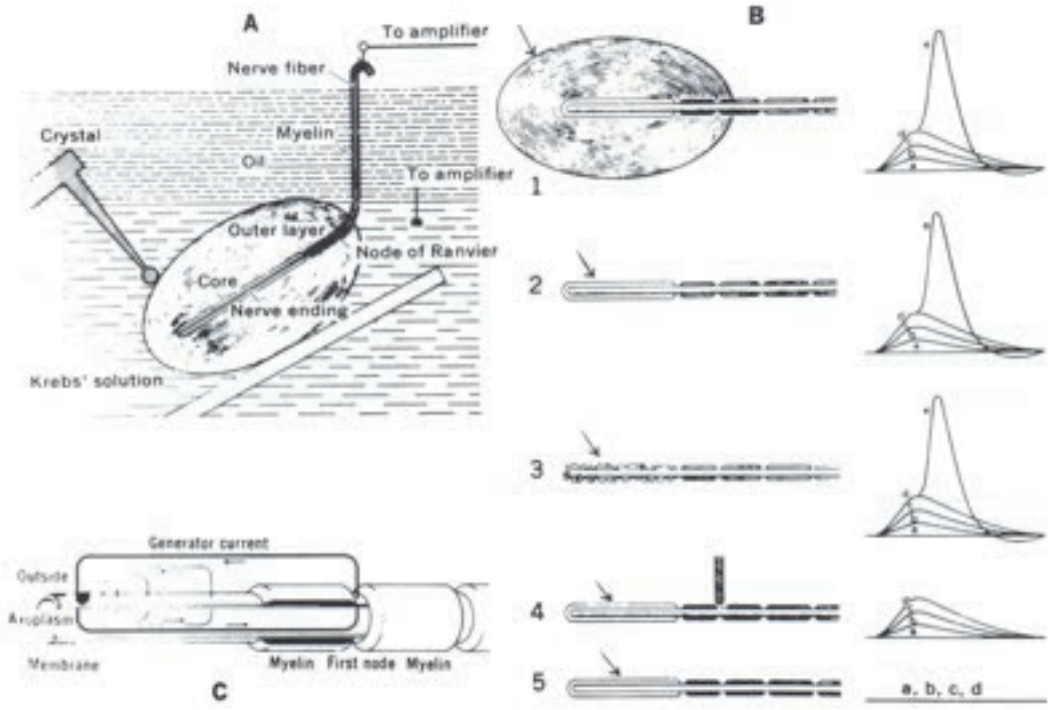

Figure 3.10. Quickly-adapting fiber/receptor system. ***A***, Method of stimulating Pacinian corpuscle. Electrical impulse drives the crystal which applies force from capsule to the axon after capsule is removed. ***B***. Records show increasing generator potentials (a, b, c, d) produced by increasing stimuli until a generator potential is produced (e) that reaches firing level for the axon resulting in a conducted action potential. In 4, pressure at the fist node of Ranvier blocks production of action potential but not generator potential. In 5, axon has degenerated after nerve section ***C***. Concept of local change in membrane permeability that results in generator potential. (Adapted with permission from V. B. Mountcastle (ed): *Medical Physiology*, ed 12. Saint Louis: CV Mosby, 1968, Ch 61-62.[5] Modified from W. R. Lowenstein: *Sci Am* 203:99-108, 1960[41])

In a further study with this model, which was the cat mesentery, an artificial capsule was made for the "decapsulated" axon. They found that they needed multilayered sheets of mesethelium (thin and elastic) with fluid between the layers to obtain good mechanical filtering.[43] They interpreted this to mean that the capsule shortens the "active" phase of a stimulus, causes rapid decay of the generator potential, and thereby limits impulse generation, i.e., the capsule is critical to rapid adaption.[43] However, a second factor was felt to be present, too, because electrical stimulation at the first node of Ranvier still produced

just a few conducted neural impulses.[43] In the summary of that paper, the statement "under these (decapsulated) conditions, the electrical response of the ending behaves as that of more slowly-adapting sensory ends: "refers to the generator potential, not the fiber's conducted response properties of adaptation. Lowenstein concluded this report with a proposed model for "high pass mechanical":

> The primary elements of this mechanical filter are the lamellae, their inter-connections and the fluid. The former two provided the structural stiffness and the elasticity, and the latter, the viscosity. The system has thus the elements of capacitative reactance (elasticity) and resistance (viscosity) … The system behaves essentially like a dashpot with pistons (the lamellae) in series. To mechanical stimuli of slow rates of use, that is, compressions of the outer surface, such a system offers relatively little viscous resistance … Elastic force is virtually the only force produced, and this is small and falls steeply from periphery to centre. With fast rising stimuli … viscous resistance is high. Hence a high viscous force is developed in addition to the elastic one. The viscous force is transmitted with relatively little spatial decrement through the system … This will give rise in the intact corpuscle to a brief pulse of pressure at the centre where the sensor is located, lasting only as long as the fast rising phase of the stimulus … During the "off-phase of the stimulus, stimulus energy stored in the elastic elements of the system is released … The sensory ending at the centre receives than during the "off-phase" pressure pulse similar to that of the "one-phase."[43]

Lowenstein[43] credits Gray[44, 45] with first describing the Pacinian corpuscle as having rapid properties of adaption.

The quickly-adapting fiber/receptor system has been studied in the cat,[14] rabbit,[14] raccoon,[21,23] monkey,[16, 27, 38, 48] baboon,[46] and human[24-27] in both hairy[14, 24-26, 37] and glabrous[16, 21, 23, 26, 27, 38, 46, 48] skin. The quickly-adapting population can be subdivided based upon the response of single fibers to peripheral vibratory stimuli.[38]

If a vibratory stimuli (an oscillating mechanical probe, electrical sine wave, or tuning fork) is applied to the peripheral receptive field of a quickly-adapting fiber, a threshold (amplitude of wave) will be found for that frequency at which the stimulus is transmitted (or perceived in an awake subject being studied percutaneously). This is the absolute threshold at which an action potential is generated. There will be higher stimulus intensity (amplitude voltage) at which stimulation of the receptive field results in a one-to-one entrainment of neural impulses in the fiber. That threshold at which the impulse frequency equals the stimulus frequency is termed the tuning point. The plot of these points for a given fiber is its tuning curve.

In a combined psychophysical experiment on humans and single-unit recording in monkeys, Mountcastle's group described the sense of flutter-vibration.[39] In brief, the quickly-adapting population of group A-beta fibers in glabrous skin contains one group most sensitive to low frequency stimuli (range of 5 to 40 cps), maximally sensitive to about 30 cps, and another group most sensitive to high frequency

stimuli (range of 60 to 300 cps), maximally sensitive to about 250 cps. Thresholds were obtained in the human volunteers, and the tuning curves from the monkeys superimposed (see Fig. 3.11). In another study, the epidermis of the human volunteers was anesthetized by cocaine iontophoresis. This raised the threshold for the low-frequency responsive group of fibers (see Fig. 3.12). It was concluded from these studies that one subset of quickly-adapting fibers existed that was responsive to low-frequency stimuli, had a receptor located in the epidermis (probably the Meissner corpuscle), and was responsible for detecting transient stimuli (movement) and flutter/ The second subset was responsive to high-frequency stimuli, had a receptor located below the epidermis (probably the Pacinian corpuscle), and was responsible for detecting transients (movement) and vibration. Furthermore, Pacinian afferents were more sensitive and had a larger receptive field (see Table 3.3).[39]

What is the distribution between these two subdivisions? In glabrous skin, several studies permit reanalysis of their published data to give an approximate answer. In monkeys, 16% of 310 quickly-adapting fibers were Pacinian afferents.[39] In baboons, 23% of 26 fibers were Pacinian afferents.[46] In humans, 6% of 15 fibers were Pacinian afferents.[27] It has been said that there are no Pacinian afferents in hair skin.[37]

A characteristic set of responses to clinical stimuli is illustrated in Figure 3.13.

It remained to be learned how the quickly-adapting populations of fiber/receptors signalled magnitude of response. It could not be by impulse frequency, as the slow adaptors do, because the rapid-adaptors' impulse frequency is related to stimulus frequency. K.O. Johnson investigated this probelm in a single-unit analysis, monkey glabrous skin model, where the site of vibratory stimulus was related to its location within the receptor field. The distance of the probe from field center was related to minimum stimulus amplitude eliciting an action potential in the fiber. These data allowed the formation of the spatiotemporal response of the population of fibers to the stimulus. Vibratory magnitude (intensity of vibratory stimulus) was found to be signalled by (1) total impulse frequency; (2) total number of active fibers; (3) total number of entrained fibers.[47]

Although it had seemed that the primate glabrous skin was too packed with sensory end organs to permit identification of the slowly-and quickly-adapting fiber’s specific mechanorecptor, recent work from Munger[48] appears to achieve this correlation. The general approach was to excise dorsal sensory ganglia, thereby diminishing the population of sensory receptors. Subsequent to ganglionectamy, single-unit analysis of median nerve fibers is related to a given peripheral receptive field, which is then biopsied. The histologic, electron microscopic, and neurophysiologic correlates found an innervated Meissner corpuscle in the rapidly-adapting field, and an innervated Merkel cell-neurite complex in the slowly-adapting field.

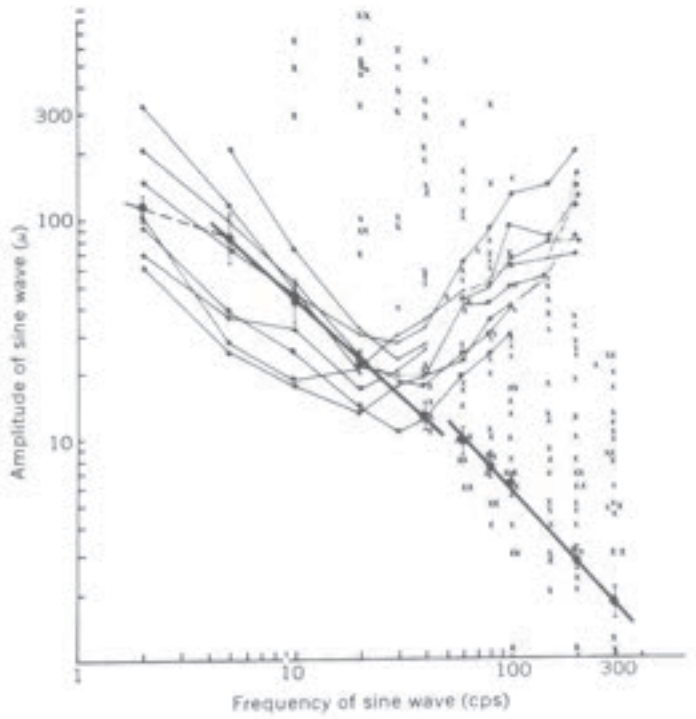

Figure 3.11 Quickly adapting fiber/receptor system. *Heavy lines* plot human threshold for perception of vibratory stimulus to index fingertip. *Lighter lines* for monkey median nerve fibers. *Crosses* plot tuning points for median nerve fibers that end in pacinian corpuscles. If the crosses were joined, tuning curves would be plotted that cover the high frequency limb of the human threshold curve. (Adapted with permission from V. B. Mountcastle (ed): *Medical Physiology*, ed 12. Saint Louis: CV Mosby 1968 Ch 61-62[5])

Summaries of the information on slowly-and quickly-adapting fiber/receptor systems are given in Figure 3.14 and Table 3.4.

CENTRAL ORGANIZATION

Spinal Cord Level

In the peripheral nervous system we saw that cutaneous sensibility is organized according to submodality specific fiber/receptor systems. These fibers are the first order afferents, and their procimal connections end within the central nervous system, synapsing with the second order afferents. The neuron for the second order afferent is in the nucleus cunneatus and gracilis. Third order afferent neurons are in the ventroposterolateral nucleus of the thalamus. Here they receive input from the second order afferents and relay this centrally to the somatosensory cortex, the postcentral gyrus of the parietal lobe[49] (Fig. 3.15).

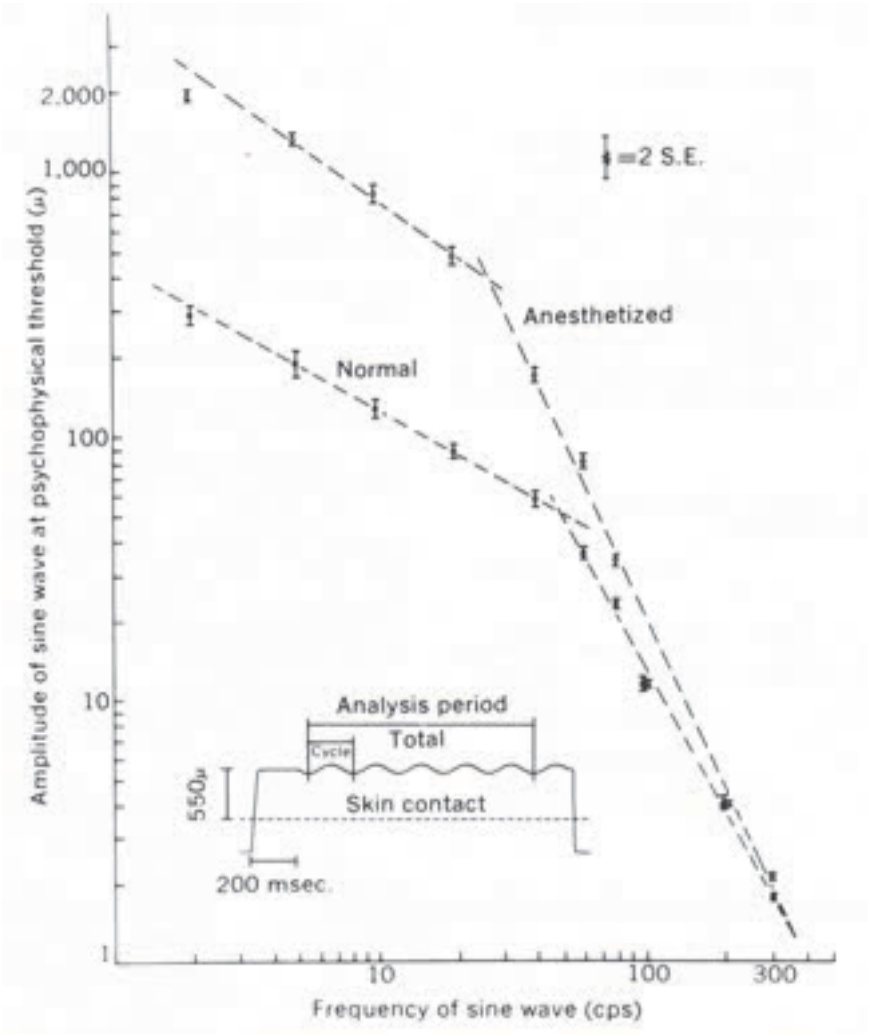

Figure 3.12 Quickly-adapting fiber/receptor system. Measurements of human thresholds for sense of flutter-vibration tested over thenar eminence in the anesthetized cure. Cocaine was applied to skin, blocking the superficial receptors. Note that this resulted in a threshold change only over the low-frequency portion of the curve. Thus, the Meissner corpuscles are the receptors for the low-frequency responsive group. (Adapted with permission from V. B. Mountcastle (ed): *Medical Physiology*, ed 12, Saint Louis: CV Mosby, 1968, Ch 61-62.[5])

Table 3.3
Quickly-Adapting Cutaneous Mechanoreceptors

	Meissner	Pacinian
Quickly-adapting	x	x
Responds to oscillation	x	x
Frequency range	10–300 cps	10–300 cps
Maximum sensitivity	30 cps	250 cps
Thresholds	Higher	Lower
Receptive field	Smaller	Larger
Receptor: proven	±	+
Location	Superficial	Deep
Axon	>1	1

There is evidence suggesting that the submodality-specific profile of neural impulses, generated at the fingertip, reaches the thalamic level essentially unchanged. That is, fiber sorting mechanisms existing within the spinal cord continue the submodality segregation.[50-53]

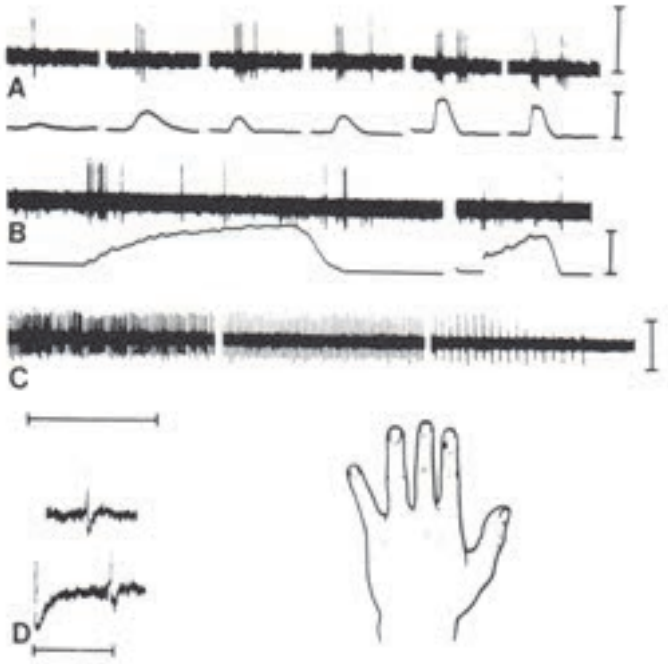

Figure 3.13 Quickly-adapting fiber/recetor example of percutaneous recording from awake human subject's response to *(A)* taps, *(B)* continuous pressure, *(C)* vibration, *(D*) mechanically (upper) and electrically (lower) induced impulse. Black spot on hand is receptive field of the recorded single fiber. Note: good response to transients (moving-touch) in *A* and *C*. Just an "on-off" type of response to constant-touch and pressure. (Adapted with permission from A. B. Valibo and K.E. Hagbarth: *Exp Neurol* 21:270-289, 1968[26])

Thalamic Level

The ventrobasal complex of the thalamus, and the ventroposterolateral nuclei in particular, receives the medial lemniscal pathway. The medial lemniscus carries the second order afferent fibers. Mountcastle's group[54, 55] recorded the evoked potentials in this nucleus after tactile stimulation of the skin. They found that the nucleus contains a detailed representation of the contralateral body and that its neurons (third order afferents) were highly specific as regards place (area of periphery stimulated) and sensory submodality (Fig. 3.16). The body pattern represented on the surface of the thalamus is distorted with respect to the relative surface area of the periphery. The area represented by the head, hands, and feet is disproportionately large. Thus, this representation is in proportion to the peripheral innervation density, not to body geometry. From point to point on the thalamic surface, there is also a partially shifted overlap of the peripheral receptive fields.

From the thalamus, this submodality specificity is projected to somatosensory cortex.

Somatosensory Cortex

The postcentral gyrus was first mapped generally in awake humans by direct stimulation by Penfield and Rasmussen,[56] and in detail in monkeys by evoked potential by Woolsey.[57] These studies yielded the familiar, distorted homonculus in which, as we saw for the thalamus, body shape was proportionate to the peripheral innervation density, with partially shifted overlapping peripheral receptive fields (Fig. 3.17).

The surface of the postcentral gyrus can be divided by the cytoarchitecture gradient that extends from anterior (within the sulcus) area 3, to the rostral half of the gyrus surface, area 1, to the caudal half of the gyrus surface, area 2, as described by Brodmann. Area 2 contains neurons primarily activated by rotation of joints, while area 1 and 3 contain neurons activated by skin stimulation.[5] Mountcastle's work[58, 59] demonstrated that the basic organization of postcentral gyrus neurons within each area was vertical. Utilizing a technique that penetrated the surface of the gyrus with a microelectrode, it was demonstrated that for a given penetration the neurons in that column of cortical tissue responded in the same manner to the same peripheral cutaneous stimulus. There was a columnar submodality-specific organization related to the same peripheral receptive field.

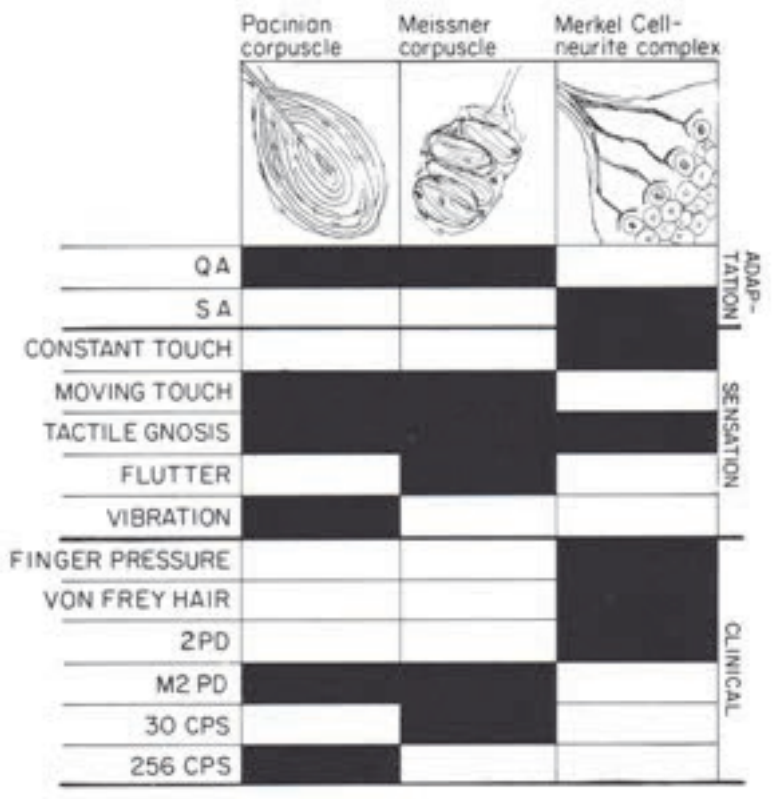

Figure 3.14 Summary diagram of slowly- and quickly-adapting fiber/receptor systems with clinical correlates.

Table 3.4
Summary

Nerve Fiber Property	Peripheral Receptor	Sensation	Clinical Test	Neurophysiologic Correlate
Slowly-Adapting	Merkel cell-neurite complex	Constant-touch Pressure Tactile gnosis (static)	Fingertip touch von Frey hair Classic two-point discrimination	Stimulus Threshold Innervation density
Quickly-adapting	Meissner corpuscle	Moving-touch Flutter Tactile gnosis (moving)	Fingertip stroking 30-cps tuning fork Vibrometer Moving two-point discrimination	Stimulus Threshold Innervation density
Quickly-adapting	Pacinian corpuscle	Moving-touch Vibration Tactile gnosis (moving)	Fingertip stroking 256-cps tuning fork Vibrometer Moving two-point discrimination	Stimulus Threshold Innervation density

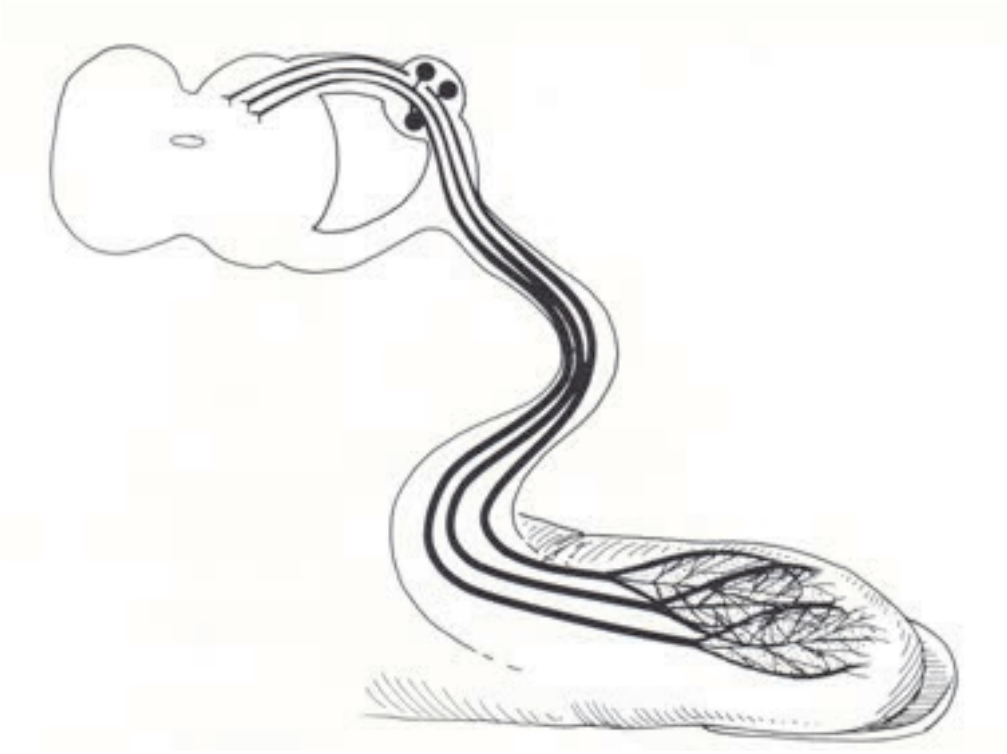

Figure 3.15 Three sets of afferent fibers transmit a submodality-specific profile or neural impulses to the somatosensory cortex. Note overlapping peripheral receptive fields.

How does the postcentral gyrus organization permit two point discrimination? During the work of Mountcastle and Powell[60] on the cortex, 53 neurons of the 593 studied were not only excited by stimulation of one skin area, but were also inhibited by stimulation of another (Fig. 3.18). They found that general anesthesia could abolish this inhibitory effect, perhaps explaining why the phenomenon had been so rarely seen (the monkeys studied had received anesthesia). Afferent inhibition, in a center-surround patter such as this, shapes and limits the profile of neural impulses (as conceptualized in Fig.

3.19). Thus a broad profile may be centrally inhibited to reveal two peaks. This mechanism may be operational in two-point discrimination.[5]

Recently, careful remapping of the postcentral gyrus by Merzenich and co-workers[61] have demonstrated a duplication of the hand area within Brodmann's areas 3 and 1. This work, in the monkey species *Macaca mulatta*, was subsequently confirmed in another species, *Aotus trivirgatus*, the owl monkey[62] and recently reviewed[63] (Fig. 3.20 and also Figs 5.11, 5.12). As first described in the macque, appropriate stimuli to peripheral receptive fields resulted on postcentral neuron responses which could be recorded as quickly-or slowly-adapting. In are 3 (within the sulcus), 56% of the responses were slowly-adapting. In area 1 (rostal half of gyrus surface), 95% of the responses were quickly-adapting.[61] This duplication was shown to occur first at this, the highest level of sensory organization, as it was not present (by horseradish peroxidase staining) in the thalamus.[64] These authors believe this dual representation is firmly established, as they have now studied 3500 recording sites in New World Monkeys.[63]

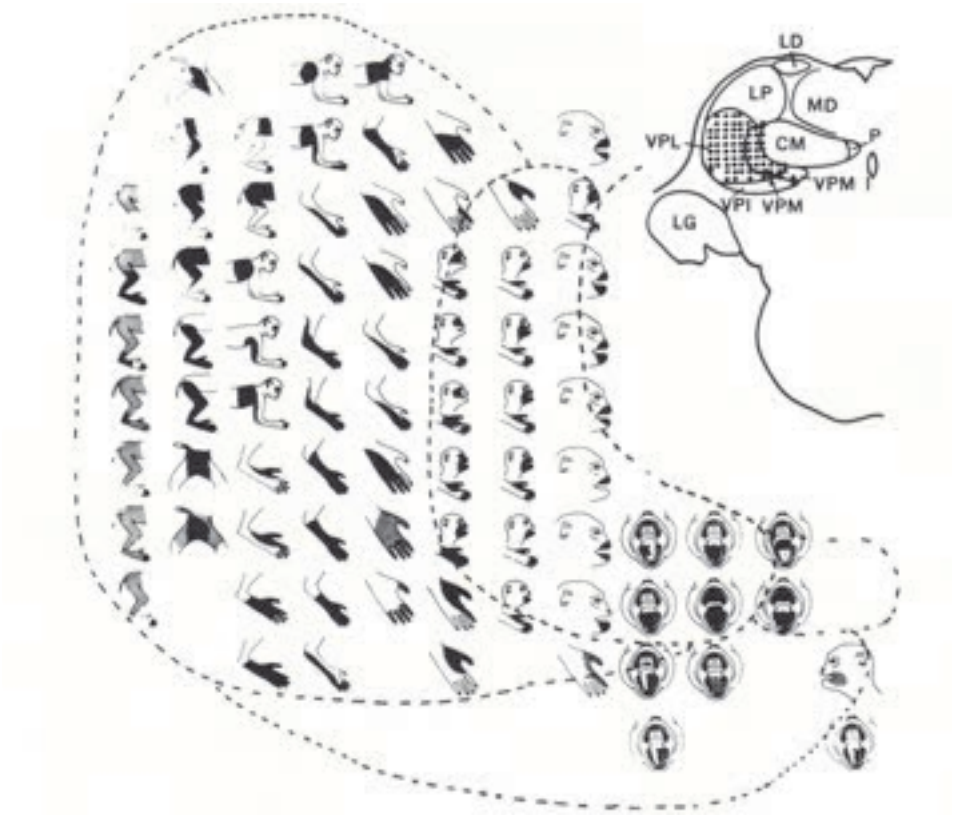

Figure 3.16 Thalamic sensory organization: Representation of cutaneous sensibility in one frontal plan of thalamus of monkey. Tactile stimulation of skin of areas marked on figurines evoked responses at points indicated. VPL. Ventroposterolateral nuclei. (Adapted from Mountcastle[54])

Figure 3.17 Postcentral cortex sensory organization: Representation of cutaneous sensibility rostral surface postcentral gyrus of monkey (area 1). Central sulcus is heavy wavy line to the right. Tactile stimulation of skin of areas marked on figurines evoked responses at points indicated. (Adapted from Woolsey.[57])

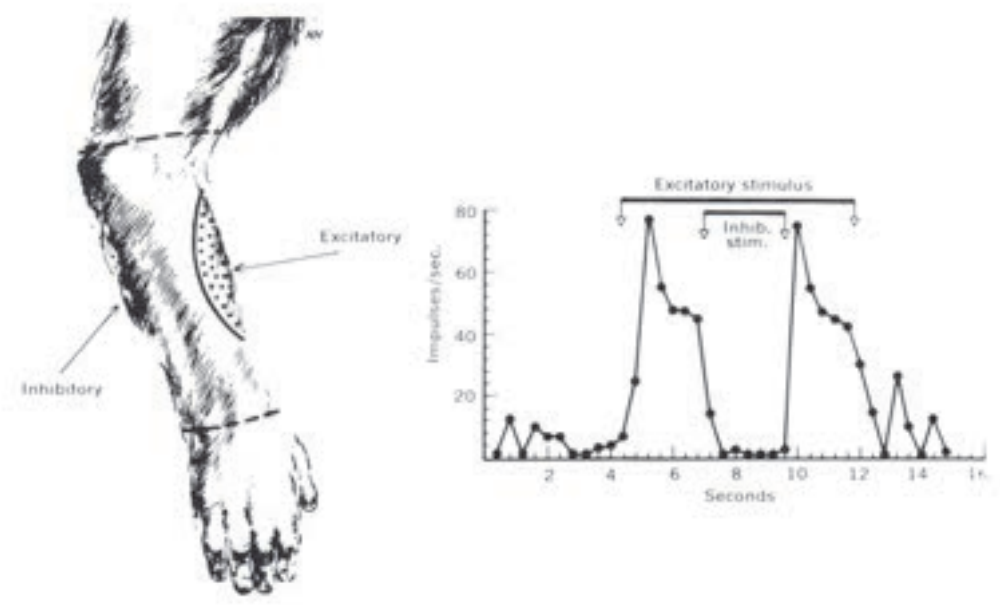

Figure 3.18 Afferent inhibition: Tracing to right is from a postcentral gyrus neuron which reacted to stimulation in the contralateral forearm excitatory zone. During this response, tactile stimulation of the zone surrounding this central excitatory zone produced inhibition of the response. (Adapted from Mountcastle and Powell.[60])

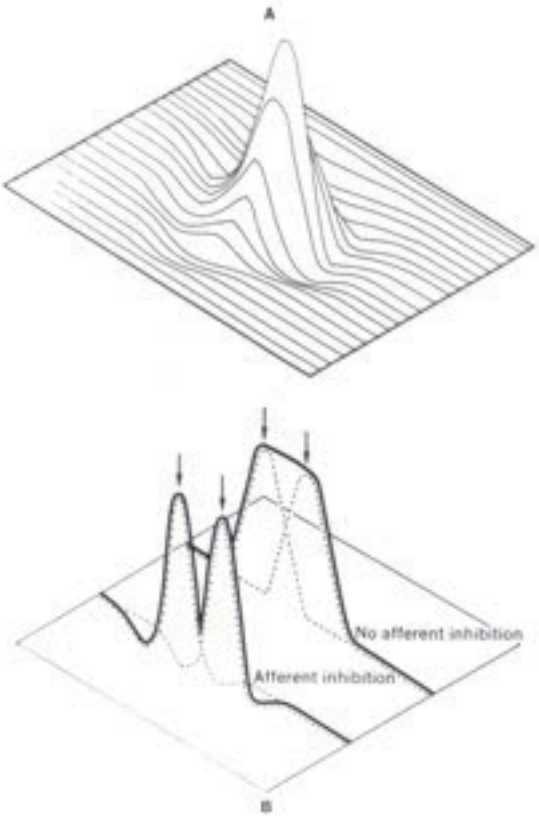

Figure 3.19 Afferent inhibition: conceptualization of the reshaping or contouring of the profile of neural impulses by afferent inhibition. This may be the mechanism operational in two-point discrimination. (Adapted with permission from V. B. Mountcastle (ed): *Medical Physiology,* ed 12. St. Louis: CV Mosby, 1968. Christianity 61-62[5])

A summary, adapted from Mountcastle, of the coding of peripheral sensibility is presented in table 3.5.

