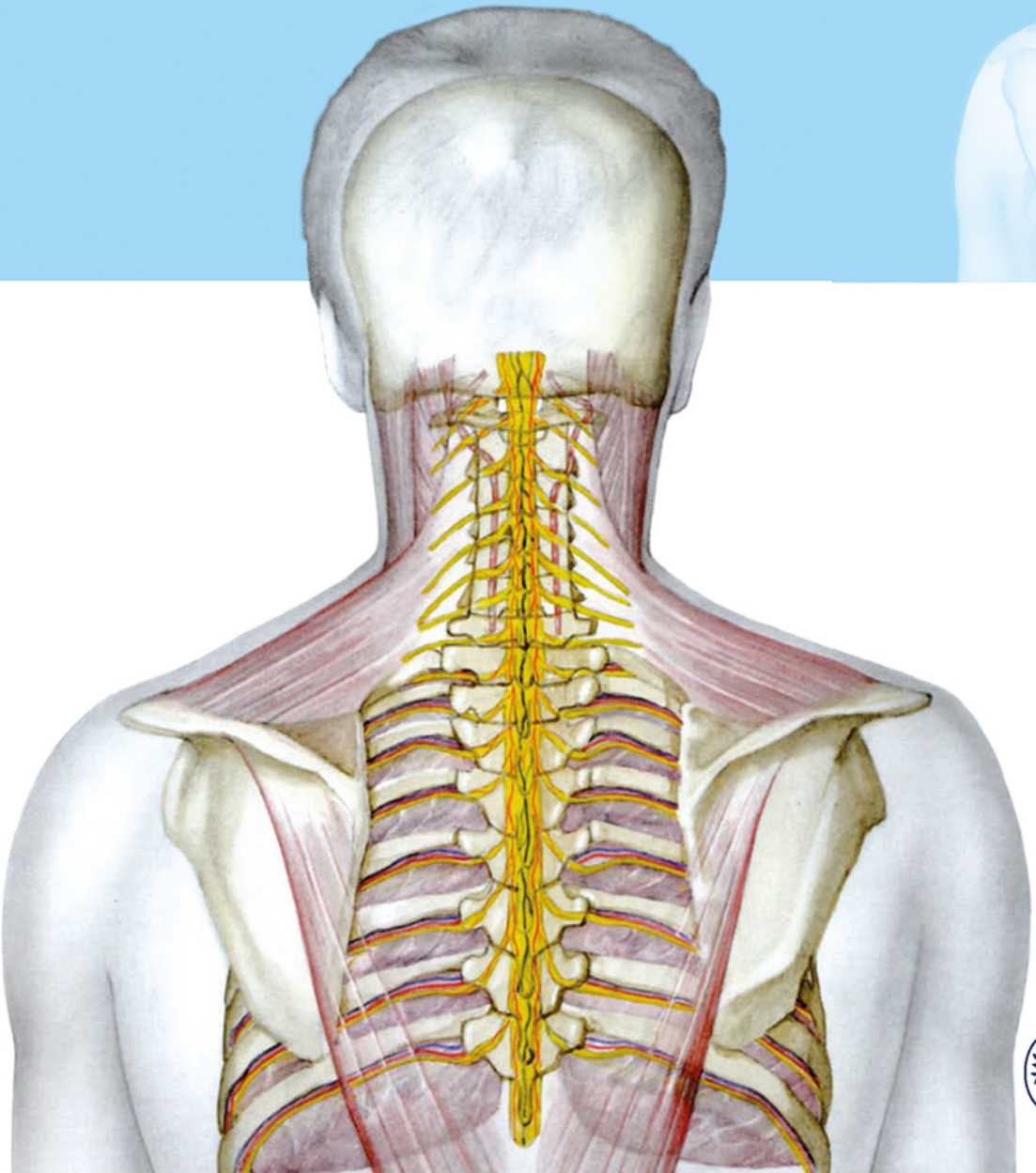
Textbook and Atlas of Neural Therapy

Diagnosis and Therapy with Local Anesthetics

Hans Barop



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Textbook and Atlas of Neural Therapy

Diagnosis and Therapy with Local Anesthetics

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182 illustrations

Thieme
Stuttgart • New York • Delhi • Rio de Janeiro

Library of Congress Cataloging-in-Publication Data is available from the publisher.

This book is an authorized translation of the 2nd German edition published and copyrighted 2015 by Karl F. Haug Verlag in MVS Medizinverlage Stuttgart GmbH & Co. KG, Stuttgart. Title of the German edition: Lehrbuch und Atlas Neuraltherapie

Translator: tolingo translation agency, Hamburg/Germany

Illustrator: Reinhold Henkel, Heidelberg/Germany

Body-Painting: Heike Dimler, MD, Hamburg/Germany

1st Italian edition 2003

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Thieme Publishers Stuttgart
Rüdigerstrasse 14, 70469 Stuttgart, Germany
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Thieme Publishers New York
333 Seventh Avenue, New York, NY 10001, USA
+1-800-782-3488, customerservice@thieme.com

Thieme Publishers Delhi
A-12, Second Floor, Sector-2, Noida-201301
Uttar Pradesh, India
+91 120 45 566 00, customerservice@thieme.in

Thieme Publishers Rio, Thieme Publicações Ltda.
Edifício Rodolpho de Paoli, 25º andar
Av. Nilo Peçanha, 50 – Sala 2508
Rio de Janeiro 20020-906 Brasil
+55 21 3172 2297 / +55 21 3172 1896

Cover design: Thieme Publishing Group
Typesetting by Ditech, India

Printed in Germany by CPI Books GmbH 5 4 3 2 1
ISBN 978-3-13-241049-7

Also available as an e-book:
eISBN 978-3-13-241050-3

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Many thanks to the brothers Ferdinand and Walter Huneke and all subsequent physicians dedicated to the development of neural therapy as a comprehensive new treatment method for the benefit of patients.

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Preface

The first observations of the "side effects" of local anesthetics started at the same time as local anesthesia was developed for surgical purposes. As so often happens in applied medicine, ultimately a new therapy concept with a very broad scope of application emerged as a result of attentive and detailed observation. Thanks to the consistent work of the physicians and brothers Ferdinand and Walter Huneke, this treatment method, initially based on individual observations with local anesthetics, was able to be developed and spread through numerous applications.

In 1963, Peter Dosch published the first comprehensive neural therapy textbook in which he summarized more than 60 years' experience in the therapeutic potential of local anesthetics, thus making this information available for teaching. Other major contributors to the spread of neural therapy are the countless doctors whose observations - to some extent even before Huneke - confirmed the efficacy of the first experiences in the therapeutic use of local anesthesics and thereby helped to stabilize the method and enable its further expansion.

The 1st German edition of my textbook "Lehrbuch und Atlas Neuraltherapie ...." was published 20 years ago. On the one hand, it was based on the enormous variety of therapeutic experience published over decades by neural therapists as reproducible "empirical medicine". On the other hand, the medical knowledge of the neuroanatomical and neurophysiological principles of the autonomic nervous system were used as the scientific basis of neural therapy.

The scientific facts about the neuroanatomy and neurophysiology of the autonomic nervous system have grown significantly in the meantime. Numerous studies and trials have shown substantial involvement of this system in the pathogenesis of various diseases (e.g. inflammation, pain, degeneration). Many anatomical and neurophysiological textbooks and individual works published in the last 20 years increasingly detail the interaction of autonomic dysfunctions in numerous diseases. Here the focus is on the regulation of microcirculation and simultaneous organ and tissue function through the autonomic nervous system. At the same time, an intensive search began for ways to therapeutically implement these findings. The current thinking primarily points in the direction of drug therapy methods.

The epistemological foundations of neural therapy have been strongly integrated with this greatly increased knowledge of the autonomic nervous system. Further experiences in the practice of neural therapy, the gradual acceptance of certain components of the method in different fields of medicine and the introduction of neural therapy as a subject for medical students at some universities indicate an increasing integration of neural therapy as an independent method of treatment.

This book can give students the opportunity to learn the basics of neural therapy and, in particular, it is designed to illustrate the influence of the autonomic nervous system on numerous diseases. Qualified physicians should use this textbook along with practical 2-year training to expand their therapeutic options in practice, independently of their specialist training.

Neural therapy offers the opportunity to answer the still-open question of the therapeutic realization of pathogenetic correlations between different disorders related to dysfunctions of the autonomic nervous system, especially the sympathetic nervous system. To this end, the decades of experience in pragmatic neural therapy are available. Through thoughtful and critical approaches, academic medicine has a proven therapy concept in the form of valuable and reliable practical experience which makes a further search for e.g. medications influencing the autonomic system unnecessary. On the other hand, neural therapy gratefully expands and confirms its theoretical foundations from comprehensive academic findings.

