Textbook of
PAIN

EDITED BY

Patrick D. Wall
Ronald Melzack

Churchill Livingstone

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EDITED BY

Patrick D. Wall

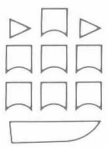
DM, FRCP
Director, Cerebral Functions Research Group;
Professor, Department of Anatomy,
University College London, London, UK

Ronald Melzack

PhD
Professor, Department of Psychology, McGill
University, Montreal, Quebec, Canada

CLINICAL CONSULTANTS

John J. Bonica MD, DSc, FFARCS
Harold Merskey DM, FRCP, FRCP(C), FRCPsych
Peter W. Nathan MD, FRCP
John P. O'Brien MBBS, PhD, FRCS (Edin), FACS
William H. Sweet MD, DSc, OHC
C.B. Wynn Parry MBE, DM, FRCP, FRCS



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Contributors

Mary J. Baines MB BCh
Consultant Physician, St Christopher's Hospice, Sydenham, Kent, UK

Allan I. Basbaum PhD
Associate Professor, Department of Anatomy and Physiology, University of California, San Francisco

Herbert Benson MD
Associate Professor of Medicine at the Beth Israel Hospital, Harvard Medical School; Director, Division of Behavioral Medicine and Hypertension Section, Beth Israel Hospital, Boston, Massachusetts, USA

Jean-Marie Besson DSc
Directeur de Recherches CNRS, Unite de Recherche de Neurophysiologie Pharmacologique, Institut National de la Santé et de la Recherche Médicale, Paris, France

Laurence M. Blendis MD, FRCP, FRCP (C)
Professor of Medicine, University of Toronto; Clinical Service Chief, Internal Medicine and Staff Gastroenterologist, Toronto General Hospital, Toronto, Ontario, Canada

John J. Bonica MD, DSc, FFARCS
Director, Multidisciplinary Pain Center, University of Washington, Seattle, Washington, USA

Anthony J. Bouckoms MB ChB
Assistant in Pathology, Massachusetts General Hospital; Instructor in Pathology, Harvard Medical School, Boston, Massachusetts, USA

Steven F. Brena MD
Professor and Director, Emery University Pain Control Center, Atlanta, Georgia, USA

Philip R. Bromage MB BS, FFARCS
Professor and Chairman, Department of Anesthesiology, University of Colorado, Denver, Colorado, USA

Stanley L. Chapman PhD
Senior Associate Chief Psychologist, Emory University Pain Control Center, Atlanta, Georgia, USA

Kenneth D. Craig PhD
Professor of Psychology, University of British Columbia, Vancouver, BC, Canada

Benjamin L. Crue, Jr MD, FACS
Clinical Professor of Surgery (Neurological) and Director, Section of Algology, Department of Neurosurgery, University of Southern California School of Medicine, Los Angeles; Director, New Hope Pain Center, Alhambra, California, USA

A. Claudio Cuello MD, MA
University Lecturer in Neuroanatomy/Neuropharmacology; E.P. Abraham Senior Fellow, Lincoln College, University of Oxford, Oxford, UK

James Cyriax MD, MRCP
Honorary Orthopaedic Physician, St Thomas's Hospital, London, UK; Visiting Professor in Orthopaedic Medicine, University of Rochester, Rochester, NY, USA

Donald J. Dalessio MD
Chairman, Department of Medicine and Senior Consultant in Neurology, Scripps Clinic and Research Foundation, La Jolla, California, USA

Marshall Devor PhD
Senior Lecturer, Life Sciences Institute, Hebrew University of Jerusalem, Jerusalem, Israel

Paul A. Dieppe BSc, MB BS, FRCP
Senior Lecturer in Rheumatology, University of Bristol; Honorary Consultant Rheumatologist, Bristol Royal Infirmary, Bristol, UK

David F. Dinges PhD
Co-Director, Unit for Experimental Psychiatry, Institute of Pennsylvania Hospital, Philadelphia, Pennsylvania, USA

David Dubuisson MD, PhD
Instructor in Surgery, Harvard Medical School; Attending Neurological Surgeon, Beth Israel Hospital, Boston, Massachusetts, USA

Richard H.T. Edwards PhD, FRCP
Head, Department of Medicine, University College London School of Medicine; Director, Charles Dent Metabolic Unit, University College Hospital, London, UK

Howard L. Fields MD, PhD
Professor of Neurology and Physiology, University of California, San Francisco, California, USA

Maria Fitzgerald BA, PhD
Associate Research Fellow, Department of Anatomy, University College London, London, UK

D.M. Grennan MD, PhD, FRCP
Senior Lecturer in Rheumatology, University of Manchester; Honorary Consultant Physician, Rheumatic Diseases Centre, Hope Hospital, Salford, Manchester, UK

Gisèle Guilbaud MD, DSc
Mâitre de Recherches, Unite de Recherches de Neurophysiologie Pharmacologique, Institut National de la Santé et de la Recherche Médicale, Paris, France

J.G. Hannington-Kiff BSc, MB BS, MRCS, LRCP, FFARCS
Director, Pain Relief Centre, Frimley Park Hospital, Frimley, Surrey, UK

James A.L. Harkness FRACP
Visiting Rheumatologist, Alfred Hospital and Royal Southern Memorial Hospital, Melbourne, Victoria, Australia

E.R. Higgs MRCP
Department of Rheumatology, Bristol Royal Infirmary, Bristol, UK

Roger A. Hitchings FRCS
Consultant Ophthalmologist, Moorfields Eye Hospital, London, UK

A.M. Hoy BSc, MB BS, MRCP, DMRT
Senior Registrar in Radiotherapy and Oncology, St Thomas's Hospital, London, UK

Edward C. Huskisson MD, BSc, FRCP
Consultant Physician, St Bartholomew's Hospital, London UK

Malcolm I.V. Jayson MD, FRCP
Professor of Rheumatology, University of Manchester, Rheumatic Diseases Centre, Hope Hospital, Salford, Manchester, UK

Mary Ellen Jeans RN, PhD
Associate Professor and Director, School of Nursing, McGill University, Montreal, Quebec, Canada

Troels Staehelin Jensen MD
Senior Registrar, Department of Neurology, Århus University Hospital, Århus, Denmark

Barton A, Jessup PhD
Regina Mental Health Clinic, Regina, Saskatchewan, Canada

Stephen R. Kirkham MA, MRCP
Medical Director, Pilgrim's Hospice, Canterbury, Kent, UK

Sheila Kitzinger MLitt
Lecturer in Community Education, The Open University, UK

J.U. Krainick MD
Professor of Neurosurgery, Schmerz-Zentrum Mainz, Mainz, West Germany

