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Macro- and Microanatomic Description of Nerve Transfers in the Distal Forearm for the Reconstruction of Hand Function

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1   Introduction

Peripheral nerve injuries are frequently encountered in clinical practice, with nearly 100,000 patients undergoing peripheral nerve surgery in Europe and the United States each year.[75] Severe nerve injury has a devastating impact on the patients' quality of life, often leading to sensory and motor function loss, partial or complete paralysis of a limb, the development of extreme neuropathic pain, or - as is often the case - some combination of these three.

The cause of nerve injuries can be grouped into four major categories: These include penetrating injury, which usually involves sharp transection; trauma-type injury, which generally involves some kind of crush component; massive tissue loss; and avulsion or traction injuries which lead to stretching or tearing of the nerve internally due to extreme tension. Other causes may include ischemia, thermal injury, electric shock or radiation.[11, 19] Most peripheral nerve injuries occur in the upper extremity of the body, where the ulnar nerve – alone or in combination- is most commonly affected.[39]

Nerves can regenerate spontaneously, depending on size and severity of the injury, but their growth can be obstructed by neuroma and scar tissue formation. If recovery fails, surgical intervention becomes necessary,[54] the aim of which is to preserve or restore innervation and function of skin, muscles, soft tissues, skeletal structure and other target organs. This repair can be done by suture or by graft. In extreme instances when the proximal stump is irreparably damaged or if the continuity between the proximal stump and the spinal cord has been ruptured, nerve transfer to the distal stump is possible. The sooner the distal segment is reconnected to the proximal segment and thus to the cell body, the better the result. The outcome of

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reconstructive surgery is largely determined by the quality of hand sensation, the contralateral hand function and the patients' motivation and ability to adapt to any sensory loss.[14]

This study will contribute anatomical and histomorphometric data for nerve transfers in the lower arm and will thereby help the surgeon to decide in which cases to use a nerve transfer and estimate the likelihood of a successful surgery.

Until the late 18th century it was believed that peripheral nerves could not regenerate at all.[74] As a consequence, all types of major nerve injury were treated nonsurgically or by amputation. Improvements in microscopic devices and staining techniques over the course of the 19th century provided the means to examine nerves and nerve tissue in greater detail and permitted researchers to lay the groundwork for a new understanding in nerve pathophysiology and repair. In 1850 Augustus Waller described what happened to a nerve once it was transected ("Wallerian degeneration")[38], Cruikshank noted the regrowth of nerves and in 1905 Cajal clarified the stages and behaviour of axon regeneration.[89]

During the 20th century nerve injuries were increasingly frequent, especially during the wars, which saw the refinement and implementation of many of the clinical and surgical techniques still used in nerve repair today. In 1915, while working with wounded soldiers from World War I, Jules Tinel characterized a tingling sensation that occurs in regenerating nerves ("Tinel sign").[3] That same year the German physiologist Paul Hoffmann described the same phenomena, a tingling sensation triggered by tapping lightly on the nerve. After World War II, Sir Herbert Seddon improved nerve surgery by using bridging grafts, cable grafts and primary and secondary closure[73]. Sir Sydney Sunderland published his new findings of nerve topography after World War II, which led to new repair techniques, among them fascicle repair.[83] Millesi

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introduced new microsurgical instruments and techniques that have facilitated tremendous improvements in nerve repair.[56, 57]

New developments and expanded knowledge about nerve pathophysiology and repair throughout the last century have had a major impact on the outcome of nerve reconstruction. However, while there is a great improvement in the results of directly repaired nerves, large nerve gap reconstruction still remains a major challenge, especially for motor recovery.[75]

1.1 Nerve Anatomy and Injuries

In order to manage nerve injuries, good knowledge about the relevant anatomy, pathology, pathophysiology, electrodiagnosis and the principles of surgical management is necessary.[19] In the following section, the basic principles of these points will be described, which are especially relevant for the planning of a successful nerve transfer.

In order to clinically assess nerve damage, careful physical examination is important. The examination must include a motor and a sensory evaluation and should focus on determining the level of nerve injury and attempt to identify complete from incomplete lesions.[65, 95] The motor evaluation should test range of motion, functionality, and strength in the functional areas of the tested nerve. Each nerve ought to be assessed individually, although all movements should be compared bilaterally for strength and range of motion.

The median nerve innervates both intrinsic and extrinsic muscles of the hand. Intrinsic function can be tested with thumb abduction, whereas extrinsic motor function can be evaluated by letting the patient flex the index finger at the distal and proximal

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interphalangeal joints, the thumb on the interphalangeal joints and the radial wrist. The ulnar nerve also shows intrinsic and extrinsic function. The extrinsic musculature can be tested using proximal interphalangeal flexion of the small finger and flexion of the ulnar wrist. The intrinsic interossei muscles are tested for intrinsic innervation. The radial nerve can be evaluated by letting the patient extend the elbow, wrist, and fingers.

Sensory evaluation evaluates basic protective sensation and 2-point-discrimination (2PD) and depicts all areas of parasthesia. The median nerve supplies index finger, thumb, and proximal palm near the thenar eminence through the cutaneous branch. The ulnar nerve innervates the ulnar side of the hand and the little finger, and the dorsal cutaneous branch supplies the ulnar region on the dorsum of the hand. The radial nerve supplies the dorsal radial aspect of the hand and the first web space.

Additional examinations can help with localizing innervation deficits, like the presence of dry, shiny skin as a consequence of denervation. The Tinel test can help to locate the ends of transected and regenerating axons. Any sign of movement or preserved sensation indicates that the nerve lesion is incomplete. In a first degree lesion the Tinel sign is elicited focally over the area of abnormality. Here, muscle atrophy does not develop (unless as a result of disuse) because there is no axon loss. In a second degree lesion the Tinel sign moves distally at approximately 1 mm/day, implying that the axonal growth cone is advancing. With these lesions, neurogenic atrophy does develop. With third degree lesions, there is atrophy and the Tinel sign indicates that the axons progress distally, but at a slower rate than expected. With fourth and fifth degree injuries, atrophy is severe and develops rapidly, and a distal progress of the Tinel sign cannot be elicited.[19]

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If the findings remain unclear after examination, electrophysiologic diagnosis should be performed, so the extent and grade of the injury can be more accurately estimated. In clinically and electrophysiologically complete lesions, the return of function is indicated by a sign of movement in the physical exam or the return of motor unit action potentials (MUAPs) in the EMG. The EMG is more sensitive than the physical examination, so evidence of reinnervation can be detected weeks to months before any movement or muscle contraction is visible.[37]

Additionally, questionnaires like the DASH-Score ("Disabilities of the Arm, Shoulder, and Hand") can be used to evaluate physical function and symptoms in people with any or several musculoskeletal disorders. It is a 30-item self-report questionnaire that can help clinicians to assess any or all joints in the upper extremity. It can be downloaded from http://www.dash.iwh.on.ca/about.htm.

The Ulnar nerve and its injuries

The ulnar nerve is the continuation of the medial cord of the brachial plexus and contains fibers from the C7, C8 and T1 roots.[36] It is a mixed motor and sensory nerve. It runs through the arm behind the medial epicondyle and into the flexor compartment. In the forearm, its motor branches innervate the flexor carpi ulnaris and the ulnar portion of the flexor digitorum profundus, which supply the ring and little fingers.[76] Just proximal to the wrist, it gives off a dorsal cutaneous branch that supplies the skin over the dorsal side of the little finger and the ulnar half of the ring finger, and then passes over into the palm superficial to the flexor retinaculum in Guyon's canal. At wrist-level, the ulnar nerve passes under the superficial part of the flexor retinaculum (in Guyon's canal) accompanying the ulnar artery, and divides into superficial sensory and deep motor branches.[78] The deep motor branch DBUN innervates most of the intrinsic muscles of the hand: hypothenar muscles, the

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interosseous muscles, the third and fourth lumbricals, adductor pollicis and the deep head of the flexor pollicis brevis. The superficial branch of the ulnar nerve (SBUN) provides sensation in the little finger and the ulnar side of the ring finger. The dorsal sensory branch (DCBUN), also supplies sensation to the part of the dorsum and the volar side of the hand at the ulnar border of the hand.[44]

Injuries of the ulnar nerve can be classified as high or low[52]. Low injuries take place distal to the origins of the motor branches of the flexor carpi ulnaris and ring and little finger flexor digitorum profundus muscles. Although the strength of the extrinsic hand muscles is not influenced, sensation is lost on the ulnar border of the hand and in the ring and little fingers, and the ulnar-innervated intrinsic muscles lose their function. Consequently this shows through a weakened thumb pinch, claw deformity, loss of the normal pattern of finger flexion, and significant loss of hand dexterity and strength.[13, 41] High injuries occur above the aforementioned place. Here, loss of active ring finger flexion, little distal interphalangeal joint flexion, and wrist flexion compound the findings; paradoxically, however, the claw deformity has a tendency to be less severe.[21]

The Median nerve and its injuries

The median nerve is a mixed motor and sensory nerve. It originates in the brachial plexus and forms a union of the terminal branch of the lateral and the median cords of the plexus.[36] It does not supply any muscles in the upper arm. It runs through the anteromedial compartment, through the cubital fossa and enters the forearm between the two heads of the pronator teres.[49, 76] In the forearm, it gives off the the anterior interosseous nerve, which supplies the flexor pollicis longus; the flexor digitorum profundus to the index finger; the pronator quadratus; and—occasionally—the flexor digitorum profundus to the long finger.[77]

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The median nerve itself passes deep into the flexor retinaculum at the wrist. Upon entering the palm, it branches into the motor or recurrent branch to the thenar muscles and the radial two lumbricals, as well as into sensory cutaneous branches that serve the palmar dimensions of the thumb, index, and middle fingers and the radial half of the ring finger.

When the median nerve is injured, it is important to restore its most important functions in the hand. For the resumption of daily activities it is crucial to restore especially the opposition of the thumb and the flexor pollicis longus and index finger profundus function, as well as sensory function– especially in the tip of the thumb.

Median nerve injuries can be classified into high and low level injuries, depending on whether the injury is located distal or proximal to the origin of the anterior interosseus nerve in the forearm. Depending on the injury, different muscles are affected. In low injuries, the thenar intrinsic muscles, the abductor pollicis brevis muscle, the opponens pollicis muscle, and the superficial head of the flexor pollicis brevis muscle are paralyzed, whereas in high injuries the pronator teres, flexor carpi radialis, all the superficiales of the fingers, the profundi of the index and middle finger, flexor pollicis longus, and pronator quadratus muscles also loose their function.[21]

The Radial Nerve and its Injuries

The radial nerve is a mixed motor and sensory nerve. It is the continuation of the posterior cord of the brachial plexus and contains fibers from C7-Th1 roots.[76] In the upper arm it runs through the spiral groove of the humerus and then passes through the upper arm where it supplies the triceps muscle, the anconeus, the brachioradialis and a part of the brachialis muscle before it enters the cubital fossa lateral to the

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biceps tendon. In the forearm its motor branches supply the extensor carpi radialis longus, extensor carpi radialis brevis and the supinator muscle before dividing into deep and superficial branches.

The deep branch innervates muscles for finger and thumb extension before turning into the posterior interosseus nerve, which runs between the two heads of the supinator muscle and passes into the extensor compartment of the forearm.
The superficial branch of the radial nerve (SBRN) branches from the main radial nerve at the lateral epicondyle and runs in the forearm with the radial artery alongside the brachioradialis muscle. It reaches the anterior compartment in the lower third of the forearm between the radius and brachioradialis muscle and bifurcates proximal to the radial styloid into two main branches, which terminate by supplying the skin over the dorsal side of the thumb, index, middle and radial half of the ring finger.[1, 44]

Radial nerve injuries create a significant disability in the hand. Extension of fingers, wrist and thumb is greatly diminished and the patient has difficulty grasping objects. Especially the loss of active wrist extension hinders the patient to have a strong grip or grasp things.[43] Whereas its motor innervation is so crucial for sustaining daily life activities, the sensory part of the radial nerve has less importance. Loss of sensibility on the radial side of the dorsum of the hand may be disturbing, but rarely poses such a strong disability. At times, a person with a complete radial nerve palsy shows no demonstrable sensory deficit. In these cases the superficial branch of the radial nerve is missing, and its function is preempted by the lateral antebrachial cutaneous nerve.[33]

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1.2 Nerve Microanatomy and Pathophysiology

The human organism is endowed with a central nervous system that alerts it to internal or external environmental changes and enables it to react accordingly. The peripheral nervous system connects the central nervous system to the peripheral sensory or executing organs. Peripheral nerves consists of motor fibers to the end plates of skeletal muscle; sensory fibers that supply skin, muscle, tendon and joints; and autonomic fibers to blood vessels, sweat glands, and hair follicle musculature.[10]

The peripheral nerve is built of the following structural features: The endoneurium is a connective tissue that surrounds individual myelinated axons and groups of unmyelinated axons. Axons bundled together form fascicles that are surrounded by the perineurium. The epifascicular (internal) epineurium lies between fascicles. The peripheral nerve is a collection of fascicles which is surrounded by the epineurial (external) epineurium. The endoneurium is longitudinally aligned, whereas the perineurium and epineurium are circumferential.[19, 83 75]

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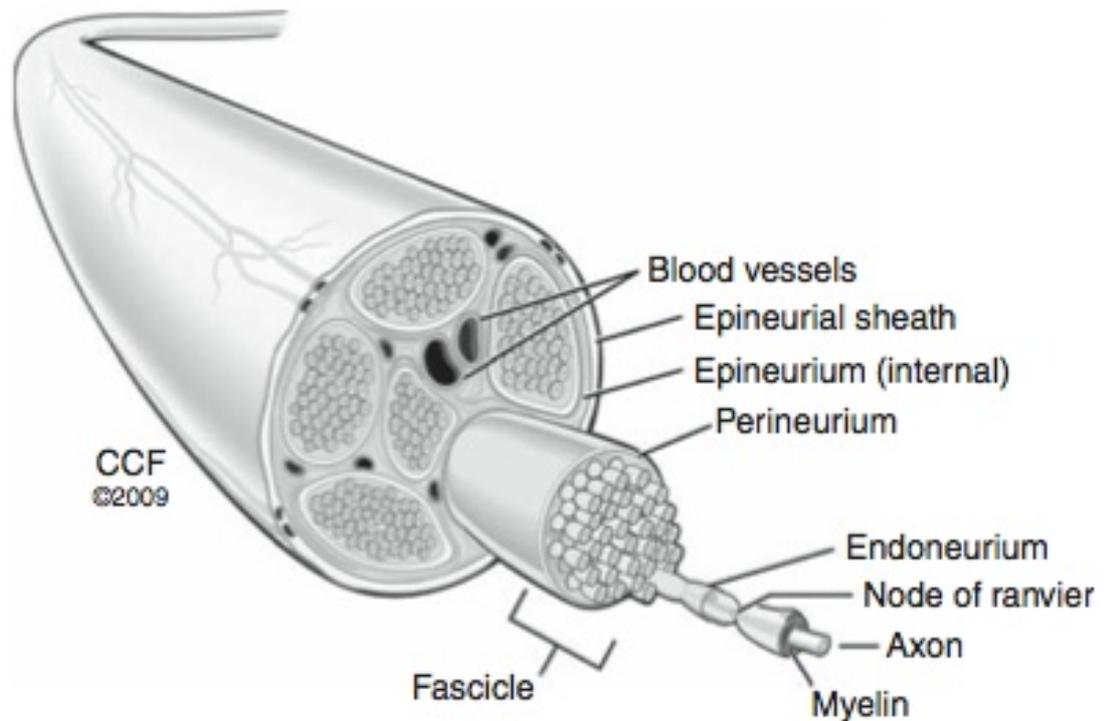
Figure 1: Schematic presentation of peripheral nerve anatomy[75]

After nerve injury, nerve regeneration and repair processes take place at different sites, including the nerve cell body, the proximal stump (segment between the neuron and the injury site), the injury site itself, the distal stump (segment between the injury site and the end organ) and the end organ.[18] Whereas the CNS cannot repair itself and function is regained through plasticity (using intact areas to take over the function for damaged areas), the PNS has three main mechanisms for self-repair. These include: remyelination, collateral sprouting distally from preserved axons, and regeneration from the site of injury.[101] In partial nerve injuries involving only 20-30% of the axons, collateral sprouting can lead to sufficient reinnervation in a two- to six-month time span. However, when over 90% of the axons are damaged, regeneration occurs primarily at the site of the injury, and success depends largely on the distance between the proximal stump and the injury site. [19]

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Soon after nerve injury attempts of regeneration take place and a cascade of events involving neurotrophic factors and cell signaling molecules occur. Axon disruption triggers Wallerian degeneration. In the distal portion of the axon, the axolemma and axoplasma begin processes of disintegration and degeneration, which develop at different rates depending on the thickness of the nerve fiber.[19, 38, 81] After degeneration takes place, phagocytosis and digestion chambers clear out degrading axons and myelin debris. Proximal to the lesion, the degeneration stops at the first internode in mild injuries, although it can progress further in more severe injuries.[19] Although the axon degenerates in the distal stump, the connective tissue basement membranes may remain, forming endoneurial tubes that are aligned by proliferating Schwann cells – thereby forming Bungner bands. The Schwann cells provide crucial basement membrane proteins, cellular adhesion molecules, and neurotrophic factors that both promote and direct the regeneration of axons.[15, 19, 27] The proximal stump of the damaged axon develops sprouts, which can find their way along the row of Schwann cells and may eventually reinnervate the original peripheral target structures. Regeneration is completed by remyelination of the axons by the surrounding Schwann cells.[15]