The second German edition of "Lehrbuch und Atlas Neuraltherapie" was expanded to include the growing evidence of neurovegetative anatomy and physiology. The anatomical details of autonomic end formation have become clearer through modern imaging methods such as immunohistochemistry, tracer techniques and electron microscopy. At the same time, the knowledge of the diversity of transmitter substances has increased, resulting in more clarity in the etiology and pathogenesis of diseases with regard to the interdependence of stimulus and stimulus response, the physiological and pathological processes that occur via the autonomic nervous system with simultaneous feedback. This not only confirms the observations by Rickers, which he summarized in relations pathology, but also illustrates the logical therapeutic conclusion which can be conceptionally rediscovered in neural therapy.

The creation of the second German edition was made possible by the cooperation and exchange of ideas between neural therapists and academic institutes of anatomy and neurophysiology, among others. The empirical data resulting from the treatment of patients can be placed on a comprehensive scientific basis in continuous discussion with academic medicine, providing both sides – neural therapists as well as researchers - with clearer ideas about the function of the autonomic nervous system, its influence on the body, and the potential for therapeutic use.

This English edition of *Textbook and Atlas Neural Therapy* grew out of the international dissemination of neural therapy, and the diagnostic and therapeutic use of local anesthetics. Neural therapy originated and developed in the German speaking world and until now, most of the literature was written in German. The growing international interest in this method has necessitated a translation of the new edition into the international medical language. It is our hope that an important gap can be filled.

Acknowledgement

First, I must thank my editor Ms. Angelika-M. Findgott, Thieme Publishers Stuttgart – Germany, for her consistently friendly support. She organized and supervised the various steps of the translation and the overall development of this textbook for which I am very grateful.

I would also like to thank Professor J. Giebel und Professor T. Koppe from the Anatomical Institute at the University of Greifswald for continuous consultation and discussion about the anatomy of the neural autonomic system both in the dissection room and in literary recommendations. For the countless detailed conversations and discussions about observations in the practice of neural therapy in conjunction with the scientific foundations, I would like to thank Professor L. Fischer, professor and chair of neural therapy at the University of Berne, author of the textbook "Neuraltherapie, Neurophysiologie, Injektionstechnik und Therapieempfehlungen" (now in its 4th edition), who continues to publish many papers on the scientific nature, efficacy and cost-effectiveness of neural therapy.

Furthermore, my special thanks go to Dr. S. Resch, neural therapist and senior physician at the Headache Clinic in Königstein, for her detailed assistance in the revision and editing of the textbook.

Last but not least, my thanks go to my patients. Each of them, as individual cases, provided me with the majority of empirical data without which the practice of neural therapy — in balance with the scientific principles — would not have been possible.

Hamburg, Fall 2017
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1 History of Local Anesthesia and Neural Therapy

1.1 Introduction

The history of anesthesia,[274] whether used prophylactically before surgery or therapeutically to treat existing pain, occupies a prominent place in medicine, because pain caused by illness or injury is one of the most common symptoms in everyday medical practice. The methods of targeted pain treatment were highly variable until the end of the 19th century. In addition to medicinal forms, various methods of localized pain reduction for surgical procedures were developed, such as tissue compression, and later nerve compression with truss pad, and the application of cold to specific sites.

A completely new form of localized pain treatment was first described in 1839 by **Lundy, Taylor**, and **Washington**. Using precursors of the modern syringe, they tried administering morphine solutions under the skin to achieve a reduction in pain. With the development of the syringe by the French **Pravaz** (1843), and the hollow cannula by the Scottish **Wood** in the same year, it was possible for the first time to achieve pain relief through targeted injections of morphine solutions into painful areas and nerves. However, local anesthesia, i.e., the complete alleviation of pain, could not be achieved with morphine solutions.

Koller, an ophthalmologist at the University of Vienna, came into contact with **Freud** in 1883 during his neurological training.[274,282] Freud had experience with cocaine, which he used to treat heart diseases and nervous exhaustion or depression. In a self-test, Freud determined the analeptic effect of cocaine in addition to its anesthetic effect on the tongue and oral mucosa, and reported this to his colleague. Koller was able to experience this anesthetic effect in his own self-test, especially when suffering from a painful gum inflammation, which he daubed with a cocaine solution on the advice of Freud.

In contrast to Freud, as a surgical ophthalmologist Koller saw the obvious potential for pain-free surgery using cocaine. He applied this property of cocaine therapeutically and, after preliminary trials with animals, performed the first cataract surgery using local anesthesia on September 11, 1884. At a meeting of doctors in Vienna on October 17, 1884, he first reported the successful use of cocaine for local anesthesia of the eye. This was also the starting point for the use of local anesthesia throughout surgery worldwide, which then evolved with breathtaking speed.

Only then was it clear to Freud what a groundbreaking discovery he had been involved in. In a report in Heitler's *Zentralblatt für die gesamte Therapie*, he had already reported on the anesthetic effect of cocaine before Koller, and considered the use of cocaine for localized painful infections. Freud was more interested in the therapeutic use than the possibility of a local anesthetic for surgical procedures. He recommended that the ophthalmologist von Königstein use cocaine on iritis and trachoma. He himself had experimentally (and unsuccessfully) attempted to treat trigeminal neuralgia with a cocaine injection targetedto the trigeminal nerve. Worth mentioning is the 1863 report published in Paris by the Peruvian general physician **Moreno y Maiz** on an animal experiment in which a bullfrog leg was anesthetized by way of cocaine infiltration.

1.2 Anesthesia and the Treatment of Pain

1.2.1 Local Anesthesia

Considering the initial phase of local anesthesia thus far, at this very early stage there were already two different pathways for the newly discovered drug, cocaine:

1. Targeted local anesthesia, i.e., anesthesia for surgical purposes, which was eagerly awaited by the world of surgical treatment.
2. Slightly overshadowed by local anesthesia, the therapeutic use of local anesthesia for existing pain, whether due to neuralgia or tissue inflammation (Freud).

When keeping this two-pronged development in mind and not allowing the concept of pure local anesthesia for surgical purposes to dominate at first sight, local anesthesia and neural therapy can be easily differentiated.

Knowledge about both pathways is still required, since the technique of local anesthesia in the implementation of neural therapy falls into the realm of the technical.

Infiltration, Block, and Spinal Anesthesia

In the rapid development of local anesthesia for surgical purposes, the names **Halstedt, Hall**, and **Hartley** are representative of infiltration anesthesia and block anesthesia, which they used in animal experiments and later in human surgery. The first major drawbacks of the drug cocaine came to light: overdoses and dependence with repeated use. Halstedt had become addicted to cocaine through numerous self-tests but was cured after undergoing detoxification; Hall, who had also become addicted, died.

On the one hand, increased experience with the drug **cocaine** resulted in successful local anesthesia for surgery; on the other hand, an increase in overdose deaths occurred. Thanks to the Parisian surgeon **Reclus**, the cocaine dosage was corrected after the initial euphoria and a number of iatrogenic deaths, and the use of cocaine for local anesthesia could be continued and developed further. The 20 to 30% cocaine solution first used for topical anesthesia resulted in severe intoxication and even death. Reclus was able to prevent both intoxication and deaths by reducing the concentration initially to 2 to 3% and later to 0.5% solutions.

Block anesthesia, the selective suppression of sensitive peripheral nerves, evolved from infiltration anesthesia,

i.e., local numbing through local infiltration of cocaine. With more centrally acting local anesthesia, **Bier** developed spinal anesthesia, which he first successfully performed on August 15, 1898. His idea was to use the more centrally implemented anesthesia to create a more comprehensive anesthesia with lesser amounts of cocaine than were used in pure block anesthesia. He achieved this by intrathecal injection in the lumbar region with 3 mL of an 0.5% solution of cocaine. Bier was also able to report on the "postspinal headache" after the self-test with this new neuraxial anesthesia.

The American neurologist **Corning** had successfully performed neuraxial anesthesia before Bier, though not in preparation for surgical treatment, but for treating existing pain. To what extent this involved true spinal anesthesia with intrathecal administration or epidural anesthesia remains unclear.

With regard to the history of local anesthesia, this meant a breakthrough in surgical development in the public eye. With the advancement of local anesthesia, the number of general narcosis procedures previously using chloroform and ether could be reduced and thus many, sometimes fatal, incidents involving general narcosis could be avoided.

Emergence of Segmental Therapy

Less exciting, however, was the development in the therapeutic use of local anesthetics, since it suffered from a lack of attention that still exists even today in the medical landscape of surgery. On closer inspection, however, it turns out that the use of local anesthetics for purely therapeutic use has at least as much potential as local anesthesia for surgery.

In the analysis of the history of neural therapy, it is useful to provide some preliminary guidance for clarifying its fundamental difference from purely local anesthesia. The names representing the beginning of neural therapy are partly the same as those for the development of local anesthesia. These are predominantly the names of surgically qualified doctors who used the injection of local anesthesia in their daily practice. The first observations pointing the way toward neural therapy were made when local anesthetic was not applied to surgical procedures but to preexisting pain.[446,469,470] Now, it was frequently observed that despite the local anesthesia wearing off, the preexisting pain symptoms were reduced or even completely disappeared.

