Nerve Injuries and their Repair

A Critical Appraisal

Sir Sydney Sunderland

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Preface

The first edition of *Nerves and Nerve Injuries* was published in 1968 and a second edition in 1978. Both have been reprinted. A continuing demand for the book raises the question of whether a new, revised and rewritten edition is required. Careful reflection has convinced the author that such an edition is not warranted at this time.

The author believes that any new edition can only be justified if most of the contents have been subjected to changes, alterations and additions that are sufficiently substantial and relevant to warrant its replacement for an earlier edition.

In the case of *Nerves and Nerve Injuries*, the bulk of the contents relate to basic factual information of considerable clinical interest and significance that will not change in centuries. Instead of a third edition, what is really needed is a satellite or companion volume to the major work that addresses itself to those areas that call for amendment and for the inclusion of new and relevant information on nerve injury and nerve repair. This will explain the title of this book, *Nerve Injuries and their Repair. A Critical Appraisal*, and the motivation behind the selection of its contents.

This book is concerned solely with the subject of nerve injury and nerve repair. Non-traumatic causes of nerve dysfunction have been omitted intentionally.

Having in mind the wide-ranging nature of the book and the fact that it will be frequently used for reference purposes it is believed that some repetition is necessary and justifiable lest too many cross references destroy the continuity of an account. It is hoped that the understanding reader will appreciate this point.

Finally, the contents are based on the experiences and thoughts of one who has been involved in the laboratory investigation, study and clinical management of nerve injuries for more than 50 years. Such studies have at all times been directed to the elucidation of those principles on which the clinical management of nerve injuries should be based.

Melbourne 1991 Sir Sydney Sunderland

Acknowledgements

Though this saga of nerve injury, regeneration and repair has been a solo effort there are some to whom the author will always remain indebted for their friendship, generous help and support.

That the book is dedicated to my wife is the best I can do, inadequate though it is, to express my indebtedness to her for her monumental contribution to the completion of the book. She has typed and checked the entire manuscript several times and without her constant support and encouragement over the years the task would never have been undertaken let alone completed.

Though in my 80th year and 15 years into retirement, the Anatomy Department of the University of Melbourne, through the kind offices of Professor Ian Darien-Smith, has provided me over the years with accommodation and facilities while Professor Graeme Ryan, Dean of the Faculty of Medicine, has thoughtfully arranged for the Faculty to fund the final preparation of the manuscript for transmission to the publishers.

Churchill Livingstone has brought its customary skills and experience to the publication of the book and for this I thank them. My thanks are also due to Mrs Meldrum, Medical Librarian at the Alfred Hospital, who has been most helpful in tracking down and checking source material.

Lastly, this is an appropriate place and opportunity to acknowledge the debt I owe to colleagues in North America, Europe and elsewhere who have always given freely and generously of their time and experience during fruitful discussions and debate at international meetings and during the course of personal visits. I have indeed been fortunate in my clinical and laboratory contacts over the past 50 years. They are too numerous to name and too important to be overlooked. Clearly I owe much to the camaraderie that exists between workers in widely separated parts of the world but linked by a common cause and interest directed to achieving the best possible result from nerve repair by way of an unremitting search for the knowledge on which this depends.

Sir Sydney Sunderland

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SECTION 1

General considerations

1. Introduction

The old order changeth, yielding place to new,
And God fulfils Himself in many ways,
Lest one good custom should corrupt the world.
Tennyson. *Morte d'Arthur.*

One of the advantages of the first, and subsequently the second, edition of *Nerves and Nerve Injuries* is that it is the work of a single author who, at the time the book was written, could claim personal involvement both as a clinician and as a laboratory investigator capable of exploiting several scientific disciplines. Under these conditions knowledge from both clinical and experimental sources could be integrated in an orderly and meaningful way so that the central theme of nerve injury and nerve repair could be pursued on a broad and coordinated front.