Ilan Kutz MD
Instructor in Medicine, Harvard Medical School, Boston, Massachusetts, USA

Barbara J. de Lateur MD, MS
Professor, Department of Rehabilitation Medicine, University of Washington School of Medicine; Physiatrist-in-Chief, Harborview Medical Center, Seattle, Washington, USA

Justus F. Lehmann MD
Professor and Chairman, Department of Rehabilitation Medicine, University of Washington, Seattle, Washington, USA

S. Lipton FFARCS
Director, Centre for Pain Relief, Mersey Regional Department of Medical and Surgical Neurology, Walton Hospital, Liverpool, UK

John D. Loeser MD
Professor of Neurological Surgery, University of Washington, Seattle, Washington, USA

Federico Lombardi MD
Established Investigator, University of Milan School of Medicine, Milan, Italy

Bruce Lynn PhD
Lecturer in Physiology, University College London, London, UK

Alberto Malliani MD
Professor of Internal Medicine, University of Milan, Ospedale L. Sacco, Milan, Italy

M.R. Matthews BSc, DM
University Lecturer in Anatomy; Fellow and Lecturer of Lady Margaret Hall, University of Oxford, Oxford, UK

Donald Meichenbaum PhD
Professor of Psychology, University of Waterloo, Ontario, Canada

Ronald Melzack PhD
Professor, Department of Psychology, McGill University, Montreal, Quebec, Canada

Harold Merskey DM, FRCP, FRCP (C), FRCPsych
Professor of Psychiatry, University of Western Ontario; Director, Education and Research Department, London Psychiatric Hospital, London, Ontario, Canada

John B. Miles MB BCh, FRCS
Consultant Neurosurgeon and Director of Neurosurgical Studies, Mersey Regional Department of Medical and Surgical Neurology, Walton Hospital, Liverpool, UK

K.R. Mills BSc, PhD, MB BS, MRCP
Senior Registrar, Department of Clinical Neurophysiology, The National Hospital, London, UK

Richard C. Monks MD, CM, FRCP (C)
Senior Psychiatrist and Consultant, Pain Centre, Montreal General Hospital; Associate Professor, Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Balfour M. Mount MD, FRCS (C)
Director, Palliative Care Service; Professor of Surgery, McGill University, Montreal, Quebec, Canada

D.J. Newham MPhil, MCSP
Research Physiotherapist, Department of Medicine, University College London School of Medicine, London, UK

William Noordenbos MD, PhD
Professor Emeritus of Neurosurgery, Amsterdam, Netherlands

John P. O'Brien PhD, FRCS (Edin), FACS
Director, Department for Spinal Disorders, The Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire, UK

M.T. Orne MD, PhD
Director, Unit for Experimental Psychiatry, Institute of Pennsylvania Hospital, Philadelphia, Pennsylvania, USA

Massimo Pagani MD, FACC
Associate in Medicine, University of Milan, Milan, Italy

Carlo Alberto Pagni MD
Professor of Neurosurgery and Director, Centre for Pain Study and Therapy, University of Turin, Turin, Italy

Marc Peschanski MD, PhD
Chargé de Recherches, Unite de Recherche de Neurophysiologie Pharmacologique, Institut National de la Santé et de la Recherche Médicale, Paris, France

Issy Pilowsky MD, ChB, FRANZCP, FRACP, FRCPsych
Professor of Psychiatry, University of Adelaide; Head, Psychiatric Service, Royal Adelaide Hospital and Consultant to Pain Clinic, Adelaide, South Australia, Australia

Jack J. Pinsky MD
Clinical Associate Professor of Surgery (Neurological), University of Southern California School of Medicine; Attending Psychiatrist, Department of Psychiatry, Cedars-Sinai Medical Center, Los Angeles, California, USA

Charles E. Poletti MD
Assistant Professor of Surgery, Harvard Medical School; Assistant Visiting Neurosurgeon and Director of the Neurosurgical Pain Service, Massachusetts General Hospital, Boston, Massachusetts, USA

Bruce Pomeranz MD, PhD
Professor, Departments of Zoology and Physiology, University of Toronto, Toronto, Ontario, Canada

Paolo Procacci MD
Professor of Medical Therapy and Director of the Pain Centre, University of Florence, Florence, Italy

Peter Rasmussen PhD
Professor of Neurosurgery, University of Århus, Århus, Denmark

Anthony E. Reading PhD
Visiting Assistant Professor, Department of Psychiatry, UCLA School of Medicine, Los Angeles, California, USA

M.J. Renaer MD, PhD, FRCOG
Professor and Head, Department of Obstetrics and Gynaecology, University of Louvain, Louvain, Belgium

Kathleen M. Rowat N, PhD
Associate Professor, School of Nursing, McGill University, **Montreal,** Quebec, Canada

Dame Cicely Saunders DBE, MA, FRCP, FRCN
Medical Director, St Christopher's Hospice, London, UK

John W. Scadding BSc, MD, MRCP
Consultant Neurologist, National Hospital for Nervous Diseases and Islington District General Hospital, London, UK

Yair Sharav DMD, MS
Professor of Oral Medicine and Head, Department of Oral Diagnosis, Oral Medicine and Oral Radiology; Dean, Hebrew University – Hadassah Faculty of Dental Medicine, Jerusalem, Israel

David G. Simons MD, MS, DSc
Director, Myofascial Pain Clinic, Veteran's Administration Medical Center Long Beach; Clinical Professor, Physical Medicine and Rehabilitation, University of California, Irvine, California, USA

M.A. Smith MA, FRCS
Consultant Orthopaedic Surgeon, St Thomas's Hospital, London, UK

Anders E. Sola MD, MS
Clinical Assistant Professor, Department of Anesthesiology and Pain Service, University of Washington School of Medicine, Seattle, Washington, USA

Erik Spangfort MD
Chief Orthopaedic Surgeon and Head of Spinal Unit, Huddinge University Hospital, Huddinge, Sweden

Richard E. Sternbach PhD
Director, Pain Treatment Center and Head, Division of Psychology, Scripps Clinic and Research Foundation; Clinical Professor of Psychiatry, University of California, San Diego, California, USA

William H. Sweet MD, DSc, OHC
Senior Neurosurgeon, Massachusetts General Hospital; Emeritus Professor of Surgery, Harvard Medical School, Boston, Massachusetts, USA

Frances Tappan BS, MA EdD, RPT
Professor Emeritus, Chair of Distinction, University of Connecticut, Storrs, Connecticut, USA

R.R. Tasker MD
Head of the Division of Neurosurgery, Toronto General Hospital; Professor, Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Lars Terenius PhD
Professor of Pharmacology, Uppsala University, Uppsala, Sweden