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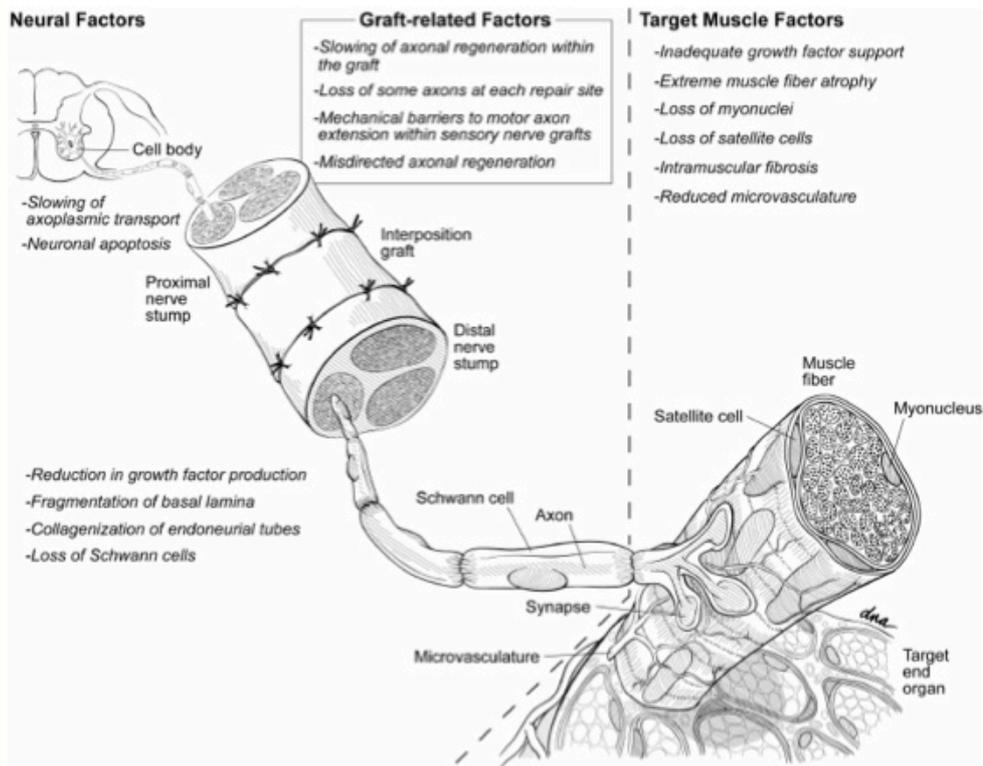
Figure 2: Illustration showing various axotomy-related changes that are deleterious to axon regeneration[15]

Different axonal regeneration rates are reported, ranging from 0.5 mm to 9 mm/day across different species and techniques. The variability depends on different factors, and regeneration is more effective in younger people and when achieved proximally. An estimated time of 1 mm/day is used in clinical contexts,[18] which only takes the production of the first axons into consideration, since full recovery takes place over a longer duration. Indeed, regeneration can often require more than two years in proximal injuries. This places considerable constraints on the outcome, which can be expected from this type of repair, since the interval which elapses between axotomy and reinnervation is one of the most significant factors affecting how successful a peripheral nerve repair will be. Denervation time plays an important role within the cell body, the distal and proximal nerve stump, and the target end organs.[26] In each of

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these instances, increased denervation time has been proven to jeopardize the likelihood of functional recovery.[15]

In nerve regeneration the basement membrane proteins and neurotrophic molecules that Schwann cells provide in the distal nerve stump are crucial to sustaining the axonal growth and direction of regenerating axons. The capacity of Schwann cells to provide such support decreases, however, in direct proportion to the prolongation of denervation, and many may suffer apoptosis.[91] Nerve repair that is delayed for a period greater than six months post-axotomy results in up to one third fewer regenerating motor neurons. Thus, protracted periods of axotomy and denervation negatively effect all facets of the neuromuscular unit.[91]

The state of the nerve end organs is also an important factor for functional recovery after nerve injury. This is especially relevant in motor nerves where the muscle end plates start to undergo atrophy after the loss of neural stimulation. Unless an appropriate number of axons are provided, their number steadily decreases with time, and 12 to 18 months post-injury they may be insufficient to restore adequate function to a muscle. This factor is combined with the expected time it takes a nerve to grow from the site of injury to the affected muscle to determine the expected functional outcome after nerve repair.[96] A result is considered positive when muscle function returns to MRC grade 3/5, meaning muscle can move against gravity, but not resistance.[19]

Thus, various considerations must be taken into account in order to time nerve repair accurately. There are, first, three crucial temporal factors. The resolution of segmental demyelination takes 8 to 12 weeks, so persisting deficits after that time period indicate that there has been axonal damage. Irreversible muscle atrophy, where surgery would not provide any benefit, is estimated to begin at 12 to 18 months.

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Schwann cells and endoneural tubes can stay viable for about 18 to 24 months. If they do not receive regenerating axons within this time frame, they degenerate. Therefore, the "time-distance-equation"[19] has two main variables: irreversible changes in the target organs within 12 to 18 months and axonal regeneration at 1 mm/day from the site of injury or surgery. Furthermore, the mechanisms of the nerve injury can influence the results of the repair. Sharp transections tend to regenerate better than crushing or avulsion nerve injuries. Age of the patient also plays a role, and children do much better than adults.[18] It has also been noted that pure motor nerves tend to regenerate better than mixed nerves, while these do better than pure sensory nerves. [18]

Electrophysiologically, nerve injuries are understood as defects that result in the disruption of a nerve such that it is no longer capable of transmitting an action potential. A wide range of injury types and severities has been classified and should be considered. Two classification schemes have been widely used by clinicians to describe nerve injuries. The first scheme was introduced by Seddon in 1943 and designates nerve injury in terms of its severity with the terms neurapraxia, axonotmesis and neurotmesis. Below is an overview of this system of classification on which all later classifications refer to.

Seddon-classification[73]:

    1. **Neurapraxia** (praxis = to do, to perform) is the mildest form of nerve injury. It is a physiological block of impulse conduction without anatomic axon disruption or degeneration of the nerve fiber. However, a certain amount of demyelination may be present. Transient loss of function exists until remyelination occurs. Spontaneous recovery is typical with this type of injury, and full function is usually restored without intervention after 12 weeks. Due to the differing extents to which the axons are

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myelinated, function is lost and regained at different times. In most cases, the impact on motor fibers outstrips that on sensory fibers: namely, they are the first to fail and the last to recover, whereas the contrary occurs with pain and sympathetic fibers. This type of injury is often seen after a prolonged application of pressure, such as a tourniquet, sleeping with pressure (e.g. Saturday night radial nerve palsy) on a nerve, or carpal tunnel syndrome.

2. **Axonotmesis** describes injuries in which the internal nerve structures are completely divided (tmesis = to cut), and although Wallerian degeneration occurs, the covering neural tubes are intact. This means the axons are disrupted and must regenerate, whereas the epineurium is intact and the nerve appears normal upon macroscopic examination. These injuries are usually due to traction of nerves wherein the inelastic internal structures rupture, but the stronger elastic nerve sheaths stay intact. Axon regeneration occurs in a reliable and predictable fashion through the retained neural tubes and the Tinel sign can always be elicited. The nerve should fully regenerate, and full motor and sensory function should be regained. Recovery times vary based on the location of damage relative to the end organs. [22, 49, 50]

3. **Neurotmesis** is the highest degree of nerve injury described by Seddon. It involves the complete transection of the nerve and all its supporting structures, including the epineurium. The separated nerve ends make it very unlikely that axon regeneration can occur from the proximal to the distal end, rendering surgical intervention necessary for the recuperation of any function. Recovery time depends on the location and severity of the lesion, as well as on other variables. The injury is usually caused by direct sharp trauma or by a very violent traction injury. A successful recovery depends on the accurate approximation of the cut nerve ends and meticulous surgical repair. A distal progression of the Tinel sign is indicative of a successful repair.[84]

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In 1951 Sunderland proposed a second schema, which overlaps with Seddon's classification, that distinguishes five degrees of nerve injury.

Sunderland Classification[29]:

First-degree: "Seddon's neurapraxia"

Second-degree: "Seddon's axonotmesis": The axon is injured, but supporting structures (including the endoneurium) remain intact. Wallerian degeneration occurs; but there is recovery at 1 mm/day as axons follow the 'tubule'. This can sometimes only be diagnosed retrospectively.

Third-degree: Here the endoneurium is disrupted, but the epineurium and perineurium remain intact. Recovery ranges from poor to complete and depends on the degree of intrafascicular fibrosis. The nerve may not appear seriously damaged on gross inspection. Surgery might become necessary.

Fourth-degree: Here all the neural and supporting elements are interrupted, but the epineurium remains intact. The nerve is usually enlarged on inspection. There is no spontaneous recovery and surgery is necessary.

Fifth-degree: "Seddons's neurotmesis"

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Sunderland	Seddon	Process	Tinel sign	Progress distally	Recovery pattern	Rate of recovery	Surgery
First degree	Neuraxpraxia	Segmental demylination	–	fast	complete	Fast (days to 12 weeks)	none
Second degree	Axonotmesis	Axon severed, but endoneurium intact (optimal circumstances for regeneration)	+	+	complete	Slow (3cm/month)	none
Third degree	Axonotmesis	Axon discontinuity, endoneurial tube discontinuity, perineurium and and fascicular arrangement preserved (disorganized regeneration)	+	+	varies	Slow (3cm/month)	Varies
Fourth degree	Axonotmesis	Loss of continuity of axons, endoneurial tubes, perineurium and fasciculi, epineurium intact (neuroma in continuity, no regeneration)	+	-	none	none	yes
Fifth degree	Neurotmesis	Loss of continuity of entire nerve trunk	+	-	none	none	yes

Chart 1: Nerve injury classification according to Seddon and Sunderland

More recently, Thomas and Holdorff[86] have developed another simplified classification scheme for nerve injuries, which divides them according to degenerative (discontinuity) and nondegenerative (conduction block).[10]

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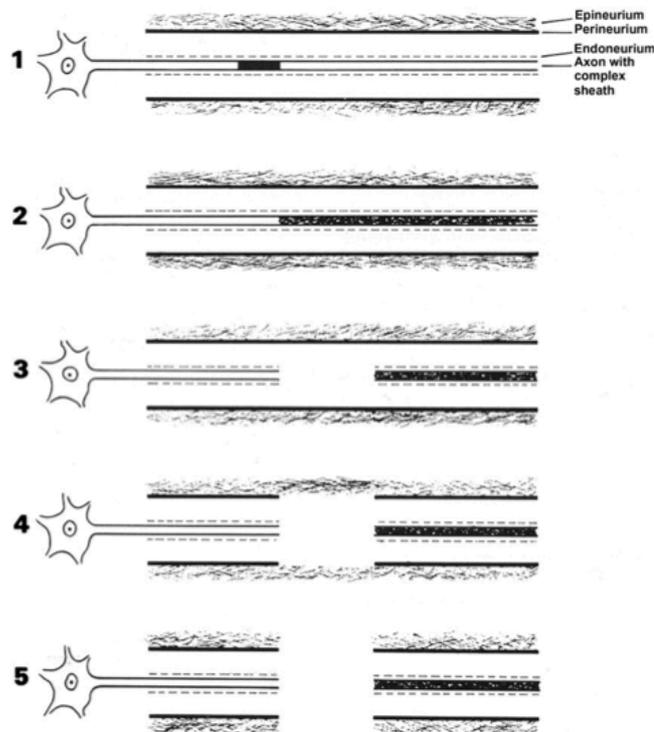
Figure 3: The five degrees of nerve injury[19]

1.3 Treatment of Nerve Injuries

Despite the progress in understanding the pathophysiology of peripheral nervous system injury and regeneration, as well as advancements in microsurgical techniques, peripheral nerve injuries still remain a major challenge.[75] There are various treatment options for surgical nerve repair for different types of injuries and clinical conditions. Nerve reconstruction aims, primarily, to reinnervate the target organs. It does so by guiding regenerating sensory, motor, and autonomic axons into proximity to the distal nerve. The outcome of peripheral nerve repair depends on many factors, which

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include: type, location, and extent of nerve injury; timing of surgery; type of repair; accurate alignment of fascicles; surgical technique; and patient comorbidities.[75]

In the following paragraph there will be an overview of the current techniques for peripheral nerve repair.
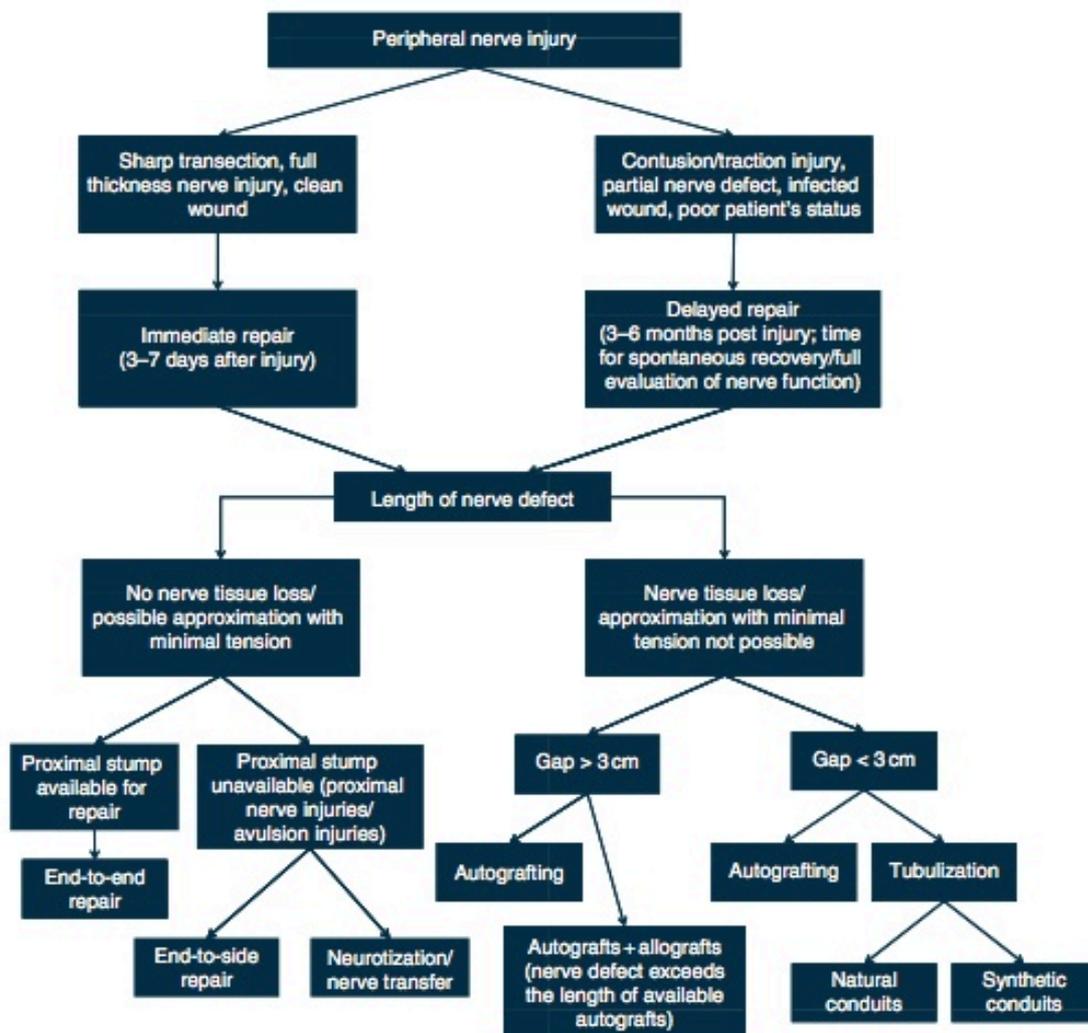

Chart 2: Algorithm of peripheral nerve repair according to Siemionow[75]

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1.3.1 Primary/ Direct nerve repair

Direct repair remains the therapy standard and treatment of choice for repairing completely or partially injured nerves, in which the gap is small enough that nerve ends can be approximated without tension and the injury site is close to the target organs. The outcome is better when the nerves are purely motor or sensory, as opposed to mixed motor/sensory nerves. To obtain optimal results and nerve regeneration, repair must be tension-free: nerve stumps must be accurately aligned and repaired atraumatically, with minimum tissue damage and a minimal number of sutures.[75] Primary nerve repair should be performed within 72 hours up until 7 days after the nerve injury.[24]

Nerve surgery is performed in a microneurosurgical technique, with magnification and 9-0 nylon (between 8-0 and 10-0).[91] The use of fibrin-based tissue glue has gained popularity when coapting nerves, especially when the coaptation site does not involve a joint.[19]

Direct repair techniques include several different techniques, such as end-to-end repair and epineural sleeve repair.

End-to-End Repair

End-to-end nerve repair can be subdivided into epineural repair, group-fascicular repair, and fascicular repair. Generally, epineural repair is used to treat sharp nerve injury and partial injuries with good fascicular alignment. Usually, the epineural sheath is sutured with 3-8 single stitches.

Grouped fascicular repair technique is usually employed in crush nerve injury or late nerve repair that requires cutting of the nerve ends, or in mixed nerves, where matching groups of fascicles are easily identified. Prior to coaptation, the epineurium

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is retracted and correlative clusters of fascicles are conjoined by means of 2-3 stitches passing through the interfascicular epineurium. To avoid scar tissue formation, a minimal number of sutures should be used.