Today the situation is different, for it is becoming increasingly difficult to preserve the closest possible integration of information pouring in from clinical and experimental sources. Spectacular developments in molecular biology, pharmacology, biochemistry, and electroneurophysiology, and the application of the complex technology required to support them, have outstripped the capacity of any one individual to handle the detail in every scientific discipline with any real authority or understanding. This largely explains why some of the subject matter in the Second Edition of *Nerves and Nerve Injuries* has been omitted from this companion volume, special attention now being given to those aspects of the subject in which the author has had a particular and lasting interest.

There is the further point that much of the recent published work in these various scientific disciplines has only an obscure relationship to the central theme of this text. Despite this, it has been possible to retain the essential objective of bringing all relevant aspects of the topics selected for inclusion together in an orderly and meaningful way.

The literature relating to nerve injury and nerve repair over the past 10 years remains a problem. Today we are confronted with a growing and confused mass of facts, often of an isolated and unrelated character, that clinicians and experimentalists pour daily in a continuous stream into the literature. As a result, the volume of papers, monographs, journals and books is approaching dimensions that are rapidly reaching the point of discouraging and defying readers.

While acknowledging that fact finding is the objective of any scientific enquiry, and that facts should be the ultimate court of appeal when an element of uncertainty, inconsistency or disagreement arises, we are now exposed to the real danger of becoming so preoccupied with accumulating new facts, often of an isolated and fragmentary nature, that too little time is left for their rational analysis. As a result, a synoptic and balanced appreciation of a subject becomes exceedingly difficult and general principles tend to become obscured in a mass of irrelevant detail.

What is also disturbing is that even a cursory examination of the current literature reveals an astonishing disregard for information that is already available, so that much of what is being reported continues to be either repetitious or irrelevant, or both, even though it may be supported in this technological age by an arsenal of gadgetry. Far too much time and effort are being spent 'rediscovering the wheel'.

Accordingly, the author has purposely refrained from including a comprehensive list of recent publications on the subject, redundant material being disregarded in favour of key references that con-

vey information that is original, has broken new ground, settled controversial issues or has introduced new and promising concepts. The intention, then, has been to retrieve from a morass of detail information of proven validity and to rescue from oblivion those facts that it is our wisdom to remember but our weakness to forget. Information does not need to be new to be important.

Finally, a persisting obstacle to improving the results of nerve repair today on a broader front is the failure by some to take advantage of information that has already been made available. The need to reduce the gap between what is known and what is practised remains a continuing challenge.

In a book of this nature there will always be the problem of deciding what to include and what to omit and such decisions must be largely a matter of personal judgement and a reflection of individual interpretation and emphasis.

Mediaeval surgeons believed that operative detail and surgical techniques could not be learnt from books but only by serving an apprenticeship under the tutelage of an experienced surgeon and by observing and assisting him in his craft. Thus, as long ago as the 15th century, Leonard of Bertapaglia wrote 'You must accompany and observe the qualified physician, seeing him work before you yourself practise, for by observing terrible accidents, you will discern the methods employed by those who treat them and thus attain the perfection of the masters.' This advice is as sound today as it was in mediaeval times and explains the omission from this text of descriptive details of operative procedures. Accordingly, the text is concerned with principles and changing attitudes and ideas regarding the management of these injuries and not with the details of changing operative techniques. At the same time the necessity for preserving and encouraging the highest standards of technical skills and achievement is obvious and is strongly endorsed.

After 50 years of unbroken endeavour in this field of activity, the preparation of this text has provided the author with an opportunity to pause and look back over the past and, by avoiding the tyranny of detail, to obtain a more general view of the subject, to contemplate its wider relations and so to crystallise his own thinking on the many problems in nerve injury and nerve repair that continue to baffle and to confuse us. In the process of doing so it becomes possible to sift the 'chaff from the grain', to discard what is outmoded and has been disproved, to include what is genuinely new and confirmed, to separate fact from fiction and fantasy, and, finally, to offer suggestions on the direction that future research might be expected to take to correct and eliminate persisting imperfections and gaps in our knowledge. Finally, where genuine doubt and uncertainty still persist, this is recognised and included as a challenge to the imagination and a stimulus to experimental initiative directed to new and more fruitful lines of investigation.

