PAIN

By
SIR THOMAS LEWIS

¶ This enquiry into the nature and mechanism of pain reviews modern ideas of the subject and brings the recent work of the author's laboratory into perspective with other observations. In order that the book may be kept within a reasonable compass, all the various pains of disease processes are not discussed, but outstanding instances are used as examples. Most of the evidence is drawn from experience with human pain rather than from that with animals, both because it is a more reliable source and because it is more directly applicable to medical problems.

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PAIN

By the Same Author

CLINICAL DISORDERS OF THE HEART BEAT

CLINICAL ELECTROCARDIOGRAPHY

THE MECHANISM AND GRAPHIC REGISTRATION OF THE HEART BEAT

THE SOLDIER'S HEART AND THE EFFORT SYNDROME

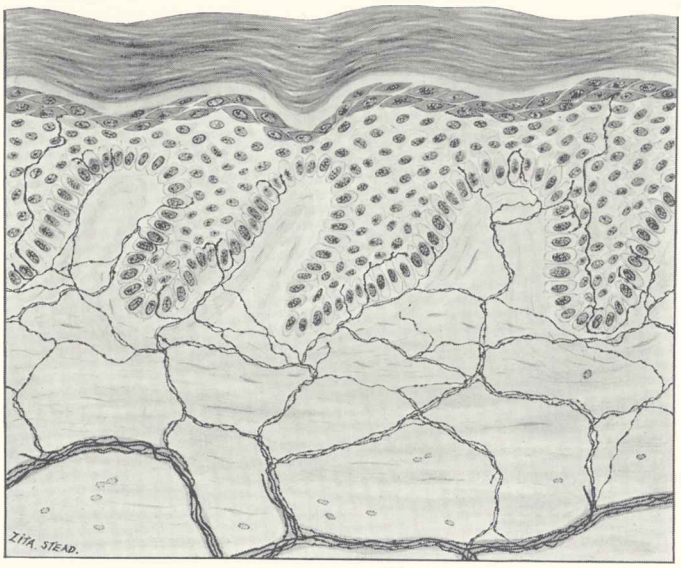
BLOOD VESSELS OF THE HUMAN SKIN AND THEIR RESPONSES

CLINICAL SCIENCE ILLUSTRATED BY PERSONAL EXPERIENCES

DISEASES OF THE HEART

VASCULAR DISORDERS OF THE LIMBS

RESEARCH IN MEDICINE AND OTHER ADDRESSES



Frontispiece. ($\times$ 500) Subepithelial plexus of nerve fibres in human skin giving rise to naked terminals in the subepidermal and epidermal layers. The intra-epidermal nerve fibres reaching the stratum granulosum have been observed only in the finger. A composite drawing from methylene blue and reduced silver preparations by the late Professor Woollard and by Dr. Weddell.

PAIN

BY

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PREFACE

Reflection tells me that I am so far from being able satisfactorily to define pain, of which I here write, that the attempt could serve no useful purpose. Pain, like similar subjective things, is known to us by experience and described by illustration. The usage of the term in this book will be clear enough to anyone who reads its pages; to build up a definition in words or to substitute some phrase would carry neither the reader nor myself farther. But in using the undefined word it is necessary to take care that it is never allowed to confuse phenomena that may be distinct; when there is such possibility, the bare word, pain, is not enough; it needs and will be given qualification.

We have no knowledge of pain beyond that derived from human experience; yet we may judge of its presence in animals by bodily reactions that human experience has brought us to recognise as its frequent accompaniments or by the use of stimuli that similar experience tells us should be painful. Often, physiological investigation is more profitably undertaken on animals; in the case of pain, this is not so. Strictly speaking, there are no reliable and usable indices of pain in animals; there are only phenomena recognised as frequent associations of pain, such as raised blood pressure, movements of withdrawal or defence, dilatation of pupil, increased respiratory depth, and cries. But some of these are manifestly spinal cord or medullary reflexes and can happen in the absence of pain; and some probably are quite independent of pain, in the sense that the initiating impulses travel by paths other than paths of pain. Even prolonged struggling and cries are no reliable criteria since they may come, not from pain, but from apprehension; and these are the least usable, for they are associated with the infliction of suffering. Sherrington (210) wrote: "In all this experimental work on animals the observer has to work through signs of subjective states incomparably inferior in most instances to the

verbal communication establishable with an intelligent human being." Our knowledge of pain, of its sources, of the nerve paths conveying it, has been built up, and will continue to be built up, chiefly by observations upon man. It is built up by tests of the sentient surface in the normal subject, tests of skin deprived deliberately or accidentally of its nerves, the innumerable probings of disease itself, stimulation of deep-lying structures during surgical operations, and ingenious forms of exploration of deep structure from without; all these sources have contributed so abundantly that I shall but rarely need to refer to evidence derived from animals. There is manifest wisdom in seeking knowledge from the direct, rather than from the indirect, source, and here the direct source is prolific; there is, too, the deep satisfaction of knowing that any evidence won from man is indubitably applicable to the human problem.

The chief purpose of this book is to review modern ideas of the mechanism of human pain and to bring into perspective with other observations the work of my own laboratory during the last ten years. While attempting to make a book of reference, one that will bring contact with the more important views, I have desired to preserve it from cumbrousness and to keep it in a readable form that will stimulate interest and enquiry. These purposes have decided against a systematic discussion of the various and many pains of human disease. Such an attempt would have multiplied the pages several times. Moreover, the task could not have been accomplished while maintaining an equal standard of definiteness, for the pains of many human ills are still mysterious. Nevertheless, I have drawn freely upon outstanding instances of pain in disease and upon examples that have been studied closely, for the evidence derived from these is often illuminating from the general viewpoint. I believe that our recent analysis of deep somatic pain can be used to explain the phenomena of visceral pain and tenderness. I had hoped to study them, under continuing peace conditions, until able more conclusively to define their mechanism. The war leaves me no alternative but to record present and more tentative views of these visceral symptoms.

The two introductory chapters of this book form chiefly a record of plain facts without much discussion. Some may prefer

to regard them as chapters of occasional reference and to begin to read at the third chapter, from which run lines of argument.

It is a pleasure to acknowledge gratefully the help I have received from Professor T. R. Elliott and Dr. Paul D. White in their careful reading of my manuscript and proofs, respectively.

T. L.

(*June, 1941*)

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PAIN

Chapter I

PAIN-SENSITIVE TISSUES

The evidence in this chapter is derived almost exclusively, and always unless otherwise stated, from tests of human beings, whence such evidence must be derived to possess final value.

In speaking of pain-sensitive tissues of the body, I mean distinctly to imply tissues that may be supposed to contain pain nerves, in that stimulation confined to such tissues gives rise to immediate pain. The forms of testing stimulus to be used in identifying pain-sensitive tissue are for the most part mechanical. In testing exposed tissues, pricking and pinching are particularly suitable because the stimulus can be applied with minimal disturbance of surrounding structures. To apply injurious heat or electrical stimulation is also valid if we can ensure that the stimulus does not spread beyond the tissue to be tested. From this point of view, chemical stimuli must be used cautiously unless, indeed, they can be employed in very small quantities and the mass of tissue to be tested is voluminous or has a large surface. I shall not here admit methods of testing that either directly, or indirectly through the responding contraction of the tissue, impose strains that may be supposed to be conveyed to other tissues. Such forms of stimulation have their experimental uses and, because they are sometimes regarded as the most natural or adequate, may not be neglected ultimately. But the effects brought about by such stimulation could not suitably be introduced into this preliminary survey, since it sets out to enumerate those tissues from which painful sensations may undoubtedly be provoked, rather than those tissues which we may be able to describe with complete finality as being without pain sense. Those who attach great importance to tension as a stimulus or to massive stimuli need have no misgiving that the exclusion of these from this chapter will falsify arguments in

later chapters; where the forms of stimulation mentioned are most likely to be concerned, they will not be neglected.

In addition to the surface of the body, there are very few somatic tissues that cannot easily and safely be reached and stimulated. A few years ago I introduced the method of passing a fine hollow needle into various tissues in order to inject into them small quantities of substances temporarily irritating to the tissue nerves but otherwise harmless. A hypertonic solution of salt was found to be the most convenient of the substances introduced. The method has greatly helped in studying pain provoked from the deeper structures of the limbs and body wall.

Superficies

Skin and mucous membranes.—The whole of the skin, the conjunctiva, most of the mucous membrane of the mouth, the mucous membrane of the nasopharynx and its sinuses (including the middle ear (121), the upper surfaces of the larynx and the anal canal) and the stratified mucous membranes of the genitalia, all give pain in response to simple forms of injurious stimulation such as are within everyday experience. Broadly speaking, pain response is found in all structures that are sentient to touch, warmth, or cold. Exceptionally, however, there are dissociations. Thus the cornea and sometimes the nasal mucous membrane contain only pain nerves; the conjunctiva, the glans penis, and usually the nasal mucous membrane are sensitive to pain and to cold, but are unresponsive to warmth and to touch (53, 181).

Deeper Somatic Tissues

Subcutaneous fat.—Afferent nerve endings are found in subcutaneous tissue. It is generally agreed, however, that, apart from cutaneous nerves penetrating it, this layer gives rise to little pain when injured by needle or by incision (5, 153). If the web between two fingers is squeezed, a stimulus involving subcutaneous tissue, pain is easily produced; it comes from nerves lying deep to the skin (228).

Deep fascia.—When a needle passing through subcutaneous tissue strikes the deep fascia, pain is often felt and is increased if the needle point is moved over the fascia; in the case of the fascia lata, pain may be severe (5, 48, 103, 235). In testing this

and other deep-lying structures with a needle, the skin should be anaesthetised beforehand.

Muscles.—The somatic muscles all give rise to pain (101, 121, 137). It is slight when elicited by needle prick or knife cut but very distinct or severe when provoked by injecting 0.02 to 0.03 c.c. of 6 per cent saline or other irritant substance (101, 137) or when induced by working the muscle under ischaemic conditions (145). It may be elicited crudely by squeezing any muscle firmly between finger and thumb.

Tendons.—Pain from such tendons as the tendo Achillis is easily produced by driving in a needle or by injecting hypertonic saline into the mass of the tendon (103, 137). The same kind of pain is given by squeezing this or other tendons, such as that of the semitendinosus muscle, between the fingers.

Periosteum.—Most observers have found the periosteum to be very sensitive (48, 121, 123); its sensitivity can be shown easily to pricks or to hypertonic saline injection (103, 137).

Bone.—Compact bone may be bored without pain (103); but when cancellous bone is reached, pain may appear (48, 103). Lennander, however, speaks of painlessly sawing through the femur (121).

Joints.—These have been explored when opened under local anaesthetics or through cannulae. The articular surfaces, tested with needle point, knife, or cautery, are insensitive; but the synovial lining of ligamentous structures is very sensitive to scratching and to hypertonic saline (48, 103, 121, 123).

Vessels.—Pain is often but not always felt when a needle, already through skin and subcutaneous tissue, is pushed on through the coats of an artery (5, 235). Puncture of a vein is nearly always painless. Pain has often been reported to occur in operations under local anaesthesia when arteries are tied; thus the thyroid arteries are said to be very sensitive (48, 176). Often but not always, arteries of the limbs can be tied without pain. Injections of irritant substances, such as barium chloride, into the arterial lumen in animals is painful, but only if the substance is allowed to reach the capillary field. Thus it is probable that the intimal layers of arteries are insensitive to pain and that in ligation pain comes inconstantly from point to point of the peri-arterial tissues (176).

Cerebrospinal Membranes and Brain Surface

In operations under local anaesthesia or in those conducted without anaesthetic, the membranes and surface of the brain have been tested by many observers. The dura mater is recognised to be insensitive to incision, scratch, cautery, and electrical stimulation except in the region of the large meningeal vessels and sinuses, from which responses may be obtained (43, 45, 48, 121, 166). Cushing (32) believed the falx and tentorium to be pain-sensitive. The pia mater and the cortex are generally regarded as insensitive to faradism, burns, and incision; but there is sensitivity of the middle cerebral, vertebral, basilar, and posterior cerebellar arteries when these are pinched or stimulated electrically (45, 120, 121). A very full account of pain-giving structures within the skull, based on numerous observations and in general agreement with those already summarised, has been published recently (193). Pain derived from dorsal structures is referred in general to a neighbouring region of the head's surface. The brain surface is generally regarded as giving little or no pain on stimulation (see p. 31). Sensitivity of nerves and that of pain-conveying tracts of the spinal cord are considered on pages 13 and 18.

Thoracic Contents

Pleura and lung.—The statement of Lennander (123) that the lung and visceral pleura are insensitive is one with which other observers agree. The passage of an exploring needle through lung is painless. The pleural surfaces have been tested by scratching them with a needle point or wire while tapping effusions. Mackenzie (153) reported both surfaces to be insensitive, but Lennander and others (23, 123, 173) found the pleural surface of the thoracic wall and diaphragm sensitive.

Pericardium.—In ectopia cordis, the surface of the heart is found to be insensitive, a fact known since Harvey's time. The sac has been explored through cannulae or through apertures made to drain it. Capps (22, 23) failed to elicit pain by scratching or pressing upon the visceral surface of the heart or by scratching the parietal pericardium. Similar observations by Alexander and his collaborators (2) agree with the observations

by Capps, though the former suggest that some of the lower parts of the sac may be supplied by pain nerves derived, perhaps, from diaphragmatic branches of the phrenic nerve.

Heart and aorta.—In dogs, tubes have been sewn, under anaesthesia, into the pericardium through the chest wall and the heart subsequently tested through these after recovery. Traction on a ligature previously passed around the descending branch of the left coronary promptly calls forth evidence of pain, the dog limping on the left forepaw (Sutton and Lueth, 222). Signs of pain are elicited by such traction, even though the artery remains patent (159), it therefore seems to come at least in part from tension on the nerves accompanying the artery. Puncturing the heart wall of the heart in dogs is said to be painless (214, 222); the aorta may be punctured painlessly (222), but signs of pain are sometimes elicited from the adventitia (214).

Oesophagus.—Hurst states (89) that the oesophagus is sensitive to touch as low as the cricoid and that warmth and cold are appreciated throughout its length. There seem to be few direct observations upon pain sense. It is said (173) that, if a faradic current is applied through a stomach tube, nothing is felt until the level of the cricoid cartilage is reached during withdrawal. My surgical colleagues inform me that they have often and painlessly removed pieces of the oesophageal wall of the conscious subject for histological examination, even including muscle with the mucous membrane.

Abdominal Contents

Peritoneum.—The relative insensitivity of the abdominal viscera in man has been recognised for over a hundred years. The question was first thoroughly explored in the present century by Lennander (120 to 123). This surgeon compiled a large series of precise notes of his patients' responses during the progress of numerous explorations of the abdomen under local anaesthesia (cocaine); his results are in general agreement with those of earlier and of later observers (10; 245; Mackenzie, 155; Morley, 169).

The parietal peritoneum with its subserous layer is recognised by surgeons operating under local anaesthesia to be very sensitive

to tension (120, 155, 169). The sensitivity of the peritoneal surface itself is more doubtful. Mackenzie states (155) that, during laparotomy in conscious subjects, he has often scratched it without reaction (see also 189). But Morley (169), relying chiefly on tests of the dome of the diaphragm, insists that the membrane is itself very sensitive. Capps and Coleman (24) explored the surface with bent wire through cannulae introduced to evacuate ascitic fluids. A rounded point was passed over the parietal surface and elicited pain when the pressure was enough to raise the abdominal wall so that the position of the point could be seen from without. It is to be gathered that a good deal of pressure is required to elicit pain with blunt points, but less with sharper ones. Both Lennander (120) and Morley (169) speak of the pain as severe when a surgical mop is passed beneath the dome of the diaphragm.

Solid organs.—It is common knowledge that the solid organs, such as liver, spleen, and kidney, can be tightly gripped, cut, or even burnt without the subject's being conscious of it (120, 155).

Gall bladder.—This sac is insensitive to clamping and to cautery (120, 123).

Duodenum and pancreas.—Morley (169) finds the peritoneal tissue overlying the pancreas to be very sensitive. Traction on the duodenum produces severe pain (Lennander, 120). I know of no satisfactory direct tests of pain sensitivity in either of these organs.

Stomach.—All parts of the wall of this organ may be cut, burnt, stretched, or clamped without pain (10, 120). It is stated (173) that faradism through a gastric tube is painless.

Jejunum and ileum.—Clamping or cutting these parts of the alimentary canal, cauterising or stretching them, is accomplished painlessly. The jejunum has been stretched between the fingers; no pain results if pull on the mesentery is avoided (Lennander, 120).

Colon.—The insensitiveness of this gut attracted early attention. Stitched to the bottom of an abdominal wound, it could later be opened by knife or cautery to complete the colotomy painlessly in the fully conscious patient. When tested through colotomy openings, the mucous membrane of the colon has been proved insensitive to the usual pain-giving stimuli, including

faradic currents adequate to produce strong contraction of the gut (121, 122, 173). Similar insensitivity of the recently exposed colon has often been recorded. The caecum and appendix are similarly stated to be insensitive to clamp, knife, and cautery (Lennander, 120; Mackenzie, 155); Kinsella (107), however, has recently said that he finds squeezing the inflamed appendix lengthwise between thumb and finger to be painful.

Rectum.—Haemorrhoids are painlessly treated by injecting the wall of the rectum above them from the anal canal in the fully conscious subject. The mucous membrane of lower colon and rectum can be reached from without, and Sir Arthur Hurst tells me they are quite insensitive to pinch or cautery. The anal canal is sensitive to pain throughout its length.

Great omentum.—Crushing or cutting this omentum is accomplished painlessly (120, 169, 189).

Mesenteries.—Lennander (120) believed the mesenteries in general to be insensitive, though he was well aware (as was Bier before him) that traction on stomach or duodenum usually produces severe pain and that pain is often complained of when similar traction is exerted on the mesocolon and mesenteries of the small intestine. He supposed this pain to be derived from traction on the posterior abdominal wall. In one instance, however, he records how gripping the mesentery of the appendix with forceps gave pain though all drag was avoided, a fact since abundantly confirmed (Kinsella, 107). Other surgeons have found the mesenteries to be sensitive (16, 245); Morley (169) describes those of small and large intestine as sensitive from their roots to a little distance from their attachment to the bowel.

Pain was said by Wilms (245) to be elicited on pinching vessels of the human mesentery within 2 or 3 cm. of the bowel. Breslauer (16) also found these mesenteric vessels sensitive to pinching, though it is not to be gathered that this is invariable.

In dogs, the region of the vessels of the mesenteries has been found particularly sensitive; ligation of a chief vessel gives signs of pain, but a second ligature causes repetition of these signs only if it is proximal to the first (96, 189, 196, 197). It is surmised, therefore, that pain nerves run with the vessels for some distance or throughout their length.

Pelvis of kidney and ureter.—A touch with a probe on the inner aspect of the pelvis of an exposed kidney may cause unpleasant pain (Lennander, 120), as does even slight distension of the pelvis (121). Mr. F. J. Barrington tells me that a catheter, when passed from the bladder, gives pain from the time it enters the ureter (consult also Papin, 178).

Bladder.—The presence of a stone upon the neck of the bladder has long been recognised to give severe pain. Similar pain is provoked when a finger, introduced through a cystotomy opening, touches the base of the bladder. The fundus of the bladder seems to be less sensitive (Müller, 173).

Testicle.—According to Lennander, the testicle and epididymis are insensitive, but he recognised the great sensitivity of the covering scrotal tissues (120). Mackenzie (155) tested the surface of the tunica vaginalis and proclaimed it to be the only sensitive serous membrane that he had detected.

Uterus and appendages.—The body of the uterus can be cut or burnt; the broad ligaments can be dissected painlessly (120, 121). It is a familiar fact that the cervix can often be gripped by toothed forceps and pierced or cauterised while the subject remains unconscious of it, though it is not clear that this insensitivity is complete and invariable.

Vagina.—It is stated (173) that this organ is insensitive after passing a centimetre or two within the orifice. Lennander (121) reported the vaginal wall to be insensitive to cautery, faradic current, incision, and clamping; many gynaecologists, however, believe the fornices to be sensitive.

Urethra.—The mucous membrane of the urethra is very sensitive at its mouth, where it can readily be tested. It is probably sensitive throughout, but I know of no tests of its upper reaches that avoid stretching its walls.

Summary and discussion of further evidence.—To sum up, there is widespread agreement among surgeons that the solid organs of the human abdominal cavity yield no pain to direct stimulation. The same statement applies to the alimentary canal (from stomach to rectum), to the gall bladder, and to the uterus; it applies to organs that are undiseased; it applies equally, according to most observers, to those that are inflamed (Lennander, 120; Morley, 169; Hurst, 89), though to this all are not agreed

(107). It is also agreed that traction upon the hollow viscera, especially upon those of the upper part of the abdominal cavity, is painful. While Lennander originally attributed this to drag on the parietes, there seems clear evidence that at least the basal parts of the mesenteries are supplied by sensory nerves and that traction can affect these. There is also evidence that pain nerves are contained within the lesser omentum and that they occur in relation to the pancreas, to the renal pelvis and ureter, and to the base of the bladder.

These observations upon man have been repeated extensively in animals. Kast and Meltzer (99, 100), using dogs chiefly, opened the abdomen under anaesthetic, closed it with stitches, and, after recovery, allowed a loop of gut to protrude. As the result of many carefully conducted experiments, they stated emphatically that, if the bowel is tested early and is kept warm and moist within or without the abdominal cavity, signs of pain can be elicited by pricking or pinching the bowel itself or by faradising it. The signs consisted of whining or cries, or of struggling. Using dogs under morphia, Ritter (196, 197) confirmed these findings for gut and included appendix, stomach, liver, and spleen, though it is clear from his protocols that the responses lacked uniformity. Ritter also reported that he had found the human bowel itself sensitive to pinches in some instances and Kinsella (107) speaks of the inflamed appendix in the same way. In unanaesthetised dogs, Kappis (96) failed to provoke signs of pain except from the vessels of the mesentery.

Kast and Meltzer believed that their observations upon dogs proved the bowel wall to be painful, and that failure to provoke similar pain in man has been due to the absorption of local anaesthetic and its action upon the central nervous system or to loss of function of the pain nerves to the bowel through exposure. When a simple solution of cocaine was the local anaesthetic used, the idea that its absorption and central action masked pain had more force. Doses of cocaine equivalent to those used by Kast and Meltzer in their experiments showing this central effect would now be regarded as unsafe by surgeons; and, in fact, such doses abolished pain responses from the parietes as well as from the viscera. In the later observations upon man, much less toxic substances, such as eucaine and novocaine, have been employed;

and their absorption has been hindered by their admixture with adrenaline—yet the apparent insensitivity of the organs has remained. Moreover, in a number of instances, operations have been carried out on man by Mackenzie (155) and others (76, 166, 189, 245), and tests made in the absence of either general or local anaesthetic; these support the general view of visceral insensitivity. Further, there is very striking evidence in the observations upon man by Lennander and his successors that, whereas the bowel and other organs are found to be insensitive, the parietes are found to be exceedingly sensitive. In view of these controls and in view of the usual insensitivity of cervix uteri, oesophageal, rectal, and colonic walls, all of which can be reached and tested in the fully sentient subject, it is safe to conclude that the viscera which Lennander names are either completely insensitive to injury or are relatively very insensitive. To insist on their complete and universal insensitivity to injury would be unwise in view of the occasional responses reported from the human gut and the more frequent responses in animal experimentation. Naturally, there is reluctance to accept the view that the sensory supply of the bowel is fundamentally different in man and animals. The seeming difference may in part depend on inability to estimate pain in animals, for a dog, fastened for tests and expecting pain, will provide a lively display in response to slight pain or even to its anticipation.

Now, although we arrive at the conclusion that, in general, the direct stimulation of the hollow viscera gives rise to little or no pain, it is manifest that contractions of these organs are responsible for severe pain. The manner in which such pain is brought about and the criticism that direct stimulation may be inadequate will be discussed more conveniently in a later chapter.

Chapter II

ANATOMICAL BASIS OF PAIN

Pain Points and Nerve Endings

Working independently, Blix (11) and Goldscheider (65) found that a fine needle may be stuck deeply into many points of the human skin without awakening pain. Goldscheider called the sensitive points pain points. But the pain points are so closely set and the strength of stimulus required to elicit response is so varying that the idea of a special end apparatus for the reception of pain impulses has found less easy acceptance than has that of specific receptors for warmth, cold, and touch. Frey (54), in contrast to Goldscheider, was insistent on the separateness of the pain and touch apparatus since he believed that each could be made to yield pure responses and disproved the old view that pain response is merely a full response to strong stimulation of other sensory systems.

The spots identified as pain points may be aggregated as closely as two hundred to the square centimetre, as is the case in the fossae of the body (supraclavicular, antecubital, inguinal, popliteal); on the tip of the nose and ear, on the sole of the foot and palm of the hand, they are much less frequent and amount to from forty to seventy to the square centimetre (220). It is interesting to note that, while touch spots are said to increase, pain points are said to decrease in frequence in passing from the base to the extremity of a limb and from the dorsum of the finger to its palmar surface.

The frequence of cold and warm spots on the skin agrees in general with the frequence of special forms of sensory nerve endings, such as Krause's corpuscles and Ruffini's endings; and the touch spots similarly agree with special endings around the hair roots and with Meissner's corpuscles (54). These various end

organs, therefore, are often regarded as specific receptors of the corresponding forms of sensory stimulus. Notable attempts to strengthen these correlations have been made in recent years and have reached a considerable, though not a full, measure of success (Bazett and McGlone, 6; Woollard, 249). These consist in marking, with utmost accuracy possible, sensory spots of different kinds on the surface of the skin and in excising or slicing off the skin and examining it microscopically.

There remain the numerous free endings of branching sensory nerves in the skin, endings long known to exist in Reptilia and Mammalia and recently recognised in adult human skin by

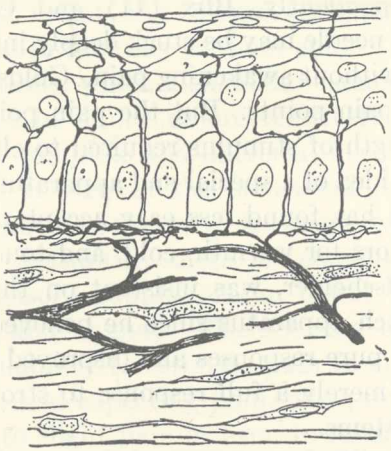

Fig. 1. (After Cajal.) Nerve terminals in the corneal epithelium of the rabbit (silver chloride preparation).

Woollard (250). These branched endings (Frontispiece) are unmyelinated, finely beaded, and often arranged in plexus form. In skin of the kitten's paw, they were depicted by Cajal as penetrating the Malpighian layer almost to the stratum granulosum. They supply the skin very freely and have seemed to be an apparatus suited to the reception of pain impulses for, as Woollard (249) said in referring to experiments in which successive thin slices of skin were removed (the new surface being each time tested), pain is of the modalities at once the most superficial and the most extended through the various cutaneous strata.[1]

[1] Waterston (234) believes the nerves of the epidermis to be touch nerves. He finds this layer may be sliced painlessly by razor; but the painless cut may be due to the small number of nerve fibres encountered.

Woollard found in his own skin, in the region of a spot marked for intense pain, an irregular plexus of finely beaded fibres. The idea that these free endings are associated with the reception of pain impulses has long been supported by the knowledge that such endings are the characteristic nerve endings of the cornea and of the mucous membrane of the nose. The cornea up to its margin, where cold may be appreciated, is pain sensitive only (54), and its nerve endings intra-epithelial (Fig. 1). The nasal mucous membrane is pain, but not touch, sensitive; and its nerves, according to Cajal (21), are of the same kind. Similar nerve endings have been described on the blood vessels, structures generally acknowledged to be pain sensitive, and probably pain sensitive only (41). There is more work to do along these lines and those investigating the presence or absence of such nerve terminations in various abdominal structures.

Nerves

It has long been known to surgeons that exposed nerves of the limbs give severe pain, whether to ligature, cut, or cautery. Pain down the arm is elicited from the ulnar nerve when this nerve is pricked or firmly pressed upon through the overlying tissues. When a needle is passed through the skin and on through the subcutaneous fat, and especially when passed where a cutaneous nerve is known to lie, momentary or longer lasting pain is sometimes felt in the skin distal to the point of puncture; evidently this pain is due to stimulation of a cutaneous nerve. Superficial nerves may readily be found (Trotter and Davies, 231) by moving across the skin a pair of electrodes conveying faradic current; when the electrodes pass over the cutaneous nerve, a fluttering feeling accompanied by a sense of tension is felt in the distal part of the nerve's distribution. If the current strength is increased, pain is experienced and the whole territory seems to be affected. If a cutaneous nerve has been found in this way, I have found that it may be stimulated very conveniently and easily, with any form of current desired, by passing down to it the first electrode (a single, fine, shellac-coated wire) through a hypodermic needle, while the second, a large indifferent electrode, is placed anywhere upon the skin (133).

Stimulation of the central ends of nerves to muscles gives in

man severe pain, according to Foerster (48), who insists that there is no such thing as a pure motor nerve or branch.

Overlap of sensory territories.—1. Overlap of cutaneous pain nerve territories.—It has long been known clinically that, if a nerve to a limb is severed, the area of total loss of cutaneous sensibility is much smaller than would be anticipated from the known anatomical distribution of the nerve. This phenomenon is due to overlapping of adjoining nerve territories. If a small cutaneous nerve of the forearm is blocked by cocaine or allied anaesthetic, the area of disturbed pain sense may be very small or negligible; so may be that of an adjacent cutaneous nerve similarly treated. But if the same two are blocked simultaneously, the disturbance may be considerable. In mapping out the complete area of disturbed sensibility from division or blocking of a single nerve, it may be possible to detect the loss of many previously existing pain points in the outer parts of the area affected and thus to gather an approximate notion of the whole area affected; but such a method is laborious and insufficiently exact. To display fully the territory of a nerve, the area which it supplies should be mapped out after blocking all nerves supplying adjacent territories.

An ulnar nerve lesion displays an analgesic territory, including the fifth finger and parts of the hypothenar eminence; but the territory of its pain fibre distribution displayed by lesions of the remaining nerves of the hand, the ulnar being untouched, is much larger (Head and Sherren, 85; and others, 48, 187). Actually, few accurate estimates of overlap of neighbouring nerve territories have been made, because of the necessity of isolating each nerve territory separately and mapping out completely the disclosed boundaries by taking in all remaining pain spots in each case. But it is clear that for limb nerves there is often overlap of one or several centimetres. If skin is tested while an interrupted but not pain-giving current is led into the nerve supplying it, the response to the cutaneous stimuli is lost or greatly diminished (66). This knowledge has been used to map out nerve territories on the forearm and the extent of overlap (225). These observations are mainly concerned with touch sense, but I can state from personal experience that pain nerve overlap can be displayed similarly.

2. Overlap of cutaneous pain with other sensibilities.—In comparing the extent of the defect in pain sense and in other sensibilities when skin is deprived of its nerve supply, it is essential to take into account the method of testing. It is common knowledge that insensitivity does not start abruptly but that between fully sensitive and insensitive skin is an intermediate zone of partial sensitivity, which may be relatively broad or narrow. A statement that the area of touch loss exceeds that of pain loss has very little value unless we know precisely how these two forms of sensibility have been tested and can conclude that the comparison is sound. There may be an area of skin quite insensitive to needle prick; there may be a larger area over which touches with cotton wool are unfelt: nevertheless, it would be inaccurate to conclude that the area of anaesthesia is larger than that of analgesia. Pricks and cotton-wool touches would be comparable only if each formed a maximal stimulus; and methods of testing are incomparable if, in one, a point and, in the other, an area are stimulated. This vital preliminary consideration is very clearly indicated in the paper in which Trotter and Davies (231) describe their precise and exhaustive studies of the effects of cutaneous nerve section. These workers used graded stimuli for touch and for pain and were thus enabled to produce maps, which portrayed not only the margins of absolute loss but which clearly indicated the zone of partial loss of sensibility. The results of this method of testing are illustrated in Figure 2. They conclude that "the changes consequent upon depriving a piece of skin of its nerve supply are distributed in a central area of absolute loss surrounded by a zone of partial loss, which is slight towards the periphery and deepens towards the centre". They find that this is the rule for pain as well as for other forms of sensibility and that, when the skin is tested at a suitable time after nerve section, "the defect of sensibility to pain is precisely similar in character and distribution to the defects in sensibility to cold, to heat, and to touch". They do not mean to convey that the area of defective touch and pain sense coincide exactly in extent, for the area of touch loss charted by them for comparison with Figure 2 is detectably though slightly the larger of the two. It is clear, however, that they believe the difference in boundaries to be small or negligible. After very

carefully studying the chief relevant papers, I regard the observations of these workers upon touch and pain defects following nerve section as the soundest we possess and accept their conclusion that the pain and touch defect is almost, if not quite, coextensive. I am the more inclined to accept it because it is consistent with the work of others (15, 113), with my own experience, and with the idea that each terminal twig of a cutaneous nerve will, in general, carry to its territory the necessary comple-

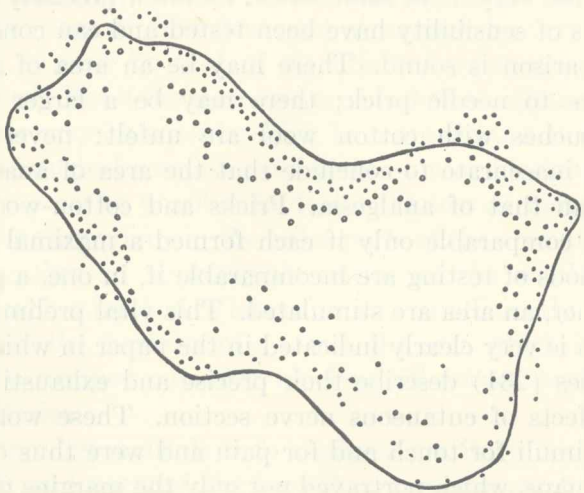

Fig. 2. (× approx. ½) (Trotter and Davies, *J. Physiol.* 38: 171, 1909. Twenty-three days after section of the external branch of the middle cutaneous nerve of the thigh. The continuous line marks the area within which there was anaesthesia to camel's hair brush.

Black dots, reacting to pressure of 1860 mg.; circles, to pressure of 2280 mg., with algometer. Thus the area responding defectively to prick is larger if the pricks are light.

ment of nerve fibres to serve touch, pain, and other sensibilities (as well as its complement of sweat, pilomotor, and vasomotor fibres) and that these do not follow distinct channels to reach almost common destinations in the skin. My personal experience is that in nerve blocks the territorial correspondence between sensory defects and sympathetic defects of the three kinds named is too remarkable to be accounted for on any other basis than conjoined distribution.

While many of the recorded statements of overlap between

touch and pain are to be explained on the basis of insufficiently precise comparison, a word remains to be said of overlaps in hand and upper limb. A nerve lesion such as ulnar transection is said to yield on the hand a smaller area of analgesia than of anaesthesia, whereas upon the base of the limb the reverse is said to occur. Thus, it has been said that in a lesion of a peripheral nerve the loss to touch exceeds that to prick, whereas in a lesion of contiguous posterior roots the loss to prick exceeds that to touch (Head, 82; Foerster, 48, 49). Two facts when taken into simultaneous consideration would explain this apparent discrepancy, which would mean that in the hand the pain overlap is greater than that of touch and that on the base of the limb the touch overlap is greater than that of pain. Firstly, it is agreed (54, 220) that pain spots decrease and touch spots increase in density as the extremity of the arm is approached. Secondly, Trotter and Davies (231) point out that in outlining touch where touch points are scattered (as on the base of the limbs), hypoaesthesia will be much diffused and it may be impossible to get a cotton-wool line. Thus, it will follow, as a result of difference in the numerical distribution of touch and pain spots, that a sharp and widely placed outline for pain defect is more likely to be obtained on the trunk and bases of the limbs; and for touch, upon the hands.

3. Overlap of cutaneous and deep pain.—Much more is known of the distribution of sensory nerves to the skin than of that to the underlying tissues; and this for the manifest reason that the deeper lying tissues are much more difficult to test. A conspicuous example of divergence between the supplies of given nerves to superficial and deep-lying territories is provided by *C*3, *C*4, and *C*5, which, while furnishing the skin of the neck and shoulder, also supply the central parts of the diaphragm with pain fibres. Similarly, thoracic nerves supply the skin of the chest wall, while underlying muscles such as the pectoral and serratus are supplied by cervical nerves.

When a small nerve is cut after penetrating the deep fascia, defects of sensibility will naturally be conspicuous in the skin only. There are clear examples of larger areas of skin being rendered insensitive by nerve section, while the nerve supply to underlying tissues remains more or less intact. One of the best

known is that described by Head (82), who found pressure to be recognised and pain to be elicited from tissues on the back of his own hand, through skin rendered anaesthetic and analgesic by section of the radial and external cutaneous nerves at the elbow. Instances of cutaneous analgesia of fingers with preservation of deep pain sense have been recorded by Thomas (224) and by Lehmann (116),[2] and similar dissociation on the trunk by Wartenburg (233). Parts of the face appear sometimes to respond painfully to deep pressure through skin rendered insensitive by division of the sensory root of the fifth cranial nerve (35). This example seems not to be invariable, however, since H. M. Davies (34) had previously failed to find evidence of deep pain sense in cases where the Gasserian ganglion had been removed.

Posterior Roots

The reception by the spinal cord of pain impressions through the portal of the posterior roots formed part of the Bell-Magendie law, under which all forms of sensation, including pain, are conveyed by these roots. These famous workers depended for their evidence on anatomy and animal experimentation. The evidence derived from man is similar to that derived from the latter. The two main facts here concerning us are that stimulation of the posterior root gives vehement pain (48), while section of a series of roots produces analgesia of a corresponding skin area on the same side. While all are agreed that evidence of this kind proves the posterior roots to be the main channel of pain impulses, the idea that they form the sole path has not remained uncriticised. We will for the moment accept the main conclusion and will return a little later to the controversial question relating to the anterior roots (p. 23).