Table 3.5
Peripheral and Cortical Coding Mechanisms for Sense of Flutter-Vibration[a]

Psychophysical Event	Peripheral Neural Code	Central Neural Code
Identification: flutter vs vibration	Place code: which set of peripheral fibers is active	Place code: which set of cortical neurons is active
Detection of flutter	Place plus frequency code: appearance of any activity in Meissner afferents	Place plus frequency code: increment in activity in a give set of cortical neurons
Frequency discrimination	Place plus temporal order code: appearance of tuned discharges in some small number of Meissner afferents	Place plus temporal order code: cyclic entrainment of activity of a given set of cortical neurons
Subjective magnitude estimate (amplitude)	Place and spatial distribution code: linear increase in size of Meissner population activated by stimulus	Place and spatial distribution code: linear growth in size of cortical cell population in which increments in activity occur

[a] Adapted from V. B. Mountcastle.[6]

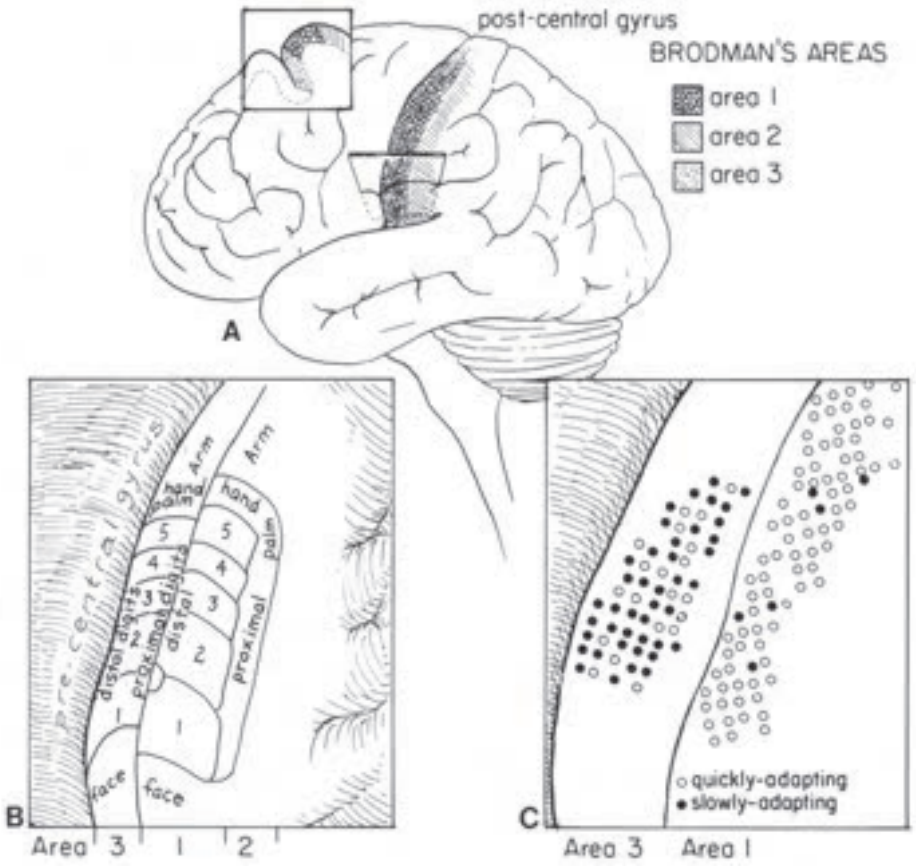

Figure 3.20 Dual representation of the hand area: A. The postcentral gyrus is cytoarchitecturally divided into Brodmann's areas: 3 (within sulcus). 1 (rostral half of gyrus surface) and 2.B. the hand area is topographically present in areas 3 and 1. C. each ○ or ● represents a direct recording from a neuron, labeled after appropriate peripheral stimulations. Area 1 was found to average 95% slowly-adapting units. (Adapted with permission from R. L. Paul et al*: Brain Res* 36: 229-249, 1972[61])

References:

1. Weber EH: Uber den Tastsinn. Arch Anat Physiol 1:152 – 159, 1835.
2. Seddon HJ: *Surgical Disorders of the Peripheral Nerves*. Baltimore: Williams and Wilkins, 1972, p viii.
3. Sunderland S: *Nerves and Nerve Injuries*. Edinburgh: Churchill-Livingstone, 1978.
4. Woodhall B, Beebe GW: *Peripheral Nerve Regeneration*. Washington, DC: US Gov Print Office, 1956.
5. Mountcastle (ed): *Medical physiology*, ed 12. Saint Louis: CV Mosby, 1968, Ch. 61 – 62
6. Mountcastle VB: The view from within: Pathways to the study of perception. Johns Hopkins Med J 136: 109 – 131, 1975.
7. Erlanger J, Gasser HS: *Electrical Signs of Nervous Activity*. Philadelphia: Univ Penn Press, 1937.
8. Mountcastle VB: Pain and temperature sensibilities, in Mountcastle VB (ed): *Medical Physiology*, ed 12. Saint Louis: CV Mosby, 1968, Ch 63.
9. LaMotte RH, Campell JN: Comparison of responses of warm and nociceptive C-fiber afferents in monkey with human judgments of thermal pain. J Neurophysiol 41: 509 – 528, 1978.
10. Campbell JN, Meyer RA, La Motte RH: Sensitization of myelinated nociceptive afferents that innervate monkey hand. J Neurophysiol 42: 1669 – 1679, 1979.
11. Dellon AL: The moving two-point discrimination test: Quantitative evaluation of the quickly-adapting fiber/receptor system. J Hand Surg 3: 474 – 481, 1978.

12. Iggo A. New specific sensory structures in hairy skin. Acta Neuroveg 24: 175 – 180, 1963.
13. Iggo A, Muir AR: A cutaneous sense organ in the hairy skin of cats. J Anat 97: 151, 1963
14. Brown AG, Iggo A: A quantitative study of cutaneous receptor and afferent fibers in the cat and rabbit. J Physiol 193: 707 – 733, 1967.
15. Iggo A, Muir AR: The structure and function of a slowly-adapting touch corpuscle in hairy skin. J Physiol 200: 763 – 796, 1969.
16. Lindblom U: Properties of touch receptors in distal glabrous skin of the monkey. J Neurophysiol 28: 966 – 985, 1965.
17. Werner G, Mountcastle VB: Neural activity in mechanoreceptive afferents: Stimulus response relations, Weber functions, and information transmission. J Neurophysiol 28: 359 – 397, 1965.
18. Mountcastle VB, Talbot WH, Komhuber HH: *The Neural Transformation of Mechanical Stimuli Delivered to the Monkey's Hand.* Ciba Foundation Symposium on Touch, Heat and Pain, de Rueck AVS, Knight J (eds). London: JA Churchill, 1966.
19. Siminoff R: Quantitative properties of slowly-adapting mechanoreceptors in alligator skin. Exp Neurol 21: 290 – 396, 1968.
20. Munger BL: The intraepidermal innervation of the snout skin of the possum: A light and electron microscopic study, with observations on the nature of Merkel's Tastzellen. J Cell Biol 26: 79 – 96, 1965.
21. Pubols LM, Pubols BH Jr, Munger BL: Functional properties of mechanoreceptors in glabrous skin of the raccoon's forepaw. Exp Neurol 31: 165 – 182, 1971.
22. Munger BL, Pubols LM, Pubols BH Jr: The Merkel rete papilla – a slowly-adapting sensory receptor in mammalian glabrous skin. Brain Res 29: 47 – 61, 1971.
23. Munger BL, Pubols LM: The sensorineural organization of the digital skin of the raccoon. Brain Behav Evol 5: 367 – 393, 1972.
24. Hensel H, Boman KA: Afferent impulses in cutaneous sensory nerves in human subjects. J Neurophysiol 23: 564 – 578, 1960.
25. Konietzny F, Hensel H: Response of rapidly and slowly-adapting mechanoreceptors and vibratory sensitivity in human hairy skin. Pflugers Arch 368: 39 – 44, 1977.
26. Valibo AB, Hagbarth KE: Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. Exp Neural 21: 270 – 289, 1968.
27. Knibestol M, Vallbo AB: Single unit analysis of mechanoreceptor activity from the human glabrous skin. Acta Physiol Scand 80: 178 – 195, 1970.
28. Harrington T, Merzenich MM: Neural coding in the sense of touch: Human sensation of skin indentation compared with response of slwly-adapting mechanoreceptive afferents innervating the hairy skin of monkeys. Exp Brain Res 10: 251 – 254, 1970.
29. Horch KW, Whitehorn D, Burgess PR: Impulse generation in type I cutaneous mechanoreceptors. J Neurophysiol 37: 267 – 281, 1973
30. Horch KW, Burgess PR: Responses threshold and suprathreshold stimuli by slowly-asapting cutaneous mechanoreceptors in the cat. J Comp Physiol 110: 307 – 315, 1976.
31. Pinkus F: Uber Hautsinnesorgane neben den menschlichen Haar (Haarscheiben) und ihre vergleickenden anatomische Bedeutung. Arch Mikrosk Anat EntwMech 65: 121 – 128, 1904.
32. Straille WE: Sensory hair follicles in mammalian skin: The tylotrich follicle. Am J Anat 106: 133 – 148, 1960.
33. Andres KH: *The Peripheral Nervous System*, Hubbard JI (ed). New York: Plenum Press, 1974, Ch12.
34. Iggo A: Cutaneous receptors, in Hubbard JI (ed): *The Peripheral System*. New York: Plenum Press, 1974, Ch. 12, pp 347 – 404 (101 references).
35. Chambers MR, Andres KH, von During M, et al: The structure and function of the slowly-adapting type II mechanoreceptors in hairy skin. Q J Exp Physiol 57: 417 – 445, 1972.

36. Biemesderfer D, Munger BL, Bink J, et al: The Pilo-Ruffini complex: A non-sinus hair and associated slowly-adapting mechanoreceptor in primate facial skin. Brain Res 142: 197 – 222, 1978.
37. Merzenich MM, Harrington T: The sense of flutter-vibration evoked by stimulation of the hairy skin of primates: Comparison of human sensory capacity with the responses of mechanoreceptive afferents innervating the hairy skin of monkeys. Exp Brain Res 9: 236 – 260, 1969.
38. Mountcastle VB: Discussion section of CIBA Foundation Symposium on *Touch, Heat and Pain*. London: JA Churchill, 1966.
39. Talbot WH, Darian-Smith I, Kornhuber HH, et al: The sense of flutter-vibration: Comparison of the human capacity with response patterns of mechanoreceptive afferents from the monkey hand. *J Neurophysiol* 31: 301 – 334, 1968.
40. Lowenstein WR, Rothkamp, R: The sites for mechanoelectric conversion in a Pacinian corpuscle. *J Glen Physiol* 41: 1245 – 1265, 1958.
41. Lowenstein WR: Biological transducers. Sci Am 203: 99 – 108, 1960.
42. Lowenstein WR: On the "specificity" of a sensory receptor. J Neurophysiol 24: 150 – 158, 1961.
43. Lowenstein WR, Mendelson M: Components of receptor adaptation in Pacinian corpuscle. J Physiol 177: 377 – 397, 1965.
44. Gray JAB, Malcolm JL: The initiation of a nerve impulse by mesentric Pacinian corpuscles. Proc R Soc Lond [Biol] 137: 96, 1950.
45. Gray JAB, Mathews PBR: A comparison of the adaptation of the Pacinian corpuscle with the accommodation of its own axon. J Physiol 114: 454 – 464, 1951.
46. Dykes RW, Terzis JK: Reinervation of glabrous skin in baboons: Properties of cutaneous mechanoreceptors subsequent to nerve crush. J Neurophysiol 42: 1461 – 1478, 1979.
47. Johnson KO: Reconstruction of population responses to a vibratory stimulus in quickly-adapting mechanoreceptive afferent fiber population* innervating glabrous skin of the monkey. J Neurophysiol 37: 48 – 71, 1974.
48. Munger BL, Page RB, Pubols BH Jr: Identification of specific mechanosensory receptors in glabrous skin of dorsal root ganglionectomized primates. Anat Rec 93: 630 – 631, 1979.
49. Wall P, Dubner R: Somatosensory pathways. Annu Rev Physiol 34: 315 – 336, 1972.
50. Whitsel BL, Petrucelli LM, Sapiro G, et al: Modality representation in the lumbar and cervical fasciculus gracilis of squirrel monkeys. Brain Res 15: 67 – 78, 1969.
51. Whitsel BL, PetricelliLM, Ha H, et al: The resorting of spinal afferents as antecedent to the body representation in the post central gyrus. Brain Behav Evol 5: 303 – 341, 1972.
52. Dreyer DA, Schneider RJ, Metz CB, et al: Differential contributions of spinal pathways to body representation in post-central gyrus. J Neurophysiol 37: 119 – 145, 1945.
53. Schneider RJ, Kulics AT, Ducker TB: Proprioceptive pathways of the spinal cord. J Neurol Neurosurg Psychiatry 40: 417 – 433, 1977.
54. Mountcastle VB, Henneman E: The representation of tactile sensibility in the thalamus of the monkey. J Comp Neurol 97: 409 – 440, 1952.
55. Mountcastle VB, Poggio GF, Wener G: The relation of thalamic cell response to peripheral stimuli varied over an intensive continuum. J Neurophysiol 26: 807 – 834, 1963.
56. Penfield W, Rasmusen AT: *The Cerebral Cortex of Man: A Clinical Study of Localization of Function.* New York: Macmillan, 1950.
57. Woolsey CN: Organization of somatic sensory and motor areas of cerebral cortex, in Harlow HF, Woolsey CN (eds): *Biological and Biochemical Basis of Behavior*. Madison: Univ Wisc Press, 1958.
58. Mountcastle VB: Modality and topographic properties of single neurons of cat's somatic sensory cortex. J Neurophysiol 20: 408 – 434, 1957.
59. Powell TPS, Mountcastle VB: Some aspects of the functional organization of the cortex of the post-central gyrus of the monkey: A correlation of findings obtained in a single unit analysis with cytoarchitecture. Bull Johns Hopkins Hosp 105: 133 – 163, 1959.

60. Mountcastle VB, Powell TPS: Neural mechanisms subserving cutaneous sensibility, with special reference to the role of afferent inhibition in sensory perception and discrimination. Bull Johns Hopkins Hosp 105: 201 – 232, 1959.
61. Paul RL, Merzenich M, Goodman H: Representation of slowly and rapidly-adapting cutaneous mechanoreceptors of the hand in the Brodmann's areas 3 and 1 of Macaca mulatta. Brain Res 36: 229 – 249, 1972.
62. Merzenich MM, Kaas JH, Sur M, et al: Double representation of the body surface within cytoarchitecture areas 3b and 1 in "S1" in the Owl Monkey (Aotus trivirgatus). J Comp Neurol 181: 41 – 74, 1978.
63. Kaas JH, Nelson RJ, Sur M, et al: Multiple representations of the body within the somatosensory cortex of primates. Science 204: 521 – 523, 1979.
64. Lin C, Merzenich MM, Sur M, et al: Connections of areas 3b and 1 of the parietal somatosensory strip with the ventroposterior nucleus in the Owl Monkey (Aotus trivirgatus). J Comp Neurol 185: 355 – 372, 1979.

Chapter 4
SENSORY CORPUSCLE AFTER NERVE DIVISION

INTRODUCTION

In 1850, August Waller described the axonal consequence of dividing the IX and XII cranial nerves of the frog.[1] Ranson's classic light microscopic[2] and more recent electron microscopic[3,4] investigations have described in great detail the axoplasmic, myelin, and Schwann' cell alterations that characterize the peripheral nerve fiber following complete nerve division, and which we call "Wallerian Degeneration." Virtually every minute detail of this process has been reviewed recently by Sunderland,[5] who cites 533 reference sources. Following complete transection of a nerve, both retrograde and antegrade changes occur. Retrograde changes include not only a variable degree of axoplasmic disintegration and absorption, but also central neuronal chromatolysis, followed by cell death (or recovery). The proximal axonal swelling represents the build up, through axoplasmic flow, of materials required for the axoplasmic sprouts to regenerate and corresponds with a central nuclear polarity during chromosynthesis or recovery. The severity of the retrograde changes is directly proportional to the severity of the injury (avulsion causes more chromatolysis than laceration) and inversely proportional to the distance between the neuron and the site of injury (shoulder level causes more chromatolysis than forearm level). The antegrade changes comprise axonal swelling, axonal breakup, myelin degeneration, Schwann-cell dedifferentiation into macrophage-like cells, phagocytosis of degenerated axoplasm and myelin, and subsequent partial collapse of the endoneurial tube. The most distal antegrade change, the counterpart of the central component of retrograde change, is not discussed. The fate of sensory corpuscles follwoing nerve division is not mentioned.

Sensory function is more difficult to asses at every level of investigation than motor function. For this reason, investigation of every phase of neuromuscular activity has preceded similar work in sensory function. Until the last 2 decades sensor function has been relatively ignored. Sunderland[6] devotes five

full chapters (with at least 550 references) to the effect of denervation upon muscle without a single reference to the effect of denervation upon sensory corpuscles!

A brief account of change in the motor system following denervation is offered for comparison with sensory material to follow. After complete nerve division, progressive gross muscle atrophy occurs, although histologically the remaining fibers retain striations and relatively normal subsarcolemmal nuclei. Atrophy is due to myofibrillar fragmentation and subsequent loss. Motor end-plates degenerate. There is a relative increase in the connective tissue component which may give the appearance of "fibrosis." Motor fiber bulk may be reduced by 80%. The pathophysiologic, biochemical, and ultrastructual changes occurring in denervation muscles are beyond the scope of this text.

EARLY SENSORY INVESTIGATION

Two basic approaches have been used to investigate the fate of denervated sensory corpuscles: (1) the nerve is injured (crushed, ligated, or transected) and previously innervated tissue examined at some point later in time. (2) The tissue containing the sensory end organs is excised and transplanted, and this transplanted tissue is the examined at some point later in time.

The series of experiments carried out in the laboratory of J. Boeke, in Utrecht, Netherlands in the 1920's and 1930's remains classic.[7,8] A succession of co-workers, including Klein, Dykstra, Heringa, and Van Straten, were present with Boeke during this time.[9] Their early work involved the mole's snout: this specialized sensory end organ (the organ of Eimer) contains expanded bulb nerve endings adjacent to epidermal papillae. The organ of Eimer was observed to "degenerate" following trigeminal nerve transection. A similar study in the duck demonstrates that the bill's corpuscle endings, Grandry corpuscles (a neurofibrillar disc morphologically analogous to a Merkel cell-neurite complex) and Herbst corpuscles (Pacinian-like corpuscles) degenerated following division of the V cranial nerve. Also in the duck, bill skin was excised and transplanted onto the foot with subsequent degeneration of these corpuscles (Fig. 4.1).

The sensory end organ most intensely studied with respect to nerve sectioning experiments has been the taste bud. Guth[10, 11] (then at the National Institutes of Health, and now at the University of Maryland's Department of Anatomy) pursued Waller's experimental design. Using a rat model, the IX cranial nerve was divided and the circumvallate papillae studied; they were found to degenerate and desquamate. Recent electron microscopy has confirmed these observations.[12,13]

In the skin graft type of study, small corpuscular sensory ending were observed to degenerate completely in pig snout transplanted to the pig's back[14] and in rabbit scrotal skin transplanted to the rabbit's ear.[15]

Although these studies suggest that denervated sensory corpuscles degenerate, recent authorities imply that sensory end organs persist, at least to the extent that the regenerating axon "re-establishes"

continuity with end organ.[16, 17] Seddon cites an example of "Pacinian and Meissner Corpuscles found in man nine months after nerve injury," documented by Lyons and Woodhall in 1949. Careful review, however, reveals a histologic section from a fingertip biopsy from the amputated arm of a soldier injured 9 months earlier. The soldier had sustained a high velocity missile injury to the axilla with laceration of the subclavian artery and brachial plexus. In the biopsy, one Pacinian and on Meissner corpuscle were found: they were described as being "aneuric and fibrotic." Though "persisting" following "nerve injury," I believe these corpuscles had degenerated.

FIG. 8. Photograph of duck's bill containing two pieces of transplanted 'scaly' skin of the foot. After Dijkstra, 1933.

Figure 4.1 Photograph of duck's bill, with two sites of successfully transplanted scaly skin from the duck's foot. No Herbst or Grandry corpuscles regenerated *de novo* in these grafts. (Reproduced with permission from J. Boeke; *The Problems of Nervous Anatomy*, London Oxford University Press, 1940.[9])

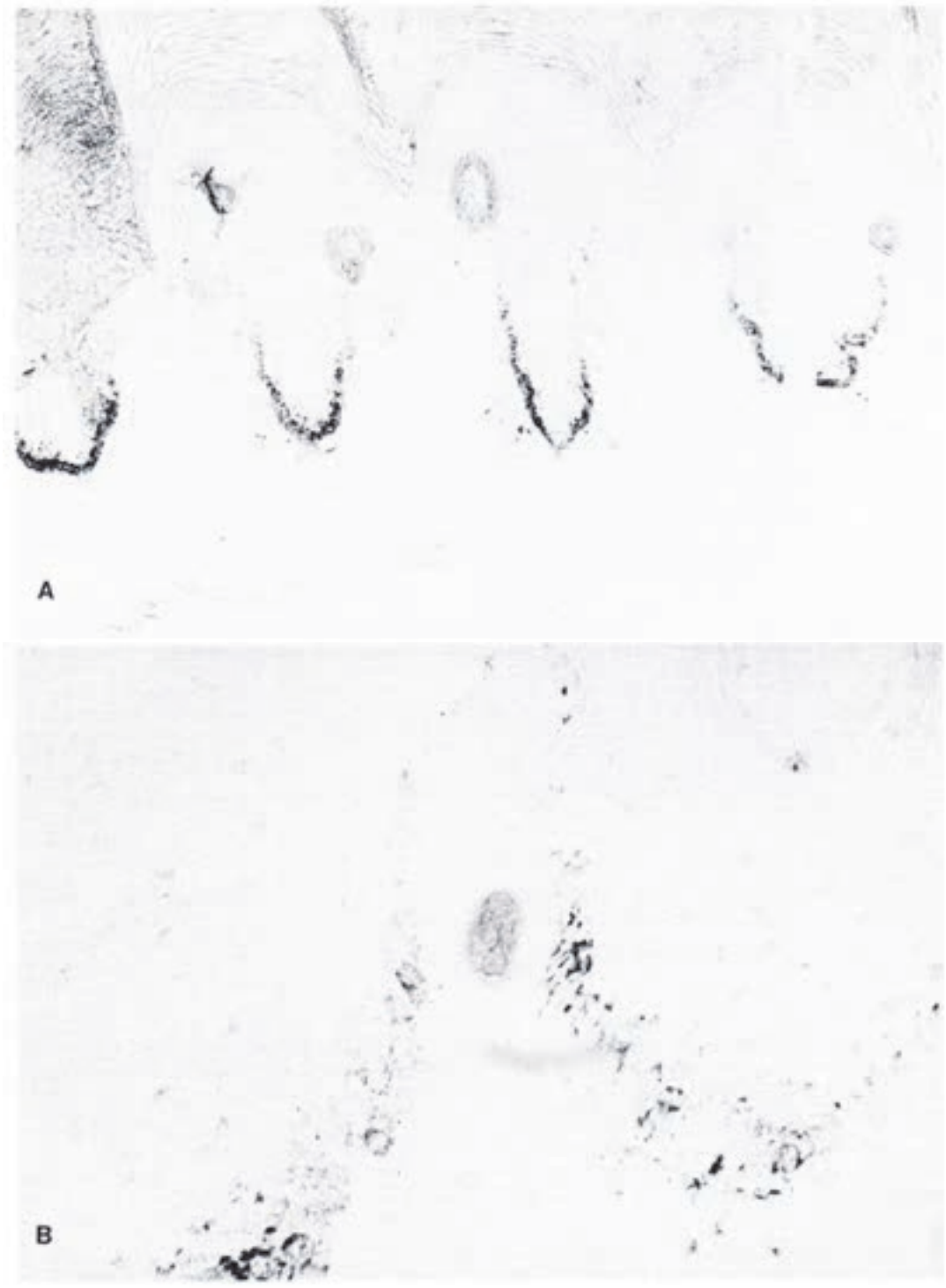

Figure 4.2 (*A*) (*B*) (*C*) Nonspecific cholinesterase staining of the Meissner corpuscle. Control sections: A at x25 and B at x100. At 4 months after denervation (*C*, x100) the corpuscle still stains well but has altered morphology.

Figure 4.2 C

Winkelman's observation of Meissner corpuscles in the toe of one dog 18 months following sciatic nerve division[19] is often quoted as demonstrating that sensory corpuscles persist following nerve division. Winkelman used a nonspecific cholinesterase histochemical technique has been utilized to study biopsy material from fingertips of patients with neuropathy.[20] Qualitative changes were observed in these disease states. The interpretation of these studies is difficult. They essentially demonstrate an aneuritic corpuscular remnant that contains an active enzyme. Application of a cholinesterase inhibitor to the skin fails to alter the clinical response to sensory testing,[21] and therefore positive non-specific cholinesterase staining does not have functional significance clinically. The positive staining material appears to be localized between the axoplasm and the Schwanncell,[22] or, by analogy, between the axon tip and the lamellar cell process in the Meissner corpuscle. No comments were made in the study of the neuropathies as to whether the numerically diminished corpuscles that remained were of normal size or atrophic! I feel that this staining technique cannot be utilized to demonstrate anything more than the location of a Meissner corpuscle, and inferences regarding corpuscles' integrity or function are not justified.[23] My own investigations with this technique also demonstrate presence of positive-staining Meissner corpuscles in denervated primate fingertips, but careful comparison with controls suggests that the overall shape of the Meissner corpuscle is distorted and smaller[24] (Fig. 4.2). I believe these observations suggest that even

though Meissner corpuscle remnants are nonspecific cholinesterase-positive in staining characteristics, these end organs are degenerating following denervation.

PACINIAN CORPUSCLE

It was natural for detailed sensory investigations to begin with the Pacinian corpuscle. As discussed in Chapter 1, this corpuscle was the first sensory end organ discovered because it is macroscopic. It is ubiquitous in mammals and quite abundant in the mesentery of the cat. Ferdinand C. Lee,[25] in a remarkable series of experiments from the Hunterian Surgical Laboratory (begun by William Stewart Halstead) at Johns Hopkins, demonstrated degeneration *in* the Pacinian corpuscle. These were reported in 1936. He divided the myelinated fiber to the corpuscle in the cat mesentery and observed, histologically, degeneration of the axon and its completion within 2 weeks. His surgery was performed under an early (Greenough) operation microscope. His short-term observation showed no change in the lamellar corpuscle. Lee also studied the physiology of the corpuscle and the effect of "regeneration" following partial excision of the corpuscle (it rounded over and contracted, not really "regenerated").

In 1949 Glees et al.[26] made long-term observations on the effect of denervation upon the Pacinian corpuscle itself. They excised Pacinian corpuscles from cat mesentery and implanted them into cat cerebrum and thigh muscle. Up to 400 days later there were no signs of degeneration of the lamellar corpuscular structure. There were also no signs of reinnervation either by cerebral axons or those "cutaneous" axons adjacent to the thigh muscle. Lowenstein's neurophysiologic studies of this receptor, discussed in detail in Chapter 3, led to a series of experiments on the effect of denervation upon the Pacinian corpuscle. Attempting to learn the relationship of the different components of this fiber/receptor system to neural conduction, Lowenstein[27] crushed and divided the myelinated axon to the corpuscle. The axon ending degenerated and the corpuscle's laminated capsule remained unchanged. In attempting "nerve union" studies, corpuscles, themselves, were still present in failed "nerve unions" 7 weeks after nerve division.

The effect of denervation upon Pacinian corpuscles has been investigated in subhuman primates.[28, 29] After nerve division, the axon terminal within the corpuscles was completely absent within 3 to 4 weeks. Specific descriptions of later corpuscle changes were not given, although noninnervated corpuscles could be "identified" at 40 weeks postdenervation. Histochemical studies demonstrated loss of acetylcholinesterase staining in the Pacinian corpuscle by 8 weeks postdenervation, while nonspecific cholinesterase staining showed no difference from controls.

Ultrastructural evaluation of the immediate events following denervation has been reported in the cat, sciatic nerve, hind footpad model.[30] These findings confirmed those discussed above and added that the lamellar cell processes were responsible for the phagocytosis of the unmyelinated portion of teh axon

within the Pacinian corpuscle's inner core, analogous to the Schwann cell phagocytosis of the myelinated portion of the axon. This suggested that the lamellar cells were modified Schwann cells.

The single reported observation, of which I am aware, in man is that described earlier[18] following brachial plexus trauma. At 9 months postinjury, fingertip biopsy demonstrated a single "aneuritic and fibrotic" Pacinian corpuscle.

It may be concluded that Wallerian degenerated occurs following division of the sensory nerve fibers to a Pacinian corpuscle. The end organ's tightly wound lamellae, probably over a great length of time, undergoes progressive degeneration. This latter process is slow and its time course remains to be defined. The relationship between the activity of the enzymes of the cholinesterase system upon neurotropism or capsular integrity remains unknown.

MEISSNER CORPUSCLE

Although the observations by Winkelman (19) of the effects of the denervation upon Meissner corpuscles (utilizing *non-specific* cholinesterase staining techniques) has been interpreted as demonstrating persistence of these corpuscles) further work has altered these interpretations. In a series of precise morphologic and histochemical investigations, Silver, Versaci, and Montagna studied control and "pathologic" biopsy material from patients' fingertips.[31, 32] These patients had various median and ulnar nerve injuries from 2 1/2 to 12 months prior to biopsy. The staining reaction to acetylcholinesterase became greatly reduced following denervation and that to butyrocholinesterase also became reduced. Nonspecific cholinesterase staining was not employed. Furthermore, serial sections of corpuscles were measured in terms of capsular height, length, and width, and volumes estimated. In two patients, 10 months and 12 months postdenervation, Meissner corpuscle volume was reduced by 53% versus control! For example, one of these patients demonstrated Meissner corpuscle degeneration from an estimated volume of 98 cu to one of 47 cu, a change statistically significant at the p less than 0.001 level.

The effect of nerve crush and division in subhuman primates was studied at 3 to 4 weeks, 6 weeks and 8 weeks postinjury utilizing acetycholinesterase and nonspecific cholinesterase and silver techniques.[27] By 3 to 4 weeks, all corpuscles were aneuritic, acetylcholinesterase staining was diminished, and nonspecific cholinesterase staining unchanged. By 8 weeks, the acetylcholinesterase staining charactersitics were returning in the crushed nerve specimens, while in the nerve division specimens the acetylcholinesterase reaction was absent and the nonspecific cholinesterase reaction was normal.

These earlier studies demonstrated that at 3 to 4 weeks the Meissner corpuscle had undergone Wallerian degeneration and that at 8 weeks postdenervation alterations in histochemical staining occurred. In at least two isolated observations, the capsular structure degenerated by 10 months.

We investigated the effects of the prolonged denervation upon the Meissner corpuscle in the Rhesus monkey, utilizing a sequential light and electron microscopic technique that permitted controlled observations.[24] In these studies, an Azzopardi silver and Masson trichrome staining technique was used to study 72-hour, 2-week, 4-month, 7-month, and 9-month postdenervation fingertip biopsies. In each monkey, the median, ulnar and radial sensory nerves were excised for a length of 1 cm at the wrist of the level to totally different the volar pads and eliminate anomalous innervation. At 72 hours postdenervation, the Meissner corpuscle had lost the pink-staining material usually present between the lamellae, and the lobular architecture was less prominent. Silver staining showed the axon terminals were fragmenting. At 2 weeks, lobular subdivisions were less evident, the lamellae appeared to be "collapsing," and no axon terminal remained. There was little further change in 4 months. By 7 months, the corpuscles were shrinking in size. By 9 months, they were markedly shrunken (Fig. 4.3 and 4.4)

Ultrastructural changes paralleled and confirmed the light microscopic observations.[24]* The electron microscopy at 48 hours showed that terminals were degenerating and being phagocytized by lamellar cell processes. At 4 months postdenervation, axon terminals were absent, lamellar cell processes had become blunt, and there was a relative increase in interlamellar substance (Fig. 4.5). The observation of lamellar cell phagocytosis of the axon terminals is analogous to the Schwann cell phagocytosis of the axon in classical Wallerian degeneration,[33] of the Dark Cell phagocytosis of the axon filaments in the rat fungiform taste bud,[12] and of those reported above in the Pacinian corpuscle.[30]

We conclude that the denervated Meissner corpuscle undergoes progressive degeneration, beginning first with its axon terminal, then with enzyme systems within the lamellar cell (e.g., acetylcholinesterase) and then with atrophy of the lamellar cell complex itself.

MERKEL CELL-NEURITE COMPLEX

During studies following discovery of the "Touch Corpuscle" in the cat, Brown and Iggo[34] observed that crushing the saphenous nerve caused the tactile cells and the nerve fibers to degenerate and the dome to flatten. Palmer[35] extended these observations to the opossum. In an abstract, he reported dividing the infraorbital nerve and observing snout Merkel cells and the axon terminals to be degenerated completely by 72 hours after nerve section. Kasprzak et al.[36] in 1970 confirmed Brown and Iggo's earlier observations on the cat's footpad.

An apparent species difference in the trophic dependence of the Merkel cell on the presence of the axon was noted by Smith.[37] In the rat, division of the cutaneous nerve caused degeneration of the axon terminals beneath the tylotrich hair, but up to 90 days later the Merkel cells remained intact. Kasprzak et al.[36] confirmed these observations in the rat.

Burgess et al in 1974[38] divided the femoral cutaneous nerve of the cat and observed its effect upon the previously identified touch dome population. This site was depilated, the domes tattooed, the domes counted under magnification, and the site photographed. The site was re-examined at intervals up to 1 year after the crush and denervation. Electrophysiologic recording was done from the nerve with simultaneous stimulation of the touch domes in the receptive fields before and after nerve crush and division. At 16 days following nerve division, the neural component of the dome was completely degenerated. By 35 days following nerve division, the entire dome had disappeared (Figs. 4.6 and 4.7)

Recently, Munger and Ide[39] have studied degeneration of the Merkel cell-neurite complex in the raccoon at the ultrastructural level. They have confirmed the neural degeneration and observed a decrease in the Merkel cells as well as decreased number of the synaptic vesicles in the Merkel cell. (see Fig. 10.7).

It may be concluded that the Merkel cell-neurite complex also undergoes progressive degeneration postdenervation.

CLINICAL IMPLICATIONS

Length of Delay Before Nerve Repair

What is the effect of delaying a nerve repair for a period of time after nerve division? In general, there is little effect for a "short delay" and a decrease in quality of recovery of function for delays greater than 4 months. But "good" recovery has been reported even after delays of 2 years.[40] One report stated that "in marked contrast to the analysis of motor recovery, it is extremely significant that the analysis here yielded no evidence that time from injury to suture influenced (sensory) recovery in any way."[41] A critical review of those studies suggesting that a long delay has no effect, however, reveals that these studies are based on an "arbitrary grading system,"[42] or they define delay as "greater than two weeks."[43] One study which suggests that delay is detrimental[44] does not distinguish between sensory and motor recovery. The distinction is essential, of course, because the motor end-plates persist in good condition for a year and muscle atrophy does not begin for an even longer period of time.[45]

If one includes only those studies that report specifically on the sensory components of the median and ulnar nerves, and then grades the degree of functional recovery (e.g S1 to S4), the results indicate a significant loss in the percentage of patients achieving a given grade of recovery and a decrease in the highest grade attained when the delay interval exceeds 4 months[46-49] (Figs. 4.8 and 4.9).