Reconsider the earliest days of local anesthesia when Freud shared with Koller his first observations on mucosa anesthesia after oral ingestion of cocaine. Freud's logical, rather intuitive decision to apply a local anesthetic for therapy and not for anesthesia would prove to be correct in the shadow of the rapid development of local anesthesia in surgery. At the same time that the French surgeon **Reclus** reduced the concentration of cocaine and ultimately prevented its decline in use due to frequent toxic complications, the German **Schleich** developed "refined local anesthesia" also by reducing the cocaine concentration, by targeted infiltration of nerves, and by additional cooling of the tissue with ethyl chloride.

This combination resulted in a radical reduction of the toxic effects of cocaine, so that the local anesthetic in this "defused form" prevailed.

Schleich also used a 0.5 to 1% strength solution of cocaine for purely therapeutic purposes.[446] In 1898, he was the first to observe that not only local infiltration of cocaine alleviated rheumatic symptoms during the anesthetized period, but also the rheumatic symptoms were alleviated for a long time thereafter, or recurred only to a lesser extent. This first documented successful application of local anesthetics for therapeutic purposes can be characterized as the birth of neural therapy. The method was refined over the next few years and developed into the first part of neural therapy, namely segmental therapy.

Independently of Schleich, **Spiess** also observed in clinical use that repeated anesthesia resulted in not only a strikingly pain-free surgical wound beyond the duration of the anesthesia, but at the same time wound healing, in this case in the throat area after a tonsillectomy, that was clearly less prone to irritation than without the repeated local anesthesia.[469,470] In addition, he observed that existing inflammatory wound healing disorders were resolved faster and without irritation. Spiess published these new clinical observations in 1906 in the "*Münchner Medizinische Wochenschrift*" ["Munich Weekly Medical Journal"] under the title "The Healing Effect of Anesthetics."[470]

1.2.2 Neural Therapy

Development

Parallel to the use of local anesthesia and neural therapy, pharmacologists were intensively researching alternative substances to cocaine with the aim of achieving comparable anesthetic quality without the toxic side effects. In 1905, **Einhorn** succeeded in producing a local anesthetic with the same anesthetic quality as cocaine, but without any addictive side effects. The substance was procaine (p. 37), which was used worldwide as a local anesthetic after 1905 and is used today for purely therapeutic purposes because of its short duration of action.

Once cocaine, which was used until 1905, was replaced with procaine, the path was cleared for the use of less dangerous local anesthesia and neural therapy. After the first reports of therapeutic applications from **Schleich** and **Spiess** made little impression, the works of **Leriche** and colleagues garnered attention.[299] Leriche's extensive neurosurgical experience certainly contributed to this, having first used the effect of local anesthesia intraoperatively.[302]

Specifically, the study of the sympathetic nervous system, at first purely surgically and later also using neural therapy, provided **Leriche** with important information on the wide range of possible applications of local anesthetic for therapy. The surgical removal of the stellate ganglion for therapeutic purposes—published in 1920—and the therapeutic "stellate infiltration," also first performed by him, basically gave comparable results; consequently,

repeated stellate ganglion block prior to the extirpation was considered by him to be a less traumatic procedure. The term "bloodless knife of the surgeon,"[301,302] as coined by Leriche, stems from the application of this method. His therapeutic recommendations resulted from impressive clinical trials involving the infiltration of local anesthetics into sympathetic nerve structures to affect diseases that could not yet be treated satisfactorily. Stellatum injections in the case of pulmonary embolism, cerebral embolism, and vascular dyskinesias after injury or for various headache disorders are just a few examples. Leriche's other observation, that the consolidation of a fracture occurred in half the time under repeated procaine infiltration, underscores the value of the sympathetic nervous system. No less important are his observations on the intra- and periarterial application of local anesthetics for the treatment of vasomotor disorders. His book *The Surgery of Pain* convincingly presents his decades of experience in neurosurgery and neural therapy.[302]

Without knowledge of the therapeutic use of local anesthetics already practiced by Leriche, **Ferdinand Huneke**, a general practitioner in Dusseldorf, unintentionally became aware of the local anesthetic procaine when he injected his migraine-suffering sister with a mixed preparation recommended by another colleague, whereby the migraine abruptly disappeared.[223] He injected atophanyl, a drug meant for the treatment of rheumatic symptoms, which was available in two versions: for intravenous injection as pure atophanyl and for intramuscular injection with the addition of procaine. He had inadvertently given the intramuscular injection intravenously, which did not lead to the complication of cardiovascular depression as indicated by the manufacturer. When the injection was repeated, the migraine did not abate as expected; this time he had used the drug intended for intravenous injection without the addition of procaine. Thus, Huneke found that the actual active substance responsible for these two different responses was procaine. In fact, on the occasion of his sister's next migraine attack, he injected pure procaine intravenously and was able to curtail the migraines. He and his brother **Walter Huneke,** who was also a general practitioner, began to use the product for a variety of disorders. In addition to traditional drug therapy through intravenous and intramuscular administration, they developed targeted injection into painful tissue structures, nerves and blood vessels, joints, and ganglia.

When the first paravenous injection of a patient with headache showed the same therapeutic effect as intravenous injection, already frequently performed, the idea developed that it was not the general distribution of procaine in the body that provided the crucial therapeutic effect, but rather this "healing process" must obviously proceed over neural structures because of their repeatedly striking rate of occurrence. The Huneke brothers suspected the autonomic system as guiding this process and published their collective therapeutic experience with procaine in the article "Unknown remote effect of local anesthesia"[223] for the first time in 1928. Over time, they characterized their therapy with local anesthetics as "healing anesthesia." They had not yet departed from the idea of anesthesia, which in this case means only the reversible suppression of pain-conducting fibers. The pharmacological basis of membrane research, which would prove the stabilizing effect of general anesthetics on each membrane and not only on nerve cells, was not known at that time. The healing processes which repeatedly proceeded analogously in a variety of diseases caused the brothers to focus on the idea of uniform involvement of the autonomic system.

Lightning Reaction—The Discovery of the Interference Field

In 1940, **Ferdinand Huneke** first observed something entirely new.[236] A female patient, who he had just treated unsuccessfully for a very painful functional disorder of the left shoulder, presented again due to exacerbated chronic recurrent osteomyelitis in the right lower leg. Knowing that inflammation could be successfully treated using procaine, he infiltrated the inflamed lower leg section with **impletol**, a 2% procaine solution with a caffeine additive. Immediately thereafter, the painful left shoulder became completely mobile and symptom-free, to the surprise of the doctor as well as the patient. The reaction in the left shoulder, which had occurred directly after the remote infiltration in the right lower leg, suggested a connection between the two diseases. The Huneke brothers focused on this result, as it was key to many chronic diseases which could not be healed with previous therapeutic procedures.

This first "lightning reaction" meant the revision of the idea formulated much earlier by **Pässler**, which had defined the focal site as bacterially contaminated tissue with metastatic distribution of bacteria and their toxins throughout the body. The speed at which the patient's left shoulder became pain-free was evidence that the nerves involved in the left shoulder disorder were controlled by the inflammation of the right lower leg. It was therefore possible that chronic diseases may be caused or maintained by focal sites and could be cured only through their "suppression" by means of local anesthetic or surgical removal (e.g., teeth), whereby the effect of the suspected focal site is only revealed after injection into the site. It is to the undeniable credit of the brothers **Ferdinand** and **Walter Huneke** that they recognized the fundamental nature of this singular observation and newly coined the term "focal site." They introduced the concept as "nerval interference field" and developed the interference field test as a therapeutic principle. This resulted in three ground rules:

1. Any chronic illness may be due to an interference field.
2. Any illness or injury can leave behind an interference field.
3. Each interference field disorder is curable only by "suppression" of the interference field.

Certainly, similar observations had been made before Huneke. Some dentists no doubt learned from their patients that after removal of a diseased tooth, for example, long-lasting back pain suddenly disappeared. As early as 1936, **Leriche** observed and described the cessation of

remote pain after infiltration of a nonirritated scar. However, the therapeutic consequences of this observation were first recognized and implemented by **Ferdinand** and **Walter Huneke**.

Term

The word "neural," previously used in context to distinguish therapeutic use from the local anesthesia practiced only for surgical procedures, was established in 1940 after the discovery of the lightning reaction by Huneke.

In 1938 **von Roques**,[430] who also worked with neural therapy like many other doctors, started the English to German translation of a book of basic principles by **Speransky.**[467] (He was familiar with the extensive neurological and experimental work that had been carried out by Speransky in Russia.) Thus, von Roques coined the term "neural therapy according to Huneke," which is still used today. Before that time, the therapeutic use of local anesthetics was paraphrased with other terms such as "procaine therapy," "impletol treatment," and "healing anesthesia." Since a particular drug is not essential to the therapy, since other local anesthetics can be used, neither is local anesthesia the basis of the therapy, but only a partial property of the local anesthetic, the term neural therapy was certainly more comprehensive.

The suffix "according to Huneke" is not primarily regarded as a tribute to the "inventor," but rather indicates that it consists of the following two parts:

1. Segmental therapy, which was practiced before 1940. It included local treatment with local anesthetics "in the diseased segment."
2. Interference field therapy; this means the ubiquitous possible therapeutic use of local anesthetics, detached from the segment, depending on the location of the suspected interference field.