U. Thoden MD
Professor, Department of Clinical Neurology and Neurophysiology, Freiburg University, Freiburg-in-der-Breisgau, West Germany

Janet G. Travell MD
Clinical Professor of Medicine Emeritus, George Washington University, Washington, DC, USA

Dennis C. Turk PhD
Associate Professor of Psychology, Yale University, New Haven, Connecticut, USA

Ian M. Turnbull MD, FRCS (C)
Division of Neurosurgery, Department of Surgery, University of British Columbia, Vancouver, BC, Canada

Robert G. Twycross MA, DM, FRCP
Consultant Physician, Churchill Hospital, Headington, Oxford, UK

Tony C. Ty MD
Assistant Professor, Department of Surgery, McGill University, Montreal, Quebec, Canada

P.J. Verrill MB BS, FFARCS, DA
Consultant Anaesthetist, University College Hospital, London, UK

Ladislav Vyklicky MD, DSc
Head, Laboratory of Cellular Neurophysiology, Institute of Physiology, Czechoslovak Academy of Sciences, Prague, Czechoslovakia

Mary M. Wagner BS, MS
Assistant Professor, University of South Carolina College of Nursing, Columbia, South Carolina, USA

Patrick D. Wall MA, DM
Director, Cerebral Functions Research Group; Professor, Department of Anatomy; University College London, London, UK

Matisyohu Weisenberg PhD
Associate Professor, Department of Psychology, Bar-Ilan University, Ramat-Gan, Israel

Patricia A. Wells BSc, MSc
Assistant Professor, School of Physical and Occupational Therapy, McGill University; Clinical Scientist (Rehabilitation)), Montreal General Hospital, Montreal, Quebec, Canada

William D. Willis, Jr MD, PhD
Professor and Director, Marine Biomedical Institute, Galveston; Professor, Departments of Anatomy and of Physiology and Biophysics, University of Texas Medical Branch, Galveston, Texas, USA

R. Withrington MB, MRCP
Senior Registrar, Department of Rheumatology and Rehabilitation, Royal National Orthopaedic Hospital, Stanmore, Middlesex, UK

B. Berthold Wolff BSc, AM, PhD, DipPsych
Research Professor of Psychology, Behavioral Sciences and Community Health; Director, Comprehensive Pain Center, New York University, New York, USA

Kathleen M Wood MD
Professor, Department of Anesthesiology, University of Colorado, Denver, Colorado, USA

Clifford J. Woolf MB BCh, PhD, MRCP
Lecturer, Department of Anatomy, University College London, London, UK

C.B. Wynn Parry MBE, DM, FRCP, FRCS
Director of Rehabilitation, Royal National Orthopaedic Hospitals, London, UK

Anthony Yates MD, FRCP
Physician in Charge, Department of Rheumatology, St Thomas's Hospital, London, UK

Manfred Zimmermann MD, FRCS (C)
Professor, Physiology Institute, University of Heidelberg, Heidelberg, West Germany

Massimo Zoppi MD
Associate Professor of Rheumatology, University of Florence, Florence, Italy

PROLOGUE

William Noordenbos

In his introduction to White and Sweet's famous monograph, Jefferson wrote the following sentence: 'Sensation in general, with pain as a part buried as it were in it, remained for a long time a difficult subject for both the practising doctor and for the physiologist.'[19] Typical for Sir Geoffry there is a sting in this sentence, about which more later, but in a general sense he was right. A lot has happened since.

There has been a tremendous surge of interest in the subject during the last decades. National and international societies have been formed, a journal is devoted exclusively to the subject. 'Pain clinics' have opened everywhere, meeting an obvious need but at the same time creating a demand. Often under the leadership of anaesthetists who, by virtue of their skill in combating the acute predictable pain as the result of surgery, consider themselves fit to face that formidable foe which is chronic pain. Neurophysiology has made tremendous strides and modern methods of staining by neuro-anatomists, which depend on active transport retrograde or anterograde, have demonstrated the wealth of connectivity. Neuropharmacology has opened vistas undreamt of. Yet the opening sentence of the introduction of a recent monograph reads: 'It is ironic that the most common symptom in the field of medicine is also one of the least understood.'[16]

Surely there must be something wrong somewhere. The Editor has asked me to write a sort of prologue to this Textbook of Pain. What were his instructions? 'I hope you will write a completely free prologue, which will itself really set the clinical as well as the basic background and foreground.' And later, after I had expressed considerable doubts about my ability to do so, further encouraging me: 'Please proceed with all sails up on your careful course' — hoping that in expressing himself in nautical terms it would have an effect on this amateur seaman. It did ring a bell.

The title reads *Textbook of Pain*. A textbook has been variously defined as a standard source of reference,[1] a symptomatic representation of the principles and vocabulary[2] or as a manual of instruction.[3] Taking all three together and applied to the present context it should therefore be representative of the state of the art today, be a guideline on how to tackle the subject and how to express yourself in such a manner that the meaning is clear to the reader who works at a less advanced level or belongs to a different discipline, and finally it should tell you how to act in a given situation.

A textbook should therefore be a guide to give you a sense of security. When we travel we usually take a guidebook which takes you to the highlights of a region and tells you how to get there. The sailor who goes to sea also takes a guide but they are called 'pilots', published in uniform volumes by the Hydrographic Departments of the different countries and covering certain circumscribed areas. They have a different character. They do the opposite, they mainly describe the, oft-hidden, dangers and instruct how to avoid them. They often make frightening reading and the amateur then feels disinclined to sail at all, until after a little experience he realizes that dangers forewarned lose their terror.

We have to travel, mentally this time, and we are all amateurs, laymen everyone of us as soon as we trespass into other disciplines, as we must do to grasp this vast material.

I once made such a journey.[4] It was a short one, starting in the periphery, via afferent nerve, dorsal horn and anterolateral quadrant up to the thalamus. This was a fairly reckless adventure and I stumbled on various obstacles, hidden problems which had to be pinpointed before being able to proceed. Many will maintain that this route has been sufficiently surveyed. I happen to disagree.

'A systematic representation of the principles + vocabulary'

The book consists of chapters written by experts for people of various levels of knowledge and experience. If these are to understand each other the use of specialized terms, characteristic of each discipline, sometimes referred to as the 'lingo' of a profession (*lingo* = a contemptuous term for the vocabularly of jargon of a class of persons), must be avoided as much as possible. This is difficult, but can be solved. The problem, however, starts earlier: the communication between the patient and his physician. This is where it starts and where our information has to be obtained. Its limits are best illustrated with lesions of the afferent system such as for instance in regenerating nerves. Many prominent investigators, dissatisfied with the unintelligible verbalisation of the sensory experiences of their patients, were sufficiently fascinated by the problem to submit to having their own nerves crushed or cut and resutured in order to observe and describe the sensory experiences during the subsequent

stages of re-innervation. Starting in 1905, these experiments were repeated by many in the subsequent 60 years. (The last one I am aware of was in 1965.)[5] None of these investigators ever agreed with each other, thereby demonstrating that it is impossible to convey the contents of a distorted message to an outside observer.