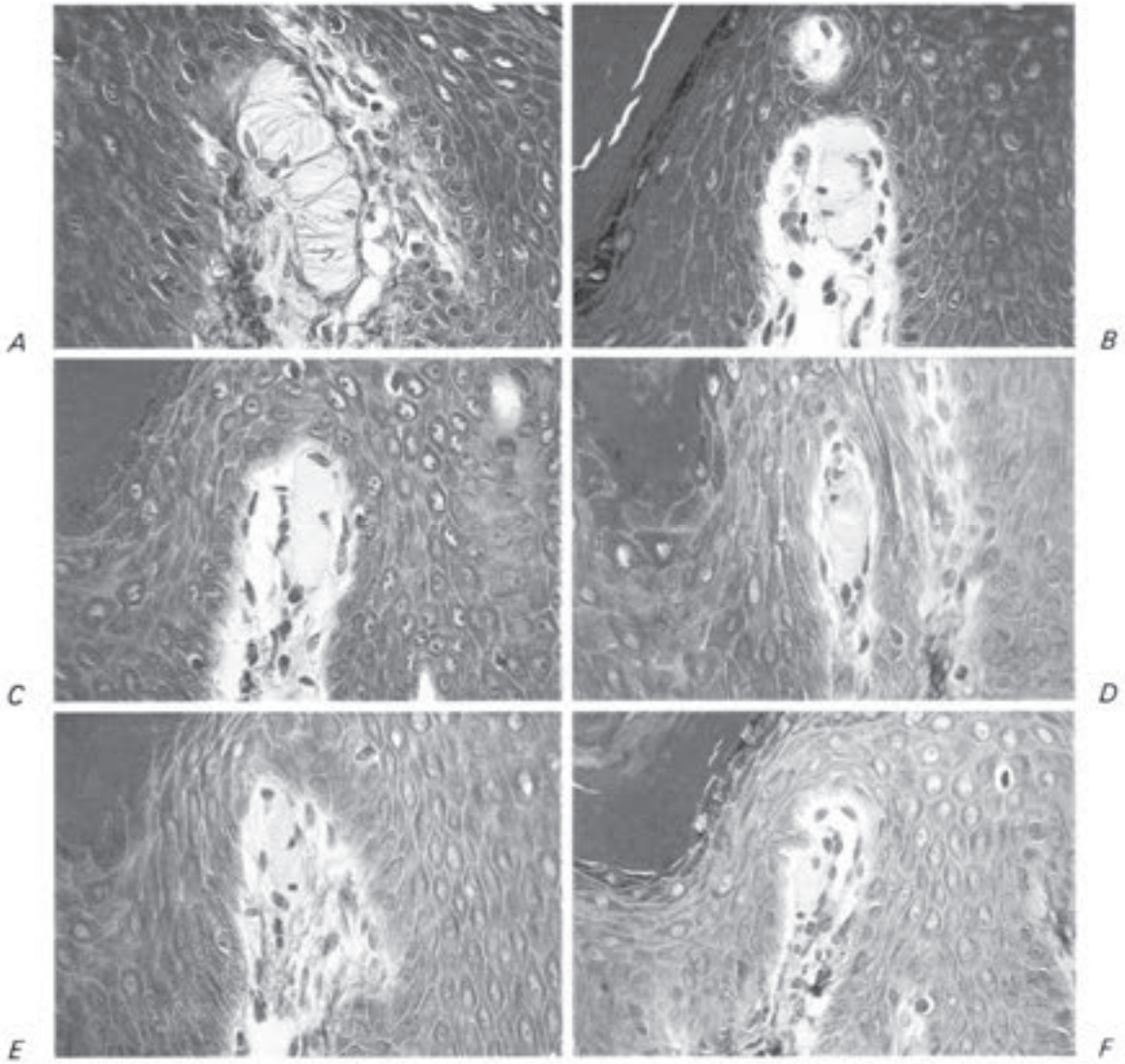

Figure 4.3 Progressive change in the Meissner corpuscle after denervation. ***A***. Representative normal Meissner corpuscle. ***B***. at 72 hours after denervation, showing early loss of lobular subdivisions and of pink-staining material. ***C***. At 2 weeks, there is complete loss of the lobular subdivision and lamellar collapse appears, with progressive diminution in the size of Meissner corpuscle is seen adjacent to the capillary in the dermal papilla (Masson trichrome, x160). (Reproduced with permission from A. L. Dellon et al, *Plast Reconstr. Surg* 56:182-193, 1975[24])

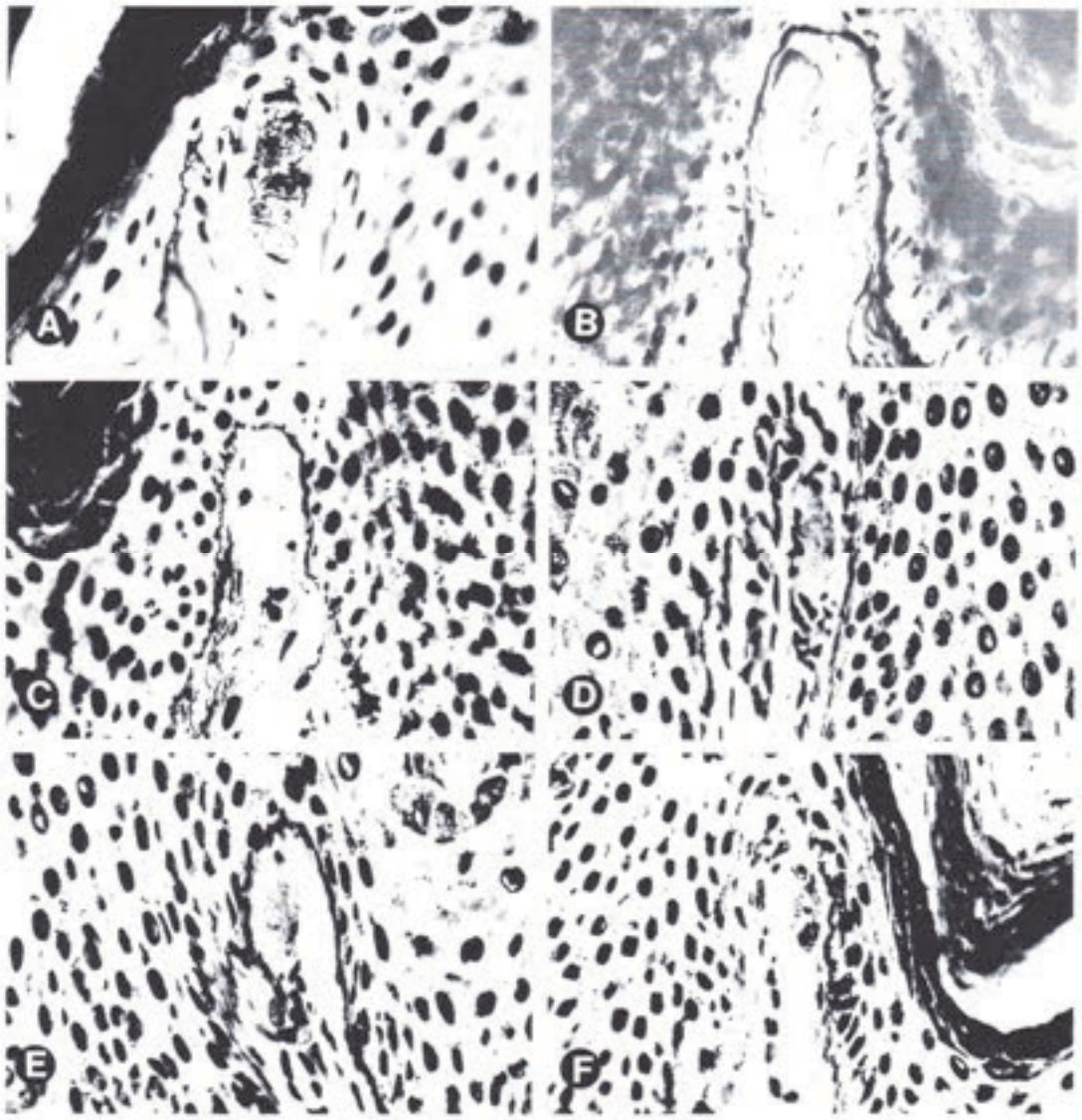

Figure 4.4 Progressive changes in the Meissner corpuscle after denervation (above left). ***A***. Representative normal Meissner corpuscle from a control fingertip; note the fine meshwork of nerve terminals within the corpuscle. The other photographs are of denervated Meissner corpuscles. ***B***. Axonal fragments remain within Meissner corpuscle at 72 hours after denervation. ***C.*** At 2 weeks. ***D***. At 4 months. ***E***. at 7 months. ***F***. at 9 months after denervation, nerve terminals are absent from the Meissner corpuscle and there is a progressive decrease in the size of the Meissner corpuscle. In the last photograph ***F*** the Meissner corpuscle is adjacent to a capillary (Silver stain, x 160). (Reproduced with permission from A.L. Dellon et al: *Plast Reconstr Surg* 56:182-193, 1975.[24])

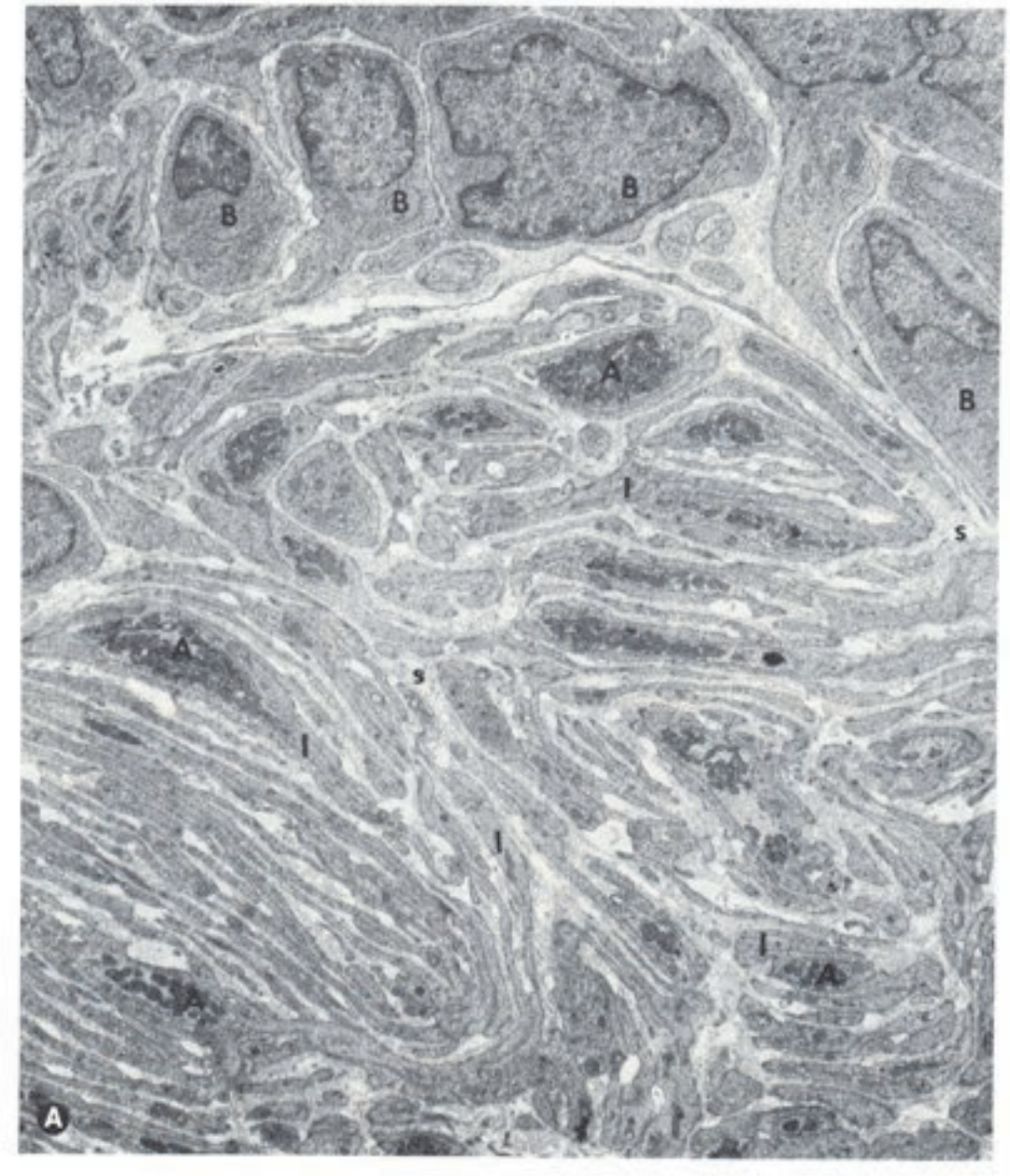

Figure 4.5 ***A.*** Electron micrograph of a normal Meissner corpuscle. In a dermal papilla beneath the epidermal basal cells (*B*), the Meissner corpuscle contains sstacks of lamellar cell processes, (l), which ensheath the axon terminals *(A)*. The axon terminals contain numerous mitochondris. Between the processes is the interlammelar substance *(s)*. (X12,450) (Reproduced with permission from A.L. Dellon et al: *Plast Reconstr Surg* 56:182-193. 1975[24])

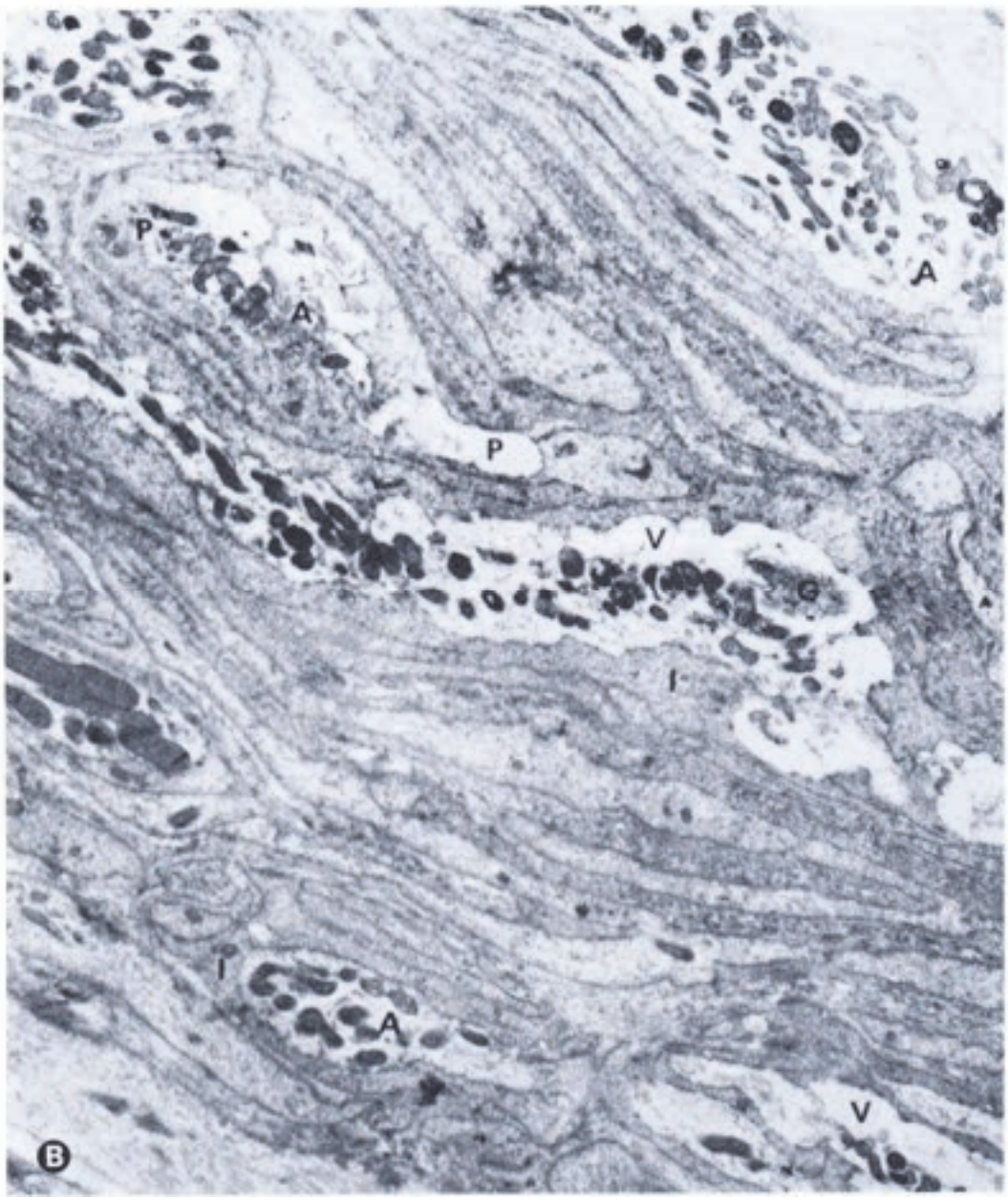

Figure 4.5. *B.* Electron micrograph of a normal Meissner corpuscle 48 hours after denervation. Degenerating axon terminals *(A)* are characterized by granular axoplasm *(G)* and vacuolization *(V)*. Possible example of axonal phagocytosis *(P)* within a lamellar cell process[24] (x21,200). (Reproduced with permission from A.L. Dellon et al: *Plast Reconstr Surg* 56:182-193. 1975[24])

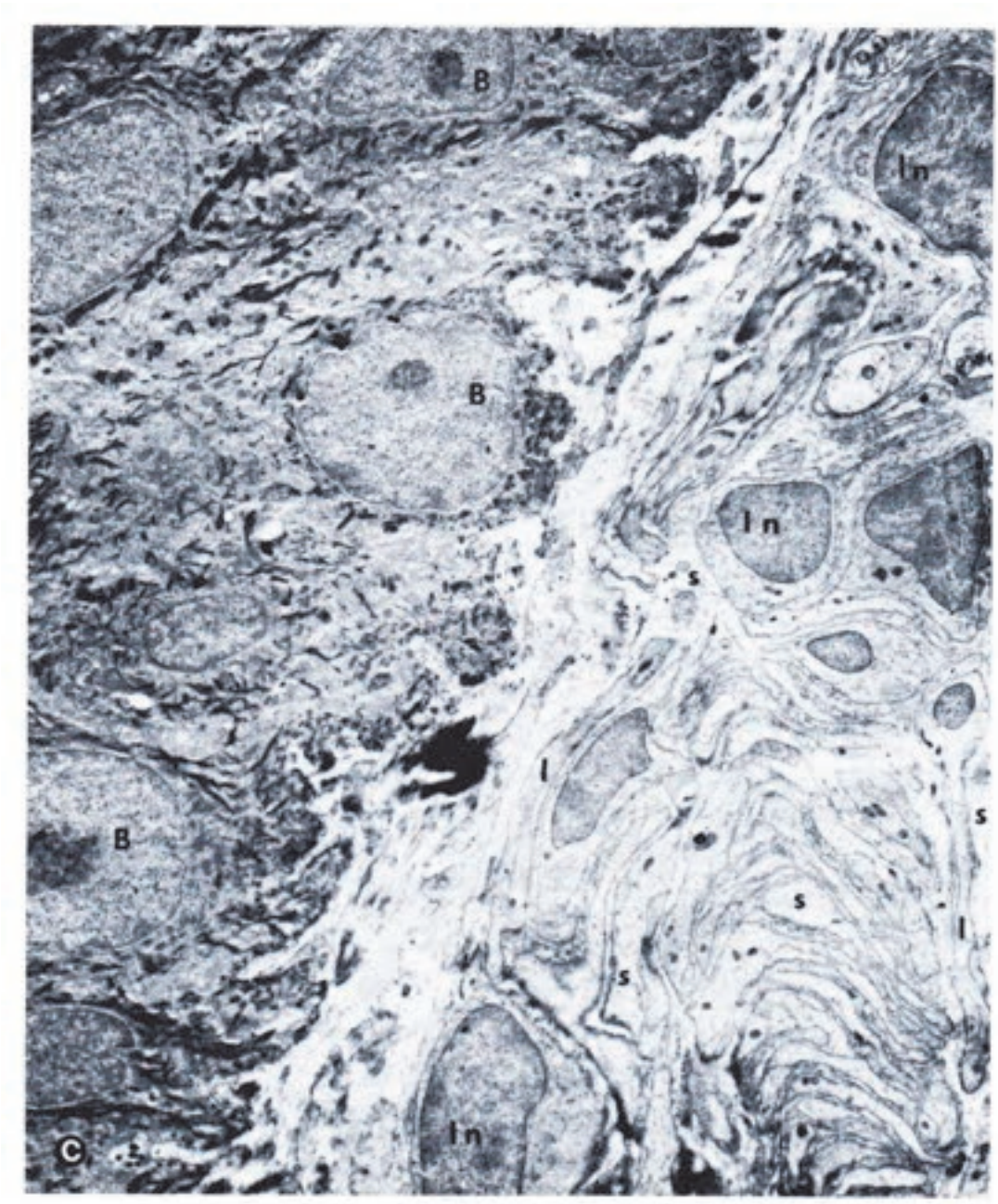

Figure 4.5 *C*. Electron micrograph of a Meissner corpuscle 4 months after denervation. Beneath the epidermal basal cells (*B*), the lamellar cell nuclei (In) are crowded together in the shrunken Meissner corpuscle. No axon terminals are present. There is a relative increase in the interlamelar substance (s) between the collapsed and narrowed lamellar cell processes (i). (x12,450). (Reproduced with permission from A. L. Dellon at: *Plast Reconstr Surg* 56:182-193, 1975[24])

Figure 4.6 Distribution of touch domes in the cat thigh before (*A*) and (*B*) division of the femoral cutaneous nerve. The squares and triangles are domes from overlapping, nonfemoral cutaneous nerves. (Reproduced with permission from P.R. Burgess et al: *J Physiol* 236:57-82, 1974[38].

These clinical observations may be explained if one assumes that the recovery of normal sensation requires a regenerating axon to reinnervate a persisting sensory end organ. During the first 6 months of denervation, the Meissner corpuscle, for example, loses its nerve fibers and its general architecture, but it has not undergone major reduction in size and it can probably still respond fully tot eh reinnervating nerve. After 6 months, the progressive retraction and collapse of lamellae, the steadily diminishing corpuscular size, and the increased collagenation probably render the Meissner corpuscle incapable of responding fully to a reinnervating axon's trophic influence. These structural changes probably prevent the Meissner corpuscle from ever regaining its normal threshold characteristics and, therefore, its potential for mechanoreception.

The Meissner corpuscle appears to be about midway in the rate of degeneration between the rapid deterioration (review above) of the Merkel cell-neurite complex and the relative stability of the Pacinian corpuscle. Thus, a period of delay of even 6 months will find the sensory end organ population in less than optimal condition to receive the regenerating axons.

How Long to Wait Prior to Re-exploration

Although you want to allow sufficient time to elapse to permit axonal regeneration across the repair site and distally to the fingertip, and allow for the patient's age, etc. you must remember the progressive degenerative changes occurring in the end organ population. If, for an injury at the wrist, the

predicted pattern of sensory recovery (see Chapter 7) is not proceeding on schedule, we believe re-exploration, between the 4th and 6th postoperative month, is indicated. To permit a greater interval to elapse is to permit such peripheral end organ degeneration that the salvage procedure (neurolysis, nerve grafts, etc.) will be handicapped severely.

Effect of the Ischemia on End Organ Degeneration

This is, essentially, unknown and remains an area for future investigation. Two recent studies are pertinent. The effect of forearm arterial injuries upon recovery of sensation from concomitant nerve injury has been reviewed.[50] The conclusion was that "associated unrepaired arterial lacerations have no apparent effect on the rate or completeness of neurological recovery following repair." Presumably, this was because "following single arterial injury in the forearm, the intact artery consistently demonstrates a compensatory increased flow." However, in these cases, significant ischemia to distal sensory end organs probably doesn't occur. More pertinent are the results of the Duke replantation experience.[51] Detailed evaluation of recovered sensibility was correlated with the replanted digit's pulse-volume recordings. Those patients who recovered less that 6-mm two-point discrimination all had pulse-volume recordings at least 85% of normal. Results of two-point discrimination, overall, in their series was not as good as that for digital nerve repairs in nonamputated digits.

I believe that the sensory corpuscles, being highly active metabolically, have a low tolerance to ischemia thereby differ from the other digital components, e.g., epidermis, tendon, bone, in their absolute requirement for oxygen. Although a replanted digit with a cold ischemia time of 24 hours may survive, we feel that even the most meticulous nerve repair will only result in axons regenerating to ischemia-injured end organs. Following prolonged ischemia, for example, the enzyme systems of the lamellar cell processes of Meissner corpuscles are probably irreversibly damaged, rendering them either unable to respond to neurotropism (these may be the same thing). Ischemia is probably the cause of the "ghost" Pacinian corpuscle observed in autografted primate volar pads,[52] while lack of ischemia is the basis of the persistent neural structures observed in the distal end of the pedicle flap.[53] My own observations (see Chapter 5) on sensory corpuscles in flaps and grafts support this view (see Figs 5.13 through 5.17)

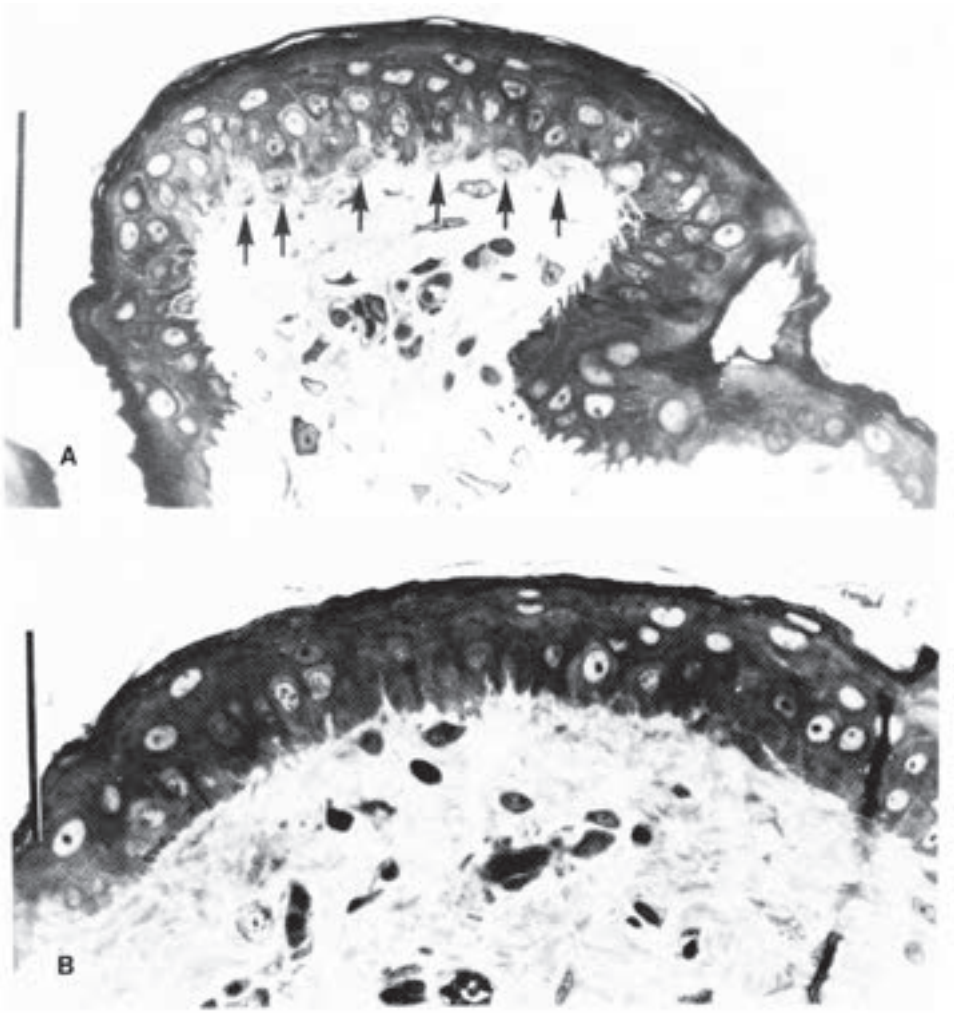

Figure 4.7 Cat touch domes before *(A)* and 22 days after *(B)* nerve division. Note complete loss of the Merkel cells (arrows, *A*) and flattening of the dome after denervation. Calibration bar (left of figures) is 50 (**m). (Reproduced with permission from P.R. Burgess et al: *J Physiol* 236:57-82m 1974[38]).

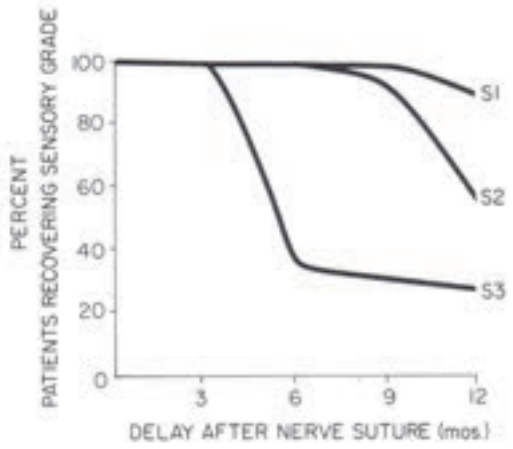

Figure 4.8 Effect of delay in nerve suture upon the degree of sensory recovery following wartime distal median nerve injuries. After delays of more than 4 months, there was a significant decrease in the percent of patients recovering to the S3 level. (Adapted from Kirklin et al[49])

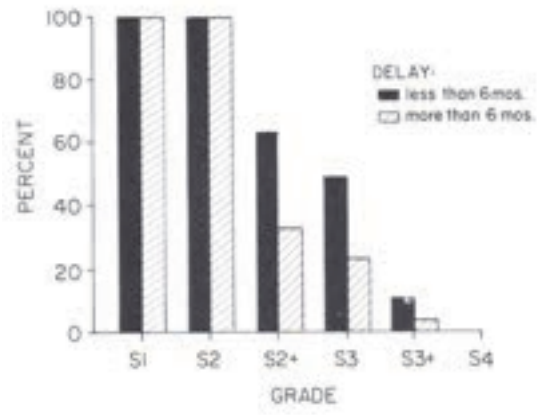

Figure 4.9 Effect of delay in repair of divided nerve upon degree of sensory recovery, for distal median nerve, wartime injuries. After delay of 6 months, there was a significant decrease in percent of patients recovering to the S2+ and S3 levels. (Adapted from Zachary.[47])

Sensory Neurotropism

The interaction between the axon and epithelial (mesenchymal) component of the sensory corpuscle is poorly understood. To what extent is the integrity of the epidermis and dermis dependent upon neurotrophic factors? Why do fingertips undergo acralsclerosis after nerve division? To what extent do the corpuscular components control the course, the ultimate destination of regeneration axons? What is the role of the synaptic vesicles in the Merkel cell, and of what significance are the various cholinesterases and their varying response to denervation? These questions and more remain to be answered. An intriguing start has been made in the reviews by Harris,[54] Werner,[55] and Drachman's multiauthored monograph.[56]

References:

1. Waller A: Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibers. Philos Trans R Soc Lond 740:423-429, 1850.
2. Ranson SW: Degeneration and regeneration of nerve fibers. J Comp Neurol 22:487-546, 1972.
3. Webster HF: The relationship between Schmidt- Lantermann incisures and myelin segmentation during Wallerian degeneration. Ann NY Acad Sci 122: 29-38, 1965.
4. Engel AG, Stonnington HH: Morphologic effects of denervation of muscle: A qualitative ultrastructural study, in Drachman DB (ed): *Trophic Functions of the Neuron*. New York: New York Academy of Sciences, 1974, pp 68-88.
5. Sunderland S: *Nerve and Nerve Injuries*, ed 2. Edinburgh: Churchill-Livingstone, 1978, Ch 7.
6. Sunderland S: *Nerve and Nerve Injuries*, ed 2. Edinburgh: Churchill-Livingston, 1978, Ch 17-20, 22.
7. Boeke J: On the regeneration of sensitive end-corpuscles after section of the nerve. K Acad van Wetenschoppen (Amsterdam) 25:319-323, 1922.
8. Boeke, J, Dijkstra C: De- and regeneration of sensible end-corpuscles in the duck's bill (corpuscles of Crandy and Herbst) after the cutting of the nerve, the removing of the entire skin or the transplantation of the skin in another region. K Acad van Wetenschoppen (Amsterdam) 35:1114-1119, 1932.

9. Boeke J: *The Problems of Nervous Anatomy*. London; Oxford University Press, 1940, pp 12-44.
10. Guth L: The effects of glossopharyngeal nerve transection on the circumvallate papilla of the rat. Anat Rec 128:715-731, 1957.
11. Guth L: Degeneration and regeneration of taste buds, in Beidler LM (ed): *Handbook of Sensory Physiology*, Vol. VI. Berlin: Springer-Verlag, 1971, pp 63- 74.
12. Farbman AI: Fine structure of degenerating taste buds after denervation. *J Embryol Exp Morphol* 22: 55-68, 1969.
13. Fujimoto S, Murray RG: Fine structure of degeneration and regeneration in denervated rabbit vallate taste buds. Anat Rec 168:393, 1970.
14. Fitzgerald MJT, Martin F, Paletta FX: Innervation of skin grafts. *Surg Gynecol Obstet* 124:808-812, 1967.
15. Orgel M, Aguayo A, Williams HB: Sensory nerve regeneration: An experimental study of skin grafts in the rabbit. J Anat 111:121-135, 1972.
16. Seddon H: *Surgical Disorders of Peripheral Nerves.* Baltimore: Williams & Wilkins Co, 1972, Ch 2,14.
17. Sunderland S: *Nerve and Nerve Injuries*, ed 2. Edinburgh: Churchill-Livingstone, 1978, Ch 31.
18. Lyon WR, Woodhall B: *Atlas of Peripheral Nerve Injury,* Philadelphia: WB Saunders, 1949, p 215.
19. Winkelmann RK: Effect of sciatic nerve section on enzymatic reactions of sensory reactions of sensory end-organs. J Neuropathol Exp Neurol 21:655-657, 1962
20. Ridley A: Silver staining of the innervation of Meissner corpuscles in peripheral neuropathy. Brain 91:539-552, 1968.
21. Hurley HG, Koelle GB: the effect of inhibition of nonspecific cholinesterase in perception of tactile sensation in human volar skin. J Invest Dermatol 31:243-245, 1958.
22. Orphanos CE, Mahrle G: Ultrastructural and ytochemistry of human cutaneous nerves. J Invest Dermatol 61:108-120, 1973.
23. Jabaley ME, Dellon AL: Evaluation of sensibility by microhistological studies, in Omer GE, Spinner M (eds): *Management of Peripheral Nerve Problems.* Philadelphia: WB Saunders, 1980, Ch 62.
24. Dellon AL, Witebsy FG, Terrill RE: The denervated Meissner corpuscle: A sequential histologic study after nerve division in the Rhesus monkey. Plast Reconstr Surg 56:182-193, 1975.
25. Lee FC: A study of the Pacinian corpuscle. J Comp Neurol 64:497-522, 1936.
26. Glees P, Mohiuddin A, Smith AG: Transplantation of Pacinian bodies in the brain and thigh of the cat. Acta Anat (Basel) 7:213-224, 1949.
27. Lowenstein WR, Rothkamp R: The sites for mechanoelectric conversion in a Pacinian corpuscle. J Gen Physiol 41:1245-1265, 1958.
28. Wong WC, Kanagastuntheram R: Early and late effects of median nerve injury on Meissner's and Pacinian corpuscles of the hand of the macaque (M. fascicularis). J Anat 109:135-142, 1971.
29. Krisshnamurti A. Kanagasuntheram R. Vy S: Failure of reinnervation of Pacinian corpuscle after nerve crush: An electron microscopic study. Acta Neuropathol (Berl) 23:338-341, 1973.
30. Karthals JK, Wisniewski HM, Ghetti B, et al: The fate of the axon and its terminal in the Pacinian corpuscle following sciatic nerve section J Neurophysiol 3:385-403, 1974
31. Silver A, Versaci A, Montagna W: Studies of sweating and sensory function in cases of peripheral nerve injuries of the hand J Invest Dermatol 40:243-258, 1963.
32. Silver A, Montagna W, Versaci A: The effect of denervation on sweat glands and Meissner corpuscles of human hands. J Invest Dermatol 42:307-324, 1964
33. Satinsky D, Pepe FA, Liu CN: The neurilemma cell in peripheral nerve degeneration and regeneration. Exp Neurol 9:441-451, 1964
34. Brown A, Iggo A: The structure and function of cutaneous "touch corpuscle" after nerve crush. J Physiol 165:28-29P, 1963.

35. Palmer P: Ultrastructural alterations of Merkel cells following denervation. Anat Rec 151:396-397, 1965.
36. Kasprzak H, Tapper DN, Craig PH: Functional development of the tactile pad receptor system. Exp Neurol 26:439-446, 1970.
37. Smith KR: The structure and function of the Haarscheibe. J Comp Neurol 131:459-474, 1967
38. Burgess PR, English KB, Horch KW, et al: Patterning in the regeneration of type 1 cutaneous receptor J Physiol 236:57-82, 1974.
39. Munger B: Personal communication (Munger B. Ide H, manuscript in preparation).
40. Sunderland S: *Nerve and Nerve Injuries*, ed 2. Edinburgh: Churchill-Livingstone, 1978, Ch 48.
41. Woodhall B, Beebe GW: *Peripheral Nerve Regeneration—A Follow-Up Study of 3635 World War II Injuries*, Veterans Administration Medical Monograph. Washington, DC: US Govt Print Office, 1956, p 309.
42. Thomson JL, Ritchie WP, French LO: A plan for care of peripheral nerve injuries overseas. Arch Surg 52:557-570, 1946.
43. Weckesser EC: The repair of nerves in the palm and fingers. Clin Orthop 19:200-207, 1961.
44. Hamlin E, Watkins AL: Regeneration in the ulnar, median and radial nerves. Surg Clin North Am 27:1052-1061, 1947
45. Sunderland S: Capacity of reinnervated muscles to function efficiently after prolonged denervation. Arch Neurol Psychiatry 64:755-771, 1950.
46. Shaffer JM, Cleveland F: Delayed suture of sensory nerves of the hand. Ann Surg 131:556-563, 1950.
47. Zachary RB: Results of nerve suture, in Seddon HJ (ed): *Peripheral Nerve Injuries.* London: Her Majesties Stationery Office, 1954, pp 254-388.
48. Nicholson OR, Seddon HJ: Nerve repair in civilian practice: Results of treatment of median and ulnar lesions. Br Med J 2:1065-1071, 1957.
49. Kirklin JW, Murphy F, Berkson J: Suture of peripheral nerves: Factors affecting prognosis. Surg Gynecol Obstet 88:719-730, 1959.
50. Gelberman RH, Blasingame TP, Feonek A, et al: Forearm arterial injuries. J Hand Surg 4:401-408, 1979.
51. Gelberman RH, Urbaniak JR, Bright D, et al: Digital sensibility following replantation. J Hand Surg 3:313-319, 1978.
52. Miller SH, Reisenas I: Changes in primate Pacinian corpuscles following volar pad excision and skin grafting: A preliminary report. Plast Reconstr Surg 57:627-636, 1976.
53. Santoni-Rugiu P: Experimental study on reinnervation of free grafts and pedicle flaps. Plast Reconst Surg 38:98-104, 1966.
54. Harris AJ: Inductive function of the nervous system. Annu Rev Physiol 36:251-305, 1974 (403 references.)
55. Werner JK: Trophic influence of nerves in the development and maintenance of sensory receptors. Am J Phys Med 53:127-142, 1974 (68 references).
56. Drachman DB (ed): *Trophic Function of the Neuron.* New York: New York Academy of Sciences, 1974.