The term "therapeutic local anesthesia," which is still in use today, was coined by **Gross**[179] after 1940 to characterize neural therapy. But this is confusing in that local anesthesia does not account for the therapy. Painless diseases without the neural therapeutically negligible side effect of a local anesthetic can also be treated, e.g., hyperthyroidism, vertigo, and chronic sinusitis.

2 Theoretical Foundations and Practice-Based Hypotheses

2.1 Introduction

In order to make the basic principles of neural therapy understandable, it is first necessary to describe the anatomical substrate that enables a diagnostic and therapeutic approach to the organism. A prerequisite is the realization that all bodily functions are linked to an information system, which coordinates these functions using control loops and ensures homeostasis. Major significance must be attributed to the autonomic nervous system with regard to causal relationships in physiological or pathophysiological functions.[69,425]

The separate analysis of an anatomical structure serves to identify it more clearly, albeit with partial loss of insight into its functional relationships. The anatomical isolation of the autonomic nervous system illustrates this particularly well, as the central and peripheral connections to other anatomical structures are extremely obvious. Knowledge of the anatomy and physiology of the autonomic nervous system is still not sufficiently disseminated in medicine and therefore does not receive the necessary consideration in diagnosis and therapy.

The basic function of the autonomic nervous system is the rapid antagonistic and coordinated control of individual tissue functions of an organism in order to enable homeostasis—or, better, homeodynamics—and to properly respond to external influences to which the organism is continuously exposed. The aim is to keep individual organ functions in balance. Thus, the autonomic nervous system represents the conductive structure on which all qualitatively uniform but quantitatively variable stimuli proceed as a steadily changing flow of information.

In order to control vital functions such as breathing, digestion, metabolism, secretion, water balance, electrolyte balance, temperature, blood pressure, and reproduction, a distribution of the system up to the terminal vascular bed and a high degree of cross-linking are necessary to enable a feedback-based information exchange between the individual organ and functional areas which are independent from one another. Thus, the autonomic nervous system requires a "nervous circulation", with afferent and efferent branches similar to the vascular system with its arterial and venous branches.

2.2 Autonomic Nervous System

2.2.1 Anatomy and Function

In terms of function, it is useful to understand the anatomy of the **stimulus pathway** in terms of both the efferent and afferent systems. The centers of the sympathetic and the parasympathetic branches can be found in the diencephalon in the hypothalamus region and represent the overriding functional link between the autonomic, somatic, and endocrine systems. Anatomical differentiation in this autonomic organization level between the sympathetic and parasympathetic parts is not possible because there is close anatomical and functional networking of both systems. The experimentally structured stimulus or severing of these diencephalic centers results in overriding antagonistic functions for entire organ areas. **Rohen** has created a table that illustrates the influences of the organ systems (▶Table 2.1).[429]

Here, Rohen develops the terms **ergotropic** (sympathetic adrenergic) and **trophotropic** (parasympathetic, cholinergic) **reaction conditions** to clarify the functional relationships. The region of the hypothalamus with the corresponding autonomic nucleic regions has an afferent and efferent interconnection with the cranial nerves, pituitary, and the cortex, and thus has a promotional or inhibitory effect on perception organs, hormone-forming organs (pituitary, thyroid, parathyroid, kidneys and adrenal glands, gonads), and somatomotor activity and somatic sensitivity. Further peripherally, the anatomy of the autonomic nervous system is far clearer, as the anatomical mapping of the segmental structure of the **sympathetic nervous system** at the level of the spinal cord becomes less complex and therefore differentiable.

Although the **parasympathetic nervous system** has no segmental distribution, its course is defined with the cranial nerves III (oculomotor nerve), VII (facial nerve), and IX (glossopharyngeal nerve) and the parasympathetic cranial ganglia (ciliary ganglion, pterygopalatine ganglion, otic ganglion, submandibular ganglion).

The most extensive parasympathetic portion is represented by the cranial nerve X, the vagus nerve. The sacral portion of the parasympathetic nervous system from segments S2–S4 completes the picture of the parasympathetic nervous system, which becomes anatomically and functionally comprehensible and thus diagnostically and therapeutically accessible by way of the described topography.

Cellular structure is common to the sympathetic as well as the parasympathetic portions. The relatively small nerve cells generally have multiple nerve fibers per cell unit, which efferently ensure the principle of divergence and combine impulses from the periphery using the afferent pathway. This is the basis for the autonomic nervous system's typical divergence, which enables widely divergent information transmission on the efferent branch and thereby has a harmonizing effect on entire organ areas. The conduction rate of the autonomic nervous system is significantly slower than that of the somatic system. Since the nerve fibers are poorly myelinated or unmyelinated and have a very small diameter in the peripheral organ distribution of up to 0.3 µm, the conduction rate is between a maximum of 25 m/s (afferent A-δ fiber) and a maximum of 0.5 m/s (C fiber).

▶ **Table 2.1** Influence of the organ systems according to Rohen[429]

Organ	Effect of the (ortho-) sympathetic nervous system (adrenergic effects)	Effect of the parasympathetic nervous system (cholinergic effect)
Eye		
• Iris	• Mydriasis	• Miosis
• Ciliary muscle	• Disaccommodation	• Accommodation
Heart		
• Rate	• Accelerating	• Decelerating
• Contraction strength	• Increased	• —
• Rhythm	• Ventricular extrasystoles, tachycardia, fibrillation	• Bradycardia, atrioventricular block, vagal cardiac arrest
• Conduction time	• Shortened	• Prolonged
Vessels		
• Coronary arteries	• Expansion	• Narrowing?
• Muscle vessels	• Narrowing	• —
• Intestinal vessels	• Narrowing	• Expansion
Lung		
• Bronchial musculature	• Slackness	• Contraction
• Bronchial mucosa	• Decreased secretion	• Increased secretion
Gastrointestinal canal		
• Peristalsis	• Inhibited contraction	• Increased
• Sphincters	• ?	• Slackness
• Glandular secretion	• Decreased	• Promoted
Extrahepatic bile ducts and gall bladder	Slackness	Contraction
Spleen (musculature)	Contraction	Slackness
Salivary glands	Secretion (thick secretion)	Secretion (thin secretion)
Pancreatic islets of Langerhans	Decreased insulin secretion	Increased insulin secretion
Liver	Glycogenolysis	Biliary discharge
Adrenal medulla	Discharge of adrenaline and noradrenaline	Reduction in the release of adrenaline and noradrenaline
Bladder		
• Musculature	• Slackness	• Contraction
• Sphincter	• Contraction	• Slackness
Cerebral cortex	General activation, increased awareness	Inhibition, loss of consciousness
General response	Ergotropic “output nerve”	Trophotropic “recovery nerve“

In addition to different cell types, the autonomic ganglia also have strong vascularization. This certainly serves not only the nutritional supply of the nerve cells, but also probably the metabolic functions mediated via neurotransmitters.[429] Switch processes take place in the ganglia, e.g., from the preganglionic to the postganglionic neurons. Not only do cholinergic synapses transmit the information further, but so do dopamine-containing cells (SIS) with dopaminergic synapses that terminate at the perikarya of the postganglionic neurons and affect their conduction through modulation.

2.2.2 Sympathetic Efferent

The nucleic regions of the sympathetic nervous system are in the intermediolateral nucleus of the spinal cord at the level of segments C8–L2 (L3). The preganglionic fibers exiting the spinal canal via the intervertebral foramen together with the anterior root portions initially course for a short distance together with the spinal nerves in order to leave them via the myelinated white ramus communicans for the paravertebral ganglion. Here, they become connected partly synaptically with the nerve cells of the ganglion cells of higher and deeper segments and leave after switching to the second neuron via the gray ramus communicans in order to extend in the direction of the periphery with the spinal nerve bundle.

This results in the **first** efferent **distribution pathway** of the sympathetic nervous system, which is directed toward the periphery all the way to the effector organs. It includes the sympathetic supply to the skin and extremities. As a result, the peripheral, segmentally structured somatomotor and somatosensory nerves always proceed

accompanied by sympathetic postganglionic fibers. These sympathetic fibers in turn originate from several paravertebral ganglia of the sympathetic chain, resulting in a wider divergence compared to the somatomotor and somatosensory innervation area. The somatosensory innervation area of skin regions is more precisely delineated, while the sympathetic supply to the skin does not have such strict, segment-bound division.

The **second distribution pathway** of the sympathetic nervous system proceeds from the intermediolateral nucleus of the spinal cord via the ganglia without switching to the prevertebral ganglia (e.g., celiac ganglion, aorticorenal ganglion, superior and inferior mesenteric ganglion). The switch to the second neuron occurs only in these prevertebral ganglia. From here, the sympathetic nervous system reaches the abdominal and pelvic organs, primarily accompanied by the arterial and venous vessels as well as free nerve bundles. The sympathetic supply of the thoracic cavity and the thoracic organs and the entire head and upper extremities proceeds via the three cervical ganglia, in which the switch to the second neuron takes place, and via the first six thoracic sympathetic ganglia; the cervical and thoracic ganglionic section receive their preganglionic fibers from the intermediolateral nuclei of segments C8–T6. The sympathetic supply of the abdominal cavity, the retroperitoneal space, the pelvis, and the lower extremities proceeds with overlap from segments T5–L2 (L3) and the associated lumbar (abdominal, sacral, coccygeal) ganglia.