Dermatomes.—Dissections of the somatic nerves have long since taught that their roots supply the skin of the trunk in successive and overlapping bands or segments. The rearrangement of the nerve fibres in the limb plexuses greatly complicates the use of this anatomical exploration in the corresponding localities. Nevertheless, from such investigations and from clinical observa-

[2] The idea that the corresponding nerve fibres belong to the anterior root system is dealt with on page 23 and that they belong to a perivascular system on page 27.

tions upon spinal cord lesions, many of the sensory cutaneous fields became defined with an approach to accuracy by earlier workers (see Ross, 201; Thorburn, 227; and others). Intense interest in this mapping out of the body surface developed among a group of independent workers in England in the nineties. Thus a very accurate study was made by Sherrington (209) on the monkey; he displayed the full territory of each root investigated by cutting a number of roots above it and below it, thus leaving an island of sensitive skin upon a background of insensitive skin. When successive roots were investigated in this way, it was found that the corresponding skin fields overlap considerably so "that each point of skin is supplied by two spinal roots, and some, it would appear, by three". Sherrington's test was a painful stimulus, and movement the observed response. Side by side with this work was that of Mackenzie (154) and Head (80) on man in 1893. Herpes zoster, at the time, was thought to result from disease of the posterior root system (4); and both Mackenzie and Head were thus separately led to the idea that the cutaneous eruptions in this affection might accurately disclose the distribution of the posterior roots to the skin, and especially to the skin of the limbs, in man. This idea found encouragement in the seeming correspondence between the zoster areas and those of the cutaneous hyperalgesias of visceral disease to which Mackenzie had recently drawn attention (152, 153); the maps provided by a large number of cases of herpes zoster were examined. Their work was in general agreement, but Head (80, 81), whose work was the more complete, soon constructed composite diagrams of almost the whole trunk of the body (see Fig. 3). The border of certain of these areas was identified with the borders of sensory loss arising out of cord lesions at known levels; with these and simple anatomical guides it was possible to number off the remaining areas of his diagrams. This method of ascertaining the human dermatomes was indirect and precarious; nevertheless, Head's areas have proved, in the light of later observations, to possess an accuracy hardly to have been expected from the methods used. They departed in a notable respect from the plan of segmental areas determined by Sherrington. They were contiguous and not overlapping, a fact noted by Head and never satisfactorily explained. Head thought

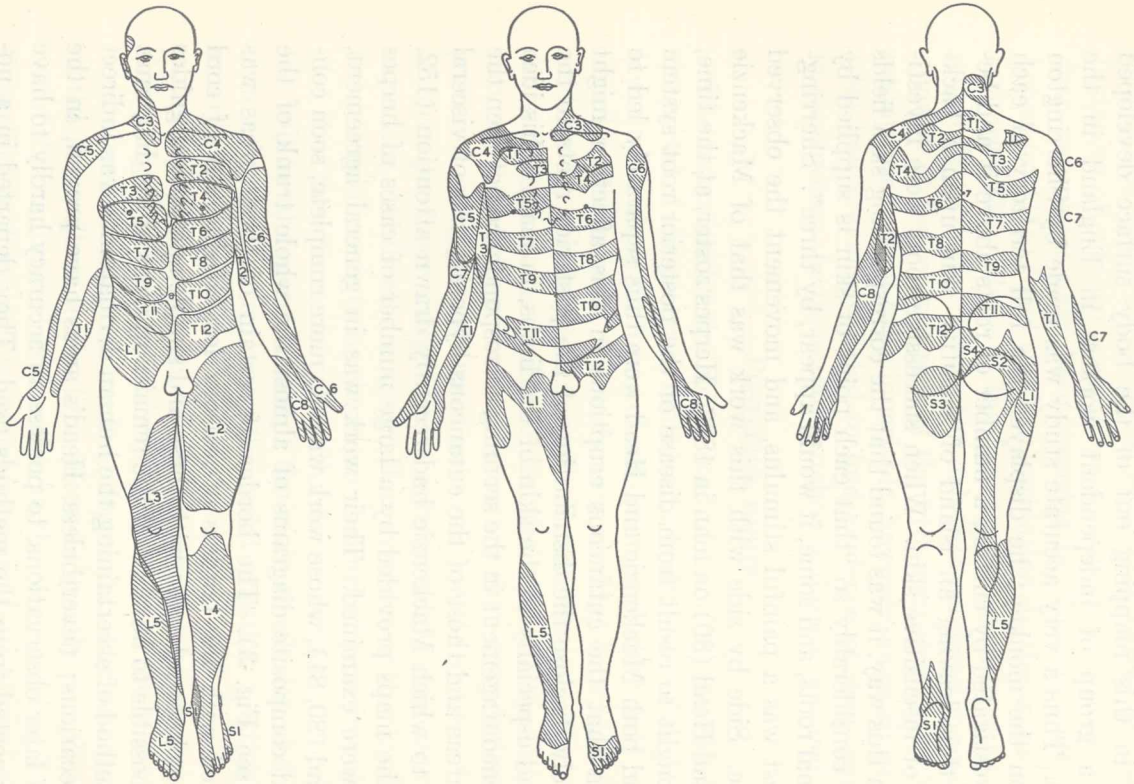

Fig. 3. The two figures to the right represent Head's cutaneous areas, as displayed in his original papers (80, 81). Small areas of *C*5 and *C*6, coinciding with *T*1 and *T*3 on the back, have been omitted. The left-hand figure has been constructed from Foerster's data (49) and represents his "dermatomes".

his areas represented segments of the cord rather than of the roots arising from them. Foerster (49) in this connection has lately expressed the idea that herpes areas are naturally smaller than the true dermatomes. But it is also to be said that the herpetic eruption may pass beyond the boundaries of Head's areas, a fact pointed out by Mackenzie at the time of their publication. Knowledge of the cutaneous segmental areas, or dermatomes, more reliable in its detail, has been obtained from the observations of Foerster. He used Sherrington's method of remaining sensibility and cut series of posterior roots in the therapeutic treatment of pain. Foerster's observations have been sufficiently extensive to allow him to map out the dermatomes of large surfaces of the human body, including the limbs, with accuracy. Thus explored, the territories corresponding to adjacent nerve roots are found to overlap extensively; so great is the overlap that section of a single root gives little or no sensory change in the skin; one dermatome sometimes overlaps not only the adjacent dermatome but also the dermatome beyond it.

The dermatome may also be identified by stimulating the peripheral end of the corresponding root and by watching the effect upon the skin, for such stimulation causes vasodilatation of the corresponding skin territory by so-called antidromic action. Foerster (48, 49) has confirmed many of the dermatomes, outlined by posterior root section, by this method; but he states that, like herpes areas, the territories so determined are less extensive than those outlined by the method of remaining sensibility.

I have compiled diagrams, as complete as they can be made, from Foerster's data; they are shown side by side with those of Head in Figure 3.[3] They differ from the latter in displaying overlap and in other particulars. Though the most accurate maps we possess, they are still to be regarded as approximations and as taking little account of variation such as is known to occur from subject to subject. They may be regarded as representing pain dermatomes with an accuracy approximating to that of touch dermatomes. Although, according to Foerster, the line of touch loss lies within that of pain loss at the boundary of

[3] Foerster's data for the back are not included; they are much less complete because of interference of the laminectomy wounds.

a denervated area, which would indicate a greater overlap of touch as compared with pain dermatomes, yet the divergence between the two lines is usually insignificant in his own diagrams.

Anterior Roots

The law formulated by Bell and Magendie long remained substantially unchallenged. But in recent times the idea has been expressed that pain impulses may be conveyed by afferent fibres through the anterior roots. That a reaction suggesting pain may appear in animals when anterior roots are stimulated has long been known and has been ascribed to occasional recurrent fibres from the posterior roots. Such fibres form no exception to the law. Schäfer (203) described some cells in the ventral roots of cats, chiefly in the dorsolumbar region; the cells closely resembled those of the dorsal root ganglion. He sought them in vain in dog and man. Piolti (185), however, found them in man in the lumbar region, and this has been confirmed (247). Nothing definite seems to be known about the axons of these cells—errant cells perhaps.

The doubts about the purely efferent functions of the anterior roots are derived from disappointment with dorsal root section as a remedy for persistent pain. On this basis, Kidd (104) seems to have been the first to insist that pain fibres must enter the cord by anterior roots also. Undoubtedly, division of the posterior roots frequently fails. It may fail to relieve pain in the arm when the resection covers the whole, or covers almost the whole, of the roots ordinarily regarded as incorporated in the brachial plexus; it may fail although the skin of the whole limb is rendered insensitive. However, such evidence clearly has no great value unless the pain is known to arise from the limb, and this is frequently unproved in the reported cases; for it is always possible that the pain has arisen in the central nervous system and not in the nerves' territories distal to their point of resection. Failure to relieve the pains of tabes (Groves, 73) is very possibly due to origin of the pain in the cord. If root section stops pain that was persistent and this pain recurs in a matter of weeks or months, the operation is rightly regarded as failing therapeutically; but the recurrence of pain in such cases cannot be used as

evidence that the original pain tract has escaped section. When a sensory nerve is divided, pain frequently starts up subsequently from the cut end; such recurrence is notorious where nerve section is used in an attempt to cure pain arising from neuromata formed on the ends of nerves in amputation stumps. Pain, indeed, is not infrequent and may be severe immediately on recovery from operations in which roots are divided; it must then often be ascribed to irritation of these roots. Such pain may persist or may pass away with healing. Another reason why pain may remain unrelieved is that, although the surgeon sets out to cut a series of roots, filaments of these roots are apt to escape the section. It is quite clear from the case records that this very easily happens (see 233): thus, Groves (73) relates a case in which filaments in each of five roots escaped, being found undivided at a second operation, and Meyer (162) relates how a whole root escaped division. Cases in which, after extensive root sections have been attempted, loss of sensibility is incomplete or the area of loss is much smaller than expected are particularly to be suspected from this point of view. And in this same connection it should never be forgotten while reading the case reports that the boundaries of dermatomes are never contiguous; they always overlap conspicuously, and it is very probable that in given cases the overlap is unusually extensive. Thus it will be seen that the argument, which relies on failure to relieve pain, is from many points of view a precarious one. It is an argument based upon a process of exclusion; the pain is not stopped by what is regarded as adequate posterior root section, and therefore it is assumed to pass by anterior roots.

Another kind of evidence is that brought by Lehmann (116, 118), who, after rendering the skin of the arm quite insensitive over large areas by posterior root section, finds these same areas sensitive to deep stimulation. Such evidence led him to believe that while superficial pain is carried by posterior roots, all deep pain is carried by anterior roots. His own two cases are unconvincing; although the roots dealt with covered or almost covered the brachial plexus, normal sensation persisted in parts of the arm as low as the hand, and overlap of areas of superficial and deep sensation (see p. 17) would account for what he found. Lehmann's hypothesis that *all* deep sensation is carried by an-

terior roots is indeed negatived by many instances (38; 162; 213; 233, cases 5 and 7) in which posterior root sections have undoubtedly rendered limbs completely devoid of deep, as well as devoid of superficial, sensation. These positive results have greater value than negative ones, in which the possibility of missed filaments or overlap in partial denervations is ever present. Foerster (48), who also bases his view on root sections in man and instances cases in which some deep pain is preserved, goes no farther than to suppose that the anterior roots are subsidiary channels for the conduction of pain. This is more consistent, than is Lehmann's view, with the usual finding, that, if—after extensive posterior root section—any deep pain is left, it is elicited only by very strong stimulation (233).

The evidence from man is nowhere inconsistent with the still generally accepted view that the posterior roots alone convey pain. More than subsidiary pain channels in anterior roots there cannot be. No evidence exists that simple section of anterior roots interferes with normal sensation or that, when posterior root section has failed to relieve pain, an added anterior root section brings success. Foerster's observation (48) that he has induced pain on stimulating the anterior root of *D*8 after cutting posterior roots *D*6 to *D*10 requires confirmation.

The controversy surrounding clinical work led to renewed animal experimentation, which presents the advantage that the source of pain impulses can be arranged. Lehmann (116 to 118) and Shaw (208) recorded experiments, the former to show that visceral pain, and the latter to show that deep somatic pain, passes by the anterior, and not by the posterior, roots. Meyer (161, 162), however, convinced himself that, if subsequent investigation showed all posterior roots divided, the limb was always rendered quite insensitive to stimulation and that, when any sensation remained, an uncut root could always be found. He quite rightly insists that no observation, human or animal, is acceptable when pain sense is not abolished, unless subsequent examination proves the appropriate roots to have been completely divided. Davis and Pollock's results (38) on the limb agree with those of Meyer; and Fröhlich and Meyer (58) disagree with Lehmann's conclusions upon visceral pain.

The evidence for the orthodox conclusion seems the more con-

vincing whether we consider the evidence from man or animals.

Visceral pain paths.—Of nerves supplying viscera, a few have been tested in conscious human subjects. Thus Jonnesco and Ionescu (94, 95) found that the cardiac nerves and the inferior cervical ganglion are painful to stimulation. Although the sympathetic chain above this level receives no white ramus and is generally regarded as possessing no afferent fibres, Leriche (125) states that he and Fontaine have elicited pain in the jaw and behind the ear by stimulating the superior cervical ganglion[4] and, from the chain lower down, pain in the shoulder. Davis and Pollock (38) saw evidence of pain on stimulating the superior ganglion in the cat; they found it necessary to cut posterior roots and sensory root of the fifth cranial nerve to prevent the reaction. They state the precautions taken to prevent escape of current and believe the pain to have arisen indirectly through efferent sympathetic fibres producing a change in skin adequate to stimulate sensory nerves. The depressor and vagus nerves carry no pain fibres; stimulation of the central end of the latter produces nausea in man (48, 95). The splanchnic nerve gives severe pain when cut (124) or when its central end is faradised (48). The presacral branches of the hypogastric plexus are also known to give pain when stimulated by tension (Learmonth, 115). The reactions of animals indicate the presence of pain fibres in the splanchnic and many other visceral nerves.

The effects of nerve section are in agreement with those just stated. It is now generally agreed that anginal pain passes through sympathetic paths. Removal of the left inferior cervical (stellate) ganglion (see Leriche and Fontaine, 126) or of the whole sympathetic chain down to this ganglion (Jonnesco and Ionescu, 95) may relieve or abolish left-sided anginal pain. This operation, however, though sometimes successful, sometimes fails; all the paths evidently do not pass through this ganglion. Kuntz and Morehouse (110) have shown that in man there are nerves joining the second, third, and fourth sympathetic ganglia to the cardiac plexuses and that these nerves contain medullated (presumably sensory) fibres. The presence of these nerves

[4] The statements of Frazier (52) about this ganglion appear to be out of harmony with each other, and I refrain from using them.

is probably responsible for persistence of anginal pain after removal of the inferior cervical ganglion, according to White (240), who succeeds in abolishing pain on the side of operation by extending the sympathectomy below the level of the fourth ganglion.[5] Corresponding evidence of sympathetic pain paths from the heart in animals is given on page 140. Visceral pain has been treated successfully by division of the splanchnic nerves (Craig, 30; Smithwick, 215). Dr. J. C. White has recently and very kindly sent me details, as yet unpublished, of a number of very clear instances of visceral pain relieved by splanchnic nerve division. Bentley and Smithwick (8) have found that the bilateral pain ordinarily provoked by distending a balloon in the upper part of the jejunum cannot be provoked on the side on which the splanchnic nerve and sympathetic chain have been excised previously. Visceral pain is also relieved by anaesthetising these nerves (98, 109). Gaza (63) and Scrimger (206) have both been able to relieve abdominal pain by cutting appropriate rami communicantes. Foerster (51), Groves and others (74), and Davis (36) have relieved the gastric crises of tabes by cutting posterior roots, and Bogaert and Verbrugge (13) by resecting these and the corresponding rami. These results, however, lack uniformity; the crises may be cured by section of as few as three roots, while in other cases much more extensive root section fails. Failure to relieve, which is explicable without invoking anterior roots, is of far less importance to the argument than is success, which can be explained only by the breaking of a pain path in the posterior roots. All pain of abdominal visceral origin is lost, according to Foerster, when the spinal cord is broken at the level of *D*6.

Thus, in man, there is evidence both from stimulation and from division that pain impulses from the viscera are conveyed by afferent nerves bound up with the sympathetic nerve trunks, through white rami communicantes, to posterior roots. This accords with the pathway recognised by physiologists as that for afferent visceral impulses in general.

Langley (111, 112) recognised the posterior root ganglia as the cell stations of afferent visceral nerve fibres because he could

[5] It is also stated that in some cases the pain is relieved or abolished by excision of superior, or superior and middle, cervical ganglia (28, 127); but these observations are less convincing.

find no evidence by degeneration experiments of afferent cell stations in the ganglia of the abdomen or sympathetic chains and because section of the posterior root beyond the ganglion causes practically all medullated fibres in the white ramus to degenerate. Curiously enough, however, there seems to be little available record that medullated fibres of the posterior root system are traced by degeneration to the viscera after extirpation of the posterior root ganglia. It is curious that there seems to be little available record of medullated fibres of the posterior root system being traced by degeneration to the viscera after extirpation of the posterior root ganglia. This anatomical evidence would be useful.

Physiological evidence that afferent impulses from the viscera pass in animals by the posterior roots is scattered in many papers. The discordant results of Lehmann, who believes visceral pain to pass through the anterior roots, have been mentioned earlier, as have those of Fröhlich and Meyer, who believe all pass through the posterior roots. The observations of Miller and Simpson (163), who used muscular reflexes as their guide, and of McSwiney and Suffolk (156), who used dilatation of the pupil, agree as to posterior root paths (see also 37, 168).

Periarterial pain paths.—In recent years it has been suggested that pain impulses from the limbs may be carried substantial distances by nerves constituting periarterial plexuses. Foerster (48, 50) relates a case in which, after posterior roots *C*7, *C*8, and *D*1 had been cut, pain sense was completely lost in the third to the fifth fingers, but deep pain sense remained; he tells how he exposed a digital nerve in the fifth finger and found it insensitive to stimulation, though stimulation of the neighbouring artery gave severe pain. He is inclined to believe the arterial pain to be conveyed by channels travelling along the whole length of the arteries of the limb rather than to interpret the phenomenon as a relatively short and local overlap between superficial and deep pain territories; but he recognised his evidence to be inconclusive. In other instances he suggests that nerve fibres concerned with pain may leave the arteries for the sympathetic trunks rather than for the segmental spinal nerves.

The idea that accessory pain paths follow the arteries for long distances has arisen largely out of attempts to explain the thera-

peutic effects of arterial decortication. There seems no doubt that stripping the adventitia off the artery of a limb is sometimes followed by relief of intractable pain, but the manner of relief is uncertain. Leriche (125) has cited many examples. Friedrich (57) relates how without success the main nerves of an arm were divided to relieve pain in an amputation stump but how the pain disappeared after arterial decortication. Dennig (40), who is critical, rightly points out that the pain did not disappear at once, as it should have done if remaining pain nerve paths had been divided. Experiments on animals (57, 87), purporting to provide evidence of lengthy, afferent, sensory channels on the walls of arteries are unconvincing. Arterial decortication leaves no obvious sensory change behind it (181, 233). It is certain, therefore, that in the limbs pain paths on the arteries are short or, if longer paths indeed exist, quite subsidiary. It is certain that deep pain from the limbs, including such pain from arteries of the limbs, is chiefly conveyed by the main nerves of the limbs and that the final portal is the posterior root (see also 168). Even if some nerve fibres concerned with pain pass directly from arterial wall to sympathetic nerve trunk at the base of the limb, these are not to be regarded as sympathetic fibres. Thomas (224) refers to the nerves as sympathetic perivascular fibres; and Zotterman (253) also seems on the point of accepting the view that deep pain (dull pain) is an affair of afferent sympathetic fibres. There is no justification for the idea that fibres of the physiological sympathetic system convey pain (see page 140). Personal observation upon cases in which the sympathetic paths to an arm have been destroyed by sympathetic ganglionectomy have shown that pain provoked by methods described earlier in this book from web, root of nail, fascia, muscle, and periosteum are similar in quality and in intensity when elicited in the normal and denervated limb. Similarly, the pain responses of the skin are unreduced; indeed, they have been described as increased (50).

Spinal Cord

The posterior root enters the cord as a number of rootlets in the line of the posterolateral sulcus; and these, in entering, break into medial and lateral filaments. In degeneration following sec-

tion of the posterior root, the main column of large myelinated fibres is traced over the top of the posterior horn into the posterior funiculus, in which the fibres form the ascending paths for vibration, position sense, touch, and so forth. The fibres of the lateral filaments are small, myelinated or unmyelinated; and they pass into Lissauer's tract where, after ascending only a short distance, they enter and end in the grey matter of posterior horn (190). These fibres are believed to include the pain-conveying fibres, for in animals a cut that breaks them where they enter Lissauer's tract but leaves the main column of root fibres intact abolishes the evidences of pain previously elicited by stimulating the whole root distal to the cut. Cutting off the main or medial part of the root has not this effect (Ranson and Billingsley, 191).

Long ago, Schiff (204) found, after section of the cervical cord in rabbits (the posterior tracts being left intact), that the animals responded unusually to simple contacts but were quite indifferent to pain-giving stimuli such as cuts or crushes. Injury of the posterior tracts in man leaves pain and temperature sense unaffected. Observations of this kind show that the root fibres mediating pain and temperature sense do not pass with those of the posterior tracts; they have separated off as have the unmyelinated afferent fibres by the time the cord is reached. Out of these facts arises the presumption that the first stage of the pain tract ends where the small myelinated or unmyelinated fibres end—in the substantia gelatinosa of the posterior horn. New neurones arising in the horn cross the midline (Fig. 4). The crossing of pain and temperature sense is evidenced by clinical experience, which shows that unilateral lesions of the cord, while evoking motor paralysis on the same side of the body, affect pain and temperature sense on the opposite side (Brown-Séquard paralysis). The ascending pain path is now identified in the spinothalamic tract. This tract arises from cells in the posterior horn and crosses through the anterior commissure to ascend as an unbroken path to the lateral nucleus of the optic thalamus. As early as 1850 and 1860, Brown-Séquard (17) was urging that sensory impulses cross to the opposite side of the cord, on the basis both of animal experiment and clinical observation; but he did not identify the observation with pain especially. In 1886,

Gowers (71), largely on the basis of a patient reported by him some years earlier (70), suggested this path as the pain tract. But the crossing of pain was still unaccepted by physiologists until early in the present century. Spiller and Martin in 1912 were the first to record deliberate and successful division of the tract for the relief of human pain (217). This operation, incising the anterolateral part of the cord, is now often carried out, and there remains no doubt that it succeeds in dividing the pain paths. It produces complete analgesia of the opposite side. Woodworth and Sherrington's experiments on cats (248) seemed to show the nociceptive impulses to pass from one side by both tracts but somewhat preponderantly by those of the crossed tract.

If further evidence, that pain impulses are conveyed antero-

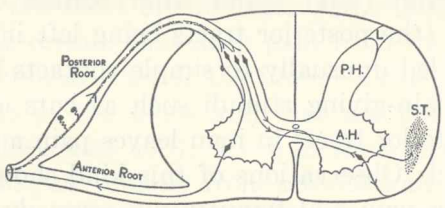

Fig. 4. Diagrammatic representation of a cord section, to show the pain paths. *A.H.* and *P.H.*, anterior and posterior horn. *S.T.*, spinothalamic tract.

laterally in the cord, were required, it would be found in the repeated observation that stimulation of this region by prick, cut, or even by touching it with a probe gives in man severe pain in the opposite leg (48).

Section of the anterolateral tract in man abolishes pain sense completely from skin and deep somatic tissues, below its level on the opposite side of the body, while touch and vibration sense are preserved. Temperature sense is also usually abolished; there is no doubt that the corresponding fibres lie within the same tract probably as a segregated group to the dorsal side of the pain fibres. Anterolateral tract section, if bilateral, prevents visceral pain also (48, 216; see 37, however, for conflicting evidence).

That the crossing of the pain tract takes place quickly after entering the cord is generally agreed. Foerster relates cases of

anterolateral incision which, at the upper border of a cord segment, gave complete analgesia to the lower border of the dermatome corresponding to the next lower segment. All, however, are not agreed with him that the crossing takes place within the segment of entry.

The fibres of the dorsal root that enter Lissauer's tract send collateral branches up and down the cord; these all shortly end in the grey substance. Such collaterals must sometimes connect, through direct synapses or through secondary neurones, with motor nuclei of the anterior horns, thus forming short channels by which appropriate muscles respond reflexly to injurious cutaneous stimuli.

In view of the usual complete analgesia of skin and deeper lying tissues from the level of the lesion downwards when the region of the anterolateral tract is cut, it seems improbable that pain paths exist in any other region of the cord. Foerster (48) states, however, that, though paraesthesiae are the rule, clear pain sometimes follows when Goll's column is touched in the cervical region.

Brain

It has been said that the spinothalamic tract proceeds without break to the lateral nucleus of the optic thalamus. Here all its fibres end. Cushing (31) could elicit no pain by faradising the cortex in the region of the Rolandic fissure in conscious men, the brain having been exposed under local anaesthesia. But Foerster (48), in more extensive observations of the same kind, reports paraesthesiae amounting to actual pain as obtainable from faradisation of the postcentral and superior parietal gyri. For this reason and because he has observed long continued disturbance of pain sense following surgical excisions of the retrocentral region, he believes that pain has some cortical representation. Penfield and Boldrey's electrical explorations (180) of the human cortex, however, yielded pain responses in little more than one per cent of stimulation and, they believe, indicate that pain has little or no true cortical representation.

There is wide agreement that the optic thalamus is closely concerned with the reception of pain impulses of all kinds. This belief follows the general experience that pure and unprogres-

sive cortical lesions are painless, while lesions of the thalamus characteristically produce profound disturbances of the pain sense, including hyperalgesia, spontaneous pain, and painful overreaction to slight stimuli. Head and Holmes (84) believe the thalamus to be the essential organ for the appreciation of pain. The cerebral cortex, in their view, controls and checks the activity of the essential centre; and the excessive response to affective stimuli, so prominent in thalamic lesions, is not regarded as due to irritation but rather to removal of cortical control through interruption of fibres uniting the lateral nucleus and the cortex. The question whether the thalamus suffices or whether the cortex must be regarded as playing an indispensable part in registering pain is to be regarded as still unsettled. The argument turns very largely upon the phenomena of cortical damage and upon their assessment in cases in which spread of the actual damage, or of irritation arising out of such damage, may be suspected to have occurred.

Chapter III

SENSORY SYSTEMS: TYPES OF PAIN

Specific Sensibilities

General theories concerning cutaneous and deep sensations are relevant to this book in so far as they place pain in perspective with other forms of sensibility. Therefore they will be dealt with briefly.

At first, pain tended to be regarded as the inevitable climax of other sensations, such as touch and warmth, since rougher contact or increased heat soon converted pleasant into unpleasant responses. Ideas began to sharpen and real interest to be aroused when Blix (11) and, a little later, Goldscheider (65) discovered that the perception of warmth and of cold by the skin are attributes not uniformly displayed by the skin but concentrated in, or confined to, tiny areas of it. In discovering this punctate distribution, Blix discovered the separate distribution of warm and cold spots. Frey (53) extended the view of Blix to touch and to pain and concluded that sensation possessed by the skin is due in each of its forms to the existence of small areas of specific sensibility. Frey went farther and attempted to correlate the different sensibilities with specific forms of nerve endings in the skin. Reference has been made in an earlier chapter to the fact and to the more notable attempts to strengthen these correlations in quite recent times. Although, as has been indicated, the attempts may not perhaps have reached a full measure of success, and although the denseness of so-called pain spots is such as inevitably to raise the supposition that pain comes from stimulating any part of an intimate plexus of nerve fibres in the skin rather than specific endings of the nerve fibres; yet the separateness of touch, warm, cold, and pain senses grew to be a clearer and sharper conception. The degree of separate-

ness has come to be regarded as of the order of that postulated by Johannes Müller in his doctrine of "specific nerve energies". Under this doctrine each modality of sensation (sight, hearing, etc.) is normally dependent upon the stimulation of a specific and appropriate form of nerve ending and is conveyed from these by corresponding nerves. The generally accepted idea today is distinctly modelled along these lines, and it regards the sensory nerve channels joining periphery to brain as all simple conductors conveying impulses of similar, or of common, pattern. Nerve fibres are of interest at their endings rather than in their length. Under natural conditions, the peripheral apparatuses are to be regarded as responding selectively to the appropriate forms of extraneous disturbances; the eye to light, the ear to sound, the touch corpuscle to touch, and so forth. The end organ selects the stimulus; the nerve fibre merely conducts the impulse to a central and specific destination; this destination is predetermined by the anatomy of the path or paths; the sensation arising in consciousness is predetermined by the specific destination. It is implicit in this induction that the process once started in a peripheral element can arouse only a given character of sensory response. And the conclusion is probably warranted that any sensation which arises in consciousness out of peripheral stimulation and which is recognised to be in its character clearly distinct—as light is clearly distinct in character from sound, and cold from touch—is, in fact, fundamentally a distinct form of sensation.

But, although the peripheral mechanism is often peculiarly adapted by the inclusion of specific end organs to the reception of the appropriate stimulus, this mechanism is capable of being activated in other ways. Possibly the end organ is not thus capable, but undoubtedly the end mechanism, which includes end organ and connecting nerve, is. Thus, it is known that cold spots can be stimulated to give a sense of cold by heat (53, 198), and touch spots to give a sense of touch by electrical stimulation (53); stimulation of the eye, mechanically or electrically, produces flashes of light. Thus, to have effect, the stimulus is not necessarily appropriate. In the case of pain, the stimulus is of extremely varied kind; but there is a common factor of injury (see p. 105).

That touch, warm, cold, and pain systems of sensation are separate entities is established first by minute exploration of the periphery; by the discovery in skin of independent small areas particularly apt to awaken the sense of touch, cold, warmth, pain; and by the finding over general surfaces, such as the cornea and the mucous membranes of the nose and glans penis, of dissociation in the sense that all forms of sensibility are not represented. Next we find evidence in examining the nerve tracts that unite skin to brain. When normal cutaneous nerves are directly stimulated, pain is the response that predominates to the usual exclusion of other forms of sensation. It has been noticed by Trotter and Davies (232), however, that during regeneration separate sensations both of touch and of cold can be awakened by stimulating the cutaneous nerve trunk. In recent times, evidence has rapidly been accumulating to show that sensory dissociation can be accomplished by influencing the cutaneous nerve trunk. Perhaps the most striking and certainly the simplest to confirm is to asphyxiate the nerve by robbing it of its blood supply for a short stretch of its course through the arm, an interference leading to complete loss of touch sense in the hand while sense of warmth, cold, and pain persist (Lewis, Pickering, and Rothschild, 146). There is, too, the much earlier demonstration of loss of pain sense while touch persists under cocaine anaesthesia (75). The order in which sensation is lost when the nerve is treated by asphyxia (146, 148), by cocaine (60, 75), or by cooling (9), may be stated broadly in tabular form.

TABLE 1

ORDER OF SENSATION LOST UNDER TREATMENT OF NERVE

Asphyxia	*Cocaine*	*Cooling*
touch	cold	cold
cold	warm	touch
warm	pain	pain
pain	touch	warm

Note. Where the different sensibilities are bracketed, statements of the order of loss are not in full agreement; differences of statement are partly due to very gradual disappearance of certain sensibilities.

Finally, certain well-known dissociations between cutaneous sensations occur in diseases of the sensory nervous system—such as tabes dorsalis, syringomyelia, and, most notably, local lesions

of the spinal cord (see p. 29)—in which sense of pain is lost alone or in which loss of pain and temperature sense occur together while touch is unaffected.

The evidence of separate representation for the sense of touch, cold, warmth, and pain in the skin, in nerve, and in central nervous system should be surveyed as a whole, for they build up a consistent and formidable case for the separateness of these different sensibilities.

Pain Systems

Qualities of pain.—Studies of pain are necessarily subjective, and our descriptions of what we feel can only attain to reasonable degrees of accuracy if the closest attention is given by the subject and comparisons are most carefully planned. A subject can present a clear description of a pain's relative severity by comparing it with other pains of similar kind and location; especially so if pains of different severity can be elicited within a short period of intervening time. The duration of pain may be recorded often with great accuracy. The two, intensity and time, may be combined to give graphic expression of the events in a time-intensity curve (see p. 176). Often the region in which pain arises may be located with precision. There is no direction in which description of pain is less definite and accuracy more difficult to achieve than when the attempt is made to convey an idea of the pain's quality or tone. A direct description is no more possible than it is in the case of sense of colour; here we use the device of exemplification or association, as when we talk of "blood red" or "orange". The frequent descriptions and comparisons of everyday life enable us to attain a high degree of accuracy in conveying by this method the idea of particular colours or tints. In describing the kind or quality of pain, we are likewise restricted to exemplification; but, in this connection, experience is infrequent and limited, unless deliberately sought, and the art of description is unpractised and unchecked. Experience may be supplied and practice obtained in the recognition of pains of different qualities and the naming of them. Common parlance has acquired a few striking terms, as when we speak of pain as "burning" or as "pricking" and quite distinctly mean to associate such pains with those provoked by burns or pricks of the skin. Here

are two instances of descriptions by exemplification achieving unusual accuracy. But many terms in use and of like origin, such as tearing, boring, cutting, stabbing, and crushing, convey between two persons no exact ideas because of the comparative infrequency of corresponding physical damages. Thus the common device of describing pain in terms linking it with various forms of injury has little scientific and, apart from a very few examples, little practical value. This method of description has been almost sterile because, as already indicated, experience of the relevant kinds of injury is uncommon and thus the terms cannot recall the appropriate sensations. It is clear that a constant type of pain is not produced by an act of crushing or of tearing, and it is known that one kind of pain can follow both a crush and a burn (Lewis, 137).

To render descriptions clearer and to focus research, it is necessary that power to recognise types of pain should be increased; it is necessary that those who seek such knowledge should have at their disposal simple tests that will elicit the chief types of pain, so that pains so elicited may form a basis of description and so that pains provoked from this structure or that, or by this means or that, may be compared. I shall begin by describing in this chapter observations upon the chief somatic structures of the body.

Skin.—When pain is derived from skin, its localisation is very accurate (see p. 118); it varies in intensity and in its duration, it may change from moment to moment, but it does not vary in quality or tone. Though this idea had been expressed by previous workers (3, 7) and is summed up in the term "bright" pain, it was not apparent when I first became interested in the matter (131, 139) that it had been at all generally acknowledged. It seemed that it would be of so much importance if true, that it deserved to be brought, if possible, to the point of demonstration. Pain can be provoked by injuring the skin in a large number of different ways, as by pricking with a sharp point, by pinching tiny folds of skin, by pulling on hairs, by burning, by the passage of electrical current, and by the application of irritant poisons. The quality of pain evoked in these several ways from skin can, in fact, be demonstrated to be unvarying in that, when the tests are properly applied, the subject is unable to decide the manner in which pain is produced.

A constantan wire 5 cm. in length and 0.25 mm. in thickness is bent at an acute angle and heated by passing through it a current of 0.8 to 1 amp. The acute angle of the heated wire is brought into quite transient contact with the skin; alternatively, the skin is pricked with a fine needle. A blindfolded subject cannot detect which of these two forms of stimulation is employed. Similarly, a quick tug upon a single hair or the make-and-break shock of a galvanic current may be used. All these will be described without distinction as pricking pain. Naturally, it is necessary that the subject should not be allowed to receive associated sensory (but unpainful) stimuli that are peculiar to the form of stimulation. Thus, if the contact of the hot wire is maintained unduly, its warmth may be felt in addition to pain, and the form of stimulation will then be detected at once. When a hair is to be pulled, it should first be isolated so that it may be grasped and pulled without the warning which simple contact with this or neighbouring hairs will give; and counterpressure should be exerted around its base so that, when the hair is pulled, the skin is not lifted. Similar counterpressure should be exerted when needle prick, hot-wire contact, or galvanic shock is compared with this form of stimulation. The greater the precaution taken to eliminate supplementary sensory stimuli or to reduce these to uniformity in comparing different forms of painful stimuli, the more successful will be the tests. The subject tested is soon aware that it is impossible to distinguish the different pain stimuli and that, where the form of stimulus is recognised, the recognition depends upon a non-painful accompanying sensation. The stimuli just discussed are all brief ones, and their effects are all called "pricking".

A prolonged stimulus gives rise to pain described as "burning"; and this is always so, whether the pain arises from heat or not. The bent wire is carried just through a small cork and thus applied to the skin, and enough current is now led through the wire to heat it appropriately. A needle point is sunk in a similar cork and from it a galvanic current of appropriate strength is turned into the skin. An isolated hair is pulled and held tense through a small slit in a cork held around it and in contact with the skin. Or a tiny fold of skin is caught up in sharp-edged forceps and pinched in similar circumstances. The subject cannot differen-

tiate between the four methods used. All these forms of stimulus give rise to pain that is described without distinction as "burning" pain. It is recognised as such, not simply from its peculiar quality, but because it is a cutaneous pain *that continues;* it is called "burning" from association. The hot stimulus applied briefly causes what is termed "pricking" pain; prolong the same stimulus and it is called "burning". The initial pull on a hair causes a "pricking" pain; but, if the hair is held tense, the pain, though quite unchanged, is now called "burning". The difference between "pricking" and "burning" pain is not one of quality or tone, it is purely one of duration.

So far, pain arising from, and ending with, brief or short stimulation of the skin has been discussed; but pain may also continue as an after-effect of injury. The most widely recognised pain of this kind is that continuing long after contact with an object hot enough to injure the skin visibly. Pain quite indistinguishable from this arises out of injuries resulting from continued friction, abrasions, crushes, freezing, ultraviolet light, and irritant substances. And here it is important to note that it is identical in quality with, though it is usually less in intensity than, the pain previously discussed—namely, that which occurs during the actual period of stimulation. A series of minute scratches, closely set, gives rise after an interval of time to a very definite continuous pain; it has precisely the same qualities as the pain that follows a burn or which occurs after mustard oil or chloroform has been held on the skin. Comparison should be made of two forms of stimulation applied symmetrically and simultaneously to two arms; the result is then convincing in the sense indicated. This and similar observations established the fact that pain of only one *quality* can be provoked from skin. When we speak of "smarting", "burning", or "stinging", we are using terms that lack precise distinction. Some think it convenient to say that smarting is less intense than burning; others describe smarting and stinging as pain that begins with relative suddenness or does not continue long at full intensity. In the last instance, the pain produced by the stings of insects or of plants clearly guides the definition. But the terms are in fact undefined and in ordinary parlance largely interchangeable; what is of chief consequence is to note that, when closely com-

pared, pain answering to these three descriptions cannot be differentiated in respect to quality. On experiencing and considering pain derived from the superficial layers of the skin in response to various stimuli, I am brought more and more firmly to believe that all such pains have but a single quality, and that the variable characteristics of such pains are merely in their intensity and in their distribution in time and space.