Chapter 5
SENSORY CORPUSCLES AFTER NERVE REPAIR

INTRODUCTION

This chapter is concerned with the most distal events by which an injured sensory nerve re-establishes contact with the external world. The process is regeneration. "Regeneration is an active invasion and displacement process in which the pushing forces of axonal streaming, increased axoplasmic pressure and central protein synthesis are opposed by distal Schwann cell proliferation, collapsed tubules and collagen accumulation.[1] This excellent general description focuses upon the nerve fiber, as has most previous investigation and writing is this field. Seddon,[2] for example, extended the process to be the periphery but was concerned only with muscle reinnervation. Suderland's comprehensive review of regeneration comprises 239 references on axonal regeneration,[3] 88 references on the pattern motor recovery associated with regeneration of motor nerve fibers,[4] but just 27 references on the pattern of sensory recovery associated with regeneration of sensory nerve fibers. Of those 27 references, only five actually describe the effect of regeneration upon sensory corpuscles. These five references have appeared in the last decade and are included in the review to follow.

Very few studies have focused on sensory receptors in fact, some of those referred to as demonstrating "end organ reinnervation" have not concerned sensory receptors for example, the series of studies by Sanders and Young in the mid 1940's[6-8] is usually quoted as showing "the importance of end organ reinnervation." What these investigators actually did was to divide mixed nerves and, in some instances, pure motor nerves (e.g., to the gastrocnemius) and then to permit some nerves to regenerate and others not to regenerate. They then studied nerve *fiber* diameter in those nerves allowed to regenerate. They never evaluated sensory receptors they concluded that although the shrunken distal Schwann tubes "restricted the diameter attained by the regenerating fibers within them"[6] "both sensory and motor nerve fibers became larger when allowed to reach their end-organs."[6] Thus, "the most powerful influence lies

not centrally but in connection with the end-organ."[6] But, these studies did not evaluate the effect of regeneration upon the sensory end organ.

One of the central areas of controversy has been whether regenerating sensory axons reestablish contact with sensory end organs, that is, reinnervate persisting sensory corpuscles, or whether regenerating sensory axons arrive at the periphery and induce the new sensory end organs that is, develop new or *de novo* sensory corpuscles. Chapter 4 established that sensory corpuscles undergo progressive degenerative changes following denervation the sensory corpuscles, therefore, do "persist" for a time after nerve injury, but if they remain without innervation sufficiently long, they are altered significantly. This chapter will attempt to answer the following questions. Can sensory corpuscles arise *de novo*? Can degenerating corpuscles be reinnervated? What happens if a persisting end organ is reinnervated by an axon that previously had innervated a different type of sensory end organ?

EARLY REINNERVATION STUDIES

BOEKE

J. Boeke's observations on the organ of Eimer in the mole snout are quoted as demonstrationg *de novo* end organ formation.[9] However, Boeke's observations were made during the mole's growth and development when the early fibers into the mole's snout (the organ of Eimer) were noted to degenerate. Following tis degeneration "entirely new innervation" was found which was identical with the adult form of this organ. Thus, these observations probably cannot be extrapolated into the primate nerve repair setting.

In ducks Boeke[10, 11] transected the trigeminal innervation and subsequently biopsied the duck's bill to evaluate the effect of the regenerating axons upon the Grandry (a morphologic analog to the Merkel cell-neurite complex) and Herbst (a morphologic analog to the Pacinian) corpuscles. He observed axons re-entering, thereby reinnervating, each of these corpuscles. The Grandry tactile cell, which had "shriveled" in size, regained normal size as the axon developed into the neurofibrillary disc. Developmentally, the tactile cells were of lemnoblastic (sheath cells) origin. Boeke specifically distinguishes what I call "reinnervation" from *de novo* origin as follows: "Besides a regeneration of the old existing sensory corpuscles, a great number of new corpuscles is formed."[11]

In duck bill-to-leg and leg-to-bill skin "transplant" experiments, graft biopsies at 2 month after surgery were observed to contain only degenerated corpuscles, including the Herbst corpuscles. These were smaller than normal and infiltrated by "blood capillaries apparently being organized by the surrounding connective tissue. No 'new' corpuscles developed in the leg-to-bill transplants by eleven months after surgery. In the bill-to-leg transplants, however, 'new' Grandry corpuscles developed and 'here and there' newly-formed Herbst corpuscles."[11]

In related experiments often quoted as demonstrating *de novo* origin of sensory end organs, Boeke's approach was to excise an area of skin, allow this area to heal "primarily," and to evaluate the end organs of this "regenerating skin." This approach was utilized in the duck's bill, where "newly formed Herbst and Grandry corpuscles "developed," in monkey fingertips and in the little fingertip of his assistant, Doctor van Straaten, where "new" Meissner corpuscles developed.[9, 11]

Boeke's laboratory carried out imaginative and excellent work and the observations will remain classics. However, as wound healing is understood today, all the work based on "primary" healing of excised wounds is fallacious Secondary healing of excised wound into the healed central, and future biopsy site (see Fig. 5.1). Recall it was only this type of study in the duck that "new" Herbst corpuscles were observed. Problems with experimental design in sensory investigations still persist. A recent study reported "new" Pacinian corpuscles regenerating" after nerve repair.[12] Analysis of that study[12] suggested wound contracture and transposition of normal adjacent Pacinian corpuscles as the source of the *de novo* corpuscles. Indeed, Boeke's own serial drawings of "primary healing" in the monkey's and in von Straaten's finger clearly show the wound contracture (Fig. 5.2). New skin did not form. *De novo* corpuscle formation did not occur.

Boeke's work does document that following nerve division, Grandry and Herbst corpuscles are reinnervated by regenerating axons. The study also apparently shows that *de novo* Grandry corpuscles arise in ducks during axonal regeneration

The extrapolation of the response of sensory end organs to denervation and axon regeneration in lower vertebrates to that of higher vertebrates is probably not justified. For example, the mole is blind and "sees" primarily with its nose for food and shelter. The duck, whose forearms are wings and whose fingertips are feathers and claws relies on its beak not only to hold its food but also to filter seeds and insects from sand, in the water and mud.[14] Although some birds, like the duck, and perhaps some mammals, like the mole, can regenerate bill or nose sensory corpuscles, increasing specialization proceeds during evolution at the expense of regenerative potential. The primates probably cannot regenerate sensory corpuscles *de novo*.

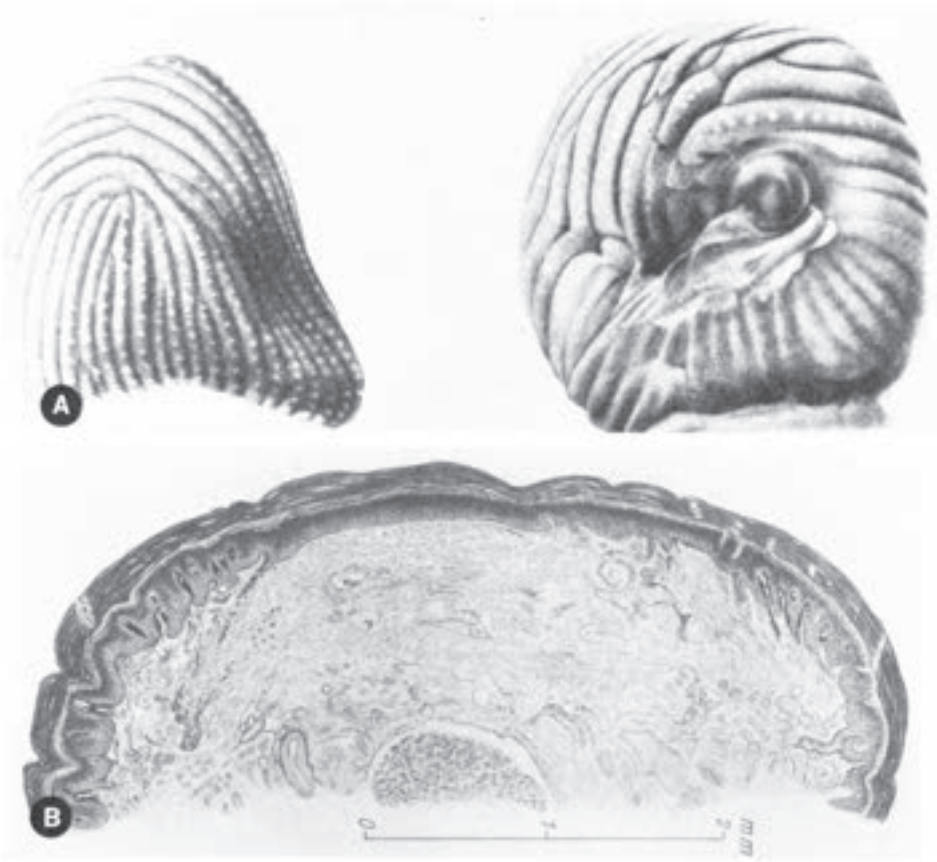

Figure 5.1. From Boeke's study of "regenerated" skin in the monkey.[9] ***A***, Note that the central, previously biopsided area, in the fingertip has not "regenerated" but healed secondarily by wound contracture. ***B***. The histologic section of this area shows not new skin but scar with sensory receptors transposed centripetally, not regenerated *de novo.*

Figure 5.2. From Booke's study of "regenerated" skin in man.[9] Note the healed central area has done so by secondary intention. Sensory corpuscles present in the histologic section of this area are pre-existing corpuscles pulled centrally by the force of wound contracture

Taste Buds

Werner[15] has reviewed the literature on the taste bud as a model of sensory receptor change during embryogenesis, denervation, and reinnervation. It is relevant that the epithelial analage of fungiform papillae in the rate develops prior to neural ingrowth into the tongue, and that these cells have ultrastructure-size vesicles that may releae a trophic substance to guide gustatory axons. Normally, taste buds are replenished on a weekly basis.[17] As reviewed in Chapter 4, taste buds degenerate completely following division of any cranial nerve carrying gustatory fibers. Repair of the divided gustatory nerve results in taste bud regeneration.[18, 19] (Additional discussion of taste buds studies is found later in this "Chapter in the Cross Innervation" section.)

Skin Grafts

The extensive literature on the reinnervation of skin grafts and flaps was the closest the researchers prior to the 1960's came to the question of sensory corpuscle reinnervation or regeneration. These studies attempted to answer two general questions: (1) By what anatomic pathway does reinnervation occur, e.g., longitudinally via pre-existing neurovascular pathways or at random through the edge of bed of the graft or flap. (2) Was that pattern of recovered sensation that of the donor or the recipient environment e.g., would abdominal skin grafted onto the fingertip eventually recover sensation more like the abdomen or like the fingertip? A corollary of the last questions was what type of sensory corpuscle present in the graft is related to the recovered sensation? A review of these areas will lead directly to the studies on the sensory end organs themselves. Aspects of these questions have been reviewed recently by Jabaley[20] and Terzis.[21]

Several studies attempting to determine which type of soft tissue coverage recovered sensation (touch, pain, temperature) earliest concluded that detached, distant pedicle flaps recovered sensation earlier than grafts, and full thickness grafts earlier than split-thickness graft.[22-24] Another study[25] reached the opposite conclusion. The controversy begun in the 1930's continued into the 1950's with observers on both the "flap first"[26, 27] and the "flap last" side of the controversy. When viewed from today's perspective, many of the differing results of these studies were due to (1) the quality of the recipient bed, (2) the time interval between injury and resurfacing and testing, (3) the testing techniques, and (4) the size and location of test area (in small test areas, perception is often through areas adjacent to the resurfaced areas). For example, in all of these studies on grafts, the donor sites were thigh and abdomen and the grafts were transferred to the trunk, face, or extremities, but not to fingertips!! Flaps were abdominal and transferred to the head and neck or hand's dorsum or palm but not to the fingertips!! Defects were frequently those with extensive deep scarring, such as burns. Thus, resurfacing tissue contained few, if any sensory corpuscles, and resurfaced areas were those with a normally low innervation density. These

early observations, some of which are meticulous, monumental and truly classic,[24, 25] nevertheless contribute little to our understanding of sensibility in the hand or the reinnervation of sensory corpuscles.

The course which the regenerating axons followed into the graft or flap generally was agreed upon. The earliest investigators[22-25] observed that in detached pedicle flaps, sensation recovered first proximally, and proceeded distally, from the edges to the center, while in grafts the recovery was more form's peripheral to central. Later studies generally concurred regarding graft innervations[29, 30], with the degree of sub dermal re-innervation being related to the conditional the graft bed.[29] Re-innervation nerve axons from proximal bundles, where aligned with neurovascular bundles in the resurfacing tissue, followed them into the graft.[29, 31] The greatest number of axon sprouts, however, entered the resurfacing tissue randomly, at the periphery and sub dermally, and traveled randomly. The ether ended as free nerve terminal, joined the cutaneous plexus of the resurfacing tissue, or, by change, re-innervated a sensory corpuscle or hair follicle.[29, 31]

The classic studies by Hutchinson, Tough and Wyburn in 1949,[32] Ponten in 1960[30], and Mannerfelt in 1962[33] established conclusively that transplanted soft tissue recovers, a sensory pattern more like its recipient bed than its donor site *if* sufficient re-innervation occurs.

The influence of Moberg[34] begins to be seen here, as Ponten's[30] studies emphasized functional recovery and recorded sensation in terms of two-point discrimination. Manerfelt's comprehensive sensory evaluation[33] on 28 patients included not only two-point discrimination testing, but the pick-up test, the coin test, and the ninhydrin test[32]. Although Ponten[30] reported examples of recovery of tactile gnosis, Moberg and Mannerfelt have stated that skin grafts never recover tactile gnosis. Skin grafts generally recover better sensation than flaps. (33) (This will be discussed further in the "Clinical Implications" section, later in this chapter.)

In the decade of the 1970's, histochemistry, electron microscopy, and sophisticated neurophysiologic recording, techniques were applied to experiments similar to those done in the preceding 40 years. Ridley[35] biopsied human fingertips previously skin grafted with forearm skin in, trauma patients. He observed no encapsulated ending, but did identify an occasional Merkel-like ending in relation to an epidermal ridge. He noted the apparent paradox that the patient had two point discrimination but no Meissner corpuscle. His results have been variously interpreted. I believe they demonstrated: (1) that regeneration sensory axons do not form de novo encapsulated corpuscles (and therefore this observation is consistent with the results of my work on the Meissner corpuscles;[36] (2) that the observed Merkel disc may represent re-innervation of a Haarscheibe by a slowly-re-innervation of a Haarscheibe by a slowly-adapting fiber (see "Cross Innervation" section); and (3) that presence of two-point discrimination and Merkel disc is the appropriate correlation (see Chapter 3).

Orgel, Aguayo, and Williams[37] studied the regeneration fiber population, observing an imbalance in favor of many more small, myelinated fibers over the larger myelinated fibers. This altered ration correlated with absent end-corpuscles in grafted rabbit ski. Terzis extended these observations by noting a decreased conduction velocity in the regeneration population of axons entering the rabbit ear grafts.

Cellin and Caoli,[38] in long review, essentially have confirmed many of the observations previously presented, as has a recent publications from Japan.[39] This latter report also documents the reinnervation of hair follicles in grafted hairy skin.

In my opinion, if the resurfaced area is a fingertip, and if the resurfacing is done primarily on a no scarred base, the perception of pain, temperature, and touch will be recovered first in the thin split-thickness graft, then in full-thickness graft, and last in a flap. The degree of recovery of functional sensation will be related to the innervation density of sensory corpuscles in the resurfacing tissue.

A separate but related question is whether the noninjured nerves in an area adjacent to the receptive field of an injured nerve can sent axon sprouts into this injured nerve's receptive field. This, reinnervation would occur from normal adjacent nerves rather than regeneration axons of the injured nerve. This question need not arise with the question of graft reinnervation because the nerves about the periphery of the graft have all been injured. Weddell, Guttmann, and Guttmann[40] in 1941, using a rabbit hind limb model and whole mount horizontal sections stained with methylene blue, concluded that into adjacent denervated areas. Hoffman demonstrated similar finding for muscle, in the rat hind limb. Adjacent normal axons sprouted to reinnervate a denervated motor end-plate[41]. Livingstone reported two cases were demonstrated by nerve block to have anomalous innervation?) By adjacent noninjured nerves, I believe that the axons in the overlap areas of receptive fields can be either stimulated by a substance released from the degenerating axon or are released from contact inhibition by the degeneration axons and can extend into adjacent areas.

PACINIAN CORPUSCLE

In 1970, Wong and Kanagasutheram[43] made preliminary observations on the effect of crushing, section, and ligating a primate (macaque) median nerve. Silver and histochemical staining techniques were done on palm biopsies using the contralateral hand as a control in a total of three animals. At 40 weeks after nerve crush, there was just an occasional Pacinian corpuscle reinnervated. I infer from the author's lack of commentary upon long-term result of the ligation and section parts of their study, that no reinnervated Pacinian corpouscles were identified. In the crush study (one nerve, crushed at the writs), cholinesterase staining was "nil to moderate" in Pacinian corpuscles.

In 1972, Lowenstein[44] studied the physiology of Pacinian corpuscle in the cat mesentery. In six cats the inferior mesenteric nerve was divided and "reunited" (autologous clot within a polycarbonate

membrane sleeve). At 30 to 40 days after "union," just eight of the 54 tested corpuscles in the mesenteries innervated by these six nerves were mechano-receptive.

During that same time period, Kanagasuntheram's group[45] further evaluated this difficulty in reinnervation the Pacinian corpuscle. This time they studied the ultrastructure of five corpuscles from the middle finger of a primate (slow loris) 75 days after median nerve crush in the forearm. They observed unremoved myelin debris and endoneurial fibrosis within the corpuscle's inner core, "preventing" reinnervation.

Jabaley[46] did not comment on Pacinian corpuscles in his biopsy study of human fingertips after nerve repair.

The study by Krishnamurti and Kanagasuntheram[45] may be criticized. Although they studied primates and employed excellent histochemical and ultrastuctural techniques, their experiment was poor. In their earlier study[43], they evaluated potential reinnervation following nerve section (technique of repair unspecified) and after ligation (regeneration theoretically may not occur at all) at the wrist with a palm biopsy. They did not totally different this area where a palmar cutaneous nerve, originating above the area of crush, or a musculocutaneous nerve might also be innervation the palm. In that study, the time chosen for postinjury evaluation, 40 weeks, was appropriate for the injury-test site separation of a few centimeters. The time chosen in their next study[45], however, was too short: the injury and test site were now widely separated (forearm to fingertip versus wrist to palm), yet the time interval was just 10 weeks! They observed alterations in the blood supply to the corpuscle, and this may explain the delayed phagocytosis and fibrosis they found.

In summary, very little experimental work has been conducted on the reinnervation of Pacinian corpuscles. The work reviewed above suggested that these corpuscles were reinnevated with difficulty, probably because of mechanical factors. My own observation (see chapter 7) indicate that Pacinian corpuscles are reinnervated in humans, but they are the last in the time sequence to be reinnevated. Although "mechanical" obstruction may block axonal regeneration to the corpuscle, I feel the basis for the above observations lies in the low probability of a regenerating axon making the proper peripheral connection where the nerve fiber to receptor ration is 1:1 (see chapter 7).

Meissner Corpuscles

In 1970, Wong and Kanagasuntheram[43], in the study described in the preceding section observed "early" Meissner corpuscle "reinnervation" 8 weeks following a nerve crush several centimeters proximal to the observation site. "The reinnervation of Meissner's corpuscle forty weeks after nerve crush was almost complete, but after nerve section (32 weeks) and nerve ligature (40 and 47 weeks) the process was less complete" (silver stain). Both nonspecific and acetylcholinesterase staining reaction were normal, with the latter having recovered normal staining characteristics first in the crush specimens.

Jabaley et al.[46] observed "reinnervated" Meissner corpuscles in 12 of 17 patient fingertip biopsies done an average of 24 months after nerve repair.

In a more detailed investigation of the effects of nerve repair upon the Meissner corpuscles, I did fasicular reparis upon the median and ulnar nerves of a different primate hand (rhesus)[36]. Sequential histologic studies including ultrastructual studies, were done up to 9 months after nerve repair, with the contralateral fingertips serving as controls. Because of the lack of physiological or functional correlates, cholinesterase stains were not employed. In addition to refining earlier observations, this study attempted to determine whether a regenerating axon reinnervated a pre-existing but degenerating, corpuscle, reversing this process, or whether the regenerating axon reached the epidermal region and induced *de novo* Meissner corpuscles. The conclusion was that "in the rhesus monkey, axons of regenerating sensory nerves reinnevate the denervated Meissner corpuscle… there was no evidence of Meissner corpuscles regenerating *de nov*. "The results of that study follow and are reported and illustrated in greater detail.

Controls. The histologic sections of the preoperative biopsies of the control and operative fingertips, as well as the contralateral fingertip controls throughout the postoperative period, contained normal Meissner corpuscles as demonstrated by both connective tissue and nerve staining techniques. The Meissner corpuscle showed segmentation into two to three lobules, each of which contained a lamellar arrangement of plump cells or spaces with many collections of pink staining material believed to be asoplasm. The nuclei of the lamellar cells usually were located peripherally. The entire Meissner corpuscle was large and almost filled with dermal papilla on a section taken near the Meissner corpuscle's longitudinal axis(Fig. 5.3 A). On silver staining, at least one and usually three or more modulated axons reached the Meissner corpuscle and arborized within it by looping between the lamellai. Axon endings appeared as coils or sprays of fine twigs under the magnification employed (Fig. 5.4 A).

Two Days after Nerve Suture. In the sections stained for connective tissues, early signs of degeneration were apparent; the lobular subdvisions were blurred, the usually distinct internal lamellar pattern was obscured, and the collections of pink-staining material were less apparent (Fig. 5.3 A). With silver staining, the axon terminals were no longer present, with the exception of a few argyrophillic fragments (Fig 5.4 B). Dermal nerve trunks demonstrated Wallerian degeneration.

Four weeks after Nerve Suture. By both connective tissue and verve stain techniques, the Meissner corpuscles in these control biopsies were denervated, demonstrating that the innervation to these fingertips had been divided. Without successful nerve repair, progressive, Meissner corpuscle degeneration could be expected.

Six Weeks after Nerve Suture. The Meissner corpuscles stained for connective tissue (Fig.5.3 C) showed more advanced signs of degeneration. There was some diminution in overall size and there

were no lobulations or collections of pink-staining material, but rather the entire Meissner corpuscle was bluish, flattened, ovoid, nearly devoid of internal architecture. The few detectable lamellar cells were not plump. With the silver staining technique (Fig. 5.4 C), most were devoid of argyrophillic material, except for the nuclei of lamellar cells; the entire Meissner corpuscle was pale. An occasional Meissner corpuscle however had a thin axon inside. The dermal nerve trunks were now primarily empty endoneural sheaths, although an occasional sheath contained a thin regeneration axon.

Three Months after Nerve Suture. With connective tissue staining, most of the Meissner corpuscles appeared as they had at 6 weeks, after nerve suture, except that most of the Meissner corpuscles were diminished in overall size (Fig.5.3D)

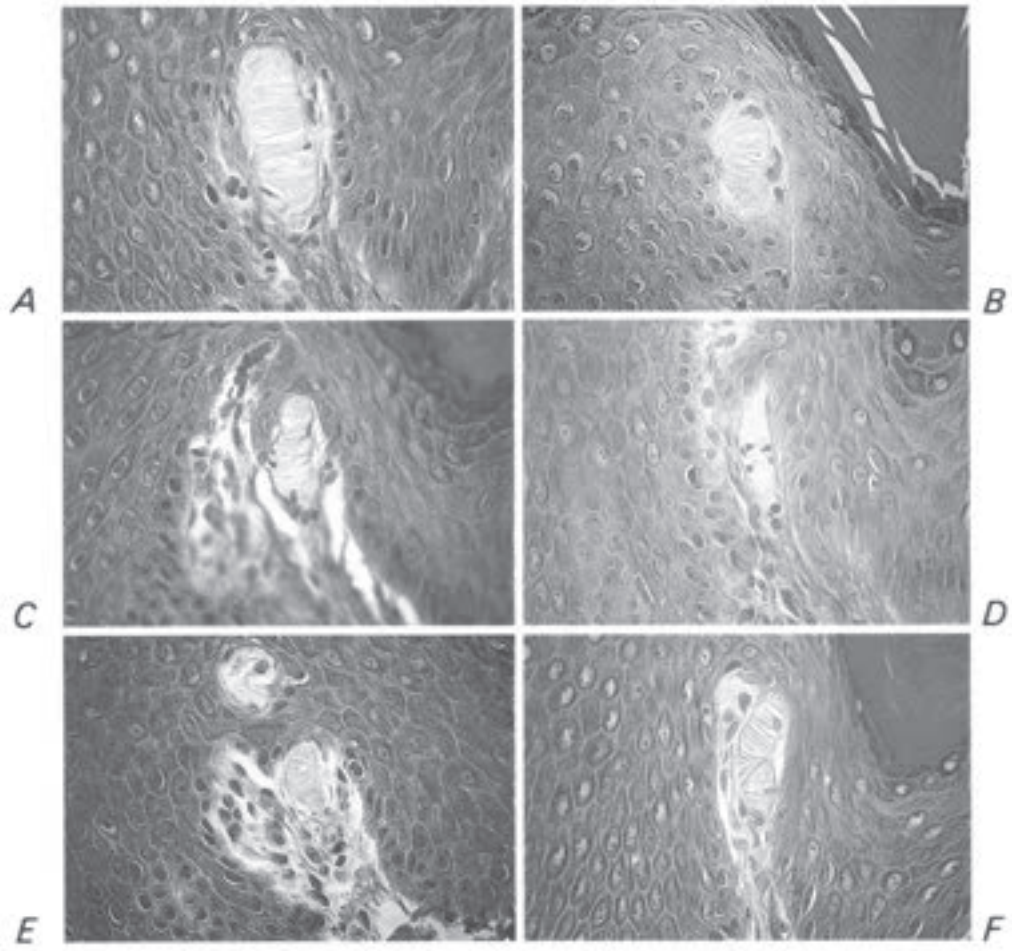

Figure 5.3. Reinnervation of denervated Meissner corpuscle. Mallory trichrome stain, x 160 ***A***. Normal. Other sections are the following intervals after nerve repair: ***B***. 48 hours; ***C.*** 6 weeks; ***D***, 3 months; ***E***, 6 months; ***F,*** 9 months. See text for description,. (Reproduced with permission from A.L. Dellon: *J Hand Surg* 1:98-109, 1976[36]).

The silver straining method demonstrated about one third of the Meissner corpuscle to be aneuritic. The remaining Meissner corpuscles, however, definitely contained axons. These were single or

multiple thin axons intertwined between the lamellar cell (Fig. 5.4, c). Most dermal nerve trunks contained thick and thin regenerating axons.

Six Months after Nerve Suture. About 70% of all Meissner corpuscles contained plump lamellar cells with collections of pink-staining material. Meissner corpuscles were increased in size and a few Meissner corpuscles were lobulated (Fig. 5.3, E). With silver staining, about 80% of the Meissner corpuscles contained axons, many of which were now of normal thickness (Fig.5.4. E). Dermal trunks appeared to be normal.

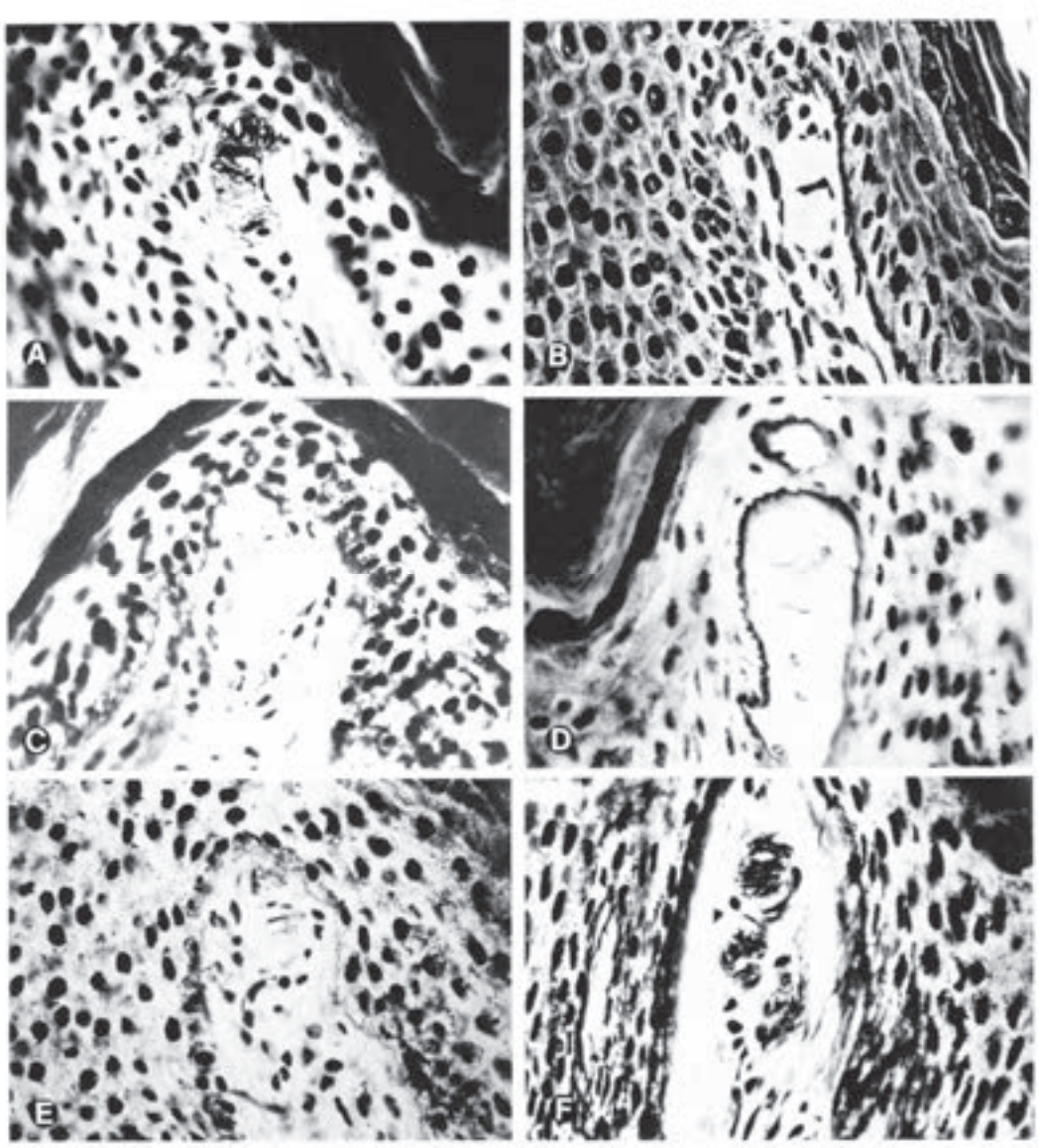

Figure 5.4. Reinnervation of denervated Meissner corpuscle. Silver stain, x160 ***A***, Normal. Other sections are the following intervals after nerve repair: ***B***, 48 hours; ***C***, 6 weeks; ***D***, 3 months; ***E***, 6 months; ***F***, 9 months. See text for description. (Reproduced with permission from A.L. Dellon: *J Hand Surg* 1:98-109, 1976.[36])

Nine Months after Nerve Suture. By both connective tissue and silver staining techniques, virtually all Meissner corpuscles appeared normal, i.e., identical with the controls (Fig. 5.3, F and 5.4, F).

About 5% of the Meissner corpuscles remained without signs of innervation, i.e., they showed progressive denervation. Whereas the control biopsies contained one Meissner corpuscle every two to three papillary ridges, the operated hand biopsies contained one Meissner corpuscle every two to six papillary ridges, i.e., the Meissner corpuscle density following nerve suture was less than or equal to but never more than the control values.

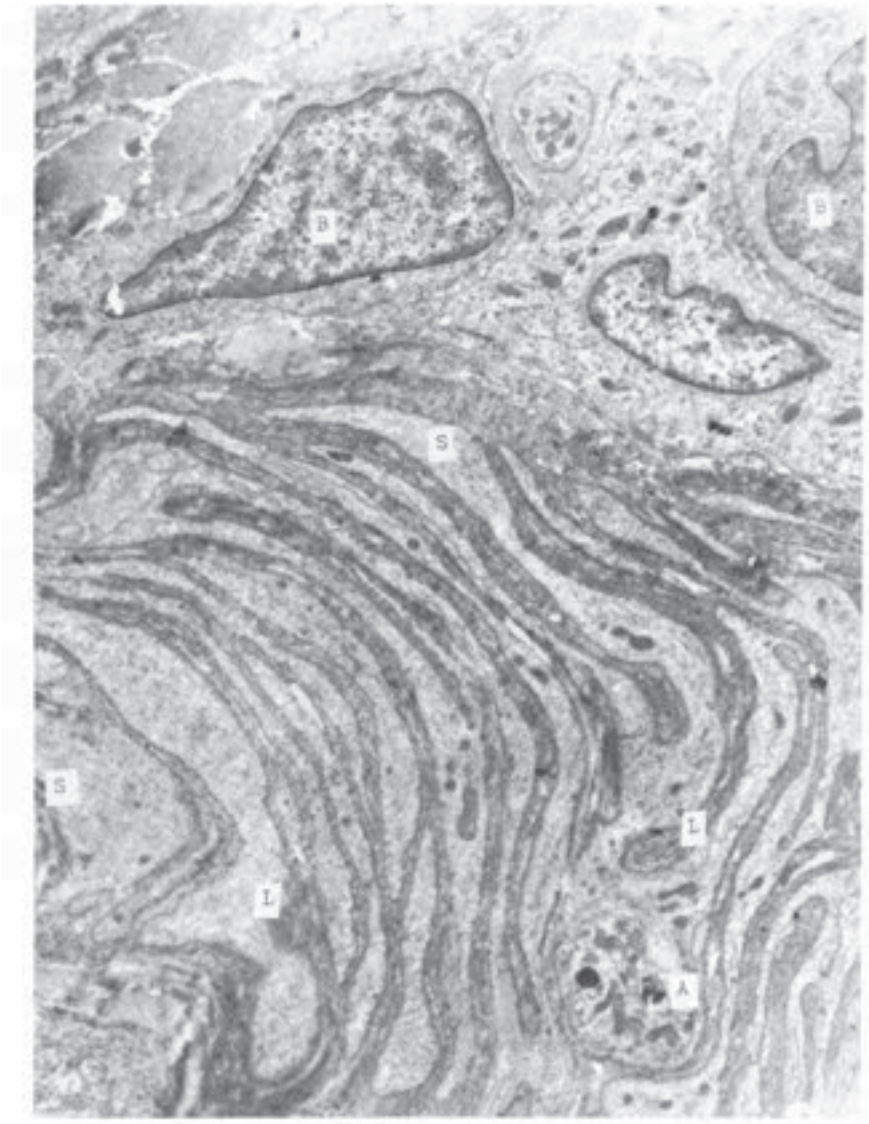

Figure 5.5 Reinnervation of denervated Meissner corpuscle. Electron micrograph, x 15,000: 3 months after nerve repair. Basal cells *(B)* are seen at top of dermal papilla. Note relative abundance of interlamellar substance *(S)* and short contracted lamellar cell processes *(L)* that characterize the degenerating corpuscle. But note the early reinnervation by the axon sprout *(A)*. (Reproduced with permission from A.L. Dellon: *J Hand Surg* 1:98-109, 1976.[36])

Electron Microscopy. Electron microscopy at 3 months after nerve repair demonstrated a degenerated Meissner corpuscle in which new axonal sprouts were seen (Fig. 5.5). At 9 months after

nerve repair, the Meissner corpuscle was indistinguishable from normal, with long, thin lamellar cell processes ensheathing thick axon terminals (Fig. 5.6).