One would think that the student is forewarned not to expect too much from the information supplied by the sensory examination of a patient. The textbooks however ignore this whole episode.

In the absence of pain this problem is possibly not all that important, except when assessing the recovery of function after nerve suture. But in the presence of pain it rears its head again when trying to analyse the nature of the lesion. It is therefore not without reason that general terms such as hyperirritability, hyperaesthesia, hyperalgesia, hyperpathia made their entrance in the clinical literature, followed by considerable confusion as to their exact significance. Serious attempts are now undertaken to define their meaning,[6] though sometimes this bears more resemblance to words being in search of a syndrome than syndromes in search of a word.

'The sense of security'

The main aim, the central theme, would have to be to provide the framework, the solid underpinning for the understanding of the mechanisms, the nature of pain and the rationale of its treatment. It is the task of the basic sciences to explain why pain behaves as it does, for only if we are familiar with its mechanisms can we institute rational treatment, in the sense that the results are predictable, permanent and without untoward risks or unwanted side-effects. We are a long way from realizing this. Our knowledge concerning the mechanisms both under normal and abnormal circumstances is deficient, incomplete and at some levels may perhaps be faulty or altogether lacking.

Section One is entitled *Basic Aspects* and therefore starts by erecting the 'framework'. It seems traditional to start in this manner and I always feel a little uneasy at this stage. It starts with the explanation of the facts before the facts are given. Facts are the various clinical manifestations of pain as it occurs in man. Unfortunately, pain is what the patient tells us he feels, and we have discussed the limits of the verbalisation of sensory experiences. What little we have concerning the actual reality of that intangible phenomenon has to be provided by whatever diagnostic means we have at our disposal. The framework has to explain the facts.

How solid are the facts and how solid is the framework going to be? The only test we have is that if we act according to the precepts, the pain should disappear. This is often successful, but frequently is not. Either there is something wrong with the facts, or we didn't act according to 'instruction' or our means of doing so are 'faulty' or there is something wrong with the 'framework'. Any of these parameters may need modification. This makes it necessary to test one against the other continuously. One way of doing this is to study the failure of a given therapy, which may be as important as the report of successful cases. This is what should be done, but it is often omitted. The trouble is that the very nature of chronic pain imposes a sense of urgency. If one method fails or the pain recurs, something else is tried and it becomes extremely difficult to study the natural history of a condition or the result of a given therapy. Moreover the consequences of iatrogenic lesions are often superimposed on the original pathology which makes subsequent analysis almost impossible.

But to start somewhere, let us begin at the beginning of this book and try and pinpoint some of the difficulties and trends of thinking as we go along. The first chapter deals with nerve fibres which respond to injury and tissue damage. Presumably the fibres so activated will have to be 'labelled'. They may be indicated by letters such as A-delta or C, but they are more commonly called 'nociceptor fibres' and the receptors from which arise as 'nociceptors'. If we now look up the definition[6] we read: 'A nociceptor is a receptor sensitive to a noxious or potentially noxious stimulus.' The word 'potentially' strikes me as being ambiguous. Is this a property of the receptors, as implied by the definition, or is it to be interpreted in terms of the result of proper conditioning of the individual? In any case a *noxious* stimulus is defined as a *tissue-damaging* stimulus. If we now refer to the definition of pain we read: 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.'

These definitions tend to become somewhat tautologous, for if we leave the loophole of the ambiguous word 'potential' out of account we read: 'Tissue-damage activates nociceptors, which cause pain', which is true in a general sense.

Unfortunately there is a tendency to reverse this statement, which now reads: 'Pain is due to the activation of nociceptors, which is the result of tissue damage.' This is certainly not necessarily true. Take visceral pain for instance: renal colic causes one of the severest pains one can experience. Is this tissue damage? Hardly, for the pain ceases immediately the stone is passed. Yet in a recent summary[7] it is written: 'Visceral nociceptors have not been well defined to date ....' Adequate visceral noxious stimuli are difficult to define. The author has obviously reversed the statement; he searches for nociceptors and the notion 'noxious stimulus' is replaced by 'adequate stimulus'.

I find the whole notion of nociceptors difficult to accept. What are these? Lying in wait like watchdogs which bark when danger arises or has arisen and being inactive otherwise? That is not what a watchdog does. It barks when there is a change in his surroundings and the farmer has learned to disregard this unless the barking is uncommonly loud and prolonged. In normal life we do not experience pain and we have learned to avoid tissue injury, and we would have to assume therefore that these fibres are inactive. Surely a system that is not regularly activated conducts less well, and there is no evidence for that. 'Nociceptors' must be regularly activated but do not give rise to pain, either because not enough of them come into action, or because their activity is suppressed early at low levels or because we pay no attention to it, which may be a form of inhibition at higher levels. It is only when activity exceeds certain levels, when inhibitory mechanisms fall short, that pain arises and our attention is focussed on what is happening. This inevitably needs

introduction of the quantitative element in the mechanism of pain.

This would be the proper place to discuss what happens when this mechanism fails, as in congenital analgesia.

To move on to the group of patients in which nerve damage is associated with pain: these were the subject of my monograph.[4] They all complained of pain. They all exhibited signs of a lesion of the afferent system, which is the end result of tissue injury which meantime has healed. When examined, the remaining cutaneous sensibility exhibits features which can be characterised by the fact that stimuli which normally do not cause pain now do so. This was originally designated as hyperaesthesia but the Taxonomy Committee adopted a new term 'allodynia': 'Pain due to a non-noxious stimulus'.[6]

A non-noxious stimulus cannot cause tissue-injury or potential tissue-damage, and if consistent we would have to conclude that therefore nociceptors cannot be activated. Yet the most excruciating pain can be caused, in extreme cases, by a light stroke of cotton wool or even the merest puff of air.

Fortunately most cases of nerve lesions complaining of pain are less extreme, but they present an additional problem. The patient is unable to identify the stimulus and therefore regards all accidental contacts as *potentially* harmful, even though the majority of these do not cause tissue-injury. In these cases we are now in difficulties. Either nociceptors are being activated or they are not. If they are, we must assume that the threshold of these nociceptors is lowered, or that they are activated in a different manner either by chemical means or ephaptic transmission or any other mechanism. In a recent article[8] it is postulated that, even before entering the CNS, for an explanation of the dysaesthesia and pain associated with injury of a peripheral nerve at least twelve sorts of physiological abnormalities must be taken in consideration.