In essence, then, this book is based on one individual's observations, experiences, and personal views and thoughts that have accumulated during half a century of personal involvement with nerve injury, nerve regeneration and nerve repair. This covers a period of unprecedented experimental and clinical activity in many countries, as the result of which much new factual information has been added to the storehouse of knowledge while many old concepts have either required amendment or been shown to be false and discarded.

Interestingly enough, the rethinking generated by all this restless activity has revealed that many contradictions disappear when the *observations* and not the *conclusions* of investigators are compared, and that, while principles might remain sacrosanct, their clinical significance and clinical application have taken on new dimensions as the point of vision has altered in a rejuvenated and greatly changed clinical setting.

Finally, this book is not a substitute or replacement for *Nerves and Nerve Injuries* which should be consulted at all times for the details that have survived unchanged, and for the established information on which categorical statements in the present work have been based.

REFERENCES

Ladenheim J C 1989 Leonard of Bertapaglia: On nerve injuries and skull fractures. Futura Publishing Company, New York

2. Terminology relating to nerves, nerve injury and nerve repair

The careless and misleading use of terms in medical reporting is a common source of confusion and misunderstanding when interpreting and comparing the observations and writings of different authors.

Often a term is used in a manner that is clearly in conflict with correct usage, the author often compounding the error by failing to specify the meaning that he is attaching to the term. While errors introduced in this way may be corrected by following the text, there are those occasions when an element of uncertainty persists. For example, *perineural* is often used when *perineurial* is intended. Perineural means about or surrounding the nerve trunk and relates to epineurial tissue. Perineurial, on the other hand, refers to the perineurium, whose structural features and physiological properties differ significantly from those of epineurial tissue.

Again, it is not unusual for a term, particularly when first introduced into the literature, to be interpreted and used in different ways by different individuals. The availability and use of several terms, all with the same meaning, also adds to the confusion.

Finally, it should be remembered that there is a considerable literature on the subject of nerve injury and nerve repair in languages other than English, each of which employs its own terminology with terms that sometimes differ in a potentially misleading way from what would be regarded as the corresponding term in English. Such differences are inevitable and should be recognised and understood if errors in interpretation are to be avoided.

Clearly, what is needed is a universally accepted standard nomenclature for terms that are in common use in peripheral nerve literature, particularly those relating to nerve injury, nerve regeneration and nerve repair. Where synonyms are available it is suggested that there are advantages in retaining one and adopting it for general use.

The sole intention of this chapter is to direct attention to the importance of this subject. Information relating to individual terms is not provided here but is included as an introductory section on terminology in those chapters in which the term is logically located and where the definitions given leave no doubt as to precisely what is meant when a certain term is used in this book.

The passage of time will, no doubt, necessitate additions to the lists which serve only as a framework to meet the needs of future developments and new information.

3. Animal experimentation and the solution of clinical problems

The proper study of mankind is man.
Pope

That animal experimentation has told us much about the biological processes involved in axon degeneration and regeneration is beyond question. Against this background of success, the conviction has now developed that animal experimentation should be the initial step in the investigation of any clinical problem from which, it is confidently expected, important clues and answers will inevitably flow.

The outstanding contributions that animal experimentation has made to progress should not, however, blind us to the fact that this approach is not without its shortcomings and limitations. Models for studying nerve injury and nerve repair, so conveniently offered by the experimental animal, seldom match those special conditions encountered in clinical practice and frequently differ from them in several significant respects. As a consequence information so obtained may have little, if any, clinical relevance and may even be misleading.

Experimental investigations have often been employed to test, inter alia, the relative merits of different methods of nerve repair using a variety of techniques and materials. In these investigations comparisons have usually been based on four sets of observations:

1. The numbers, and histological features, of regenerating axons in the nerve below the repair.
2. The distance covered by regenerating axons within a given time.
3. The application of neurophysiological techniques to detect, study, and track regenerating axons as they grow down the nerve.
4. The recovery of function based on the study of reflex responses, muscle contraction, and forepaw and hind limb movements.