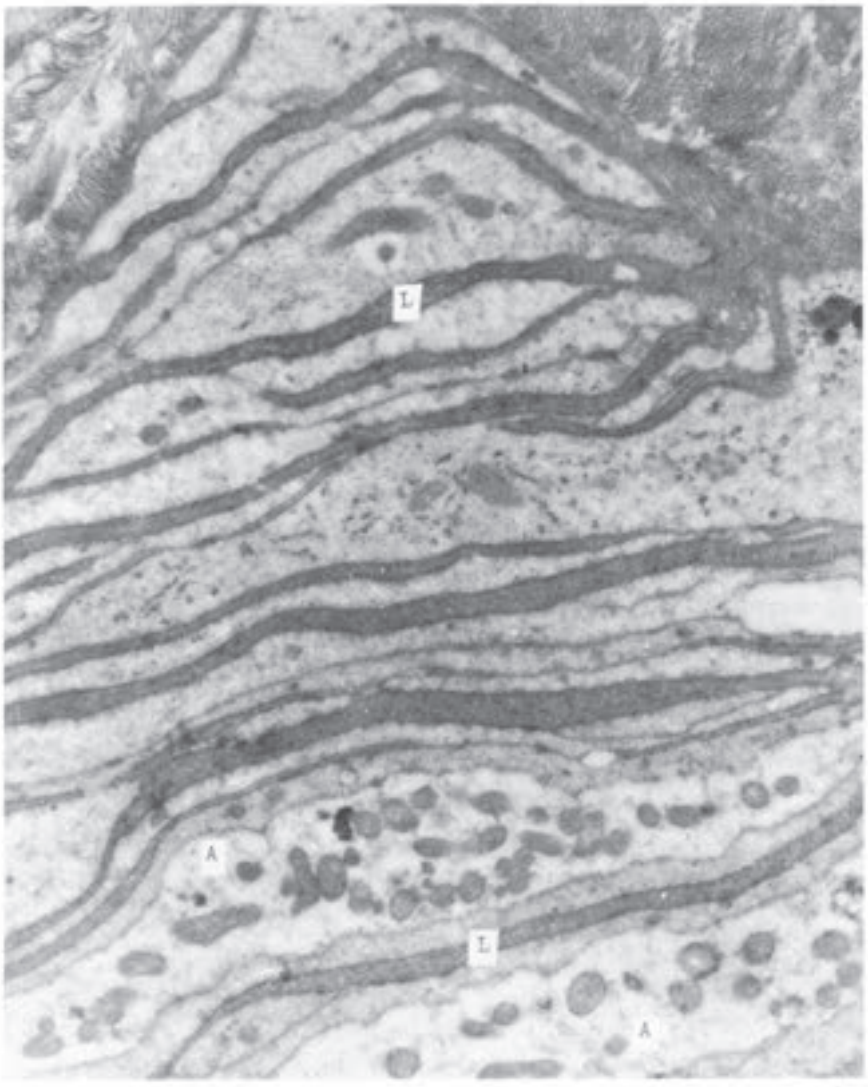

Figure 5.6. Reinnervation of denervated Meissner corpuscle. Electron microscopy, x32,000: 9 months after nerve repair. Advanced reinnervation demonstrated by thick axon terminations *(A)* being ensheathed by lamellar cell processes *(L).*

MERKEL CELL-NEURITE COMPLEX

During investigations into the function of his "touch corpuscle" in the cat, Iggo[47] observed the effect of crushing the saphenous nerve. The corpuscles degenerated progressively. By 16 to 20 days after nerve crush, axonal branches reappeared among the capillary tufts and dermal papillae that represented the former touch corpuscles. By 25 to 30 days after crush, tactile cells are present again, and by 100 days the "tactile corpuscles appeared normal." By 30 days after the crush, mechanostimulation of the corpuscles and electrical recording from the saphenous nerve demonstrated that a low threshold slowly-

adapting fiber/receptor system had been reestablished. (A low-threshold, quickly-adapting fiber/receptor system – the hair follicle – also was re-established.) This report was in the form of an abstract in the *Proceedings of the Physiological Society* in 1963 and received scant attention.

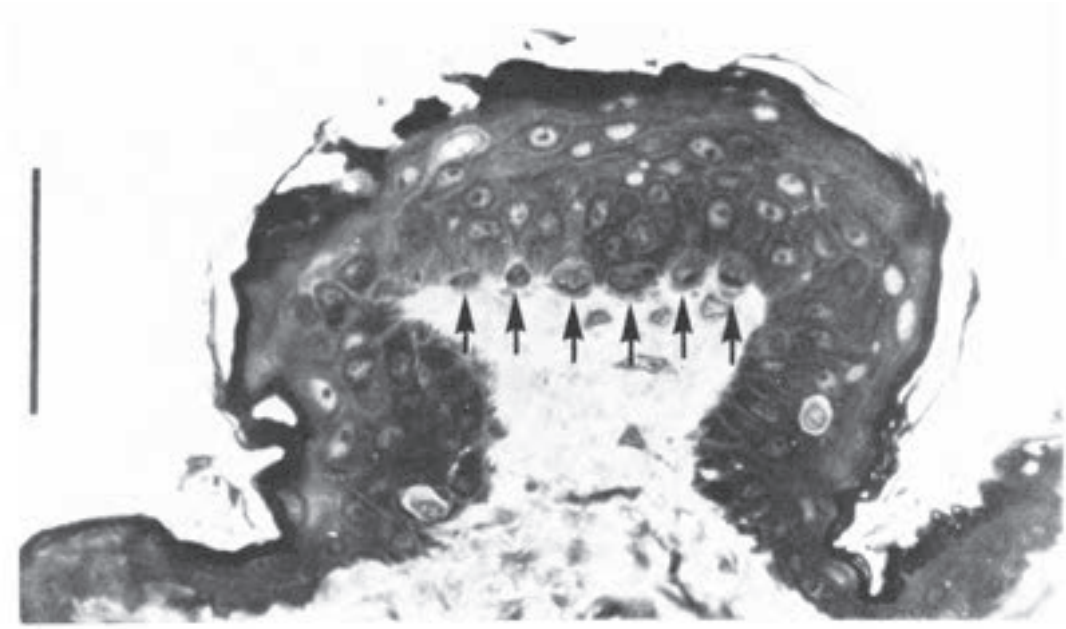

Figure 5.7. Reinnervation of denervated Merkel cell-neurite complex in the cat touch-pad. Following nerve crush, the degenerated Merkel cell-neurite complex becomes reinnervated and histologically is indistinguishable from normal (for comparison see Fig 4.7.). (Reproduced with permission from Burgess et al.: *J Physiol* 236:57-86, 1974.[48])

A decade later, Burgess and Horch et al.[48-49] reported a series of carefully controlled neurophysiological and morphological investigations into the touch dome fiber/ receptor system of the cat. Sural nerves were repaired and single unit recordings done after regeneration. These recordings were compared to the preoperative control recordings and dome population locations. Nineteen percent of control fibers were type I alpha fibers, innervating touch domes. The average fiber innervated two to four domes. Of the 445 regenerated fibers studied, just 11% were type I alpha fibers. Their mean conduction velocities were unchanged. Rates of adaption to maintained deformation were unchanged. The only difference observed was that the regenerated fiber innervated just one dome, and its peripheral receptive field, instead of being confined exclusively to the dome, extended to the skin immediately surrounding the dome[48](Fig. 5.7).

Burgess and Horch's next investigations[49] attempted to learn whether the pattern of domes following nerve repair was similar to that following nerve crush. The skin of the posterior thigh and the femoral cutaneous nerve was studied. Dome patterns were tattooed with ink under 25X magnification, and drawings made of the patterns. The femoral cutaneous nerve was electrically recorded, while this mapped area was tested to be sure no touch domes had been missed. One year later, the cats were studied

again. Each touch dome was stimulated and the femoral cutaneous nerve recorded to demonstrate that the dome was actually innervated by that nerve. Control observations on dome "stability" demonstrated 87o/o of domes were in the identical position in which they had been observed 4 months previously. When touch domes that had been tattooed directly were evaluated, a 91 to 95% "stability" of the population was found. In the nerve *crush* study, one animal, retested 689 days after nerve crush, had all femoral cutaneous domes in the original femoral cutaneous field, while all other domes were outside the field (Fig. 5.8). Following nerve transection in five animals, the areas were retested between 393 and 1010 days after the surgery. The average preoperative field had 69 domes, the average postoperative field had 46. But in one field, there were actually more domes postoperatively (50 before versus 76 after). Eliminating this animal, the average animal recovered just 51% of its domes. Only 71% of the domes present at the postoperative test, however, were innervated by the regenerated femoral cutaneous nerve! This suggested that new domes had appeared due to activity of adjacent cutaneous nerves. Many of these new, non-coincidental domes were part of a "cluster." These clustered domes were smaller, had a closer inter dome distance, and frequently the domes in the cluster were innervated by more than one nerve. These "new" domes had normal morphology by light and electron microscopy. The most recent study utilizing the cat touch dome model from the University of Utah Physiology Department, extends the analysis to the relationship of individual nerve fibers to their touch domes.[50] In the nerve crush type experiment, virtually all nerve fibers regenerated to the same two to four touch domes originally innervated (Fig. 5.9). In the nerve transection experiment, an average of only 60% of the fibers regenerated and each fiber reinnervated only half the number of previously innervated domes (Fig.5.10). The dome to fiber ratio after nerve transection dropped from 2.6 to 1.3. The overall number of reinnervated domes was 35% of the original number.

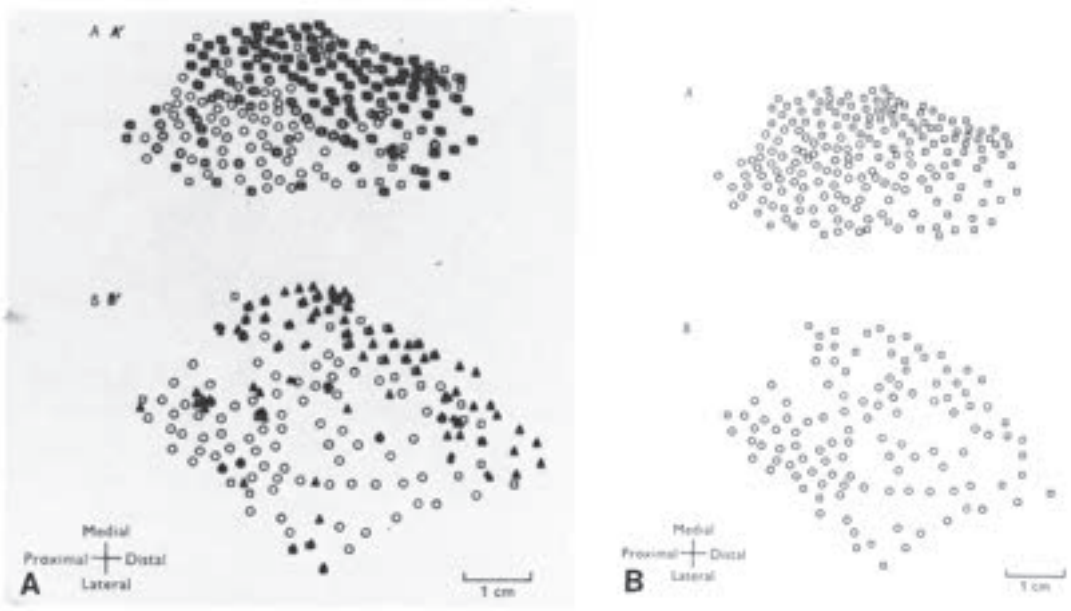

Figure 5.8 Reinnervation of denervated Merkel cell-neurite complex in the cat touch-pad. Following nerve crush, the pattern of touch domes originally present *(B)* is almost completely recovered *(A)*. in *A, A*' and *B*' is an overlay of the regenerated pattern onto the preoperative pattern of two separate cats, *A* and *B*. The nontemporal cutaneous nerve was the nerve crushed. (Reproduced with permission from Burgess et al.: *J Physiol* 236:57-86, 1974.[49])

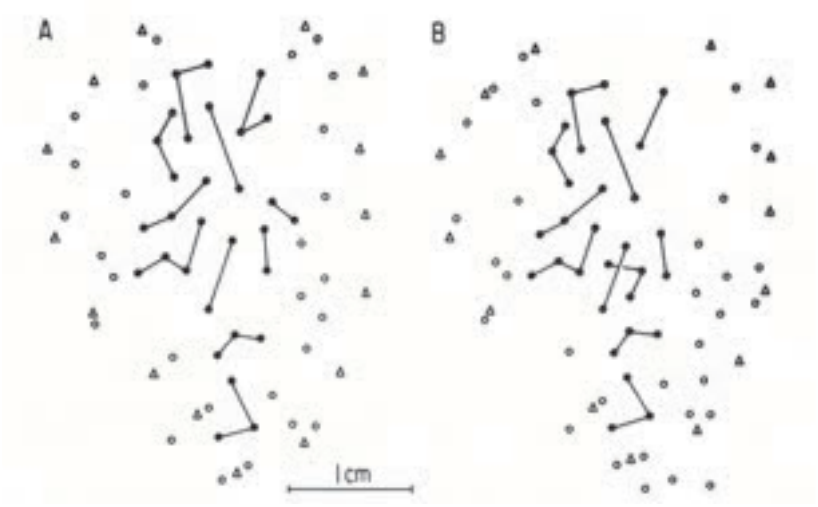

Figure 5.9. Reinnervation of denervated Merkel cell-neurite complex in the cat touch-pad. Individual nerve fiber recordings before *(A)* and after *(B)* nerve *crush* demonstrate that not only are patterns of domes almost identical postregeneration, but also the relationship of individual fibers to touch domes is almost identical post-regeneration. . (Reproduced with permission from K.Horch: *J neurophysiol* 42:1437-1449, 1979[50])

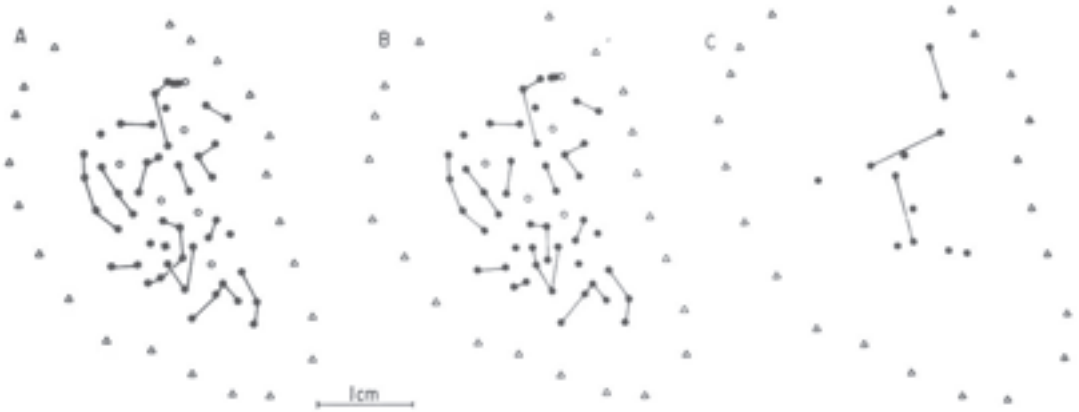

Figure 5.10. Reinnervation of denervated Merkel cell-neurite complex in the cat touch-pad. Crush versus nerve division. Note difference in number of recovered domes (just 23%) and number of fibers (40%) relating to domes in *B* versus *A* (crush versus normal) and *C* versus *A* (division versus normal). (Reproduced with permission from K.Horch: *J Neurophysiol* 42:1437-1449, 1979[50])

In summary, it is clear that *in the cat,* the Merkel cell-neurite complex recovers virtually completely after nerve crush and to a lesser extent after nerve repair. The high coincidence between the location of the recovered touch dome and its location prior to nerve injury and the relationship between the regenerating fiber after transection and the dome it reinnervates after nerve transection, suggest a specificity in the pattern of the end organ recovery. In the cat, by 1 month, the renervated dome essentially "disappears" including the apparent loss of the Merkel cell. In the nerve crush study, the 100% coincidence pattern reflects the rapid regeneration of axons to the periphery before the complete degeneration of domes and therefore 100% complete reinnervations. In the nerve transsection studies, the slowly regenerating axon has no end organ left to reinnervate. To explain the coincidence of recovered domes in this case, an "intrinsic specificity" may be hypothesized, in which only certain areas of the skin can differentiate into domes. Axons regenerate down the pre-existing Schwann tubes to the periphery area, and via some "trophic" influence this specific area is induced to form another dome. This is a borderline position between reinnervation of a denervated structure and *"de novo"* origin of the end organ. (Burgess et al.[49] rejected the *de novo* hypothesis because they found domes recovered in areas of previously excised domes following nerve transections. However, they, as Boeke before them, failed to realize that wound contracture could have pulled an area of "intrinsic specificity" into that excised area.) The alternative hypothesis, "extrinsic specificity" which Burgess et al.[49] favor, implies that a regenerating axon can induce a dome anywhere. This seems to me, at least in primate glabrous skin, to be untenable. If this hypothesis were so, the number of recovered domes in each of their animals should have been near 100%, with simply a low coincidence. They found the opposite: only half the original number of domes recovered and among these recovered domes the percent coincidence was high (average 63%). I believe these results in cat hairy skin are compatible with "intrinsic specificity."

One additional finding from Burgess et al.[49] deserves comment. Recovered touch domes were found within the peripheral field of the regenerating femoral cutaneous nerve fibers that were not innervated by the femoral cutaneous nerve. They suggested that axons "sprouted" from adjacent nerve territories to account for this. This is consistent with the earlier discussion in this chapter and previous observations.[40-42]

In primate, glabrous skin, the analog of the touch dome, the Merkel cell-neurite complex is found only beneath intermediary ridges. The time course of degeneration following nerve division in primates has not been documented, but, extrapolating from the above, the Merkel cell-neurite complex probably degenerates more quickly than the Meissner corpuscle. Therefore, it would less likely be present to be reinnervated by a regenerating axon. Since we know that constant touch is recovered following nerve repair, we may assume, in the absence of any previous documentation, that Merkel cell-neurite complexes are reinnervated after repair. We feel the "intrinsic specificity" theory is consistent with this observation, in that a regenerating slowly-adapting fiber emerges from the sub-papillary plexus and moves Hat random" toward the epidermis. Trophic factors, either from the once apparent Merkel cell, or from the axon, or both, result in the regeneration of this fiber/receptor system in the specific regions about sweat ducts in the intermediate ridge. (For further discussion of trophic neural mechanisms, refer to Werner[15] and Drachman[51] reviews.)

CROSS-REINNERVATION STUDIES

Among Cross-Reinnervation Studies the intriguing questions of sensibility is whether a nerve fiber that once innervated one type of sensory end organ could innervate a different type of sensory end organ *and* result in a functional fiber/receptor system; if it could, which function, that of the fiber or of the end organ, would result? I feel that this question has never been answered clearly. I will review the few types of studies that have been done, suggest explanations for their results based upon the neurophysiologic and morphologic principles developed so far in this text, and suggest some definitive avenues of investigation.

One of the earliest studies demonstrated an interaction between the central neuron of a regenerating axon and the distal Schwann sheath into which it was regenerating.[52] Ventral rami of spinal nerves, containing large myelinated fibers in the rabbit, were sutured distally to the anterior mesenteric nerve, which had contained small unmyelinated fibers. Small myelinated fibers appeared following the nerve repair. Suture of the ventral rami to the greater sphlanic nerve, which had contained small myelinated fibers, resulted in regenerating axons of intermediate thickness and myelinated. Thus, the neuron and its regenerating axon could induce myelination by the Schwann cells distally and even cause some enlargement of the endoneural sheath, while the sheath, in general, did restrict regenerating axon

diameter below normal. The first clinical experiment was war-inspired and involved transferring the proximal radial sensory nerve into the distal median nerve at the level of the wrist for irreparable median nerve loss[53] Turnbull[53] reported four clinical cases, three of which were nerves repaired by the fibrin clot technique of Tarlov. The patients had their final reported evaluation at 16, 29, 34, and 52 months, respectively, after nerve transfer. All regained the perception of pain, temperature, and sudomotor function (sweating). The two patients followed the least amount of time could not perceive "touch." In alt point localization was poor. In all, most stimuli were interpreted as being from the radial innervated area, although some central transfer had occurred. Recently, Chacha et al[54] reported results of this operation in six monkeys: two had the superficial radial sensory, two had dorsal ulnar sensory, and two had both nerves transferred into the distal median nerve in otherwise deafferented hands. At 3 weeks, the animals' median nerves and thumb and index fingertips were biopsied. They were stained with specific and nonspecific cholinesterase, as well as silver staining. Reinnervated Meissner corpuscles were observed and their cholinesterase staining reaction (specific and nonspecific) were normal. Reinnervation occurred in the two monkeys in whom both nerves were transferred into the distal median nerve. No observations were made on Merkel cell-neurite complexes, Pacinian corpuscles, or dermal nerve networks. No single unit nerve recordings were done.

One of the most frequently cited references is Lowenstein's[44] in which the proximal segment of the greater sphlanic nerve of the cat was "united" with the distal segment of a transected inferior mesenteric nerve in the cat. The "autonomic nerve" regenerated distally along the mesenteric axonal sheaths and subsequent histologic evaluation of the Pacinian corpuscles demonstrated that about one third had been reinnervated. These corpuscles, when given mechanostimulation, were demonstrated by single unit neurophysiologic analysis to function like the normally innervated Pacinian corpuscle.

More recently, Paul, Merzenich, and Goodman[55 56] have reported a series of studies in which the brain's somatosensory area, the postcentral gyrus, was mapped in terms not only of individual finger-area representation but also of slowly- and quickly-adapting nerve fiber/receptor systems in the monkey. A duplicate hand representation (as discussed in more detail in Chapter 3) was found (Fig. 5.11). One area (Brodmann's area 1) on the rostral surface of the postcentral gyrus had very few slowly adapting fiber/receptor spots (5%), whereas the other area (Bradmann's area 3) on the posterior bank of the central sulcus had a much higher percentage (56%) of these. In six monkeys, then, median and ulnar nerves were transected, and sutured, to their own respective ends, utilizing an 8-0 nylon, microsurgical (presumably epineural) repair. Although not a cross-union of nerves as described above, regenerating median (for example) axons did regenerate down a significant number of different endometrial sheaths. Cortical mapping after nerve regeneration demonstrated a significant number of multiple field responses, not seen in the control hemispheres (Fig. 5.12). Thus, there were central neurons following nerve regeneration that

could be stimulated by more than one peripheral receptive field (heterogenous submodalities). This mixed input was presumed due to "cross regeneration at the periphery." Of note is the greater incidence of multiple field responses in area 1 (rostral surface where 95% of responses are normally quickly-adapting) than in area 3, 31% versus 11%. There was also an absolute decrease in the number of slowly-adapting responses in area 3 from 56 to 28% while there was no significant change in percentage of quickly-adapting responses in area 1.

The most recent approach to cross-regeneration again comes not from suturing different peripheral nerves together but from comparing the neurophysiologic properties of regenerating fiber groups. The data of Dykes and Terzis[57] suggest that following nerve crush, a regenerating axon, by means of its multiple sprouts, may still enter two separate peripheral receptive fields, each of which has a different response characteristic (see Fig.12.12). This peripheral nerve single unit data is exactly analogous to that described by Paul et al.[56] as central multiple field responses of the heterogenous submodality type.

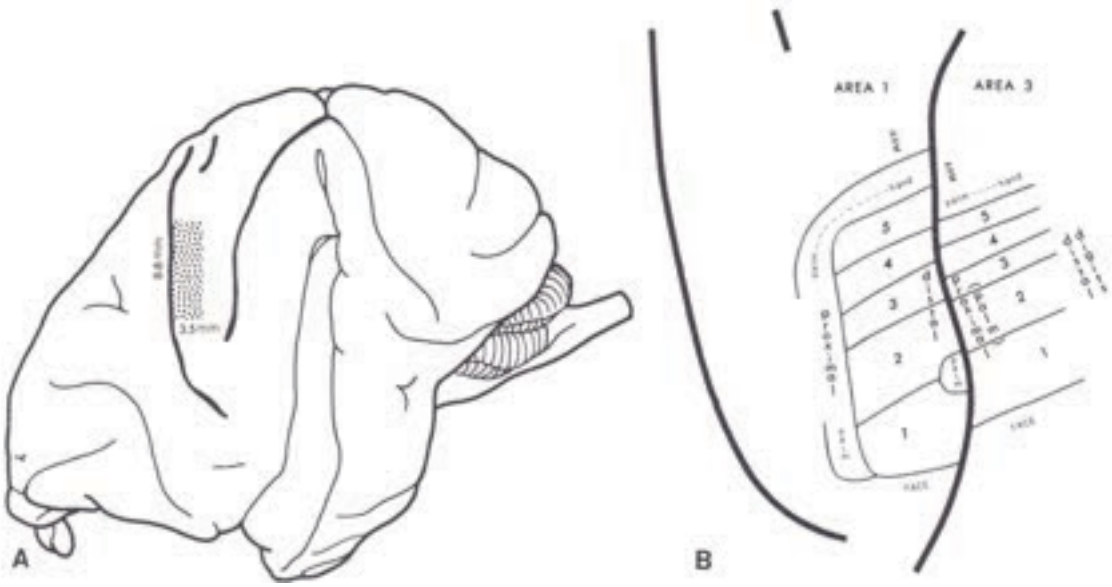

Figure 5.11 Dual representation of hand in sensory cortex. *A*, The sensory cortex, the postcentral gyrus, is posterior to the dark line, the central sulcus. The area of the gyrus within the sulcus is Brodmann's area 1. *B*. With the sulcus surface imagined as opened p area 1 and area 3 are seen as dual hand areas. Area 1, however, was found to have mostly slowly-adapting receptors (56%). (Reproduced with permission from R. L. Paul et al.: *Brain Res* 36:229-249, 1972[55])

Other examples of cross-innervation include the classic taste bud studies. Cranial nerves carrying gustatory fibers could induce taste buds following cross-innervation, whereas nongustatory cranial nerves, autonomic nerves, and somatic sensory or motor nerves could not.[18, 58] While these studies seem to demonstrate the absolute requirement of the specific axon, tongue germinal epithelium will develop taste buds when transplanted to the eye's anterior chamber.[59] McLachlean, et al.[60] noted that denervated

skeletal muscle is reinnervated at the site of the old (degenerated), motor end-plates. Bennett et al.[61] pursued this work using avian muscle. The fast muscle fibers were associated with "en grappe" type endings at the motor end-plates, while slow muscle fibers were associated with "en plaque" type. In the crossed nerve studies, regenerated fast muscle fibers grew into the slow muscle and formed "en plaque" type endings. Regenerating slow muscle nerve fibers grew into fast muscle and "en grappe" endings were found.

We may now try to infer the answers to the questions (1) can, for example, a regenerating axon from a slowly-adapting fiber/ receptor system reinnervate a different type of receptor, for example, a Meissner corpuscle, and, if it can, (2) will it function as a slowly- or as a quickly-adapting fiber/receptor system? The studies reviewed suggest that for the fast/slow muscle groups, for the myelinated/ unmyelinated axons regenerating into distal unmyelinated/myelinated sheaths and for taste bud systems, there is a mutual influencing of the cross-innervating structures. Taken together, these studies suggest that a regenerating axon can reinnervate a different type of end organ. The results of the studies on response characteristics of regenerating fiber populations and on cortical neuron responses after peripheral nerve regeneration suggest that the reinnervated end organs that were cross-innervated do function. I interpret the available data to mean that the function is determined by the end organ's original function.

The results of many of the studies referred to earlier may be better explained or reinterpreted by applying the neurophysiological correlates developed previously in this text. For example, Lowenstein's cross-innervation study is usually quoted as demonstrating that a receptor can be reinnervated by a different type of axon and yet function without change.[44] Actually, only one-third of the Pacinian corpuscles were reinnervated by the nerve that originally innervated the bladder. Was this because the results of the nerve "union" were poor, allowing only one-third of the axons to regenerate successfully? Alternatively, we know that the bladder innervation contains fibers that respond to stretch, relay muscle tone, etc. Is it not possible that some of these fibers are quickly-adapting and that these fibers reinnervated the Pacinian corpuscles and reproduced the functioning fiber/receptor system? If so, then Lowenstein's study did not demonstrate what it is usually cited as having shown.

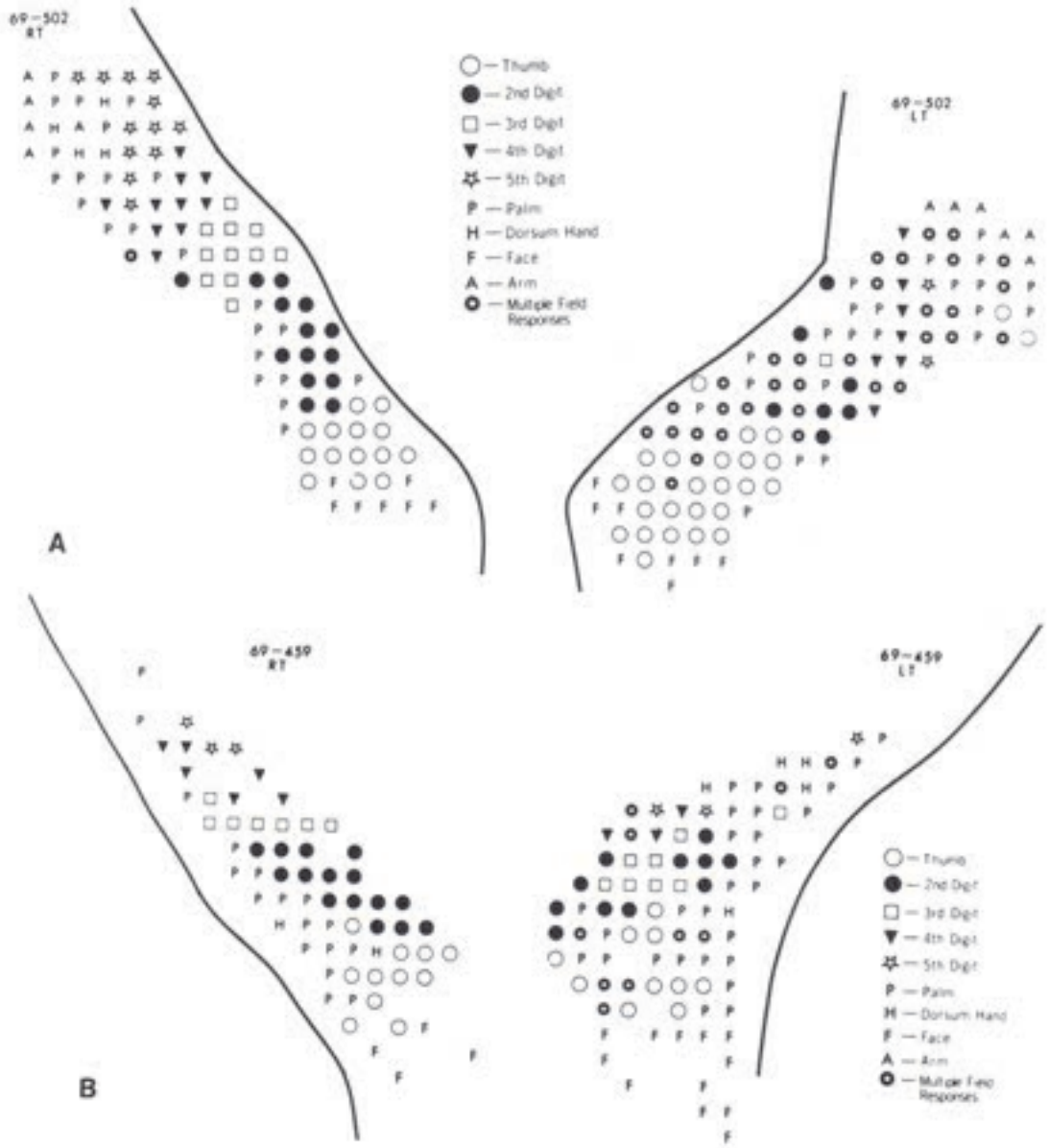

Figure 5-12 Central manifestation of cross-regeneration of peripheral nerve fibers. Median and ulnar nerves were transected and repaired. Central responses were later recorded by stimulating peripheral receptive fields. In both Brodmann's area 1 *(A)* and area 3 *(B)* the experimental hemispheric recordings (*right side* of diagram) demonstrated cortical neurons that responded to more than one peripheral field and were of both the slowly- and quickly-adapting response type. (Reproduced with permission from R. L. Paul et al.: *Brain Res* 39:1-10, 1972.[56])

The clinical cross-innervation studies of radial into median nerve showed overall poor recovery of functional sensation. Protective sensation was recovered. The relatively few fibers in the radial sensory branches were distributed to the entire median nerve territory. This had to result in too low an innervation density for tactile localization, no less discrimination. The free nerve endings, subserving pain and temperature, successfully reached the periphery, and needing no end organ, re-established protective sensation, albeit with false localization (stimuli referred back to the dorsoradial skin). The experimental

cross-innervation studies of radial plus dorsal ulnar sensory into median provided a greater number of regenerating axons, and histologic confirmation of a sensory end organ reinnervation was achieved. The functional significance of this is unknown because the cholinesterase series of staining techniques is unrelated to sensory perception.

There are examples, however, of cross-finger flaps transferring dorsal skin, recovering good functional sensation when transferred to the (volar) fingertip.[55] How can this be explained? I believe that "hairy skin" has receptors (the hair follicles) that can be reinnervated by glabrous skin's quickly-adapting fibers and Haarscheibe, or follicles with a Merkel cell-neurite complex, that can be reinnervated by glabrous skin's slowlyadapting fibers to form functional fiber/receptor systems. Conversely, I believe that the quickly-adapting fibers that innervate hair follicles, and the slowly-adapting fibers that innervate Haarscheibe (or Merkel cell-neurite complexes about hair follicles) in the hairy skin, could reinnervate Pacinian/ Meissner corpuscles or Merkel cell-neurite complexes, respectively, in the cross-innervation radial-to-median studies.

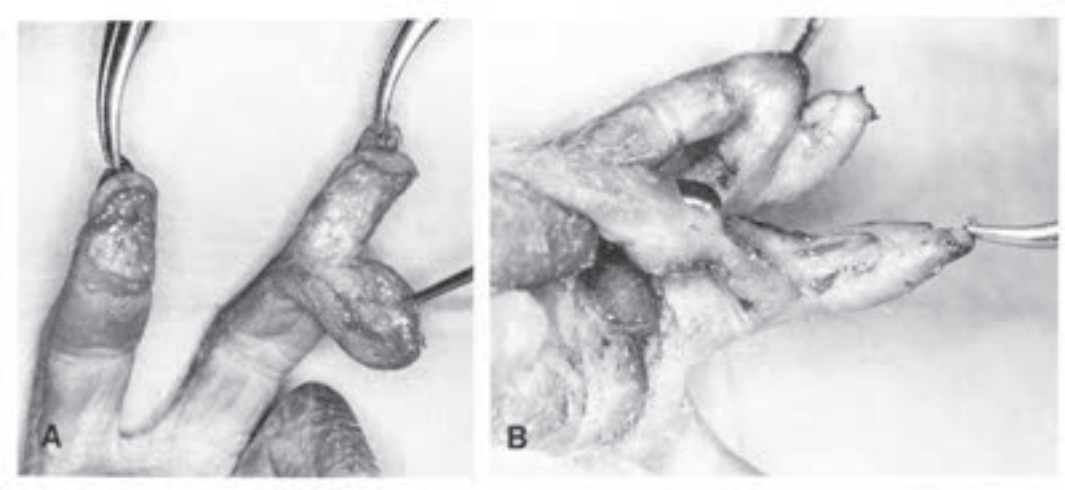

Figure 5-13 Monkey skin graft/flap study: *A.* Volar full thickness skin grafts were exchanged between the thumb and index finger. A hypothenar flap was done on the little finger. *B.* Dorsal view of the dorsal cross-finger flap from the middle finger to the ring fingertip. There is a forearm skin graft on the middle fingertip and dorsal flap donor site.