Thus, the efferent sympathetic nervous system proceeds together with the brain and spinal nerves as well as with the blood vessels up to the capillary end flow path in order to reach the periphery. This anatomically describes its ubiquitous distribution. Therefore, the efferent sympathetic nerve supply to the periphery proceeds together with spinal nerves and blood vessels down to the capillary system. The parasympathetic nervous system does not have this generalized distribution, since—according to current knowledge—it is not involved in the supply of the extremities and the skin.

The **third distribution path** of the sympathetic nervous system can be called interganglionic. Over the beadlike connection of the 23 individual ganglia, there are homolateral connections in cranial and caudal directions, as well as in the contralateral direction via interganglionic nerve branches to the para- and prevertebral sympathetic ganglia. The 23 paravertebral and 5 prevertebral ganglia groups only face 15 sympathetic nucleic origin areas in the spinal cord. Thus, in accordance with the divergence, numerous preganglionic fibers of a spinal segment must be switched to the second neuron in several ganglia. This results in greater "security" of the impulse transfer in the vertical homolateral direction, i.e., the failure of a ganglion does not cause any significant restriction in function of the sympathetic nervous system. However, at the spinal level with unilateral sympathetic stimulation, the co-reaction—albeit limited—of the sympathetic nervous system on the contralateral side is possible through the horizontally extending interganglion branch. This explains why the degeneration of the hip joint, which is linked to reduced blood supply—i.e., increased sympathetic stimulation, among other things—initially occurs on one side and later on the other side; it also explains the clinical observation that CRPS (complex regional pain syndrome) on one side of the body can also occur like a "mirror image" on the contralateral side, or explains the phenomenon of "contralateral pain therapy" in which segmental therapy on the "healthy side" mirrors the therapeutic effect on the "affected side."

Special consideration needs to be given to the sympathetic nervous system in the periphery, i.e., in the **area of the terminal vessels**, in which the conducted impulse at the axon terminal is to be transmitted to the target organ. Around 1925, Stoehr was the first to deal with the anatomy of the autonomic nervous system in the area of the terminal vessels, i.e., with the terminating fiber portion in the periphery. He created the concept of the "**terminal reticulum**" which describes the fact that the finest unmyelinated autonomic nerve endings terminate in the interstitial space as inextricable fiber material without direct contact with other cells.[477,478] Thus, the transmission of information via the autonomic nervous system to the organs to be supplied proceeds via the interstitium.

Pischinger et al managed a further significant step.[399,400] They described the terminal autonomic fiber materials as a component of the interstitium to be defined as a system. As further components, they combined the three capillary structures (arterial, venous, lymphatic), the cellular portion (fibrocyte, macrophage), and the extracellular fluid (ground substance) into the so-called interstitial regulation system (p. 13). Thus, the efferent sympathetic nervous system ends as a free "synapse" in the interstitium where the impulse transmission of nerve fibers proceeds through the release of neurotransmitters into the extracellular fluid and thus influences both the capillary system and the cell system of the interstitium.

In addition to the free termination of the efferent sympathetic nervous system, in numerous animal species Fujita et al reported synapses between the end formation of the sympathetic nervous system and the so-called paraneurons.[154] These are special cells in the epithelial lining of hollow organs, glandular ducts, and blood vessel walls that produce transmitters, whose release is modulated by direct autonomic synapses. Similar conditions are found in the skin and mucosa in the dendritic cells, whose function, among others, is the modulation of immunological processes (monocyte–macrophage system) through the absorption of antigenic material and transfer to the lymphocytes.

The description of the function of the efferent sympathetic nervous system incorporating the interstitial regulation system and the paraneurons emphasizes its ubiquitous distribution in the whole organism. On this neurophysiological basis, the sympathetic nervous system can engage as an information system in regulatory activity of all tissue structures.

2.2.3 Sympathetic Afferent

The classification of nerve fibers into A, B, and C fibers does not allow a complete description of the fiber portions allocated to the afferent sympathetic nervous system. Clearly defined is the **sympathetic efferent**, which proceeds from its nucleic regions in the intermediolateral nucleus of the spinal cord (segments C8–L2), over the anterior root, the white ramus communicans of the sympathetic trunk, and the prevertebral ganglia together with the vessels and spinal or cranial nerves. The preganglionic fibers make their way as myelinated fibers to the para-and prevertebral ganglion, and the postganglionic fibers as slightly myelinated or nonmyelinated fibers to the interstitium of the target organ. The **sympathetic afferent** is identified not only through the fiber characteristics (little or no myelinization), but also primarily from its afferent function. (Remaining questions on the microanatomy of this region can currently only be addressed via the clinical, physiological, and pathophysiological functions.)

This divisive view of the efferent sympathetic nervous system and sole designation of the efferent as the sympathetic nervous system[436] is to be challenged, since the designation of the sympathetic nervous system comes from its function. This can only be inferred from the consideration of efferent **and** afferent, i.e., via the neural conduction arc. By analogy, it is equally useful to construct the term "vascular system" from the efferent arterial branch and the venous and lymphatic afferent branch in order to satisfy the related purpose of the vascular system.

Thus, the sympathetic afferent does not result in a uniform picture when considering only the fiber quality. Rather, a sensible approach considers the direct or indirect informing function of the afferent via the posterior horn to the efferent nucleic region in the spinal cord, the reticular formation in the brain and in the hypothalamus. In this respect, fiber quality of the sympathetic afferent results in a mixed picture:

- A-fibers: for pressure, warmth, and stretching (heart, veins, arteries, and lungs).
- B-fibers: for visceral sensitivity, atria, and lungs.
- C-fibers: for warmth, cold, itching, dull surface pain, deep protopathic pain, and visceral pain.

The afferent impulses are conducted from the periphery toward the center and form the reflex arc with the sympathetic efferent fibers. They are connected with the somatic nervous system through numerous circuits and generally course in the same nerve bundles as the corresponding efferent sympathetic nerve fibers. In this case, the identical, now converging, distribution pathway is defined as in the diverging—efferent—sympathetic system.[69] The fiber course thus proceeds via:

- Sensory fibers of the spinal nerves via spinal ganglion and posterior root to the spinal cord.
- Sensory nerves, but then via the white ramus communicans to the ganglion and the gray ramus communicans; then via the anterior and posterior root to the spinal cord: the corresponding ganglion cells are in the spinal ganglion, but probably also in the sympathetic trunk ganglia and the para- and prevertebral sympathetic ganglia.
- Pure autonomic nervous bundles; visceral branch, splanchnic nerves directly to the sympathetic trunk.
- Sympathetic perivascular plexuses to the sympathetic trunk and further via the rami communicantes to the anterior and posterior root of the spinal nerves to the spinal cord.

The afferent fiber processes and the associated localization of the synaptic connections result in the complex transfer of information within the sympathetic nervous system, and especially between the somatosensory and somatomotor systems in the head and the cranial nerves. This is how the autonomic functional area regulates itself in pure autonomic connectivity. The purely autonomic self-regulation is relativized where there are neural connections to the somatic nervous system. In some cases, these narrow autonomic and somatic connections are already at the receptor organ, e.g., at the lamellar bodies. These proprioception organs discharge both an afferent myelinated and unmyelinated afferent autonomic fiber, so that the autonomic nervous system receives both functional and somatosensory supply from one and the same "information organ."[69] Similar relationships are found, among others, in the muscle spindles, on Dogiel's corpuscles, and at Krause's end bulbs.[69]

The functions of the sympathetic afferents are highly variable. They impart the feeling of discomfort (e.g, distension of the bladder) up to pain (overfilled bladder), or vascular pain with irritation of the sympathetic perivascular plexus (e.g., from an infection). When the sympathetic trunk of the throat or the sympathetic carotid plexus is stimulated, the afferent sympathetic branch responds with head, face, neck, tooth, and ear pain.[69]

Considering the comprehensive supply of the entire organism through the efferent sympathetic nervous system, which reaches both the individual organs and the vascular system, the influence of the sympathetic nervous system becomes clear. The efferent sympathetic nervous system modulates organ function in two ways: on the one hand, it controls organ function directly via the interstitial distribution in the interstitial regulation system; on the other hand, it controls the microcirculation of the same organs via the vasomotor system. The efferent role of the sympathetic nervous system along with the afferent impulse inputs not only ensures the purely sympathetic conduction arc, but it also exists in numerous direct and indirect afferent contacts with the parasympathetic nervous system (e.g., intestinal lining) and the somatosensory and somatomotor systems. These functions illustrate the capacity of sympathetic nervous system throughout the whole body. Quite simply, no other peripheral nervous system has the functional range of the sympathetic nervous system.