We are in the midst of controversies and you can choose which is your favorite theory. I am strongly in favour of loss of inhibition, but that does not exclude other possibilities. We can only conclude that the notion of nociceptors does not fit in well in cases of lesions of the afferent system accompanied by pain.

Finally we have the problem of the pain in psychiatric patients. Here the concept of nociceptors completely loses significance, for whatever the mechanism, we can only designate the patient to this group when 'organic symptoms' are negative or of such minor nature that they are unlikely to be the cause of their suffering. Therefore a preliminary approach by identifying fibres activated by tissue injury fits the facts in some categories, is doubtful in others, may possibly lead astray or have no bearing on the problem in another group.

There is an additional reason why it would be inadvisable to stress the notion 'nociceptor activity = pain' too strongly and ascribe all the characteristcs of pain to their action. There is no doubt that many of them have a high threshold. But before they are activated, low-threshold receptors must have come into action. The eventual outcome, the localisation and subsequent correct identification of the focus, must depend on the total afferent spectrum which travels centrally. External stimuli which do not cause pain can be localised with fair accuracy and a strong case can be made that this function is subserved by fast-conducting, oligosynaptic pathways.[9]. Correct localisation of a painful internal focus may be a quality of the nociceptors but could equally well depend on the simultaneous activity of other available systems. This would lead to the conclusion that: 'The sensation of pain and the ability to localize its source are not subserved by the same fibre systems'.

Inability to localise a painful focus may be due to the absence or insufficient numbers of fibres which subserve this function. It may be useful to discuss the manifestations of painful foci in different tissues in terms of the fibre spectrum which is present and the manner in which it is activated.

Inevitably on entering the CNS and before travelling upwards, we meet the GATE. This is an interesting story. This mechanism was implied very early, with Head's thesis that the epicritic system inhibited the protopathic system of nerves, based purely on clinical arguments, long before action potentials could be demonstrated[18] Similar arguments were presented by Foerster[17] with the effect of *Empfindung Systeme* on *Schmerz Systeme*, again as the result of clinical observations. This was further elaborated by others,[10, 4] but only gained wide acceptance in 1965 when the Gate Theory was published.

It became extremely popular. I think for two reasons. In the first place by the use of the word *Gate* which admirably indicated the overall effect in a single term, and secondly by the use of a simple diagram which graphically illustrated the principle and made the idea understandable. As was to be expected, it was also subject to many attacks. But these were aimed at the diagram and not at the overall effect. What was meant as an illustration was taken as the true state of affairs.

This problem is not unusual and has been met elsewhere: H.A. Lorentz, one of our great physicists, said in 1878: 'If somebody is introduced to the study of physics, it is desirable to be as clear and illustrative as possible in this difficult field. This can be overdone and in being illustrative one can overshoot one's aim. What is meant as a model comes so much to the foreground that it is taken as the true state of affairs.' Replace the word 'physics' by 'CNS' and the quotation illustrates the difficulties that face us today. There is a fair consensus on the overall effect of events in the dorsal horn, but the manner in which this takes place is still the subject of intense investigation. In fact a whole symposium has been devoted exclusively to the Dorsal Horn.[11] The mechanisms are so complicated that it is useless to attempt to represent them in a simple diagram. The diagram should be abandoned but there is every reason to retain the term *Gate*.

If we now move to the origin, course and destination of the pathways in the cord we meet similar problems. The history of the development of the knowledge of the pathways in the antero-lateral quadrant has been admirably described by Keele[12] and was largely obtained from clinical observations. It was the serendipitous observation of the case of bilateral tuberculomas in the antero-lateral quadrant which led to the development of the antero-lateral

chordotomy. The spino-thalamic tract emerged, usually represented as a circumscribed bundle in the anatomy textbooks. It soon proved, however, that the result of these iatrogenic lesions fell short if these diagrams were taken as authorative and that much larger lesions were needed in order to obtain the desired effect. At the same time the paucity of numbers of fibres that reach the thalamus and the large variety of different destinations of the oligo-synaptic fibres became known. If moreover it is realized that those direct fibres are phylogenetically very recent, there is every reason to postulate that chains of short neurons forming a multisynaptic afferent system (MAS)[4] on which lower mammals depend, have an important function in the conduction of impulses which give rise to pain in *man*. It is clear that instead of a simple tract we are dealing with a very complicated system. The multisynaptic system is no more than the revival of the old notion of the 'final common pathway'. It is making a hesitant and in my opinion necessary re-entry in the clinical literature,[13, 14] but is largely ignored by basic science and with very good reason. It cannot be followed as a functional unit by the anatomist, and similar difficulties beset the neuro-physiologist. The fact, however, that proof of its functional existance cannot be obtained by means of the present methods cannot be a valid reason to reject the notion.

The function attributed to the ascending system in the antero-lateral quadrant is usually stated in terms of functions lost when conduction is blocked: noxious and thermal stimuli cannot be identified on the opposite side of the body below the lesion. If however it is stated in terms of functions retained if this is the only region that remains intact, as we were able to observe in a unique case[15] this again proves to be a gross simplification: a surprising number of functions are retained.

Textbook representation of tracts and the description of their function are really simplified models of the true state of affairs. Such representation is an absolute necessity otherwise neuro-anatomy and neurophysiology cannot be taught at all. There is therefore no reason to scorn simplification, but every reason to mistrust it.

In a way this is a rapid, relatively short journey for it has hardly reached the thalamus or brain stem. On the way, certain problems were pinpointed with little attempt at a solution, though this would really be necessary to assure a safe passage. One thing is certain, the higher we ascend the more complicated it becomes.

The biggest problem of all has not been touched upon, that is the word *pain*. Under what conditions can it arise?

These can be subdivided in four main categories:

1. *Pain due to external events* (special senses excepted). This has the following features:
   a) It always involves the skin.
   b) The pain is of short duration, except when tissue injury is the result.
   c) Localisation, identification or verification of its cause is usually possible by the subject.
   d) Withdrawal is possible (if prevented we are dealing with torture).
   e) The NS is intact, conduction is not interfered with, modulating factors are fully operative. This category includes the majority of methods of experimentally-produced pain. It represents the conditioning mechanism which teaches the individual to avoid injury. It includes the clinical sensory examination which ascertains whether this function is intact.
2. *Pain due to internal events*. Receptors are activated whatever their nature or the mechanism of this activation may be. An afferent pattern is set up which is perceived as pain.

   This group has the following features:
   a) The skin is usually not involved, except when directly injured or in referred pain.
   b) The pain is of longer duration. It lasts until the source is ascertained and if possible adequately dealt with.
   c) Localization and identification of the source by the patient is often impossible.
   d) Withdrawal is not possible, or only partially so (i.e. not moving an injured joint).
   e) The NS is intact: the focus or pathological process is peripheral to the receptors. Conduction is normal, modulating factors are operative.