The radial nerve to median nerve cross-innervation provides the perfect model for experimental investigation of these problems. I suggest that all radial sensory fibers be sutured to the volar digital nerves to a single finger. This maximizes the possibility that the fibers of the sensory radial nerve, which are- fewer than the total number of sensory fibers in the median nerve, will have an innervation density sufficient to reinnervate the dense population of sensory receptors in the fingertip. Prior to fingertip biopsy, and obtaining light and electromicroscopy, single unit nerve recordings can be obtained from the sensory radial nerve at the wrist. This regenerated fiber population can be compared to the normal radial

sensory and median sensory population. Peripheral rnechanostimulation should incorporate moving and constant touch, as well as vibratory stimuli.

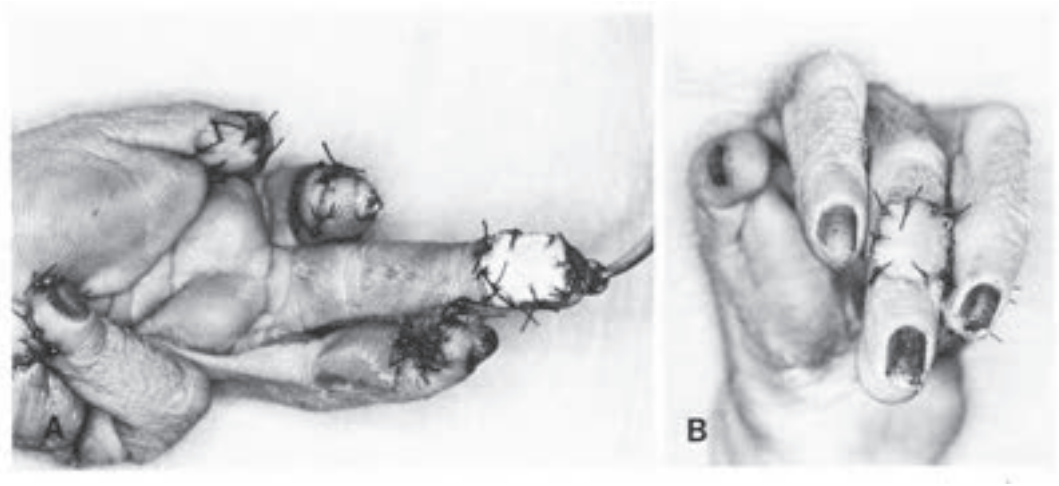

Figure 5-14 Monkey skin graft/flap study. *A*. Volar cross-finger flaps were done from the middle finger to the index fingertip, and from the ring finger to the thumb. *B*. Completed procedure showing also the hypothenar flap to the little finger.

Figure 5-15 Monkey skin graft/flap study. The monkey's hand was protected with a cast of acrylic poured over plaster (Reproduced with permission from A. L. Dellon and R. E. Terrill: *Hand* 8:165-166, 1975.[71]

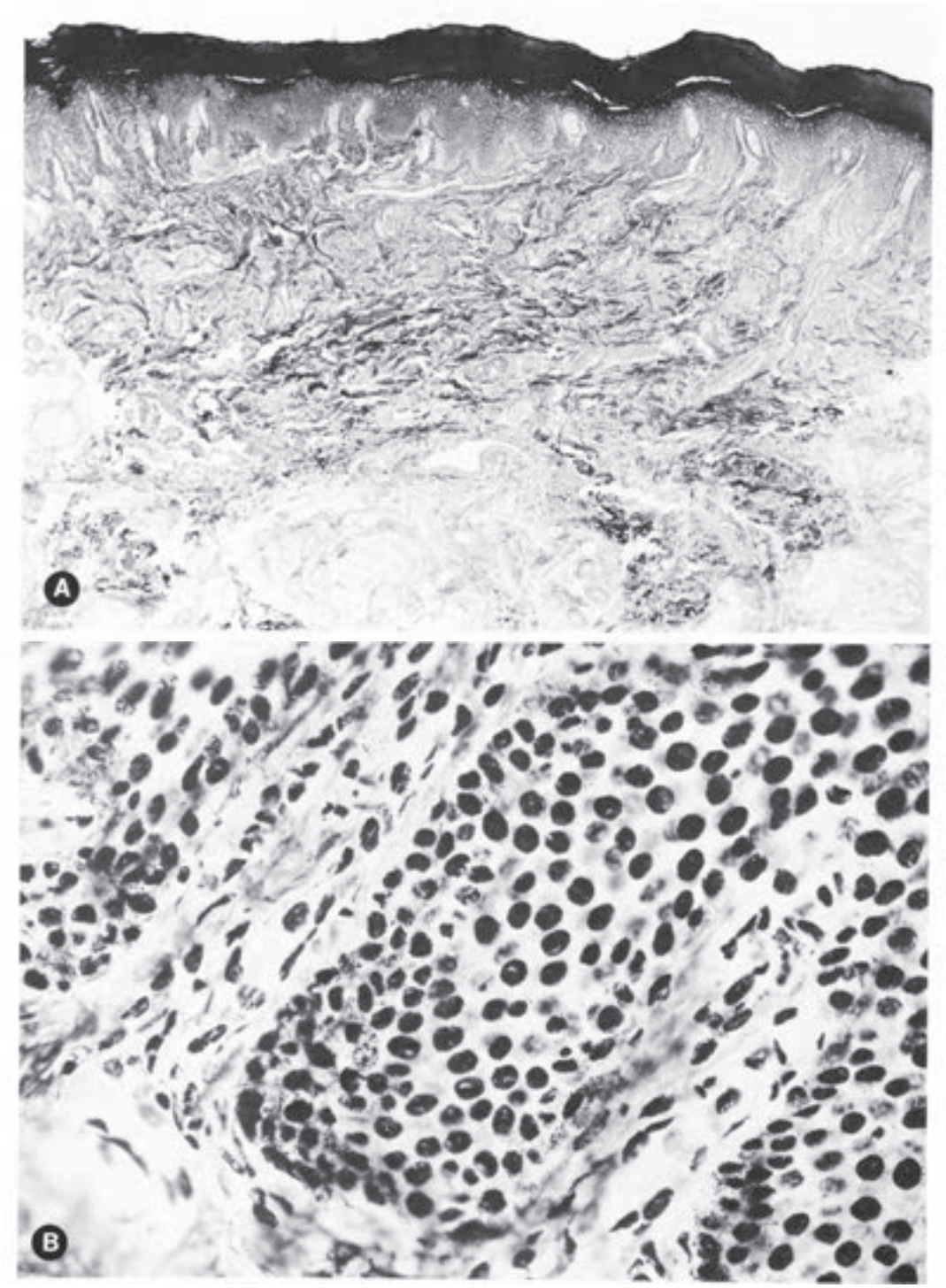

Figure 5-16 Monkey skin graft/flap study. Sensory end organs were best preserved in flaps where they were protected relatively from ischemia. *A*. Note row of innervated Meissner corpuscles (Silver stain, x16) *B.* Note early reinnervation of two Meissner corpuscles and Merkel cell-neurite complex (Silver stain, x300) both are from a volar cross-finger flap in monkey biopsied 4 months after flap inset.

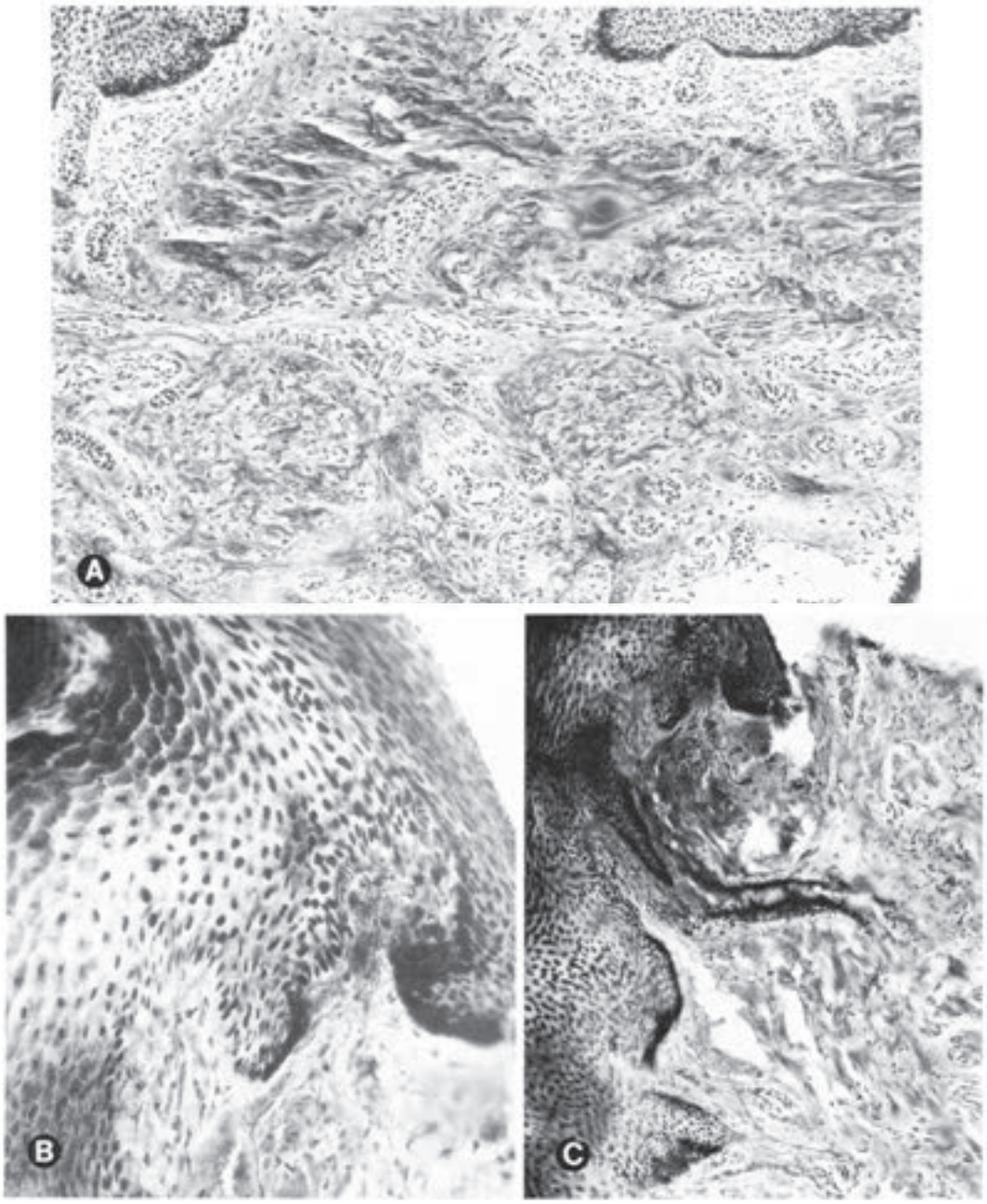

Figure 5-17 Monkey skin graft/flap study: The volar (glabrous) full thickness skin graft had excellent reinnervation of the dermal nerve networks (*A* and C),but the ischemic period before graft "take" resulted in significant, probably irreversible, loss of end organs. Note the "ghost" Pacinian *(A)* and "ghost" Meissner corpuscle *(B)*. There was partial reinnervation of some remaining Meissner corpuscles in these biopsies taken 4 months after the graft *(C)* (Silver stain, x150).

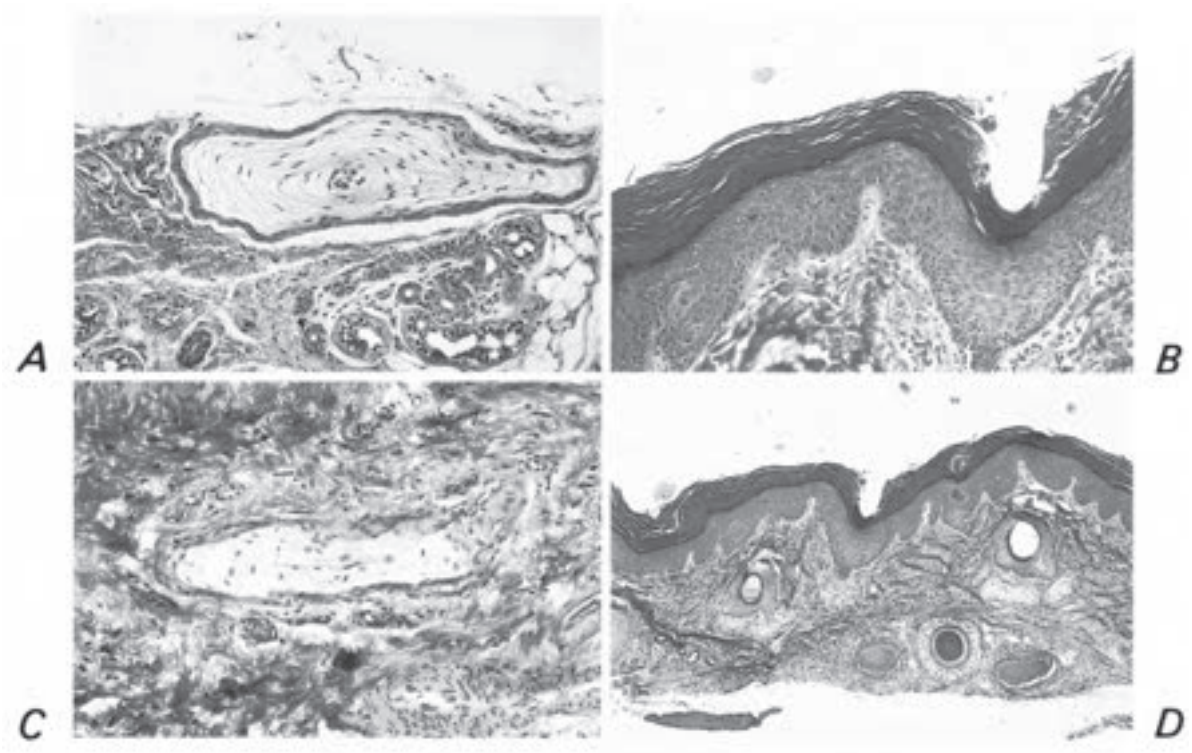

Figure 5.18. Monkey skin graft/flap study: Dorsal finger skin contains Meissner-like corpuscles and hair touches (Trichrome stain, x64)

CLINICAL IMPLICATIONS

What is the ideal soft tissue resurfacing material for the fingertip? The results of this review suggest the following approach to this problem. Since normal fingertip sensory function requires the presence of peripheral mechanoreceptors capable of high fidelity transduction of sensory stimuli, it becomes clear that sensory axons must not only regenerate in maximum numbers into the donor tissue but also must reinnervate a suitable mechanoreceptor. There is no evidence that human mechanoreceptors, e.g., Meissner corpuscles, regenerate *de novo* after an axon regenerates into the dermis. To provide optimal potential for sensory recovery, the before, it follows that the donor skin must contain the suitable mechanoreceptors. This implies that skin most resembling fingertip skin should be used. Such skin, i.e., hairless (glabrous) skin containing papillary ridges, is found only on the palm of the hand and fingertip and the sole of the foot and toes. A close approximation of this skin is dorsal fingertip skin which has modified papillary ridges and contains an occasional Meissner corpuscle.[63, 64]

I propose the following hypothesis: The highest potential for recovery of normal sensation is provided by skin with papillary ridges and the highest density of mechanoreceptors, i.e., distal glabrous skin. This hypothesis can be tested indirectly by reviewing the reported clinical experience with the treatment of fingertip injuries. The poorest recovery of sensation is found with distant pedicle flaps, e.g., abdominal and pectoral donor sites. Perhaps slightly better, but still poor, sensation is recovered when

forearm or thigh thick split-thickness grafts are used. The best results are achieved with local pedicle flaps, e.g., thenar, hypothenar, and dorsal cross-finger flaps.[33, 65-67] A recent report using dorsal cross-finger flaps combined with a program of sensory re-education (see Chapter 12) has resulted in recovery of virtually normal sensation subjectively and by two point discrimination testing. With smaller pulp losses, of course, virtually normal sensation has been recovered using split thickness skin grafts[68] or conservative management.[69] In these cases, the normal skin surrounding the injury ultimately becomes the re-surfacing "donor" tissue, by wound contracture is the latter case and by "graft" contraction in the former. The myofibroblast is probably at the "bottom" of both these processes and the distinction is probably already archaic.

Further support of the hypothesis that the degree of functional sensation recovered is proportional to the density of mechanoreceptors in the donor tissue comes from Kleinert's study.[62] With dorsal cross-finger flaps, 90% of his youngest patient group (6 to 13 years old) recovered less than 6-mm two-point discrimination in contrast to just 40% of his oldest patient group (greater than 40 years old). I presume it is more than coincidence that this result parallels the decline in sensory end organ density with increasing age: the Meissner index (density of Meissner corpuscles) in the fingertip is more than twice as high in a population less than 15 years old than it is in a population greater than 40 years old.[70]

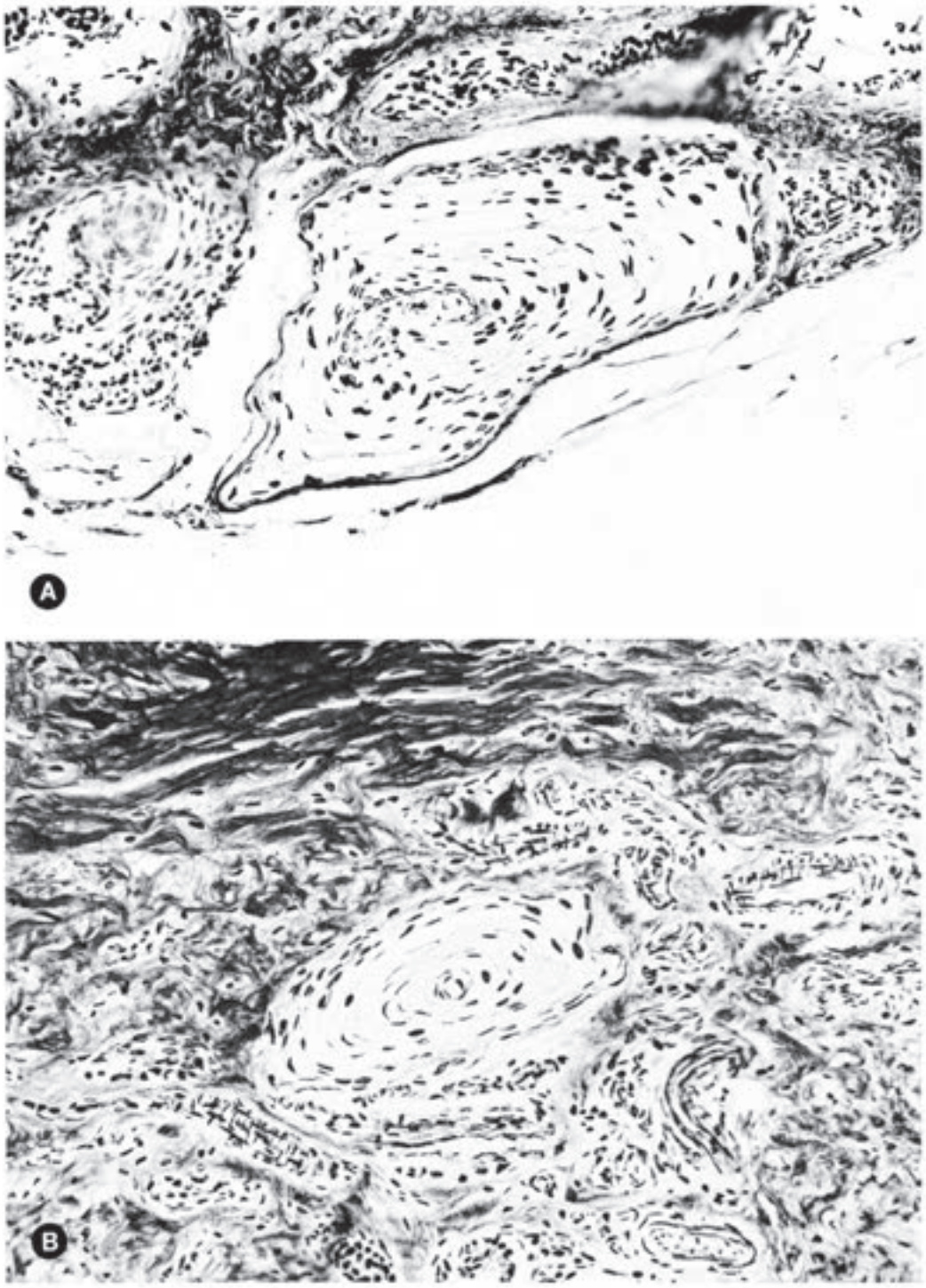

Figure 5.19 Monkey skin graft/flap study: This partially reinnervated specimen permits statement that the pink component of the trichrome stains axoplasm. Reinnervated *(A)* and noninnervated *(B)* Pacinian corpuscle (*A*, Silver stain; *B* trichrome stain; x 64)

In 1975, while a Clinical Associate in the Surgery Branch of the National Cancer Institute, National Institutes of Health, I designed a series of grafts and flaps in monkeys to test the effect of

ischemia and axonal regeneration upon the sensory end organ population. The study has remained unpublished because time constraints have prevented the necessary detailed evaluation of the thousands of serial sections. In two monkeys, the operations consisted of: (1) full thickness volar skin grafts switched between thumb and index finger; (2) dorsal cross-finger flap from middle finger to ring fingertip; (3) hypothenar flap to little finger; and (4) forearm skin grafts to flap donor site on middle finger dorsum and to middle fingertip (Fig. 5.13). In two more monkeys, the operations were: (1) volar cross-finger flaps from middle to index finger and ring finger to thumb, and (2) hypothenar flap to little finger (Fig. 5.14). Flaps were' divided and inset at 3 weeks and were protected until that time in acrylic casts[71] (Fig. 5.15). This study demonstrated reinnervation of the dermal nerve networks in both grafts and flaps (Figs. 5.16 and 5.17). No Meissner or Pacinian corpuscles *or* Merkel cell-neurite complexes were identified in forearm skin grafted to the fingertip, although hair follicles were reinnervated well. None of these sensory end organs were identified in dorsal finger skin transferred to the fingertip, although hair follicles were reinnervated. An occasional Meissner-like structure was identified as well as subpapillary plexus nerves in search of end organs beneath the hairy skin epidermal ridges (Fig. 5.18). Perhaps of greatest consequence were the two following observations: (1) the volar cross-finger flap was the best reinnervated, with the best preservation of pre-existing sensory end organs (Fig. 5.16); and (2) the glabrous skin grafts demonstrated ischemic damage to the sensory corpuscles (ghost Meissner and Pacinian corpuscles) with poorer reinnervation than the volar cross-finger flap (Fig. 5.17) .One partially reinnervated, serially sectioned specimen allowed the following confirmation of my earlier suspicion[36, 72] that the pink-staining component in the trichrome stain identifies axoplasm (Fig. 5.19).

In summary, the preliminary results of this monkey skin graft/flap study demonstrated that skin containing sensory end organs is the best resurfacing material, and that a local flap of this tissue permits greater end organ survival than a full-thickness graft, presumably because the end organs are relatively protected from ischemia. Applications of these concepts are illustrated at the end of Chapter12.

References:

1. Remensnyder JP: Physiology of nerve healing and nerve grafts, in Krizek TJ, Hoopes JE (eds): *Symposium on Basic Science in Plastic Surgery*. Saint Louis: CV Mosby, 1976, Ch 24.
2. Seddon, H: *Surgical Disorders of the Peripheral Nerves*. Baltimore; Williams & Wilkins, 1972 Ch 2.
3. Sunderland S: *Nerves and Nerve Injuries*, ed 2. Edinburgh: Churchill-Livingstone, 1978, Ch 8.
4. Sunderland S: *Nerves and Nerve Injuries*, ed Z. Edinburgh: Churchill Livingston, 1978, Ch 23, 26.
5. Sunderland S: *Nerves and Nerve Injuries*, ed 2. Edinburgh: Churchill Livingstone, 1978 Ch 31, 32.
6. Samders FK, Young JZ: The role of the peripheral stump in the control of fibre diameter in generating nerves. J Physiol 103:119-136, 1944.
7. Aitkens JT, Sharman M, Young JZ: Maturation of regenerating nerve fibres with various peripheral connections. J Anat 87:7-22, 1947.
8. Sanders FK, Young JZ: The influence of peripheral connections on the diameter of regenerating nerve fibres. J Exp Biol 22:203-272, 1947.

9. Boeke J: *The Problems of Nervous Anatomy*. London: Oxford University Press, 1940, pp 72-44.
10. Boeke J: On the regeneration of sensitive end-corpuscles after section of the nerve. K Acad van Wetenschoppen (Amsterdam) 25:319-323, 1922.
11. Boeke J, Dijkstra C: De- and regeneration of sensible end-corpuscles in the duck's bill (corpuscles of Crandry and Herbst) after the cutting of the nerve, the removing of the entire skin or the transplantation of the skin in another region. K Acad van Wetenschoppen (Amsterdam) 35:1114-1119, 1932.
12. Miller SH, Rusennas I: Changes in primate Pacinian corpuscles following volar pad excision and skin grafting. Plast Reconstr Surg 57:627-636, 1976.
13. Dellon AL: On changes in primate Pacinian corpuscles after volar pad excision and skin grafting. Plast Reconstr Surg 58:614-615, 1976.
14. Marshall Al (ed): *Biology & Comparative Physiology of Birds*. New York: Academic Press, 1960, pp 33, 44, 210.
15. Werner JK: Trophic influences of nerves on the development and maintenance of sensory receptors. Am J Phys Med 53:127-142, 1974.
16. Farbman AI: Electron microscopic study of the developing taste bud in rat fungiform papillae. Dev Biol 11:110-135, 1965.
17. Biedler LM, Nejad MS, Smallman RL, et al: Rat taste cell proliferation. Fed Proc 19:302, 1960.
18. Guth L: Taste buds in the rat's circumallate papillae after reinnervation for the glossopharyngeal, vagus, and hypoglossal nerve. Anat Rec 130:25-37, 1958.
19. Fujimoto S, Murray RG: Fine structure of degeneration and regeneration in denervated rabbit vallate taste buds. Anat Rec 168; 393-414, 1970.
20. Jabaley ME: Recovery of sensation in flaps and skin, in Tubiana R (ed): The Hand. Philadelphia: WB Saunders, 1981.
21. Terzis JK: Functional aspects of reinnervation of free skin grafts. Plast Reconstr Surg 58:142-156, 1976.
22. Kredel FE, Evans JP: Recovery of sensation in denervated pedicle and free skin grafts. Arch Neurol Psychiatry 29:1203-1221, 1933.
23. Davis L: The return of sensation to the transplanted skin. Surg Gynecol Obstet 59:533-543, 1934.
24. Davis, JS, Kitlowski EA: Regeneration of nerves in skin grafts and skin flaps. Am J Surg 24:501-545, 1934
25. McCarroll HR: The regeneration of sensation in transplanted skin. Ann Surg 108:309-320, 1938.
26. Lofgren L: Recovery of nervous function in skin transplants with special reference to the sympathetic functions. Acta Chir Scand 102:229-239, 1952.
27. Reid DAC: Experience of a hand surgery service. Br J Plast Surg 9:11-16, 1956.
28. Barclay TL: The late results of fingertip injuries. Br J Plast Surg 8:38-43, 1955.
29. Adeymo O, Wyburn GM: Innervation of skin grafts. Transplant Bull 4:152-153, 1957.
30. Ponten B: Grafted skin: Observation on innervation and other qualities. Acta Chir Scand [Suppl] 257:1- 78, 1960.
31. Fitzgerald MJT, Martin F, Paletta FX: Innervation of skin grafts. Surg Gynecol Obstet 124:808-872,1967.
32. Hutchinson J, Tough JS, Wynburn GM: Regeneration of sensation in graft skin. Br J Plast Surg 2:82-94,1949.
33. Mannerfelt L: Evaluation of functional sensation of skin grafts in the hand area. Br J Plast Surg 15:136-154,1962.
34. Moberg E: Objective methods of determining the functional value of sensibility in the hand. J Bone Joint Surg [Suppl] 40-B:454, 1958.
35. Ridley A: A biopsy study of the innervation of forearm skin grafted to the fingertip. Brain 93:547-554,1970.
36. Dellon AL: Reinnervation of denervated Meissner corpuscles: A sequential histological study in the monkey following fascicular nerve repair. J Hand Surg 1:98-109, 1976.

37. Orgel M, Aguayo A. Williams HB: Sensory nerve regeneration: An experimental study of skin grafts in the rabbit. J Anat 111:121-135,1972.
38. Celli L, Caroli A: La ripresa della sensibilita nei trapianti, ed. innesti cutanei della mano. Riv Chir Mano 8:23-62,1970.
39. Terui A: Reinnervation in the free skin graft. Jpn J Plast Reconstr Surg 18:392-399, 1975.
40. Weddell G, Guttmann L, Guttmann E: The local extension of nerve fibres into denervated areas of skin. J Neurol Neurosurg Phychiatry 4:206-225, 1941.
41. Hoffman H: Local re-innervation in partially denervated muscle: A histo-physiological study. Aust J Exp Biol Med Sci 28:384-398,1950.
42. Livingstone WK: Evidence of active invasion of denervated areas by sensory fibers from neighboring nerves in man. J Neurosurg 4:140-145,1947.
43. Wong WC, Kangasuntheram R: Early and late effects of median nerve injury on Meissner's and Pacinian corpuscles of the hand of the Macaque. J Anat 109:135-142, 1971.
44. Lowenstein WR: Development of a receptor on a foreign nerve fiber in a Pacinian corpuscle. Science 177:712-715, 1972.
45. Krishnamurti A, Kanagasuntheram R, Vij S: Failure of reinnervation of Pacinian corpuscle after nerve crush: An electron microscopic study. Acta Neuropathol (Berl) 23:338-341, 1973.
46. Jabaley ME, Burns JE, Orcutt BS, et al: Comparison of histologic and functional recovery after peripheral nerve repair. J Hand Surg 1:119-130, 1976.
47. Brown AG, Iggo A: The structure and function of cutaneous "touch corpuscles" after nerve crush. J Physiol 165;28P-29P, 1963.
48. Burgess PR, Horch KW: Specific regeneration of cutaneous fibers in the cat. J Neurophysiol 36:101-114,1973.
49. Burgess PR, English KB, Horch KW, et al: Patterning in the regeneration of type I cutaneous receptors. J Physiol 236:57-86, 1974.
50. Horch K; Guidance of regrowing sensory axons after cutaneous nerve lesions in the cat. J Neurophysiol 42:1437-1449, 1979.
51. Drachman DB (ed): *Trophic Functions of the Neuron*. New York: New York Academy of Sciences. 1974.
52. Simpson SA, Young JZ: Regeneration of fiber diameter after cross-unions of visceral and somatic nerves. J Anat 79:48-64, 1944.
53. Turnbull F: Radial-medial anastamosis. J Neurosurg 5:562-566, 1948.
54. Chacha PB, Krishnamurti A, Soin K: Experimental sensory reinnervation of the median nerve by nerve transfers in monkeys. J Bone Joint Surg 59A:386-390, 1977.
55. Paul RL, Merzenich M, Goodman H: Representation of slowly- and rapidly-adapting cutaneous mechanoreceptors of the hand in Brodmann's areas 3 and 1 of Macaca mulatto. Brain Res 36:229-249, 1972.
56. Paul RL, Goodman H, Merzenich M: Alterations in mechanoreceptor input to Brodmann's areas 1 and 3 of the post-central hand area of Macaca mulatto after nerve section and regeneration. Brain Res 39: 1-19, 1972.
57. Dykes RW, Terzis JK: Reinnervation of glabrous skin in baboons: Properties of cutaneous mechanoreceptors subsequent to nerve crush. J Neurophysiol 42:1461-1478, 1979.
58. Zalewski AA: Combined effects of testosterone motor, sensory or gustatory nerves on reinnervation of regeneration of taste buds. Exp Neurol 24:285-297, 25:29-37, 1969.
59. Zaleski AA: Regeneration of taste buds after transplantation of tongue and ganglia grafts to the anterior chamber of the eye. Exp. Neurol 35:519-528, 1972.
60. Mclachlean EM, Taylor RS, Bennett MR: The site of synapsis formation in reinnervation and cross-reinnervation mammalian muscle. Proc Aust Physiol Pharmacol Soc 3:62-69, 1972.
61. Bennett MR, Pettigrew AG, Taylor RS: The formation of synapsis in reinnervated and cross-reinnervated adult avian muscle. J Physiol 230:337-357, 1973.

62. Kleinert HE, McAllister CG, MacDonald CJ, et al: A critical evaluation of cross-finger flaps. J Trauma 14: 756-763, 1974.
63. Cauna N, Mannan G: Development and postnatal changes of digital Pacinian corpuscles (corpuscular lamellosa) in the human hand. J Anat 93:271-286, 1956.
64. Cauna N: Nature and functions of the papillary ridges of the digital skin. Anat Rec 119:449-468, 1954.
65. Sturman ML Duran RJ: Late results of fingertip injuries. J Bone Joint Surg 45A:289-298, 1963.
66. Smith JR, Bam AF: An evaluation of fingertip reconstruction by cross-finger and palmar pedicle flaps. Plast Reconstr Surg 35:409-418, 1965.
67. Porter RW: Functional assessment of transplanted skin in volar defects of digits: A comparison between free grafts and flaps. J Bone Joint Surg 50A:955-963, 1968.
68. Brady CS, Cloutier AM, Woolhouse FM: The fingertip injury-an assessment of management. Plast Reconstr Surg, 26:80-90, 1960.
69. Holm A, Zacharias L: Fingertip lesions: An evaluation of conservative treatment versus free skin grafting. Acta Orthop Scand 45:382-392, 1974.
70. Ridley A: Silver staining of the innervation of Meissner corpuscles in peripheral neuropathy. Brain 91: 539-552, 1968.
71. Dellon AL, Terrill RE: A protective acrylic cast for use in experimental hand surgery. Hand 8:165-166, 1975.
72. Jabaley ME, Dellon AL: Evaluation of sensibility through microhistological studies, in Omer GE, Spinner M (eds); *Management of Peripheral Nerve Problems*. Philadelphia; WB Saunders, 1980, Ch 23.