2.2.4 Parasympathetic Efferent

In contrast to the sympathetic nervous system, which has preganglionic neurons present in the intermediolateral nucleus of the spinal cord in segments C8–L2/L3, the preganglionic neurons of the parasympathetic nervous system are found in various nucleic regions. Unlike the sympathetic nervous system, with the exception of the vagus nerve, these neurons do not form any independent nerves and use cranial and sacral spinal nerves as conductors. Since there is no parasympathetic trunk in which the switching takes place on the second neuron, the fiber length of the preganglionic neurons is very long in contrast to those of the sympathetic nervous system. The switch to the second neuron takes place either shortly before the target organ in parasympathetic ganglia or in the target organ itself.

There is differing information about the location of the source cells of the parasympathetic branch. Clara differentiates cranial, spinal, and sacral components, which is no longer found in modern anatomy textbooks.[69] These three components are taken into consideration in another form through the definition of the "continuous" postganglionic neurosecretion of acetylcholine. This is a defining feature of the parasympathetic nervous system and signifies its difference from the sympathetic nervous system, which secretes noradrenaline.

Also included in this new definition are the names of "sympathetic adrenergic" and "sympathetic cholinergic" efferent innervation that are based on the immunohistochemical detection of the neurotransmitters of the sympathetic and parasympathetic nervous systems.[420,428]

The cranial parasympathetic portion extends in four cranial nerves: oculomotor, facial, glossopharyngeal, and vagus nerves. The parasympathetic preganglionic fibers, which course with the oculomotor nerve, originate from the Edinger–Westphal nucleus, are switched in the ciliary ganglion, and supply the sphincter pupillae and ciliary muscles.

The preganglionic fibers coursing with the facial nerve originate in the superior salivatory nucleus, are switched in the pterygopalatine ganglion, and supply the tear ducts and the glands of the nose and palate via the zygomatic nerve. In the pterygopalatine ganglion, there are further neurons that modulate cerebral circulation intracranially as vasodilators with the cranial nerves (internal carotid artery).[558]

Further parasympathetic fibers from the facial nerve course via the chorda tympani to the lingual nerve, are switched to the second neuron in the submandibular ganglion, and supply the glands at the base of the oral cavity. Finally, parasympathetic fibers course with the peripheral branches of the facial nerve and supply a part of the facial sweat glands.

The preganglionic parasympathetic fibers, which course with the glossopharyngeal nerve, originate from the inferior salivatory nucleus and extend to the otic ganglion, where they are switched to the second neuron, and supply the parotid gland as well as the lip and cheek glands.

The vagus nerve forms the largest cranial part of the parasympathetic nervous system, whose source lies in the dorsal nucleus of the vagus nerve. The area supplied includes the chest and abdomen, whereby the switching to the second neuron takes place in the ganglion of the vagus nerve itself (superior ganglion and inferior ganglion) or in ganglia directly before or within the target organs. The main task of the vagus nerve is the motor supply of the palate and pharynx muscles as well as the entire larynx muscles; the sensory supply of the posterior fossa, a portion of the tympanic membrane, a portion of the skin of the external auditory meatus, the outer ear, and the larynx; and the sensory, secretory, and motor supply of all thoracic and abdominal organs up to the middle third of the transverse colon (Cannon–Böhm point). The rest of the large intestine and the pelvic viscera is supplied via the sacral parasympathetic nervous system.

The second section of the parasympathetic nervous system is the spinal portion of C1–S1 with its root cells from the midportion of the spinal cord, which send their nerve fibers over both the posterior and the anterior root of the spinal cord.[69] The efferent, thin-caliber myelinated fibers of the posterior root have a skin-vasodilating, perspirant, and pilomotor effect. Immunohistochemical studies of the abundant innervation of the sweat glands, sebaceous glands, hair follicles, and arrector pili muscle confirm the NO secretion, as is typical of the parasympathetic nervous system, but refer to them as "sympathetic-cholinergic." In smaller amounts, "sympathetic-adrenergic" fibers and parasympathetic fibers are found in connection with blood vessels of the skin.[74,428]

The efferent fibers, which extend across the anterior root, cannot be distinguished from the sympathetic fibers in the chest and upper lumbar spinal cord. Their function is partly in segment-related sweat secretion, and they may also be significant with regard to muscle tone.

The third parasympathetic section is the sacral portion and includes the segments S2–S4. From the sacral intermediolateral nucleus, the efferent nerve fibers radiate as pelvic nerves into the pelvic plexus via the anterior root. The question remains whether the parasympathetic efferents in their course with the spinal nerves and the blood vessels penetrate all the way into the skin, analogous to the sympathetic nervous system. Clinically, irritation of the skin over the sacrum (S1–S5) can lead to reactions of the rectum (e.g., diarrhea) as an indication of increased parasympathetically induced colon activity. The switch to the second neuron takes place in the pelvic ganglia and in the intramural ganglia of the target organs. The area supplied by the sacral parasympathetic portion comprises the last third of the transverse colon, descending colon, sigmoid colon, rectum and anus, the bladder with urethra, and internal and external sex organs. Bowel and bladder emptying is supported by muscular contraction and relaxation of the internal sphincter muscles. The pelvic splanchnic nerves relax the blood vessels of the external genitals, resulting in blood filling the corpus cavernosum.

The distribution proceeds partly with the vessels, similar to the sympathetic system, in some cases freely without vascular accompaniment via the mesentery and the hollow organs. On and in the hollow organs, myelinated fibers—which are preganglionic up to that point—are switched to the second neuron in numerous intramural ganglia. They supply both the myenteric plexus (Auerbach), which innervates the smooth muscles of the gastrointestinal tract, and the submucosal plexus (Meissner), which is responsible for the mucosa of the gastrointestinal tract. A stimulation of the efferent cholinergic parasympathetic system therefore results in an increased peristalsis and an increased secretion of mucous, with simultaneous cholinergic-induced vasodilation of the supplying blood vessels. On the one hand, the outgoing parasympathetic fibers terminate blindly in the interstitial space. On the other hand, as already described in the sympathetic system, according to Heine[204] and Fujita et al,[154] there are numerous synaptic connections to the paraneurons that are located in the network of the mucosal lining of the hollow organs. The question remains whether the paraneurons receive impulses from both the sympathetic and the parasympathetic system or only from one of these two branches. Given the large number of neurotransmitters formed by the paraneurons, which are transmitted both to the intestine and in the interstitium underneath the basement membrane, the sympathetic and parasympathetic innervation of paraneurons is quite conceivable. The intramural nervous system ensures a separate autonomy for the gastrointestinal tract. Consequently, an isolated, vessel-supplied intestinal segment continues to maintain directed peristalsis as well as mucous membrane function and thus, inter alia, can be used for bladder reconstruction surgery or intestinal interposition.

2.2.5 Parasympathetic Afferent

Although center-directed, the parasympathetic afferents show the same course as the efferents, i.e., an efferent parasympathetic nerve bundle also guides afferent fibers simultaneously. These converge in the vagus nerve and the pelvic nerves (▶Fig. 2.1). The view expressed in several textbooks that the afferent fibers of the parasympathetic nervous system form only an insignificant proportion of the neural structure is in contrast to the published 1994 studies of Linda Rinaman (University of Pittsburgh, Pennsylvania, United States) and Grundy (University of Sheffield, South Yorkshire, England). The study results indicate that approximately 80% of the fibers of the vagus nerve have an afferent function and only about 20% have an efferent function. This means that there is a very close relationship between the entire gastrointestinal tract, the brain stem, and the hypothalamus. A portion of the afferent fibers of the vagus nerve connects with the spinal nucleic regions of the trigeminal nerve, but especially with the terminal nucleus of the spinal tract and the posterior column of the first and second cervical segments.[69] Therefore, through irritation of the afferent parasympathetic fibers, illness in the area supplied by the vagus nerve can lead to irritation of the spinal nucleic regions of the trigeminal nerve and the posterior column at the first to third cervical segments, with corresponding clinical symptoms (facial pain, cervicocephalgia).

The sensory supply of the intestine is ensured by the afferent sympathetic system, which is to be regarded as an actual pain-conducting structure, while the afferent parasympathetic system rather imparts specific organic sensations. Thus, the pain of cholecystitis or gastritis is transmitted by the sympathetic nervous system, while malaise, nausea, and vomiting proceed via the parasympathetic afferents.