The quality is the same if the pain is produced by stimulating nerve endings or nerve fibers. While anaesthetising by hypodermic injection a small cutaneous nerve previously and accurately located, it is not very unusual for the needle point to touch the nerve; a pricking or burning pain is then felt in the area of the nerve's distribution, and in quality it is indistinguishable from that produced by injury of the skin itself.

Muscle.—The second example of pain to be considered is that derived from muscle. Experiments in which pain is deliberately provoked from skin are easy to devise and to control. Deeper lying structures such as muscle require different and appropriate tests. A needle may be passed through muscle, or muscle may be incised, almost if not quite painlessly. If the circulation to a limb is stopped and a group of muscles is exercised voluntarily or if a single muscle is forced to contract by direct electrical stimulation, pain is produced after a time in the limb. This pain, as Pickering, Rothschild, and I proved (145), is derived from the muscle, and we put forward abundant evidence to show that it is due to a chemical or physicochemical pain factor arising out of muscular metabolism (see Chap. VIII). This pain is disagreeable, it is rather diffuse and difficult to locate, it is continuous, and it is thought by most to waver a little in its intensity. Its quality is indescribable. But the pain is distinctive in the sense that it is impossible to confuse pain from skin and pain from muscle when once you know the two.

When convinced that pain derived from skin has a constant quality or tone, I turned to muscle and, in personal experiences, tested this to see if pain originating from it possessed similar constancy (137). I first used isotonic acid solution (phosphoric acid and disodium hydrogen phosphate mixture of *p*H 5.0 to 6.5), injecting 0.3 c.c. through a fine needle into a dorsal muscle of the forearm and comparing the resulting pain with that produced

simultaneously in the symmetrical muscle by working this under ischaemic conditions. The two pains were indistinguishable. I subsequently used hypertonic solutions (5 per cent sodium chloride), injecting a similar quantity of this or, alternatively, of 0.5 per cent potassium chloride with enough sodium chloride to render the solution isotonic; these injections also gave identical pain. Pain can be provoked mechanically by squeezing muscle firmly between finger and thumb. It can easily be elicited by light pressure over muscle that has been much used the day before; similar pressure exerted upon the more superficial tissues is without similar effect. Pain induced from muscle by this means was again found to be indistinguishable from that provoked by the same muscle worked under ischaemic conditions. As an experimental method of producing muscle pain, the injection of a minute quantity of a salt solution is the most satisfactory; it is very simple and harmless, the stimulus is confined to a small mass of muscle, and it is invariably effective. We have seen in the case of skin that pain, though it is of one kind, may be provoked for an instant or for indefinitely long periods. I have not succeeded in provoking very brief pain from muscle; once it appears in the field of consciousness, it seems always to last for at least a few seconds.

We have in this instance of muscle a second example of tissue from which pain of only one kind can be provoked. In making these observations, I was impressed by the way in which pain provoked from muscle is often referred to a distance, and they led to the researches from this standpoint described in Chapter X.

Web, tendon, periosteum, joint.—Thunberg (228) distinguished a form of pain, which he called "dull" pain and which was probably derived from subcutaneous tissues. As he pointed out, pain of this quality is readily produced by tightly squeezing the short web of skin between two adjacent fingers. It is a very unpleasant rather diffuse pain, lasting as long as the squeeze; it gives the impression of being less superficial than skin pain.

The quality of two pains is not always quite easy to compare if they are derived from unsymmetrical structures. Despite this fact, I believe that pain derived from squeezing the web and from squeezing tendons, such as the tendo Achillis or that of the

biceps flexor cruris, can be recognised to be of one quality. Here it is to be said that I find pain from a tendon to have exactly the same quality, whether induced by pressure or by the injection into the tendon of a small quantity of hypertonic salt solution or of buffered acid solution.

In the same class as pain from tendon, I would place also pain derived from periosteum (137). In eliciting the latter, I anaesthetise a little piece of skin over the tibia and carry a needle through this until it impinges on the bone. Each time the needle is jabbed against the tibia, a disagreeable diffuse pain is produced and lasts at its height for an appreciable time. Similar pain is provoked but is longer lasting if a small amount of hypertonic saline is injected while the needle point is against the bone. This pain, presumably arising from periosteum, is similar to, if not indistinguishable from, web and tendon pain.

If a joint is strained in rough walking, pain is felt subsequently at each movement of the joint. It is an intermittent and rather short-lasting pain, but its quality is the same as that here described.

The pain elicited from deep fascia and aponeurosis is also of the same kind.

The quality of pain derived from all these deep-lying somatic structures is similar to that derived from muscle. The latter is more apt to waver in intensity, but otherwise the pains are alike. It is these deep pains which, in their less severe forms, are generally described as aching pains.

Mucous membranes.—1. Buccal membrane.—This membrane, where it covers lips, cheeks, tongue, and palate, is highly endowed with touch, warm, and cold senses. It is endowed with pain to a more limited extent than is skin. The threshold is, by comparison, high; and from many parts a pain response is obtained only with heavy pressure on the needle point. Indeed, a patch on the cheek has been described (105) as free from pain spots. From the cheek, little folds of membrane can often be picked up with forceps and squeezed or even torn away painlessly. To needle point, the response, when it comes, is similar to that from skin, being felt as a simple prick and easily tolerated. Squeezing a little fold of tongue or palate, as with sensitive parts of lip and cheek, gives burning pain.

2. Bulbar conjunctiva.—The mucous membrane covering the sclerotic and the cornea are usually reputed to be devoid of touch and warm spots; they are richly endowed with pain nerves, and cold spots are found from the margin of the cornea outwards (53). Very light touches with a needle or even with a blunt point give pain responses; the surface of the eyeball is notoriously sensitive in this respect.

3. Nasal membrane.—The mucous membrane is easily tested over the inferior turbinal, septum, and floor of the nose. It responds readily to cold but not to warmth; warm sense scarcely penetrates the nose; there are hair-covered areas in the vestibule where warmth is unappreciated. When touched lightly with a needle or blunt point, the response if felt is painful; like the cornea, though less in degree, it presents a pain-sensitive surface (181).

4. Glans penis.—The sensitivity of this mucous membrane was described by Frey (53). Pain and cold spots but no warm spots, except around the meatus, and complete insensibility to touch were found. The pain is described as having a different character from that of skin, being boring and deeper. Rivers and Head (198), who confirmed Frey, described the threshold of pain as raised as compared with skin and the response, when it comes, as excessively unpleasant.

The threshold to prick is indeed raised, but the surface is nevertheless a tender one, responding painfully to touches with the head of a pin if these drag along the surface.

5. Sensitive membranes.—If we consider the outer part of the cornea, the bulbar conjunctiva, the mucous membrane of the nose, and that of the glans penis, sensibilities in these are found to have very much in common. It is remarkable that all are devoid of touch and warm sense. All are endowed with cold and pain sense. The resemblances do not end here. All these surfaces are hypersensitive in that simple contacts or the lightest friction give painful responses; this they have in common although in relation to skin the threshold to prick is in some instances very low (conjunctiva) and in some very high (glans). In all instances, the pain that comes even in response to a weak stimulus, has relative to skin a surprising intensity and is very disagreeable in quality; though fairly well localised, it has an

element of diffusion, but it never radiates in the true sense. If the pain responses from these membranes are taken in succession and all compared, their remarkable similarity in quality can be recognised; and this quality is, in my judgement, the same as that of pain derived from the web and from other deep-lying somatic structures and not of that derived from skin.

It has been seen in the case of a sufficient number of examples that pain derived from any one structure is of uniform quality. It has further been shown that pain derived from skin and buccal mucous membrane is of one kind, while that from representative somatic tissues lying at a deeper level is of another and distinct type. It places pain derived from web, tendon, periosteum, aponeurosis, joint, muscle, and sensitive mucous membranes together in one division. We may anticipate by saying that comparisons of pain provoked from the deep-lying somatic tissues with pain of visceral origin lead similarly to the belief that these also are of one kind. Such comparisons also bring us to a conclusion very similar to that expressed many years ago by Alrutz (3): there are but two classes of pain, the superficial and the deep. However, there are different ways of regarding the two forms of painful sensation described.

The separateness of superficial and deep pain.—Speaking of sensation generally, the nerve ending is specialised to receive particular forms of stimulus and to convert these into nerve impulses. There is reason to think that all these nerve impulses are fundamentally alike and that the nerves are mere conductors of a common pattern of excitation thrown into them by the end apparatus. If this is indeed so, then the sensorium, which ultimately receives these impulses, alone determines the form of sensation, be it light, sound, or pain. The kind of pain which skin is capable of awakening is common to all parts of the skin and to certain mucous membranes; the corresponding nerves evidently belong to a common system and connect to a common centre.

The difference in the qualities of skin pain and of deep pain is so clear and each belongs so exclusively to the corresponding structures that it would perhaps seem unsafe to class both together under the one unqualified term "pain". It has been the usage; but these two sensations have not been shown to possess

the common properties which the use of a single term would imply. If we are right in believing that the system of fibres subserving cutaneous pain passes to an appropriate and exclusive part of the sensorium, which determines this particular sensation, we are brought to consider whether or not fibres subserving pain derived more deeply connect to a distinct part of the sensorium. Although both follow the path of the anterolateral tract, as shown by the abolition of both in cases in which this tract has been divided surgically, we should bear in mind the possible serious fallacy of regarding both types as represented in a common centre.

It is usual today to refer almost all peripheral sensations to the four specific systems—touch, pain, warm, and cold—and to ascribe tickle and itch to the touch or pain nerve system. This is arbitrary and has arisen out of a surrender to simplicity rather than from the dictates of evidence. Conceivably the correct view, it is not necessarily true, and we should be on guard. The difference in the quality of pain derived from skin and from deeper structures has led me to suppose it possible that these are separate forms of sensation. In reviewing all the facts and thinking along these lines, it would seem safe to regard them as having a degree of separateness equal, at least, to that displayed in the appreciation of different colours by the organs of vision. But the distinction to be made is possibly more fundamental.

The idea suggested, that the two corresponding systems of peripheral nerves must establish different connections within the central nervous system, is supported in other ways. Painful stimulation of the skin is well known to awaken quick protective reflexes. Painful stimulation of deeper structures does not appear to possess this association. Thus, stimulation of a decerebrated frog's toe results in instant withdrawal by flexion of the limb; so, too, will stimulation of any other part of the skin of the limb. But, if care is taken to avoid escape to cutaneous nerves, such reflexes do not seem to be obtainable from muscle or periosteum of the leg, or from abdominal viscus (Lewis, 137). So, too, are the results obtained by stimulating various parts of the decapitated cat; rubbing the skin of the shoulder gives the scratch reflex; injury to the skin gives vigorous kicking movements; while stimulating deeper somatic and visceral structures gives, predom-

inantly, local contractions of the trunk musculature, such as never follow stimulation of the skin (Lewis and Kellgren, 140). While painful sensations derived from the human skin are associated with brisk movements, with rise of pulse rate, and with a sense of invigoration, those derived from deeper structures are often associated with quiescence, with slowing of the pulse, a fall of blood pressure, sweating, and nausea. The last phenomenon, nausea, is responsible for the common designation "sickening", which is applied to pain derived from the deeper structures but never to cutaneous pain. This syndrome, or vasovagal response, to deep pain occurs frequently when joints are painfully stimulated; it has also been witnessed in painful stimulation of muscle, deep fascia, and periosteum and in puncturing arteries (181). It occurs in association with all the chief severe visceral pains—such as angina, gallstone, renal, and bowel colic—and in blows on the testicle and bladder pain. It never occurs, apparently, with cutaneous pain (181).

It will be observed that pain of the kind derived from skin is also derived from other ectodermal structures, such as the mucous membrane of mouth and anus. Deep pain, on the other hand, is derived from mesodermal structures, while the endodermal structures are either devoid of pain fibres or contain very few. There is this general morphological relationship, but it is not strict in detail. The main exceptions are the sensitive membranes (see p. 43).

We have considered the separateness of superficial and deep pain. This is one view. The other that I shall consider accepts pain as of one order or kind but regards it as modified by concomitant responses.

Protopathic and epicritic systems.—Head (82) believed that cutaneous sensibility is of two kinds, namely: "Protopathic sensibility, capable of responding to painful cutaneous stimuli, and to the extremes of heat and cold"; and "Epicritic sensibility, by which we gain the power of cutaneous localisation, of the discrimination of two points, and of the finer grades of temperature, called cool and warm".

The first group comprised pain and the responses cold and warm to temperature below 26° C. and above 37° C., respectively. The second group comprised touch and the responses cold

and warm to stimulation within the range of 26° to 37° C. These forms of sensibility were regarded as depending peripherally upon two separate systems of nerve fibres and end organs—which often overlapped in their distribution in the skin—so that, in lesions of cutaneous nerves, dissociation of the two forms of sensibility would occur. The first system was regarded as the more primitive. It was believed to possess the greater overlap in supplying skin of the extremities and, therefore, to become exposed as marginal areas of pure protopathic supply after a peripheral cutaneous nerve section. It was thought to be the first system to regenerate after nerve section and thus temporarily to establish large areas of purely protopathic supply. Further, in the case of temperature, the protopathic system was supposed to be alone in supplying the endings responsible for punctate temperature sensibility. Lastly, pain was supposed to vary in its characteristics, being altered or inhibited by the coexistence of epicritic sensibility. According to this view pain from deep-lying structures would be regarded as unaltered; and skin pain would be regarded as fundamentally the same but modified to our perception by simultaneous reception of touch or other impression.

In the form in which it was presented (32, 85, 198), and especially because of the postulation of a dual mechanism for the sensations of warm and cold, the hypothesis, though not grossly inconsistent with the main and generally accepted theory of specific sensibilities of touch, warm, cold, and pain, tended at the time to overshadow and confuse that theory. Actually, the protopathic-epicritic hypothesis with its full implications has itself achieved no general acceptance. As Trotter and Davies showed (231, 232), the condition of sensibility in areas of partial loss immediately following nerve section and its condition in areas showing recovery during the early stages of regeneration are, when submitted to adequate analysis, by no means identical as they should be if, according to hypothesis, both resulted from an undiluted protopathic nerve supply. The meticulously careful and repeated observations of these workers failed to confirm Head at vital points—notably, Trotter and Davies disagreed that there is any material divergence between the areas of touch and pain loss when peripheral nerves are cut or in the rate of their recovery. They were able to deny that areas of what Head

called purely protopathic nerve supply became exposed, and they explained the observed facts upon quite different lines (see p. 86). They disagreed also that there are two separate types of heat and of cold sensation. Their effective criticisms of the original observations and of the generalisations drawn from these can leave no doubt of the precariousness of Head's hypothesis as a whole, if, indeed, Trotter and Davies are not to be regarded as destroying it. The general correctness of Trotter and Davies's observations have been confirmed adequately by later workers (15, 113). Head's hypothesis, fascinating in the breadth of its conception, nevertheless formed a powerful stimulus to new observational work and still influences speculation.

Chapter IV

TWO SYSTEMS OF PAIN NERVES IN SKIN

In studying with Pickering and Rothschild (146) the effects of asphyxia upon the arm, I found that nerves of touch lose their function earlier than do those of pain and that, when actual anaesthesia has developed, the pain response to needle prick seems to be delayed. More recently, while testing the ischaemic limb for pain sense and attending closely to the pain produced by needle prick on normal ischaemic fingers, Pochin and I (147) observed that the pain produced from the normal finger is two-fold, a first pain coming almost at once, and a second following after a period of delay. It was found that a similar observation had been made previously.

A double response to a single stimulus was, in fact, first described by Rosenbach in 1884 (199). Gad and Goldscheider (59), using needle pricks to stimulate, emphasised the first response as touch and the second as pain; and they explained the double response by supposing that the first response travels by the posterior columns and that the second is delayed in the grey matter of the spinal cord. Thunberg (228) clearly recognised that both responses may be painful and that the double response may be elicited not only by prick but by heat. His view was that the first response is due to stimulation of nerve fibres, and the second to stimulation of nerve endings, a hypothetical process intervening between the stimulus and the excitation of nerve ending. This explanation of the second response also appealed to Frey (55) (see p. 109).

The Double Response

If a fine needle is used and the skin just proximal to a finger nail is stabbed quickly but lightly (preferably by using the needle point set up on a bristle bending under tensions of two

to four grams), the contact usually gives a slight but brief flash of pain. After a little interval, a second pain, lasting longer and being usually more intense than the first, is felt. Heavier jabs with a needle give two pain responses, the first of which is the more apt to attract attention. Thus, to elicit the phenomenon clearly with a needle, relatively light pricks should be employed. But stimuli, if too light, will give only the second pain response, the threshold for which is much the lower. The threshold for the second response is indeed remarkably low; touching the skin at the base of the nail with the blunt point of a lead pencil is usually enough to elicit the second pain if observation is intent.

Fig. 5. (*Clinical Science* 3: 68, 1937–38). A copper cylinder 4 cm. long and 5 cm. in diameter; a mass of metal from which a shorter cylinder 1 cm. diameter projects. The metal is heated to the desired temperature in a water bath. The flat surface, large or small, may be applied to the skin, the mass of metal forming a sufficient reservoir of heat for several tests in succession.

Perhaps the most certain method of displaying the double pain is by the use of a metallic contact (Fig. 5); the metal should be at 60° to 65° C., and the contact very brief (about 0.3 sec.). Such a contact is usually just long enough to give an immediate brief sting, which, after contact is broken, is followed by an echo—a flash of pain of greater intensity.

Meaning of the Double Response

As soon as the apparent delay in the response to needle prick in asphyxia was considered in relation to the fact that normally there is a first and a second response to a single stimulus, the idea arose that the delayed response in asphyxia might be the second response standing by itself; measurement of the latency in the two was consistent with this idea within reasonable margin of error (Zotterman, 253; Lewis and Pochin, 147).

Now Gasser and Erlanger (61), in their well-known experiments on animals, have shown that the fibres of peripheral nerve trunks conduct impulses centrally at very different rates. Studied by Gasser's methods, the fibres separate themselves into

groups, which he terms α, β, γ. Gasser and his colleagues (62) had also shown that cocaine, in acting on the nerve trunk, abolishes first the function of the slower conducting (or γ) fibres. When he came to use our method of asphyxia (27), he found, on the contrary, that this first abolishes the function of the faster conducting fibres (α and β). Cocaine had long been known to abolish pain sensibility before touch (see p. 35), and it had been shown in my laboratory that asphyxia abolishes touch before pain. Gasser therefore suggested (60) that our delayed pain response, since recognised as the isolated second response, might be due to the functional survival of slow conducting fibres. This suggestion at once became more acceptable when it was found that the second pain response in man is abolished, while the first response is retained, when either the skin or the nerve supplying it is brought under the early influence of cocaine (Lewis and Pochin, 147). There was now a very clear and suggestive accord between Gasser's observations and our own; for he found fibres of fast conduction rate, while we found fibres conducting the first pain response, to be more susceptible to asphyxia; similarly, he found fibres of slow conduction, while we found fibres conducting the second pain response, to be the more susceptible to cocaine. The idea, which now definitely emerged, that the two pain responses are carried by fibres of different conduction rate, could be submitted to decisive experiment in man. If it were correct, then the interval between the first and second responses should increase with the length of nerve traversed; and, because of its slow conduction, the second response should be delayed very notably when the nerve path is long. These expectations proved easy to demonstrate. If heat, the most suitable stimulus, is used and the point of stimulation is moved in steps from the finger up the arm to the shoulder, the interval between the two responses gradually diminishes until, near the shoulder, the responses fuse. Similarly, when the foot is stimulated, the interval between the responses is remarkable for its length; this interval decreases until, near the hip, the two responses are indistinguishable. The average lag of the second response at the toe is 1.9 sec., at the knee, 1.3 sec., and at the top of the thigh, 0.9 sec. The significant change in passing up an extremity to the trunk precludes Thunberg's view

that the "between process" can be held appreciably to account for the lag of the second response. The appropriate calculations show that the rate of conduction of the second response in nerve is about 0.5 to 1 m. per sec. That of the first response is, at the very least, twenty times as fast. These values are of the same order as those found by Gasser and his colleagues for the slow and fast conducting fibres of peripheral nerves.

The parts of the body over which the two responses cannot be distinguished are shown black in Figure 6, the border of the

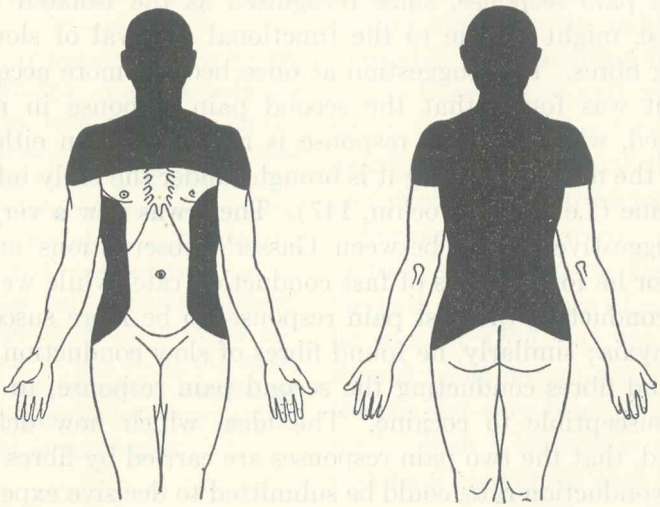

Fig. 6. (*Clinical Science* 3: 73, 1937–38.) A subject of 5 ft. 8 in. in height. The blackened areas are those that gave a single response to brief painful stimulus, the unblackened areas gave double responses, the interval between the two gradually increasing as the stimulus was moved peripherally on arm or leg.

blackened area being the boundary at which they first become indistinguishable. It will be manifest from the example of the diagram that the cord can contribute little to lag of one pain response behind the other, for the boundaries at which the double response fuses into one stand everywhere at approximately the same distance, measured along nerve trunks to their points of entrance to the cord; and this is so whether the measurement is to the cervical or to the sacral region of the cord. The interval is caused by the presence of two sets of pain nerves, one of fast, and one of slow, conducting power.

It is to be remarked that the incidence of fibres of different conduction rates is not a diffuse scatter or simple transition from fast to slow. The fibres are more or less sharply grouped into very fast and very slow conducting types; otherwise the two pain responses would not be distinct, as they are.

Further Observations

It will be realised that, having distinguished two systems of pain nerves in skin, it becomes important to reinvestigate pain responses from this standpoint. Some, but by no means all, of this work has been done.

The quality of the pain awakened from skin by these two systems is the same. The two types of response are equally well localised (Lewis and Pochin, 147).

Both slow and fast travelling impulses reaching the cord cross over and ascend in the anterolateral tract, for both are abolished when this tract has been cut and leaves crossed analgesia (181).

The apparent delay in the response to pinprick by patients suffering from locomotor ataxia has been shown by my collaborator Pochin (186) to be due to the extinction of the first response. Using patients of this kind, in which only second responses are present, we have recently attempted to discover if reflex withdrawal of the foot when painfully stimulated is associated exclusively with the nerves of quick rather than of slow conduction. In normal subjects, instant and uncontrollable withdrawal happens if very hot metal is brought into contact with skin of the foot. In these tabetics, such withdrawal is not found; and often the limb remains still although the subject complains and, if the metal is not withdrawn, the skin may subsequently blister. Sometimes the limb is withdrawn by the subject when the delayed pain response is felt; the manner of this withdrawal generally indicates a voluntary, rather than a reflex, act. The results are not, I think, entirely conclusive; but they distinctly suggest that, in normal subjects, reflex withdrawal is associated, as might be anticipated, only or particularly with the quickly conducted pain impulses.

While we may be sure of two systems of pain nerves where skin responses are concerned, in the case of deep somatic pain uncertainty remains. Most pain responses obtained from deep-

lying structures, such as web, tendon, and so forth, come slowly and are prolonged; and there could be little hope of distinguishing first and second responses occurring with a relatively short interval between them. But, if we accept the nerves supplying the glans penis as belonging exclusively to the deep system, then the presence of both slow and fast conducting types must be acknowledged. This point of stimulation is rather near to the boundary so that the two responses are close together; but that there are two is not infrequently and distinctly recognisable to needle prick.

Relation of Fibre Size, Conduction Rate, and Sensibility

It has long been suspected, and more recently it has been shown, that there is a relation between the size of the fibre of an excitable tissue and its rate of conduction. In the Linacre lecture of 1921 (128), I used the knowledge that, when the four different forms of muscle in the mammalian heart are arranged in the order of decreasing diameter, they form a series in which the rate of conduction also decreases. I regarded this relation as fundamental, and it led me to postulate my "Law of cardiac muscle". Six years later, Gasser and Erlanger (61), in studying the action potential curve from a mixed nerve trunk, were able to show, by their very admirable observations with the cathode ray oscillograph, that this curve owes its form to the presence of three groups of fibres (α, β, and γ) of different conduction rates and that these comprise a series in which velocity is determined by diameter. Their conclusions relating to conduction rate and size of nerve fibre have been generally accepted and have formed the basis of attempts to correlate morphology with the sensibility subserved.

The association of pain with fibres of small size was suggested and emphasised by Ranson. The posterior roots contain afferent nerves of very different sizes, many myelinated and many more showing little or no myelination. The fine fibres pass from root to cord through the lateral filament of the root, and division of them was found by Ranson and Billingsley (191) to abolish the reflexes usual to painful stimulation. This evidence, though very suggestive, is of course indirect; it assumes that ascending

impulses producing certain reflexes are inevitably pain-giving impulses. It would be unreasonable to overemphasise this criticism, but it is one that must be kept before our minds. Ranson collected evidence (190) to show that nerves to pain-giving structures—such as skin, muscle, cornea, and dental pulp—contain small fibres, finely myelinated or unmyelinated (other than sympathetic), in a proportion consistent with expectation, on the view that these convey pain. In later work, however, in which nerves supplying skin of various parts of the body were examined, the same worker found (192) that the large myelinated fibres were far too few to supply the touch spots in areas heavily endowed with touch sensation, thus leaving open the possibility that small, as well as large, myelinated fibres participate in this function. Ranson's views on the size of fibres subserving pain have received some support from observations made on man. Heinbecker, Bishop, and O'Leary (86) stimulated human nerves by using an apparatus calculated to excite fibres of different sizes and compared these with the sensations elicited. With stimuli of rising strength, they found threshold for two distinct sensations, namely, touch and pain; they ascribed the first to stimulation of large, and the second to stimulation of smaller, fibres.

Accepting a fundamental relation between fibre size and conduction rate, then a relation between conduction rate and the sensibility subserved would be anticipated. There is some direct evidence from this standpoint. Adrian (1) found in the frog that touch yields large rapidly conducted impulses, while an injurious stimulus calculated to give pain yields a discharge of slowly conducted impulses only. His very convincing records are republished in Figure 7. Earlier in this chapter it has been stated that, acting on the nerve trunk, cocaine blocks the slower (62), and asphyxia blocks the faster, conducting impulses first (27); in man it has been found that cocaine abolishes pain before touch and that asphyxia abolishes touch before pain. Here would seem to be satisfactory evidence that touch is carried by fast, and pain by slow, conducting fibres. Nevertheless, despite the evidence reviewed, it will be manifest that this conclusion cannot be drawn without considerable reservations. It has not been shown that all pain passes by slow conducting fibres; we possess

direct evidence for man that pain is conveyed at both fast and slow rates (first and second response). Thus, although at first the simple conclusion seemed to be promised, it is now clear that a strict relation between sensibility, on the one hand, and fibre size and rate of conduction, on the other, cannot be established. As Gasser (60) himself expresses it, the fibres belonging to different modalities must be widely distributed through the various fibre sizes. It is probable that pain is carried by fibres of the β and γ order, the latter being responsible for the second pain response to prick.

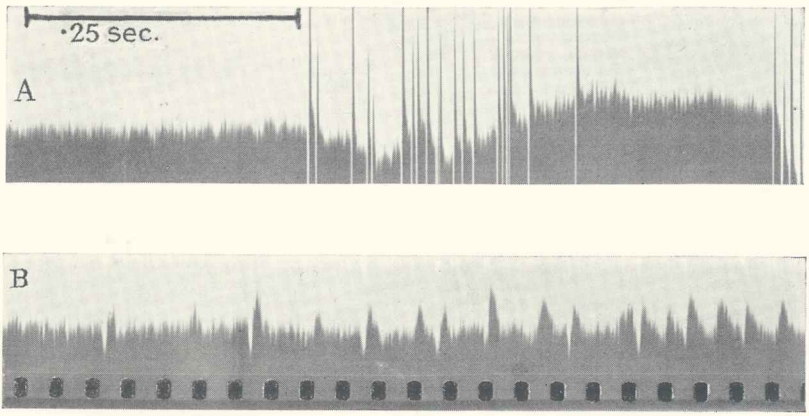

Fig. 7. (Adrian, *Proc. Roy. Soc.*, London, s. B. 109: Fig. 7.) Dorsal cutaneous nerve of the frog. *A*. Large rapid action potential waves due to touch. *B*. After the surface layers of the skin had been removed by scraping, a crush gives discharge consisting entirely of slow impulses.

Note. The rate at which the individual potential wave is completed is a measure of the rate at which it is travelling past the electrodes.

Chapter V

ERYTHRALGIA

That many forms of injury of the skin are followed by local redness and tenderness is very well known. One of the most obvious instances is that produced by exposure of white skin to sunlight. Hours later the skin becomes red, the friction of clothing against it is painful, and often, even though untouched, there is a sense of burning in the skin. Now this condition of skin is not peculiar to sunlight burns, since similar lesions can be produced in many ways; it exemplifies a common and fundamental type of sensitive skin which, when submitted to appropriate investigation, provides facts of much practical and theoretical significance.

Methods

To bring an area of skin into this erythralgic state, as I have called it, a number of methods has been used in my laboratory in a thorough exploration of this important condition (139).

Scratching.—One of the simplest ways of injuring skin is to scratch it methodically. An area two centimetres square is marked out on the forearm and the point of a needle drawn across it in ten parallel lines; ten more are drawn at right angles, and a final ten obliquely. The skin is thus crosshatched by little scratches, each giving a tiny white line of broken horny layer but none sufficiently injurious to draw blood. The injured region at once displays the usual reactions of the triple response—local redness, a little swelling, and a surrounding flare. This lesion is at first painless, but in about 15 to 20 min. a little burning may be noticed in it. Next day the skin is usually red, swollen, tender, and still burning a little from time to time; this state lasts for another whole day and sometimes longer.

Burns.—A convenient way of burning skin is to use molten

wax. The end of a small stick of sealing wax is softened in a flame and pressed quickly against the previously moistened skin. After a little experience, burns of a suitable intensity can be produced in this way (the wax being at about 60° to 65° C. when applied) with little or no subsequent blistering of the skin. The application is painful. Pain as an after-effect may begin at once, but often an interval of 10 to 30 sec. or even a minute after the withdrawal of the wax passes without pain. In about 10 min. the skin is red, a little swollen, and tender and is giving constant burning pain; this state continues for many minutes, an hour, or more.

Freezing.—An area of skin one and one-half centimetres square is frozen by applying to it a bar of copper maintained at about —15° C. for 20 to 25 sec. (141). This produces a thin but hard plate of frozen tissue, which can be grasped by the fingers and lifted. After they have thawed, such areas give full whealing of the skin, whealing which subsides in an hour or two. In about eight hours, the reddened skin has become painful and later is swollen again. It remains in this state for four or five days.

Ultraviolet light.—If an area of skin is exposed appropriately, the skin will be reddened in a few hours and perhaps a little tender. Within twelve hours, it is a little swollen and painful and so continues for five or more days.

These instances are by no means exclusive; a similar erythralgic state can be induced by crushing the skin, by strongly faradising it, or by applying irritant substances such as chloroform or mustard oil.

The condition of the skin developed from all these kinds of injury is found on examination to be much the same. A notable variation is the early appearance of spontaneous burning pain when the skin has been injured by heat and its late development in the ultraviolet burn. But this difference is one of degree rather than of kind. The heat burn is the most severe of the injuries and is the quickest in the making; the ultraviolet lesion has the longest latent period. If the freeze has been harder, pain may begin almost in the moment of thawing. We may say that, in all these conditions, the skin passes sooner or later into what may be termed, from the standpoint of pain, a susceptible

or hyperalgesic state. Such a state begins at varying times, according to the agency employed and the grade of injury, and may be delayed from a few seconds to many hours. Once established, it usually lasts for days.

The Hyperalgesic State

It will be convenient to summarise the common phenomena of this hyperalgesic state before proceeding to examine certain of them in more detail.

Threshold responses.—Skin so affected is truly hyperalgesic, in the sense that it responds to needle pricks that are too light to awaken pain in surrounding unaffected skin. Further, the response, when it is aroused, is of unusual intensity; and it seems to possess a certain diffuseness, though it is never referred to a remote region. On the toe, it is possible to distinguish that increased intensity concerns both the first and second response to the prick; the threshold of the first response is certainly lowered, but lowering of that of the second response has not been observed. Pain is easily induced by friction, by warming, and often by cooling the affected skin.

There is no hypersensibility to light touch and none to warmth or cold unless such stimuli arouse pain.

Responses to friction.—The hyperalgesia is usually first noticed through painful response to light contacts such as are imposed by the friction of clothing. Friction in part produces this pain by setting the skin on the stretch. The response to deliberate friction or to an act of stretching is peculiar. A single, rough frictional movement elicits unpleasant burning during the act. It subsides almost at once but is followed after a clear interval of 10 or 15 sec. by a recurrence of similar pain (*recurrent pain*) lasting 1 to 3 min.

Responses to high and to low temperatures.—A striking and early method of detecting the hyperalgesia is to immerse the skin in warm water.[1] The most suitable temperature for test purposes is 40° C. Normally, water at this temperature is pleasantly warm to skin, and it is not until the level reaches or sur-

[1] The only previous statement I have found is by Rein (194), who, in discussing the pain threshold for heat, states incidentally that it is lowered by chemical and mechanical stimulation of the skin.

passes 43° that the first detectable element of "sting" or pain is introduced into the response. Pain is not severe until temperatures of about 48° are reached. A temperature of 50° will often scald the skin; immersion of the arm in water at this temperature is not tolerated.

When skin is entering the hyperalgesic state, immersion at 40° gives a painful response. Susceptibility increases as time passes; tests at 40° produce increasing and often very severe pain, and pain is provoked by lower temperatures. The response to heat is not simple. Both the actual temperature and the gradient of change count. Thus, if the susceptible skin is brought to 30° or to 20° alternately before immersing at 40°, pain elicited by the change from 30° to 40° comes quicker and more intensely than by the change from 20° to 40°. In the latter transference, the gradient of rising skin temperature is, in general, the steeper. But over the relevant period of time, namely, the first 6 sec., during which pain is most severely felt, the temperatures in the former case are actually higher, and the gradient is actually steeper for the same range of temperatures. If the skin is warmed from 30° to 40° C. and from 32° to 42° C., the intensity of pain is conspicuously greater in the second test, though the number of degrees of rise and the rate of rise cannot be very dissimilar in the two. As previously stated, the intensity of pain produced is governed both by the height of the actual temperatures and by the steepness of gradient.

Instead of testing with water, the flat end of a copper cylinder (5 cm. diam.) withdrawn from a bath at 40° may be used; it is a more convenient and more universally applicable test. The pain produced is more intense than in the corresponding water test, for the gradient of temperature rise is steeper owing to the high conductivity of the metal.

Skin in this hyperalgesic state can also be provoked into displaying pain by severe cooling. Thus, if the skin is at 20°, a metallic contact at 0° may give severe burning pain, and pain is often elicited by contacts at 5°, 10°, or even 15°.

Spontaneous Pain

Spontaneous pain occurs especially in skin rendered hyperalgesic by heat injury, and here it is felt very soon after the injury

has occurred. It is familiar knowledge that, when it has come, it is enhanced by warming and relieved or abolished by cooling. But spontaneous pain is not confined to heat injury; it occurs in suitable circumstances with each of the forms of injury described. The pain after heat injury is described as burning pain; it has exactly the same quality in the case of the other injuries. In all, it is continuous. In all, increased temperature enhances, and decreased temperature allays, it. The common idea that the after-effect of heat injury is peculiar to heat is quite erroneous.

Relation to temperature.—The occurrence of spontaneous pain depends largely upon the actual temperature of the affected skin. It may be ascertained, by immersing the skin at 25° C. and very gradually raising its temperature, that the critical temperature for most injuries, such as a scratch, bruise, freeze, or ultraviolet burn, lies between 32° and 34°. These are the temperatures at which spontaneous pain is first detected, and the levels explain why the corresponding lesions do not display pain constantly, for these minimum levels are above those at which the skin of the extremity often stands. In natural circumstances, the critical level is only reached by the skin of an extremity from

TABLE 2

MINIMAL TEMPERATURE FOR PAIN EXEMPLIFIED

Injury	*Pain begins at*
1. Finger hit with hammer causing blood blister, previous day	32.5° C.
2. Skin damaged by freezing, on previous day	32.5°
3. Six ultraviolet burns, at their height	32.0° to 34.3°
4. Heat burn, 1 hr. old, blistering a little subsequently	29.0°
5. Heat burn of foot, 1 hr. old, small blister	30.3°
Same at 3½ hrs., no longer paining spontaneously	32.4°

time to time. But the temperature of the injured skin is not far below the critical level, and so the increased warmth of bed or of a well-warmed room is often enough to tip the balance, and spontaneous pain results. In injuries from burning heat, pain usually appears at lower levels of temperature, namely, about 29° or lower; this is the form of injury in which "spontaneous" pain is most obtrusive. Injuries produced by heat are liable to be more severe than those arising in other ways; more often than with other forms of injury, the damage is not so nicely

graded as to be adequate without causing subsequent blistering. It is clear, however, that the severer the lesion from any cause, whatever be its kind, the lower is the temperature required to induce spontaneous pain.