   This group may be subdivided according to which type of tissue is involved: ectodermal, mesodermal or endodermal,[7] each having their own particuular type of afferent innervation.

   This group also includes pain due to physiological events such as labour pains.
3. *Pain associated with lesions of the NS*, especially the afferent system.
   a) The skin is often involved, which makes correct identification of external events difficult if not impossible.
   b) Localisation of the source may be faulty.
   c) The pain is prolonged, may last years or even a whole lifetime.
   d) Withdrawal is impossible.
   e) The NS is not intact. Conduction is faulty. Modulating mechanisms have become disrupted.

   In these cases the lesion is proximal to the receptors. It may involve peripheral nerves, the spinal cord or higher levels. It may be localised or of a systemic nature.

   This group represents the real problems, the Puzzles of Pain (postherpetic neuralgia, causalgia, phantom limb pain, plexus avulsions, thalamic syndrome). It may be of a more general nature, as in polyneuropathies.
4. *Neither 1 nor 2 nor 3:* the pain associated with psychological, social or environmental factors. In each of these categories we have to take cognitive and emotional aspects into account though the emphasis will differ markedly, depending how the pain arises.

These four groups represent different problems but they have one thing in common: the result can be described by the single word 'pain'. Just because of that single word there is the tendency to think that in each of these different categories we are dealing with similar mechanisms and that observations and conclusions in one group are transferable to another. This is manifestly not the case. If textbooks are

consulted in trying to interpret the symptoms found in the individual patient, it is as well to keep this in mind. My personal preference has always been the study of lesions of the afferent system associated with pain, believing that the study of abnormal conduction might yield some of the secrets of normal conduction. The single most important finding is that stimuli which normally do not cause pain now do so. That is the sting in Sir Geoffry's sentence: 'Sensation in general has pain as it were buried into it.'

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Contents

Introduction

Patrick D. Wall

So long as one person remains in pain and we cannot help, our knowledge of pain remains inadequate. However, there are reasons for optimism because there is at present a real increase of knowledge which comes in part from the abandoning of old concepts which were wrong and which held the subject in a strait-jacket. The editors and authors of this book try to express where these new facts and attitudes have brought us.

The book is in three parts. In the first, the major areas of basic knowledge are summarised. In the second, clinicians describe the various conditions in which pain predominates and discuss diagnosis and prognosis. In the third part, the primary aim is to describe different therapies with their rationale, applicability, effectiveness and side-effects. The authors are well aware that they have attempted a difficult task in reviewing subjects in rapid transition. Old, incorrect, inappropriate and sometimes dangerous concepts and therapies still linger on and merge with novel ones which have yet to be subjected to proper criticism. The study and treatment of pain emerges as a subject in its own right, although of course understanding the fundamental cause of the pain must remain the ultimate target. This book describes the situation from which the new subject is emerging.

A definition of pain

The dominating nature of pain with its imperative need for action sets it aside from other sensations. A changing attitude can be seen in the migration of the definition of pain. Mountcastle (1968) wrote simply 'Pain is that sensory experience evoked by stimuli that injure'. The taxonomy committee of the International Association for the Study of Pain chaired by Merskey (1979) defined pain as 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. They added crucial notes to this sentence:

> Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. It is unquestionably a sensation in a part of the body but it is also always unpleasant and therefore also an emotional experience.
>
> Many people report pain in the absence of tissue damage or any likely pathophysiological cause, usually this happens for psychological reasons. There is no way to distinguish their experience from that due to tissue damage, if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.

Nociception: the detection of injury by peripheral nerve fibres

Dubner, Iggo and Perl and their associates have defined a group of afferent fibres in the skin which only respond as tissue damage approaches (See Chapter 1.1). These nociceptors, once fired, change their properties, some become more sensitive and some less sensitive (Campbell et al 1979, 1981, Lamotte et al 1982). Even neighbouring nociceptors which were not initially excited may become sensitive (Fitzgerald 1979). Thus when injury occurs the central nervous system will receive a barrage in these specialised fibres which varies with time and with the nature of the injury, and of course it will also receive messages in the lower threshold afferents which respond to both large and small stimuli. When nerve itself is damaged, it is unfortunate that the growing sprouts and dorsal root ganglion cells generate chronic afferent barrages which act as false signals which may be interpreted by the central nervous system as if injury is in progress (Wall 1983).

The activity in visceral afferents is very much more difficult to study and seems different from cutaneous afferents. It is described in a number of chapters particularly by Malliani (Chapter 1.7). It has not yet been possible to locate specific nociceptors coming from such organs as the heart. Instead, it appears that sensory fibres gradually increase their discharge frequency as conditions move from normal to abnormal. Here central mechanisms would have to set a threshold above which emergency reactions would be triggered.

The relationship of injury to pain

Given signals in the afferent barrage which announce the

presence of abnormal conditions, the next crucial question is how the central nervous system handles the messages. We urgently need to be able to analyse the factors and mechanisms which lead to the variability of the relationship of injury to pain (Wall 1979). Adding to these problems is the fact that central cells can generate false signals when they receive unusual messages from damaged peripheral nerves, roots or tracts (Wall 1983). These problems have been faced by the most eminent of this century's neurologists and scientists including Head, Adrian, Sherrington, Zotterman, Livingston and Noordenbos. Melzack and I have attempted to join their concepts with more recent facts and have produced the gate control theory (Melzack & Wall 1965, Wall 1978). It incorporates the now accepted fact that the messages concerned with pain transmitted from the first central cells in the spinal cord depend on three factors: 1) the arrival of nociceptive messages; 2) the convergent effect of other peripheral afferents which may exaggerate or diminish the effects of the nociceptive message; 3) the presence of control systems within the CNS which influence the first central cells. We emphasise that convergent controls decide the fate of arriving messages as they pass through every level of the central nervous system and eventually produce reaction, sensation and movement. Our data were derived from the standard physiological preparations but it is now possible to record the firing of first order central cells in the trigeminal system of alert behaving monkeys (Dubner et al 1981). Here one sees the remarkable subtlety of the brain. With an abrupt isolated stimulus to a naive animal, the first central cells respond in a classical and predictable way whether the animal is awake or even anaesthetised. However, the response changes radically if other events are in progress. For example, some cells 'learn' to respond not only to the stimulus but also to the alerting signal which tells the animal that the noxious test stimulus will soon follow. Facts such as these show us that the signalling of injury by even the first central cells is dependent not only on the arrival of nociceptive afferent impulses but on the signalling of other peripheral events and on the setting of excitability by central nervous system mechanisms. These contingent controls offer an explanation for the variable response to injury. The presence of such controls means that they themselves may become locked into a pathological position and exaggerate or create pain. More optimistically the existence of these controls offers the possibility of a therapeutic decrease of pain by means other than the simple interruption of pathways transmitting information about noxious events. These therapies have already begun with peripheral nerve stimulation, TENS, which Wall & Sweet (1967) began as the first obvious test of the gate control theory and have been extended into stimulation of central structures (Chapters 3.D.3 and 3.D.4). Even ancient therapies such as narcotic analgesia seem likely to act by mimicking existing control mechanisms (Chapters 1.10 and 1.11).