Fascicular repair is not widely used anymore, due to higher scar tissue formation as a result of more suturing. It requires the dissection of the interfascicular epineurium and a separation of the fascicles; the sutures are placed within the perineurium. Both the grouped fascicular and the fascicular repair grant more accurate alignment of the fascicles and thereby decrease the misdirection of regenerating axons. On the other hand, these techniques require more dissection and sutures relative to epineural repair, which can lead to higher scar tissue formation and decreased intraneural bloodflow. When functional outcomes are compared, group fascicular repair does not out-perform epineural repair.[75]

End-to-Side Repair

End-to-side nerve repair is a technique in which the distal stump of an injured nerve is coapted to the side of an uninjured donor nerve. This technique is promising when the proximal nerve stump is either unavailable or at a significant distance from the target, or in cases where a greater nerve gap exists. Its major advantage is that the injured nerve recovers function without compromising the function of the donor nerve, thereby avoiding donor-site morbidity.[67, 72] Additionally, the distance between the regenerating axons and their target muscle can be shortened. However, various studies show that results range from good to poor. The authors assume that end-to-side technique can be useful, but the outcomes are unpredictable and depend heavily on the surgical technique itself.[75]

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1.3.2 Secondary Nerve Repair

In delayed nerve repair or in nerve gaps that require relatively large tension in order to perform direct coaptation, repair should not be performed through direct repair techniques. If the dimension of the nerve injury is unclear, repair should be delayed for two to three weeks until fibrosis in the area of injury has taken place and the degree of injury can be assessed more easily. If direct repair is not possible due to nerve retraction or large defects, secondary nerve repair becomes necessary: this includes nerve grafting or the application of tubulization techniques. Currently, tubulization techniques (conduit repair) are only feasible in short nerve gaps that do not exceed 3-4 cm.[47, 74, 75] For larger nerve defects, nerve grafting, tendon transfer, or nerve transfer is required.

Nerve Grafting with Autologous Grafts

Nerve autografting is currently the surgical procedure most commonly used to repair nerve defects that cannot otherwise be coapted without tension. This technique exhibits superior results when compared to nerve coaptations performed under excessive tension leading to nerve ischemia. The success of autografts depends on the presence of Schwann cells and basal lamina endoneural tubes, which provide neurotrophic factors and endoneural tube surface adhesion molecules to regenerating axons.[74]

To choose the best autograft, the surgeon has to consider the following factors: the length of the nerve defect, the caliber of the nerve to be repaired, and donor site morbidity.[75]

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Donor nerve	Available length (cm)	Hypesthesia
Medial antebrachial cutaneous nerve (MACN)	10-12 (above elbow), 8-10 (below elbow)	Medial forearm
Lateral antebrachial cutaneous nerve (LACN)	10-12	Lateral forearm
Superficial sensory branch of the radial nerve (SSRN)	20-30	Radial dorsal hand
Dorsal cutaneous branch of the ulnar nerve (DCBUN)	4-6	Ulnar dorsal hand
Sural nerve	30-50	Lateral foot

Chart 3: Examples of donor nerves available for autografting[75]

The disadvantages of autografting include the loss of function at the donor site, multiple surgery sites, donor site morbidity (scarring, pain, and neuroma-forming), and difficulties associated with matching the donor nerve's caliber to the recipient nerve.

Nerve Grafting with Allografts

Nerve allografting is an alternative to nerve autografting. While it remains the main technique for larger nerve gap repair, nerve autografting has its limitations: donor site morbidity and the limited amount of available graft material remain major challenges. In several cases, allograft material from cadaver donors or xenografts (from animal cadavers) offer a reasonable alternative, insofar as they circumvent donor site morbidity and make an unlimited length of nerve tissue available for transplantation. Furthermore, the recipient's injured nerve can be replaced with the same nerve type from the donor, which is discussed as leading to a more effective recovery.[58] However, they require immunosuppression and their success rate is not very high.[82]

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Conduit Repair

In injuries that are chronic, or in which tensionless nerve repair is not feasible, autografts have traditionally been the preferred method of treatment. Decellularized allografts and conduits have been introduced as substitutes for autografts. These conduits overcome donor site morbidity, as well as functional loss at the donor area in cases of autografting, and immune reaction from transplants or unprocessed allografts.[70] Various neural conduits can be used to repair nerve gaps and may help in the treatment of acute and chronic nerve injuries. These conduits can be made of biological materials such as muscle, vessels, or tendons; nondegradeable materials such as silicone tube; or biodegradeable synthetic materials.[74] They provide an environment for outgrowing axons, growing Schwann cells and neurotrophic stimulation by the distal stump, all of which are crucial to optimal nerve regeneration.[55, 75] However, presently conduits can only be used in nerve gaps that do not exceed 3 cm (4cm).[74]

1.3.3 Palliative nerve surgery

Tendon Transfer

Tendon transfer surgery is another option for restoring muscle function after the loss of nerve innervation. Generally, nerve repair should always be favored prior to tendon transfer. Despite the progress in microsurgical nerve repair techniques, often enough unsatisfactory results maintain. In these cases tendon transfers can be indicated for improving the hand function. The indication for tendon transfer surgery depends heavily on the personal and professional profiles of the individual patient. Tendon transfer procedures alleviate the suffering from functional hand impairment by

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regaining motor activity and at the same time by providing a superior alternative to permanent external splints. Various transfer procedures have been described for every nerve trunk of the upper extremity, and their prognosis depends mainly on the severity of nerve loss, local effects of the trauma (e.g. involvement of soft tissues, joints), and the physiological characteristics of the transferred muscle. Tendon transfers are possible due to the redundancy that exists among the actions of the upper-extremity musculature. Potential donors for tendon transfers are muscles with adequate power to motor the recipient tendon, similar tendon excursion to the recipient, and synergy with the recipient.[69] Despite outcomes that may ultimately fall short of those achieved in isolated motor nerve lesions, tendon transfers remain a vital instrument for recuperating hand function in instances of complex nerve damage, and are often the only option for doing so.

1.4 New Approaches in Treating Nerve Injuries - Nerve Transfer

Nerve transfer is becoming a more common strategy for repairing peripheral nerve injuries and is a versatile reconstructive technique, although the idea of transferring an uninjured nerve to the distal stump of an injured nerve is not new. Narakas described early work[59], and Addhas and Midha wrote an important review in this field.[2]

According to Narakas, "in neurotization or nerve transfer, a healthy but less valuable nerve or its proximal stump is transferred in order to reinnervate a more important sensory or motor territory that has lost its innervation through irreparable damage to its nerve".[60] Hence, nerve transfer involves the sacrifice of a normally functioning nerve (donor), which is transferred to neurotize the distal stump of a more important

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nerve (recipient).[51] Especially in cases of extensive proximal nerve injury that usually have a poor prognosis,[6] it may be the only technique by which motor and sensory function can be restored. Contrary to common reconstructive techniques like nerve grafts and tendon transfers, distal motor and sensory nerve transfers in middle- and high-level injuries have the advantage of allowing surgery in unscarred and uninjured tissue, minimizing regeneration time and distance and reinnervation of muscles in their native location before degeneration of the motor endplates occurs. Generally, patients in the following circumstances are candidates for nerve transfer surgery: 1.) in cases where the proximal nerve stump is unavailable for reconstruction or inadequate; 2.) in cases where the time necessary for regeneration through other treatment options is unacceptable; and 3.) in cases where there is restraining difficulty of surgery in the injury zone and/or an undefined level of nerve injury or lesion.[99]
When choosing the optimal donor nerve, the donor's quantity of motor axons compared to that of the recipient is important.[91, 93, 99]

Optimal muscle reinnervation depends on a sufficient quantity of regenerating motor axons reaching their target muscles within approximately one year of the injury. Hence, the results of proximal nerve repair or reconstruction with grafts are frequently poor because of the irreversible loss of the target motor endplates through degeneration and fibrosis. [15, 17, 32, 91]

 "Time is muscle"[91]- so in order to prevent muscles from irreversible changes it is crucial to choose a donor nerve that is in close proximity to the target muscle(s), thereby substantially reducing regeneration distance and time.
Nerve transfer should always be weighed against other treatment alternatives. All nerve transfers carry the risk of donor nerve impairment, which should always be taken into consideration. Depending on the donor nerve under consideration, one

should carefully evaluate the risk-to-benefit ratio of nerve transfer versus tendon transfer.

Generally donor nerve selection is limited by human anatomy and human ingenuity. The selection of the ideal donor nerve should take the following principles into account:[93, 99]

- The motor function of the donor nerve should be as unadulterated as possible in cases in which motor function is the objective; it follows that if sensory function desired, the donor nerve's sensory function should be as pure as possible.

- The functional loss that may follow a transfer of the donor nerve should be negligible: it should never be commensurate with, much less exceed, the anticipated function of the recipient nerve.

- The mobilized length of the donor nerve should be sufficient to permit a direct tension free coaptation to the recipient nerve.[99] Ideally, this mobilized length should place the recipient nerve as close as possible to the target organ, always following the dictum: "Donor distal, recipient proximal."[16, 91]

- Donor and recipient nerves should approximate one another in both diameter and microanatomic structure.

- The function of the recipient nerve should be synergistic with the donor nerve's normal function.

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1.4.1 Motor Nerve Transfers

Various options for nerve transfers have been reported for different levels of nerve injury in the upper extremity. A direct end-to-end method is preferred for motor nerve transfers.[91]

The number of motor axons, proximity to the target muscle, and synergy of muscle function all contribute to selecting the ideal donor nerve for motor nerve transfer. It is preferable to choose donor nerves that either function as nerve branches that exclusively innervate muscle, or as motor fascicles that can easily be neurolysed from a mixed nerve, such as the flexor carpi ulnaris fascicle of the ulnar nerve or the medial triceps nerve.[24, 53] Postoperative rehabilitation and motor re-education benefit from the use of donor nerves that innervate the expendable muscles in synergy with the target muscle. Such nerves, moreover, heighten the probability of success. On the other hand, a nonsynergistic or even antagonistic donor muscle will frustrate and lenghten the process of rehabilitation, resulting in a less satisfactory—if usually successful-- outcome.[52]

1.4.2 Sensory Nerve Transfers

Motor nerve transfer is more widespread than nerve transfer as a technique for restoring sensibility.[98] Ideally sensory nerve transfers are carried out end-to-end for critical sensation, but limited donor availability may necessitate that they be performed end-to-side for noncritical sensation, which will yield some protective sensation. For sensory transfers, a nerve branch that innervates a noncritical sensory area is sacrificed to restore critical digit sensation, for example the contact surfaces

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of the thumb and index fingers.

In cases in which the ulnar or median nerve can serve as a donor for the other, sensory nerve transfers more frequently take place at the level of the distal forearm or palm, either alongside motor nerve transfers or ancillary. Distal level transfers enable a faster return of sensation, which eases postoperative therapy and rehabilitation.[91]

In proximal nerve injuries and relatively large nerve gaps, reconstruction with orthotopic nerve grafts can lead to some degree of protective sensibility that is perceived as topographically appropriate. A conscientious program for sensory rehabilitation can further augment the result. However, it is extremely rare that the sensibility restored through sensory nerve transfer aligns topographically with the recipient nerve zone.[79] Rather, the sensibility is perceived in the topography of the donor nerve, which disorients and discomfits the majority of patients. This may diminish the functional usefulness of this nerve transfer.[99]

1.4.3 Previous Works

Shoulder

Many nerve transfers with different donors and recipients have been described for brachial plexus injuries. In the case of shoulder abduction and external rotation, the transfer of the accessory nerve to the suprascapular nerve has been described. Useful donor nerves for shoulder abduction with the axillary nerve as a recipient are the medial triceps branch, the medial pectoral nerve, the thoracodorsal nerve, and intercostal nerves. For scapular winging and instability transfers from the

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thoracodorsal nerve, pectoral fascicle of C7/ middle trunk and of intercostal nerves to the long thoracic nerve have been described.[9, 91]

Elbow

Oberlin's restoration of elbow flexion through a nerve transfer from a fascicle of the ulnar nerve directly to the branch of the muculocutaneous nerve, thereby innervating the biceps brachii, marked the beginning of an increase in distal nerve transfers.[62, 63] Potential donor nerves for transfers restoring elbow flexion are the ulnar and median nerve fascicles (double fascicular transfer to the biceps and brachialis muscles), the medial pectoral nerve branches, the thoracodorsal nerve, the distal accessory nerve, and intercostal nerves with the musculocutaneous nerve as the recipient nerve.[90, 91] For elbow extension the FCU fascicle of the ulnar nerve, ECRL fascicle of the radial nerve, and intercostal nerve transfers to the triceps branch of the radial nerve have been described.[91]

Hand

In order to regain function of the hand after an irreparable median or ulnar nerve lesion, it is essential that sensibility in the hand is restored. The loss of sensation to the dorsal side of the hand is not considered disabling; however, the loss of sensation to vital areas of the hand (i.e. the ulnar border of the thumb, the radial border of the index finger, and the ulnar border of the small finger) cause severe disability. The loss of sensation in the thumb, for example, is seen to decrease hand function by 20%.[66] In the hand, various motor and sensory transfers have been described. In cases of loss of pronation, the extensor carpi radialis brevis (ECRB) branch of the radial nerve and the FDS or flexor carpi radialis (FCR)/Palmaris longus (PL) branch of the median nerve transfers to the pronator teres branch of the median nerve were performed.

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Transfers from the FDS, FCR/PL branches of the median nerve to the ECRB, PIN branches of the radial nerve have been reported for wrist and finger extension, as well as for finger flexion transfers from the brachialis branch of the musculocutaneous (MCN) nerve or the ECRB, supinator branches of the radial nerve to the anterior interosseous nerve (AIN) of the median nerve.[91] To restore intrinsic hand function, the transfer from the distal AIN to the deep motor branch of the ulnar nerve (DBUN) has been described and successfully performed.[16, 97]

Various donor options exist for sensory reconstruction. If possible, the distal end of the sensory donor nerve should be sewn dto an adjacent normal sensory nerve or to a sensory nerve awaiting reinnervation.[23]

1.5 Objective of this Research

This study focuses on the anatomic and histomorphometric background for possible nerve transfers at the hand. Three different transfers were examined and this study seeks to deepen the current understanding of the anatomic and histomorphometric basis necessary for the successful performance of nerve transfers. This is shown macroscopically by describing relevant anatomic landmarks for tension-free coaptation sites, as well as microscopically by comparing donor and recipient nerves in terms of their diameter, axon density, and fascicle numbers. The results are intended to provide surgeons with data relevant for predicting the success of a given operation.

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2   Material and Methods

2.1   Anatomic Dissection

This study was performed on 15 limbs of fresh cadavers (N=15). There were 5 male and 10 female upper limbs transected right above the epicondyle. For all the specimens, gender, weight, height, and age were recorded. None of the specimens had a history of neurological disease. All forearms were measured from the medial epicondyle to the os pisiforme and the medial epicondyle to the processus styloideus ulnae, as well as from the lateral epicondyle to the os scaphoideum and the lateral epicondyle to the processus styloideus radii. The forearms were dissected, and skin and subcutaneous tissue were removed. The nerves were then carefully exposed.

The donor nerve was examined in the following manner: the most distal point where the nerve was transected was first exposed and described by anatomic landmarks; next, the proximal point from where the donor was moved (with and without interfascicular dissection) was also exposed and described by anatomic landmarks.
The recipient nerve was similarly examined. The following points were exposed and described by anatomic landmarks: the point most proximal to the site of the nerve's transection for coaptation (with and without interfascicular dissection), and the distal point around where the recipient nerve was moved.

All measurements were documented, and photographs were taken of each nerve and nerve transfer. At the coaptation sites, nerve specimens were extracted for histomorphometric evaluation.

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2.1.1 Anterior Interosseus Nerve Transfer to the Deep Motor Branch of the Ulnar Nerve

The anterior interosseus nerve (AIN) was identified along with its accompanying anterior interosseous artery on the interosseous membrane in the deep midportion of the forearm, where it enters the pronator quadratus muscle (PQ) both proximally and centrally. It was separated from the surrounding tissues in the proximal direction at a length of approximately 3 - 4 cm, transected and transposed to the ulnar border of the PQ. The DBUN was identified by opening the Guyon's canal. The neurovascular bundle was medially swept aside, exposing the ulnar nerve. The ulnar nerve was then traced proximally into the forearm until the takeoff of the dorsal cutaneous branch. It was microsurgically and interfascicularly dissected from the superficial branch of the ulnar nerve (SBUN) in a retrograde manner to the height of the AIN. There the nerve coaptation was performed and its location described by measuring its relevant distances to anatomic landmarks (Fig. 4). The distances between the medial epicondyle and the pisiform, the takeoff of the dorsal cutaneous branch of the ulnar nerve (DCBUN), and the height of the coaptation were recorded.