It is immaterial how temperature is raised in injured skin, whether by radiant or conducted heat or by local vasodilatation; pain will result if the temperature rises high enough.

Relation to tissue tension.—If the skin of the foot is injured sufficiently to render it painful at ordinary temperatures, then raising the foot to the horizontal decreases or abolishes the pain. Hanging the foot down determines pain or increases it if it is already present. This change does not depend on any change of temperature of the foot that might be supposed to accompany change in its position; observations actually show that no such temperature change happens, even in injured skin. It is due to increased tension in the tissues caused by hydrostatic increase in the pressure within the vessels. Thus, the same effects can be obtained by artificially raising venous pressure in a limb that is kept at rest and horizontal. Whether it results from hanging the limb down or from throwing a pressure of 60 mm. Hg upon the veins, the pain does not appear at once but only after the lapse of an interval of ¼ to 2 min., times entirely consistent with the gathering of adequate tension in the veins. When pain is provoked by posture or by deliberately obstructing of the venous return, it can be reduced or abolished by occluding the common femoral artery; it is similarly reduced or abolished by directly applying to the affected skin a pneumatic pressure sufficient to counterbalance the pressure in the cutaneous veins.

The effect of tension can usually be shown by placing the skin directly on the stretch with the fingers; burning pain results immediately when tension has reached a certain point, and it subsides rapidly when the tension is released. The pain produced by tension from tissue already rendered predisposed is characteristically a pain that comes at once with the provocative stimulus. Presumably that is why the pulse produces in many circumstances throbs of pain synchronously with its beats, though actually, in erythralgia, throbbing of the skin is unusual.

A clear understanding of this particular hyperalgesic state, so that it may be recognised in skin in which it occurs, is very

important clinically. It is associated with a large number of different conditions, including painful chilblains, frostbite, lesions arising out of defective blood supply, herpes zoster, and many small inflammatory lesions of the skin; it is often responsible for severe, and sometimes for intolerable, pain in the extremities, such pain being related to temperature and posture. Mitchell (165), who presented a picture of certain of these cases, gave the impression of a specific disease in which painful vasomotor storms occurred in the extremities. This clinical side has been dealt with elsewhere (Lewis, 131). As has been indicated, the hyperalgesia discussed is associated particularly with inflammatory redness of the skin, and, for that reason, I have described it under the distinctive term erythralgia. In again using this term, however, it is necessary to state that distinct redness of the skin is not a quality on the presence of which we can rely; there are clinical instances of this same type of hyperalgesia in which redness is not much, or not always, in evidence. It is difficult to select quite adequate terms; and, when speaking further of erythralgia or of erythralgic tenderness in this book, I desire to convey the idea of a peculiar form of painful skin commonly associated with inflammatory reddening rather than to confine the term to reddened skin.

Cause of Hyperalgesia and Pain in Erythralgia

Recognising that in erythralgic skin the threshold is lowered to all forms of painful stimulus, we may conclude that the pain nerve endings are in a state of hyperexcitability. How this comes about deserves further enquiry.

We know that skin is not brought to this state at once by such physical injuries as scratching or freezing but only gradually after an interval of minutes or even hours. The hyperalgesia cannot be due to damage of nerve endings occurring at the time of injury and lasting, but must result from something arising gradually out of injury after a lesser or greater period of delay. It evidently involves some preparatory process in the tissues, a process probably associated with a certain stage of inflammation, since it is usually delayed at least until clear signs of the latter are established, a fact prominently exemplified in the instance of ultraviolet light. The hyperalgesic skin is often

a little swollen; but excess of tissue fluid is not the cause of hyperalgesia. Thus it is the rule, in the case of ultraviolet burns, for hyperalgesia to occur before swelling can be detected. Hyperalgesia is not usual in urticarial wheals when these form, although the tension of tissue fluids is greater in them than in the skin we are considering; moreover, the area, which was without tenderness when whealed, may be tender next day after the wheal has subsided. As these observations show, the hyperalgesia is not due to such a simple physical cause as tension.

Chemical Factor Underlying Hyperalgesia

In relatively mild injuries, the precise area damaged (scratched, frozen, or reddened by ultraviolet light) becomes hyperalgesic. But if the injury is more severe, hyperalgesia is almost always found outside it next day and on days following. With Zotterman, I described (150) how an area of skin injured and reddened by ultraviolet light or by freezing becomes surrounded by a stable diffusion flush, and how lymphatic channels may become marked out on the proximal side of the lesion by red streaks, which are in the skin and which lead away from the lesion. The flush and the streaks were attributed to the movement of vasodilator substances out from the injured, into uninjured, skin. The failure of hyperalgesia to confine itself to the actual region of injury suggested that it results similarly from products of injury,[2] which influence the pain nerve endings not only within the injured area but also in the surrounding skin into which they are conveyed. There is approximate, though not

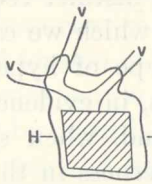

Fig. 8. (*Clinical Science* 1: 53, 1933–34.) An ultraviolet burn was put down over the area shaded (2.5 × 2.5 cm.) two days previously. The diagram shows the relation of the area of hyperalgesia to the chief veins of the region. The burn was on the dorsum of the right foot, and the upper edge of the chart is proximal.

[2] The injury product inducing redness has been thought to be histamine or a histamine-like substance; the pain substance is not regarded as histamine, which, when introduced, gives itching and not pain.

precise, correspondence between the area of added redness and that of added hyperalgesia. It is the rule for the chief extension of hyperalgesia to be up the limb, in the direction of lymphatic drainage, and sometimes the course of the chief subcutaneous veins of the region seem to be followed for short distances. Only exceptionally, however, is the relation to veins as precise and convincing as is illustrated in Figure 8. Although it still seems probable that the correct explanation of hyperalgesia established as a narrow band around the central lesion and extending chiefly up the limb is that given, its value as evidence of a pain-giving substance moving out into surrounding skin has been decreased by my subsequent discovery of a more widespread form of hyperalgesia arising through local nervous channels around many injuries of the skin (see next chapter). The possible relation of these two forms of hyperalgesia is further discussed on page 80.

Chemical Factor Underlying Pain

Pain in rubbed skin.—If skin has been rendered hyperalgesic by crisscross scratching or by ultraviolet light, it is painful when rubbed. A single rough rub is accompanied by pain which, as has been stated, subsides. After a clear interval of fifteen or more seconds, recurrent pain is felt, and this may last one or more minutes. The preliminary free interval, the gradual rise of pain to a maximal intensity, and its long continuation are incompatible with its origin as a direct response to rubbing. It is a delayed after-effect of the rubbing, and the manner of its onset and even slower decline clearly suggest that the friction causes the discharge of some pain-giving substance into the intercellular spaces, which, first accumulating and then slowly dispersing, accounts for the curious and interesting time relations that the pain displays.

This idea is confirmed by observing the effect that arresting the limb circulation has upon the reaction. If this is done directly before rubbing the injured skin, the immediate pain and the free interval come as before, but the recurrent pain rises to greater intensity and remains at this intensity while the circulatory arrest is maintained, usually to be finally lost a minute or more after the release. The recurrent pain is prolonged by

circulatory arrest in a manner to be expected if it were due to a relatively stable pain-giving substance released into, and held within, the tissue spaces.

Effect of simple occlusion.—If skin, injured and rendered hyperalgesic by ultraviolet light or in other ways, is giving rise to no spontaneous pain, pain can be induced in it by simple arrest of the circulation to the limb. This local pain comes after one-half to one minute and gradually increases in intensity, only to disappear quickly when the circulation is released again.

Quite severe pain may be induced in a recent blister of the hand, the result of hard usage, by arresting the bloodflow to the hand, although previously little or no pain was to be felt in it.

Pain from freezing and thawing.—If skin is mildly frozen and thawed, the skin so treated itches and wheals subsequently; but, if it is frozen harder, then severe burning pain may be felt on thawing, and in such the skin blisters. It is tempting to suppose that the difference in these reactions is due to the kind of substance released, a histamine-like substance in the first case, and a pain-producing substance in the second.

Hyperalgesia and Pain; the General Argument

The hyperalgesic skin, according to my theory, is one which has been brought to this state by the action of certain tissue substances upon the pain nerve endings, the latter being rendered hyperexcitable. It is suggested that these substances are the outcome of processes following at varying intervals according to the nature and severity of tissue injury; the interval is short after a cut or burn and long after ultraviolet light. Pain nerve endings in this unusually responsive state react to warmth as do normal nerves to higher temperature; they react unusually to pinpricks and to light friction and to increased tension placed upon the skin directly or through vascular distension. The pain awakened from the tender skin in any of the several ways described is of one kind, and it is felt at the time of the interference, or almost so, and quickly subsides. There is in this time relation a strong suggestion that the immediate stimulus is direct and physical or that, if any intermediate process is set up, this must be a highly unstable or quickly reversible process.

But this is not the only mechanism that brings pain from this hyperalgesia. The immediate pain response of rubbing or stretching subsides; but, after a little time, a second pain appears and lasts. The immediate pain must differ fundamentally from that of the recurrent pain. That the mechanism of the two differs is proved by the observation that previous arrest of the circulation to the skin in no way modifies the first, while it prolongs the duration of the second.

When the susceptible skin is rubbed, the accompanying pain may be ascribed to direct stimulation of hyperexcitable pain nerve endings; the recurrent pain I attribute to a stable determinant of pain, the intercellular content of which is increased by rubbing. The prolongation of this recurrent pain by circulatory arrest follows naturally upon the maintenance of this raised content while the bloodflow remains obstructed.

When pain is produced in injured skin simply by arresting the bloodflow to it and when the pain quickly subsides on releasing the circulation, I suppose that the substance has been passing out slowly into the tissue spaces, that it reaches an adequate concentration during circulatory arrest, and that the concentration rapidly declines to its former level at the release. As the concentration rises and falls, so does the excitability of the pain nerve endings, high concentration bringing stimulation and pain.

Chapter VI

NOCIFENSOR TENDERNESS

Diffuse Hyperalgesia from Local Injury of Skin

Many subjects, but by no means all, become conscious of soreness of skin surrounding a small area of injury. In some it is a very conspicuous phenomenon, and in these it is most easily investigated.

I first noticed it on my own arm after stimulating it locally with a faradic current. It awakened my keen interest, and I have made very many observations upon it (133, 135, 136).

The current must be of painful intensity and be continued for several minutes, a useful guide to strength being its capacity to provoke and maintain local goose skin. At the end of stimulation, little or no soreness of the surrounding skin can be detected; but, after a time, soreness develops and may be outlined. As time passes, the soreness becomes more conspicuous and spreads. An example is illustrated by Figure 9. Stimulation of the forearm lasted 5 min., and soreness was definite and was outlined as shown at the 6th min., by which time the stimulated skin had whealed (*W*). The soreness increased and spread up and down the arm, the enlarging area being mapped at the 9th, 11th, and 16th min. A curious tongue of soreness extended up the arm and covered three chief superficial veins converging to the antecubital fossa. The total area extended over 18 cm. in the length of the forearm and was as much as 7 cm. in width. The soreness lasted for several hours. After an interval of several days, to ensure full recovery, the stimulus was repeated in exactly the same way and at the same place. The area of soreness when fully developed corresponded closely with that previously recorded, even to the extension up the skin covering the veins.

This example represents a full reaction; it well illustrates the chief features of such reactions. The area of soreness is not fortuitous; it can be made to repeat itself. It always has its

long axis in that of the arm; it spreads proximally more than distally when the stimulated point lies near the wrist, and distally more than proximally when the point is near the elbow. Extension to skin overlying veins is frequent. A full reaction develops in about 15 or 30 min., the skin being sorest near the stimulated

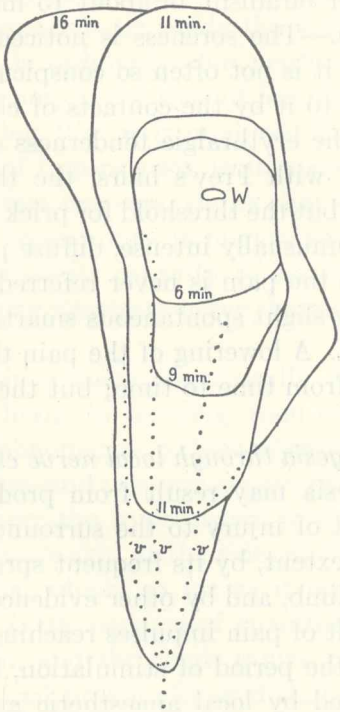

Fig. 9. (× ½) (*Clinical Science* 2: 376, 1935–36.) Faradic stimulation of skin a little above the wrist. The wheal produced is shown at *W*. The area of hyperalgesia, which developed subsequently, is indicated by solid lines, with the times in minutes at which the corresponding outline was mapped out. The letters *v*, *v*, *v* indicate the centre lines of three subcutaneous veins. The marks made on the skin have been traced in the case of this and similar diagrams on cellophane laid down subsequently on the arm.

In this and subsequent charts, the top edge of the chart represents its distal margin.

point and least sore at the periphery of the area. In full reactions, this soreness lasts for eight or twelve hours and sometimes for as much as one or two days.

Similar areas of soreness follow other injuries. A simple and

very useful method of injuring is to catch up a tiny fold of skin[1] with strong but tapered forceps and to crush the skin. In this instance, the hyperalgesia may begin as early as 10 sec. in the skin immediately surrounding the crush; it spreads at the rate previously described, the area being complete, but not so extensive as after faradism, in about 15 min.

The hyperalgesia.—The soreness is noticed when the skin is lightly rubbed, but it is not often so conspicuous that attention is constantly called to it by the contacts of clothing; it is much less obvious than the erythralgic tenderness of the actually injured skin. Tested with Frey's hairs, the threshold for touch sense is unchanged, but the threshold for prick is slightly lowered. Needle pricks give unusually intense, diffuse pain of longer than usual duration, but the pain is never referred. When there is a full reaction, a very slight spontaneous smarting is felt diffusely over the whole area. A lowering of the pain threshold to heat is suspected to occur from time to time; but the effect, when present, is slight.

Origin of hyperalgesia through local nerve channels.—The idea that this hyperalgesia may result from products conveyed directly from the seat of injury to the surrounding skin is placed out of court by its extent, by its frequent spread down the limb as much as up the limb, and by other evidence.

It is not the result of pain impulses reaching the central nervous system during the period of stimulation, for, if a cutaneous nerve is first blocked by local anaesthetic and the stimulus is placed on the resultant insensitive skin, hyperalgesia of usual extent is discovered as soon as the nerve block recovers. Moreover, similar hyperalgesia forms around an area of skin that has been painlessly but hard frozen and thawed.

If a small button is formed in the skin by injecting one per cent novocaine intradermally, faradic or mechanical stimulation may be applied quite painlessly to the centre of the little anaesthetised area. This local anaesthesia, while it lasts, prevents hyperalgesia from developing. When the local anaesthesia clears

[1] Years ago, Goldscheider (68, 69) reported that hyperalgesia appears around a fold of skin pinched by a small clamp. This hyperalgesia was associated with the pain produced by clamping; it disappeared when the clamp was removed. His observations were made during the period of painful clamping. My own observations concern hyperalgesia following as a long-lasting after-effect of injury.

away, it does so first at its edges. No trace of hyperalgesia can be found in the surrounding skin until the point of actual stimulation recovers; then hyperalgesia begins to appear and to spread in the usual fashion. Thus the local anaesthetic delays the hyperalgesia; and, if the anaesthetic is given with adrenaline, the delay may be a very long one. The failure of hyperalgesia to appear while the anaesthetic holds the nerves shows that the hyperalgesic state is ordinarily due neither to spread of substances in the skin nor, in the case of faradism, to spread of the original stimulus, but that it is produced through these nerves. The development of hyperalgesia in its usual manner from the time local anaesthesia recovers, shows that a local condition of the skin resulting from injury is maintained during the anaesthetic period and that its capacity to set up hyperalgesia at a distance as soon as the necessary nerve channels become free is retained.

If the tiny crush is made eccentrically over the anaesthetic button, the anaesthesia, in receding, soon exposes the crush. A very interesting phenomenon is then observed; a first patch of hyperalgesia appears, and it comes always in the skin on the side where the crush lies; the hyperalgesic area enlarges, but for a time it does not invade skin at the sides of, or beyond, the patch of local anaesthesia, which, so far as it remains, constitutes a barrier (Fig. 10). Little barriers of anaesthetic skin may be arranged on the skin, and the crush injury placed quite near to them; whether placed proximally or distally to the barrier, the effect is the same; until the anaesthetic skin recovers, hyperalgesia appears only on the side of the barrier on which the crush has been placed. If, however, the skin is crushed one centimetre or a little more from the barrier, then the latter is less effective, hyperalgesia appearing beyond the barrier from the start or after less delay. These experiments considered together indicate the kind of arrangement the relevant nerves possess. They indicate that the impulses from a small area of damaged skin are conveyed at first through nerves lying in the skin itself, and they indicate that these nerves are in the form of arborisations rather than of a network.

If we picture nerve axons forming finely branching, rich end plexuses lying mainly or entirely within the skin, and if we picture

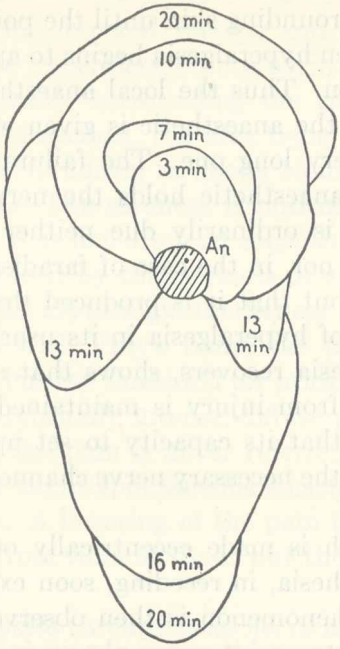

Fig. 10. (× ⅔) (*Clinical Science* 2: 397, 1935–36.) Crush placed eccentrically over anaesthetised skin.

A circular area of skin (*An*) is anaesthetised by intradermal injection of 1% novocaine. The area of analgesia is mapped out, and it is noted that there is no surrounding hyperalgesic skin 2 min. later.

0 min. A tiny piece of skin (indicated by a dot) lying within but near the distal margin of the anaesthetised area is crushed. The crushing is painless.

3 min. The area of analgesia is receding at its margin; it still just includes the crushed skin. An area of hyperalgesia has appeared and gradually extends to the contours marked by corresponding times.

7 min. The crushed skin is now just outside the area of receding analgesia.

10 min. Hyperalgesia still extends; there is still a barrier of analgesia between the crush and the proximal skin, in which sensation is normal.

16 min. The injected skin has almost recovered and by 20 min. has completely recovered; hyperalgesia now surrounds the crush widely in every direction.

the parent axons lying deeper and themselves running into common subcutaneous stems, such a system would explain adequately the diffuseness of the hyperalgesia, the gross interference caused by near-by intracutaneous barriers, and the lesser interference by more distant barriers, such as have been described.

Hyperalgesia from Stimulating Cutaneous Nerve Trunks

The effects hitherto described are due to injury of the skin. This is to be emphasised for the reason that experiments are about to be described showing similar effects arising from direct nerve stimulation. The two series, though related, must be kept separate. The more dramatic effects of this second series should not be allowed to obscure the greater importance and more immediate relevance of the first series to hyperalgesia arising pathologically. Faradic stimulation of nerves is wholly artificial; small injuries of the skin are natural to everyday usage.

A suitable nerve is the anterior branch of the external cutaneous shortly after it emerges from the deep fascia. It is found and its course marked on the forearm by using preliminary faradism (see p. 13).

The nerve may be stimulated through the skin or directly by using a special and fine subcutaneous electrode. Stimulation for 1 to 2 min. suffices to produce subsequent hyperalgesia. This hyperalgesia does not differ in any way from that described on page 70. The area involved may be less than that of the nerve's cutaneous distribution, or it may fill this territory completely and very accurately, as shown by comparing it with the area of diminished and lost sensibility following anaesthetisation of the same nerve. The hyperalgesia develops to its maximal degree and extent in about 10 or 15 min. and is maintained for hours, a day, or longer.

When the marked course of the nerve is of sufficient length, the nerve may be stimulated, after blocking it by a small injection of novocaine, either above or below the point stimulated. If it is blocked below the point stimulated (Fig. 11), hyperalgesia does not develop subsequently in the nerve's territory, though the central nervous system receives the full sensory stimulus. If it is blocked above the point stimulated (Fig. 12), the

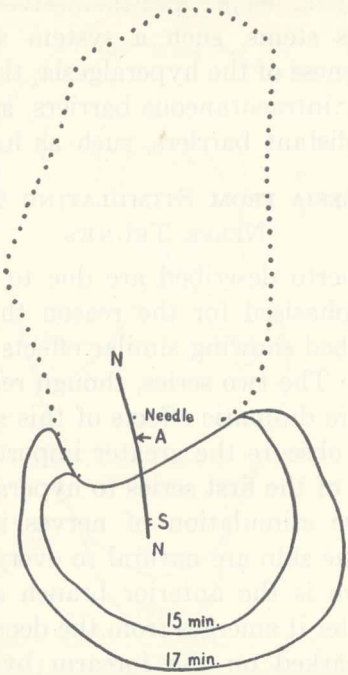

Fig. 11. (× ½) (*Clinical Science* 2: 386, 1935–36.) Stimulation of anterior branch of the external cutaneous nerve (*N*) through skin; nerve blocked below.

0 min. The region of the nerve was injected at *A* with 1 c.c. of 1% novocaine.

6 min. Area of anaesthesia and hypaesthesia fully developed and mapped out (dotted line).

8 min. Faradic stimulation at *S*, with coil at usual strength, for 2 min.; goose skin maintained in surrounding skin throughout. The stimulus very painful locally, and fluttering pain felt during the whole period along the nerve's territory.

15 min. An area of hyperalgesia has developed around the point of stimulation and is charted.

17 min. The nerve block is recovering. The area of hyperalgesia has increased a little.

19 min. A little spontaneous burning felt around region of stimulation, but nowhere else; the nerve block has quite recovered and skin sensation in the corresponding area is perfectly normal and remains so for the next hour of observation.

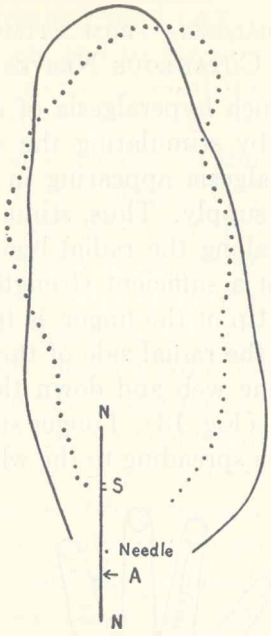

Fig. 12. (× ½). (*Clinical Science* 2: 387, 1935–36.) Stimulation of nerve through skin, nerve blocked above. The course of the anterior branch of the external cutaneous nerve had been marked on the left forearm days before.

0 min. The region of the nerve injected (at *A*) with 1 c.c. 1% novocaine, the needle being inserted where shown.

5 min. The resultant area of anaesthesia and hypaesthesia has fully developed and is mapped out (dotted line).

9½ min. Faradic stimulation at *S* in line of nerve for 2 min. Current of usual strength; goose skin throughout stimulation in surrounding skin. The current felt as a slight local tingle; no fluttering along the nerve. At the end of stimulation the area of anaesthesia and hypaesthesia is unchanged in extent and degree.

25 min. The anaesthesia and hypaesthesia have disappeared and a large area of hyperalgesia has appeared (solid line).

current, while passing, is unfelt or at the most gives a little local tingling; but hyperalgesia is found over the whole, or a large part, of the nerve's territory when the nerve block recovers. The result is the same whether the nerve is stimulated through the skin or subcutaneously and directly without implicating the skin.

Diffuse Hyperalgesia from Stimulating Small Cutaneous Nerves

Another way in which hyperalgesia of exactly the same kind may be provoked is by stimulating the short branch of a cutaneous nerve, hyperalgesia appearing in the much larger area of the parent nerve's supply. Thus, stimulation over the digital nerve, where it runs along the radial border of the fifth finger, for several minutes at a sufficient strength to give considerable pain radiating to the tip of the finger, is found to yield hyperalgesia, which involves the radial side of the fifth finger and gradually spreads up to the web and down the ulnar border of the fourth finger to its tip (Fig. 13). Longer stimulation of the nerve may yield hyperalgesia spreading to the whole distribution of the

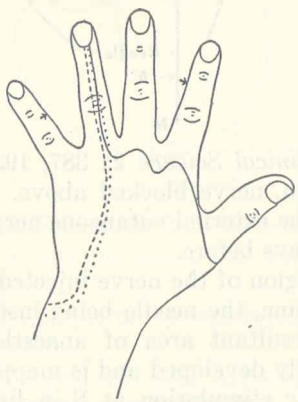

Fig. 13. (*Clinical Science* 2: 423, 1935–36.) *June the* 12*th.* The left ulnar nerve when anaesthetised at elbow gave an area of anaesthesia and hypoaesthesia indicated by the broken line. The previously marked digital nerve to the radial side of the little finger was then stimulated where marked by arrow for 5 min. with a strong faradic current, which was unfelt. The resultant full area of hyperalgesia was mapped out after recovery of the nerve block (dotted line).

June the 24*th.* The digital nerve to the ulnar side of the index finger was faradised with a strong current for 5 min. where indicated by the arrow. The full area of hyperalgesia subsequently developing on the fingers is shown by the solid line.

The subject of this experiment was ignorant of the anatomical distribution of the main nerves (ulnar, median, and radial) to the hand.

ulnar nerve in the fingers and hand, namely, to all of the fifth and half of the fourth fingers and to the ulnar border of the hand, dorsal and palmar, up to the level of the wrist. It may be accompanied by perceptible smarting of the same area, and it may last for twenty-four hours or more. If the digital nerve is stimulated while the ulnar nerve is blocked by local anaesthetic at the elbow, hyperalgesia of similar extent is found when the ulnar block recovers. Undoubtedly these effects are produced through nerve paths, though the central nervous system is not involved.

Diffuse hyperalgesia, following stimulation of skin over the digital nerve, is in part derived from local injury to the skin and in part from stimulation of the actual nerve twig. The latter can be excited by using a fine subcutaneous electrode passed down to the nerve. Much weaker current suffices, in this case, to give the full ulnar area of hyperalgesia.

The main comment to make at this stage is upon the length of the paths through which the stimulus must travel to render distant skin hyperalgesic. It is clear that, on stimulating the middle of the fifth finger, the impulses must pass up that finger and subsequently down the fourth finger, a total distance of not less than 10 cm. The paths followed to reach the skin, if the back of the hand is involved, must be 20 or 25 cm. in length. This is, of course, a minimal statement of the possibilities; if the ulnar nerve supplied forearm skin, this might also display involvement. Briefly, the full extent to which spread can happen is still unknown, but the paths we are already forced to consider are of remarkable length.

There are cases in which a finger has been crushed, torn, or otherwise injured and in which, though healing occurs, intractable tenderness and pain develop and spread to the adjoining finger. This reference to an adjoining finger probably happens through a mechanism similar to that here described (Lewis, 135).

Cutaneous Hyperalgesia from Stimulating Deeper Lying Tissues

Hyperalgesia of the kind discussed may be provoked in skin not only by stimulating skin and the nerves supplying it but by stimulating deeper lying somatic tissues or the nerves supplying these. This has been shown by stimulating, with appropriately

curved electrodes, the mucous membrane of the maxillary antrum through an old aperture in its internal wall. In the subject explored, it was quite easy to stimulate the mucous membrane covering any part of the antral wall; and it was possible, by directing the electrodes to the anterior and lateral parts of the floor, to pick up nerve branches passing to different teeth. The current that can be tolerated over the nerves is naturally much less in strength than over the membrane, but what can be tolerated is enough to produce very definite effects. The current is passed for about 3 min. When stimulation ends, nothing un-

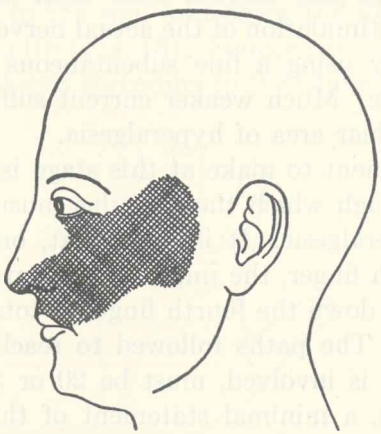

Fig. 14. (*Clinical Science* 2: 393, 1935–36.) A diagram of the face showing the area of hyperalgesia developing on stimulation of the mucous membrane or dental nerves within the left maxillary antrum.

usual can be felt, and sensation in the skin of the face is quite normal. At about the 8th to the 10th min., a little smarting is felt in the region of the malar process and lower eyelid of the same side. The lower eyelid and, a little later, the malar region are the first to exhibit hyperalgesia; this increases in degree and in extent until most of the cheek becomes involved, a little of the temple, the ala of the nose, and the whole of the skin of the upper lip. This hyperalgesia is at its height in about 40 to 60 min. and may often continue till next day (Fig. 14).

The effects are the same if mucous membrane is stimulated or if the electrodes lie over nerves to the incisor or molar teeth.

The area becoming hyperalgesic is the whole territory of the second division of the fifth nerve; spread beyond the middle line or invasion of the territories of the first or third division of the nerve has not been observed. The exposed mucous membrane of the upper lip may become sore; and, upon rolling the eyes, a little unilateral pain may be felt momentarily in the orbit of the same side. A just perceptible flush may appear on the corresponding cheek.

An exactly similar area of hyperalgesia was repeatedly observed to be set up by catarrh of the antrum in the subject in which these observations were made (133).

The manner in which the hyperalgesia develops and its long duration when established can leave no doubt that it is similar to the hyperalgesia previously described. This instance is of special interest, however, because it shows that cutaneous hyperalgesia of the sort discussed can be provoked from somatic tissues lying deeply beneath the skin. Other instances are referred to in Chapter XIII.

The Effector Mechanism

The hyperalgesia described in this chapter may be produced either by injuring the skin, by stimulating a cutaneous nerve trunk, or by stimulating a small branch of the cutaneous nerve. The distant effect is essentially the same in all three cases, namely, hyperalgesia tending to fill the cutaneous nerve territory within which the stimulus falls. In all three cases, the hyperalgesia is brought about through the local nerves; because this is so and because the hyperalgesia is always of the same kind (being associated with a little smarting which develops slowly and being long lasting), it must be concluded that the same system of nerves is involved and that, whether the original nervous impulses descend directly to the periphery or first ascend and then descend, the same effector mechanism is called into play and establishes in the skin the same process or state.

It has been said that if skin of the forearm is anaesthetised locally before it is injured, the diffuse hyperalgesia does not develop; this is evidence that the distant skin is influenced through local nerves. But, if the local anaesthesia is used after the skin has been injured and the distant hyperalgesia has developed, the

hyperalgesia is unaffected. Thus, once developed, its maintenance over a considerable period of time does not require a continuous flow of nervous impulses from the original source of disturbance. The interesting conclusion is reached that the original injury sets up, through nervous channels, a relatively stable state in skin lying at a distance, a state conducive to hyperalgesia. The long duration of the reaction strongly suggests that some process, such as the release of stable chemical products (or a change in the skin whereby such release occurs and is maintained), happens at the effector endings concerned. The hyperalgesia arising from stimulation of a cutaneous nerve trunk must be regarded as produced similarly by a process at its endings. For this nerve trunk stimulation, clear evidence exists that, at the point stimulated, there is no durable change which could be held to maintain an influence through the nerve upon the skin, since nothing develops in skin guarded during stimulation by peripheral nerve block when that block is released. I asked Professor Foerster if, in his many observations upon stimulation of distal ends of posterior roots and of cutaneous nerves in man, his patients ever complained of burning pain in the skin; he replied, to my great interest, that it does occur and that he had recorded it (47). It is to be remembered that, in his observations, the direct pain path was broken, the nerve being cut and its distal end stimulated. Foerster, in speaking of the pain that nevertheless occurs, records the additional fact that it is abolished by section of the nerve that, overlapping, supplies the same territory. I think it probable that the nerve stimulation changes the skin supplied so that it liberates substances and that these act on the pain receptors of the overlapping cutaneous nerves.

Common Basis for Two Forms of Hyperalgesia

A possible if not probable relation exists between the diffuse hyperalgesia specially discussed in this chapter and the erythralgic hyperalgesia of the last chapter. The idea will obtrude itself that these may be manifestations of states differing from each other merely in degree. It may be stressed that both states have now been ascribed, on independent evidence, to the release of pain-producing substances in the skin. The hyperalgesic skin in the two states is similar; but the resemblance would be more

significant if it could be shown that the diffusely hyperalgesic skin displays recurrent pain to friction or that the threshold of the pain response to heat is lowered. The position is this. In diffusely hyperalgesic skin, a very little smarting is sometimes brought to light or is increased by local friction. When brought to light in this way, it follows upon the friction after a little period of delay, but it is a very inconspicuous affair compared with the unpleasant recurrent pain that follows friction of the erythralgic skin. Again, in most instances in which skin presenting the diffuse hyperalgesia is tested with copper at 40° C., no definite difference can be found between it and normal skin; but, in the more prominent examples, it is noticed that the warmth is more readily appreciated and its glow is longer felt. The reaction can be interpreted as a borderline one. It will be apprehended that neither in the case of recurrent pain nor in the response to warmth is the result emphatic. But, in each case, there seems to be a departure from normality in the apposite direction, thus bringing some support to the general conception that the underlying state in the two forms of hyperalgesia is the same, though differing in the degree to which it has progressed. It is conceivable that the same pain-producing substance is released in the skin but that, where the release happens through nervous channels, it is very much smaller than in the case of direct injury. The view is hypothetical and has against it the failure to obtain more emphatic resemblance when nerve stimulations have been increased in strength and duration.

The Nocifensor Nerves

Hyperalgesia of the kind discussed in this chapter is to be regarded as the result of a reduction in the threshold of the pain nerves of the skin; but this interpretation should not mislead us into believing that pain nerves form the system through which the local state underlying the hyperalgesia is provoked. When hyperalgesia fills a large part of the territory of a cutaneous nerve in response to a local skin injury, the stimuli provoked in a small area of skin spread to a much larger one. As there is clear evidence that this provocation occurs through nervous channels, it follows that nerve paths must connect the small territory of stimulation to all parts of the larger one. Both for this reason and also

from the evidence provided by barriers, we are brought to conclude that the skin possesses a system of nerve axons connecting every part with almost every other part within the territory of a given cutaneous nerve. It is very difficult to understand how painful stimuli could be accurately located on the surface of the skin, as they are (see p. 118) through a richly arborising nerve system of this kind. Other strong reasons for rejecting the pain nerves as those concerned are that there is evidence to show that the nerve fibres concerned are paralysed very early by asphyxia, while pain nerve fibres are paralysed late; and that weak cocaine will paralyse the pain nerve fibres of skin while leaving the apparatus through which hyperalgesia is spread intact (136).

The fact seems to be that the pain nerves appear merely to register, through sensations that we call hyperalgesia, a state of skin for which they themselves are not responsible.

The argument that, because painful cutaneous stimuli can be located by the subject, the pain nerves do not provoke the state underlying hyperalgesia applies with equal force to nerve fibres subserving touch, warm, and cold sensibilities, for impulses conveying these impressions are all well located. Thus, it would seem as if the sensory nerves generally can be dismissed. There remain of known nerves to the skin only sympathetic nerves; and, incidentally, these do form, in the skin, branching plexuses of an appropriate kind (Lewis and Marvin, 142). Yet it may be said at once that the sympathetic nerves are not concerned, for diffuse hyperalgesia is observed in skin completely deprived of them by degeneration after sympathetic ganglionectomy.

There is good evidence that the skin is supplied only by sympathetic nerves and nerves belonging to the posterior root system. That the latter are all concerned with sensory function is an idea for which there is no sure foundation. We have come to recognise given systems of cutaneous nerves by their manifestations; first, the sensory nerves and, afterwards, the vasomotor, pilomotor, and sudorific nerves, as changes in blood supply, erection of hairs, and sweating became recognised as being under separate nerve governance. It will be evident that any system of nerve fibres which, in the exercise of its function, gives

rise to no obvious and distinctive external manifestations will tend to escape recognition. The fact that a system of nerves, which I conclude to be present and to belong to the posterior root system, has previously escaped recognition is no argument against its existence; the need to postulate a new system has now arisen to explain hitherto unrecognised phenomena. Because the nerves are associated with local defence against injury and because they seem to belong to the same general system which is responsible for the local flare surrounding skin injuries, I have named them "nocifensor nerves" to distinguish them.

The type of hyperalgesia described in this chapter is unquestionably provoked through nervous channels. The system to which these channels belong is a distinct matter, more problematic, and one that cannot be pursued appropriately in this book. I have confined the discussion to evidence which implicates them in the production of hyperalgesia; their possible relation to vascular reactions and to "trophic" changes has been discussed elsewhere (135).

Chapter VII

CUTANEOUS TENDERNESS AND NERVE INJURIES

Of all cutaneous sensibilities, pain is recognised to be the sensibility most easily disturbed, especially in the direction of increase. Increase to warmth, cold, or touch is rare; increased pain response occurs in a variety of circumstances. Some forms of tenderness have already been considered; others, and especially those associated with nerve injuries, are to be considered in this chapter, in which also an attempt will be made in certain instances to correlate different forms of tenderness from the standpoint of underlying mechanism.

Now it is to be observed in the first place that there are two factors in tenderness; pain may be felt in response to a stimulus that ordinarily gives none, or the pain response may be abnormally unpleasant or intense. It is usual to confine the term hyperalgesia to the first form, usage relying upon the response of the skin to pricks of measured strength; for this purpose, the testing point is attached to bristles having different bending strains, as used by Frey and others. While using the term hyperalgesia only in this way, it should be pointed out that reliance upon the pricking test is not comprehensive, for some occasions occur when the threshold to friction is lower, but the threshold needle prick is higher, than in corresponding tests on normal skin (see p. 43). The second factor in tenderness, namely, exaggerated response, is the more important clinically; it may occur apart from the first or in conjunction with it.