The subtle modifiability of the transmission pathways offers some explanation for the subtleties of man's behaviour in response to injury. Scientists rightly started their study of pain in man by presenting trained volunteers with the simplest possible situation of intense isolated stimuli under the subject's control (Chapter 1.16). As the stimulus increases, a pain threshold is reached. Studies of single units in peripheral nerve show that this sensory threshold is associated either with the appearance of activity in particular nociceptors or with these fibres reaching some threshold level of firing (van Hees & Gybels 1972, Lamotte et al 1982). These studies must be accepted as cautiously and conservatively as their authors claim. They show that an afferent barrage in high threshold afferents can be associated as *one* of the factors leading to pain. Even the experimental findings on normal subjects show that other factors are involved and we will mention only three here:

1. The relationship between the intensity of the pain and the intensity of the stimulus varies over a very wide range in different laboratories (Sternbach & Tursky 1964). This shows that unsuspected differences of instruction, preparation and expectation are sufficient to alter the relationship of stimulus to response even in highly trained subjects. The role of semantics is shown by Gracely (1979) who found quite different responses if subjects had to report either on painfulness or on intensity of the same stimuli.

2. The same amount of pain may be produced by differing levels of activity in nociceptors. Van Hees & Gybels (1972) show that pain produced by heating the skin is associated with a lower level of afferent barrage than the same degree of pain produced by pressure on the skin. Here we see the sensory consequences of convergence in the spinal cord of messages both from nerve fibres signalling temperature and pressure (the polymodal nociceptors) and from fibres signalling pressure (the mechanoreceptors). The latter partially inhibit the effects of the former (Handwerker et al 1975). The sensory end result is determined in part by the activity in nociceptors and in part by activity in other types of fibre.

3. Pain has different sensory and affective qualities (Melzack 1975) and on the contrary quite different types of afferent barrage may result in indistinguishable pains. Grossly different painful chemical stimuli may be indistinguishable (Ong et al 1980). Similarly, man is unable to differentiate punctate injuries produced by heat or cold or mechanical destruction (Chery Croze & Duclaux 1980) and by the firing of different types of nociceptor (Campbell et al 1979, 1981).

The challenge of pain appears in the unravelling of these multiple factors. Injury and the nerve fibres specialised to detect injury represent one of the factors and so do other events in the periphery and so does the set of the central nervous system which actively controls the reception of the incoming messages. The importance of each factor can be assessed by assigning them roles in explanation of the various pain states and then exploiting them to bring pain under control. The onset of pain may be abrupt and rapid and must certainly be explained by the arrival of an afferent barrage of nerve impulses. This then passes through a gate control system. The mechanisms can be explained in terms of the classical types of synaptic transmission with their inhibitions and excitations and chemical transmitters. However clinically important pain changes with time and the important factors may differ from those during the

initial onset.

The rest of this introduction will examine the special challenges which appear as time passes. It will be argued that chronic pain is not simply a prolongation of acute pain. I will discuss the tissue, the nerve terminals, the peripheral axons, central axons, central cells, and finally sensation and behaviour, all in terms of the time dimension. The acute and chronic phases of response at each of these stages will be investigated and it will be shown that chronic pain is not simply a prolongation of acute pain but involves new events in the PNS and CNS.

1. IMMEDIATE AND CHRONIC EFFECTS OF INJURY ON TISSUE

Damage to tissue may directly excite nerve ends by mechanical, thermal or chemical effects on nerve membrane. Damage also sets in progress the sequence of events recognised as inflammation with pain as one of its characteristics. As we will see in the next section, the nerve ends themselves contribute to the inflammatory process. There has been an intense search for the compounds which could be the chemical components responsible for inflammatory pain (Keele & Armstrong 1964). A list of naturally-occurring pain-producing substances would include:

	Lowest known effective concentration
Acetyl choline	2.5×10^{-8} mol, close arterial, afferent nerves
Histamine	3×10^{-8} mol, close arterial, afferent nerves
5-Hydroxytryptamine	10^{-8} mol, close arterial, afferent nerves
Bradykinin	5×10^{-11} mol, close arterial, afferent nerves
Hydrogen ions	3.2×10^{-7} mol, parenteral injection
Potassium ions	8×10^{-6} mol, close arterial, afferent nerves
Prostaglandin E_1	3×10^{-8} mol/kg, intraperitoneal, animal
Prostaglandin E_2	3×10^{-10} mol/min, intravenous, man
ATP	blister base

From Chahl 1979

In spite of the enormous work done on these compounds there is no generally agreed conclusion on their actual role in inflammatory pain. The question is not simply one of intellectual curiosity but has great practical importance. If the agent or agents which are responsible for exciting nerves could be identified, it would be possible to design specific and true analgesics. It is apparent that general anti-inflammatory agents such as the steroids or those which interrupt part of the inflammatory process such as aspirin have a highly effective analgesic action. However, we are all too well aware that the very effective action of these compounds in blocking necessary reparative processes makes them unacceptable for many forms of analgesia associated with tissue damage. We must therefore ask a series of questions to analyse why we are not further ahead.

Could it be that a crucial pain producing substance has been missed?

The reader will quickly recognise that each of the substances listed above has its own scientific history. They were isolated for various reasons from various tissues. After that process, the substance was then tested to determine if it was pain-producing, but relevant concentrations were not known. It is obvious with this process of identifying pain-producing substances that crucial compounds could have been missed. Ischaemic muscle is intensely painful but we do not know which aspect of altered chemistry is responsible (Chapters 1.7, 2.B.1 and 2.B.2). In conditions such as osteoarthritis or herniation of an intervertebral disc, we do not even know which exact tissue is responsible for the pain.

Given these problems, a logical approach would seem to be to analyse the abnormal environment around nerve endings in damaged tissue and then to recreate that environment around normal nerve endings to see if nerve impulses and pain result. Modern science has the tools for this approach. There are already cues that important factors may have been missed. Perl et al (1976) have investigated the cause of the sensitisation of unmyelinated sensory afferents and have eliminated acetyl choline, histamine, 5-hydroxytryptamine, bradykinin, hydrogen ions, potassium ions and prostaglandins. This sensitisation is one of the factors likely to produce pain which outlasts the injury, but it is evident that we do not understand its chemistry.