COMBINED REFERENCES

1. Adamson JE, Horton CE, Crawford HH: Sensory rehabilitation of the injured thumb. Plast Reconstr Surg 40: 52-57, 1967
2. Adeymo O, Wyburn GM: Innervation of skin grafts. Transplant Bull 4:152-153, 1957.
3. Adrian ED, Umrath K: The impulse discharge from Pacinian corpuscle. *J Physiol* 78:139 - 154, 1929.
4. Adrian ED, Zotterman Y: The impulses produced by sensory nerve endings. Part 3. Impulses set up by touch and pressure. *J Neurophysiol* 61:464 - 483, 1926.
5. Adrian ED, Zottermann Y: The impulses produced by sensory nerve endings: The response of a single nerve organ. J Physiol (Lond) 61:151 – 171, 1926.
6. Aitkens JT, Sharman M, Young JZ: Maturation of regenerating nerve fibres with various peripheral connections. J Anat 87:7-22, 1947.
7. Almquist E, Eeg-Olofsson O: Sensory nerve-conduction velocity and two-point discrimination insutured nerves. J Bone Joint Surg 52A: 791-796, 1970
8. Almquist EE: The effect of training on sensory function, in Mickon J, Moberg E (eds): *Traumatic Nerve Lesions of the Upper Limb*. Edinburgh: Churchill Livingstone, 1975, pp 53-54
9. Anderson S, Jones JK: *Recent Mammals of the World: A Synopsis of Families*. New York: Ronald Press, 1967.
10. Andres KH: *The Peripheral Nervous System*, Hubbard JI (ed). New York: Plenum Press, 1974, Ch12.
11. Bach-y-Rita P, Collins CC, Saunders FA, et al: Vision substitution by tactile image projection. Nature 221: 643-644, 1969
12. Bach-y-Rita P: Plastic brain mechanisms in sensory substitution, in Zulch KJ, Creutzfeldt O, Galbraith CC (eds): *Cerebral Localization.* Berlin: Springer-Verlag, 1975, pp 203-216
13. Bach-y-Rita P: Plasticity of the nervous system, in Zulch KJ, Creuzfeldt O, Galbraith GC (eds): Cerebral Localization Berlin: Springer-Verlag, 1975, pp 314-327
14. Bach-y-Rita P: Visual information through the skin-a tactile vision substitution system. Trans Am Acad Ophthalmol Otolaryngol 78: OP729-740, 1974
15. Badim J, Lessa SF, Vieiro RC, et al: Regiao hipotenar coma area doadora para as lesoes de palpa digital. Rev Bras Chir 62: 163-166, 1972
16. Barclay TL: The late results of fingertip injuries. Br J Plast Surg 8:38-43, 1955.
17. Bell JA: Sensibility evaluation, in Hunter JM, Schneider LH, Mackin EJ, et al (eds): *Rehabilitation of the Hand*. St Louis: CV Mosby, 1978, Ch 25
18. Bennett MR, Pettigrew AG, Taylor RS: The formation of synapsis in reinnervated and cross-reinnervated adult avian muscle. J Physiol 230:337-357, 1973.
19. Berger A, Meisse G; Innervated skin grafts and flaps for restoration of sensation to anesthetic areas. Chir Plast (Berl) 3: 33-37, 1975
20. Biedler LM, Nejad MS, Smallman RL, et al: Rat taste cell proliferation. Fed Proc 19:302, 1960.
21. Biemesderfer D, Munger BL, Binck J, et al: The Pilo-Ruffini complex: A non-sinus hair and associated slowly-adapting mechanoreceptor in primate facial skin. Brain Res 142:197 – 222, 1978.
22. Blackwelder RD: Classification of the Animal Kingdom. Carbondale, III: Southern Illinois Univ Press, 1963.
23. Blix M: Experimenteia bidrag till Lösning of fragan om hudnervernas specifiko energi. Ups Lakarefor Forhandlingar 43:427 - 441, 1882.
24. Boeke J: On the regeneration of sensitive end-corpuscles after section of the nerve. K Acad van Wetenschoppen (Amsterdam) 25:319-323, 1922.
25. Boeke J: *The Problems of Nervous Anatomy,* London: Oxford University Press, 1941 pp 12-44.
26. Boeke, J, Dijkstra C: De- and regeneration of sensible end-corpuscles in the duck's bill (corpuscles of Crandy and Herbst) after the cutting of the nerve, the removing of the entire skin or the transplantation of the skin in another region. K Acad van Wetenschoppen (Amsterdam) 35:1114-1119, 1932.
27. Bolton CF, Winkelmann RK, Dyk PJ: A quantitative study of Meissner's corpuscles in man. Neurology 16: 1-9, 1966
28. Bora FW Jr, Pleasure DE, Didizan NA: A study of nerve regeneration and neuroma formation after nerve suture by various techniques. J Hand Surg 1: 138-143, 1976
29. Bora FW Jr: Peripheral nerve repair in cats: The fasicular stitch. J Bone Joint Surg 49A: 659-666, 1967
30. Boring EG: Cutaneous sensation after nerve division Q *J Exp Physiol* 10:1-95, 1916.
31. Boswick JA, Schneewind J, Stromberg W: Evaluation of peripheral nerve repairs below the elbow. *Arch Surg* 90: 50-51, 1965
32. Botezat E: Die Apparrate des Gefühlssinnes der nackten und behaarten Saügetieshaut, mit Berucksechtegung des Menschen. Anat Anz 42:278 - 318, 1912.
33. Bowden REM: Factors influencing function recovery, in Seddon HJ (ed): *Peripheral Nerve Injuries.* London: Her Majesty's Stationery Office, 1954, CH VII, pp 298-354.
34. Brady CS, Cloutier AM, Woolhouse FM: The fingertip injury-an assessment of management. Plast Reconstr Surg, 26:80-90, 1960.
35. Braillar F, Horner RL: Sensory cross-finger pedicle graft. J Bone Joint Surg 51A: 1264- 1268, 1969
36. Breathnach AS: An Atlas of the Ultrastructure of Human Skin. London: JA Churchill, 1971.

37. Breathnach AS: Electron microscopy of cutaneous nerves and receptors. J Invest Dermatol 69:8 –26, 1977.
38. Brooks D: The place of nerve grafting in orthopedic surgery. J Bone Joint Surg 37A: 299-326, 1955
39. Brown A, Iggo A: The structure and function of cutaneous "touch corpuscle" after nerve crush. J Physiol 165:28-29P, 1963.
40. Brown AG, Iggo A: A quantitative study of cutaneous receptor and afferent fibers in the cat and rabbit. J Physiol 193: 707 – 733, 1967.
41. Brushart TM, Terzis JK: Dorsal horn projections of normal and repaired sensory nerves. Presented at the Plastic Surgery Research Council Meeting, Hershey, Pa, April 27, 1980
42. Buncke HJ, Rose EH: Free toe-to-fingertip neurovascular island flaps. Plast Reconstr Surg 63: 607-612, 1979
43. Buncke HJ: Digital nerve repairs. Surg Clin North Am 52: 1267-1285, 1972
44. Bunnell S: surgery of the nerves of the hand. Surg Gynecol Obstet 44:145-152, 1927.
45. Bunnell S, Boyes JH: Nerve grafts. Am J Surg 44: 64-75, 1939
46. Burgess PR, English KB, Horch KW, et al: Patterning in the regeneration of type 1 cutaneous receptor J Physiol 236:57-82, 1974.
47. Burgess PR, Horch KW: Specific regeneration of cutaneous fibers in the cat. J Neurophysiol 36:101- 114,1973.
48. Cabaud HE, Rodkey WG, McCarroll HR Jr, et al: Epineural and perineural fascicular nerve repair: A critical comparison. J Hand Surg 1: 131-137, 1976
49. Campbell JN, Meyer RA, La Motte RH: Sensitization of myelinated nociceptive afferents that innervate monkey hand. J Neurophysiol 42: 1669 – 1679, 1979.
50. Carter MS: *Re-education of Sensation*. Presented at the Hand Rehabilitation Symposium, Philadelphia, March 23, 1980
51. Cauna N: Nature and functions of the papillary ridges of the digital skin. Anat Rec 119:449-458, 1954
52. Cauna N: Nerve supply and nerve endings in Meissner's corpuscles. Am J Anat 99:315-350, 1956
53. Cauna N: structure of digital touch corpuscles. Acta Anat (Basel) 32:1-23, 1958
54. Cauna N, Mannan G: Development and postnatal change of digital Pacinian corpuscles (corpuscular lamellose) in the human hand. J Anat 93:271 – 286, 1956.
55. Cauna N, Ross LL: The fine structure of Meissner's touch corpuscles of human fingers. J Cell Biol 8:467 – 482, 1960.
56. Celli L, Caroli A: La ripresa della sensibilita nei trapianti, ed. innesti cutanei della mano. Riv Chir Mano 8:23-62,1970.
57. Chacha PB, Krishnamurti A, Soin K: Experimental sensory reinnervation of the median nerve by nerve transfers in monkeys. J Bone Joint Surg 59A:386-390, 1977.
58. Chambers MR, Andres KH, von During M, et al: The structure and function of the slowly-adapting type II mechanoreceptors in hairy skin. Q J Exp Physiol 57: 417 – 445, 1972.
59. Clark FJ, Burgess PR: Slowly-adapting receptors in cat knee joint: Can they signal joint angel? Neurophysiol 38: 1448-1463, 1975
60. Clark FJ, Horch KW, Bach SM et al: Contributions of cutaneous and joint receptors to static knee-position sense in man. J Neurophysiol 42: 877-888, 1979
61. Cohen LH, Lindley SR: Studies in vibratory sensibility. Am J Psychol 51: 44-51, 1938
62. Collins CC, Bach-y-Rita P: Transmission of pictorial information through the skin. Adv Biol med Phys 14: 285-315, 1973
63. Conomy JP, Barnes KL, Cruse RP: Quantitative cutaneous sensory testing in children and adolescents. Cleve Clin Q 45: 197-206, 1978
64. Corkin S, Milner B, Rasmussen T: Somatosensory threshold: Contrasting effects of post-central gyrus and posterior parietal lobe excision. Arch neurol 23: 41-58, 1970
65. Cosh JA: Studies on the nature of vibration sense. Clin Sci 12: 131-151, 1953
66. Cramer LM, Chase RA: *Symposium on the Hand*. St. Louis: V Mosby, 1971
67. Currier RD: Nervous system in Zuidema GD, Judge RD (eds): *Physical Diagnosis: A Physical Approach to the Clinical Exam,* ed 2. Boston: Little, Brown, 1968, pp 409-410, 424-425
68. Curtis RM, Dellon AL: Sensory re-education after peripheral nerve injury, in Omer G, Spinner M (eds): *Management of Peripheral Nerve Injuries*. New York: WB Saunders, 1980, pp 769-778
69. Curtis RM, Eversmann WW Jr: Internal neurolysis as an adjunct to the treatment of the carpal tunnel syndrome. J Bone Joint Surg 55A: 733-740, 1973
70. Curtis RM: Sensory re-education after peripheral nerve injury, in Frederick S, Brody GS (eds): Symposium on the Neurological Aspects of Plastic Surgery. Saint Louis: CV Mosby, 1978, pp 47-51
71. Daniel CR, Bower JD, Pearson JE, et al: Vibrometry and neuropathy. J Miss State Med Assoc 18: 30-34, 1977
72. Daniel RK, Terzis JK: *Reconstructive Microsurgery*. Boston: Little, Brown, 1977, p 324
73. Daniel RK: Microsurgery: Through the looking glass. N Engl J Med 300: 1251-1257, 1979
74. David WB: The life of John Staige Davis, M.D. Plast Reconstr Surg 62:368-378, 1978
75. Davis JS, Kitlowski EA: Regeneration of nerves in skin graft and skin flaps. Am J Surg 24:501-545, 1934.
76. Davis JS: *Plastic Surgery, Principles and Practice*. Philadelphia: Blakiston, 1919.
77. Davis L: The return of sensation to the transplanted skin. Surg Gynecol Obstet 59:533-543, 1934.
78. Davis RD: Some factors affecting the results of treatment of peripheral nerve injuries. Lancet 1: 877-880, 1949
79. Dawson GD: The relative excitability and conduction velocity of sensory and motor nerve fibres in man. J Physiol 131: 436-451, 1956

80. Dellon AL: Changes in primate Pacinian corpuscles after volar pad excision and skin grafting (Letter to the Editor). Plast Reconstr Surg 58:614-615, 1976
81. Dellon AL, Curtis RM, Edgerton MT: Evaluating recovery of sensation in the hand following nerve injury. *Johns Hopkins Med J* 130:235 – 243, 1972.
82. Dellon AL, Curtis RM, Edgerton MT: Program for sensory re-education in the hand following nerve injury, in Marshall E (ed): *Hand Rehabilitation*. Brookfield, Illinois: Fred Sammon, 1977, pp 110-112
83. Dellon AL, Curtis RM, Edgerton MT: Re-education of sensation in the hand following nerve injury. *Plast Reconstr Surg* 53:297 – 305, 1974.
84. Dellon AL, Curtis RM, Edgerton MT: Re-education of sensation in the hand following nerve injury. (abstr). J Bone Joint Surg 53A: 813, 1971
85. Dellon AL, Jabaley ME: Re-education of sensation. Clin Orthop, in press 1981
86. Dellon AL, Munger B: Correlation of sensibility evaluation, hand function and histology, in press 1981
87. Dellon AL, Terrill RE: A protective acrylic cast for use in experimental hand surgery. Hand 8:165-166, 1975.
88. Dellon AL, Witebsky FG, Terrill RE: The denervated Meissner corpuscle: A sequential histologic study after nerve division in the Rhesus monkey. Plast Reconstr Surg 56:182 – 193, 1975.
89. Dellon AL: Clinical use of vibratory stimuli to evaluate peripheral nerve injury and compression neuropathy. Plast Reconstr Surg 65: 466-476, 1980
90. Dellon AL: Evaluation of sensibility and re-education of sensation, in Mansat M (ed): *Proceedings: Symposium on Upper Extremity Sensory Problems*, June, 1980
91. Dellon AL: Reinnervation of denervated Meissner corpuscles: A sequential histological study in the monkey following fascicular nerve repair. J Hand Surg 1:98-109, 1976.
92. Dellon AL: Results of internal neurolysis in peripheral nerve compression, in press 1981
93. Dellon AL: Subcutaneous pedicle flap technique for fingertip reconstruction, in press 1981
94. Dellon AL: The extended volar advancement flap for thumb reconstruction, in press 1981
95. Dellon AL: The moving two point discrimination test: Clinical evaluation of the quickly adapting fiber-receptor system. *J Hand Surg* 3:474 – 481, 1978.
96. Dellon AL: The paper clip: Light hardware for evaluation of sensibility in the hand. Contemp Orthop 1:39-42, 1979.
97. Dellon AL: The plastic ridge device and moving two-point discrimination (Letter to the Editor). *J Hand Surg* 5:92 – 93, 1980.
98. Dellon AL: The vibrometer, in press 1981
99. Dellon AL: Two-point discrimination and the Meissner corpuscle (Letter to Editor). *Plast Reconstr Surge* 60:270 – 271, 1977.
100. Denny-Brown O, Brenner C: Paralysis of nerve induced by direct pressure and by tourniquet. Arch Neurol Psychiatry 51: 1-26, 1944
101. Dickens WN, Winkelmann RK, Mulder DW: Cholinesterase demonstration of dermal nerve endings in patients with impaired sensation. Neurology (Minneap) 13:91 – 100, 1963.
102. Drachman DB (ed): *Trophic Function of the Neuron.* New York: New York Academy of Sciences, 1974.
103. Dreyer DA, Schneider RJ, Metz CB, et al: Differential contributions of spinal pathways to body representation in post-central gyrus. J Neurophysiol 37: 119 – 145, 1945.
104. Dyke RW, Terzis JK: Reinnervation of glabrous skin in baboons: Properties of cutaneous mechanoreceptor subsequent to nerve crush J Neurophysiol 42:1461-1478, 1979.
105. Edshage S: Experience with clinical methods of testing sensation after peripheral nerve surgery, in Jewett DL, McCarroll HR Jr (eds): *Nerve Repair and Regeneration*. St. Louis: CV Mosby, 1980, pp 244-249
106. Edshage S: Peripheral nerve suture. Acta Chir Scand [Suppl] 331: 1-101 (99 references), 1964
107. Egger M: De la sensibilite osseuse. J Physiol (Paris) 1: 511-520, 1899
108. Elliott FA: *Clinical Neurology*. Philadelphia: WB Saunders, pp 419-420, 1964
109. Engel AG, Stonnington HH: Morphologic effects of denervation of muscle: A qualitative ultrastructural study, in Drachman DB (ed): *Trophic Functions of the Neuron*. New York: New York Academy of Sciences, 1974, pp 68-88.
110. English KB: Cell types in cutaneous type 1 mechanoreceptors (Haarscheiben) and their alterations with injury. Am J Anat 1:205 – 126, 1974.
111. English KB: Morphogenisis of Haarscheiben in rats. J Invest Dermatol 69:58 – 67, 1977.
112. Erlanger J, Gasser HS: *Electrical Signs of Nervous Activity*. Philadelphia: Univ Penn Press, 1937.
113. Eskilden P, Morris A, Collins CC, et al: Simultaneous and successive cutaneous two-point threshold for vibration. Psychon Sci Sect Hum Exp Psychol 14: 146-147, 1969
114. Farbman AI: Electron microscopic study of the developing taste bud in rat fungiform papillae. Dev Biol 11:110-135, 1965.
115. Farbman AI: Fine structure of degenerating taste buds after denervation. *J Embryol Exp Morphol* 22: 55-68, 1969.
116. Fess EE, Harmon KS, Strickland JW, et al: Evaluation of the hand by objective measurement, in Hunter JM, Schneider LH, Mackin EJ, et al (eds). *Rehabilitation of the Hand*. Saint Louis: CV Mosby, 1978, Ch 5
117. Fitzgerald MJT, Martin F, Paletta FX: Innervation of skin grafts. *Surg Gynecol Obstet* 124:808-812, 1967.
118. Flynn JE, Flynn WF: Median and ulnar nerve injuries. Ann Surg 156: 1002-1009, 1962
119. Forster FM, Shields CD: Cortical sensory defects causing disability. Arch Phys Med Rehabil 40: 56-61, 1959

120. Foucher G, Braun JB: A new island flap transfer from the dorsum of the index to the thumb. Plast Reconstr Surg 63: 344-349, 1979
121. Foucher G, Merle M, Maneaud M, et al: Microsurgical free partial toe transfer in hand construction: A report of 12 cases. Plast Reconstr Surg 65: 616-626, 1980
122. Fox JC, Klemperer WW: Vibratory sensibility. Arch Neurol Psychiatry 48: 622-645, 1942
123. Fredricks S, Brody GS: *Symposium on the Neurologic Aspects of Plastic Surgery*. St. Louis: CV Mosby, 1978
124. Freshwater MF: The principles and purpose of plastic surgery-past and present, in Krizek TJ, Hoopes JE (eds): *Symposium on Basic Science in Plastic Surgery*. Saint Louis: CV Mosby, 1976, pp. 3-13
125. Fujimoto S, Murray RG: Fine structure of degeneration and regeneration in denervated rabbit vallate taste buds. Anat Rec 168:393, 1970.

126. Gammon GM, Bronk DW: The discharge of impulses from Pacinian corpuscles in the mesentery and its relation to vascular change. *Am J Physiol* 114:77 – 84, 1935.
127. Gaul JS Jr: Radial-innervated cross-finger flaps from index to provide sensory pulp to injured thumb. J Bone Joint Surg 51A: 1257-1263, 1969
128. Gelberman RH, Blalsingame JP, Fronek A, et al: Forearm arterial injuries. J Hand Surg 4:401-408, 1979.
129. Gelberman RH, Urbaniak JR, Bright D, et al: Digital sensibility following replantation. J Hand Surg 3:313-319, 1978.
130. Geldard FA: The perception of mechanical vibration: IV. Is there a separate "Vibratory Sense"? J Gen Psychol 22: 291-308, 1940
131. Gelfan S, Carter S: Muscle sense in man. Exp Neurol 18: 469-473, 1967
132. Gellis M, Pool R: Two-point discrimination distances in the normal hand and forearm. Plast Reconst Surg 59:57-63, 1977
133. Gilmer B von H: A study of the regeneration of vibratory sensitivity. J gen Psychol 14: 461-462,1936
134. Gilray J, Meyer JS: *Medical Neurology*. Toronto: MacMillan, 1969, pp 2,4,59,60
135. Glees P, Mohiuddin A, Smith AG: Transplantation of Pacinian bodies in the brain and thigh of the cat. Acta Anat (Basel) 7:213-224, 1949.
136. Gordon I: The sensation of vibration with special reference to its clinical significance. J Neurol Psychopathol 17: 107-134, 1936
137. Gottschaldt KM, Lausmann D: Mechanoreceptors and their properties in the beak skin of geese (Anser anser). Brain Res 65:510 – 515, 1974.
138. Grabb WC, Bement SC, Koepke G: Comparison of methods of peripheral nerve suturing in monkeys. Plast Reconstr Surg 46: 31-38, 1970
139. Gradenigo G: A new optical method of acoumetrie. J Laryngol Rhin Otol 14: 583-585, 1899
140. Grandis V: Sur la mesure de l'acuite auditive au moyen de valeurs physiques entre elles. Arch Ital Biol 37: 358-376, 1902
141. Gray JAB, Malcolm JL: The initiation of a nerve impulse by mesentric Pacinian corpuscles. Proc R Soc Lond [Biol] 137: 96, 1950.
142. Gray JAB, Mathews PBR: A comparison of the adaptation of the Pacinian corpuscle with the accommodation of its own axon. J Physiol 114: 454 – 464, 1951.
143. Gray RC: Quantitative study of vibrations sense in normal and pernicious anemia. Minn Med 15: 647-680, 1932
144. Green D (ed): *Operative Treatment of Nerve Problems*. Edinburgh: Churchill Livingstone, 1981
145. Grigg P, Greenspan BJ: Response of primate joint afferent neurons to mechanical stimulation of knee joint. J Neurophysiol 40: 1-8, 1977
146. Grigg, P, Finerman GA, Riley LH: Joint-position sense after total hip replacement. J Bone Joint Surg 55A: 1016-1025, 1973
147. Gruber H, Zenker V: Acetylcholinesterase: Histological differentiation between motor and sensory nerve fibers. Brain Res 51: 207-2l4, 1973
148. Guth L: Degeneration and regeneration of taste buds, in Beidler LM (ed): *Handbook of Sensory Physiology*, Vol. VI. Berlin: Springer-Verlag, 1971, pp 63- 74.
149. Guth L: Taste buds in the rat's circumallate papillae after reinnervation for the glossopharyngeal, vagus, and hypoglossal nerve. Anat Rec 130:25-37, 1958.
150. Guth L: The effects of glossopharyngeal nerve transection on the circumvallate papilla of the rat. Anat Rec 128:715-731, 1957.
151. Hakistian RW: Funicular orientation by direct stimulation; an aid to peripheral nerve repair. J Bone Joint Surg 50A: 1178-1186, 1968
152. Halata Z: The ultrastructure of the sensory nerve endings in the articular capsule of the knee joint of the domestic cat (Ruffini corpuscle and Pacinian corpuscles). J Anat 124:717 – 729, 1977.
153. Halata, Z: Spezifische innervation, Ch. 6, in Orfanos CE (ed): *Haar and Haarkrankheiten*. Stuttgart: Gustav Fischer Verlag, 1979.
154. Hamlin E, Watkins AL: Regeneration in the ulnar, median and radial nerves. Surg Clin North Am 27:1052-1061, 1947
155. Harrington T, Merzenich MM: Neural coding in the sense of touch: Human sensation of skin indentation compared with response of slwly-adapting mechanoreceptive afferents innervating the hairy skin of monkeys. Exp Brain Res 10: 251 – 254, 1970.
156. Harris AJ: Inductive function of the nervous system. Annu Rev Physiol 36:251-305, 1974 (403 references.)

157. Hashimoto K: Fine Structure of the Meissner corpuscle of human palmar skin. J Invest Dermatol 60:20 – 28, 1973.
158. Head H, Sherren J: The consequences of injury to the peripheral nerves in man Brain 28:116-337, 1905.
159. Head H: Studies in Neurology. Cited by Fox JC, Klemperer WW: Vibratory sensibility. Arch Neurol Psychiatry 48: 623-645, 1942
160. Head H: The afferent nervous system from a new aspect. Brain 28:99 - 115, 1905.
161. Heinrichs RW, Moorehouse JA: Touch perception in blind diabetic subjects in relation to the reading of Braille type. N Engl J Med 280: 72-75, 1969
162. Henderson WR: Clinical assessment of peripheral nerve injuries. Tinel's test. Lancet 2: 801-805, 1948
163. Hensel H, Boman KA: Afferent impulses in cutaneous sensory nerves in human subjects. J Neurophysiol 23: 564 – 578, 1960.
164. Hoffman H: Local re-innervation in partially denervated muscle: A histo-physiological study. Aust J Exp Biol Med Sci 28:384-398,1950.
165. Holevich J: A new method of restoring sensibility to the thumb. J Bone Joint Surg 45B: 496-502, 1963
166. Holm A, Zacharial L: Fingertip lesions: An evaluation of conservative treatment versus free skin grafting. Acta Orthop Scand 45: 382-392, 1974
167. Holmes W: Histologic observations on the repair of nerves by autografts. Br J Surg 35: 167-173,1947
168. Honner R, Fragiadakis EG, Lamb DW: An investigation of the factors affecting the results of digital nerve division. Hand 2: 21-31, 1970
169. Horch K: Guidance of regrowing sensory axons after cutaneous nerve lesions in the cat. J Neurophysiol 42: 1437-1449, 1979.
170. Horch KW, Burgess PR: Responses threshold and suprathreshold stimuli by slowly-adapting cutaneous mechanoreceptors in the cat. J Comp Physiol 110: 307 – 315, 1976.
171. Horch KW, Whitehorn D, Burgess PR: Impulse generation in type I cutaneous mechanoreceptors. J Neurophysiol 37: 267 – 281, 1973
172. Horch KWM, Burgess PR, Whitedorn D: Ascending collaterals of cutaneous neurons in the fasiculus gracilis of the cat. brain res 117: 1-17, 1976
173. Horch KWM, Tucket RP, Burgess PR: A key to the classification of cutaneous mechanoreceptors. *J Invest Dermatol* 69:75 – 92, 1977.
174. Hulliger M, Nordh E, Thelin AE et al: The response of afferent fibers from the glabrous skin of the hand during voluntary finger movements in man. J Physiol 291: 233-249, 1979
175. Hunter JM, Schneider LH, Mackin EJ, et al: *Rehabilitation of the Hand*. St. Louis: CV Mosby, 1978
176. Hurley HG, Koelle GB: the effect of inhibition of nonspecific cholinesterase in perception of tactile sensation in human volar skin. J Invest Dermatol 31:243-245, 1958.
177. Hutchinson J, Tough JS, Wynbum GM: Regeneration of sensation in grafted skin. Br J Plast Surg 2: 82-94, 1949
178. Ide C: The fine structure of the digital corpuscle of the mouse toe pad, with special reference to nerve fibers. Am J Anat 147: 329 – 356, 1976.
179. Iggo A, Muir AR: A cutaneous sense organ in hairy skin of cats. J Anat 97:151, 1963.
180. Iggo A, Muir AR: The structure and function of a slowly-adapting touch corpuscle in hair skin. J Physiol 200:763 – 796, 1969.
181. Iggo A. New specific sensory structures in hairy skin. Acta Neuroveg 24: 175 – 180, 1963.
182. Iggo A: Cutaneous and subcutaneous sense organs. Br Med Bull 22: 97 – 102, 1977.
183. Iggo A: Cutaneous receptors, in Hubbard JF (ed): *The Peripheral Nervous System*. New York: Plenum Press, 1974, Ch12, pp 374 – 404.
184. Ito T: *Surgery of the Peripheral Nerve*. Tokyo: Igaku Shoin, 1977
185. Jabaley ME, Burns JE, Orcutt BS, et al: Comparison of histologic and functional recovery after peripheral nerve repair. J Hand Surg 1:119-130, 1976.
186. Jabaley ME, Dellon AL: Evaluation of sensibility by microhistological studies, in Omer G, Spinner M (eds): Management of Peripheral Nerve Problems. Philadelphia: WB Saunders, 1980, Ch23, 62.
187. Jabaley ME, Wallace WH, Heckler FR: Internal topography of major nerves of the forearm and hand: A current review. J Hand Surg 5: 1-18, 1980
188. Jabaley ME: Recovery of sensation in flaps and skin, in Tubiana R (ed): The Hand. Philadelphia: WB Saunders, 1981.
189. Jewett DL, McCarroll HR Jr: *Nerve Repair and Regeneration*. St. Louis: CV Mosby, 1980
190. Johnson KO: Reconstruction of population response to a vibratory stimulus in quickly-adapting mechanoreceptive afferent fiber population innervating glabrous skin of the monkey. J Neurophysiol 37: 48-72, 1974
191. Johnson RK, Inverson RE: Cross finger pedicle flaps in the hand. J Bone Joint Surg 53A: 913-919, 1971
192. Joshi BB: A sensory cross-finger flap for use on the index finger. Plast Reconstr Surg 58: 210-213, 1976
193. Joshi BB: Neural repair for sensory restoration in a groin flap. Hand 9: 221-225, 1977
194. Kaas JH, Nelson RJ, Sur M, et al: Multiple representations of the body within the somatosensory cortex of primates. Science 204: 521 – 523, 1979.
195. Kappers CVA, Huber GC, Crosby EC: *The Comparative Anatomy of the Nervous System of Vertebrates, including Man*. New York: Hafner, 1960.

196. Karthals JK, Wisniewski HM, Ghetti B, et al: The fate of the axon and its terminal in the Pacinian corpuscle following sciatic nerve section J Neurophysiol 3:385-403, 1974
197. Kasprzak H, Tapper DN, Craig PH: Functional development of the tactile pad receptor system. Exp Neurol 26:439 – 446, 1970.
198. Kawamura T, Nishiyama S, Ikeda S, et al: The human haarscheibe, its structure and function. J Invest Dermatol 42:87 – 90, 1966.
199. Kawamura T: Fine struture of the dendritic cells and Merkel cells in the epidermis of various mamals, Jpn J Dermatol 81:343 – 351, 1971.
200. Keim HA, Grantham SA: Volar flap advancement for thumb and fingertip injuries. Clin Orthop 66: 109-112, 1969
201. Kim KL, Pasch JL: Island flap innervated by radial nerve for restoration of sensation in an index stump. Plast Reconstr Surg 47: 386-388, 1971
202. Kingsley NW, Stein JM, Levenson SM: Measuring tissue pressure to assess the severity of the burn induced ischemia. Plast Reconstr Surg 63: 404-408, 1979
203. Kirklin JW, Murphy F, Berkson J: Suture of peripheral nerves: Factors affecting prognosis. Surg Gynecol Obstet 88:719-730, 1959.
204. Kleinert HE, Juhalo CA, Tsai T, et al: Digital replantation-selection, techniques, and results. Orthop Clin North Am 8: 309-318, 1977
205. Kleinert HE, McAlister CG, MacDonald CJ, et al: A critical evaluation of cross finger flaps. J Trauma 14: 756-763, 1974
206. Knibestol M, Vallbo AB: Single unit analysis of mechanoreceptor activity from the human glabrous skin. Acta Physiol Scand 80: 178 – 195, 1970.
207. Konietzny F, Hensel H: Response of rapidly and slowly-adapting mechanoreceptors and vibratory sensitivity in human hairy skin. Pflugers Arch 368: 39 – 44, 1977.
208. Krag C, Rasmussen KB: The neurovascular island pedicle flap for defective sensibility in the thumb. J Bone Joint Surg [Br] 57B: 495-499, 1975
209. Kredel FE, Evans JP: Recovery of sensation in denervated pedicle and free skin grafts. Arch Neurol Psychiatry 29:1203-1221, 1933.
210. Krishnamurti A, Kanagasuntheram R, Vij S: Failure of reinnervation of Pacinian corpuscle after nerve crush: An electron microscopic study. Acta Neuropathol (Berl) 23:338-341, 1973.
211. LaMotte RH, Campbell JN: Comparison of responses of warm and nociceptive C-fiber afferents in monkey with human judgments of thermal pain. J Neurophysiol 41: 509 – 528, 1978.
212. LaMotte RH, Mountcastle VB: Capacities of humans and monkeys to discriminate between vibratory and stimuli of different frequency and amplitude: A correlation between neural events and psychophysical measurements. J Neurophysiol 38: 539-559, 1975
213. LaMotte RH, Mountcastle VB: Disorders in somesthesia following lesions of parietal lobe. *J Neurophysiol* 42: 400-419, 1979
214. LaMotte RH: Psychophysical and neirophysical studies of tactile sensibility, in Hollies N, Goldman R (eds): *Clothing Comfort: Interaction of Thermal, Ventilation, Construction and Assessment Factors.* Amer Arbr Sci, Amer Arbor, 1977 by report to the international union, LaMotte R, Mountcastle B: Symposium on "Active Touch," Beaune, France, 1977
215. Landau W, Bishop GH: Pain from dermal, periosteal and fascial endings and from inflammations. Arch Neurol Psychiatry 51: 1-26, 1944
216. Lansen RD, Posch JL: Nerve injuries in the upper extremity. Arch Surg 77: 469-482, 1958
217. Lee FC: A study of the Pacinian corpuscle. J Comp Neurol 64:497-522, 1936.
218. Lefkowitz M: *A Model of the Glabrous Skin of the Fingertip*, Master's thesis. Johns Hopkins University, Baltimore, 1979.
219. Lesavoy MA: The dorsal index finger neurovascular island flap. Orthop Rev 9: 91-95, 1980
220. Levin S, Pearsall G, Ruderman RJ: von Frey's method of measuring pressure sensibility in the hand: An engineering analysis of the Weinstein-Semmes pressure aesthisiometer. J Hand Surg 3:211-216, 1978.
221. Lewis T, Pickering GW, Rothschild P: Centripetal parapysis arising out of arrested bloodflow to the limbs. Heart 61: 1, 1931
222. Lin C, Merzenich MM, Sur M, et al: Connections of areas 3b and 1 of the parietal somatosensory strip with the ventroposterior nucleus in the Owl Monkey (Aotus trivirgatus). J Comp Neurol 185: 355 – 372, 1979.
223. Lindblom U: Properties of touch receptors in distal glabrous skin of the monkey. J Neurophysiol 28: 966 – 985, 1965.
224. Lindblom V, Meyerson BA: Influence on touch, vibration and cutaneous pain of dorsal column stimulation in man. pain 1: 257-270, 1975
225. Lindsay WK: Hand injuries in children. Clin Plast Surg 3: 65-75, 1976
226. Lister G: *The Hand: Diagnosis and Indications.* Edinburgh: Churchill Livingstone, 1977, p 73
227. Livingstone WK: Evidence of active invasion of denervated areas by sensory fibers from neighboring nerves in man. J Neurosurg 4:140-145,1947.
228. Lofgren L: Recovery of nervous function in skin transplants with special reference to the sympathetic functions. Acta Chir Scand 102:229-239, 1952.
229. Lowenstein WR, Mendelson M: Components of receptor adaptation in Pacinian corpuscle. J Physiol 177: 377 – 397, 1965.