There are several reasons why extrapolation to the clinical situation of animal data obtained in these ways should be treated with considerable caution.

1. To generalise, it appears from a survey of the literature that neuroscientists are primarily concerned with axon regeneration as a biological phenomenon, whereas the clinician's principal concern is the restoration of function. However, for axon regeneration to be functionally effective it is essential that regenerating axons should reach and re-establish connections with their original, or at least functionally related, end organs and this they often fail to do.

Among the many complex anatomical and pathological processes involved in axon regeneration, some have the potential to obstruct and misdirect axons during their growth. Where this occurs the restored pattern of innervation is left incomplete and imperfect in comparison with the original and function suffers accordingly.

Of special significance in this respect is whether there are neurotropic influences generated at the distal nerve stump that counteract this loss of axons by sorting out and organising axon growth in such a way as to ensure that each axon re-establishes its original, or at least a functionally related, terminal relationship. Such selectivity would simplify the surgeon's task in that neurotropic influences would ensure the restoration of functionally useful connections.

Because of its crucial importance to nerve repair, a separate chapter (p. 155) is devoted to this subject in which it will be shown that there are no such neurotropic influences operating to direct axons back to their old end organs.

All this means that the presence of regenerating axons in a mixed nerve below the repair is no guarantee that those axons are destined for functionally relevant destinations. This explains why:

a. the quality of the recovery after nerve repair is determined by the final destination of regenerating axons;
b. it is possible to have good axon regeneration but a poor functional result;
c. it is essential to draw a distinction between useful and wasteful regeneration;
d. the mere presence of regenerating axons below the repair is, in itself, an unreliable guide to the functional outcome of that regeneration. It is for this reason that, after the repair of a mixed nerve, an advancing Hoffmann–Tinel's sign, that registers the descent of sensory 'axon' tips, is of doubtful prognostic significance.

To recapitulate, while such experimental methods reflect the potential for axon growth they fail to differentiate between useful and wasteful regeneration, provide no clue as to the final destination of the regenerating axons and leave unanswered the all-important question of the recovery of function.

2. With animal experimentation, man has the advantage of dictating the terms and conditions of the experiment whereas in the clinical situation this is denied him.

In the experimental animal, trauma to the limb is minimal, the nerve is cleanly transected, and steps are taken to prevent wound infection and to ensure that the repaired section of the nerve is left occupying a satisfactory bed. These artificially created conditions are in marked contrast to the mutilating injuries commonly occurring in civilian accidents and battle casualties. In such injuries a considerable length of the nerve may have been destroyed or severely lacerated, the neighbouring tissues extensively damaged, and the wound infected. Residual scarring may also result in the formation of restrictive adhesions and an unsatisfactory bed for the nerve.

3. In man, both the repair of the nerve and the outcome of axon regeneration are subject to constraints imposed by the complex multifasciculated structure of peripheral nerves. These conditions cannot be matched in animals commonly selected for experimental studies. In the latter, nerves have a simple fascicular structure, usually in the form of a single fasciculus. This arrangement favours fascicular apposition when the nerve ends are united, thereby greatly simplifying the repair and reducing the chances of axons growing into, and becoming lost in, the interfascicular epineurial tissue of the distal stump.

4. When evaluating the quality of the recovery after nerve repair, movements of the forepaws and hind limbs of experimental animals bear little, if any, relation to the human situation, where manual dexterity in particular and the refined elements of discriminative sensibility and the stereognostic sense, as we understand them, are peculiarly human attributes.

5. In experimental procedures, the repair of a transected nerve involves only the simple restoration of nerve trunk continuity with evaluations of functional recovery that, in the clinical context, are inadequate and of limited value.