In dealing with tenderness arising from injuries of nervous structures, I shall do no more than indicate the chief features of tenderness in thalamic disease. The excessive responses coming from skin in which the threshold may be raised—responses that are explosive and very widely referred—result both from

painful and non-painful stimuli and contain so large an emotive or affective element that they are regarded as being in a category of their own. They are interpreted as resulting from disturbance of the parts of the brain concerned in the reception of sensory impressions and especially, according to Head and Holmes (84), with parts that form the centre of consciousness for the affective side of sensation (disagreeable or pleasurable).

Forms of cutaneous tenderness, which arise from nervous structures and are relevant to other matters discussed in this book, come chiefly from injuries of the main nerves or root ganglia.

Tenderness at Time of Nerve Degeneration

A few days after section of a cutaneous nerve, the subject notices that the skin around the anaesthetic area attracts attention by its increased sensitiveness to friction (Head, 82). Measurement shows a true hyperalgesia, and the response is rather diffuse and lasting, though it is not referred. It lacks uniformity of distribution. Trotter and Davies (231) write, "it may be said for the most part to lie outside the line of anaesthesia to the brush, to extend for a less distance inside the line and to appear in detached islets in the midst of the analgesia." The hyperalgesia is patchy and curiously tends to be distributed in the neighborhood of subcutaneous veins. It lasts a few weeks but gradually vanishes, although it maintains to the last its relation to the veins. This is from the descriptions of Trotter and Davies, who suggest "that it is a secondary process due to the presence of some irritating substance produced as the result of the division and degeneration of the nerve." [1] They believed that toxic substances are produced during the degeneration of nerve fibres.

Nerve Regeneration and Altered Pain Sense

After an experimental section and resuture of cutaneous nerves, recovery of sensation is found to begin in about fifty to eighty days and to continue for several months subsequently. The pain

[1] It should be pointed out that, in the view of these writers, the hyperalgesia which they describe and which they rigidly separate from the sensitiveness of skin during the phase of nerve regeneration was believed by them to have been confused with the latter by Head and his associates.

responses of the recovering skin in such experiments are abnormal and were first described by Head and Rivers (82, 198). They found that, although the measured threshold to prick is raised (an unusual pressure on the point being required to elicit response), yet the response, when it comes, is of increased intensity; it is unusually unpleasant, diffuses from a point, and tends to be referred to remote parts. This reference is not fortuitous but can be repeated time and again. Trotter and Davies in their later description (231, 232) emphasise the same points, namely, hypoalgesia, intensification (associated with a desire to rub and relief on rubbing), and reference. They add that the reference is peripheral; in the most proximal part of the affected area, pinpricks are referred to the peripheral part of the area. This intensification and reference of returning sensibility is not confined to pain; both series of workers are agreed that it is conspicuous with cold, the reaction being explosive when it comes, and that it is present in lesser degree with warm and touch responses. They differed in their explanations of these phenomena.

For Head and his co-workers (82, 85, 198), the recovering area was one displaying only "protopathic" sensation; they believed that recovery of response to touch and intermediate thermal stimuli is delayed, thus exposing pure protopathic reactions, to which these curious characteristics of intensiveness, diffuseness, and reference are supposed to be natural. They further believed that the eventual return of the "epicritic" sensation modifies protopathic responses by a process of central inhibition (see p. 87) and that thus the curious characteristics become lost and each response becomes localised.

To Trotter and Davies, this explanation was unacceptable because, out of their wider personal experience of recovering areas, they disagreed on vital points of fact. They found no delay in the return of touch, but that touch, cold sense, and pain recover simultaneously. Thus the intensification and reference of cold and pain responses could not be attributed to lack of touch (epicritic) sensibility in the initial stages of recovery. They state emphatically that "intensification and peripheral reference bear no relation to hypoaesthesia and persist long after restoration of sensory acuity is complete."

Trotter and Davies found reference of cold and pain responses usually to the distal margin of the affected area and also found that the phenomena of peripheral reference are always to be obtained in their most marked form in the near neighbourhood of the regenerating nerve. They believed they had shown, by testing the known region of a regenerating nerve trunk in its course before the distribution of its cutaneous fibres, that, during regeneration, its excitability is increased. They concluded that peripheral reference is due to nerve fibre stimulation and that, in an area where recovery is in progress, the regenerating fibres show increased accessibility to direct stimulation—there is difficulty here in reconciling increased excitability or accessibility of fibres with the raised threshold in the tests, unless regenerating fibres and fully established end fibres are kept as separate conceptions. They suggest that the restoration of the local sensibility may be due to the re-establishment of the connection between nerve fibre and end organ. The intensification of sensation in the recovering area was ascribed by Trotter and Davies (232) to the regenerating fibres' being subject to chronic irritation consequent upon contact of the new nervous tissue with surrounding non-nervous tissues. This would imply that these fibres are spontaneously discharging impulses while regenerating (see 113 also). Their explanation remains in the stage of interesting hypothesis.

The reaction of cutaneous areas of nerve regeneration is interesting as an instance of special overreaction. In comparing it with other forms of painful skin, it should be noted particularly that there is in it no true hyperalgesia and that it is notably distinguished by the phenomenon of peripheral reference.[2]

Tenderness and Inhibition

It is agreed that during recovery from cutaneous nerve section, curious features of the pain response, namely, increased intensity,

[2] It is not entirely clear from Trotter and Davies's work that intensification may occur for warm sense. That there is hypersensitiveness of warm spots to heat is an interpretation placed upon the observation that certain spots in the recovering area give a pure pain response to temperatures which normally give not only completely painless but actually pleasant responses (231, 232). The temperature given is 50° C., but this is a test with a metal rod of small diameter. Boring (15), however, states definitely that there is a supernormal phase in the recovery of warm sense. The same worker states that hyperalgesia occurs in response to heat (43°, 113th day).

diffuseness, and reference to distant points, are present. According to the view of Head and his collaborators (82, 198), these features are due to the withdrawal of epicritic sensibility. They adopted this view largely upon the basis of a belief that intensification and reference are abolished and normal responses resumed as soon as the part becomes sensitive to cutaneous tactile stimuli and to intermediate degrees of temperature (which are comprised in epicritic sensibility). It is supposed that protopathic sensibility is normally diminished or "inhibited" by the epicritic response.[3] The case of recovering skin is almost certainly a special one, for it exhibits reference of pain to a distance. But Trotter and Davies are insistent that, during their personal experiences of recovery from nerve section, intensification and reference persisted long after sensory acuity (including touch) was completely restored. The vivid and radiating reaction could not in that case be due to loss of another sensibility but only to change in the pain response itself. Foerster (47) states that isolated lesions of the posterior columns of the cord give hyperalgesia of the corresponding skin; but I know of no confirmatory observations.

Rivers and Head believed the glans penis to be an example of tissue endowed with protopathic sensibility only; agreeing with Frey (53) that it is devoid of touch sense, they added their own belief that it gives no cold response above 26° C., a point vital to their thesis. This has not been substantiated; on the contrary the glans gives a local cold response as high as 34° if its temperature, when tested, is maintained at 41° or 42° (181).

Undoubtedly there are remarkable associations between an intense and rather diffuse response to prick and absent touch sense. As has been related, this association is normally found on the cornea and on the nasal mucous membrane as well as on the glans. In none of these instances, however, is there any distinct reference to a distant point, and in this they differ remarkably from skin recovering from nerve section. A much simpler and more satisfactory explanation of the association discussed than

[3] In general support of this hypothesis of inhibition, Rivers and Head (198) gave several instances. A chief instance was that immersion of the glans penis in water at 45° C. was said to give a sensation of vivid cold and of pain, both of which disappear when, on including the corona, warm spots become stimulated. The observation has not been confirmed.

that put forward by the protopathic-epicritic hypothesis is possible. It is that these mucous membranes are naturally provided with special innervation, touch nerves being absent (cf. Trotter and Davies, 232); I suggest that the pain nerves are derived from the deep, and not from the superficial, system and that to this the disagreeable and diffuse nature of the pain are due.

Tenderness in Asphyxial Paralysis

Another instance of the association discussed—and one readily observed—is encountered when continued asphyxia of the nerves of the upper arm anaesthetises the fingers (Lewis and Pochin, 148), for, as touch becomes lost in these, the intensity of pain response increases and it becomes a little diffuse, though again it is never referred and the threshold to pricks is not appreciably lowered.[4] This also might be explained as due to a withdrawal of inhibition. It is to be noted, however, that the pain does not change its quality but remains, in this instance, a pricking or burning pain according to the duration of the stimulus. It is also to be recorded that when the response to prick becomes more vivid in this asphyxial experiment, a remarkable increase occurs in the pain responses from deeper lying tissue; thus web pain becomes intense, and even slight pressure on the nail bed may give painful response. Here there can be no question that loss of epicritic sense is responsible, because these nerves are postulated by Head as supplying the superficies only.[5] Consequently, it is again difficult to accept imbalance between protopathic and epicritic systems as an explanation of these phenomena of asphyxia.

An alternative and adequate explanation is that the more intense and diffuse response to peripheral stimulation is due to an initial irritability preceding the loss of function, a loss which

[4] In the same article, an example is given of a similar association following pressure paresis of a digital nerve—paresis in which touch sensibility declined and tenderness increased on warming the site of injury and in which these changes were reversed on cooling.

[5] It should be said that Stopford (218) believes deep sensation to be divisible into epicritic and protopathic elements, as Head thought cutaneous sensation to be. Stopford (219), however, explains the deep hyperalgesia occurring in the period of regeneration following nerve section as due to heterogenous connections formed between pain nerve fibres and endings, such as those of touch, with lower thresholds of stimulation than those of pain. This idea is obviously inapplicable to this deep hyperalgesia when it develops during asphyxia.

the pain nerves are to suffer as asphyxia proceeds. This irritability is not pictured at the nerve endings but in the nerve trunk, especially in that section of it which lies beneath the compression cuff; the effects are the same if loss of circulation is confined to this stretch of nerve and the circulation to forearm and hand is maintained (Lewis and Pochin, 148). Thus, in this example, in which asphyxia is confined to a stretch of the nerve trunk, this stretch may be supposed to have its threshold of excitability lowered and to be giving rise to spontaneous discharges as described by Lehmann in cat's nerve (119), or these discharges may be regarded as being provoked by other impulses ascending from the stimulated skin in adjacent groups of fibres as described by Jasper and Monnier (92) for crustacean nerve. In either case, tenderness might then be supposed to result from a summation of the two series of impulses, each by itself inadequate to produce pain. The mechanism will be similar, though including a greater length of nerve, when the whole arm is asphyxiated.

Such an initial increase of excitability as we have suggested on the sensory side has been shown to occur on the motor side in asphyxia of the human arm up to the twelfth minute of asphyxia (Thompson and Kimball, 226).

Causalgia

One of the earliest clinical descriptions of this malady, which is considered because of the important problems it poses relating to pain, was that of Paget (177); it was followed by the fuller descriptions of Mitchell and his collaborators (164, 167). The cases are, for the most part, due to wounds; the nerve usually affected is the median, and less often the sciatic, the nerve being bruised or partly cut through. Within a few days or weeks, pain develops in the territory of the nerve and increases in severity. It is characteristically burning in quality, a fact to which the malady owes its name. The pain is associated with extreme tenderness of the corresponding territory, in median nerve lesions the radial side of the hand. Pain is elicited by the slightest contact, but by friction rather than by direct pressure; it is very easily provoked by warmth and also by real cold. The pain is so easily provoked and so severe when it comes that the subject perpetually guards the limb by shrinking at once from all threatened

contacts. Many patients continually moisten the skin to obtain relief.

After the malady has continued, the skin of the tender parts assumes a deeper blood colouration with a red or purplish tint; the skin becomes smooth to very glossy, devoid of wrinkles and hair, and often wet with sweat. These changes are no doubt partly, though not wholly, due to disuse. In most cases in which temperature has been mentioned, the fingers have been overwarm or hot[6] (Mitchell, 167). In some, a few blisters or a more definite herpes-like eruption develops, the latter even in successive crops.

There are two ways of regarding this extraordinary malady. The pain and tenderness may be regarded as arising directly out of the changes at the site of nerve injury. Ascending impulses started by warming or by light friction of the finger—impulses normally awakening no pain—may be supposed, on reaching the damaged area, to release other impulses in pain nerve fibres; or, alternatively, to summate with pain impulses discharging spontaneously from the region of injury (see asphyxial tenderness). A similar explanation would apply in all instances of tenderness arising out of nerve injury, for example, in cases of pressure on nerve roots within or without the spinal canal.

There is, however, in the instance of causalgia, another important phenomenon. In addition to hyperalgesia, there are objective changes in the skin to explain. Consideration of these brings us to the second way of regarding the malady. If a nerve supplying the skin is cut and the distal end is stimulated, the skin of its territory becomes flushed and warm. This is the so-called "antidromic" vasodilatation; there is evidence that it results from the release of vasodilator products peripherally (Lewis and Marvin, 143; Lewis, 135). This vasodilatation in man may be accompanied by itching and also by burning pain. The pain impulses seemingly ascend adjoining pain nerves, the territories of which overlap that of the affected nerve, for Foerster declares that the pain is abolished by section of the adjoining nerves. In

[6] Professor Paterson Ross has kindly supplied me with convincing readings of raised temperature from affected and control fingers in two patients. In two characteristic cases, which I have repeatedly examined in recent times, the affected fingers or toes were regularly warmer than the corresponding unaffected ones.

the conception that I have suggested (134), redness, heat, and tenderness of the skin in causalgia are all due to the release of substances peripherally; the release is supposed to bring the corresponding skin into a condition similar to what has been called the erythralgic skin (Chap. V). In support of this view is the fact that either warmth or cold applied to the skin induces pain in causalgia, as in erythralgia. In a characteristic case following median injury, a case which I recently examined, it was quite easy to ascertain that a single stroke of the tender skin elicited not only immediate pain but, after a pain-free interval, the recurrent pain. Two distinct pains cannot always be so demonstrated, though it is then usual for such pain as is elicited to be remarkable for its duration. These observations clearly point to the fundamental similarity of erythralgic and causalgic skin. There is a further argument in support of this conception of causalgia. The pain is always burning in character, a fact which is consistent with its origin from skin itself, as is the superficial incidence of all stimuli producing pain. If the pain arose directly by irritation of sensory fibres in the main nerve trunk, it might be anticipated that pain of the deep variety would also be felt from time to time and that deep stimuli would be painful. This does not seem to be the case. In accord, too, is Tinel's emphatic statement (229) that section of the nerve *distal* to the lesion may relieve the pain, when section proximal to the lesion has already failed to do so. This observation, of vital importance if true, requires further confirmation (see Leriche, 125, p. 156). Head and Sherren's observation (85) of glossy skin disappearing, within five days of section and freshening of the ends of a damaged ulnar nerve, strongly supports the idea that the skin changes result from an irritative nerve lesion. The presence of herpetic eruptions is not inconsistent, for we are obliged to consider a similar peripheral state arising out of nerve action in herpes zoster. It may be objected that the fingers are not always warm or hot; but we have no knowledge that "antidromic" vasodilatation can be maintained over periods of days without compensating factors intervening; and disuse by itself is certain to bring with it a large measure of cooling (see Lewis and Pickering, 144).

Thus, there is much evidence to support the idea that all

symptoms of causalgia arise at the periphery in response to changes caused there by centrifugal impulses. It would be wrong, however, to convey the impression that this manner of origin is proved.

According to Leriche the pain of causalgia may be abolished by sympathectomy. A case coming within my own observation convinces me that he is right; both pain and severe tenderness may disappear very quickly after this operation. The action is unclear. Sympathectomy leaves sensation in the normal unaltered, a fact easy to determine in the skin of those sympathectomised. When skin pain and tenderness such as typify causalgia disappear after sympathectomy, it is hardly open to us to suppose that sensory nerve fibres passing from skin to spinal cord have been divided. Similarly, it is difficult to suppose that relief comes through interruption of nocifensor nerve paths—for normal nocifensor reactions in skin are likewise uninfluenced by sympathectomy—unless we accept the improbable idea that nocifensor fibres traverse the sympathetic chain on their way to the periphery and have their cell stations at a lower level. Thus a process of reasonable exclusion would seem to bring us to the view that when sympathectomy relieves causalgia it does so by depriving the skin of sympathetic nerve supply; persistently increased bloodflow through the cutaneous vessels consequent upon loss of vasomotor tone appears to be the only way of explaining the relief that is consistent with our remaining knowledge.

Herpes Zoster

Causalgia and herpes zoster have much in common. Baerensprung in 1863 (4), on the basis of histological changes, attributed this malady to an affection of the posterior root ganglia. His work was consolidated and extended by Head and Campbell (83); the ganglion (or ganglia) is the seat of an acute inflammatory and haemorrhagic process; and these workers believed zoster to be an acute specific malady. In recent times, as is well known, it has been believed to result from a virus thought to be identical with that producing chicken pox.

There are two ways of regarding the cutaneous manifestations of the malady. The first view is that the main and primary disturbance is in the ganglion and that reddening, whealing, and

blistering of the skin are all secondary phenomena brought about by centrifugal impulses passing out, releasing substances (Lewis and Marvin, 143), and setting up an erythralgic state in the skin. The second view is that the virus spreads along the nerve channels, reaches the skin, and then directly provokes an inflammatory reaction. This second view is based upon the work of Teague and Goodpasture (223). These workers inoculated the tarred skin of guinea pigs with the virus of herpes simplex (labialis) and provoked a herpetic eruption of segmental type from which the virus could be recovered. It was suggested that herpes zoster has a similar underlying mechanism; but Cole and Kuttner (29) and a more recent worker (207), using fluid from the vesicles of herpes zoster, have repeatedly failed to infect rodents by employing similar methods.

Supposing that herpes zoster proves to result from a virus that spreads along the cerebrospinal nerve, such a mechanism would nevertheless be consistent with the idea that the skin lesions arise out of irritation of this nerve and the centrifugal impulses awakened. Moreover, the case for this mechanism does not depend solely on a supposed virus malady. Identical skin lesions may follow the invasion of a posterior root ganglion by malignant disease or their involvement by injuries, such as gunshot wounds (Head and Campbell, 83; Elliott, 42; Morton, 172); and very similar lesions occur, as has been said earlier, when the median or sciatic nerve has been injured. Thus, the clinical evidence that herpetic eruptions may arise out of lesions of root ganglion or nerve, lesions that are not infected or not specifically infected, is very strong. The experimental evidence is inconclusive. The phenomenon of "antidromic" vasodilatation is generally accepted, and this has been shown to result from release of appropriate substances; but neither in my experiments with Marvin nor in later attempts on man, have I succeeded in producing more than redness and tenderness. It is necessary to the hypothesis that centrifugal nerve impulses should be capable of provoking a full erythralgia and ultimately swelling or even blistering of the skin. This is relevant both to the case of causalgia and zoster. In zoster, as in causalgia, the skin reacts painfully not only to friction but to warmth (40° C.); I have observed this excessive reaction to warmth and that of recurrent pain to friction over very wide areas of skin adjoining those actually reddened or

blistered, and the reddened areas themselves are exceedingly hypersensitive. The reason why similar hypersensitivity, or swelling of the skin, has not been observed experimentally in man or animal is very possibly due to our inability to maintain nerve stimulation sufficiently long. The erythralgic skin of causalgia and of herpes does not come in a matter of minutes or even of hours; it is an affair of days or of weeks. But, although a full erythralgia has not been produced experimentally so far by nerve stimulation, it is quite clear that local reddening proceeding to wheals of the skin can be brought about in certain people by stimuli descending through cutaneous nerves (Grant, Pearson, and Comeau, 72).

To sum up, although the observations of Teague and Goodpasture suggest the possibility of another mechanism for zoster, the evidence still distinctly favours the idea that the skin lesions of causalgia and of zoster are the result of long-continued centrifugal nerve impulses.

Differentiating Forms of Tenderness

To be able to differentiate clinically between tenderness of the skin when this results from changes in the skin itself and tenderness resulting from lesions of the peripheral nerves would be important. In instances of primary change in the skin, whereby the local nerve endings are rendered hyperexcitable to stimulation, two phenomena appear. First, such skin responds painfully to warmth (40° C.); and second, rubbing the skin or stretching it produces not only immediate pain but recurrent pain after an interval of many seconds. This recurrent pain lasts. In cases of "neuritis" in which pain and tenderness is distributed in the territory of given limb nerves or in which tenderness is known to result from pressure on given nerve roots, the tender skin behaves differently. Warmth does not precipitate pain and, though friction is painful, there is no recurrent pain. These distinguishing features seem to have practical validity and usefulness (Lewis, 131). Theoretically, however, a hard distinction is less warranted, for, in certain forms of nerve injury or disease (causalgia and herpes), peripheral states of the skin are set up which resemble erythralgic skin; such states certainly give the response to warmth and recurrent pain to friction.

Chapter VIII

PAIN AND TENDERNESS IN ISCHAEMIC MUSCLE

Pain in Ischaemia

It has long been known to clinicians that, when a limb is exercised while the blood supply to it is kept arrested, the limb becomes painful. At first, inability to use the limb was thought to be due to developing weakness. So thought Burns (20), in describing exercise of the ligated limb, as long ago as 1809. Charcot (25, 26), after studying cases of "intermittent claudication" in man, and Potain (188) both recognised pain to be the predominant symptom. Two views have been held as to the origin of this pain; the one, that it arises from the arteries, these vessels developing a condition of spasm (44, 252); the other, that it comes from the muscles. Charcot believed in a cramp of the muscles, which he compared with cadaveric rigidity. MacWilliam and Webster (157) spoke of muscular metabolites. All these views, however, were speculative. In actual fact, there had been little or no work upon which to base conclusions before my observations with Pickering and Rothschild were published (145). These will now be described.

To arrest the blood flow and keep it arrested in the arm, we used the armlet of a sphygmomanometer connected at will to a large reservoir under a pressure well above systolic blood pressure. The flexor muscles of the forearm and hand were exercised by vigorous gripping movements. We found, as had previous observers, that after a time the arm becomes the seat of a disagreeable aching pain, gradually becoming so nearly intolerable that the exercise must be brought to an end.

The idea that the pain arises from spasm of the arteries of the limb was excluded in preliminary experiments by releasing the

bloodflow at the height of the pain and measuring, by a volumetric method, the rate of inflow into the limb during the first few seconds. It was found that, even with the first pulse beat, the inflow rate is greatly in excess of normal, a finding incompatible with constricted arteries.

The Muscular Origin of the Pain

In the standard test, almost maximal voluntary gripping movements, which develop a tension of 20 to 28 lbs. weight, are made (Fig. 15); they are carried out rhythmically at the rate of usually

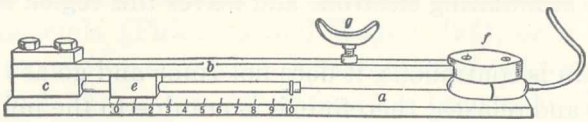

Fig. 15. (*Heart* 15: 368, 1929–31.) Apparatus used for registering the grip. The experimenter sits grasping the edge of a small table; the thumb and thenar eminence press on the table top, the index finger is flexed upon its under surface. To record this isometric contraction, the apparatus figured is used. Upon a metal base *a*, a piece of tempered steel *b* is bolted upon a block *c*. A second block *e*, sliding on a bar, controls the length of tempered bar brought into play. The plate *f*, on the end of the bar, presses on a thick-walled rubber bulb, from which a tube leads to an inscriber. Upon the bar, a receiver *g*, shaped to take the finger, is screwed. In use, the flat base of the apparatus is fastened to the under surface of the table, and the index finger lies in the trough of *g*. The grip is thus exerted between table top and the tempered bar and is recorded.

one a second. Such rhythmic movements can be undertaken painlessly for very many minutes, provided that the circulation to the limb is free; but, if the circulation is stopped before exercise begins, pain is soon felt. It begins after 24 to 45 sec. (or the same number of contractions) and quickly grows in intensity until it renders the exercise so disagreeable that the exercise is stopped at a point between 60 and 80 sec. Using uniform conditions and adequate periods of intervening rest between tests, it is surprising how constant is the time taken to reach the intolerable point in repeated tests on a given individual. The pain is rather diffuse, once it has come, and it gathers steadily in intensity as the test proceeds. It is easy to ascertain that the pain, though diffuse,

appears largely in the region of the muscles used. Thus, in the standard test, the pain is felt mainly over the flexor surface of the forearm; some may be felt over the thenar eminence. The most convincing examples are those in which small muscles and simple movements are employed, such as opposition of the thumb or abduction of the little finger. All such movements cause pain and deep tenderness in the region of corresponding muscles. Sharp location of the pain and tenderness may be obtained by using a faradic current and stimulating thenar or hypothenar eminence for 5 min. continuously. The pain then develops beneath the stimulating electrode and leaves this region sore subsequently.

The pain is continuous, it does not come and go as the muscle contracts and relaxes; therefore, it is not due to the imposition of tension upon nerve elements. Cramp does not occur; there is no recognisable increase in the tone of the muscles involved during their relaxations. Although muscular spasm has occasionally been reported to have accompanied an attack of "intermittent claudication", it is not ordinarily seen in these patients and it is clearly unessential to the production of pain.

If the circulation to the limb is released when exercise ends, the pain vanishes completely within about 3 sec.; but if exercise ends and the circulation is kept arrested, the pain persists until the flow is released, when the pain again vanishes within a few seconds. During the arrest, the pain persists unchanged and at or about the intensity (whether slight, moderate, or severe) to which it has been brought by the previous exercise. This is a most significant fact, and it led us (145) to conclude from these observations that the pain discussed is determined by a chemical or physicochemical stimulus developed in the muscle mass during its exercise and remaining stable during simple arrest of blood flow.

Since the pain develops when the muscle contracts under almost anaerobic conditions, it was natural to suspect it to be connected with lack of oxygen. But lack of oxygen by itself is an insufficient factor; a warm limb to which the circulation is arrested becomes deeply cyanotic in 5 min.; yet arrest for periods of 15 or 20 min. fails in the resting limb to produce the pain under consideration. Moreover, preliminary arrest of bloodflow to a

limb does not recognisably expedite the onset of pain in a subsequent exercise test. Such experiments placed the direct effect of lack of oxygen out of court and brought the argument to the point of showing that the process leading to pain is one starting within the muscle and is connected with its contraction process. But they did not exclude the possibility that deficiency of oxygen promotes, or hastens, the process that leads to pain. Actually it has since been shown by those who have extended our observations that lack of oxygen is in this sense responsible, since pain may develop in working muscle that is well supplied by blood provided that this blood is deficient in haemoglobin, as in cases of anaemia (Pickering and Wayne, 184), or is made deficient in oxygen by supplying the subject with a breathing mixture in which the oxygen percentage has been reduced (Kissin, 108).

The relation of pain to the amount of exercise is easy to demonstrate. If the rhythm of the muscular contractions remains constant but the tension developed is increased, the beginning of pain is correspondingly expedited (see Fig. 16). If the tension at each contraction is kept constant but the rhythm of contraction is doubled, then the period of exercise is halved. In other words, the same number of contractions is required to produce a given degree of pain, whether these occur in quick or in slow succession.

It is concluded that the stimulus responsible for pain when muscular exercise is taken in the absence of blood supply arises directly or indirectly out of the contraction process.

Factor P.—For reasons that will appear and because the appropriate nerves are found histologically (88, 190), we are bound to assume that the stimulus causing pain acts in the tissue spaces. When muscle contracts, changes, such as a release of metabolites, occur within its fibres. An obvious possibility is that such metabolites diffuse out and stimulate the sensory nerve endings in the spaces. But, since it is also possible that changes within the fibre may induce secondary and distinct changes within the spaces, it is expedient to keep the relevant changes within and without the fibre as separate ideas. Thus it is convenient to call the latter "factor *P*"; it is the stimulus to pain. So long as there is no bloodflow, factor *P* remains stable. It is cumulative during

work and increases with each muscular contraction but not with time. It rises first to a level adequate to bring pain, then to higher levels associated with increasing pain; and, because it is stable during the arrest of bloodflow, it maintains the pain between contractions and also after exercise has ceased.

Recovery.—In the standard test on the normal arm, the time taken for pain to develop from its beginning to its intolerable point is about 35 sec. The amount of factor *P* responsible for

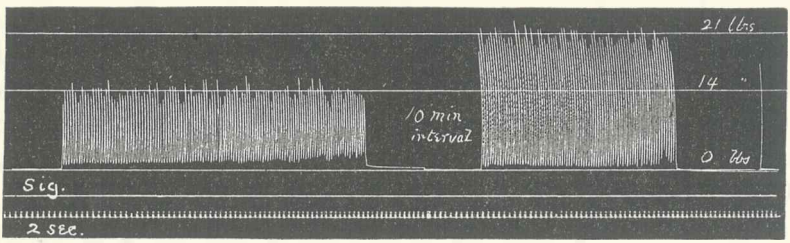

Fig. 16. (× ¾) (*Heart* 15: 373, 1929–31.) A record of two series of rhythmical gripping movements (at rate of 1 per sec.) each ended by intolerable pain. Each series was undertaken during arrest of circulation to the arm, and an interval of 10 min. rest with free circulation to the limb intervened between them. In the first series, the tension developed was 14 lbs; and in the second series, 21 lbs. The first series was ended by pain in 119 sec., and the second series in 76 sec. Time in 2 sec.

this development of pain is dispersed within about 3 sec. of restoring the flow of oxygenated blood to the muscle. Factor *P* might be regarded as being comprised in a process rapidly reversible in the presence of fresh blood or as being a substance that passes easily through the vessel wall to be dispersed by the circulating blood. Recent observations emphasise the importance of a return of oxygenated blood to the muscle as necessary for quick relief of pain and therefore support the first hypothesis.

The prompt relief of pain on releasing the circulation is not to be interpreted as meaning that there is complete recovery of the underlying process within the muscle fibre, but only that the accumulation of factor *P* outside the fibre has been reduced below the pain level. If the standard test is repeated without an adequate intervening rest period (although this period may be more than enough to abolish all pain), then, in the second test,

pain appears more rapidly than in the first; and it appears all the more rapidly, the shorter the rest period.

Muscular exercise with free circulation.—When the muscular exercise of the ordinary test is undertaken with the circulation free, there may be a little ache in the arm, but pain clearly identifiable with that studied here does not arise. From this, it is not necessarily to be concluded that factor *P* fails to develop in these circumstances, since conceivably it rises with the contractions and falls in the intervals and thus fails to reach the pain-producing level. From this standpoint, it is important to ascertain the influence of a preliminary muscular exercise, with free circulation, upon the subsequent development of pain, with circulation arrested. The time taken for pain to develop is found to be reduced, thereby showing that the process fundamental to the production of pain is natural to the working muscle while fully supplied with aerated blood. Within reasonable limits, the longer the period of the preliminary exercise, the shorter is the time required for pain to develop in the standard test; during the preliminary exercise, there is a process of accumulation.

Latent pain.—The experiments now to be described were those which led us to conclude, as foreshadowed, that the pain factor acts, not in the muscle fibre, but in the tissue space. It has just been shown that, during muscular exercise with circulation free, a process of accumulation relating to the development of pain occurs; this accumulation may be regarded as happening within the muscle fibre itself. If the exercise is done and the circulation is then stopped, there is no pain at the instant exercise ends, but pain develops distinctly after a latent period of 20 or 30 sec. and may become severe within a minute. This latency is not to be attributed to a natural delay in the development of factor *P*, for no such delay is suggested by other relevant observations. Thus, when similar exercise is carried out during circulatory arrest and pain comes, the pain does not increase if exercise is stopped; and, if exercise is carried to a point just short of producing pain, pain does not appear subsequently. The observations decidedly suggest that, while exercise is proceeding, factor *P* accumulates during circulatory arrest to given levels, and these levels, whether pain producing or not, are maintained if exercise ends and the circulatory arrest continues. But, if the blood is flowing during

exercise, then, although the chemical changes in the fibre will be cumulative to a certain level, factor *P* will not necessarily accumulate correspondingly in the tissue spaces or to a level sufficient to stimulate the nerve endings. According to this view, the latent period from occlusion to the appearance of pain is a period during which factor *P* is rising in the tissue spaces to a level corresponding to the state of the fibre. Thus, the fuller hypothesis takes the following form:—that a product of muscular contraction is directly or indirectly responsible for pain; that, when successive muscular contractions occur in the absence of bloodflow, the state of the muscle alters progressively and *pari passu* factor *P* accumulates in the tissue spaces; but that, when the muscular contraction occurs in the presence of bloodflow, although the same change happens in the muscle fibre, factor *P* cannot rise to the corresponding level in the tissue space. Clear support for this idea is obtained from a related observation. The exercise is undertaken with the circulation arrested for a fixed period, which is sufficient to produce considerable pain. The circulation is now released for a chosen period of time and re-arrested, and the time at which pain reappears and the intensity it reaches are noted. The period of release is suitably varied in distinct observations. It is found that the period of latency is less according as the period of release is less, and that the intensity reached by the pain, and subsequently maintained, is greater, the shorter the period of release. This is readily explained on the ground that the state within the muscle fibre at the instant the bloodflow is re-arrested will vary with the previous duration of that bloodflow. After a short release, recovery in the muscle will be slight; on re-arrest, factor *P* will rise quickly to the pain-producing level and subsequently to a high level in the tissue space; pain will then be considerable. After a long release, recovery will be greater; on re-arrest, factor *P* will rise more slowly to the pain-producing level and ultimately to a lesser height; pain will then be slight.

As previously indicated, the quick disappearance of pain on release of circulation in the standard test is to be interpreted as due to the prompt reduction of the level of factor *P* in the tissue spaces and not to recovery of the muscle mass as a whole. The ordinary failure of pain to appear in muscular exercise with in-

tact circulation may be attributed to adequate interchange between tissue space and vessel in which oxygenated blood is flowing rapidly and to the transformation of factor *P* so that it is no longer pain producing. For the purposes of this book, it would not be very relevant to discuss further the nature of factor *P* and the evidence for its being lactic acid or otherwise.

Muscle Tenderness

When pain is induced by working muscles under ischaemic conditions, tenderness also appears. It is deep to the skin and is easily detected by pressing or gently squeezing the muscle that has been used (145). If a small muscle or small group of muscles like those of the thenar or hypothenar eminence is employed, the sharp limitation of tenderness to such muscle is easy to observe. The tenderness develops with the pain and is maintained if exercise ceases but arrest of bloodflow continues; it disappears very quickly, as does the pain, when the flow of blood returns. Thus, there can be little reason to doubt that the factor which underlies the pain also underlies the tenderness. The example is one of deep tenderness clearly resulting from a metabolic cause.

Although it is usual for the whole of the tenderness to vanish on releasing the circulation, a little tenderness may remain for an hour or more if the test has been repeated several times; the mechanism of such tenderness is presumably different and more akin to that associated with what is ordinarily termed "stiffness" after hard muscular work (181).

Comment

The experiments relating to the pain and deep tenderness of muscular ischaemia have been described here at some length because they were the first in which any substantial evidence was brought to show that pain and tenderness can result from the accumulation of a factor arising out of natural tissue processes. They therefore mark a very distinct step forward in our understanding of the mechanisms of pain and tenderness.

The pain of muscular ischaemia is met with clinically in the condition known as "intermittent claudication". It occurs from

time to time in all kinds of conditions in which pathological obstruction of arteries of the limbs occurs. Lastly, since the publication of the evidence relating to somatic muscle pain and the suggestions arising therefrom (Lewis, 130), the pain of angina pectoris has become very generally accepted as arising out of similar processes in the heart muscle.

Chapter IX

EXCITANTS OF PAIN NERVES

Relation of Pain to Tissue Injury

Cutaneous pain has long been known to be produced by many different kinds of strong stimuli. Frey (54) recognised the high threshold of pain points and compared it with the much lower threshold of touch points. The experiences of everyday life inevitably teach that painful stimuli are, in general, strong enough to be injurious. The idea has been expressed in different forms for many years. Weber (238) in 1846 tried to make the relation precise by calling attention to the grade of heat required to produce pain and by stating it to be of a degree that, working for a little time on nerve, limits its conduction; the temperature given was 48.7° C. Exactitude in stating the relation between pain and injury is, in fact, very difficult to attain. Pain in the normal skin is produced by much lower grades of heat than Weber suspected; his measure was of surface temperature, to which, owing to the free supply of blood to the papillae, the nerves of the skin are not exposed. A temperature of 43° C. is intolerably painful to most skins if, by arresting the circulation to the limb, this grade of heat is allowed to penetrate. The same may be shown by heating the skin with circulation intact and registering the temperature beneath the skin; the heating becomes intolerable when this rises to 42°–43° C. (Lewis and Love, 141). As the temperature of skin is raised, the sensation of warmth sooner or later has pain added to it. The element of pain *begins* to appear when the surface of the skin is raised to about 43° or when the subcutaneous temperature is about 38° (Fig. 17). Temperatures very close to these levels are the lowest to produce a distinct arteriolar flare in the skin of the neighbourhood; that is to say, they are the temperatures at which we can be certain that injury to the skin cells is happening and H-substance (i.e., a histamine-like sub-

stance) is being released to give the axon reflex. But there are indications, in the form of persistent local reddening of the skin in response to heat, which would place the earliest damage even at slightly lower points.

If the skin of the front of the forearm is pricked with a needle point, just sufficiently hard enough to elicit pain, most if not all of these pricks will subsequently show the signs of tissue damage

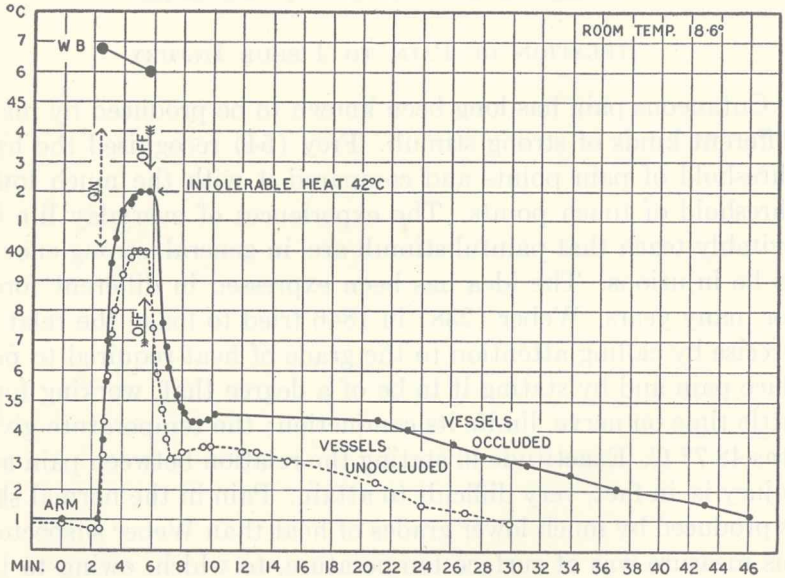

Fig. 17. (Lewis and Love, *Heart* 13: 53, 1926.) A comparison of the effects on subdermal temperature of plunging the arm into hot water, with the vessels to the limb occluded and unoccluded. The temperatures of water bath (*W.B.*) and of a subdermal point in the arm are given.

in the form of little circles of redness with or without perceptible wheals. Indeed, these local reactions may occur from point to point pricked even in the absence of pain response.