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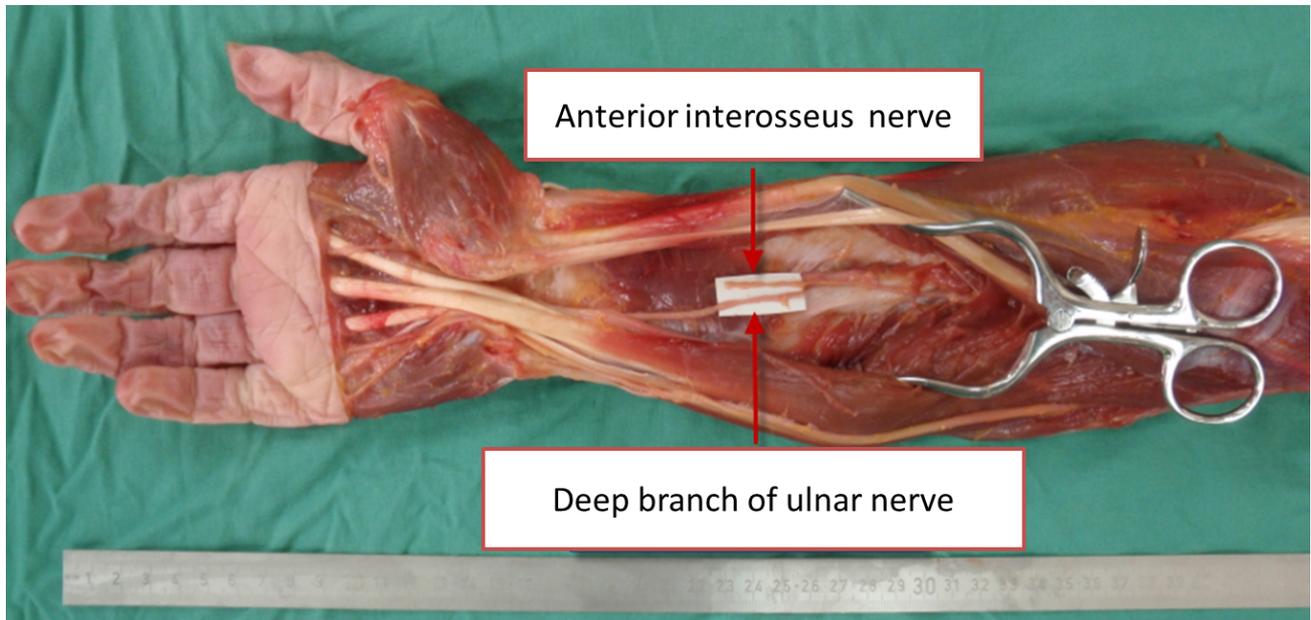
Figure 4: Transfer of the AIN to the DBUN.

The AIN was dissected at the proximal border of the PQ and transposed to the ulnar proximal border of the PQ. The DBUN was interfascicularly dissected from the SBUN in a retrograde fashion beginning at the pisiform. After the coaptation of the nerves was performed, nerve samples from each nerve were collected at the height of the coaptation. The location of the coaptation and the length of neurolysis were measured in reference to relevant landmarks, the medial epicondyle of the humerus and the pisiform. (n = 15)

2.1.2 Superficial Branch of the Radial Nerve Transfer to the Ulnar and Median Nerve

2.1.2.1 Superficial branch of the radial nerve transfer to the superficial branch of the ulnar nerve

After carefully removing the skin and subcutaneous tissue, the superficial branch of the radial nerve (SBRN) was exposed in the distal radial forearm, from where it crosses underneath the brachioradialis muscle and continues to separate distally into its smaller branches. It was transsected at its most distal point prior to its first

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bifurcation and then mobilized from its sourrounding soft tissue over a length of approximately 5-7 cm. It was then transposed underneath the extensor carpi radialis longus and brevis muscles towards the recipient nerves.

The ulnar nerve was exposed by opening the Guyon's canal, where the division of the ulnar nerve into the superficial branch and the deep motor branch can usually be seen around the pisiforme bone. Beginning at their division point, the SBUN was separated in a retrograde manner until it could be connected without tension to the SBRN, which had been placed between the superficial and deep flexors. The coaptation site is found where the SBRN can reach the SBUN without any tension, ideally after it has separated from the DBUN. If that is not possible, the SBUN has to undergo interfascicular dissection until it reaches the SBRN.
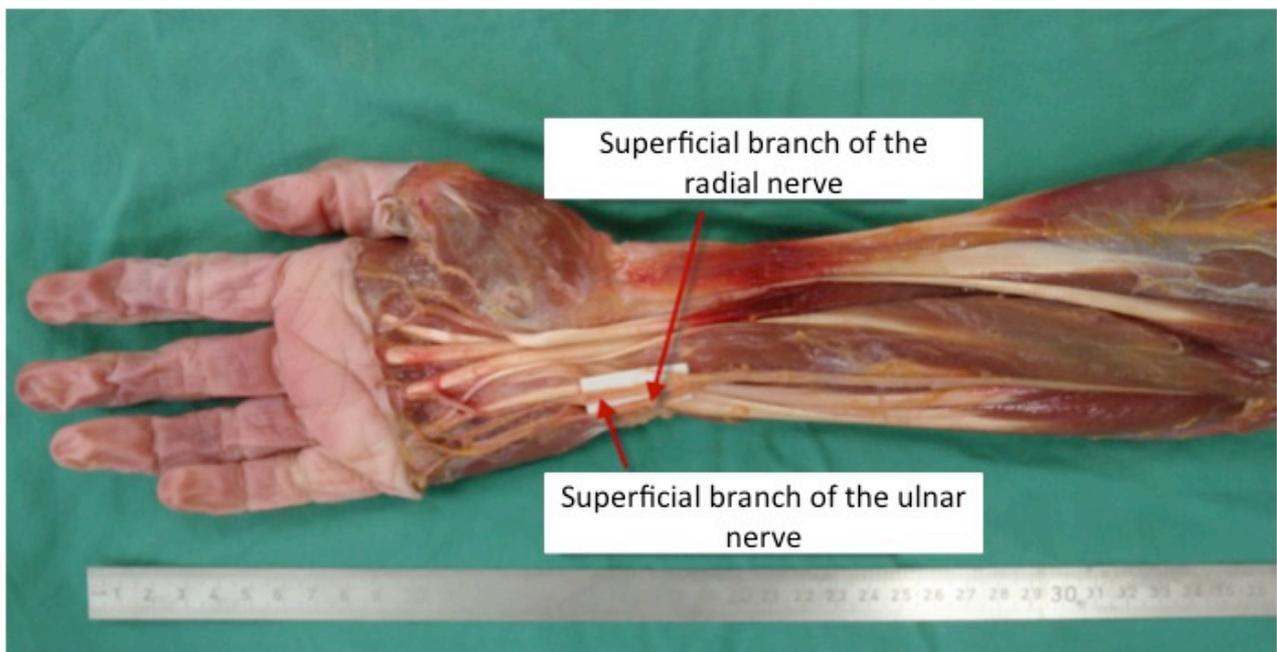

Figure 5: Transfer of the SBRN to the SBUN

Transfer of the SBRN to the SBUN was performed in 15 fresh specimens. The SBRN was dissected proximally to its first bifurcation at the distal radial forearm. Mobilizing it in the proximal direction permitted the nerve to be transferred toward the SBUN. In order to maximize its nerve length it was

placed between the superficial and deep flexors to reach the SBUN along its course at the ulnar side of the wrist. The SBUN and DBUN were identified in the Guyon's canal and separated from each other in a retrograde manner until tension-free coaptation of SBRN and SBUN could be achieved. The location of the coaptation, the bifurcation of the SBRN, the location of the diversion of the SBUN and DBUN and the required length of neurolysis of SBUN and DBUN were described in relevance to the anatomic landmarks, the lateral epicondyle of the humerus, the styloid process of the radius and the pisiform bone. (n = 15)

2.1.2.2 Superficial branch of the radial nerve transfer to the sensory part of the median nerve

The superficial branch of the radial nerve (SBRN) was exposed from that point at which it passes beneath the brachioradialis muscle to the point at which it separates distally into its smaller branches in the hand. The MN and its thenar branch were exposed by opening the carpal tunnel. Then they were separated from each other. The SBRN could be coapted to the sensory part of the median nerve by passing it under the radial flexors. The most distal part of the SBRN should be that which precedes its division into smaller branches, in order that sufficient sensory axons may be provided. The coaptation should be performed as distally as possible.

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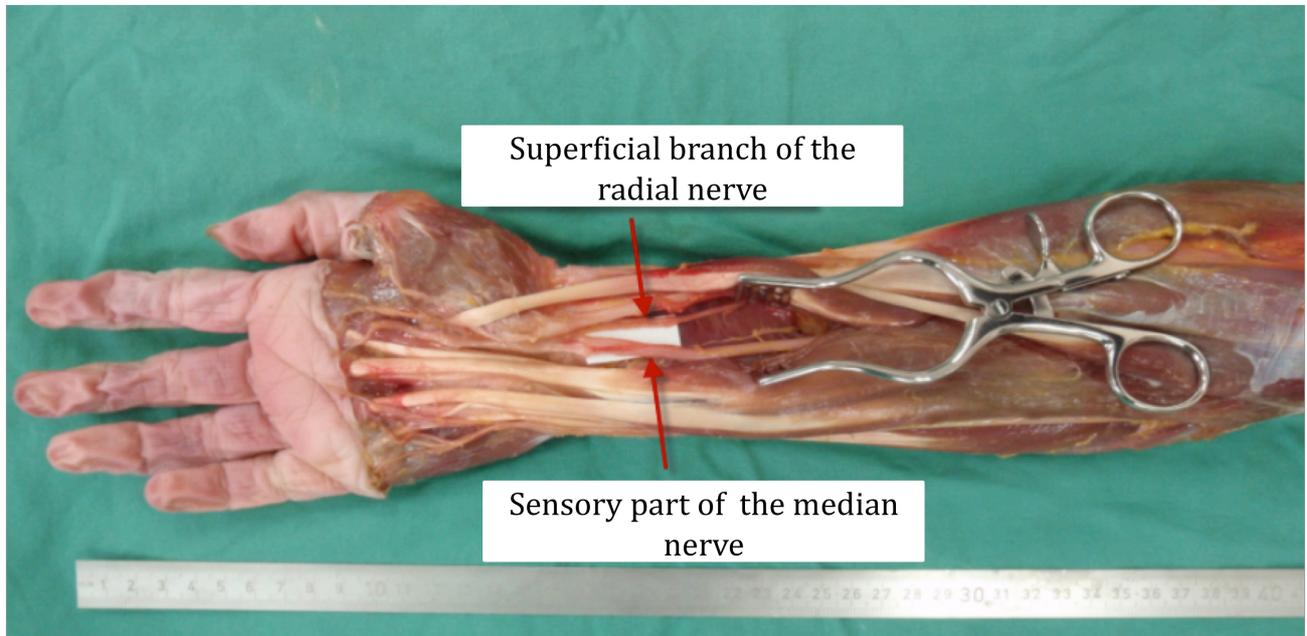
Figure 6: Transfer of the SBRN to the sensory part of the MN

Transfer of the SBRN to the MN was performed in 15 fresh specimens. The SBRN was dissected proximally to its first bifurcation at the distal radial forearm. Mobilizing it in the proximal direction permitted the nerve to be transferred toward the MN. In order to maximize nerve length it was tunneled under the extensor carpi radialis longus and brevis muscle to reach the MN along its course. After exposing the MN and its thenar branch by opening the carpal tunnel, they were separated from each other until a tension-free coaptation of MN and SBRN was possible. The location of the coaptation, the bifurcation of the SBRN, the takeoff of the thenar branch, the length of neurolysis and the overall length of the forearms were measured in relevance to the anatomic landmarks: the lateral epicondyle of the humerus, the styloid process of the radius and the pisiform bone. (n = 15)

2.2 Histomorphometric Analysis

At the coaptation sites, 2-3 mm of each nerve were extracted and fixed at 4° Celsius in a 3% glutaraldehyde/ 3% paraformaldehyde in PBS solution (Science Services GmbH, Munich, Germany). The nerves were postfixed in 1% osmium tetroxide and

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embedded perpendicular to the face of the block in epoxy resin (EPON, Merck, Darmstadt, Germany). Semithin transverse sections of 1 μm were cut on an ultramicrotome (Ultracut E by Reichert-Jung, Munich, Germany) with a DIATOME diamond knife. The sections were mounted on glass slides and stained with a 1% solution of toluidine blue, then viewed using a light microscope. Stained sections were scanned at 20x magnification (Mirax Scanner; Carl Zeiss, Jena, Germany) and the diameters of the complete nerves and individual fascicles were measured (Figure 9 A, D). The cross- sectional areas were measured using a polygon approach (Pannoramic Viewer 1.15, 3DHistech, Hungary), meaning that the total fascicle areas were calculated as the sum of the cross-sectional surfaces of all fascicles. Myelinated axons were counted semi-automatically at a 600x magnification (ImageJ version 1.42; NIH, Bethesda, MD, USA) (Fig.9 B,C,E,F). The low cut-off value for inclusion of axons was set at 4 μm. The density of the axons was calculated as the ratio of total axon number and total fascicle area. For histomorphometric comparison, the data of all nerve parameters was described as a donor to recipient ratio. For each of the specimens, an individual axon count donor-to-recipient ratio was calculated.

A two-tailed t –Test was used for statistical analysis by which to compare donor and recipient. $p \leq 0.05$ was considered significant. All data is given as the Mean ± Standard Error of the Mean (SEM).

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3   Results

3.1   Anterior Interosseus Nerve Transfer to the Deep Branch of the Ulnar Nerve

3.1.1   Anatomic Dissection

In all cadavers, the AIN and the DBUN were identified without anatomic variations. After transsection, the AIN could be transferred without tension to the ulnoproximal border of the PQ without any relevant loss of length. Following interfascicular neurolysis of the DBUN and nerve mobilization, a tension-free coaptation was possible in every specimen (Fig. 7).
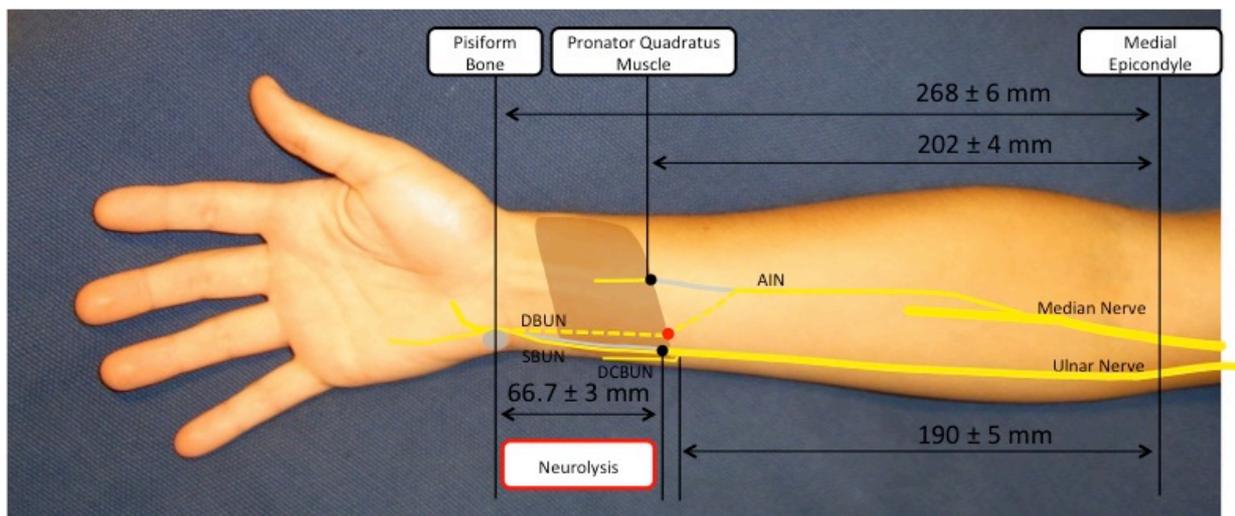

Figure 7: Schematic presentation of the measurements of the transfer from the AIN to the DBUN

Following interfascicular neurolysis of the DBUN and SBUN beginning at the pisiform over a length 66.7 ± 3 mm both nerves are being dissected (black dots). The nerves are transposed towards each other and a tension-free coaptation is possible at 202 ± 4 mm distally to the medial epicondyle of the

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humerus. The dorsal cutaneous branch of the ulnar nerve was not affected by the neurolysis as its takeoff from the ulnar nerve was seen at 190 ± 5 mm distally to the medial epicondyle. The grey area shows the courses of the AIN and DBUN before their transposition. The dotted lines indicate their positions after the transfer, and the red dot marks the site of the coaptation. In the service of precision, the median nerve is shown just to the level shortly beyond the takeoff of the AIN. The pronator quadratus muscle is highlighted in brown, the pisiform in grey.

The ulnar proximal border of the PQ appears to be a site favourable to coaptation. The measurements situated this point at 202 ± 4 mm distal from the medial epicondyle of the humerus. The superficial and the deep ulnar branches had to be separated in a retrograde fashion from their division at the pisiform over a length of 66.7 ± 3 mm in order to reach the coaptation site. At the DBUN's height of dissection, it lay dorsal to the SBUN.

The length of neurolysis of the deep and superficial branch of the ulnar nerve never extended to the height of the takeoff of the DCBUN. It was therefore possible to preserve this branch in every case. It is located about 190 ± 5 mm distal to the medial epicondyle of the humerus. The nerve diameters at the height of the coapation site were 0.79 ± 0.07 mm for the AIN and 1.60 ± 0.10 mm for the DBUN (Fig 8). Microsurgical suture of the nerves was possible despite the difference in size.

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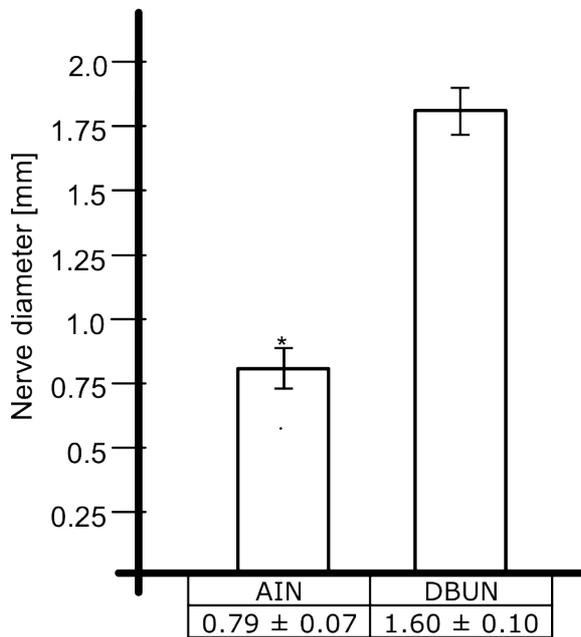
Figure 8: Comparison of donor (AIN) to target (DBUN) nerve diameter. All data presented as Mean ± SEM

Nerve diameters (Fig.8), cross-sectional nerve areas (Fig.10), fascicle numbers (Fig.11), total cross-sectional fascicle areas (Fig.12), axon numbers (Fig.13) and axon densities (Fig.14) were compared between AIN as the donor (left column) and DBUN as the target (right column). The AIN had significantly ($p < 0.05$) lower values in all parameters. All data presented as Mean ± SEM.