Clinically, the ground rules are very different and far more demanding. The restoration of function is now the objective of the exercise and this requires a carefully planned and executed repair designed to minimise wasteful and abortive axon regeneration and to maximise useful regeneration, the re-establishment of functionally effective pathways, and the restoration of patterns of innervation that approximate as closely as possible to the original. The extent to which this is achieved determines the extent to which complex and delicately co-ordinated motor and sensory mechanisms are restored, and with them the efficient and effective performance of a wide range of normal daily activities. This scenario has no experimental counterpart.

6. In experimental studies on nerve grafting, the length of nerve excised to accommodate the interpositional graft is usually of the order of 10 mm or less and is rarely extended to 30 mm. However, it has been demonstrated experimentally that regenerating axons in large numbers are quite capable of crossing, independently and unaided,

defects in nerves of at least 30 mm and of then entering the distal nerve stump and continuing on to effectively reinnervate previously denervated muscles (Chapter 16). There is much supporting clinical evidence to this effect in the literature.

Experiments to study the relative merits of different grafting techniques and materials have rarely included controls in which a gap of corresponding length has been left unbridged in order to test the capacity of regenerating axons to cross the gap unaided in comparison with the effectiveness of the graft material as a bridging tissue. This adds to the difficulty of interpreting and evaluating the contribution that the graft has made to axon regeneration, reinnervation and functional recovery.

7. Experimental animals are usually small. This means that, regardless of the level of nerve repair, the distances to be travelled by regenerating axons in order to reach the periphery are short in comparison with the much greater distances in man. Consequently, in animals usually used in experiments, delays before the reinnervation of the periphery are much shorter than in man. In the latter the affected parts may remain denervated for considerable periods, particularly after high lesions, thereby introducing complications rarely seen in the experimental animal.

8. Axon length, and the distance of the growing axon tip from the cell body, are factors influencing the calculation of rates of axon regeneration after nerve injury. Measurements over the short distances obtaining in the experimental animal have been interpreted as demonstrating a constant rate of axon advance. However, when this feature was investigated in man, it became clear that regenerating axon tips advance down the nerve at a progressively diminishing rate, the rate declining as the distance from the parent cell body increases. The distances available in experimental animals were too short to reveal this feature of axon regeneration.

9. There is always the risk that species differences in the reaction to injury, and in the biological processes involved in axon regeneration and nerve repair, could invalidate the free transfer of data from one species to another, and particularly from animal to man. The size of an animal, and whether it is warm or cold-blooded, are also factors of established significance and there are others. Cajal (1928) in his writings suggested that species, as well as age, influence the rate of regeneration following nerve section but he did not elaborate on this observation.

In a comprehensive study of the response to nerve injury in various species, Kline et al (1964) found that species differences in response to nerve crushing were minimal. On the other hand, the differences were more apparent after nerve transection and repair, and related to connective tissue proliferation, disorganisation of axonal growth at the suture site, remyelination of the distal segment and restoration of a functional threshold of conduction.

The potentially misleading effect of species differences should never be underestimated when transposing experimental data from the laboratory to the study of nerve injury and nerve repair in man.

10. Even among individuals within a given species, there is a range of variation in the nature of the response to injury, in the behaviour of axons during regeneration, and in the many factors that combine in an exceedingly complex manner to influence the outcome after nerve repair. This adds to the difficulty of correctly interpreting the results of experiments undertaken to determine the relative merits of different procedures and materials available for the repair of a severed nerve. This, of course, applies equally to both clinical and experimental investigations. However, whereas such a possible source of error is generally recognised in clinical practice, it is too often overlooked in animal experimentation.

11. Many electrophysiological methods used in experimental investigations reveal what the nervous system *can do* rather than what it *does do*.

12. It is common in laboratory procedures to select one particular feature of nerve injury and repair for study and, when analysing the results, to exclude from consideration those many other co-existing factors that influence axon regeneration and the quality of functional recovery. As FMR Walshe (1951) has reminded us:

> The isolation of a phenomenon involves its abstraction from the total reality under study yet in nature all things are connected and nothing is isolated or torn from its context and in the hands of those