230. Lowenstein WR, Rothkamp, R: The sites for mechanoelectric conversion in a Pacinian corpuscle. *J Glen Physiol* 41: 1245 – 1265, 1958.
231. Lowenstein WR: Biological transducers. Sci Am 203: 99 – 108, 1960.
232. Lowenstein WR: Development of a receptor on a foreign nerve fiber in a Pacinian corpuscle. Science 177:712-715, 1972.
233. Lowenstein WR: On the "specificity" of a sensory receptor. *J Neurophysiol* 24:150 - 148, 1961.
234. Lunborg: Structure and function of the intraneural microvessels as related to trauma, edema formation and nerve function. J Bone Joint Surg 57A: 938-948, 1975
235. Lyons WR, Woodhall B: *Atlas of Peripheral Nerve Injury,* Philadelphia: WB Saunders, 1949, p 215.
236. Major RH, Delp MH: *Physical Diagnosis,* ed 6. Philadelphia: WB Saunders, 1962, pp 320-323.
237. Mann SJ, Straille WE: Tylotrich (hair) follicle: Association with a slowly adapting tactile receptor in the cat. Science 147:1043 – 1045, 1965.
238. Mannerfelt L: Evaluation of functional sensation of skin graft in the hand area. Br J Plat Surg 15:136-154, 1962.
239. Mansat M, Delprat J: Reeducation de la sensibilite de la main. Ann Med Physique 18: 527-538, 1975
240. Maquieric NO: An innervated full-thickness skin graft to restore sensibility to fingertips and heels. Plast Reconstr Surg 53: 568-575, 1974
241. Marshall Al (ed): *Biology & Comparative Physiology of Birds*. New York: Academic Press, 1960, pp 33, 44, 210.
242. Matsen FA, Mayo KA, Kriegmire RB Jr, et al: A model compartmental syndrome in man with particular reference to the quantification of nerve function. J Bone Joint Surg 59A: 648-653, 1977
243. Matsen FA, Wenquist RA, Krugmire RB: Diagnosis and management of compartment syndromes. J Bone Surg 62A: 286-291, 1980
244. May JW Jr, Chait LA, Cohen BE, et al: Free neurovascular flap from the first web of the foot in hand reconstruction. J Hand Surg 2: 387-393, 1977
245. May JW Jr, Daniel RK: Great toe to hand free tissue transfer. Clin Orthop 133: 140-153, 1978
246. Mayamoto Y: Experimental study of results of nerve suture under tension vs. nerve grafting. Plast Reconstr Surg 64: 540-549, 1979
247. Maynard J: Sensory re-education after peripheral nerve injury, in Hunter J, Mackin E, Schneider L, et al (eds): *Rehabilitation of the Hand*. Baltimore: Williams & Wilkins, 1977
248. McCarrol HR: The regeneration of sensation in transplanted skin. Ann Surg 108:309-320, 1938.
249. McEwan LE: Median and ulnar nerve injuries. Aust NZ J Surg 32: 89-104, 1962
250. McFarlane RM, Moyer JR: Digital nerve grafts with the lateral antebrachial cutaneous nerve. J Hand Surg 1: 169-173, 1976
251. Mclachlean EM, Taylor RS, Bennett MR: The site of synapsis formation in reinnervation and cross-reinnervation mammalian muscle. Proc Aust Physiol Pharmacol Soc 3:62-69, 1972.
252. McQuillan W: Sensory recovery after nerve repair. Hand 2: 7-9, 1970
253. McQuillan WM, Neilson JMM, Boardman AK, et al: Sensory evaluation after median nerve repair. Hand 3: 101-111, 1971
254. Meissner G: Beiträge sur Kenntnis der Anatomie and Physiologie der Haut. Leipzig: Leopold Voss, 1853, p 47, and Untersuchungen uber den Tostsuin. Z Rat Med 7:92 - 119, 1859. Cited by Winklemann RK: Nerve Endings in Normal and Pathological Skin. Springfield: Charles C Thomas, 1960.
255. Melvin JL, Harris DH, Johnson EW: Sensory and motor conduction velocities in the ulnar and median nerves. Arch Phys Med Rehabil 47: 511-519, 1966
256. Merkel F: Tastzellen and Tastkorperchen bei den Hausthieren und beim Menschen. Arch Mikrosk Anat 11:636 – 652, 1875.
257. Merzenich MM, Harrington T: The sense of flutter-vibration evoked by stimulation of the hairy skin of primates: Comparison of human sensory capacity with the responses of mechanoreceptive afferents innervating the hairy skin of monkeys. Exp Brain Res 9: 236 – 260, 1969.
258. Merzenich MM, Kaas JH, Sur M, et al: Double representation of the body surface within cytoarchitecture areas 3b and 1 in "S1" in the Owl Monkey (Aotus trivirgatus). J Comp Neurol 181: 41 – 74, 1978.
259. Michon J, Moberg E: *Traumatic Nerve Lesions of the Upper Extremity*. London: Churchill Livingstone, 1975
260. Micks JE, Wilson JN: Full thickness sole-skin grafts for resurfacing the hand. J Bone Joint Surg 49A: 1128-1134, 1967
261. Miller MR, Ralston HJ, Kasahara M: The patter of cutaneous innervation of the human hand. Am J Anat 102: 183 – 201, 1958.
262. Miller SH, Reisenas I: Changes in primate Pacinian corpuscles following volar pad excision and skin grafting: A preliminary report. Plast Reconstr Surg 57:627-636, 1976.
263. Millesi H, Meisse G, Berger A: The interfascicular nerve-grafting of the median and ulnar nerves. J Bon Joint Surg 54A: 727-750, 1972
264. Millesi H, Rinderes D: A method for training and testing sensibility of the fingertips. Proc World Fed Occup Ther 7: 122-125, 1979
265. Milliesi H, Meisse G, Berger A; Further experience with interfascicular grafting of the median, ulnar and radial nerves. J Bone Joint Surg 58A: 209-2l8, 1976
266. Minor L: Uber die Localisation used klinische Bedeutung der sog. "Knochensensibilitat" oder das "Vibrationgefuhls". Neuro; Centralbl 23: 146-199, 1904

267. Mirsky IA, Futterman P, Brohkahn RH: The quantitative measurement of vibratory preception in subjects with and without diabetes mellitus. J Lab Clin Med 41: 221-235, 1953
268. Mitchell SW: *Injuries of Nerves and Their Consequence*, 1872, American Academy of Neurology Reprint Series. New York: Dover 1965, pp 179, 183.
269. Moberg E: Aspects of sensation in reconstructive surgery of the upper extremity. J Bone Joint Surg 46A:817-825, 1964
270. Moberg E: *The Upper Limb in Tetraplegia.* New York, Grune& Stratton, 1978
271. Moberg E: Criticism and study of methods for examining sensibility in the hand Neurology 12:8-19, 1962
272. Moberg E: *Emergency Surgery of the Hand,* New York: Churchill Livingstone, 1968.
273. Moberg E: Fingers were made before forks. hand 4: 201-206, 1972
274. Moberg E: Future hope for the surgical management of peripheral nerve lesions, in Michon J, Moberg E (eds): *Traumatic Nerve Lesions*. New York: Churchill Livingstone, 1975
275. Moberg E: Methods for examining sensibility in the hand, in Flynn JE (ed): *Hand Surgery,* ed 1. Baltimore: Williams & Wilkins, 1966, pp 435-439.
276. Moberg E: Objective methods for determining the functional value of sensibility in the skin. J Bone Joint Surg [Br] 40B: 454-476, 1958
277. Moberg E: Reconstructive hand surgery in tetraplegia, stroke and cerebral palsy: Some basic concepts in physiology and neurology J Hand Surg 1:29-34, 1976.
278. Montagna W: Comparative anatomy and physiology of the ski. Arch Dermatol 96:357 – 363, 1967.
279. Morrison WA, O'Brien B, Macleod AM: Evaluation of digital replantation-a review of 100 cases. Orthop Clin North Am 8: 295-308, 1977
280. Mountcastle (ed): *Medical physiology*, ed 12. Saint Louis: CV Mosby, 1968, Ch. 61 – 62
281. Mountcastle VB, Darian-Smith I: Neural mechanisms in somesthesic, in Mountcaslte VB (ed): *Medical Physiology*, ed 12. Saint Louis: CV Mosby, 1968, Ch 62.
282. Mountcastle VB, Henneman E: The representation of tactile sensibility in the thalamus of the monkey. J Comp Neurol 97: 409 – 440, 1952.
283. Mountcastle VB, Poggio GF, Wener G: The relation of thalamic cell response to peripheral stimuli varied over an intensive continuum. J Neurophysiol 26: 807 – 834, 1963.
284. Mountcastle VB, Powell TPS: Neural mechanisms subserving cutaneous sensibility, with special reference to the role of afferent inhibition in sensory perception and discrimination. Bull Johns Hopkins Hosp 105: 201 – 232, 1959.
285. Mountcastle VB, Talbot WH, Darian-Smith I, et al: A neural base for the sense of flutter-vibration. Science 155:597, 1967
286. Mountcastle VB, Talbot WH, Komhuber HH: *The Neural Transformation of Mechanical Stimuli Delivered to the Monkey's Hand.* Ciba Foundation Symposium on Touch, Heat and Pain, de Rueck AVS, Knight J (eds). London: JA Churchill, 1966.
287. Mountcastle VB: Discussion section of CIBA Foundation Symposium on *Touch, Heat and Pain*. London: JA Churchill, 1966.
288. Mountcastle VB: Modality and topographic properties of single neurons of cat's somatic sensory cortex. J Neurophysiol 20: 408 – 434, 1957.
289. Mountcastle VB: The view from within: Pathways to the study of perception. Johns Hopkins Med J 136: 109 – 131, 1975.
290. Muller J: Uber die phantastischen Gesichtsercheiningen. Koblenz: J Holscher, 1826.
291. Munger BL, Page RB, Pubols BH Jr: Identification of specific mechanosensory receptors in glabrous skin of dorsal root ganglionectomized primates. Anat Rec 93: 630 – 631, 1979.
292. Munger BL, Pubols LM, Pubols BH: The Merkel rete papilla – a slowly adapting sensory re3ceptor in mammalian glabrous skin. Brain Res 29:47 – 61, 1971.
293. Munger BL, Pubols LM: The sensorineural organization of the digit skin of the raccoon. Brain Behav Evol 5:367 – 393, 1972.
294. Munger BL: Neural-epithelial interactions in sensory receptors. J Invest Dermatol 69:27 – 40, 1977.
295. Munger BL: Patterns of organization of peripheral sensory receptors, in Lowenstein WR (ed): *Handbook of Sensory Physiology*. Berlin: Springer-Verlag, 1971, Ch 17.
296. Munger BL: The comparative ultrastructure of slowly and rapidly adapting mechanoreceptors, in Dubner R, Kawamuro Y (eds): *Oral-Facial Sensory and Motor Mechanisms*. New York: Appelton-Century-Crofts, 1971, Ch 6.
297. Munger BL: The intraepidermal innervation of the snout skin of the possum: A light and electron microscopic study, with observations on the nature of Merkel's Tastzellen. J Cell Biol 26: 79 – 96, 1965.
298. Murabeck SJ, Owen CA, Hargen AR, et al: Acute compartment syndrome: Diagnosis and treatment with the aid of a wick catheter. J Bone Surg 60A: 1091-1095, 1978
299. Murray JR, Ord JVR, Gavelin GE: The neurovascular island flap pedicle flap. J Bone Joint Surg 49A: 1285-1297, 1967
300. Napier JR: The significance of Tinel's sign in peripheral nerve injuries. Brain 72: 63-82, 1949
301. Narakas A: Surgical treatment of traction injuries of the brachial plexus. Clin Orthop 133: 71-90, 1978
302. Naso SJ: Full-thickness skin grafts from thenar eminence to cover volar avulsions of fingers. Orthop Rev 7: 127-I29, 1978
303. Newman HW, Corbin KB: Quantitative determination of vibratory sensibility. Proc Soc Exp Biol 35: 273-276, 1936
304. Newton I, 1675. Cited by Boyes J: *On the Shoulders of Giants. Notable Names in Hand Surgery*. Philadelphia: JB Lippincott, 1976

305. Nicholson OR, Seddon HJ: Nerve repair in civilian practice: Results of treatment of median and ulnar lesions. Br Med J 2:1065-1071, 1957.
306. Nielsen JB, Torup D: Nerve injuries in the upper extremities. Dan Med Bull 11: 92-95, 1964.
307. Nishi K, Oura C, Paillie W: *Fine structure of Pacinian corpuscles in the mesentery of the cat*. J Cell Biol 43:539 – 552, 1969.
308. Norris TR, Poppen NK, Buncke HJ: Restoration of sensibility and function with microvascular transplants from the toe to the hand. Presented at Am. Soc Surg Hand Meeting, Feb 5, 1980
309. O'Brien B, Macleod AM, Sykes PJ, et al: Microvascular second toe transfer for digital reconstruction. J Hand Surg 3: 123-133, 1978
310. Oester VT, Davis L: Recovery of sensory function, in Woodhall B, Beebee GW (eds): *Peripheral Nerve Regeneration.* Washington DC: US Gov Print Office, 1956, Ch 5
311. Omer GE, Spinner M: *Management of Peripheral Nerve Problems*. Philadelphia: WB Saunders, 1980
312. Omer G: Injuries to nerves of the upper extremities. J Bone Joint Surg 56A: 1615-1624,1974
313. Omer GE Jr, Day DJ, Ratliff H, et al: Neurovascular cutaneous island pedicles for deficient median nerve sensibility. J Bone Joint Surg 52A: 1181-1192, 1970
314. Omer GE: Sensation and sensibility in the upper extremity. Clin Orthop 104: 30-36, 1974
315. Omer GE: Sensibility of the hand as opposed to sensation in the hand. Ann Chir 27: 479- 483, 1973
316. Omer GE: Sensibility testing, in Omer GE, Spinner M (eds): Management of Peripheral Nerve Problems. Philadelphia: WB Saunders, 1980, Ch 1.
317. Onne L: Recovery of sensibility and sudomotor function in the hand after nerve suture. Acta Chir Scand [Suppl] 300: 1-70, 1962
318. O'Rain S: New and simple test of nerve function in the hand Br Med J 3:615-616, 1973
319. Orgel M, Aguayo A, Williams HB: Sensory nerve regeneration: An experimental study of skin grafts in the rabbit. J Anat 111:121-135, 1972.
320. Orgel MG, Terzis JK: Epineurial vs. perineurial repair: An ultrastructural and electrophysiologic study of nerve regeneration. Plast Reconstr Surg 60: 80-91, 1977
321. Orphanos CE, Mahrle G: Ultrastructural and ytochemistry of human cutaneous nerves. J Invest Dermatol 61:108-120, 1973.
322. Osborne G: The surgical treatment of tardy ulnar neuritis (abstr). J Bone Joint Surg 39B: 782, 1957
323. Osler W: The student life, in Franklin AW (ed): *A Way of Life and Selected Writing of Sir WIlliam Osler*. New York: Dover, 1958, pp 172 - 173.
324. Owen R: *On the Archetype and Homologies of the Vertebrate Skeleton*. London: J. Van Roost, 1848. Cited by Freshwater MF: The principles and purpose of plastic surgery-past and present, in Krizek TJ, Hoopes JE (eds): *Symposium on Basic Science in Plastic Surgery*. Saint Louis: CV Mosby, 1976, p 3
325. Pacini F: Nuovo Giralle Letherali, 1836, p 109. Cited by Winkelmann RK: Nerve Endings in Normal and Pathological Skin. Springfield: Chrles C Thomas, 1960.
326. Palmer P: Ultrastructural alterations of Merkel cells following denervation. Anat Rec 151:396-397, 1965.
327. Parry CBW, Salter M: Sensory re-education after median nerve lesions. Hand 8: 250-257, 1976
328. Parry CBW*: Rehabilitation of the Hand.* London: Butterworths, pp 92, 107-109, 112-113, 1966
329. Patton H: Split-skin grafts from hypothenar area for fingertip avulsions. Plast Reconstr Surg 43: 426-429, 1969
330. Paul RL, Goodman H, Merzenich M: Alterations in mechanoreceptor input to Brodmann's areas 1 and 3 of the post-central hand area of Macaca mulatto after nerve section and regeneration. Brain Res 39: 1-19, 1972.
331. Paul RL, Merzenich M, Goodman H: Representation of slowly- and rapidly-adapting cutaneous mechanoreceptors of the hand in Brodmann's areas 3 and 1 of Macaca mulatto. Brain Res 36:229-249, 1972.
332. Pearson GHJ: Effect of age in vibratory sensibility. Arch Neurol Psychiatry 20: 482-496. 1928
333. Pease DC, Quilliam TA: Electron microscopy of the Pacinian corpuscle. J Biophys Biochem Cytol 3:331 – 342, 1957.
334. Penfield W, Rasmusen AT: *The Cerebral Cortex of Man: A Clinical Study of Localization of Function.* New York: Macmillan, 1950.
335. Perry JF, Hamilton GF, Lachenbuch PA, et al: Protective sensation in the hand and its correlation to the ninhydrin sweat test following nerve laceration. Am J Phys Med 53:113-118, 1974.
336. Phelps PE, Walker E: Comparison of the finger wrinkling test results to established sensory tests in peripheral nerve injury Am J Occup Ther 31:565-572, 1977.
337. *Physical Diagnosis: A Physiologic Approach to the Clinical Examination.* Boston: Little Brown, 1968, Ch 20, pp 408-410
338. Pinkus F: Uber Hautsinnesorgane neben den menschlichen Haar (Haarscheiben) und ihre vergleickenden anatomische Bedeutung. Arch Mikrosk Anat EntwMech 65: 121 – 128, 1904.
339. Ponten B: Grafted skin: Observation on innervation and other qualities. Acta Chir Scand [Suppl] 257:1- 78, 1960.
340. Poppen NK, McCarroll HR Jr: Reply.J Hand Surg 5:92-93, 1980
341. Poppen NK, McCarroll HR Jr, Doyle JR, et al: Recovery of sensibility after suture of digital nerves. J Hand Surg 4:212-226, 1979.
342. Porter RW: Functional assessment of transplanted skin in volar defects of digits: A comparison between free grafts and flaps. J Bone Joint Surg 50A:955-963, 1968.
343. Porter RW: New test for fingertip sensation. Br Med J 2: 927-928, 1966

344. Posch JL, dela Cruz-Saddul F: Nerve repair in trauma surgery: A ten-year study of 231 peripheral injuries. Orthop Rev 9: 35-45, 1980
345. Posch JL, Marcottte DR: Carpal tunnel syndrome: An analysis of 1,201 cases. Orthop Rev 5: 25-35, 1976
346. Posner MA, Smith RJ: The advancement pedicle flap for thumb injuries. J Bone Joint Surg 53A: 1618-1621, 1971
347. Powell TPS, Mountcastle VB: Some aspects of the functional organization of the cortex of the post-central gyrus of the monkey: A correlation of findings obtained in a single unit analysis with cytoarchitecture. Bull Johns Hopkins Hosp 105: 133 – 163, 1959.
348. Powell TPS, Mountcastle VB: The cytoarchitecture of the post-central gyrus of the monkey Macaca multta. Bull Johns Hopkins Hosp 105: 108-131, 1959
349. Pubols LM, Pubols BH Jr, Munger BL: Functional properties of mechanoreceptors in glabrous skin of the raccoon's forepaw. Exp Neurol 31: 165 – 182, 1971.
350. Ranson SW: Degeneration and regeneration of nerve fibers. J Comp Neurol 22:487-546, 1972.
351. Reid DAC: Experience of a hand surgery service. Br J Plast Surg 9:11-16, 1956.
352. Reid DAC: The neurovascular island flap in thumb reconstruction. Br J Plast Surg 19: 234-244, 1966
353. Reid RL, Werner J, Sunstrum C: Preliminary results of sensibility re-education following repair of the median nerve. Am Soc Surg Hand Newsletter 15, 1977
354. Remensnyder JP: Physiology of nerve healing and nerve grafts, in Krizek TJ, Hoopes JE (eds): *Symposium on Basic Science in Plastic Surgery*. Saint Louis: CV Mosby, 1976, Ch 24.
355. Renfrew S, Melville ID: The somatic sense of space (choraesthesia) and its threshold. Brain 83: 93-112, 1960
356. Renfrew S: Fingertip sensation: A routine neurological test. Lancet 1: 396-370, 1969
357. Ridley A: A biopsy study of the innervation of forearm skin grafted to the fingertip. Brain 93:547- 554,1970.
358. Ridley A: Silver staining of nerve endings in human digital glabrous skin. J Anat 104:41 – 48, 1969.
359. Ridley A: Silver staining of the innervation of Meissner corpuscles in peripheral neuropathy. Brain 91:539-552, 1968.
360. Rivers WHR, Head H: A human experiment in nerve division. Brain 31:323 - 450. 1905.
361. Roland PE: Asterognosis: Tactile discrimination after localized hemisphere lesions in man. Arch Neurol 33: 543-550, 1976
362. Rorabeck CH, Clarke KM: The pathophysiology of the anterior tibial compartment syndrome: An experimental investigation. J Trauma 18: 229-304, 1978
363. Rosen JM, Kaplan EN, Jewett DL, et al: Fascicular sutureless and suture repair of the peripheral nerves: A comparison study in laboratory animals. Orthop Rev 8: 85-92, 1979
364. Rosenberg G: Effect of age on peripheral vibratory perception. J Am Geriatr Soc 6: 471- 481, 1958
365. Rothschild NMV: A Classification of Living Animals. New York: John Wiley & Sons, 1961.
366. Ruch TC, Fulton JF, German WJ: Sensory discrimination in monkey, chimpanzee and man after lesions of parietal lobe. Arch Neurol Psychiatry 39: 919-938, 1938
367. Rumpf J: Ueber exinem Fall von Syringomjlie nebst Beitragen zur Untersuchung der Sensibilitat. Neurol Certralbl 8: 183-190, 222-230, 1890
368. Rydel A, Seifer W: Untersuchungen ueber das Vibrationsgefuhl oder die sogenannte Knochensensibilitat (Pallasthesie), Arch Psychiatr Nervenkr 37: 488-536, 1903
369. Sakellarides H: A follow-up study of 173 peripheral nerve injuries in the upper extremity of civilians. J Bone Joint Surg 44A: 140-148, 1962
370. Salisbury RE, Taylor JW, Levine NS: Evaluation of digital escarotomy in burned hands. Plast Reconst Surg 58: 440-443, 1976
371. Sanders FK, Young JZ: The role of the peripheral stump in the control of fibre diameter in generating nerves. J Physiol 103:119-136, 1944.
372. Sanders FK, Young JZ: The influence of peripheral connections on the diameter of regenerating nerve fibres. J Exp Biol 22:203-272, 1947.
373. Sanders FK: Histopathology of nerve grafts, in Seddon HJ (ed): *Peripheral Nerve Injuries*. London: Her Majesty's Printing Office, 1954, pp 134-155
374. Santoni-Rugiu P: Experimental study on reinnervation of free grafts and pedicle flaps. Plast Reconst Surg 38:98-104, 1966.
375. Satinsky D, Pepe FA, Liu CN: The neurilemma cell in peripheral nerve degeneration and regeneration. Exp Neurol 9:441-451, 1964
376. Saxod R: Developmental origin of the Herbst cutaneous sensory corpuscle. Experimental analysis using cellular markers. Dev Biol 32:167 – 178, 1973.
377. Schlenker JD, Kleinert HE, Tsai T: Methods and results of replantation following traumatic amputation of the thumb in sixty-four patients. J Hand Surg 5: 63-70, 1980
378. Schneider RJ, Kulics AT, Ducker TB: Proprioceptive pathways of the spinal cord. J Neurol Neurosurg Psychiatry 40: 417 – 433, 1977.
379. Seddon H: *Surgical Disorders of Peripheral Nerves.* Baltimore: Williams & Wilkins Co, 1972, Ch 2,14.
380. Seddon HJ, Medawar PB, Smith H: Rate of regeneration of peripheral nerves in man. J Physiol 102:191-215, 1943.
381. Seddon HJ: Methods of investigating nerve injuries, in Seddon HJ (ed): *Peripheral Nerve Injuries.* London: Her Majesty's Stationery Office, 1954, Ch I, pp 1-15.

382. Seddon HJ: The use of autogenous grafts for repair of large gaps in peripheral nerves.Br J Surg 35: 151-167, 1947
383. Seddon HJ; Nerve grafting and other unusual forms of nerve repair, in Seddon HJ (ed): *Peripheral Nerve Injuries.* London: Her Majesty's Printing Office,1954, pp 389-417
384. Shaffer JM, Cleveland F: Delayed suture of sensory nerves of the hand. Ann Surg 131:556-563, 1950.
385. Silver A, Montagna W, Versaci A: The effect of denervation on sweat glands and Meissner corpuscles of human hands. J Invest Dermatol 42:307-324, 1964
386. Silver A, Versaci A, Montagna W: Studies of sweating and sensory function in cases of peripheral nerve injuries of the hand J Invest Dermatol 40:243-258, 1963.
387. Siminoff R: Quantitative properties of slowly-adapting mechanoreceptors in alligator skin. Exp Neurol 21: 290 – 396, 1968.
388. Simpson SA, Young JZ: Regeneration of fiber diameter after cross-unions of visceral and somatic nerves. J Anat 79:48-64, 1944.
389. Smith HR: The ultrastructure of the human haarscheibe and Merkel cell. J Invest Dermatol 54:150 – 159, 1970.
390. Smith J: Microsurgery of peripheral nerves. Plast Reconstr Surg 33: 317-329, 1964
391. Smith JR, Bom AF: An evaluation of fingertip reconstruction by cross-finger and palmar pedicle flaps. Plast Reconstr Surg 35:409-418, 1965.
392. Smith KR: The structure and function of the Haarscheibe. J Comp Neurol 131:459 – 474, 1967.
393. Snow JW: The use of a volar flap for repair of fingertip amputations: A preliminary report. Plast Reconstr Surg 40: 163-168, 1967
394. Spencer PS, Schaumberg HH: An ultrastructural study of the inner core of the Pacinian corpuscle. J Neurocytol 2:217 – 235, 1973.
395. Spindler H, Dellon AL: Results of electrodiagnostic studies in a well defined popularion of peripheral compression neuropathies, in press 1981
396. Spinner M: *Injuries to the Major Branches of the Peripheral Nerves of the Forearms,* ed 2. Philadelphia: WB Saunders, 1978, pp198-202
397. Stopford JSB: An explanation of the two-stage recovery of sensation during regeneration of a peripheral nerve. Brain 49: 372-386, 1926
398. Stopford JSB: *Sensation and the Sensory Pathway*. London: Longsmans, Green, 1930, Ch XI.
399. Straille WE: Sensory hair follicles in mammalian skin: The tylotrich follicle. Am J Anat 106: 133 – 148, 1960.
400. Strauch B, Tsur H: Restoration of sensation to the hand by a free neurovascular flap from the first web space of the foot. Plast Reconstr Surg 62: 361-367, 1978
401. Stromberg WB, McFarlane RM, Bell LL, et al: Injury of the median and ulnar nerves. J Bone Joint Surg 43A: 717-730, 1961
402. Sturman MJ, Duran RJ: Late results of fingertip injuries. J Bone Joint Surg 45A: 289- 298, 1963
403. Sunderland S: Rate of regeneration in human peripheral nerve Arch Neurol Psychiatry 58:251-295, 1947
404. Sunderland S: *Nerves and Nerve Injuries*, ed 2. Edinburgh: Churchill-Livingstone, 1978, Ch 8.
405. Sunderland S: Capacity of reinnervated muscles to function efficiently after prolonged denervation. Arch Neurol Psychiatry 64:755-771, 1950.
406. Sunderland S: Funicular suture and funicular exclusion in repair of several nerves. Br J Surg 40: 580-587, 1953
407. Sunderland S: The pros and cons of funicular nerve repair. J Hand Surg 4: 201-211, 1979
408. Swanson, AB, Goran-Hagert C, Swanson GD: Evaluations of impairment of hand functions, in Hunter JM, Schneider LH, Mackin EJ, et al (eds). *Rehabilitation of the Hand.* Saint Louis: CV Mosby, 1978, Ch 4
409. Symns JLM: A method of estimating the vibratory sensation, with notes on its application in diseases of the central and peripheral nervous system. Lancet 1: 217-218, 1918
410. Talbot WH, Darian-Smith I, Kornhuber HH, et al: The sense of flutter-vibration: Comparison of the human capacity with response patterns of mechanoreceptive afferents from the monkey hand. *J Neurophysiol* 31: 301 – 334, 1968.
411. Tallas R, Staniforth P, Fisher TR: Neurophysiological studies of autogenous nerve grafts. J Neurol Neurosurg Psychiatry 41: 677-683, 1978
412. Terui A: Reinnervation in the free skin graft. Jpn J Plast Reconstr Surg 18:392-399, 1975.
413. Terzis JK: Functional aspects of reinnervation of free skin grafts. Plast Reconstr Surg 58:142-156, 1976.
414. Thompson JS: Free hypothenar full-thickness grafts for distal digital defects. Johns Hopkins Med J 145: 126-130, 1979
415. Thomson JL, Ritchie WP, French LO: A plan for care of peripheral nerve injuries overseas. Arch Surg 52:557-570, 1946.
416. Tilney F: A comparative sensory analysis of Helen Keller and Laura Bridgman: Mechanisms underlying sensorium. Arch Neurol Psychiatry 21: 1227-1269, 1929
417. Tomson WB: The general appreciation of vibration as a sense extraordinary. Lancet 2: 1299, 1890
418. Torebjork HE, Halin RG: Perceptual changes accompanying controlled preferential blocking of A and C fiber responses in intact skin nerves. Exp Brain Res 16: 321-332, 1973
419. Treitel L: Arch Psychol Bd, 29: 633, 1897. Cited by Merzenich MM: Some observations on the encoding of somesthetic stimuli by receptor populations in the hairy skin of primates, doctoral dissertation. Baltimore: Johns Hopkins Univ (Physiol), 1968,pp 145-179
420. Trotter WB, Davies HM: Experimental studies in the innervation of the skin. J Physiol 38: 134-246, 1909

421. Trotter WB, Davies HM: The peculiarities of sensibility found in cutaneous area supplied by regenerating nerves. *J Psychol Neurol* 20:102 - 131, 1913.
422. Truex RC, Carpenter MB. *Human Neuroanatomy,* ed 5. Baltimore: Williams & Wilkin, 1964, pp 149, 203-212.
423. Tsatsos C: Address by His Excellency, President of Hellenic Republic, to the Institute of Management Science, Athens, Greece, July1977, quoted by Conomy JP, Barnes KL, Cruse RP: Quantitative cutaneous sensory testing in children and adolescents. Cleve Clin Q 45: 197-206, 1978
424. Turnbull F: Radial-medial anastamosis. J Neurosurg 5:562-566, 1948.
425. Valentin G: Ueber die Dauer der Tasteindrucke. Arch Physiol Heilk 11: 438-478, 587-621, 1852
426. Valibo AB, Hagbarth KE: Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. Exp Neural 21: 270 – 289, 1968.
427. VanBuskirk C, Webster C: Prognostic value of sensory defect in rehabilitation of hemiplegics. Neurology 5: 407-411, 1955
428. Vierck CJ Jr, Jones MB: Size discrimination on the skin. Science 163: 488-489, 1969
429. Vinograd A, Taylor E, Grossman S: Sensory retraining of the hemiplegic hand. Am J Occup Ther 5: 246-250, 1962
430. von Frey M: Beitrage zur Physiologie des Schmerzsinns, II. Ber Sachs Ges Wiss 46:283 - 296, 1894.
431. von Frey M: Beitrage zur Physokogie zur Sinnesphysiologie der Haut, III. Ber Sachs Ges Wiss 5:166 - 184, 1895.
432. von Frey M: Physiologische versuche uber das Vibrationsgefuhl. Biol 65: 417-427, 1915
433. von Frey M: The distribution of afferent nerves in the skin. JAMA 47: 645-648, 1906
434. von Frey M: Untersuchungen über die sinnesfunktionen der menschlichen Haut. Abh Sächs Ges (Akad) Wiss 40:175 - 266, 1896.
435. von Prince K, Butler B Jr: Measuring sensory function of the hand in peripheral nerve injuries. Am J Occup Ther 21: 385-395, 1976
436. Wall P, Dubner R: Somatosensory pathways. Annu Rev Physiol 34: 315 – 336, 1972.
437. Wallace WA, Coupland RE: Variations in the nerves of the thumb and index finger. J Bone Joint Surg 57B: 491-494, 1975
438. Wallace WA: The damaged digital nerve. Hand 7: 139-144, 1975
439. Waller A: Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibers. Philos Trans R Soc Lond 740:423-429, 1850.
440. Walsche FMR: The anatomy and physiology of cutaneous sensibility: A critical review. Brain 65:45 - 112, 1942.
441. Walton R, Finseth F: Nerve grafting in the repair of complicated peripheral nerve trauma. J Trauma 17: 793-796,1977
442. Weber E: Ueber den Tatsinn. Arch Anat Physiol, Wissen Med (Muller's Archives) 1:152-159, 1835.
443. Webster HF: The relationship between Schmidt- Lantermann incisures and myelin segmentation during Wallerian degeneration. Ann NY Acad Sci 122: 29-38, 1965.
444. Webster N: *The Living Webster Encyclopedic Dictionary*. Chicago: English Language Inst of America, 1975.
445. Weckesser EC The repair of nerves in the palm and fingers. Clin Orthop 19: 200-207, 1961
446. Weckesser EC: *Treatment of Hand Injuries*. Chicago: Western Reserve Press, 1974
447. Weddell G, Palmer E, Palli W: Nerve endings in mammalian skin. Buil Rev 39:159 - 195, 1955.
448. Weddell G, Sinclair DC, Feindel WH: Anatomical basis for alterations in quality of pain sensibility. *J Neurophysiol* 11:99-109, 1948.
449. Weddell G, Guttmann L, Guttmann E: The local extension of nerve fibres into denervated areas of skin. J Neurol Neurosurg Phychiatry 4:206-225, 1941.
450. Weddell G, Palmer E, Palli W: Nerve endings in mammalian skin. Biol Rev 30:159 – 195, 1955.
451. Weddell G, Sinclare DC: "Pins and Needles": Observation on some of the sensations aroused on a limb by the application of pressure. L Neurol Neurosurg Psychiatry 10: 26-46, 1947
452. Weddell G: Multiple Innervation of sensory spots in skin. J Anat 75:441 – 446, 1941.
453. Weeks PM, Wray RC: *Management of Acute Hand Injuries.* St. Louis: CV Mosby, 1973, pp 302-303
454. Weeks PM, Wray RC: *Management of Acute Hand Injuries; A Biological Approach*, ed 2. St. Louis: CV Mosby, 1978
455. Weiland AJ, Villarreal-Rios A, Kleinert HE, et al: Replantation of digits and hands: Analysis of surgical techniques and functional results in 71 patients with 86 replantations. J Hand Surg 2:1-12, 1977.
456. Weinstein S: Tactile sensitivity in the phalanges. Percept Mot Skills 14:351-354, 1962.
457. Werner G, Mountcastle VB: Neural activity in mechanoreceptive afferents: Stimulus response relations, Weber functions, and information transmission. J Neurophysiol 28: 359 – 397, 1965.
458. Werner JK: Trophic influence of nerves in the development and maintenance of sensory receptors. Am J Phys Med 53:127-142, 1974 (68 references).
459. Werner JK, Omer GE Jr: Evaluating cutaneous pressure sensation of the hand. Am J Occup Ther 24: 347-356, 1970
460. Whitesides TE, Haney TC, Harado H, et al: A simple method for tissue pressure determination. Arch Surg 110: 1311-1313, 1975
461. Whitsel BL, Petricelli LM, Ha H, et al: The resorting of spinal afferents as antecedent to the body representation in the post central gyrus. Brain Behav Evol 5: 303 – 341, 1972.
462. Whitsel BL, Petrucelli LM, Sapiro G, et al: Modality representation in the lumbar and cervical fasciculus gracilis of squirrel monkeys. Brain Res 15: 67 – 78, 1969.
463. Wilgis EFS, Maxwell GP: Distal digital nerve grafts: Clinical and anatomic studies. J Hand Surg 4: 439-443, 1979

464. Williamson RT: The vibratory sensation in diseases of the nervous system. Am J Med Sci 164: 715-727, 1922
465. Winkelmann RK, Breathnach AS: The Merkel cell. J Invest Dermatol 60:2 – 15, 1973.
466. Winkelmann RK: Effect of sciatic nerve section on enzymatic reactions of sensory reactions of sensory end-organs. J Neuropathol Exp Neurol 21:655-657, 1962
467. Winkelmann RK: *Nerve Endings in Normal and Pathologic Skin*. Springfield, III: Charles C Thomas, 1960.
468. Woolard HH, Weddel G, Harpman JAL Observations on the neurohistologic basis of cutaneous pain. J Anat 74:413 - 419, 1940.
469. Woltman HW, Wilder RM: Diabetes mellitus: Pathologic changes in the spinal cord and peripheral nerves. Arch Intern Med 44: 576-603,1929
470. Woltman HW: Neuritis associated with acromegaly. Arch Neurol Psychiatry 45: 680-682, 1941
471. Wong WC, Kanagastuntheram R: Early and late effects of median nerve injury on Meissner's and Pacinian corpuscles of the hand of the macaque (M. fascicularis). J Anat 109:135-142, 1971.
472. Woodhall B, Beebe GW: *Peripheral Nerve Regeneration—A Follow-Up Study of 3635 World War II Injuries*, Veterans Administration Medical Monograph. Washington, DC: US Govt Print Office, 1956, p 309.
473. Woolsey CN: Organization of somatic sensory and motor areas of cerebral cortex, in Harlow HF, Woolsey CN (eds): *Biological and Biochemical Basis of Behavior*. Madison: Univ Wisc Press, 1958.
474. Yahr MD, Beebe GW: Recovery of motor function, in Seddon HJ (ed): *Peripheral Nerve Regeneration.* Washington DC: US Gov Printing Office,1956, Ch III, pp 71-202
475. Young VL, Wray CR, Weeks PM: The results of nerve grafting in the wrist and hand. Ann Plast Surg 5: 212-215, 1980
476. Zachary RB, Holmes W: Primary suture of nerves. Surg Gynecol Obslet 82: 632-651, 1946
477. Zachary RB: Results of nerve suture, in Seddon HJ (ed): *Peripheral Nerve Injuries.* London: Her Majesties Stationery Office, 1954, pp 254-388.
478. Zaleski AA: Regeneration of taste buds after transplantation of tongue and ganglia grafts to the anterior chamber of the eye. Exp. Neurol 35:519-528, 1972.
479. Zalewski AA: Combined effects of testosterone motor, sensory or gustatory nerves on reinnervation of regeneration of taste buds. Exp Neurol 24:285-297, 25:29-37, 1969.
480. Zollmann PE, Winkelmann RK: The sensory innervation of the common North American raccoon (Procyon loto). J Compt Neurol 119:149 – 157, 1962.

INDEX