If a galvanic current is applied to the skin through a needle point acting as cathode, pain is experienced with currents of about three hundred microamperes; this pain is due to the electrolytic release of minute gas bubbles in the skin (Lewis and Zotterman, 151).

When chloroform is held on the skin, it gives rise, after a time, to burning pain; in these circumstances, intense local reddening

occurs and will proceed, if the chloroform is maintained, to blistering.

These observations[1] all tend to emphasise a close relation between pain and damage to the cells of the skin rather than damage to pain nerve endings. In emphasising the relation between pain and injury, it would be undesirable to create the impression that the relation is absolute. When there is pain, there is injury; but, when there is injury, there is not always pain: skin may be frozen painlessly, and it may be damaged painlessly in extreme cases of urticaria factitia by stroking with a finger.

Writing about pain nerves of skin after he had noted that mechanical thermal, chemical, and electrical stimuli give response, Sherrington (211) said "that these agents, regarded as excitants of skin-pain, have all a certain character in common, namely this, that they become adequate as excitants of pain when they are of such intensity as threatens damage to the skin." This capacity to be excited by a wide range of different kinds of nocuous stimuli is linked with the naked nerve endings and the absence of any highly evolved specialised end organs. The naked endings are better adapted to a wide range of stimuli than is a special end organ. From an evolutionary standpoint, a "low threshold was not required because the stimuli were all intense, intensity constituting their harmfulness; but response to a wide range of stimuli of different kinds was required, because harm might come in various forms."

The very close adjustment that exists between pain and injury ensures a serviceable response to the former, for cutaneous pain promotes withdrawal, abrupt or more deliberate according to the measure of the threat.

Direct Stimulation of Pain Nerve Endings

In stating that the nerve endings are excited by a wide range of different nocuous stimuli, thus linking them with naked endings to the exclusion of special endings, our conception primarily takes the form of direct stimulation. This conception of physical agencies, which regards them as immediately pain producing, is the predominantly, if not the universally, held view today;

[1] And similar observations upon cold might be cited, see Brit. M. J., Dec. 1941, p. 795.

for all such physical agencies as pricking, cutting, crushing, heating, and electrical excitation provoke pain whether applied to skin or to cutaneous nerve itself; and of irritant chemical substances the same may be said.

Tension.—A frequent and, from the clinical standpoint, important physical factor in the production of pain is that of tension. The pull that must be exerted upon skin before pain appears is naturally considerable when the area affected is broad. But pulling upon a hair is quickly effective and owes its response, in all probability, directly to tension on pain nerve endings. When skin is inflamed and its pain nerves are thus rendered hyperexcitable, deliberate stretching of it is a most effective stimulus. It is a stimulus natural to forms of inflammation associated with much exudation, as in the painful boil before pus issues from it. In these forms, the increased tension induced by each heart beat may bring its pulse of pain, as also in the pulsating toothache and throbbing headache, on which Pickering (183) has published many excellent observations. Certainly each includes a potent tension factor.

Indirect Stimulation; Chemical Factors; Malnutrition

Frey (54) commented upon the delay that may occur in the pain response of skin to the mechanical stimulus of pricking. He placed a sharp point on the skin and maintained it there under a given pressure. If the pressure is suitable, the first contact gives a sense of touch and, after a delay, a pain response appears. He says that Gad and Goldscheider (59) had noticed a similar phenomenon earlier and had ascribed the delayed pain response to a summation of impulses in the cord. This phenomenon has been dealt with in Chapter IV. To a single prick on the finger, there is a touch followed by a pain response. Or, with stronger stimulation, two flashes of pain are felt in quick succession; these are alike, though the second may seem slightly more prolonged than the first. It has now been shown (Lewis and Pochin, 147) that these two pain responses are due to the excitation of two sets of pain fibres, the one conducting much more quickly than the other. Thus, although we are dealing in the two cases with immediate and simultaneous excitation, the corresponding and very similar messages are not simultaneously received by the

sensorium. Consequently, there is no need to introduce an intermediate local process to account for the delay of the second response, which is otherwise fully explained. But Frey's comments (55), repeated in 1922, were interesting. He speaks of the nerves of the epidermis lying between the cells and of fluids issuing from the cells, changing the concentration of substances in the spaces, and exciting the nerves; he explains the lag in the production of the second pain along these lines. Thunberg (228), in explaining the same double pain response of skin, quotes Frey and adopts a similar explanation. Thunberg believes it probable that, where there is a latency, there is an intermediate process but that, when the stimulus is strong enough, it breaks through without this process intervening. This view of Frey and Thunberg was a speculation and, applied to the lag of the second response to a brief cutaneous stimulus, it has proved untenable. However, it is of much interest in being, so far as I can ascertain, the first suggestion that pain arising by mechanical injury of the skin may not be a direct response of nerves to injury but may result from an intermediate process dependent on epidermal damage.

It seems to me probable that Frey was not exclusively observing the Goldscheider phenomenon, though he does not recognise the fact. He confused itch with pain and regarded the former as merely differing quantitatively from the latter; and so he sometimes uses the sensation of itch or of slight burn, either of which appear and continue for a time after a prick and either of which is relieved by rubbing, to support the idea of a chemical stimulus (55). For reasons that will be stated, I think it quite clear that itch and pain must be considered separately. A slight continuous sting sometimes follows for a few seconds a prick of the skin, especially a prick of the cheek; this sting resembles itch in being relieved by friction and is very possibly due to an intermediate chemical stimulus, though I know of no evidence to support the idea other than the suggestive fact of its continuation.

A more dramatic example of pain continuing after injury and requiring an explanation distinct from that of direct excitation of nerves is that resulting from burning heat. If considerable heat is transiently applied to any point of the skin, a burning

pain is felt momentarily during the application and quickly subsides. This pain is probably due to direct physical excitation of the pain nerve endings by heat. But, if the heat is just sufficient to scorch the skin visibly, a similar burning *returns at an interval* of perhaps 10, 15, or 20 sec., after the removal of the source of heat. This pain is the familiar pain that lasts for many minutes after small slight burns; the delay in its onset is overlooked unless attention is directed to it. It is not a flash of pain like the original one; it is long maintained. Transmission through the same cutaneous system of nerve fibres to a common centre adequately accounts for the similarity of the two pains. But the recurrent pain cannot be ascribed to the direct effect of heat; it is a delayed effect appearing after the heat has been dispersed, and it is necessary to explain the interval of time that intervenes before this pain comes. Something in the nature of a chemical or physicochemical change is happening within the skin during this interval and is rising to a level adequate to provide a stimulus.

This example, and the suggested explanation of it, links with those described in detail in Chapter V on the erythralgic skin. We have there seen how tension or friction applied to such skin produces immediate pain and how, after an interval, pain recurs and lasts for minutes. And we have seen that the deliberate test of arresting the circulation brings evidence that the process underlying the recurrent pain, unlike that underlying the immediate pain, is a stable affair in these circumstances. The pain of a prick, of tweaking a hair, of an induction shock, are immediate and fleeting upon skin deprived of its circulation; the recurrent pain continues while circulatory arrests lasts. By itself, this evidence carries beyond the stage of hypothesis the idea that sensory nerve endings may be stimulated through natural chemical or physicochemical tissue changes. It does not stand alone. Equally notable evidence has been afforded in the case of muscle pain, described in Chapter VIII. This case of muscle pain, with its underlying *P* factor, is to be stressed as the first instance in which convincing evidence for the indirect stimulation of pain nerves by tissue change was brought forward. Another example is that of nocifensor tenderness, described in Chapter VI and believed to result, with its occasional slight spon-

taneous pain, from chemical changes at the effector endings of the corresponding nerves.

Threshold changes.—In interpreting the manner in which pain nerves are excited by physical agencies, it is very important to remember that the threshold strength of the pain stimulus is not unvarying. It has been stated that inflammation alters the threshold, and much of Chapter V has been devoted to this subject. Slight degrees of tension and grades of heat that are actually within the range of normal body temperature become adequate. It has been concluded that hyperexcitability has been produced by released substances playing upon the nerve endings; it may be perhaps less accurate to regard the low grade of heat as the stimulus rather than the released substance itself, in such circumstances. Had we evidence that, under conditions of inflammation, the temperatures and tensions injurious to the tissues may be definitely lower than those injurious to normal tissues, heat and tension might still be regarded as primary agents; but we have not such evidence, and we still remain without an intimate conception of the processes. It will, however, be clear that this factor of threshold change may be essential to the occurrence of pain resulting not only in inflammation of skin, where its influence is manifest, but in the case of more deeply seated disease, inflammatory or otherwise. There may possibly be circumstances in which temporary states of altered metabolism or of tissue interchange are adequate to excite pain, for example, from such tissues as aponeuroses, joint capsules, and ligaments, in the absence of any identifiable structural change.

Nature of chemical or physicochemical stimulus.—In the present state of our knowledge, any discussion of the nature of the chemical or physicochemical stimulus responsible for pain must be tentative and directed to stimulating more enquiry rather than to suggesting final views.

We are perhaps nearest to a solution in the case of muscle pain, for, in this instance, it has been shown (145) that the stimulus arises out of the activity of muscles and that it is probably dependent upon the production of metabolites during contraction; such metabolites, in the presence of a supply of well-oxygenated blood, are removed, not by diffusion, but by reversal of the initial process.

The close relation between production of pain and injury of the cells in the case of cutaneous stimulation at once raises the idea of release of normal cell constituents. There is here such clear parallelism between the production of what we call itch and what we call burning pain, that it will be profitable to devote preliminary attention to the former.

It is known that any kind of injury producing what has been described in previous publications as the "triple response" (Lewis, 129) will also produce itching. Thus this response is given by slight mechanical injuries, by freezing, by heat, by galvanism, and by a variety of injurious substances. To obtain this effect and to obtain itching, it is necessary that the injury be graded carefully so that it does not pass a certain grade of severity (Lewis, Grant, and Marvin, 138). There is abundant evidence, now generally accepted, to show that this "triple response" results from the release of a histamine-like substance from the cells of the skin (129). Such a substance can be extracted from skin and, when it is reintroduced into normal skin, produces the full triple response and itching (78). This itching, however produced, may last for a minute or two. But, if the circulation to the skin is arrested, it lasts much longer. Where histamine has deliberately been introduced into the skin, we naturally conclude that this prolongation of itching is due to histamine's being retained at the site of introduction. Similarly, when it is ascertained that the itch produced by such minor injuries as have been cited is also prevented from subsiding by arresting the circulation to the skin, we are driven to conclude that the continuation of itching is the result of retention of the released H-substance (138). This observation and the corresponding observation in the case of burning pain emphasise the similarity of behaviour; the similarity is ascribed to the supposition that both itch and pain are the result of a release of stable substances from skin cells by injury. Again, it is known that, if any of the physical forms of stimuli named as inducing itching is increased in strength, pain will appear. Increase the heat stimulus; instead of itching following, prolonged burning pain is felt and, more likely than not, the skin will blister. A notable instance is found in the case of freezing. Freeze and thaw the skin, and it is the rule for the skin to wheal and to itch

intensely. Increase the hardness of freezing or prolong it and, when the skin thaws, burning pain will be felt; from the moment this pain appears, it is known that the skin will subsequently blister (Lewis and Love, 141). Neither itch nor pain waits upon whealing or upon blistering, respectively. Each appears before wheal or blister has come; each can appear before there is any possible output of fluid from the blood vessels if, during thawing, the circulation to the part is kept arrested. The sensation arising, itch or pain as the case may be, is connected with the grade of tissue damage; it appears to be a question of how freely cell contents are liberated. Here there would seem to be suggestive evidence that the itch, with its associated wheal, and the pain, with its associated blister, are but grades of the same process. Indeed, Frey (55) thought that itch and burning pain are merely different intensities of the same sensation. But in this I cannot agree. Each occurs and is distinctly recognisable as such through a considerable range of intensity; burning pain is identified as such when it is so slight as to be only just appreciated. Itch and pain may arise together from the same skin and yet each be recognised distinctly. Immersion of skin at 40° to 41° C. quickly abolishes itch, but burning pain is intensified (Lewis and Hess, 139).[2] Thus there is abundant evidence that, though similarly produced, itch and pain are separate phenomena. Though both are due to release of tissue substances, they are not both due to the release of the same substance.

Histamine pricked into the skin produces itching; it does not produce pain. Used in the usual form of the acid phosphate, the solutions are distinctly acid in high concentration and must be buffered carefully; if this is done and the histamine is introduced by a simple needle prick, itching is the result, whether the concentration is 1 in 30,000 or 1 in 30 (181).[3]

[2] Inability to provoke itching from nasal mucous membrane or glans penis I hesitate to cite again, because it now appears probable that the pain nerves supplying these do not belong to the cutaneous but to the deep system; and therefore it might be held that, for this reason, conveyance of the itch sensation fails.

[3] Rosenthal and Minard (200) obtained pain from histamine, but their methods differed from mine. An application to a raw surface of skin is unsuitable in testing normal sensory responses, for such skin is already very hyperalgesic. Intradermal injection, too, is much less suitable in the case of histamine than is pricking, for it introduces far larger quantities of histamine and directly injures the skin far more than does the prick. The natural content of human skin is equivalent

It is to be emphasised not only that itch and burning pain can be recognised as separate subjective phenomena but that, in my view, they are not produced by the same released substance; the two series of observations are consistent with each other and mutually supporting. There is but one difficulty in this conception of twofold release; but it is not, I think, insurmountable. It is hard to suppose that, in the two instances, the itch and the pain substance are released merely by increase in the permeability of the same cell wall. If it were to be supposed that the size of the molecule of the histamine-like substance is smaller than that of the pain substance, then we could suppose that mild injury would release the former and severe injury would release both. But we should still be in difficulty in explaining why the pain response is not usually mixed with itching in these instances. It is possible that the pain is usually severe enough to disguise underlying itch. It is also possible that release of the histamine-like substance happens in some other way than that of the pain substance or that they are released from cells of different type.

To return to the pain substance, it is concluded that such a substance is released and accounts for continuous pain in severe damage of the skin and for recurrent pain when the erythralgic skin is rubbed. Reasons have been given on page 80 for believing that the substance responsible for nocifensor and erythralgic tenderness may be identical.[4] The nocifensor reaction, therefore, is also included.

When it is asked what the nature of the pain substance is, the answer remains speculative. It has been suggested (14) that potassium ions may be responsible for cutaneous pain; it

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to about 1 in 50,000 histamine base; and it is clear that quantities of higher concentrations, such as were injected in the observations cited, are not to be regarded as comparable to natural H-substance release. Actually, it is not my experience that small intradermal injections of histamine of 1 in 30,000 or greater strength produce pain; they will do so occasionally, but the predominant sensation is undoubtedly itching.

[4] Rosenthal and Minard (200) have misunderstood me in thinking I have ascribed nocifensor hyperalgesia to H-substance release. I have regarded it as due to an appropriate but distinct substance. The misunderstanding seems to have arisen out of my comparing an "antidromic" H-substance release, causing vasodilatation, with distal hyperalgesia from nerve stimulation and out of speculating that the nerve fibres underlying these two reactions possibly belong both to the same broad nocifensor system. But I had no intention of identifying these two reactions with each other or of suggesting for the two a common underlying chemical release.

has also been thought (64) it might be due to change in hydrogen-ion concentration. But such speculations could not be accepted on the basis that solutions of potassium salts or phosphate solutions of ascertained low *p*H cause pain when introduced into the skin.

If freshly excised human skin is frozen, crushed, and extracted by the addition of an equal or smaller volume of distilled water, and the extract centrifugalised, the fluid obtained gives pain when injected intradermally in small quantities (0.02 to 0.03 c.c.).[5] Smarting comes after a short delay and increases in intensity; it is usually mild but may be severe and lasts usually for several minutes. It is sometimes mixed with itching, for this extract contains H-substance and wheals the skin into which it is introduced. Many experiments have been conducted along these lines (Lewis, 133). They are consistent with the belief that there is present in normal skin a substance that is capable of giving rise to pain. Professor C. R. Harington has given me his help in showing that the extract does not owe its potency to changed *p*H or to altered tonicity. The pain is not due to protein, to potassium, to histamine, or to acetylcholine.[6] These are negative results, but there is no specific conclusion as yet to replace them.

Relation of arterial spasm to pain.—That pain nerves occur in the walls of many arteries is known (see Chap. I), though it is not clear that they occur in all; thus, the aorta and main arteries of a limb may be ligatured painlessly (James, 91; Murray, 174; Odermatt, 176).

In different guises, the idea has arisen and persists that pain may result from arterial spasm. I shall consider this matter briefly because it may be applied so generally.

The idea begins to develop in Erb's writings (44) on the symptoms arising when a limb is worked in the absence of adequate blood supply, in which relation the view has been stated in an emphatic form by Zak (252). This problem has been investigated fully in recent times (Lewis, Pickering, and Rothschild, 145); and it has been concluded that, when this pain develops, the arteries are not contracted, but dilated, and that the pain

[5] In this instance, since pricking in the plain solution is without effect, larger quantities must be used.

[6] The original papers contain data giving the strength of potassium, the range of *p*H, and the hypertonicity of sodium chloride solution that will give pain.

comes from the muscles engaged in work (see Chap. VIII). Pain appearing in acute embolism is also to be ascribed usually, perhaps always, to loss of blood supply to the muscles of the limb (Lewis, 132).

A second phenomenon to which frequent references are found in modern writings is Raynaud's disease, in which, through spasm of the digital arteries, the fingers temporarily lose their blood supply; it has long been known that the malady may be an extremely painful one. The arterial spasm has been regarded as the direct cause of pain. Now this is not so. Patients suffering from the more benign forms of Raynaud's disease, though they exhibit the full signs of digital arterial spasm, complain very little of pain. It is the patient in whose fingers nutritional changes and small areas of recent necrosis have appeared that chiefly suffers, and the complaint is not limited to the period of the spasmodic attack. The areas of deficient nutrition are at all times tender; they become severely painful when accidentally knocked and whenever the fingers become cold. The arterial spasm is induced by cold, and cooling may subsequently continue to a low point. Penetration of cold into normal fingers causes severe aching pain at low temperatures (5° to 10° C.); it causes severer pain in inflamed fingers. Thus, one of the causes of pain of the attack in Raynaud's disease is the exposure of damaged tissue to low temperature; it is not due, except very indirectly, to arterial spasm.

A second cause of pain in this malady (Lewis, 131) is probably the chief cause of very severe pain. It is brought about by the release of arterial spasm and the sudden discharge of warm blood into a cold finger. If the circulation to a normal finger is stopped and the finger is cooled by immersion in ice-cold water for 5 min. and if it is then transferred to a bath at 36° to 38° and the blood flow released, burning pain starts in about 15 to 20 sec. and lasts for a minute or so. It varies in degree in different subjects but is sometimes very severe and may leave the finger tender for hours. It occurs, though not usually with the same severity, when the finger is warmed without restoring the circulation and can be stopped quickly by returning the finger to the cold bath. I have seen a man who presented Raynaud's disease with healing necroses of a finger reduced to a state of quivering sobs by rais-

ing the temperature of his finger quickly from 15° to normal; he experienced similar pain during recovery of his hands from the discolouration of his spontaneous attacks.

Intractable and severe pains occur in some amputation stumps; resection of the neuroma which has formed on the end of the cut nerve will give temporary relief, thus indicating that the pain arises from this neuroma. As Leriche (125) has taught us, pain in these cases may be abolished by breaking the sympathetic paths to the limb. Similar results are known in causalgia and less clearly defined conditions. The orthodox explanation of these effects is that they depend upon increased blood flow to the limb tissues that are provoking pain, and not that they release an unnatural and painful vascular spasm or that pain impulses passing from the limb through sympathetic channels are blocked.

To sum up, there is no evidence that arterial spasm directly produces pain; there is abundant evidence that pain may arise out of malnutrition of tissues consequent upon reduced blood flow.

Chapter X

REFERRED PAIN

Localisation of Somatic Pain

The power to localise the source of pain perceived, a power often essential to the avoidance of repeated injury by the same agent, will be discussed from the standpoints that are relevant to the rest of the subject matter of this book. We may begin by considering this localisation from the standpoint of fact and in the tissues where it is most highly developed.

Skin and mucous membrane.—1. Skin.—The older studies of localisation in skin concerned themselves almost exclusively with tactile sensibility, which is alone easy to arouse in pure form; it is universally recognised that light touches are localised with great accuracy. Our power to recognise the source of pain is less easy to test. When skin has been blistered or when an irritant substance has been placed upon it, burning pain may be felt, and the region giving rise to it can be found without great error through this sensibility only. For finer work, a smaller source of pain and pain of shorter duration is required. The site of a needle prick is very accurately judged upon the finger, but it is unsafe to assume that judgement comes only through pain sensibility while touch is simultaneously involved. In using needle pricks, I have avoided any possibility of guidance from tactile or deep pressure sensibility by arresting the blood flow to a limb kept warm in water at 37° C. for a suitable period previously. Thus treated, the hand loses all appreciation of simple contacts, light or heavy, within 25 or 30 min., but needle pricks are still felt. The pricks on fingers and hand are localised with an error less than one centimetre in almost every test (Lewis, 133); there is no appreciable difference in the accuracy of localisation in the normal and in this ischaemic hand. In earlier and later stages

of the asphyxia, graded pricks allow the first and second responses to be tested separately on the anaesthetised finger. Both are well localised.

2. Mucous membranes.—Pricks with needle point, testing which involves tactile sensibility, are localised very accurately on lips, gums, and tongue.

Tests of the glans and nasal mucous membrane are uncomplicated by touch sensibility. On the glans, pricks, though giving a more diffuse sensation than from skin, are localised sufficiently well for them to be recognised as right- or left-sided, dorsal or ventral, proximal or distal. In the nose, stimulation of right and left is appreciated; but, beyond this, localisation seems to be very imperfect.

Subcutaneous tissue.—In Head's experiment (198) in which his radial and external cutaneous nerves were divided, an area of skin upon the back of the hand became completely insensitive while leaving responses, including pain, to deep pressure. These responses were stated to be accurately localised. Using the hand rendered, by its asphyxiation, completely insensitive to touch and light pressure, pain is easily elicited by squeezing the webs of skin separating the different fingers. The web stimulated is usually recognised; but this is not always so; the pain, while rather diffuse, is sometimes localised incorrectly in a neighbouring web. Pain arising from a tiny quantity of 5 per cent saline injected into the subcutaneous tissues of the back of the hand is usually well localised but is sometimes felt at curiously distant points (Lewis, 137), as in the case of web pain.

Fascia.—Kellgren (101) elicited pain from the gluteal fascia or from that overlying the tibialis anticus by passing a hypodermic needle through the anaesthetised skin and allowing the point to impinge on the fascia or injecting the fascia with a little hypertonic saline. He found the resulting pain confined to the region stimulated; it was localised by the subjects tested at, or more usually a few centimetres distal to, the needle.

Tendons.—Those tendons which have been tested by similar methods by Kellgren and by myself (103, 137)—namely, the tendo Achillis and the tibialis anticus tendon, both of which are superficial—have given local pain in the region of the stimulus or a little distal to it.

Muscles.—In preliminary observations, by using small injections of 5 per cent saline or squeezing the belly of the muscle, I found that pain arising from muscles, though felt in the general neighbourhood of the point stimulated, is usually very diffuse and is often felt at a distance. Thus, pain provoked from the lower part of the triceps often extends down the inner side of the forearm as far as the little finger, and that provoked from the trapezius usually extends into the region of the occiput (Lewis, 137). I was fortunate in interesting Kellgren in these reactions and suggested to him that he should systematically investigate the accessible muscles. From a long series of researches in my laboratory, he has since formulated some very striking principles underlying the reference of pain from muscles (101).

He found that the pain induced by the injection of a given muscle is felt over definite areas seemingly following a segmental pattern. The distribution for a given muscle is similar in different individuals. Naturally, the segmental pattern is best seen on the trunk; thus, if intercostal muscles are injected, the pain areas form narrow bands differing in level by the width of a space and rib. They tend to break into dorsal and ventral patches (as in Fig. 18). Appropriate segmental patterns also appear on the limbs (Fig. 19). There may be variation, the pain being felt in different subjects with greater or less intensity in proximal (dorsal) or distal (ventral) parts of the segmental areas affected; there is also variation in proximal and distal intensity according to the part of the muscle injected. But distribution within the relevant segment or segments is, in general, maintained unless pain is very severe, when it seems to spread to adjoining segments. Kellgren concluded that the segmental areas displayed are determined by the nerve roots involved in supplying the corresponding muscles, so that different muscles supplied from a common root source will yield a common general field of pain distribution. Thus, in Figure 18, pain is produced by injecting the multifidus dorsally, the rectus ventrally, and the intercostal laterally, all within the supply of the ninth intercostal nerve; the pain is distributed similarly in the three instances, though felt more severely and diffusely in front with the rectus, and in the back with the multifidus, injection.

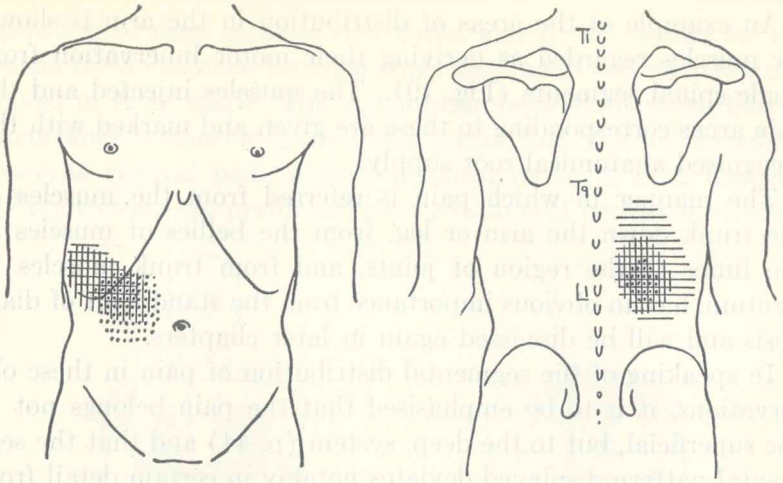

Fig. 18. (Kellgren, *Clinical Science* 3: 181, 1937–38.) Showing the areas of pain on injecting different muscles supplied by the 9th thoracic nerve. Horizontal hatching = injection of multifidus opposite 9th spine. Vertical hatching = injection of 9th intercostal space in midaxillary line. Stippled = injection of rectus abdominis 3 cm. above umbilicus.

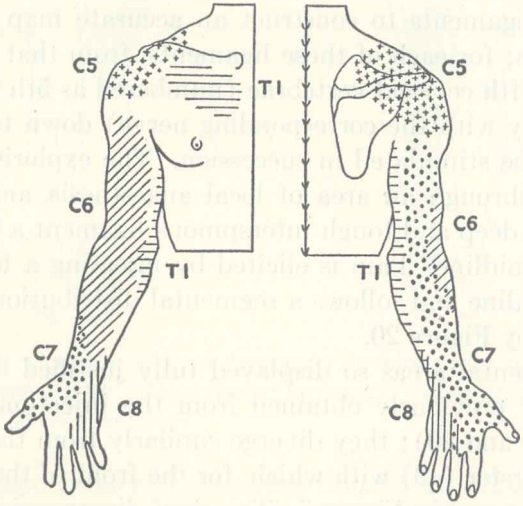

Fig. 19. (Kellgren, *Clinical Science* 3: 183, 1937–38.) Distribution of pain from injection of: rhomboids = crosses; flexor carpi radialis = oblique hatching; abductor pollicis longus = stippling; 3d dorsal interosseus = vertical hatching; 1st intercostal muscle = horizontal hatching.

An example of the areas of distribution in the arm is shown for muscles regarded as deriving their motor innervation from single spinal segments (Fig. 19). The muscles injected and the pain areas corresponding to these are given and marked with the recognised anatomical root supply.

The manner in which pain is referred from the muscles of the trunk down the arm or leg, from the bellies of muscles in the limbs to the region of joints, and from trunk muscles to scrotum, has an obvious importance from the standpoint of diagnosis and will be discussed again in later chapters.

In speaking of the segmental distribution of pain in these observations, it is to be emphasised that the pain belongs not to the superficial, but to the deep, system (p. 44) and that the segmental pattern displayed deviates notably in certain detail from the sensory segmental pattern demonstrated for skin by Head and by Foerster. On this point, more will be said directly.

Interspinous ligaments.—Kellgren (103) in further explorations found that stimulation of the deep interspinous ligaments of the vertebral column yields pain distributed in a manner similar to that obtained from muscles of the back. He thereupon used these ligaments to construct an accurate map of the segmental areas; for each of these ligaments, from that uniting the fourth and fifth cervical vertebrae (numbered as 5th *C.* ligament in uniformity with the corresponding nerve) down to the sacral region, can be stimulated in succession. The exploring needle is introduced through an area of local anaesthesia and is carried down to the deep and tough interspinous ligament a little to one side of the midline. Pain is elicited by injecting a few drops of 6 per cent saline and follows a segmental distribution illustrated in the map by Figure 20.

The segmental areas so displayed fully justified the numbering of those previously obtained from the injection of muscles (cf. Figs. 19 and 20); they diverge similarly from the segmental areas of Foerster (49) with which, for the front of the body, they may be compared in Figure 3. The chief divergencies are found, not in the trunk, but in the limb; certain segments, notably *T*1 and *T*2, extending less freely into the upper, and *L*2 and *L*3, less freely into the lower, limb. Kellgren suggests that these areas for deep pain correspond with the distribution of the segmental in-

nervation of deep somatic structures, and in this would lie the reason for divergence between superficial and deep patterns displayed in these maps. The distribution between the two has its importance because it is the latter rather than the former which concerns visceral pain, a matter considered in a later chapter.

Periosteum.—In preliminary explorations of periosteum (137),

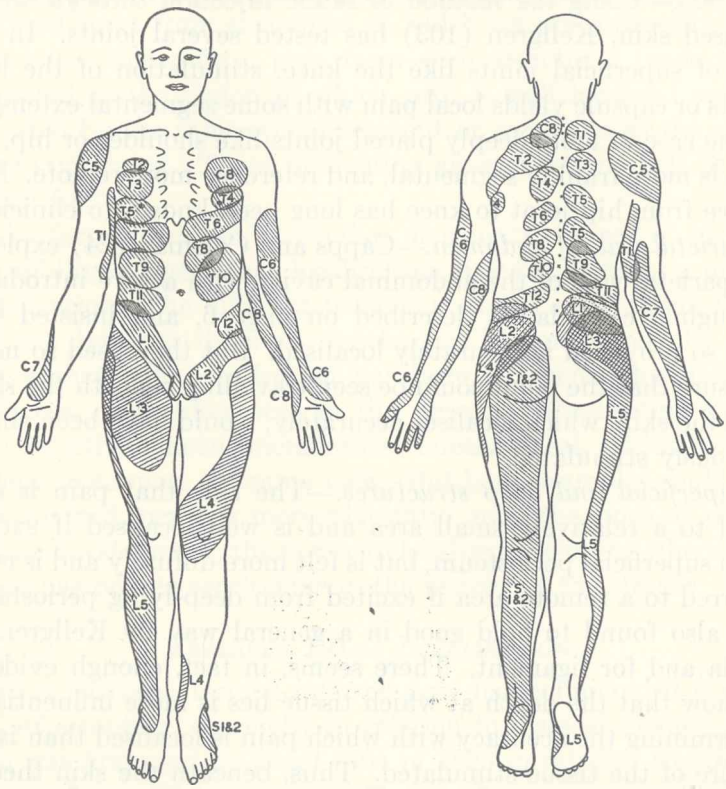

Fig. 20. The segmental areas of deep pain developed by the injection of the corresponding interspinous ligaments; diagrams constructed from Kellgren's material.

I used the superficial surface of the tibia by running a hypodermic needle through the anaesthetised skin and jabbing the periosteum or injecting a little 5 per cent saline against it. The pain provoked was a little diffuse but accurately localised.

Kellgren (103) explored the periosteum more thoroughly. He found pain, accurately or a little less accurately localised, on

stimulating any subcutaneous periosteum, such as tibia, patella, sternum, acromion, and olecranon. Deeply situated periosteum, like that of the infraspinous fossa of the scapula, the lamina of vertebra, or the pelvis, where well covered, gave more diffuse pain, which might be referred to an area at a little distance; thus the infraspinous fossa yields pain over the tip of the shoulder.

Joints.—Using the method of saline injection through anaesthetised skin, Kellgren (103) has tested several joints. In the case of superficial joints like the knee, stimulation of the ligaments or capsule yields local pain with some segmental extension. In the case of more deeply placed joints like shoulder or hip, the pain is more frankly segmental, and reference more remote. Reference from hip joint to knee has long been known to clinicians.

Parietal wall of abdomen.—Capps and Coleman (24) explored the parietal wall of the abdominal cavity with a wire introduced through a cannula, as described on page 6, and insisted that pain so provoked is accurately localised. But they used so much pressure that the point could be seen travelling beneath the skin; thus the skin, which localises accurately, would have been simultaneously stimulated.

Superficial and deep structures.—The rule that pain is confined to a relatively small area and is well localised if excited from superficial periosteum, but is felt more diffusely and is often referred to a remote area if excited from deep-lying periosteum, was also found to hold good in a general way by Kellgren for fascia and for ligament. There seems, in fact, enough evidence to show that the depth at which tissue lies is more influential in determining the accuracy with which pain is localised than is the nature of the tissue stimulated. Thus, beneath the skin there is a second sensitive layer, in which pain may be localised with fair accuracy; it consists of deep fascia encasing limbs and trunk and any periosteum, ligament, or tendon that is subcutaneous; on the other hand, all the structures deep to this layer give rise to diffuse pain, which seems to come from a region deep to the skin and which is of more or less segmental distribution (Kellgren, 103).

General.—Pain elicited from somatic structures may be focal; that is to say, it is felt at a point or in a very small area, or it may be a little or much more diffuse. If focal or a little diffuse,

its source may be well localised by the subject; or the localisation may show an error of several centimetres. Diffuseness is, in general, associated with inaccuracy and, ultimately, with the appearance of pain in, or its extension to, remote regions. According to Kellgren, localisation characterises the superficial coverings and the joints, parts of the body of which we are naturally most conscious, while pains that are so diffuse as to be poorly localised come from structures of which we are ordinarily little conscious. The diffuse pain from such structures tends to be projected to the region in which pain is well localised and innervated by the same spinal segment or segments as the structures stimulated. These interesting generalisations will be discussed further.

The facts displayed by studies of somatic tissues of varying accessibility suggest that localisation may be, in part, a matter of education. The different behaviour of the same tissue (periosteum) lying at different depths can be understood by supposing that pain localisation has been sharpened by past experiences. The differences in the power of localisation in the pain-sensitive mucous membranes (buccal, nasal, genital) might be held to support the same view. But both examples could also be explained, perhaps more plausibly, upon the lines of phylogenetic development, the power to localise developing where such power has proved serviceable in the history of the species.

Referred Pain; Localisation

What has been termed *referred pain* has commanded a great deal of attention, especially in relation to visceral disease. The term was first used by Head (80) in 1893 in relation to visceral disease. Dana (33) wrote in 1887 of "reflex or transferred pain", that is, pain felt at a distant point; he had in mind a spinal linkage between sympathetic and cerebrospinal nerve systems. Waterston (235), disliking the possible confusion arising from using the word "referred", suggested the terms "homotopic" and "heterotopic" to indicate pain felt locally or at a distance from the point where the disordered process is at work; this seems a mere substitution of terms. Morley (170) suggested that the term should be limited "to pain resulting from stimulation of a somatic sensory nerve and referred to a remote part of the dis-

tribution of that nerve or of the segmental sensory distribution with which it is connected." Such a definition could only gain acceptance by those convinced that a similar reference never happens from stimulation of visceral nerves.

The term "referred" has no accepted definition and is used to cover clearly separate phenomena. Thus, when a nerve is stimulated in its length, sensations are evoked that appear to come from the extremity of the nerve's territory. It would seem adequate to regard this false localisation of the source as the natural result of the breaking in, and interpolation of, messages upon a well-worn line of communication. The message deceives because it arrives by a channel hitherto exclusively used for messages from a distinct and recognised source. Some would include this example in the category of referred pain, others would not. I use the word "referred" in this book as one of common parlance with no attempt to narrow its meaning.

There is good evidence, to be discussed in the next chapter, for believing that the false localisations of pain arising from deep-lying somatic tissues, such as muscle, are of essentially the same kind as those happening in visceral disease, so that the term "referred pain" may be used as appropriately for the one as for another. There is certainly no reason to doubt that the study of referred pain where somatic tissue is the source is relevant to that where a viscus is the source. A useful purpose may here be served by pointing out that referred pain can be studied without recourse to the viscera; that somatic tissues, which are more accessible to safe experiment, may be used instead.

As has been demonstrated, when deep somatic structures are stimulated, pain may be confined to the immediate locality, may be felt diffusely in a remote locality, or may be felt in many ways which form a perfect transition between these two. From this comes the idea that referred pain may be fundamentally natural and not, as has often been thought, something apart from, and dependent upon, a distinct and abnormal mechanism. The transition in the case of deep somatic pain should encourage us to look at the matter differently and to attempt to discover the basis of localisation rather than the basis of reference. Had we to deal merely with localisation of varying degrees of accuracy and variation within a limited range, the idea of a change in

mechanism in passing from accurate to less accurate localisation would not be contemplated. It is the large step from localisation in skin to the remote references of visceral disease which has prompted such ideas as those of spread in the cord.