3.1.2 Histomorphometric Results

At the coaptation sites, nerve specimens were extracted for histomorphometric evaluation. In the figure below stained semithin sections of the nerve specimens are depicted.
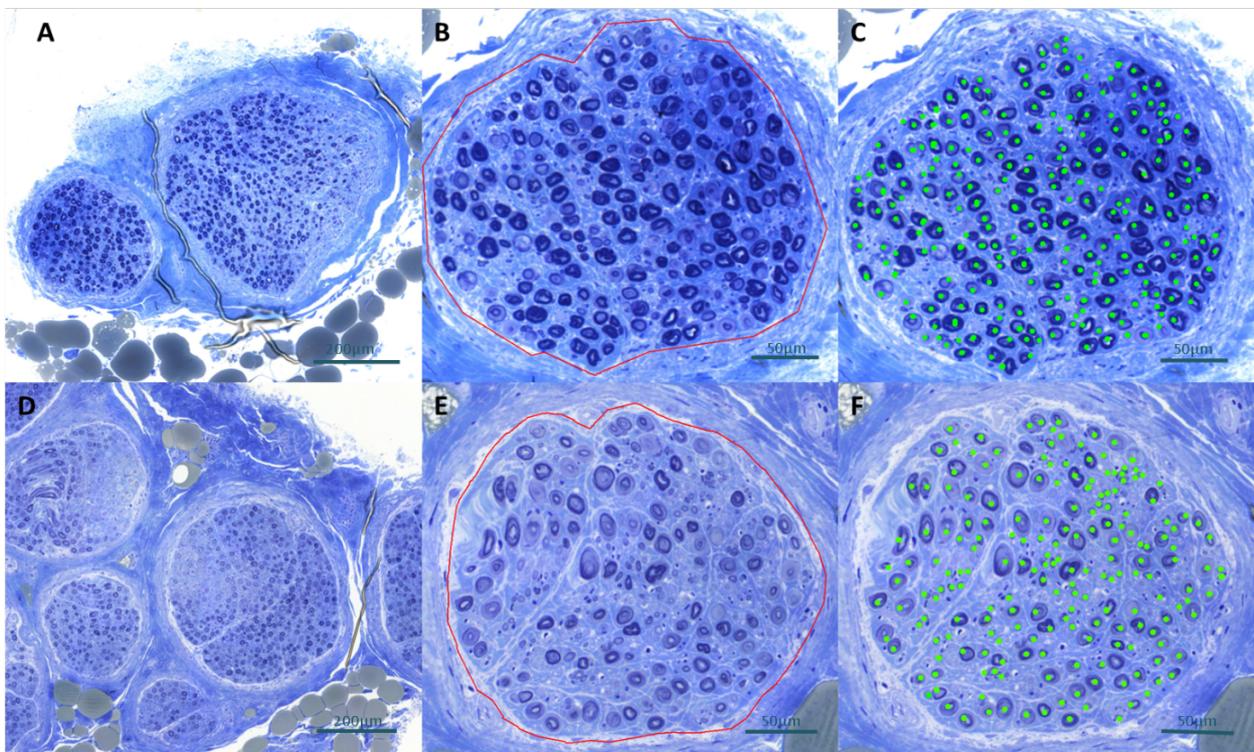

Figure 9: Histologic pictures of stained nerve sections from the AIN and the DBUN

Semithin sections of the AIN (A,B,C) and the DBUN (D,E,F) from the coaptation site were fixed in glutaradehayde, postfixed in aqueous osmium tetraoxide, dehydrated and embedded in Epon before they were stained with toluidine blue. The nerve diameters, cross-sectional nerve areas and fascicle numbers were measured at ×200 magnification (A,D). A semiautomatic count of myelinated axons (low cut-off for inclusion: 4 µm) and the cross-sectional areas of individual fascicles was undertaken at ×600 magnification (B,C,E,F) (n=14).

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The cross-sectional nerve area measured to be 0.52 ± 0.08 mm^2 in the AIN and 1.81 ± 0.19 mm^2 in the DBUN (Fig.10). The AIN had 2.29 ± 0.40 fascicles, while the DBUN had 8.57 ± 1.39 fascicles (Fig. 11). The total area of the fascicles added up to 0.26 ± 0.03 mm^2 for the AIN and 0.94 ± 0.10 mm^2 for the DBUN (Fig.12). The axon count showed 606 ± 68 myelinated axons in the AIN and 2893 ± 280 myelinated axons in the DBUN, respectively (Fig. 13). The densities of axons were calculated to 2400 ± 220 fibers / mm^2 for the AIN and 3270 ± 190 fibers/mm^2 for the DBUN (Fig. 14). Comparison of the donor to recipient nerve revealed that the AIN has a smaller nerve diameter, smaller nerve and fascicle cross-sectional areas, fewer fascicles and axons, and smaller axon density (Fig. 9 A-F, Chart 4). All differences were significant with respect to $p \leq 0.05$. Individual donor to recipient axon count ratios for each specimen revealed that most of the specimens (8 out of 14) had a ratio of about 1 : 4 to 1 : 5. Two specimens presented with very poor ratios of about 1 : 13 (Fig. 15).
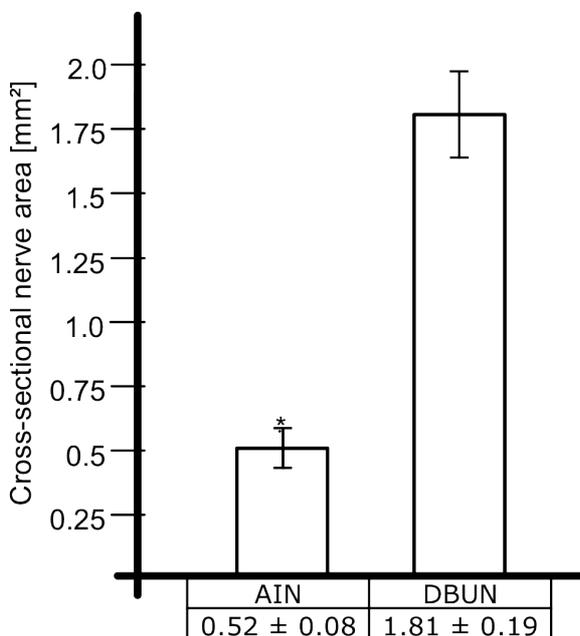

Figure 10: Comparison of donor (AIN) to target (DBUN) cross sectional nerve area.

**All data presented as Mean ± SEM. *represents p<0,05.**

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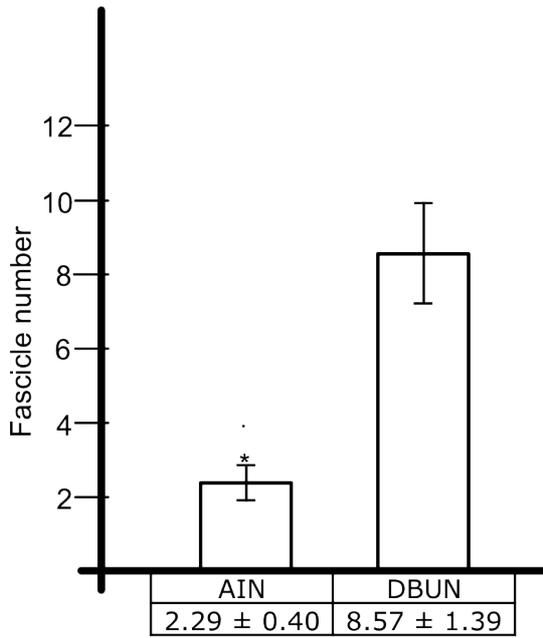
Figure 11: Comparison of donor (AIN) to target (DBUN) fascicle number.

**All data presented as Mean ± SEM. *represents p<0,05.**
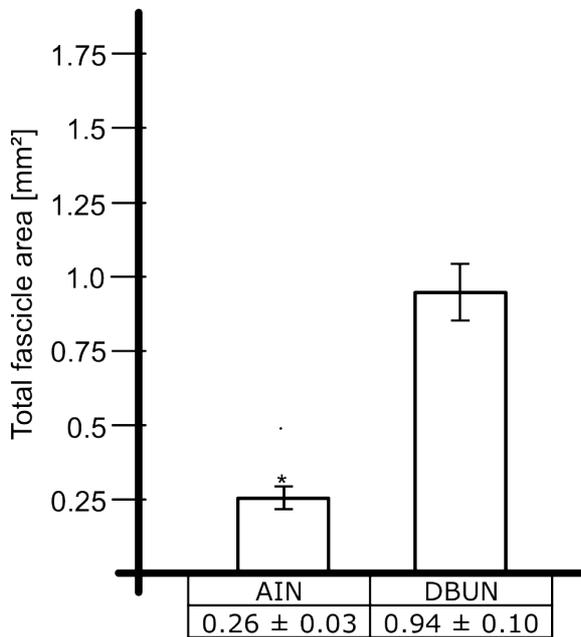
Figure 12: Comparison of donor (AIN) to target (DBUN) total fascicle area. All data presented as Mean ± SEM. *represents p<0,05.
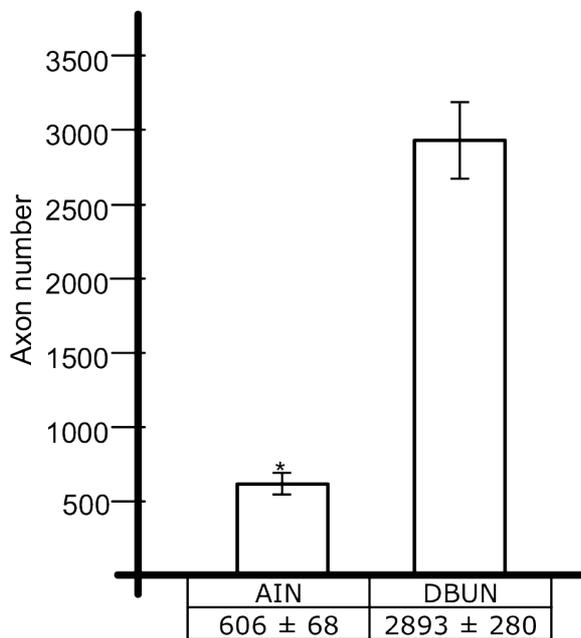

Figure 13: Comparison of donor (AIN) to target (DBUN) axon number.

**All data presented as Mean ± SEM. *represents p<0,05.**

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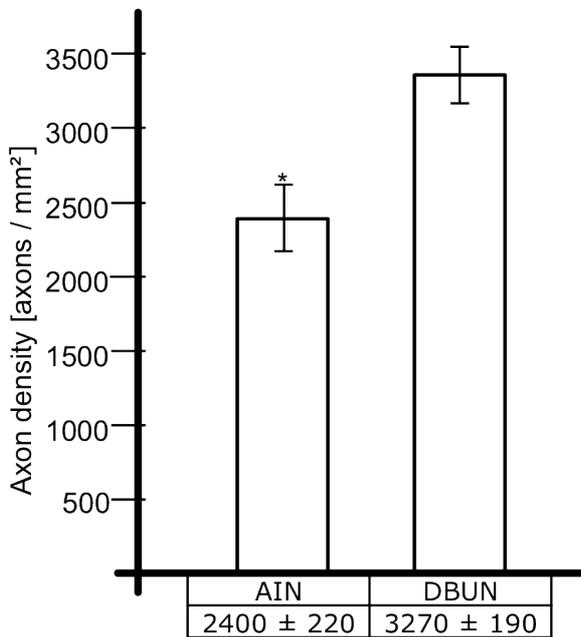
Figure 14: Comparison of donor (AIN) to target (DBUN) axon density.

All data presented as Mean ± SEM. *represents p<0,05.
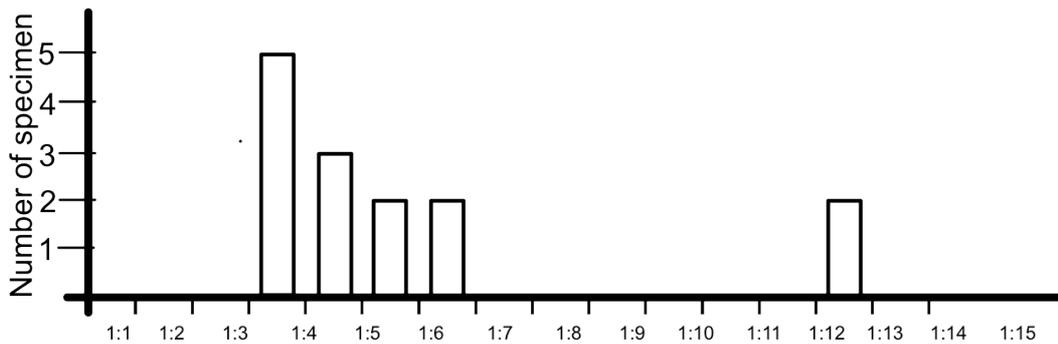
Figure 15: Frequency distribution of individual donor-to-target axon count ratios

The axon ratio of donor (AIN) to target (DBUN) was calculated for each individual specimen. This Figure illustrates the frequency of the individual ratios. No specimen had a ratio that exceeded the threshold of 1: 3 but the ratio of most specimens (8 out of 14) fell within a range of 1: 4 to 1: 5. Two specimens presented with very poor ratios of about 1: 13.

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	AIN : DBUN
Nerve diameter [mm]:	1 : 2.0
Cross-sectional nerve area [mm²]:	1 : 3.5
Fascicle number	1 : 3.7
Fascicle area [mm²]:	1 : 3.6
Axon number:	1 : 4.8
Axon density [axons / mm2]:	1 : 1.4

Chart 4: Donor-to-target (AIN: DBUN) ratios of histomorphometric nerve characteristics

Nerve diameters (Fig.8), cross-sectional nerve areas (Fig.10), fascicle numbers (Fig.11), total cross-sectional fascicle areas (Fig.12),axon numbers (Fig.13) and axon densities (Fig.14) were compared between AIN as the donor (left column) and DBUN as the target (right column). The AIN had significantly ($p < 0.05$) lower values in all parameters. All data presented as Mean ± SEM.

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3.2 Superficial Branch of the Radial Nerve Transfer to the Ulnar and Median Nerve

3.2.1 Anatomic Dissection

3.2.1.1 Superficial Branch of the Radial Nerve Transfer to the Superficial Branch of the Ulnar Nerve
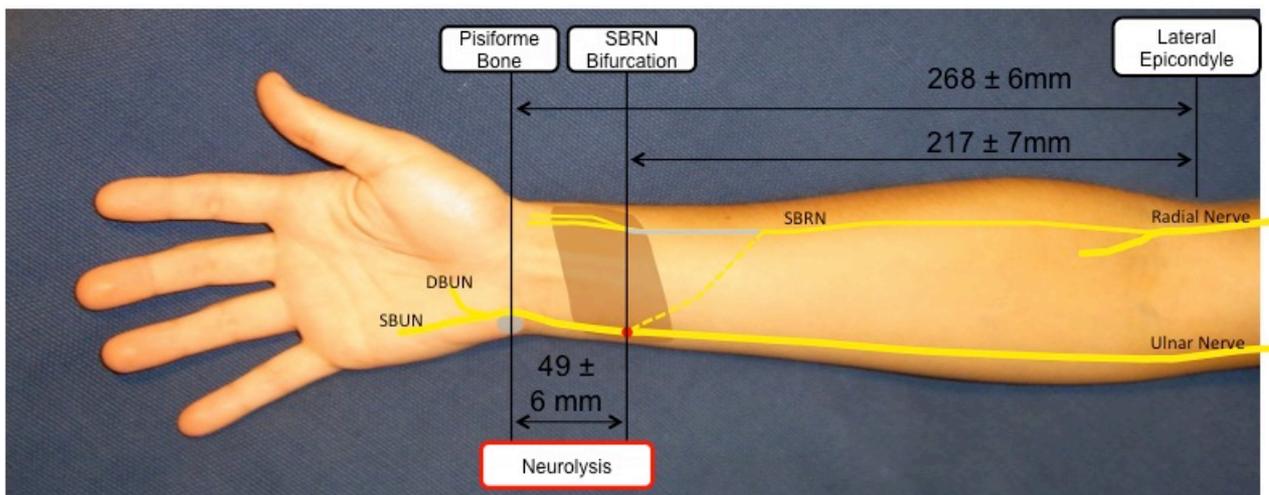

Figure 16: Schematic presentation of measurements of the transfer from the SBRN to the SBUN

The SBRN was dissected proximal to its first bifurcation which was found 217 ± 7.1 mm distally to the lateral epicondyle of the humerus and 34.7 ± 5 mm proximal to the styloid process of the radius. For coaptation with the SBUN the SBRN was transposed to the ulnar side of the wrist. SBUN and DBUN were identified in the Guyon's canal, distally to the pisiform bone which was found at 268 ± 6.0 mm distance to the lateral epicondyle. Starting at the Guyon's canal, SBUN and DBUN were separated over a length of 49.4 ± 5.5 mm to allow tension-free coaptation. The course of the SBRN before the transposition is shown in grey. Its course after transposition is depicted by an interrupted line and the coaptation is shown as a red dot. Other highlighted structures are the pronator quadratus muscle

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(brown) and the pisiform bone (grey). The radial nerve is depicted just to the level shortly beyond the takeoff of the SBRN for reasons of clarity. All data presented as Mean ± SEM, (n=15).