Could it be that more than one pain producing substance acts simultaneously?

a) Evidence for independent action. Keele & Armstrong (1964) worked mainly on the production of cutaneous pain by applying substances to the base of blisters. They extended their work to include classical pharmacological investigations to determine the nature of the excitatory action. Where specific antagonists existed, as for example against acetyl choline, they showed that these antagonists worked against the induced pain in the expected manner. Where tachyphylaxis occurred, there was an additional way to test if these agents were affecting nerve endings in the traditional way. Here the tissue was desensitised by repeated application of one agent and then tested to discover if another agent was still capable of producing pain. Since there was no crossed tachyphyllaxis between many of the agents, they concluded that these agents were reacting with independent and specific receptors. This raises the question of whether there are separate specialised nerve fibres, each capable of detecting a single chemical, or if the receptors were distributed on the same fibres.

b) Evidence for co-operative action. There are a number of examples of substances which are not by themselves pain-producing but which act to lower the threshold of afferent nerve fibres in their response to another substance. For example Chahl & Iggo (1977) found that prostaglandin E_1 alone had little effect on their preparations of rat cutaneous nerves. However a 10-minute intra-arterial infusion of low doses of prostaglandin E_1 resulted in a clear ability of bradykinin to evoke an afferent barrage. Similarly, Taira & Nakano (1974) found that 5-hydroxytryptamine increased the response of nociceptors to the action of both acetyl choline and bradykinin. The potentiation of the effect of bradykinin by prostaglandin has also been reported in different situa-

tions by Ferreira et al (1973) and by Juan & Lembeck (1974). There are a number of examples in the literature of apparent synergy between differing algogens. This evidence has to be taken into account along with the evidence from Keele & Armstrong (1964) and from Khayutin et al (1976) and others that the algogens are acting on specific receptors. Since interactions have been observed while recording from single peripheral units, one may conclude that single fibres may react to more than one substance.

c) An alternative suggestion. It may be best to consider certain types of afferent fibre in tissue as being comparable to olfactory or gustatory sensory fibres. They would be continually 'tasting' the chemical composition of the extracellular fluid in tissue. Single units from nose and tongue do not react specifically to single classes of chemicals. This observation seems a paradox since it is obvious that man and animals are capable of differentiating between various tastes and between various smells. This has been resolved by suggesting that the poorly-tuned detectors feed a temporal and spatial pattern of impulses to the brain which decodes these patterns (Erickson 1963). In the presence of injury, there will be many chemical abnormalities in the tissue some of which evoke pain. There are at least two classes of nerve fibres, the A delta and C fibres, and probably many subdivisions of these classes, which respond to injury. The brain may then group together different patterns of afferent barrage and interpret them as a single class of events. This would lead to different types of injury signalled by different types of afferent being indistinguishable as has been shown to occur with certain noxious events (Ong et al 1980, Chery Croze & Duclaux 1980). On the other hand, pain is not a uniform sensory experience but has many different qualities (Melzack 1975) which may be extracted from the afferent messages which contain detailed information in addition to the announcement of the presence or absence of injury. I have described elsewhere reasons to propose that pain is more related to guiding recovery from injury rather than the avoidance of injury (Wall 1979). On occasions, widely differing injuries may evoke identical sensations and lead to similar behaviours conducive to recovery from the injuries, such as rest or limping. On other occasions, sensation and behaviour may demonstrate that the brain has extracted differences in closely related injuries and set off differing sensations such as itching, burning or stabbing and differing behaviours such as scratching, rubbing or holding still.

2. THE EFFECT OF INJURY ON NERVE TERMINALS (Fig. 1)

a) Immediate effects

Mechanical injury evokes impulses in nerve fibres of all sizes. Which of all these are involved in pain?

A beta fibres (large myelinated fibres)

Low-level electrical stimulation of peripheral nerves selectively activates these fibres and evokes non-painful sensations. However, there are four ways in which they relate to pain. Afferent barrages in these fibres inhibit the response of cord cells to noxious stimuli and decrease pain (Wall & Cronly-Dillon 1960, Wall 1964, Wall & Sweet 1967). This observation was one of the major leads to the gate control theory. If the electrical stimulus is raised to include the smaller fibres of this group, the inhibition of painful sensation and of the flexor reflex to noxious inputs is replaced by a facilitation (Willer et al 1980). In pathological states such as trigeminal neuralgia pain may be evoked by stimulation of A beta afferents (Kugelberg & Lindblom 1959). In areas to which pain is referred and in tender areas distant from injury, light mechanical stimuli may evoke pain and there is no good reason yet to question that the A beta fibres contribute to the tenderness.

A delta fibres (small myelinated fibres)

When a single electrical shock to a nerve is sufficiently large to fire these fibres, there is intense and prolonged firing and facilitations of many spinal cord cells and intense pain (Mendell 1966, Collins et al 1960). This group of fibres includes several physiological types but many are nociceptors (Chapter 1.1).

C fibres (unmyelinated afferents)

There is no doubt that the majority of these fibres are nociceptive (Chapter 1.1). There is also no doubt that selective stimulation of these afferents produces pain (Collins et al 1960, Sinclair 1981). These two facts have reasonably led to a particular emphasis on C fibres as afferent triggers of pain and the evidence is good. However, a series of facts leads to suggestions that C fibres have additional roles which may be crucially important in understanding reactions to injury.

Reasons to doubt that pain is the only result of C fibre action

(i) Numbers. Some 70% of all dorsal root afferents are unmyelinated and the majority are nociceptors (Willis & Coggeshall 1978). These numbers are so vast that one may reasonably question if their only function is to trigger pains.

(ii) Conduction speed. Many C fibres conduct at 0.25 m/s, which means that a horse spinal cord receives impulses in such fibres 8 seconds after events on the hoof. This slowly arriving volley has been used to explain first and second pains but the correlation of this phenomenon with particular fibres has serious problems (Sinclair 1981). Even if it were true it would raise the next question which is why we need a double pain-triggering system.

(iii) Redundancy. The A delta and C fibres both signal many of the same aspects of tissue damage. Differential stimuli which excite only A deltas or only Cs both evoke pain but that is no explanation of why we need duplicated systems. In most real situations it is not yet possible to say if the perceived pain is produced by A deltas or Cs or both. However, in the best studied case, the hyperpathia which follows a heat injury at 55°C, strong evidence proposes that the pain is due to the activity of A deltas and not of Cs (Campbell et al 1981). A particular challenge to C fibres as playing a dominant role in pain comes from the use of