We know, in fact, little upon which to base a secure theory of localisation. We assume that a unit area of skin must transmit, by its special path, sensory impulses to the sensorium, which is able to recognise this unit as the source of the message. For skin, such a mechanism would perforce be one of very detailed representation. Tissues supplied by deep pain nerves may be regarded as endowed with a similar but simpler form of mechanism, the tissues being represented more in bulk and collectively. The coarsest form of such representation would be that in which many tissues in a given segment were represented in such a way that no fine distinctions would be possible in localisation; or, at the most, the tissues in the dorsal part of the segment would give a slightly different pain distribution to those in the ventral part. Now this, admittedly, is a speculation, but it shows that alternative explanations can be found without difficulty to account for variations in the power to localise when different tissues are involved; and that, considered from the standpoint of tenderness or pain arising in somatic tissues, the introduction of such an abnormal factor as an irritable focus in the cord or of spread from one system of afferent nerves to another within posterior root system or posterior horn, is really redundant and therefore unnecessary. It seems important to stress the possibility that such theories have arisen from the desire to explain what is regarded as a special and peculiar phenomenon, referred visceral pain, and that they are not needed to explain what may be regarded as imperfect development, phylogenetic or otherwise, of deep localisation.

The results of recent explorations of deep somatic localisation have profoundly altered the outlook to localisation as a whole. The application of these experiences to visceral pain will be discussed in following chapters.

Chapter XI

REFERRED MANIFESTATIONS OF SOMATIC AND VISCERAL ORIGIN COMPARED

Responses to Stimulation of Interspinous Ligaments; Rigidity and Tenderness

In an earlier chapter, I have described observations of Kellgren, which have shown that pain provoked from deep-lying somatic structures is distributed segmentally. Among his observations was that illustrated by Figure 21. It includes the distribution of pain arising from stimulation of muscles of the first lumbar seg-

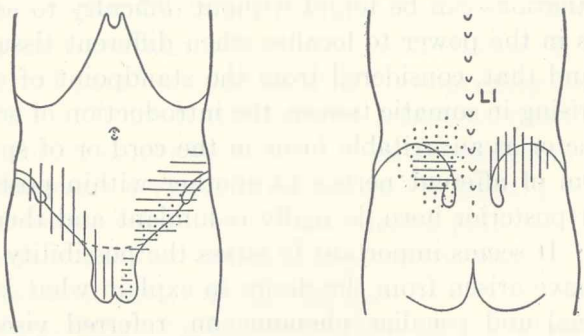

Fig. 21. (Kellgren, *Clinical Science* 3: 182, 1937–38.) Distribution of pain in 1st lumbar segment, when provoked from testis = vertical hatching; from abdominal obliques = horizontal hatching; and from multifidus = stippling.

ment and from the testicle, and shows how closely pain distribution in these two cases may resemble each other. None familiar with the pain of renal colic can fail to be impressed by this picture. It was recognised that these observations would acquire much clearer significance if they could be correlated decisively with the referred phenomena well known to manifest themselves in visceral disease. In the original studies in which

interspinous ligaments were stimulated, attention was concentrated chiefly upon the distribution of pain; muscular rigidities and cutaneous hyperalgesia were not noticed. As both these phenomena occur in association with the pain of visceral disease, they were now looked for as responses to interspinous ligament injection (Lewis and Kellgren, 140).

We first used the first lumbar ligament because of the known likeness of its pain distribution to that of renal colic (Fig. 21). Injecting this ligament, we looked for retraction of the testicle on the same side, because this is a phenomenon long known to

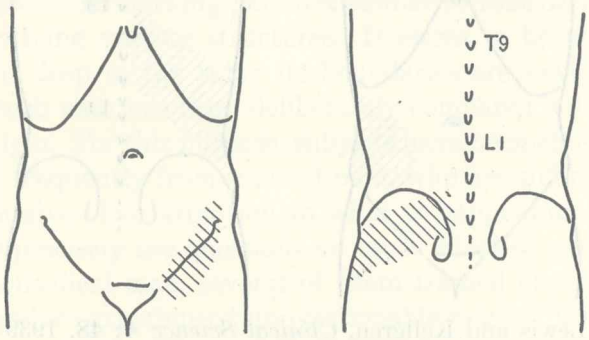

Fig. 22. (Lewis and Kellgren, *Clinical Science* 4: 48, 1939.) Area of cutaneous tenderness following injection of 1st lumbar interspinous ligament.

happen in attacks of renal colic (Ross, 201). We saw this retraction occur unmistakably and repeatedly; the retraction becomes maximal as the pain swells to its height and gradually disappears as the pain subsides during the next 3 to 5 min. The same injection gives palpable rigidity and deep tenderness of the lowest part of the abdominal wall of the corresponding side; such rigidity and tenderness also pass away with the passing of the pain. Testicular tenderness is not infrequent. Slight cutaneous tenderness usually develops over the areas shown in Figure 22.

Injection of the ninth thoracic ligament gives pain along the segment marked *T9* in Figure 20. With the pain, the muscles of the upper abdominal quadrant—and notably the upper belly of the rectus—become rigid, and deep tenderness develops; an obvious phantom tumour may form here when pain is severe;

and the subject may be conscious of the rigidity and experience a sense of fixation of the chest. Flattening of the lower ribs and diminished movement may be displayed clearly by the side affected. These signs disappear hand in hand with the passing of the pain. Cutaneous tenderness also develops, and its area is illustrated in Figure 23.

There are two features of these areas of cutaneous tenderness to which attention should be drawn. Firstly, they do not develop, as does deep tenderness, with the pain. There is a delay of many

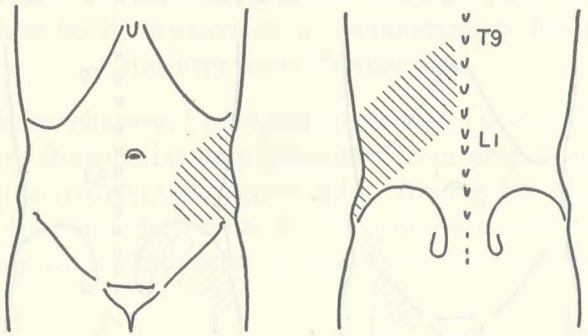

Fig. 23. (Lewis and Kellgren, *Clinical Science* 4: 48, 1939.) Area of cutaneous tenderness following injection of 9th thoracic interspinous ligament.

minutes, during which pain may actually subside, before the tenderness can be observed; and, having come, the tenderness lasts for considerable periods, such as one to several hours. In these respects, it resembles the nocifensor tenderness of Chapter VI. Secondly, the areas of cutaneous and of deep tenderness do not necessarily correspond with each other, the cutaneous area occupying, in these instances, a slightly lower level.

It became clear from these and other examples that, by appropriately stimulating such somatic structures as the interspinous ligaments, it is possible to reproduce pain having the segmental distribution characteristic of forms of visceral disease simultaneously with the superficial and deep tenderness and the muscular rigidity which frequently accompany such pain and which were described by Mackenzie (152, 155) under the terms viscerosensory and visceromotor reflexes. The unilateral rigidity of the abdominal muscles and the unilateral retraction of the

testicle are the more remarkable because they cannot be brought about by voluntary effort. As in visceral disease, it is found, in tests at different levels, that rigidity and skin tenderness are more in evidence upon trunk than upon limb.

Pain of Somatic and Visceral Origin Compared

Personal experiences tell us that the pain produced by injecting saline into the ligaments of the spine has certain characteristics. At its height, it is unvarying, continuing smoothly at one level of intensity; it has a peculiar and indescribable quality quite distinct from burning pain but similar to that derived from other deep-lying somatic structures. It seems to be not on the surface but deep to the skin; its boundaries are never sharply defined. Such pain has been deliberately compared with that of visceral origin. For this purpose, subjects have been chosen (140) who suffer frequently from visceral pain, who are sufficiently interested to give close attention to what is happening, and who appreciate precisely the questions at issue. Most of our subjects have been medical men, several of them trained observers who have themselves experienced unquestionable angina pectoris and in whom the pain has been unilateral in the chest and referred down the inner side of the left arm. Such a subject is asked to recall his pain as clearly as he can and is the more able to do so if he has suffered, or has been induced to suffer, from it recently. He is then asked to compare this pain, to which he is used, with the pain provoked by injecting the left eighth cervical or first dorsal interspinous ligament. Such an injection produces pain in the upper interscapular region, over the left breast, and down the inside of the left arm.

The distribution of the two pains is not identical because the injection provokes some pain in the back near the site of injection, while, in the anginal attack, pain in the front of the chest is the most prominent. But apart from this natural difference, it has been clear that the subjects themselves have definitely been impressed by our ability to induce a pain which, in its onset, continuation, deep and segmental localisation, and character, closely resembles that from which they came complaining. The pain from the injection may be accompanied by numbness and tingling of the hand, by a sense of constriction in the chest, or by

subsequent hyperalgesia of the skin of the inner side of the arm; and in detail these associated symptoms have repeated those of the anginal pain of effort and its associated symptoms in the same subjects. Muscular rigidity has not been detected.

Similarly, the pain of intestinal colic may be compared with that produced by injecting salt solution bilaterally into the belly of the rectus muscle just below and outside the navel. Such injections yield continuous pain of unpleasant severity, having a character not to be distinguished from that of colic, though naturally the time-intensity curve is different. The pain is diffuse and, though located in the front of the body, is felt deeply below the surface of the abdomen, as it is in colic.

In the light of these experiences, it is difficult to entertain the idea that pain derived from deep-lying somatic structures is distinct in character from that to which visceral disturbances give rise.

A manifest and simple explanation of these remarkable resemblances, which include the pain phenomena and the associated rigidities and tendernesses, is the existence of a common, though complex, mechanism which is stirred into activity by afferent impulses derived either from deep-lying somatic structures or from disturbance of a viscus.

The comparison has been made on human beings and, so far as pain and tenderness are concerned, is admittedly subjective. But the muscular rigidities are objective, and these may also be provoked and studied in animals.

Muscular Reflex of Somatic and Visceral Origin

For this comparison, Sherrington's decapitated cat (212) has been employed. When a very small quantity of 10 per cent saline is injected into the muscles of the back, a little to one side of the middle line and in the lower dorsal region, an immediate contraction occurs in the upper belly of the rectus abdominis and adjacent muscles (Fig. 24). This contraction is long sustained (5 or 10 min.), as is that following a similar injection in man. A shorter reflex response of the same muscles, and of similar character, may be obtained by pinching the exposed spinal muscles with forceps instead of injecting them. The saline injections have been used to bring the human and animal responses

into line with each other, both reactions being prolonged. The pinch stimulus has been used when comparing the response from somatic and visceral tissues in the cat; it is the more convenient form of stimulus for repeated use.

Before considering these results, it should be stated that, after Mackenzie described what he termed the visceromotor reflex, he enlisted Sir Charles Sherrington's help, and the latter was able

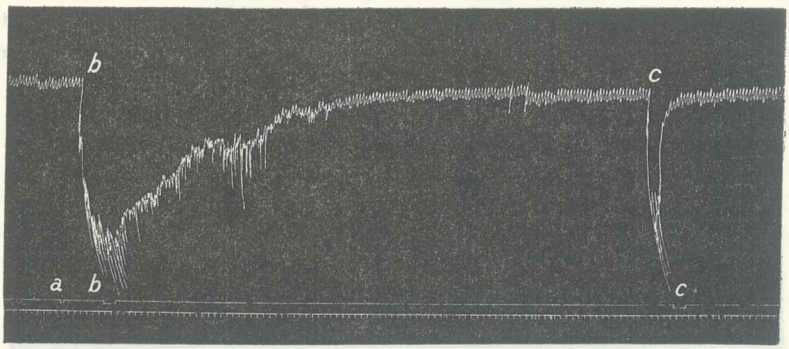

Fig. 24. (× approx. ½) (*Clinical Science* 4: 52, 1939.) Cat. Record of contraction of right abdominal oblique muscles (mid-region): *a*, insertion of needle into muscles of back, right side, at level of 13th thoracic spine; *b*, injection of 0.1 c.c. 10% saline; *c*, after the index marks, shows the response of the abdominal muscles to a pinch of the same dorsal muscles. Time in this and subsequent figures in 5 sec. intervals.

to produce movements of the abdominal wall by stimulating the gall duct or the central end of the superior mesenteric nerve (personal communication; see also Mackenzie, 155). Further work was subsequently done by Miller and Simpson (163). They have described rigidity of the abdominal wall developing in response to traction on the stomach or its mesentery, to stretching a loop of small intestine, to stimulating the central ends of nerves supplying stomach or liver, and to other means.

In my work with Kellgren (140), I found that the localised contraction of the abdominal wall cannot be obtained as a reflex from skin; but it is readily obtained by stimulating the central ends of branches of the thoracic nerves as these proceed across the abdominal wall or by pinching muscles of the back or lateral wall of the abdomen. It is equally well obtained from certain

of the abdominal contents and notably from the pancreas. The duodenum in the cat forms a simple loop suspended on a long mesentery. The central part of this mesentery holds the main vessels to the loop of gut; the rest of it contains the long ribbon of pancreas, which runs parallel to the gut throughout the loop and sends a long tail into the great omentum. A vigorous motor reflex is obtained from any part of this pancreas by pinching it; but severe pinches of the gut itself are without effect, though they cause the gut to contract strongly. Alternate pinches of pancreas and of the spinal muscles, some stimuli being shorter

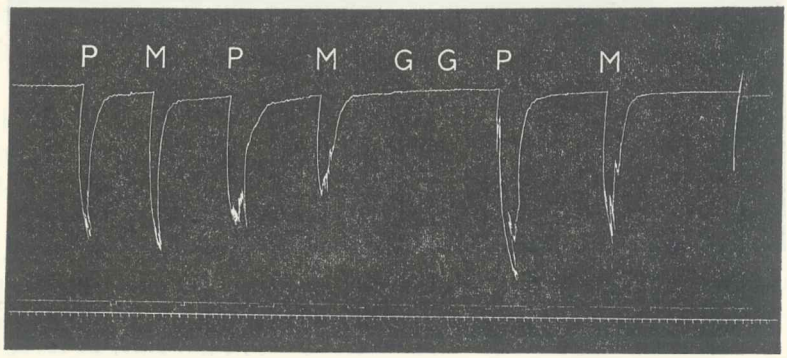

Fig. 25. (× approx. ½) (*Clinical Science* 4: 61, 1939.) Cat. Record of contraction of right upper abdominal rectus. A series comparing result of stimulating pancreas and back muscles. P = responses to pinching pancreas. M = responses to pinching back muscles at level of 12th thoracic spine. G = no response to pinch of gut wall, causing strong contraction of gut.

and some longer, give responses which may be compared. Such a group is seen at the beginning of Figure 25. All such stimuli, whether of pancreas, spinal muscle, or gut, are accompanied by small rises of blood pressure; but, since pinching the gut gives vasomotor effect only, the vasomotor effect evidently depends upon a separate reflex from the motor effect. The motor reflex from the pancreas passes through the splanchnic nerves, as Miller and Simpson (163) found the gastric reflex to pass; it is abolished by section of these nerves and especially by section of the right nerve, but the reflex from the spinal muscles continues unchanged. The motor reflex occurs also when the central end of the cut splanchnic nerve is stimulated.

Similar motor reflexes to those from the pancreas can be obtained occasionally from the mesenteries of ileum, jejunum, and large intestine, especially when the pinch includes the vessels of the mesentery; they are readily and constantly obtained from the main gall duct. The solid organs, the alimentary tract itself in its whole length, and the gall bladder fail to give the motor reflex.

To sum up, the strictly objective comparison of reflexes arising out of stimulation of spinal muscles, on the one hand, and of a viscus, on the other, shows that the responses are indistinguishable in all essentials. This evidence is the more notable because it is known that the entering path of the first reflex is the somatic nerve and that the entering path of the second reflex is along the sympathetic trunk through its splanchnic branches. It is known for both that the ultimate path of entry is the posterior nerve root.

The foregoing observations, derived from distinct sources of experiment, are all relevant to the long controversy concerning the manner in which the pain of visceral disease and the associated tenderness and muscular rigidity arise and are referred. They establish the important fact that identical phenomena of all these kinds can be provoked both from somatic and visceral structures.

Chapter XII

PAIN OF VISCERAL DISEASE

The controversy relating to pain originating in visceral disease has depended largely upon the views expressed by Ross (201) and, after him, upon those expressed by Mackenzie (155). It was Sturge (221) who, in 1883, explained the radiation of pain in angina as resulting from extension of sensory impulses in the grey matter of the spinal cord. Ross was fascinated by Sturge's hypothesis and used it to explain what he called the somatic pains of visceral disease in general. He believed that pain may be derived directly from a viscus, and he called this "splanchnic" pain. He believed with Sturge that a second pain is derived from the viscus by spread in the cord to the roots of the somatic nerves; and he called this "somatic" pain. Lennander's work (120) followed; Mackenzie, having studied this, was convinced by it and by his own observations that the viscera are wholly insensitive. Consequently, he refused Ross's belief that pain impulses are conveyed directly from the viscus (Ross's splanchnic pain) and, proceeding farther than Ross, explained all visceral pain as the result of non-painful impulses ascending from the viscus to the cord, impulses which, by spreading to sensory tracts, set up pain referred along the peripheral territories of the latter. Mackenzie's extension of Sturge's hypothesis has never received full acceptance; there have always been those who have remained convinced that pain may arise directly from the viscera (Hurst, 89; Ryle, 202; Morley, 169; Leriche, 125).

Many and diverse views have been held, and discussion has become so intricate that, if it is to be understood, it is necessary to reduce the problem to certain simple issues.

Pain Arising Directly from Visceral Structures

The first simple issue I shall discuss is whether or not pain can arise *directly* from visceral structures. We have seen that

Mackenzie denied it, for he accepted Lennander's conclusion of the insensitivity of visceral organs and he believed that all pain arising from the viscera comes indirectly through a change in the cord set up there by afferent, though not pain-giving, impulses. I shall not allow the question as to the manner in which pain originates from visceral disorder to intrude itself here. This is a question that would but complicate the present discussion, and it can be deferred conveniently to a later point. I begin with the statement that, without doubt, pain can be provoked directly from certain visceral structures if not from viscera themselves. The most conclusive example is of pain produced by direct and circumscribed stimulation of regions of the mesentery (see Chap. I). Other examples are the pains evoked by touching the calices of the kidney from within (Lennander, 120), by passing a sound into the ureter from the bladder (Papin, 178), or by touching the urethral region of the bladder. All these pains are elicited at once; there is no appreciable delay, such as would be expected if they were provoked indirectly.

Afferent Paths of Segmental Pain

Sturge—and, after him, Ross and Mackenzie—believed that segmental pain in visceral disease arises directly, or through painless afferent impulses, from the viscus itself. For Morley, segmental pain in abdominal visceral disease is always due to the action of the diseased viscus on the parietal wall (see p. 157) or from the extension, into the organs, of sensory nerves properly belonging to the somatic system. The two views are in obvious conflict.

Morley has very rightly and usefully emphasised segmental pain arising from the diaphragm. Pain, referred to the shoulder in disease of the diaphragmatic pleura, has long been known (Peter, 182). It can be provoked in man by stimulating either the upper or lower surface of the diaphragm mechanically, for example, by introducing a long probe through a cannula in tapping fluid in the serous cavities (Capps, 23) or by passing a surgical mop over the surface of the dome during an abdominal operation under local anaesthesia (Morley, 169). The pain, conveyed by impulses passing through the phrenic nerve, is referred within the more superficial territories of the third, fourth, and

fifth cervical nerves from which the phrenic nerve derives its fibres. To this very clear example of pain referred segmentally within the somatic system of nerves, we are able to add a whole series of equally convincing examples described in Chapter X; and we now recognise that segmental reference is the rule whenever pain is provoked from any deep-lying somatic structure. Thus, without prejudicing the question of what precise mechanism starts up the original impulses which lead to a display of segmental pains in visceral disease, we must concede at once that any adequate stimulation by a diseased viscus of adjacent somatic structures, such as the abdominal parietes, is capable of originating the pains considered. Whether such stimulation happens, or is usual, in visceral disease, will be discussed briefly in the next chapter. All we need note at the moment is that the origin of segmental pain in this fashion is very possible.

What then of segmental pain originating from a visceral structure without the intervention of somatic stimulation?

A classical instance is renal colic; a stone within the ureter gives rise to pain in the loin, in the iliac fossa, in the region of external abdominal ring, and in the scrotum. My colleague, Mr. F. J. Barrington, whose precise observations upon ureteral and bladder conditions are well known, assures me that the pain of renal colic has the same distribution at whatever level in the ureter the stone is situated, provided it is above the bladder. It is not a question of pain descending as the stone descends but of characteristic pain in segments *L*1 or *L*2 (see Fig. 20) provoked from the ureter in its length. As my colleague also tells me, it is now well known that, when a catheter is passed into a ureteric opening from the bladder, pain is referred to the region of the external abdominal ring.

A second classical instance is that of stone impinging upon the urethral region of the bladder, the pain being referred to the perineum and tip of the penis. Such pains can be reproduced when a finger, introduced through a suprapubic cystotomy wound, makes direct contact with this region of the bladder (Morley, 169).

Now the exact way in which pains of ureteral calculus are started is not known with certainty. Though usually regarded as arising out of muscular contraction, it is conceivable that

pains result from stimulation of nerves in surrounding connective tissue. And in the case of the trigone of the bladder, this is known to be directly supplied by the spinal nerves of the sacral plexus. Thus, although, with these examples before us, we may say that pain of segmental distribution can undoubtedly be excited from viscera, we may be tempted, as Morley has been, to stress the possibility or probability that the segmental reference is, in these instances, a function of somatic sensory nerves and to make the generalisation that segmental reference never arises through any other system. Such a generalisation could have value only if it were associated with one of two beliefs: firstly, that there are no pain nerves proper other than those comprised in the somatic nerves; or, secondly, that two physiologically distinct systems of pain nerves supply visceral structures. Neither of these views can be upheld. The first is disproved by the immediate occurrence of pain on stimulating sympathetic nerve trunks or ganglia. The second rests on the very generalisation the truth of which is under discussion, namely, that only nerves of the somatic or cerebro-spinal series yield referred or segmental pain.

Actually, the generalisation can be disproved. When Foerster (48) and Leriche (124) stimulated the central end of the cut splanchnic nerve, the patients experienced unilateral pain that was referred; Foerster records maximal reference to the sixth space just below the nipple and says that, when the current was increased, the pain spread over the whole of the zone *T*6 to *T*9. Other instances will be found in Leriche's book (125, pp. 34–36). The very convincing example of anginal pain may also be instanced. Now the heart is suspended within the pericardium; it is a viscus with purely visceral contacts and connections. There can be no doubt that this organ originates segmental pain, pain usually distributed over the sternum, pectoral region, and inner side of the arm, mainly on the left side (*T*1, *T*2, and *T*3). The evidence for the cardiac origin of the pain, regarded collectively, appears to be quite conclusive (Lewis, 130). I place in the foreground (1) the well-known occurrence of such segmentally referred anginal pain in fresh thrombosis or embolism of the branch of a coronary artery; (2) the characteristic change in the electrocardiogram in the direction of the curve of ventricular muscle injury during anginal seizures, discovered by

Feil and Siegel (46) and since abundantly confirmed (see Wilson, 246); and (3) the whining of the dog with limping on the left forepaw when a branch of a coronary artery is pulled upon (Sutton and Lueth, 222). Just as anginal pain in man is relieved by resection of the sympathetic nerves (see p. 25), so the manifestation of pain in these dogs is relieved. Sutton and Lueth excised the left stellate ganglion;[1] but White and his coworkers (242) found excision from stellate to the fourth thoracic ganglion inclusively to be more efficacious.

Thus, while there is conclusive evidence for the somatic origin of segmental pain, so is there for its visceral origin; and the attempt to distinguish fundamentally, on the ground of reference, between sensory nerves attached to somatic or to sympathetic systems breaks down.

One or Two Systems of Afferent Nerves

The notion that nerves conveying pain impulses from the viscera are in some way peculiar may profitably be examined further. In part, though not in whole, this idea has resulted from a confusing terminology. The term sympathetic is used in two senses. It may be applied to an anatomical system of nerves composing the paravertebral chains and their connections and including both afferent and efferent nerve fibres. It may also be applied to a physiological system of nerve fibres having cell stations in the sympathetic ganglia; this nerve fibre system is all efferent. When writers use the terms "sympathetic sensory" or "sympathetic afferent" nerves, they may mean merely that sensory or afferent fibres run temporarily in the anatomical sympathetic system. But the use of such expressions is likely to convey the false idea that a special system of sensory or afferent nerve fibres exists and belongs exclusively to the physiological sympathetic system. There is no evidence of such fibres, and the use of the above terms is therefore confusing and ill-advised.

Evidence has already been presented that pain may be elicited at once by stimulating certain visceral structures. It is known

[1] These workers spoke of removing the annulus of Vieussens, but it is clear from information Dr. Sutton has kindly given me that the ganglion was removed.

that pain occurs when the splanchnic nerve and other parts of the sympathetic nervous system are stimulated, and that the pain impulses passing through the anatomical sympathetic nervous system are conveyed to the spinal cord through the posterior roots, as are all afferent impulses from the viscera (see Chap. II). There is no physiological sanction for regarding the pain nerves of the sympathetic system as distinct from those supplying deep-lying somatic structures. The onus of proof lies quite definitely on those who hold the different view that a special form of visceral pain originates through afferent nerves of a different order. There is no reason and no gain in distinguishing in any fundamental way between nerves conveying pain from deep somatic structure or from any sensitive visceral structure. Physiologically and anatomically, pain fibres supplying the two types of tissues are alike; and the fact that those from somatic structures at first use the channel of the spinal nerve, and that those from visceral structures at first use the channel of the anatomical sympathetic system before entering the posterior roots, is really immaterial.

When, earlier in the last chapter, pains derived from visceral disturbance were compared with those provoked from somatic structures like the interspinous ligaments, no difference could be found in the quality of such pains; neither could any fundamental difference in their distribution be discovered; it is the rule that both are referred segmentally. It is really a matter of very little theoretical importance whether, in the case of renal colic, pain is derived from ureteric wall or from tissues closely surrounding the ureter. No apparent advantage is to be obtained from dividing sensory nerve fibres according to their anatomical distribution, as to whether they run to the cord through the somatic nerves or pass first through the sympathetic chain.

And now let us broaden the discussion and speak, not of pain nerves, but of afferent nerves. In the last chapter, a comparison was instituted between reactions arising from visceral and those arising from somatic structures. This comparison concerned not only pain but all the associated manifestations, such as cutaneous tenderness and muscular rigidity; throughout, the comparison elicited close resemblances but no substantial differences. The objective demonstration that the same muscular reflexes and

same blood pressure rises can be provoked by direct stimulation of erector spinae, pancreas, or central end of the splanchnic nerve conclusively links the general manifestations together.

To summarise broadly, there is a general afferent supply common to deep-lying somatic and to certain visceral structures; pain arising from one or the other is derived from the direct stimulation of a common system of pain nerves, namely, the nerves of deep pain described in Chapter III. The pain impulses are either identical with, or are generally associated with, afferent impulses that set up reflexly a common series of motor and sensory reactions. It is largely a matter of indifference whether the nerve fibres stimulated supply visceral or deep-lying somatic tissue; it is a matter of indifference whether they pass to the posterior roots by way of an anatomical path grouped as somatic or sympathetic; the result will depend (apart from strength and duration of stimulus) chiefly upon the segmental derivation of the afferent fibres concerned.

This relatively simple generalisation carries with it the practical conclusion that the fundamental mechanism (or mechanisms) underlying pain and associated reflexes, being common to both somatic and visceral disturbance, may be studied in either. So long as pain of visceral origin is to be regarded as fundamentally peculiar, then it would seem to be incapable of thorough experimental investigation, owing to the inaccessibility of the tissues concerned in man. But, if it differs only in the source from which it is derived, then the main problems can be probed in accessible somatic tissues, for they are problems concerning the general mechanism of pain derived from any deep-lying tissue.

True Visceral Pain

This phrase, "true visceral pain", is used not infrequently but remains undefined. For some, it would mean merely pain arising from a viscus. For others—and I believe this has been the usual usage—it means a pain that arises in a viscus and is localised in that viscus (Ross's splanchnic pain). Finally, it is used in the belief that there is a form of pain of special significance or one depending upon a special underlying mechanism. We may deal with these three notions separately.

That pain can arise directly from visceral impulses has already been discussed sufficiently on pages 136 to 139.

I come to the second point of view, that there are pains arising in, and localised in, a viscus. Now it is quite obvious that pains arising in visceral structures are not so localised as a general rule; on the contrary, they are usually diffuse and rather ill-defined in position, frequently referred to distant points, or even—as in the case of anginal pain—frankly segmental (see p. 139). Yet the belief in accurate localisation persists; renal colic and the curious extension of its pain has sometimes been responsible. I am assured by careful observers who have suffered from this severe malady that the pain does not gradually travel downwards; it is now in the loin and, as it swells, appears in front and in the region of the groin also. When a medical man experiences such pain, his anatomical knowledge may readily convince him that the pain follows the course of the stone down the ureter (see Leriche, 125, p. 444). But the reasoning is false Few medical men could, in fact, accurately map the course of the ureter on the surface. And renal colic does not strictly adhere to the ureteral sphere; the ureter ends in the bladder and not in the groin or scrotum. The pain is segmental and can be provoked just as well from the erector spinae muscles. Moreover, the whole segmental distribution may be displayed in response to a stone fixed in the upper end of the ureter. I use this and the illustration that follows to show how easily fanciful but plausible explanations may arise. Brüning (18) came to the opinion that pure visceral pain, such as intestinal colic, is not localised at the point from which it arises but in a sympathetic ganglion lying at a higher level. This idea was supported by another surgeon (19) who was convinced by contemplation of his own intact belly, which often gave rise to colic, that the pain was referred to the coeliac ganglion.

True visceral pain is most often illustrated by the alimentary tract. Where the guts are concerned, the pain is generally over the front of the abdomen and is either central or more diffusely spread and bilaterally symmetrical. The regions of the stomach, duodenum, and ileum are represented above the umbilicus and the colon below it; the appendix, at the umbilical region. These broad facts of reference from the alimentary tract were first de-

scribed from clinical observations; they were well known to Mackenzie. They have since been established by investigations in which practically all the regions of the gut have been distended separately by rubber balloons introduced within them (12, 93); such distension produces discomfort or actual pain, though the latter is never severe. It is abundantly clear from these and other researches that sensations arising are predominantly midline or bilateral; and Bloomfield and Polland (12), whose observations were conducted in a conspicuously thorough fashion, conclude, apart from the broad manner of reference already indicated, that there is no definite relation between the site of stimulus and the site to which the pain is referred. In particular, the gut stimulated may lie to right or left of the midline, and the reference will be the same (see also Mackenzie). This is so for the whole gut, including the colon in all its parts. It is but natural that the gut should yield bilateral pain; it has a bilateral innervation. The fact which has not been explained is that the pain is referred to the front of the abdomen. For the same workers, the conclusion also applies to the oesophagus, though here they are in disagreement with Hurst (89). Is visceral pain ever localised at its source? To answer such a question affirmatively would require information which we do not usually possess. Clearly, it would first be necessary to be sure of the precise source of pain. Thus, in the case of a part of the alimentary tract, we should know whether the pain arises from gut or from its mesentery. Focal pain from the viscera is rare. Usually we can do little more than point to the region of pain and indicate whether it is felt behind or in front; we know that it is deep to the skin. The pain is not beneath a point, and its accurate localisation in inches below the surface is impossible. When the region of pain coincides more or less precisely with a region in which the suspected organ is thought to be, it is probable that this approximation to accurate localisation is largely fortuitous. Pains derived from organs (including the gall bladder) lying in the upper half of the abdomen are localised chiefly above the navel; those from organs (including the urinary bladder) lying in the lower half of the abdomen are localised chiefly in the lower parts of the abdomen. But this degree of coincidence can usually be explained as well by limited

segmental reference as by propinquity. Pain may be localised more accurately in the region of the diseased organ for a special reason. It is well recognised that the first pain of appendicitis is a midline pain, and it is equally well recognised that it subsequently settles down in the iliac fossa. The explanation generally accepted is that the local pain results when neighbouring somatic structures become involved.

I come to the final point, namely, the distinction between two types of pain, which has already been discussed at some length and is here dealt with by summary comment. If the terms "visceral" and "somatic" pain were used to convey merely the idea that the pain impulses come, on the one hand, from a viscus or its supports and, on the other hand, from the body wall, then there would be no harm in their survival. But they are not used in this strictly limited sense; they are used in a manner to imply:

a) That the corresponding systems of nerves are distinct physiologically; that visceral pain is subserved by "afferent autonomic nerves", while somatic pain is subserved by sensory nerves proper to the somatic system. Reasons have been given already (p. 140) for the belief that there is but one system of pain nerves to deep-lying tissues.

b) That the second of these systems of nerves is alone capable of displaying referred phenomena, an idea dealt with on page 138.

c) That the kind of stimulus which affects the two systems of nerves is quite different, the somatic nerves alone responding to ordinary stimuli. But if it is asked why the nerves entering the base of the mesentery are not to be regarded as visceral nerves, the answer is perilously near to being that they respond to ordinary stimuli.

d) That visceral pain has a distinctive quality. Reasons against this view are given on page 141.

Meaning of Referred or Segmental Pain

The difficulty of understanding how pain, supposedly starting in the heart, is referred to the territory of the nerves of the arm led Sturge (221) to think of "an extension of commotion from one small patch of grey matter more or less intimately associated with it." He remarks that such an extension is familiar in

epilepsy. The extension is thought by him to depend upon the intimate association of one nerve cell with others by means of commissural interpolar fibres passing from cell to cell. What possible nervous communication can there be between heart and the arms? "The region of the spinal cord which gives origin to the brachial plexus gives origin also to the greater part of the fibres which eventually find their way to the heart." Thus wrote Sturge, and his views were adopted by Ross (201). Mackenzie (155), accepting and modifying the same views, regarded all the impulses emanating from the viscera as non-painful; enough has been said already to show that this modification is itself unacceptable.

The original hypothesis that pain impulses from a viscus, having reached the cord, can spread in the grey matter and thus disturb pain tracts reaching the same region of the cord from more superficial tissues, would explain the segmental reference of deep pain generally. There is, however, little or no evidence directly supporting it; and there is something to oppose it. The analogy of epilepsy may be misleading, since the latter may result from an extension of a process, such as vascular disturbance, initiating the attack. For segmental reference as it is usually encountered, there seems to be a simpler explanation, namely, that it is a form of faulty localisation. If we suppose that certain tissues are represented in great detail in the sensorium, we can also understand that pain arising in these tissues may be localised with accuracy. But in other tissues having only a massive central representation, localisation may be expected to be less accurate. Segmental reference of deep pain may mean no more than that, centrally, the deep tissues supplied by a given cord segment have a general, but little detailed, representation. Thus, the impulses received, whether these are derived from viscus or from deep somatic tissue, would tend to awaken very similar sensory impressions and to be localised over a general sphere or spheres having no very precise margins. And it may be regarded as natural enough that the general reference should be to regions that are relatively superficial, regions from which we are habitually receiving sensory impression and which are endowed with some positional sense. It must be obvious that no sensation can be located accurately in tissue that has not this

positional sense. Thus, a coil of bowel giving rise by its contraction to pain in the midline of the body can hardly be expected ever to do otherwise even if it lies, as Mackenzie observed it, twelve inches from the midline. The viscera are organs of which we are normally almost completely unconscious, and none of them is endowed with sense of position. Full realisation of these facts makes it seem less remarkable that, while pain arising in the viscera is referred to somatic structures belonging to the same segment, pain arising from the somatic structures is not referred to the region of the viscus. Yet there would be no apparent reason why the latter form of reference should not occur if reference were merely dependent upon extension of a commotion from one area of grey matter to the next. This hypothesis of spread within the cord is also difficult to accept, in view of there being no segmental spread when skin is stimulated. However strongly a point of skin is stimulated, pain arising from it diffuses very little; and, if it seems to diffuse, it does so radially and equally. Why do not pain impulses derived from skin set up this supposed commotion in the cord? The answer seems to be that the commotion is hypothetical and not real and that reference is a phenomenon which goes hand in hand with inability to localise. Segmental reference is a phenomenon of the deep pain system and is not found in the cutaneous pain system.

The unusually wide reference of very severe pain derived from deep structures is probably purely a central phenomenon.

In dealing with referred segmental pain, I have deliberately divorced it from the question of referred tenderness for reasons that will appear.

Segmental pain and superficial anaesthesia.—Weiss and Davies (239) reported that they were able to abolish pain of visceral origin by anaesthetising the skin in the region to which pain is referred. The idea here is that the pain is due to normal impulses ascending from the skin to play on an "irritable focus" in the spinal cord. This, of course, is not the original conception of Sturge and that subsequently held by Mackenzie. For them, visceral *pain* was due to spread of impulses in the cord to sensory tracts. It was hyperalgesia that was regarded as the result of normal impulses, such as those deliberately provoked, playing on

an irritable centre. Pain can arise at once out of visceral impulses and requires an explanation consistent with this. The establishment of an irritable focus presumably requires time, a delay which can be made consistent with the onset of hyperalgesia but hardly with that of pain. The distinction emphasises the importance of discussing pain and hyperalgesia separately.

To return to the observations brought in support of this extension of Sturge's hypothesis, the evidence presented is to my mind far from convincing. It is clearly important, if the effect of superficial anaesthesia upon visceral pain is to be used, to know without doubt whence the pain arises. Of Weiss and Davies's examples, that of anginal pain is perhaps the most certainly visceral in source. They report three cases in which pain was relieved by their method; but, in one case, anaesthetising skin of the chest also relieved pain in the arm; and, in another case, the relief of pain was associated with a large fall of pulse rate, to which fall the relief was doubtless due. I have myself conspicuously failed to alter, in the least, anginal pain in an eminently suitable patient in whom the referred pain was focused over the sternum and could be provoked, with regularity and by a constant amount of effort, both before and after thoroughly anaesthetising the affected part of the body wall. Another instance given is that of pain, believed to be renal colic, radiating from loin and urethra; this was abolished over the whole of its extent by injecting the corresponding loin; but it was also relieved by injecting the opposite loin. In many instances given, the injection was made too near to the possible source of pain to have clear evidential value; in other instances, local infiltration caused the pain to migrate mysteriously to other places but did not stop it. Where pain thought to be derived from a viscus and referred to somatic structure has been abolished by local anaesthetisation of the latter, it is probable that the pain has really arisen superficially and not from the viscus. Examples of pain so relieved have been published by Kellgren (103) and have also come within my personal experience.