3.2.1.2 Superficial Branch of the Radial Nerve Transfer to the Sensory part of the Median Nerve

In all specimens, the concerned nerves presented without anatomic variations. The overall length of the forearm, measured from the lateral epicondyle of the humerus to the styloid process of the radius, was 252 ± 6.3 mm. In both nerve transfers, the SBRN was dissected proximal to its first bifurcation. This bifurcation was located 217 ± 7.1 mm distal to the lateral epicondyle of the humerus and 34.7 ± 5 mm proximal to the styloid process of the radius. By separating the SBRN from its surrounding tissue in a retrograde fashion over a distance of approximately 5-7 cm and by tunneling it under the extensor carpi radialis longus and brevis muscles, maximum length was achieved and transposition to the recipient nerves was possible without loss of length. For transfer to the SBUN, the SBRN was placed between the superficial and deep flexors to reach the ulnar aspect of the wrist. Before coaptation, the MN and the SBUN were dissected from their accompanying motor parts. The MN was separated from the thenar branch over a distance of 82.1 ± 5.7 mm. The SBUN and the DBUN had to be separated over a length of 49.4 ± 5.5 mm beginning in the Guyon's canal — whose associated landmark, the pisiform bone, was located at 268 ± 6.0 mm distal to the lateral epicondyle. In no forearm did this preparation affect the dorsal cutaneous branch of the ulnar nerve (DCBUN), which branches away from the ulnar nerve at approximately 7-9 cm proximal to the pisiform. The recipient nerves did not have to be transposed to enable coaptation, since mobilisation of the SBRN was sufficient to reach them within their normal anatomic course without any difficulty. The height of the coaptation was defined by the maximum obtainable length of the SBRN, which

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extended to 34.7 ± 5 mm proximal to the styloid process of the radius. In all cases, the coaptation was possible in a zone beginning at the height of the styloid process of the radius and ranging up to 5 cm in the proximal direction. The difference in nerve calibres was noticeable when the coaptation was performed.
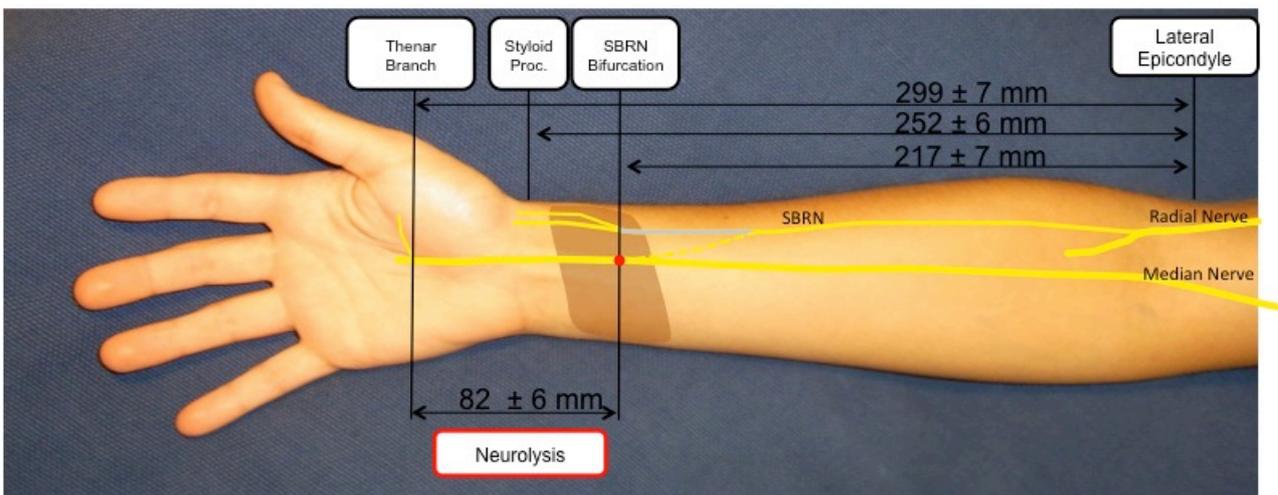

Figure 17: Schematic presentation of measurements from the transfer of the SBRN to the sensory part of the MN

The SBRN was dissected proximal to its first bifurcation which was found 217 ± 7.1 mm distally to the lateral epicondyle of the humerus and 34.7 ± 5 mm proximal to the styloid process of the radius. For tension-free coaptation, the MN had to be separated from the thenar branch over a distance of 82.1 ± 5.7 mm. The course of the SBRN before the transposition is shown in grey, while its course after transposition is shown as an interrupted line and the coaptation is shown as a red dot. Other highlighted structures are the pronator quadratus muscle (brown) and the pisiform bone (grey). The radial nerve is depicted just to the level shortly beyond the takeoff of the SBRN for reasons of clarity. All data presented as Mean ± SEM, (n=15).

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3.2.2 Histomorphometric Results

The total areas of the cross-sectional nerve fascicles were 0.64 ± 0.14 mm^2 for the SBRN**,** 1.27 ± 0.33 mm^2 for the MN, and 1.0 ± 0.19 mm^2 for the SBUN (Figure 21). The number of axons was 2310 ± 528 for the SBRN, 2450 ± 630 for the MN, and 3150 ± 674 for the SBUN (Figure 22). No significant differences ($p < 0.05$) were found when comparing the donor to both recipients in terms of cross-sectional fascicle area and absolute axon numbers (Chart 5). The SBRN had the highest axon density (3310 ± 396), followed by the SBUN (2970 ± 265) and the MN (2160 ± 231) [all in axons / mm^2] (Figure 23). The axon density of the SBRN was significantly higher than the axon density of the median nerve ($p < 0.05$).

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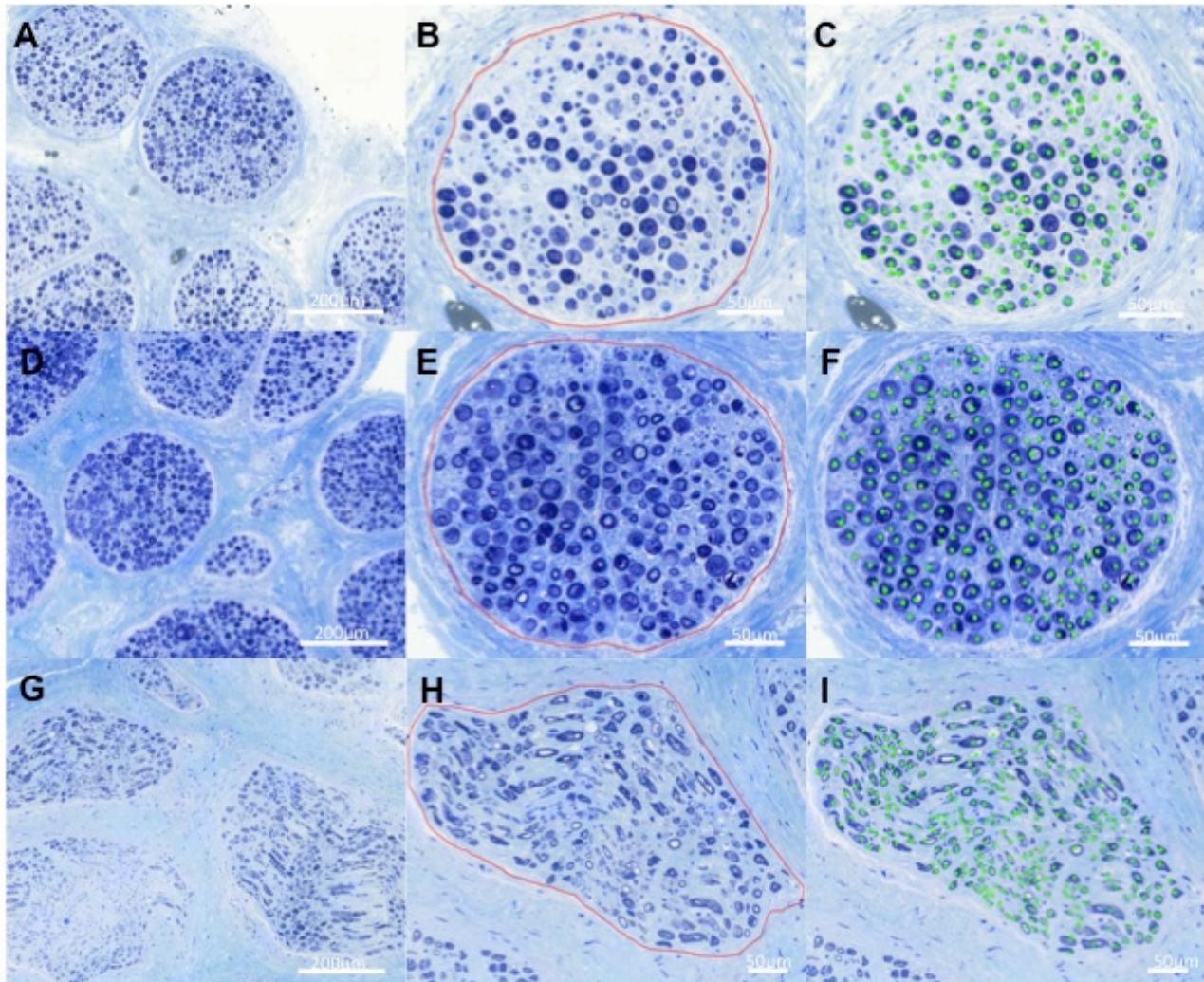
Figure 18: Histologic pictures of stained nerve sections from the SBRN, SBUN and sensory part of the MN

Samples from the SBRN (A,B,C), SBUN (D,E,F) and MN (G,H,I) were collected at the height of the coaptation. Samples were fixed in glutaraldehyde, embedded in epoxy raisin, cut to 1 µm semithin sections and stained with toluidine blue. At x200 magnification, general nerve structure and fascicles were observed (A,D,G). At ×600 magnification, cross-sectional areas of individual fascicles were determined by a polygon approach (B,E,H) and axons were counted semiautomatically with a low cut-off value for inclusion of 4 µm (C,F,I).

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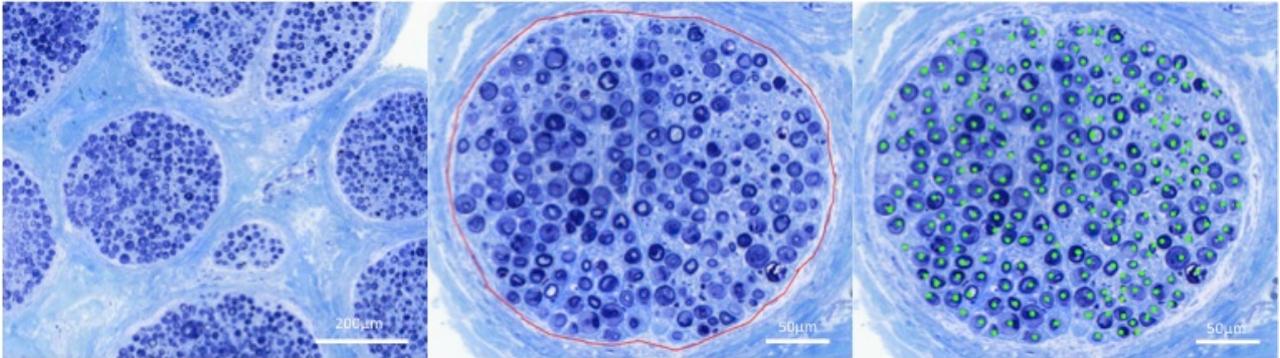
Figure 19 (= Figure 18 D, E, F): The SBUN at the height of the pisiforme
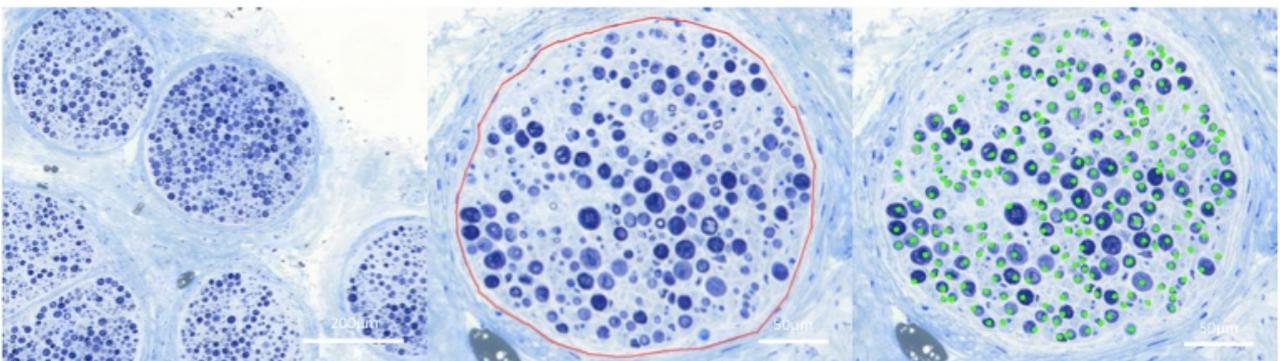
Figure 20 (= Figure 18 G, H, I): The SBRN before its division

	SBRN	MN	SBUN
	0.64 ± 0.14	1.27± 0.33	1.0 ± 0.19
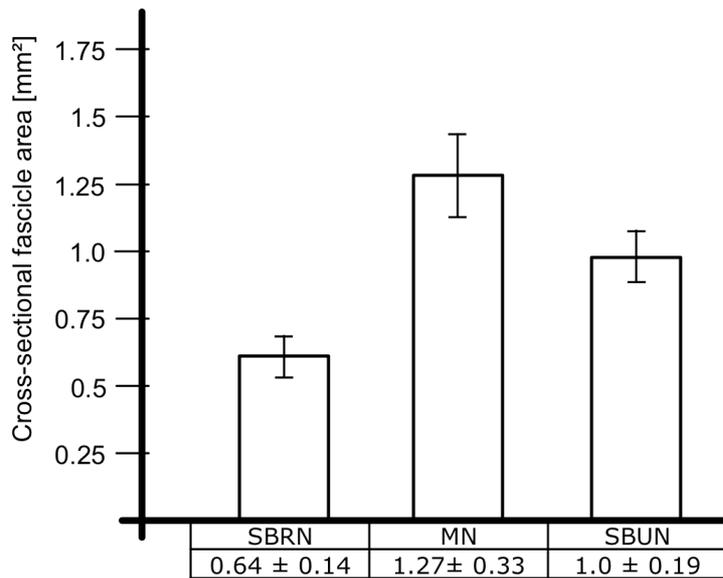
Figure 21: Comparison of donor (SBRN) to target (MN) and (SBUN) Cross-sectional nerve area

All data presented as Mean ± SEM.

	SBRN	MN	SBUN
	2310 ± 528	2450 ± 630	3150 ± 674
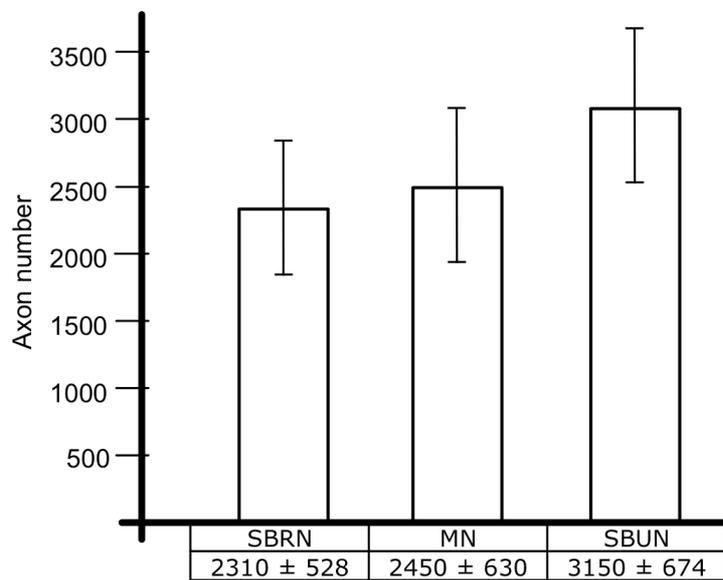
Figure 22: Comparison of donor (SBRN) to target (MN) and (SBUN) Axon number

All data presented as Mean ± SEM.
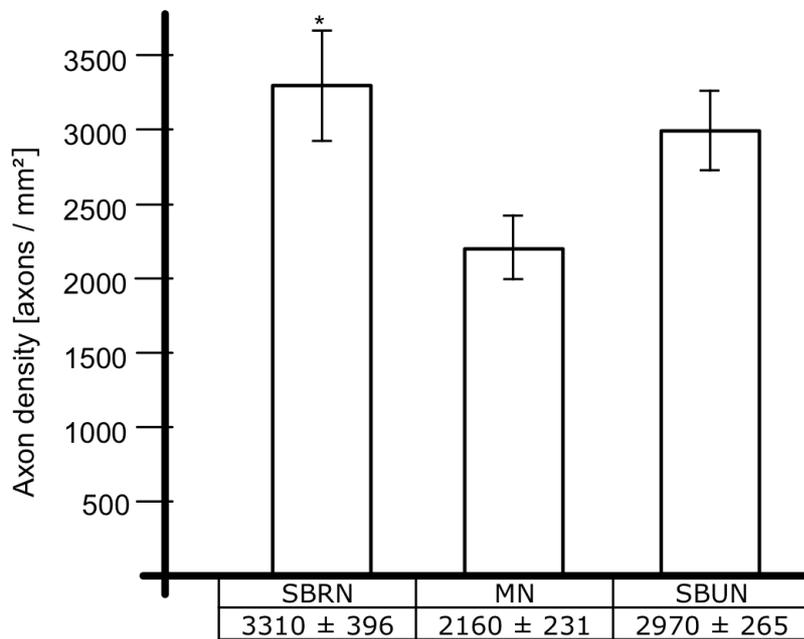
Figure 23: Comparison of donor (SBRN) to target (MN) and (SBUN) Axon density

Cross-sectional fascicle areas (A), axon numbers (B) and axon densities (C) were compared between of the donor (SBRN, left columns) and the targets (MN, middle columns; SBUN, right columns). Cross-sectional fascicle areas and absolute axon numbers showed no significant differences. Axon density was highest in the SBRN, exceeding significantly the axon density of the median nerve. All data presented as Mean ± SEM, (n=10), (p < 0.05).