2.2.6 Afferent of the Phrenic Nerve

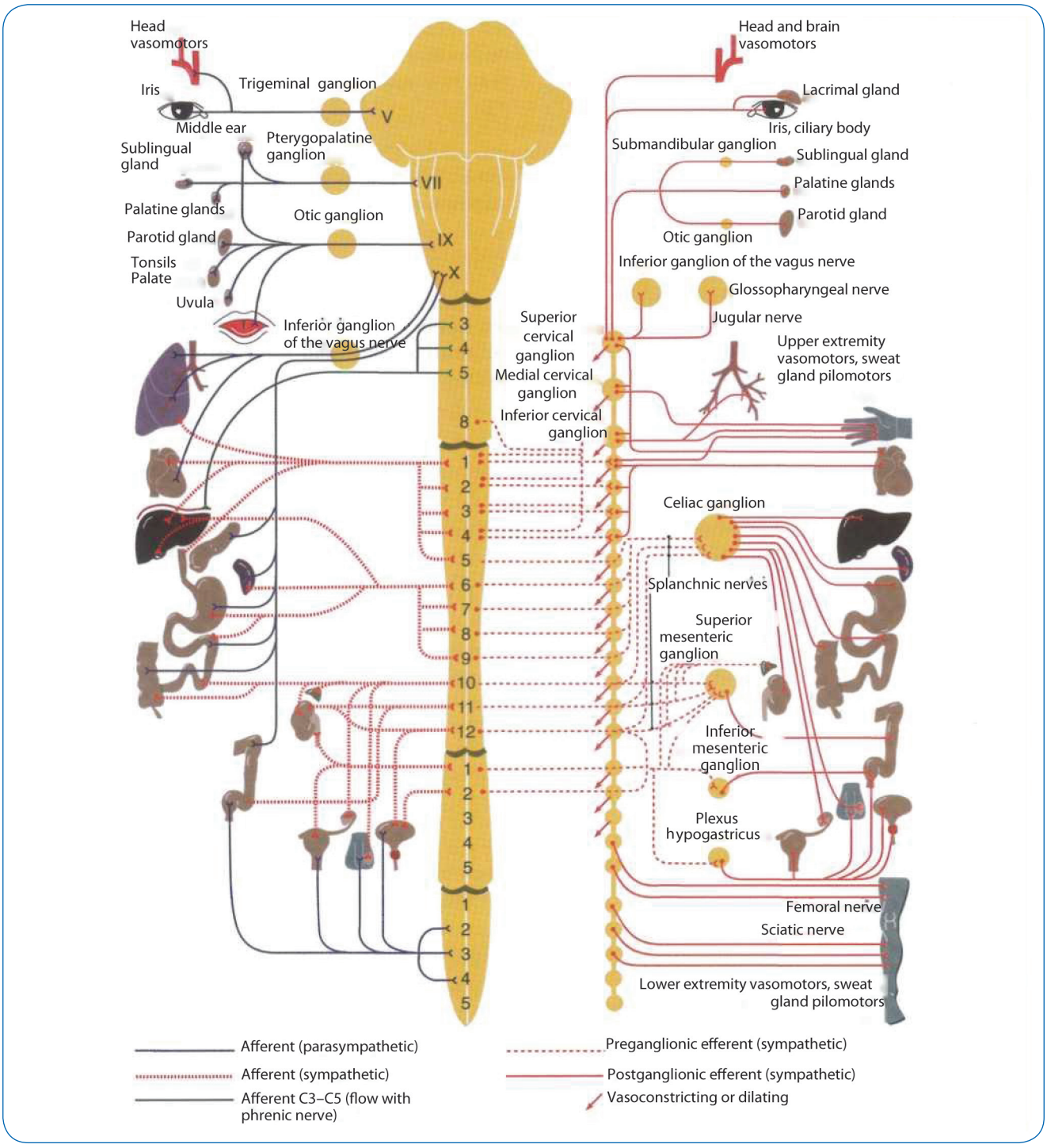
A peculiarity which involves the phrenic nerve and does not affect the autonomic nervous system should be mentioned here because it has clinical relevance. The main task of the phrenic nerve is motor supply to the diaphragm. In addition, the following course in the phrenic nerve: sensory afferents of the lower pleura, pericardium, and subdiaphragmal peritoneum as well as the peritoneal lining of the liver and the pancreas. Further clinical observations suggest that a more extensive afferent supply through the phrenic nerve seems likely, especially since shoulder pain and sensorimotor disorders in the third to fifth cervical segments, the nucleus of the phrenic nerve, occur not only with inflammation of the thoracic space and the upper abdomen, but also in diseases of the organs in the small pelvis (adnexa, uterus, seminal vesicles, and prostate). Since the nucleic regions of the phrenic nerve are not only constantly formed in the third to fifth cervical segments, but also time and again distributed over the segments C3–C7 or C8, reflex symptoms in these corresponding neck segments can occur with abdominal disorders.[69]

This somewhat detailed description of the topography, in particular that of the peripheral autonomic structures, is designed to convey to the reader the multiplicity of distribution channels of the sympathetic and parasympathetic systems and to clarify that the structures associated with the course of the peripheral autonomic nervous system can be used for diagnostic and therapeutic applications of local anesthetics.

Note

The topography of the autonomic nervous system is one of the foundations of neural therapy and a prerequisite for the entire injection technique.

Knowledge of the macroscopic and microscopic anatomy and neurophysiological relationships helps to clarify pathogenetic and etiologic correlations of diverse symptomatics of "idiopathic diseases." The differentiated use of this system for diagnosis and therapy enables a multidisciplinary application.



▶ **Fig. 2.1** Visceral efferent/afferent innervation as the basis of the meso-rhombo-spinal organization of the autonomic reflexes (modified from Fulton).

3 Interstitial Regulation System According to Pischinger and Heine

3.1 Introduction

"*The cell concept is, strictly speaking, only a morphological abstraction. Biologically speaking, it cannot be considered without the milieu of the cell.*"[399,400] This quote by **Pischinger** illustrates the difference between Virchow's cell theory and today's mindset of placing the cell in a functional relationship with the whole organism. **Virchow** believed that each cell of an organism on its own constitutes an elementary organism, which enables the function of the whole through a networked division of labor. According to Pischinger, this view neglects the milieu that is the basis of existence for each cell.

The milieu essentially represents the result of cellular function and therefore, according to Virchow, can be attributed to the cell as the elementary organism. The difference between the mindsets of Virchow and Pischinger is that Virchow considers the cell itself as the source unit of an organism, while Pischinger uses the specific cell efficiency as a starting point. Virchow's mindset created the basis for today's explanation—extending up to the molecular level—regarding the composition of the elementary organism cell, while Pischinger and Heine succeeded in a clarification—extending to molecular sizes—of the function of the nonspecific connective tissue.

Both viewpoints are important for applied medicine. The rather static view of the pathologist Virchow is useful for identification and description of the pathologic structure, while the dynamic mindset of the physiologist and anatomist Pischinger is useful for recognizing disease processes. The consequence of Virchow's cell theory is the linear thinking in diagnosis and therapy which is common today, with the risk that the causal relationships, in particular for chronic illness, are not recognized or incompletely recognized due to lack of consideration of the high level of cross-linking for all organic systems. The result can be found primarily in the symptomatically oriented treatment of chronic diseases by medications (antihypertensives, anti-inflammatory drugs, antipyretics, etc.) that steadily suppress the symptoms of the illness, which also means that the symptoms reoccur when the medication is discontinued. In contrast, harking back to Pischinger, the simultaneous consideration of the interstitial regulation system function in diagnostics and therapy allows for the influence of diseased organs and organ systems through the use of the intrinsic regulation of the organism.

Before Virchow and Pischinger, the pathologists **Bordeu** from Paris (1767) and **Reichert** (1854) from Dorpat indicated the significance of connective tissue, which functions in microcirculation and metabolism between capillaries and the cell system, in addition to its mechanical and supportive function. **Pischinger** recognized that not only the connective tissue played a static filtering role in the cell supply, but also, due to the uniform composition of the extracellular space, a structure had been found that pervades the entire organism and is involved in all cellular functions of the organism as well as the internal and external stimuli affecting it.