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	SBRN : MN	SBRN : SBUN
Cross-sectional fascicle area [mm²]:	1 : 2.0	1 : 1.6
Axon number:	1 : 1.1	1 : 1.4
Axon density [axons / mm²]:	1 : 0.7	1 : 0.9

Chart 5: Donor-to-target (SBRN : MN and SBRN : SBUN) ratios of histomorphometric nerve characteristics

Comparison of donor to target cross-sectional fascicle area shows inferiority of the SBRN as donor. When comparing by absolute axon numbers, the difference is not as striking, which is due to axon density which reveals the SBRN as having a higher density than both the targets. The axon ratio is far below the commonly accepted threshold for successful nerve transfers of a 1 : 3 ratio. From a histomorphometric perspective both nerve transfers can be expected to be successful.

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4   Discussion

4.1   Clinical Situation

Despite considerable progress towards understanding the pathophysiology of peripheral nervous system injury and regeneration, and in addition to advancements in microsurgical techniques, peripheral nerve injuries remain a major challenge in the field of reconstructive surgery. There are various treatment options for surgical nerve repair, depending on the type of injury and the relevant clinical conditions. The primary goal of nerve reconstruction is to enable the reinnervation of the target organs by guiding regenerative sensory, motor and autonomic axons into the vicinity of the distal nerve. The outcome of peripheral nerve repair depends on many factors, among them the type, location, and extent of nerve injury; the timing of the surgery; the type of repair; the accuracy of fascicle alignment; the surgical technique practiced; the patient's age and comorbidities.[75] Primary suturing of injured nerves is considered the gold standard, but because of the limited results observed in many cases, alternative treatment methods have been explored and developed.

For a variety of reasons, there has been increased enthusiasm in recent years for nerve transfers in upper extremity peripheral nerve reconstruction. In general, the indications for this procedure include the following: high-level proximal upper extremity nerve injuries; nerve lesions for which successful recovery is unlikely due to the large distance between the injury site and the target motor end-plate, or a gap requiring a graft greater than 10 cm; and nonreconstructible nerve lesions with root avulsion or a missing proximal nerve segment.[99]

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The role of nerve transfer can be extended beyond the reconstruction of the brachial plexus, for which it is well established, to the reconstruction of specific peripheral nerves that may not be suitable candidates for graft repair, or that have a very poor prognosis through graft repair.

The most established nerve transfers are used in adult traumatic brachial plexus injuries or in nonreconstructible upper limb mononeuropathies. However, other successful neurotization procedures have been reported over the years and are gaining popularity in obstetrical plexus injuries and in facial paralysis.[25, 34, 40, 45] Nerve transfers have been creatively applied in multiple contexts: intercostal nerve transfers to the second and third sacral nerve roots have been used to reinnervate neurogenic bladders, for instance, and intercostal nerve transfers to the phrenic nerve have been used to reanimate the diaphragm in patients with high cervical tetraplegia.[42, 46]

4.2 Advantages of Nerve Transfers

The key advantage of nerve transfers is that they significantly shorten the amount of time required for reinnervation by reducing the distance from injury to target organ.
One of the most limiting factors in peripheral nerve repair is the time that elapses between the injury itself and the reinnervation of the target organ.[15] During this time, a process of degeneration takes place on both sides of the injured nerve, as well as in the muscle. Proximal to the axotomy, the nerve stump creates regenerating axons, which decrease over time and reach one-third of the initial number within six months of the injury.[26] Distal to the nerve injury, Schwann cells provide a regenerative environment that promotes axonal growth for a limited time period before they

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degenerate.[4, 27] "Time is muscle"[91], so choosing a donor nerve in close proximity to the target muscle will reduce both the distance and the amount of time required for regeneration, and it will help to reinnervate the muscle before irreversible changes take place.[96] The shortened regeneration time and distance and increased probability of successful reinnervation achieved by microsurgical nerve transfers is especially crucial for motor nerve transfers.[96] In cases of sensory nerve transfer, the time span between injury and reinnervation does not seem to be as critical[15], with some reports stating that successful sensory reinnervation is possible even after 20 years.[66] The long-term results of sensory nerve repairs could be attributed to the survival of mechanoreceptors long after axotomy, as was true in the case of Pacinian corpuscles.[64, 100] Another advantage of nerve transfers is that they permit surgery in unscarred and uninjured tissue. In cases in which tissue damage is severe or the proximal nerve stump is unavailable, nerve transfers are becoming a well-established alternative.

4.3 Criteria for Successful Nerve Transfers

However, when considering whether to perform a nerve transfer, certain criteria must be fulfilled. First, when selecting optimal donor nerves, they should be in close proximity from the donor muscle (especially in motor nerve transfers) to the target muscle, and therefore reduce regeneration distance and time.[91] Secondly, the use of donor nerves that innervate muscles that provide a synergistic function to the target muscles will promote post-operative rehabilitation and motor re-education and help to increase the possibility of successful results.[52] Thirdly it is of great importance that all nerve transfers are free of tension. To ensure this, it is necessary that both donor

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and recipient are mobilized as much as possible and that the donor nerve is cut as distally as possible, while the recipient nerve is cut as proximally as possible, so as to obtain adequate length.[16] Furthermore, when considering a nerve transfer, it is crucial that the impairment due to the loss of function of the donor nerve is less consequential than the loss of function sustained as a result of the recipient nerve's lesion. The risk-to-benefit ratio must be carefully weighed out before the surgery and is often a highly individual decision. Finally, the quantity of the donor's motor axons as compared to the recipient's plays an important role. Per a study published by Totosy et al.[87], clinically relevant muscle force can be achieved with a minimum of 30% of the original motor neuron pool.

To evaluate if these criteria are met, this study examines three nerve transfers in terms of anatomic feasibility (distance, synergy, tension free coaptation, donor site morbidity) as well as the histologic background of axon ratios from donor to recipient. This study shows the anatomic and histomorphometric background for the motor nerve transfer from the anterior interosseous nerve to the deep branch of the ulnar nerve, as well as for two sensory nerve transfers from the superficial branch of the radial nerve to the median and ulnar nerve for sensory reanimation for the palmar side of the hand.

4.4 Transfer from the Anterior Interosseus Nerve to the Deep Motor Branch of the Ulnar Nerve

4.4.1 Anatomic Dissection

For the neurotization of the AIN to the DBUN, the AIN was harvested right before it enters the PQ (Figure 4: transfer from the AIN to the DBUN). Some authors have suggested harvesting it from further within the muscle (See chart 7).[16, 99] However,

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while this may be appropriate in some individual cases, it is preferable that—due to the branching pattern within the PQ—to harvest the AIN right before it enters the muscle, where axon numbers are highest, and in order to retrieve representative and reproducible data. The AIN could be carefully separated from its surrounding tissue in the proximal direction, enabling a length of about 3-4 cm to be obtained, so that the nerve could then be transferred to the ulnar border of the PQ without any loss of nerve length. While mobilizing the nerve, there was no interference with its branches to the flexor pollicis longus or the flexor digitorum profundus of the index finger, since preservation of the muscle branches is crucial to avoiding an iatrogenic Kiloh-Nevin syndrome.

In order to obtain the DBUN, the SBUN and DBUN were divided at their division point in a retrograde manner, after opening the Guyon's canal. At the height of the coaptation site, the DBUN was found lying dorsal to the SBUN, as is consistent with previous reports.[20] There are different opinions about the interfascicular neurolysis of the DBUN and the SBUN: some reports state that the DBUN can be traced by sight and then cut and sutured to its donor.[24] Others share the idea that physical neurolysis of the DBUN and SBUN is more reliable to surely identify the parts from each other. This study measures the length of interfascicular neurolysis at 67±3 mm, which allowed for the preservation of the sensory DCBUN (Figure 7). Thereby any additional trauma to the DCBUN was avoided and sensory innervation in the dorsum of the hand was preserved. Additionally, the DCBUN stays available for other sensory nerve transfers.[7, 16]

As stated above, successful reinnervation is highly dependent on the proximity of the nerve to the target muscle, which shortens regeneration distance and thereby reduces the regeneration time before the target organ undergoes atrophic changes.[96] Usually, peripheral nerve regeneration occurs at a speed of approximately 1 mm per

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day.[18] Measurements in this study state the location of the coaptation 202 ± 4 mm distal to the medial epicondyle (Figure 7), which allows one to estimate an approximate reinnervation time and distance for this specific nerve transfer. The approximate reinnervation time for ulnar nerve lesions at the elbow level is around 6.5 months. By summing up the distance from the coaptation site to the pisiforme bone (66.7 ± 3 mm) and from there to the target muscles (about 3 cm), one is able to estimate that approximately 100 days would elapse between surgery and reinnervation of the target organs. This is important information regarding the limited time window for successful nerve transfers.

There was a difference in caliber among the nerves at the coaptation site, but the neurotization was nevertheless feasible. The anatomic measurements in this study are in accordance with the literature and are valid for the end-to-side version of this transfer as well, which has been recommended for second- and third-degree ulnar nerve injuries.[5, 30, 88]

In order to perform this surgery, it is recommended to start with the identification of the AIN, followed by the neurolysis of the SBUN and DBUN to the point at which a tension-free coaptation is possible. The SBUN and DBUN occasionally demonstrate an irregular amount of interchanging nerve fibers, which—if they are minor—may be cut.[16] In case of a dense nerve plexus, it is suggested performing one of the following alternatives: if the plexus is near the end of the seperation of the branches and therefore close to the coaptation site, the AIN should be harvested from further within the PQ to gain extra length; if this is not feasible, the interposition of a graft—i.e. from the sural nerve—or a nerve conduit are options.

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4.4.2 Histomorphometric Analysis

The choice of the optimal donor nerve depends on its proximity to the target organ, the synergy of the muscle function, and its quantity of axons compared to the recipient nerve. A commonly accepted method for predicting the likelihood of a successful nerve transfer is to examine the histomorphometric characteristics, such as axon number, cross-sectional nerve area and diameter of donor and recipient nerve.[12, 71] Whereas absolute numbers of semiautomatic axon counts can vary due to inclusion criteria, axon ratios should be comparable throughout studies.[68]

In this study, nerve samples were extracted from the coaptation site and analyzed histomorphometrically in terms of nerve diameter, cross-sectional nerve area, fascicle number, total fascicle area, axon number, and density. (Figures 8-15).

The data shows that the AIN has a significantly lower, but still comparable axon density, while it is only half the diameter of the DBUN. The donor-to-recipient ratios for the cross-sectional nerve area, fascicle number, total fascicle area and axon number reveal that the AIN is significantly smaller than the DBUN. (Chart 4/6). Successful reinnervation is nevertheless possible even when the donor has significantly fewer axons than the recipient.[87] Due to the potential for collateral sprouting in the proximal stump, the axon number can be amplified by 3-4[35], which allows the motor unit to expand up to 3-5 times its initial size.[28] Research shows that clinically relevant muscle force can be achieved with a minimum of 30% of the original motor neuron pool.[87] Other authors compared different donor-to-recipient axon ratios in rabbits, showing that stronger muscle contraction and effective motor recovery are associated with an increasing donor side axon number.[48] Based on these studies, this data's axon ratio of 1 : 4.8 can be regarded as critically low.

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Donor to recipient axon ratios were calculated for this nerve transfer from axon numbers of other studies to the following ratios: 1 : 1.3; 1 : 1.5; 1 : 2 and 1 : 4.1 (See chart 7).[16, 61, 94, 97] It was notable that in two of the studies, the DBUN nerve samples were taken at the height of the pisiform, far away from the actual coaptation location.[94, 97] In contrast, in this work DBUN samples were taken directly from the height of the coaptation, which is 6.7 cm proximal to pisiform. The idea here is that samples for axon ratios should be taken at the height of the coaptation in order to ensure the accurate evaluation of nerve transfers. The other two studies did not disclose the location of sample collection.[16, 61] In the current study 8 of 14 specimens (57%) presented with ratios of 1 : 4 and 1 : 5 and can be considered only slightly below the threshold of 1 : 3. Among the cited studies, which state their sample size, the current study has the highest sample size.

Poor axon ratios that occur sporadically might explain reports of poor clinical results in some cases.[97] In two cadavers, individual donor-to-recipient axon ratios showed extremely poor ratios of approximately 1 : 13 (Fig. 15). One of these had the smallest AIN in this study, exhibiting the smallest nerve diameter and fascicle area, as well as the lowest axon number by far (98). The other cadaver, with a 1:13 axon ratio, had the third-largest DBUN axon number (3657) and the second-lowest AIN axon number (267).

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	AIN : DBUN
Nerve diameter [mm]:	1 : 2.0
Cross-sectional nerve area [mm²]:	1 : 3.5
Fascicle number:	1 : 3.7
Fascicle area [mm²]:	1 : 3.6
Axon number:	1 : 4.8
Axondensity [axons / mm²]:	1 : 1.4

Chart 6: Donor-to-target (AIN: DBUN) ratios of histomorphometric nerve characteristics

The AIN has a comparable axon density but only half the diameter of the DBUN. The ratios for the cross-sectional nerve areas, fascicle numbers, total fascicle areas and axon numbers show that the AIN is consistently inferior. Since clinical relevant success of nerve transfers is commonly expected in ratios of higher than 1: 3, the donor-to-target axon ratio of 1: 4.8 in this study must be considered critically low. (n=14).

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	n	AIN : DBUN	Location of sample collection AIN	Location of sample collection DBUN
Current study	n = 14	1 : 4.8	Proximal to Pronator quadratus (at the coaptation)	Proximal to Pronator quadratus (at the coaptation)
Wang et al. 97	n = 7	1 : 1.5	Proximal to Pronator quadratus	Pisiform bone
Üstün et al. 94	n = 10	1 : 1.3	Proximal to Pronator quadratus	Guyon's canal
Brown et al. 16	not given	1 : 2	not described	not described
Novak et al. 61	not given	1 : 4.1	Proximal to Pronator quadratus	not described

Chart 7: Comparison of donor-to-target axon ratios in other publications

Donor-to-target axon ratios for the AIN to DBUN nerve transfer were calculated from axon numbers published by other groups. Comparing calculated ratios reveals inhomogeneous results. When comparing the location of sample collection, it is worth noting that in at least in two of the four studies the DBUN samples for the histomorphometric analysis were extracted at the height of the pisiform, rather than at the height of coaptation, as in the current study. Comparison of sample size shows highest sample size in the current study.

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4.4.3 Conclusion

The anatomic results present the AIN as an appropriate donor for the DBUN and should offer recommendations for planning this procedure. In a preponderance of cases, the donor-to-target axon ratio fell slightly short of the commonly accepted threshold of 1: 3. Targeting the motor-to-motor branch directly seems to bear greater relevance to the clinical outcome. Hence, clinical reports of satisfactory outcomes could be evidence of that fact that in this particular nerve transfer lower axon ratios are sufficient.[16, 25, 51, 52, 97] The low ratio could be compensated for by transferring the AIN to selected DBUN fascicles which are expected to be most beneficial to the individual patient's hand function.

When the functional gain of the nerve transfers examined in this study is compared against their functional loss, all donors seem sufficient. Considering the AIN, reduced pronation force due to loss of PQ function is counterbalanced by the opportunity to regain intrinsic hand function by reinnervating the DBUN. Furthermore, the pronation force provided by the pronator teres and brachioradialis muscles compensates somewhat for the PQ function.

4.5 Transfer from the Superficial Branch of the Radial Nerve to the Ulnar and Median Nerve

The loss of sensation in the palmar side of the hand significantly diminishes patients' ability to work, participate in social activities, and maintain a decent quality of life. Indeed, losing sensation in the thumb alone means a 20% reduction in hand function.[85] Reports of dorsal to palmar nerve transfers were among the earliest nerve transfers ever recorded, which speaks to the crucial importance of palmar sensation. In his 1921 analysis of the way in which nerve injuries sustained by soldiers were

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treated during the First World War, R.I. Harris—the father of peripheral nerve transfers—reported successful transfers of the SBRN to the MN.[31] Since then, numerous sensory nerve transfers—including variations of the dorsal to palmar nerve transfer and heterodigital nerve transfers—have been reported.[8, 17, 64, 92] Presently, however, we lack evidence of sensory nerve transfers performed as part of a large clinical series. For heterodigital nerve transfers, documented success rates range from 72% to 85%.[66, 80] Özkan and colleagues reported a two-point discrimination of less than 10 mm in 15 out of 25 cases in which median and ulnar nerve injuries were treated with mainly heterodigital digital nerve transfers.[66] Bertelli presented a series of 8 patients who had sustained plexus injuries, for whom cutaneous branches of the median nerve to the palm were successfully transferred to the ulnar digital nerve of the small finger.[8]

4.5.1 Anatomic Dissection

For both transfers, the SBRN was harvested prior to its first bifurcation in order to maximize axon number on the donor side and, consequently, to improve donor-to-recipient histomorphometric ratios. Mobilization of the SBRN, as well as passing it under the extensor carpi radialis longus and brevis muscles to the middle and ulnar aspect of the distal forearm, prevent the creation of a hypomochlion and allow for transposition without loss of length. Accordingly, the location of the coaptation is defined only by the height of the SBRN bifurcation, and the recipient nerves can be reached within their normal anatomic course. At the level of the wrist, the recipient ulnar and median nerves are mixed sensory and motor nerves, whereas the SBRN is a purely sensory nerve. To avoid motor and sensory axon mismatching, the recipient nerves were separated from their accompanying motor parts, beginning at their

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separation into motor and sensory branches at the height of the carpus. Maximum attention should be given to atraumatic separation of the nerves to avoid nerve injury.