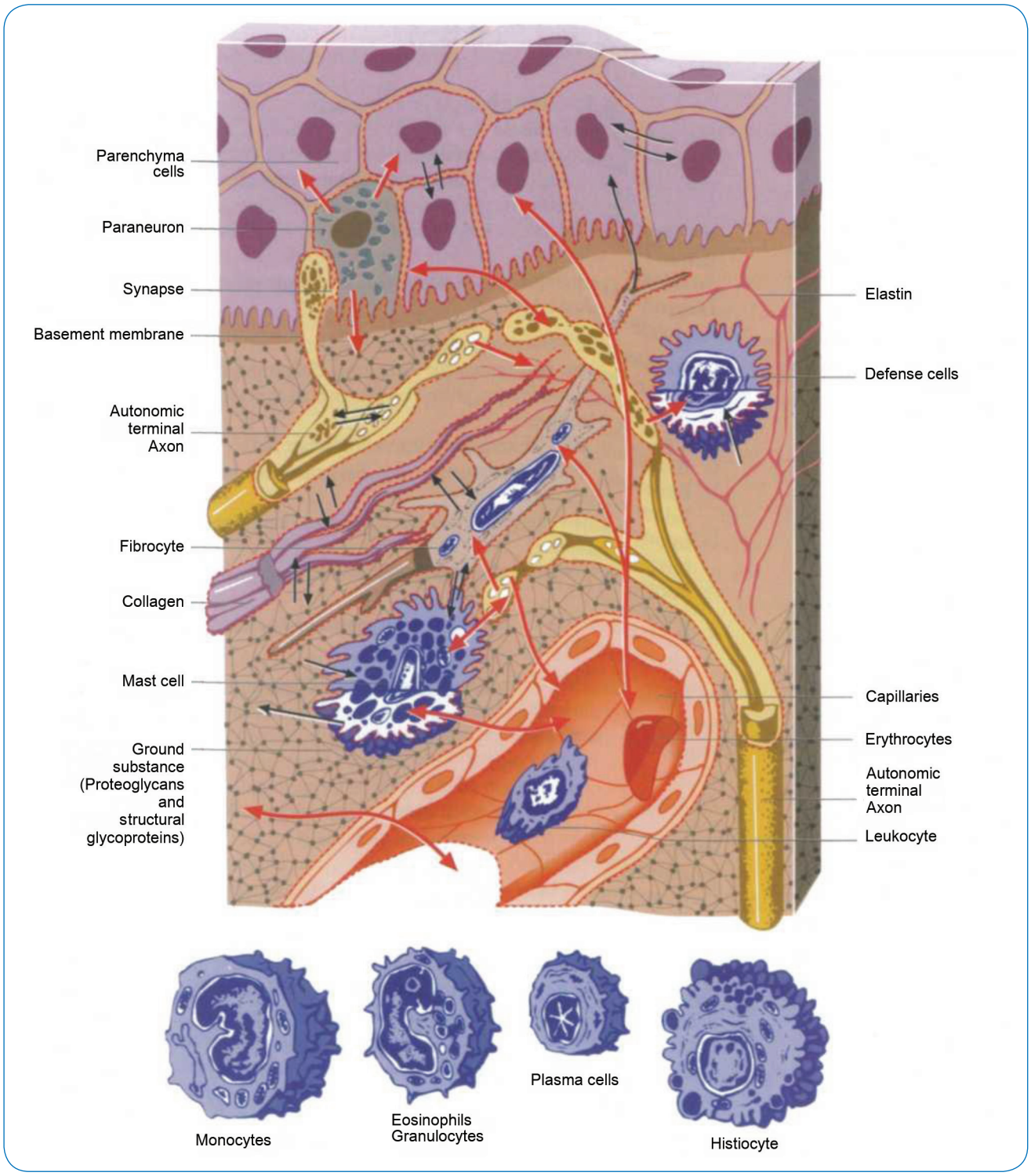
The interstitial regulation system is shown in the schematic drawing (▶Fig. 3.1). The cutaway single capillary represents the capillary branch consisting of arterial, venous, and lymphatic capillaries. The inflow and outflow of oxygen and nutrients, messenger molecules, and cell metabolites as well as cells for immunological processes takes place via the vascular system.

The autonomic end formation is represented by two terminal axons whose efferent impulse delivery and neurotransmitters (acetylcholine, adrenaline) enable the afferent impulse uptake, modulated by changes in the basic substance (e.g., metabolites, hormones, neuropeptides). According to **Fujita et al**[154] and **Heine**,[204] there are also synaptic connections of the autonomic end formation with so-called paraneurons, which use the release of transmitters to influence specifically operating cell systems and also have a feedback effect on the interstitium. The free cellular component of the interstitial regulation system is represented by the pluripotent fibrocyte, which communicates via its cell processes with about 30% of all fibrocytes and is responsible for the synthesis of the ground substance and the production of collagen and elastin, as well as the formation of new cells—among others, the immunocompetent cells— represented by the mast cell as an example of a tissue hormone-producing cell and by the defense cell (macrophage), which is responsible for the immunological processing and dissemination of degradation products, viruses, and bacteria. Other cells that have an immunological function and dispose of the ground substance are shown in ▶Fig. 3.1.

The ground substance is represented as a homogeneous extracellular fluid in a network of glycosaminoglycans (hyaluronic acid and heparin) weaving through the entire interstitium as elongated polysaccharide chains studded with brush-shaped, short-chain proteoglycans. Due to their charge and structure, this network is capable of water binding and ion exchange, i.e., for isotonicity, isoiony, and isoosmy. The interstitial regulation system can be found in the entire organism as the interstitium.

3.2 Structure and Function

The **intercellular structure** basically consists of the pluripotent **fibrocytes**, which are responsible for the synthesis of structural components (collagen, elastin) and the intercellular substance of the interstitium, **the macrophages**, whose main function is the phagocytosis of pathological intercellular structures (viruses, bacteria),



▶**Fig. 3.1** Schematic diagram of the interstitial regulation system modified according to Pischinger and Heine, based on the functional unit of capillaries, autonomic end formation, free cells, and the ground substance.

the **capillaries** (arterial, venous, lymphatic), the **free autonomic nerve cell endings**, and the structured **intercellular substance** verified by Heine, consisting of proteoglycans and structural glycoproteins.

This system, first formulated by Pischinger as the interstitial regulation system (p. 13), has the following functions:

- Supply of energy to the cells.
- Delivery of building blocks for cells and cell products.
- Removal of cell products (e.g., hormones), cell detritus, and phagocytosis of metabolic products.
- Uptake and transfer of immunological stimuli via macrophages (antigens).
- Initiation of cellular repair or regeneration after injury or disease.
- Information transfer via the capillaries (slow, e.g., by hormones, neuropeptides).

- Information transfer via autonomic nerves (fast, e.g., by neurotransmitters).
- Production of the self-regulated ground substance as needed via fibrocytes.
- Regeneration of the interstitial regulation system.

With the interstitial regulation system, the organism has an available structure through which ultimately every cell of the body is informatively and energetically connected to all other cells. The uniform structure of this system means that a stimulus reaching the organism is answered from the interstitial regulation system in a uniform manner, regardless of its location within the organism; the response is then specified as a second step by the cellular system of the interstitium and the specific tissue (organs). In a feedback process, the interstitial regulation system with all of its parts is influenced by the organ tissue, so that the functional condition of the organs can also be incorporated in the autonomic conduction arc and can be thus modified if necessary. Through this system, the various organs are hemodynamically coordinated.

Note

The normal, undisturbed functioning of the interstitial regulation system provides the basis for the body's health and ability to regenerate. The temporary disruption of this function leads to temporary illness, and chronic disruption leads to chronic illness.

According to present knowledge, factors of this chronic disturbance are all the things that stress the individual components of the interstitial regulation system beyond predetermined tolerance limits. These include chemical, physical, viral, and bacterial noxa as well as endogenous toxicants that are discharged to the interstitium by the interstitial cells and the specific working parenchymal cells.

3.3 Significance of Autonomic End Formation

The part of the interstitial regulation system that is essential to neural therapy is the end formation of the autonomic nervous system in the interstitium. The efferent transfer of information is carried out by the following neurotransmitters in the intercellular space:

- Acetylcholine.
- Vasoactive intestinal peptide (VIP; parasympathetic nervous system).
- Adenosine triphosphate.
- Noradrenaline.
- Neuropeptide γ (sympathetic nervous system).

From the intercellular space via the corresponding cell membrane receptors of the interstitial cells and the parenchymal cells, the corresponding cell function is modulated in an inhibitory or facilitative manner depending on which receptors can take up the stimulus. Ideally, the result of this efferent impulse transmission is the balanced stimulus response of the specific tissues. The physiological state probably results from the continuous equalization of internal and external stimuli, because the body responds permanently to fluctuations in its environment.

This condition, which can be best described by the physical concept of oscillation, only becomes balanced if the change in condition created by the autonomic end formation via the efferent pathway triggers centrally oriented information feedback. This is ensured through the afferent branch of the autonomic end formation.

Although it is not possible to differentiate efferent autonomic neurofibrils from afferent in the interstitium, further centrally the already bundled information flow of the afferent inputs can be interrupted at the ganglionic level, for example, by way of a local anesthetic, with a change in clinical symptoms of the target organs supplied by the autonomic end formation.

The physiological function of the autonomic stimulus conduction system is the electrical stimulus transfer (0.5–2 m/s) and the neurosecretion (norepinephrine/acetylcholine) linked to this. In a physiological functional state, this provides the afferent–efferent coupling that ensures **homeostasis**. If the tolerance range of this system is exceeded over a longer period due to excessive stimulation or increased irritability of the sympathetic nervous system, both the electrical stimulus profile and the neurotransmitter profile change as a result. This causes a change in the microcirculation, which leads to an altered metabolic state of the interstitium and the parenchymal cells/organs:

- Oxygen and nutrient deficiency.
- Change in pH value.
- Release of inflammatory mediators (silent inflammation).
- Activation of nociceptors (e.g., pain).

Interstitial dysregulation with simultaneous disruption of microcirculation leads to a disruption of organ function (e.g., pain based on "silent inflammation") as well as structural changes (e.g., degeneration) in the case of chronicity. In summary, a chronic disease process can thus be explained to be a result of chronic pathological stimulation of the sympathetic nervous system.

3.4 Interstitial Regulation System and Autonomic Nervous System

The balanced physiological impulse emission of the autonomic efferent ensures physical microcirculation, which is essential for the exchange of physiological energy and materials. At the same time, the activity of macrophages is modulated, immunological processes are activated or attenuated. The fibrocytes, which are about 30% connected with each other via their cell processes in the organism, are adaptively regulated with regard to their interstitial function and cell formation, the production of ground substance, collagen and elastin, and the "repair" of