The retrograde separation of the MN and the thenar branch was performed, starting from within the carpal canal. For tension-free coaptation to the donor, the median nerve had to be interfascicularly separated over a distance of 82.1 ± 5.7 mm, which carries with it the risk of damaging both components of the nerve. This preparation does not only avoid misdirection of axons but will conserve the function of the thenar nerve in rare cases in which it is not affected by the median nerve injury. If the thenar branch is affected, it is suggested performing the nerve transfer as an addition to an opponensplasty. Separation of the ulnar nerve was begun from within the Guyon's canal, where the SBUN and the DBUN can be safely identified and performed over a length of 49.4 ± 5.5 mm. Considerable efforts should be dedicated to preserving the DBUN in order to either preserve its intact function or to keep it available as a recipient for an anterior interosseous nerve transfer.[16] If interchanging fibers between SBUN and DBUN appear very dense, a sural nerve graft can help to avoid nerve damage by separation of the branches.[40]

The obvious macroscopic size difference of donor and recipient nerves raises the question of special suturing techniques, familiar from the microsurgical suturing of blood vessels of varying diameters.

4.5.2 Histomorphometric Analysis

The regeneration of axons in the recipient nerve, through donor axons that travel across the nerve coaptation, is crucial for the result of sensory and motor nerve transfers. Most of the knowledge of histomorphometric data was gained in correlation

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and clinical results of nerve transfers by investigating motor nerve transfers.[12] One can assume that the methods of donor to recipient comparison are valid for sensory transfers. Commonly accepted methods for estimating the results of nerve transfers are donor-to-recipient comparisons of histomorphometric nerve characteristics such as axon numbers or nerve cross-sectional areas[48], though successful reinnervation is known to occur even when the donor is smaller than the recipient.[35, 87] A commonly accepted threshold for successful motor nerve transfers is a donor-to-recipient axon ratio of 1 : 3, due to the fact that the axons of the proximal nerve stump can undergo collateral sprouting [48] Nerve samples of the donor and the two recipient nerves were taken and then cross-sectional fascicle areas, axon numbers, and axon densities were analyzed (Chart 8). Observed cross-sectional areas are in line with the clinical experience that the MN is larger than the SBUN, which in turn is larger than the SBRN (Figure 21). In evaluating absolute numbers of the cross-sectional fascicular size, it must be remembered that the true nerve size is larger because of perifascicular tissue and because of volume lost due to fixation, dehydration, and embedding of the specimen.

In this study, the SBRN to MN axon ratio was 1 : 1.1, and the SBRN to SBUN axon ratio was 1 : 1.4 (Chart 8). Both ratios are better than the commonly accepted threshold of 1 : 3. The axon density of the SBRN (3310 ± 396) exceeds the MN (2160 ± 231) and the SBUN (2970 ± 265) (Figure 23). From this data, it can be concluded that the SBRN is a suitable donor for both recipients. The macroscopically observed inferiority of the SBRN in size can be misleading in judging its qualities as a donor, because its significantly higher axon density balances out the discrepancy in size to some extent.

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	SBRN : MN	SBRN : SBUN
Nerve diameter [mm]:	1 : 1.4	1 : 1.2
Cross-sectional nerve area [mm²]:	1 : 1.5	1 : 1.2
Fascicle number:	1 : 0.8	1 : 1.6
Fascicle area [mm²]:	1 : 2.0	1 : 1.6
Axon number:	1 : 1.1	1 : 1.4
Axondensity [axons / mm²]:	1 : 0.7	1 : 0.9

Chart 8: Donor-to-target (SBRN : MN and SBRN : SBUN) ratios of histomorphometric nerve characteristics

4.5.3 Conclusion

The anatomic and histological data leads to conclude that the SBRN is a suitable donor for the MN and the SBUN. The anatomic measurements demonstrate the feasibility of the transfer and will assist in refining the technique of the operation. The histomorphometric results reveal the SBRN as a sufficient donor. The macroscopically observed inferiority of the SBRN's size can be misleading when endeavoring to assess its quality as a donor. The high axon density of the SBRN partly outweighs its smaller cross-sectional area. The presented nerve transfers can be considered to be promising treatment options for reviving sensibility in the thumb and fingers.

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The loss of sensation to the dorsal side of the hand is not considered as heavily disabling; however, loss of sensation to important regions of the hand (i.e. the ulnar border of the thumb, the radial border of the index finger, and the ulnar border of the small finger) cause severe disability. Loss of sensation in the thumb, for example, results in a 20% loss of function in the hand.[66] Therefore, the SBRN is to a certain extent expendable, depending on the chances of regaining sensation in more relevant regions of the hand.

However, it is extremely rare that the sensibility restored through sensory nerve transfer aligns topographically with the recipient nerve zone.[79] Rather, the sensibility is perceived in the topography of the donor nerve, which disorients and discomfits the majority of patients. This may diminish the functional usefulness of this nerve transfer.[99]

Nonetheless, one must always take care never to sacrifice a viable nerve to a nerve with nonvital function. Therefore, thorough preoperative examinations are absolutely crucial.

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5 Summary

Extensive peripheral nerve injuries and their resultant motor and sensory deficits remain a major challenge within the field of reconstructive surgery. There are various treatment options for different levels of nerve injury, but nerve transfers have gained popularity among surgeons for several reasons. Chief among them are the limited results seen in high-level injuries, large nerve defects, and cases in which the proximal nerve stump is unavailable.

This treatment option offers advantages over direct repair or the grafting of proximal injuries because it reduces the distance between the regenerating nerve and the target organ. Essentially, this converts a high-level injury into a low-level injury. Reducing the distance for reinnervation with a distal nerve transfer will thereby shorten the time required for nerves to regenerate and permit the recovery of motor or sensory function before target organs undergo irreversible atrophy. It also enables surgery in unscarred tissue, which improves the results.

Of course, nerve transfer poses certain hazards as well. The primary disadvantage of nerve transfer is that it involves sacrificing a viable nerve for the sake of an injured one. Therefore, the procedure must be meticulously planned, and the risk-to-benefit ratio must be taken into consideration. However, in most nerve transfers the donor site defect is neglectable.

In order to perform a nerve transfer and to accurately predict its success, the surgeon has to have exact knowledge of the donor and recipient nerves' anatomic and histomorphometric backgrounds.

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This study seeks to evaluate, in an experimental context, the feasibility of restoring distinct motor and sensory functions in the hand. It accomplishes this by examining three transfer options in terms of their anatomic and histologic requirements.

For the motor nerve reconstruction, the transfer of the AIN to the DBUN was examined. For sensory reconstruction, the transfer of the SBRN to the SBUN, as well as the transfer from SBRN to the sensory part of the MN, were examined.

The study was performed on 15 fresh cadaver specimens. The nerves were identified, and the nerve transfer was performed. A favorable site for coaptation was chosen, and its location was described using relevant anatomical landmarks. Nerve samples from the donor and recipient nerves were extracted at the coaptation site for histomorphometric evaluation.

The anatomic results identify the AIN as a suitable donor for the DBUN. The favorable site for coaptation appears to be just proximal to the pronator quadratus muscle, 202 ± 4 mm distal from the medial epicondyle of the humerus. In order to reach the coaptation site, the superficial and deep ulnar nerve branches have to be separated by interfascicular dissection by a length of 66.7 ± 3 mm. The dorsal cutaneous branch of the ulnar nerve could be preserved in all specimens. The AIN presented with smaller nerve diameter, smaller fascicle and nerve cross-sectional areas, and fewer fascicles and axons; its axon density, however, was comparable. The histomorphometric inferiority of the AIN raises the question of whether it should be transferred solely to selected parts of the DBUN. The functional loss of the AIN is outweighed by the chance of compared to the functional gain.

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Regarding the sensory transfers, a suitable location for the dissection of the SBRN was identified prior to its first bifurcation. Coaptations were possible near the pronator quadratus muscle, approximately 22 cm distal to the lateral epicondyle of the humerus. The MN and SBUN had to be separated by interfascicular dissection for a length of over 82 ± 5.7 mm and 49 ± 5.5 mm, respectively. Histomorphometric analysis reveals sufficient donor-to-recipient axon ratios for both transfers and identifies the SBRN as a suitable donor with high axon density. This significantly higher axon density balances out the discrepancy in size to some extent. The anatomic and histomorphometric results indicate that the SBRN is a suitable donor for the MN and SBUN at the wrist level.

It is yet to be determined whether enhanced techniques for nerve coaptation and improvements in the speed and quality of nerve regeneration, thanks to pharmacologic and genomic advances, will serve to increase and expand the use of nerve transfers in the future. So far, it is clear that nerve transfers are an important new tool for reanimating paralysed muscles and for restorating functional sensibility. In the last years this led to a shift of perception from anatomical peripheral nerve repair with autologous grafts towards extraanatomical nerve repair by means of nerve transfers. However, further research into the anatomic and histologic basis of nerve transfer is necessary to deepen current understandings of the anatomic nuances and will enable the peripheral nerve surgeon to safely and reliably restore function in the deficient target organ in a more efficient manner.

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5.1   Zusammenfassung

Schwere Nervenverletzungen und daraus resultierende motorische und sensorische Einschränkungen stellen nach wie vor eine große Herausforderung in der rekonstruktiven Chirurgie dar. Je nach Schwere der Nervenverletzungen gibt es unterschiedliche Behandlungsoptionen, wobei sich Nerventransfers aus mehreren Gründen zunehmender Beliebtheit bei Chirurgen erfreuen. Die wichtigsten Gründe hierfür sind schlechte Behandlungserfolge von Nervenverletzungen die sehr proximal liegen, langstreckig sind oder wenn der proximale Nervenstumpf fehlt.

Diese Behandlungsoption hat gegenüber der direkten Wiederherstellung oder der Verwendung von Nerventransplantaten bei proximalen Verletzungen den Vorteil, dass sie die Distanz zwischen dem sich regenerierenden Nerv und dem Zielorgan reduziert. Somit wird eine proximale Verletzung in eine distale Verletzung überführt. Durch Verkürzung der Reinnervationsstrecke mit einem distalen Nerventransfer, verkürzt sich die Reinnervationszeit und ermöglicht die Wiederherstellung der motorischen und sensorischen Funktion, bevor die Zielorgane irreversibel atrophieren. Zudem kann die Operation in narbenfreiem Gewebe durchgeführt werden, was verbesserte Ergebnisse erwarten lässt.

Nerventransfers bergen jedoch auch Risiken. Der größte Nachteil eines Nerventransfers besteht darin, dass ein funktionsfähiger Nerv für einen verletzten Nerv geopfert wird. Deshalb muss die Vorgehensweise sorgfältig geplant und zwischen Risiko und zu erwartendem Erfolg sorgfältig abgewogen werden. Bei den meisten Nerventransfers kann man die Schädigung an der Entnahmestelle vernachlässigen.

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Um einen Nerventransfer durchzuführen und den Erfolg präzise abzuschätzen, muss der Chirurg über genaue Kenntnisse der Anatomie und Histomorphometrie der Spender- und Empfängernerven verfügen.

Ziel dieser experimentellen Arbeit ist die Untersuchung verschiedener Rekonstruktionsmöglichkeiten von bestimmten motorischen und sensiblen Funktionen der Hand. Hierfür wurden drei Transferoptionen hinsichtlich ihrer anatomischen und histologischen Erfordernisse untersucht.

Als motorische Rekonstruktion wurde der Transfer des Nervus interosseus anterior auf den Ramus profundus des Nervus ulnaris untersucht. Als sensible Rekonstruktion wurden der Transfer des Ramus superficialis des Nervus radialis auf den Ramus superficialis des Nervus ulnaris sowie der Transfer des Ramus superficialis des Nervus radialis zum sensiblen Teil des Nervus medianus untersucht.

Die Untersuchung erfolgte an fünfzehn frischen Leichenpräparaten. Die Nerven wurden identifiziert, die Nerventransfers durchgeführt, geeignete Stellen für die Koaptation ausgewählt und ihre Position mittels relevanter anatomischer Orientierungspunkte beschrieben. Sowohl von Spender- als auch von Empfängernerven wurden an den Koaptationsstellen Proben zur histomorphometrischen Untersuchung entnommen.

Die anatomischen Ergebnisse identifizieren den Nervus interosseus anterior als geeigneten Spender für den Ramus profundus des Nervus ulnaris. Eine geeignete Koaptationsstelle scheint unmittelbar proximal des Musculus pronator quadratus und 202 ± 4 mm distal des Epicondylus humeri medialis zu liegen. Um diese Koaptationsstelle zu erreichen, müssen der Ramus superficialis und Ramus

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profundus des Nervus ulnaris interfaszikulär auf einer Länge von 66,7 ± 3 mm voneinander getrennt werden. Bei allen Präparaten konnte der Ramus dorsalis des Nervus ulnaris erhalten werden. Der Nervus interosseus anterior hat kleinere Nervendurchmesser, kleinere Nerven- und Faszikelquerschnittsflächen, weniger Faszikel und Axone, aber seine Axondichte ist vergleichbar. Die histomorphometrische Unterlegenheit des Nervus interosseus anterior führt zu der Frage, ob der Nerv vielleicht besser nur an ausgewählte Anteile des Ramus profundus des Nervus ulnaris transferiert werden sollte. Der funktionelle Verlust durch den Transfer des Nervus interosseus anterior wird durch die potentielle funktionale Verbesserung des reinnervierten Ramus profundus des Nervus ulnaris überragt.

Bei den sensiblen Nerventransfers wurde zum Absetzen des Ramus superficialis des Nervus radialis die Stelle unmittelbar vor seiner ersten Gabelung als geeignet identifiziert. Koaptationen waren somit in der Nähe des Musculus pronator quadratus, in etwa 22 cm Entfernung zum Epicondylus humeri lateralis möglich. Der Nervus medianus sowie der Ramus superficialis des Nervus ulnaris mussten durch interfaszikuläre Faszikolyse über eine Länge von 82 +/- 5,7 mm bzw. 49 +/- 5,5 mm getrennt werden. Die histomorphometrische Analyse ergibt ein ausreichendes Axon-Verhältnis von Spender zu Empfänger für beide sensiblen Transfers und stellt den Ramus superficialis des Nervus radialis als geeigneten Spender mit hoher Axon-Dichte dar. Die Diskrepanz der Nervendurchmesser wird durch diese signifikant höhere Axondichte zu einem gewissen Teil ausgeglichen. Das anatomische und histomorphometrische Ergebnis lassen den Ramus superficialis des Nervus radialis als geeigneten Spender für den sensiblen Teil des Nervus medianus und den Ramus superficialis des Nervus ulnaris im Bereich des Handgelenks erscheinen.

Die Zukunft wird zeigen, ob es durch weiterentwickelte Nervenkoaptationstechnik und durch pharmakologische und gentechnische Fortschritte zu einer schnelleren und

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erfolgreicheren Nervenregeneration und in Folge zu einer häufigeren und breiteren Anwendung von Nerventransfers kommen wird.

Nerventransfers spielen mittlerweile eine wichtige Rolle bei der Reanimierung von gelähmten Muskeln und der Wiederherstellung funktionaler Sensibilität. In den letzten Jahren hat es bei einer Vielzahl von Indikationen eine Entwicklung weg von der anatomischen Wiederherstellung durch ein autologes Nerventransplantat hin zur extraanatomischen Wiederherstellung durch einen Nerventransfer gegeben. Allerdings ist weitere Forschung auf dem Gebiet der Nerventransfers notwendig, um das anatomische und histologische Verständnis zu vertiefen und es dem Chirurgen zu ermöglichen, die Funktion des geschädigten Zielorgans effizienter wiederherzustellen.

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7 Appendix

List of all products, devices and drugs:

Epoxy resin	(Merck, Darmstadt, Germany)
Glutaraldehyde	(Science Services, Munich, Germany)
ImageJ version 1.42	(NIH, Bethesda, MD, USA)
Mirax Scannner	(Carl Zeiss, Jena, Germany)
Osmium tetraoxide	(Science Services, Munich, Germany)
Pannoramic Viewer 1.15	(3DHISTECH, Hungary)
Propylene oxide	(Science Services, Munich, Germany)
Sodium cacodylate buffer	(Science Services, Munich, Germany)
Toluidine blue	(Sigma-Aldrich, Taufkirchen, Germany)
Ultramicrotome	(Reichert Technologies, Munich, Germany)

8 Figures

9   Charts

10 List of Abbreviations

AIN	anterior interosseus nerve
DBUN	deep motor branch of the ulnar nerve
DCBUN	dorsal cutaneous branch of the ulnar nerve
CNS	central nervous system
PBS	phosphate buffered saline
PNS	peripheral nervous system
PQ	pronator quadratus muscle
MN	median nerve
SBRN	superficial branch of the radial nerve
SBUN	superficial branch of the ulnar nerve
SD	standard deviation
2 PD	two point discrimination
MRC	Medical Research Council

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Eidesstattliche Versicherung

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