Some similar examples of pain referred from somatic structures and the effect of local anaesthesia upon them are available. Thus, in two patients who were suffering from perforated duodenal ulcer and in whom right shoulder-tip pain was present,

Morley found the pain abolished or relieved by anaesthetising the right-shoulder-tip area. But the most striking phenomenon in each case was the marked difference between the intensity of the pain produced in the two shoulders by stimulating the dome of the diaphragm with a swab on the two sides; in each, it was less on the side anaesthetised. Morley states with confidence that none of the novocaine solution was injected near the trunk of the phrenic nerve.

Woollard, Roberts, and Carmichael (251) experimented with phrenic nerves exposed for the purpose of their avulsion under local anaesthesia. Stimulation of the nerve caused flinching, and severe pain localised to a small area near the acromioclavicular joint. In no case was the referred pain altered in character or intensity by anaesthetising the area of reference. Similarly, Kellgren (101), who produced referred pain on the back of the hand by stimulating the extensor muscles of the forearm, could not modify it by local anaesthetisation. In the instance of deliberate stimulation of the diaphragm, which gives immediate shoulder pain, could we possibly accept the idea that this pain is due to a flow of impulses from the shoulder itself? Could we entertain the idea that stimulating the phrenic nerve (end branches or trunk) produces pain other than by directly involving pain fibres of that nerve; and, if it involves such fibres, could interruption of anything but the direct path possibly prevent the passage of painful impulses? These are questions that arise naturally in the mind but need not be allowed to preoccupy us so long as there is seemingly a conflict in the evidence bearing upon them.

Views of Visceral Pain

In considering and comparing past and present views of pain derived from visceral disease, it is important to recognise that these views usually incorporate two distinct considerations, namely, the source from which pain is thought to be derived and its localisation. It may be helpful if I display in tabular form the chief views that have been held and thus bring them into relation with each other and to the views expressed in this book. These views are four in number.

True visceral pain.—This pain is supposed to start in the viscus

and is usually regarded as being localised in the viscus. It is the equivalent of what Ross called "splanchnic pain" and is still accepted by Morley and others.

TABLE 3

PAIN IN VISCERAL DISEASE

Pain	*Derivation*	*Localisation*	
1. True visceral	Viscus	Viscus	Ross ("splanchnic pain"), Morley and others
2. Visceral referred	Viscus	Segmental	(*a*) Reference due to spread of impulses in the cord segment (Sturge, Ross) (*b*) The same, the original afferent impulses being painless (Mackenzie) (*c*) Reference due to imperfect central localisation (Author)
3. Parietal referred	Parietes	Segmental	Lennander, Morley, Author
4. Parietal local	Parietes	Local	Generally acknowledged

Visceral referred pain.—Such pain is supposed to arise directly or indirectly out of visceral afferent impulses and to be referred segmentally.

a) Impulses travel to the cord and diffuse from the grey matter representing the viscus to that representing somatic structures of the same segment. This is Sturge's hypothesis, subsequently adopted by Ross.

b) A similar hypothesis is that of diffusion in the cord, but it is one in which the original afferent impulses from the viscus are emphasised as giving rise to no pain directly. This is Mackenzie's hypothesis.

c) The impulses from the visceral structure on reaching the sensorium are interpreted as pain, and the pain is referred to the segment in default of sharper localisation. This is the hypothesis adopted in this book.

Parietal referred pain.—This is interpreted as pain arising when a diseased viscus directly stimulates the parietal wall with which it is in contact or when the disease spreads to the parietal

wall; the parietal pain is referred segmentally. This view was originated by Lennander; it has found its chief modern advocate in Morley. I accept this mechanism of pain when visceral disease has spread to the parietes.

Parietal local pain.—This pain is supposed to appear when disease spreads from a viscus to the parietes, thus giving rise to local pain. Its occurrence is generally acknowledged.

Unexplained References

There are referred pains and referred tendernesses that remain unexplained. The manner in which pain sometimes spreads to the jaw and neck in angina has been mentioned already. Purely somatic reference having unusual remoteness is found in glomus tumour beneath the fingernail; pain in this condition arises from a minute focus, is easily provoked, and may spread as far as the tip of the shoulder or even into the neck. I have observed another curious instance of distant reference. The subject had suffered some years previously from a single attack of "neuritis", pain, numbness, and tingling in the first three fingers of a hand. The condition had not recurred, but distinct pain and tingling in this hand were always felt at the moment of evacuating a full bladder. Mackenzie (155) mentions some instances of the lighting up of chronic pain when the subject was startled; here, however, the explanation is very probably to be found in sudden and general tightening up of the muscles.

Curious areas of tenderness in face and scalp were described by Head (81). He associated these with disorders of various viscera; but such references have not been generally recognised.

Chapter XIII

TENDERNESS AND RIGIDITY IN VISCERAL DISEASE

Cutaneous Tenderness

Sturge in 1883 noticed, as others had before him, that attacks of angina pectoris leave behind them tenderness in the skin of the chest over the left side (221). Speaking of a spinal centre, he explains this tenderness by assuming that the centre is "left by the attack in an irritable condition, so that ordinary stimuli produce an over-action in the centre." Here is the original conception of the "irritable centre" in the cord, a conception which Head (80) accepted to explain hyperalgesia and which played so large a part in Mackenzie's philosophy (155) of this and other referred phenomena.

It will be observed that Sturge's idea of an irritable focus in the cord was introduced to explain not referred segmental pain but referred cutaneous tenderness. The first problem has been considered, the second should be kept distinct from it. Pain impulses reaching the cord from a viscus are supposed to spread in the grey matter of the cord in that segment, thereby rendering hyperexcitable the sensory elements supplying somatic structures of the corresponding segment. As a result, natural impulses subsequently reaching this centre from the skin and ordinarily incapable of producing pain now induce pain because of the unnatural condition of the centre. Mackenzie and Head both systematically investigated areas of cutaneous tenderness (see Chap. II) and were able to show that these appear in many forms of visceral disease. The soreness of the skin is detected by lightly stroking the skin with the head of a pin, or by moving hairs, or by picking up a fold of skin in the fingers. Mackenzie believed the cutaneous areas to conform less strictly to the dermatome than did Head; Mackenzie described them as never

limited to the full extent of one segment and as often spreading to two or more segmental areas without completely covering any one. "Cutaneous hyperalgesia will usually be found in an ill-defined patch occupying portions of the field of distribution of one or more spinal nerve roots." Though their illustrations were mainly of hyperalgesia in visceral disease, both recognised similar hyperalgesia originating from disease of somatic structures. Thus, Mackenzie spoke of hyperalgesia of the skin of the cheek in toothache; and Head (81) gave an elaborate description of areas of hyperalgesia appearing on the head and neck in diseases of eye, tooth, ear, tongue, nose, and other parts. Neither of these workers distinguished between forms of hyperalgesia according to whether the source is somatic or visceral but evidently regarded the two as originating similarly.

In Chapter VI, an investigation is described in which hyperalgesia of distant skin develops in response to painful stimulation of skin or cutaneous nerves. A cutaneous nerve is blocked, and a current is used to stimulate it above or below the block. If above the block, then the central nervous system receives the full discharge of pain-producing impulses lasting for several minutes. Never in these circumstances does peripheral hyperalgesia develop. But if the nerve is stimulated below the block, although the cord is guarded from the pain impulses during the whole period of stimulation, widespread hyperalgesia is found in the skin as soon as the block recovers. Now the interpretation of these experiments is clear; the hyperalgesia is not due to a process taking place in the cord; it results from a process at the nerve terminations. The observations throw serious doubt upon the idea that painful impulses ascending to the cord can set up such an "irritable centre" as may give rise to cutaneous hyperalgesia (Lewis, 133). They go farther. Similar hyperalgesia is provoked by stimulating skin itself; this is produced through a local nervous apparatus and referred to distant skin, again without the intervention of the central nervous system. Hyperalgesia, which we cannot doubt to be produced through similar mechanism, also results in the skin of the face when the mucous membrane of antrum or nerves of the teeth are stimulated. The last observations link up the experimental hyperalgesias with those described by Head and Mackenzie in the case of the teeth. It

is hardly to be questioned that, in all these instances, we are dealing with simple variations of one phenomenon. In speaking of the close similarity of the several segmental hyperalgesias discussed, I have in mind not only the common character of this hyperalgesia but particularly the peculiar and distinctive time relations to stimulation. The hyperalgesias appear after a period of delay and sometimes last many hours after the provocative stimulus has ceased. So does the hyperalgesia appearing after stimulation of an interspinous ligament with salt solution, and so does that following a short severe attack of angina pectoris. Another point of resemblance is the clear relation of all these hyperalgesias to nerve or segmental territories.

Thus a train of evidence of a most suggestive kind points to a common mechanism for all instances of referred hyperalgesia. It is to be remarked, incidentally, that these hyperalgesias do not necessarily depend upon pain-giving stimuli; a non-painful injury of skin suffices; so does a painless infection of the maxillary antrum. Skin tenderness may also appear without pain in visceral disease.

It would perhaps be premature to apply this hypothesis of referred hyperalgesia to direct visceral impulses without more questioning and study. One objection to it that may be raised is that of distance. In the studies of skin, tenderness might appear as far as 15 cm. in a direct line from the point stimulated; and in the case of reactions within the hand, it might be necessary to assume axon reflex paths as long as 25 cm. I know of no anatomical studies to support axon paths subtending such distances; that, however, is not to say that such do not exist, for the physiological evidence seems in these instances unequivocal. Similar evidence in the case of reference from interspinous ligament ($L1$) to the front of the abdomen would be exceedingly difficult to obtain and has not actually been sought; it would be still less possible to obtain where reference from viscera is concerned. The point here is that, if we postulate axon reflexes in these instances too, the distances are so great as to become difficult of credence though, in fact, we have no knowledge, anatomical or physiological, which sets a final limit to the length of an axon reflex. There is another possibility. The evidence is that hyperalgesia may come out of an axon reflex. That does

not preclude its origin out of reflexes passing through posterior root ganglion or even through spinal cord; we possess no direct evidence of such, but it is to be remembered as a definite possibility. In any case, I have in mind a hyperalgesia set up through a process developed locally in the skin.

If we believed hyperalgesia to depend upon axon reflexes passing through pain nerves, it might be difficult to explain how the impulses become transmitted from the deep system of pain nerves to a distinct system (see p. 44) supplying the skin. The difficulty, however, would not exist if the reflex were accepted as passing through a special system of nocifensor nerves (see p. 68) common to superficial and deep tissues. Given the possibility of a spinal cord reflex as opposed to an axon reflex, passage from one system of nerves to another could occur, and again the difficulty discussed would not arise.

A word more must be said about the hyperalgesia of the shoulder tip described by Morley (170), who relates that, in patients in whom he deliberately stimulated the diaphragm, hyperalgesia appeared instantly at the shoulder tip and vanished at once when stimulation ceased. The stated time relations cannot be regarded as establishing a fundamental distinction between this hyperalgesia and the hyperalgesia I have described. It can hardly be doubted that cutaneous hyperalgesia derived from ligaments of spine and of diaphragm are similarly brought about, for both are derived from deep-lying somatic structures and the one serves as well as the other as example; yet, in the case of interspinous ligaments, we have found the hyperalgesia to take some time to develop and much time to subside. Again, Capps and Coleman (24), in similar tests of the diaphragm, found hyperalgesia distinctly to outlast the pain.[1] Thus, there is disagreement about the duration of hyperalgesia provoked by stimulating different deep-lying somatic structures. Perhaps it will prove more accurate to say that the intensity and duration of hyperalgesia varies from subject to subject. Variation when skin is stimulated is considerable (Lewis, 133). In some subjects,

[1] It is not always made abundantly clear in such experiments that skin tenderness and deep tenderness are distinguished; the distinction is important from our standpoint, as we have no evidence that the two forms of tenderness owe their origin to similar mechanisms.

it fails to provoke a neighbouring cutaneous hyperalgesia; in some, too, itchy skin appears instead. Moreover, when the hyperalgesia appears, in some it lasts many hours, in others it lasts for shorter periods. Goldscheider (68) described it as disappearing instantly with the pain. Thus, there is as much discord in the description of what is found after skin stimulation, as after stimulating deeper lying structures; and the similar variations in the two instances become, in reality, a further point of resemblance between them. The presence of hyperalgesia of the skin in one patient with abdominal disease and its absence from another, despite pains of similar intensity and duration in both, might be explained plausibly along the same lines.

There is a minor point requiring new observation. In speaking of nocifensor hyperalgesia in Chapter VI, it has been said that the tender skin is not very definitely hypersensitive to warmth, as is erythralgic skin, but that there is a borderline reaction. No very deliberate observations from this standpoint have been made on tenderness referred from visceral disease, but Head (80) mentions incidentally that such skin may be hypersensitive to moderate warmth, the patient flinching from the contact. The presence or absence of this hypersensitivity to warmth is very probably related to the grade of cutaneous hyperalgesia; the point may be of importance and should be re-examined.

Muscular Rigidity

As is well known, muscular rigidity is often found in the abdominal wall, sometimes more or less overlying a diseased organ, such as gall bladder or appendix; at other times, at points remote from the seat of disturbance, as in the case of the contracted cremasteric muscle described by Ross in renal colic (201). Such rigidities may last for hours, days, or even weeks. They do not necessarily, or even usually, affect a whole muscle but only a limited part of it, thus producing what has been called "phantom" tumour. While muscular rigidities have been described in the main as being in the abdominal wall, Ross thought there was rigidity of the upper intercostal muscles in angina, and Mackenzie ascribed the sensation of gripping in the chest to intercostal spasm. It is interesting that, in visceral disease, the reflex is never seen to affect muscles in the limbs. In the decapitated cat,

the latter can be produced readily enough by stimulating the proximal end of the cut phrenic, a somatic nerve; but in these observations with Squire (149), I was unable to elicit any such reflex from the heart or aorta.

Muscular rigidities in visceral disease were carefully studied by Mackenzie, who regarded them as reflexes started as responses to visceral stimuli. He also recognised that similar muscular rigidities happen in response to stimuli received from somatic tissues, such as painful joints or peritoneum. For Morley (169), these muscular reflexes always owe their origin to impulses received from somatic structures. But experiment shows that there is an apparatus whereby both viscus or parietal wall may be the source of a spinal reflex setting up local and unilateral muscular contractions in the abdominal wall, and that the impulses travel in the one case by sympathetic, and in the other by somatic, nerve paths (see p. 132). There is evidence in the case of visceral disease itself that a reflex may be started from the visceral or from the parietal structure (see p. 165).

In deliberately provoking rigidities reflexly in man (140)—as by injecting saline into an interspinous ligament—the contraction is found to appear and to subside with the pain provoked; pain in this form of stimulation lasts some minutes, and so does rigidity. Because there is this time relation between pain and rigidity, we cannot assume it will so strictly prevail in states of disease. Muscular rigidities are here maintained for very long periods of time and in states where pain has not always the same severity as in the acute experiment. It is possible, as is the case with referred tenderness, that the end phenomena may appear or be maintained in the absence of actual pain.

Deep Tenderness

Deep tenderness as an association of visceral disease provides a problem of complexity. For Mackenzie, who made the important observation that it occurs in the abdominal wall, it was largely muscular (153, 155). He found that, after attacks of anginal pain, pinching the sternomastoid, or the borders of trapezius, or pectoral muscles may elicit pain, as will squeezing the edge of the rectus abdominis muscles when the fingers can be carried around and behind the edge in cases of abdominal

visceral disease. Mackenzie (153, 155) was emphatic in his belief that the deep tenderness was in the parietal wall and never in the viscus, for the reason stated and because it seemed to him to be fixed in position even when the underlying organ moved, as with respiration; he attributed this deep tenderness which he had discovered to excitation of an abnormally sensitive spinal cord by stimuli that normally would produce no painful sensation. Morley agrees that the tenderness is in the parietal wall but believes that it comes chiefly from the parietal peritoneum directly stimulated by the diseased viscus. For Kinsella (106, 107), as for Hurst (90), the diseased viscus may itself be tender. This last view can be considered more conveniently in the next chapter.

When severe pain is aroused by injecting hypertonic salt solution into the ninth thoracic interspinous ligament and a phantom tumour appears in the upper part of the rectus abdominis of the same side, the region of this tumour displays deep tenderness (140). This deep tenderness disappears as the pain subsides. That the tenderness is elicited from the abdominal wall tissues deep to the skin cannot be doubted, and that it is elicited from the affected muscle is highly probable. Muscles may become both pain-giving and distinctly tender towards the end of a period of steady, firm, voluntary contraction of two or more minutes' duration. Similar, though more conspicuous, phenomena are developed when muscle works under completely ischaemic conditions (145). In both instances, the pain and the tenderness rapidly disappear when full blood supply is restored and the muscle is relaxed. The recovery is complete unless the painful contraction has been longer maintained, when a measure both of pain and of tenderness may remain. The amount and duration of this remnant largely depends upon the duration of previous muscular contraction. Thus, the contemporary tenderness of the experimental phantom tumour is very probably muscular tenderness resulting from the tonic contraction. Tenderness developing in muscle that has undergone continuous contraction for many hours or days might be expected to outlast the actual contraction, as common experience tells us it does in the stiffness which follows prolonged, and especially unaccustomed, exercise.

But deep tenderness is not always muscular. Tenderness appears over the testicle in renal colic and after injections of the first lumbar ligament. It lies deeper than the skin and is presumably elicited from the deep tissue of the scrotal wall or from the tunica vaginalis. Kellgren (101) found that a saline injection into the extensor muscles of the fingers produced pain and deep tenderness on the back of the hand. This tenderness was undiminished by anaesthetising the overlying skin; it was abolished, but the pain was not, by anaesthetising deep structures as well. It is exceedingly difficult to explain unless we assume that there is a summated effect of impulses travelling to a common region of the sensorium from injected muscle, on the one hand, and from the distant tissue in which the tenderness has been found, on the other. An alternative possibility, on the lines of the nocifensor hyperalgesia in skin but applied to deep tissues, meets with the objection that the tenderness in these experimental examples does not outlast the pain. This hypothesis of summation is not equivalent to that of Sturge's irritable centre in the cord; the latter is a stable condition, while what we are here considering is a condition in which temporarily two series of impulses, one pain-giving and the other subthreshold, exert a combined effect on a common region of the sensorium.

It will be clear from what has been said that tenderness appearing in the region of a reflex rigidity of the abdominal wall, though probably the outcome of muscular contraction, may possibly possess other contributory causes. It requires further investigation.

Root Representation of Visceral Tenderness and Pain

Head (80), following Mackenzie's example, systematically studied areas of cutaneous tenderness associated with painful disease of various viscera and, relying on Ross's hypothesis, concluded that "the nerve roots along which reference takes place enable us to map out the sensory supply, which the affected organs receive by means of the sympathetic. For on this hypothesis the viscera receive their sensory fibres from that segment of the spinal cord from which the somatic sensory roots arise along which pain is referred." Using areas of tenderness displayed in visceral disease and comparing these with his enu-

meration of segmental skin areas (see Fig. 3), Head drew up a tabular statement purporting to represent the sensory root supply of many of the viscera in man. This will not be reproduced fully because I cannot regard his representations as sufficiently approaching to finality; but many of Head's data are incorporated in the accompanying table. I have used his text rather than his tabular statement.

There is a second method of approach, namely, that introduced by Läwen (114). He injected novocaine into the region of the sympathetic chain ganglia and succeeded, by so doing, in relieving different forms of visceral pain. I say regions of the ganglia because these "paravertebral" injections, as they have been called, often cause segmental anaesthesia of the skin and it is not clear at precisely what point the visceral afferent path is interrupted—whether in ganglion, white ramus communicans, or nerve root.

TABLE 4

ROOT REPRESENTATION OF VISCERAL TENDERNESS AND PAIN

	Head (tenderness)	*White & Läwen* (pain)	*Kappis & Gerlach* (pain)
Anginal pain	*T*1 to *T*5 *T*6 to *T*9 (and cervical areas)	*T*1 to *T*4 (*T*5 to *T*8 also)	
Gastric pain	*T*7 to *T*9	*T*7 to *T*8	*T*6 to *T*8
Gall stones	(*T*6, *T*7) *T*8 to *T*9 (*T*10)	*T*10	*T*9 to *T*10 (*T*11)
Renal colic	*T*10 to *T*12 (*L*1)	*T*12 to *L*1 (*L*2, *L*3)	*T*12 to *L*2

Note. The numbers in parentheses are of roots sometimes involved.

Head tabulated the root representation of many other organs, thus: Intestine, *T*9 to *T*12; rectum, *S*2 to *S*4; bladder fundus, *T*11 to *L*1; neck, (*S*1) *S*2 to *S*4; testicle and ovary, *T*10 to *L*1; uterus contracting, *T*10 to *L*1; os uteri, (*L*5, *S*1) *S*2 to *S*4.

Pain from duodenum, pyloric end of stomach, and gall passages is conveyed chiefly or exclusively by nerves of right side (Läwen; Kappis and Gerlach).

White (241) mainly used alcohol injections and tabulates forty cases in which he has treated anginal pain. From this valuable collection and from the earlier novocaine blocks of Mandl (158), it is clear that blocking *T*1 to *T*5 on the left side usually abolishes anginal pain and that blocking *T*1 to *T*4, or

even *T*1 to *T*3, may have the same effect but that sometimes it is necessary to carry the injections lower down and even below *T*6. It is interesting that pain, though abolished on the left side, is sometimes noted to persist on the right side after these left-sided injections. In agreement is the usual effectiveness of excision of the left inferior cervical ganglion, though pain sometimes persists on the right side after this procedure also.

Läwen states, on the basis of numerous experiences, that gastric pain in man is relieved by injecting *T*7 and *T*8 on the right side; that injecting *T*10 on the same side abolishes or relieves most examples of gall stone pain; and that renal colic is relieved by blocking *T*12 to *L*1 but that sometimes the injections must be carried as low as *L*3. With these results, those of Kappis and Gerlach (98), obtained by the same method, are in good agreement.

When Head's associations are compared with those derived from nerve block, it will be seen that there is a broad agreement.[2] There is not precise agreement in detail. The correspondence is closest in the upper dorsal region, where, indeed, it is to be expected since segmentation of the somatic tissues is clearest here; and the first root known on anatomical grounds to carry visceral afferent fibres is *T*1. For the rest, there is a definite tendency for Head's representation of the supply to lie at a higher level than those obtained by nerve block. If Head's representation is corrected to bring it into conformity with the later map of Foerster (see Fig. 3, p. 20), the discrepancies become less, because this correction would have, as a chief effect, the lowering of Head's segments *T*11 to *L*1 by one segment. Even so, discrepancy does not disappear.

The comparison made will suffice to show the direction that observations are taking, though even today we are far from being able to present a complete and accurate plan of the sensory root supply of the main viscera in man.

In investigating this problem of visceral root representation and in applying the results of observation, it is desirable to dis-

[2] Segmental values given by Gaza (63) are sometimes also quoted, but these appear to be derived from Läwen and from Head and must not be regarded as confirming these latter.

tinguish between areas of superficial tenderness and regions of pain. The first is more objective, and it is a cutaneous effect. The second is subjective, and the pain is not felt on the surface. It is a pain having no resemblance to cutaneous pain, which is felt in the skin and is readily localised. Visceral pain has the quality of other pains from deeply lying tissues—it is diffuse, it cannot be localised sharply, and it seems to be beneath the skin.

The area of superficial tenderness, when it occurs, does not mark out on the surface with any accuracy the region in which pain is felt; not infrequently there is a conspicuous divergence between the two. For example, take angina pectoris, in which pain frequently descends as low as the fingers but in which tenderness is rare even to the level of the elbow. Take renal colic, in which tenderness is frequent in loin and even groin; but, though there is no tenderness of the scrotal skin, pain is not unusual in the testicle. In estimating the sensory root supply of visceral pain, it is not the cutaneous maps of Head or of Foerster that must be used but the maps of deep segmental pain (Fig. 20, p. 123). When we use these maps, we shall still be content to regard the usual distribution of anginal pain as over *T*1 to *T*4; but we shall associate renal colic with *T*12 to *L*2, including the testicle, and thus agree closely with Läwen's observations.

Chapter XIV

SOURCE OF PAIN AND ASSOCIATED REFLEXES IN VISCERAL DISEASE

Visceral and Parietal Source

Two main views have been held respecting the anatomical source of pain, tenderness, and rigidity in visceral disease. The first is that these three phenomena come from impulses arising in the viscus itself. The second is that the impulses start from other structures, which are affected by visceral disease. The latter originated with Lennander (120), who, after recognising the insensitivity of the chief viscera, came to the conclusion that the pain of abdominal visceral disease comes from the parietal wall, through adhesions, by general stretching of the parietal wall or by drag on the attachments of the mesenteries, involved or not in lymphangitis. In his later work (123), he emphasised the front parietal wall. Lennander, however, concerned himself little with tenderness or rigidity.

The first view, because it was held too rigidly by Mackenzie (155) and despite his appreciation that reflex rigidity and tenderness may appear in local peritonitis, led him into difficulty in attempting to explain the phenomena of appendicitis. He knew that the early symptom of this disease is midline pain and ascribed it to overaction of the appendicular muscle. He fully recognised, however, that the predominant symptoms are those following in the right iliac fossa; and, though confessing inability to account for their being so one-sided, he yielded to the pressure of a generalisation and explained them as visceral reflexes. Incidentally, the idea that pain or reflexes arising in structures developing in the midline will present themselves as midline or bilateral phenomena, can be carried too far. Thus the gall bladder and common bile duct belong to this category; yet, in the decapitated cat, distension of the duct yields ab-

dominal muscular reflexes that are chiefly right-sided and pass chiefly through the right splanchnic nerve (37, 149, 205). Similarly, the heart is developed in the midline, but anginal pain predominates on the left.

The second view, that the parietal wall is the source, leads equally to difficulty if held too generally. Thus, it would seem impossible, because of the isolation of the organ, to accept any theory of cardiac pain and its referred tenderness built up on these lines. Again, Morley (169) is brought to believe that the deep tenderness and rigidity over an overdistended and inflamed gall bladder arise reflexly out of stimulation of the parietal peritoneum by the contact of the inflamed organ, and that these symptoms shift correspondingly with any movement of the organ consequent upon its further distension, a difficult idea to accept. This direct stimulation of the parietal peritoneum by diseased organs has become an essential feature of his views whenever reflex or referred phenomena are to be explained; and thus he is led to suggest that the parietal peritoneum is affected in this manner by a congested liver, through some chemical process on its surface, or by a gastric ulcer, though this is making no obvious contact with the parietal wall. "When the sensitive parietal peritoneum is pressed down by the examining finger into closer contact with the ulcer, it receives a painful stimulus", again thought to be chemical. "With each change of its position relative to the abdominal wall, a fresh area of parietal peritoneum is stimulated, with a fresh group of nerve endings, and the accurate localisation of the tender point over the ulcer is explained."

Morley's conviction of the large part played by the parietal wall is influenced by his belief in great sensitivity of the parietal peritoneum. In Mackenzie's experience (155), the parietal peritoneum was not a very sensitive structure: it can be incised and stretched painlessly, he says, but the loose connective tissue lying immediately outside is very sensitive. Morley, on the other hand, found that light stimulation of the parietal peritoneum from within causes severe pain. Such sensitivity must surely be exceptional or confined to inflamed peritoneum; the hobnailed liver and craggy carcinomata of stomach pass up and down under the examining hand painlessly, and there was no complaint of severe pain in Capps' experiments (24) in which the parietal

peritoneum was scratched or rubbed with a wire introduced through an exploring cannula. In the decapitated cat, muscular reflexes are not very readily provoked from the peritoneal surface; they are more readily induced from the tissues lying outside it (Lewis and Kellgren, 140).

Important evidence bearing upon this discussion is to be found in Kappis and Gerlach's statement (98) that rigidity of the abdominal wall arising out of visceral disease disappears when the reflex arc is broken by paravertebral injections. Now these injections may catch the sympathetic ganglia and break afferent paths travelling through these ganglia or their rami, or they may catch the segmental somatic nerves, which run also in the vicinity. Thus the injection might break the reflex path, whether the afferent channel was from visceral or from parietal structure. But these workers state that rigidity is often relieved without loss of touch sense in the corresponding segments, a clear indication that the somatic paths have escaped and that the reflex is, in such cases, started in the visceral structure. This evidence is supported by similar evidence (Kulenkamff, 109) in the case of successful anaesthetisation of the splanchnic nerve for visceral pain; muscular rigidity in gall stone colic may disappear at once when this pain-carrying nerve is blocked. Kappis and Gerlach and also Kulenkamff state further that the whole of the rigidity does not disappear in all patients and that, in those in whom it does not disappear, the remnant is to be ascribed to a reflex arising in the parietes.

It is not fundamental unsoundness that renders either the first or the second view unacceptable, since each contains a large element of truth; it is their presentation as general laws, each exclusive of the other, which is objectionable. I believe that referred pain and associated phenomena are started sometimes in a visceral structure (not necessarily in the actual viscus) and sometimes from the anterior or posterior wall of the body cavity. The evidence that they can so start has been given and is, I think, in both cases conclusive. It seems clear that anginal pain and gall stone colic, with their attendant phenomena, arise directly from the viscus concerned; it seems equally clear that the shoulder pain of diaphragmatic peritonitis and the late pain of appendicitis arise from the parietal wall. In given visceral

diseases, the source of the impulses—whether parietal or visceral —must be determined in each instance on individual grounds. It does not belong to the province of this book to study exhaustively the sources in the case of all organs but rather to use these as illustrations in a general discussion.

True Visceral Tenderness

Mackenzie departed from usual opinion in concluding that deep abdominal tenderness is not in the viscus itself. This view of his was based not only upon the frequent possibility of demonstrating the tenderness to be in the wall of the abdomen but on visceral insensitivity, as shown by Lennander, himself, and others. The main viscera are insensitive even when inflamed. Lennander (120) speaks of the inflamed intestine and gall bladder as being as insensitive as healthy ones; the insensitiveness of the inflamed appendix is generally agreed upon, though Kinsella (107) says it is usually sensitive if squeezed in its long diameter;[1] Morley (169) records how he squeezed and pinched with forceps a duodenal ulcer without eliciting pain (see also 16, 160). Another reason why Mackenzie refused to accept the idea of true visceral tenderness was that he believed he could demonstrate, in the case of organs moving freely with respiration, that deep tenderness remains stationary while the diseased organ moves. Gastric ulcer has usually formed the basis of this discussion. It was Hurst (90) who, though once (89) agreeing with Mackenzie, stated that there is also a true visceral tenderness and that this is finally settled so far as ulcers are concerned. He concluded on the basis of X-ray examinations that, in a large majority of cases, the actual ulcer is found to be the seat of localised tenderness, the position of tenderness changing as the ulcer changes with alteration of posture and during manipulation of the abdomen. Morley and Twining (171), after a very carefully conducted research controlled by X ray, confirmed Hurst's finding (90) that the point from which deep tenderness can be elicited by pressure overlies the ulcer and moves with it. Their explanations, however, are different, for, whereas Morley believes the

[1] This must be difficult to accomplish, however, without interfering in the least with the sensitive mesentery.

tenderness to be a changing parietal tenderness (see p. 164), Hurst expressed belief in tenderness of the ulcer itself.

Between Mackenzie, on the one hand, and Hurst and Morley, on the other, there might seem to be a contradiction of fact; but it is reasonable to conclude that both points of view may have been right and that sometimes there is movement of the point of deep tenderness and sometimes there is not; and, with Hurst, that sometimes the deep tenderness is in the body wall and that sometimes it lies deep to it.

To accept Hurst's view that an ulcer itself is tender when pressed upon through the abdominal wall is, however, very difficult while the evidence we possess speaks for the insensitivity of ulcers when exposed and tested. The conclusion that it is tender to pressure through the wall depends on the assumption that the stimulus of pressure is localised to the ulcer, which, clearly, is never the case. Mackenzie very properly said that no conclusion should be drawn as to the sensitiveness of an organ which has been stimulated through a structure itself sensitive; and I would add that none should be drawn if stimulating pressure is exerted through the organ on structures which may be sensitive. Is it not possible that tenderness in cases of gastric ulcer is sometimes in the attachments of the stomach to the posterior abdominal wall? To resolve the question here discussed is important to the problem of visceral pain for, if we admit that true visceral tenderness occurs, then we simultaneously agree that pain can arise directly from a viscus.

Origin of Pain from Contraction of the Bowel

It is a commonplace that solid organs of the abdomen like the liver, kidney, and spleen become the seats of local inflammation, gross fibrosis, or new growth, without the production of pain. Pain, in fact, is not regarded as a symptom usual in, or proper to, disease of these viscera. Pain arising from abdominal organs is known to arise mainly from the hollow muscular-walled viscera; this was recognised by Traube (230), and Mackenzie (153) emphasised such organs as the source of some of the most severe pains experienced by man.

We will not consider the hollow viscera individually (that would carry us too far into detail), but the intestine will be dis-

cussed at some length. This is the most readily investigated and has been the most closely studied; what is shown for the intestine is applicable to other, probably to most, hollow abdominal viscera.

The term "colic" reflects the long-established belief of pain derived from the large bowel, and no very acute observation is required to relate severe spasms of colic with its movements. The synchronism of the pain with bowel contraction, as the latter begins and ceases, was reported by Nothnagel (175). Mackenzie (155) watched a loop of bowel contract after being withdrawn from the abdomen; and, with each contraction, the unanaesthetised subject complained of simultaneous pain. The hardening of the fundus uteri is easy to feel at each pain during labour. Thus, it is conclusively known that spasms of pain, and of severe pain, arise out of the contraction of the walls of such hollow viscera and of the bowel in particular. This knowledge, when coupled with the observation that the same viscus is insensitive to injury, posed a problem of fertile interest. Lennander (120) boldly concluded that, although the pain is provoked by bowel contraction, it does not arise in the bowel. We shall return presently to the evidence and to his views.

Nothnagel disagreed and early suggested that, although the bowel may not react painfully to stimuli such as cuts or burns, other stimuli may be more adequate. After abandoning the idea that contraction of the bowel presses on nerves contained within its walls, he put forward the hypothesis that the pain stimulus arises out of the anaemia of contraction; this second idea is scarcely acceptable in view of the rapidity with which pain succeeds contraction. In a similar but not identical argument, it has been urged more recently that special organs respond only to specific stimuli—the eye to light, the ear to sound, and so forth —and that cutting or burning, being unnatural forms of stimulus to apply to such a viscus as the bowel, may be incapable of initiating pain, while pain may be derived from the development of tension in its walls (Hurst, 89). In this form, the argument cannot pass. The test is not of an end organ like the retina; it is of nerve fibres. All nerve fibres that have been tested respond appropriately to cross section; the optic nerve, when cut, gives flashes of light; a motor nerve gives motor response; and pain

nerves give pain. The idea here is failure of all but appropriate stimuli. But an adequate stimulus may be such from its quantity rather than from its quality. It is inconceivable that the viscera are permeated by pain nerves and that these cannot be stimulated by cross section (97); it is, however, conceivable that the nerves are so scattered that a cut or a crush damages too few to register as pain. And, in this connection, it is to be remembered, as stated in Chapter I, that we are not quite in a position to insist on the complete and universal insensitivity of the bowel to such stimuli. We have to consider if contraction or tension affecting a length of bowel might not stimulate adequately, in virtue of the length of bowel and numbers of nerve fibres involved.

Summation.—In discussions on bowel pain, it has been thought that pain may result from summation of impulses. It is known, of course, that spinal cord reflexes can be provoked by several stimuli where a single stimulus of the same strength fails. It happens when several subthreshold stimuli are released together into different afferent nerve fibres; it also happens when a number of subthreshold stimuli are arranged in succession. The term "summation" has been used for both these phenomena, the one spatial, the other temporal.

In regard to the first, Weber (238) stated long ago that the development of pain from skin, when it is heated or severely cooled, depends on the extent of surface involved. Though it seems clear that more pain is experienced when the area from which it is derived is increased, there is no evidence that the threshold for pain is lowered by increasing the number of pain fibres stimulated; on the contrary, it would seem that pain first appears with the same strength of stimulus (radiant heat, for example) whether the area stimulated is small or large (Hardy, Wolff, and Goodell, 77). This form of summation will be referred to again in discussing the adequacy of the stimulus provoking colic, especially in relation to the length of bowel involved.

In regard to the second, I find it difficult to agree that summation in this sense has been shown conclusively for pain. The papers usually cited are those of Richet (195), Watteville (236), and especially Goldscheider (59, 67). It seems very possible that, in this early work, the response of the skin to successive shocks was often the result of decrease in the electrical resistance of the

skin with the repeated stimulation. Goldscheider, who applied his results theoretically to visceral pain, investigated the second pain described on page 108. He believed this to be a summation phenomenon. Hauck and Neuert (79), in recent work, follow Watteville's method of stimulating a cutaneous nerve through the skin. The observations should be repeated by using a subcutaneous electrode in close contact with the nerve.

Tension of Gut Wall or Mesentery

This theoretical discussion could serve no useful purpose unless it was followed by a further consideration of observation and of experiment. For Lennander (120, 123), bowel pain was derived exclusively from the walls of the abdominal cavity; movements or distension set up strains stretching the parietal wall where the mesentery is long or tugging at the root of the mesentery where the mesentery is short. He recorded an instance in which a coil of bowel slipped out from an abdominal wound and soon showed such violent contraction that its lumen was obliterated. The patient was unconscious of this; but, when another couple of coils protruded and contracted in the same way, pain was felt in the interior of the abdomen. There were adhesions between bowel and parietal peritoneum as well as at the root of the mesentery. Deliberate stretching of the gut without pulling on its mesentery is painless, according to the same surgeon; but slight forward strain gives pain referred to the umbilicus. He instanced two cases in which dragging on an appendix and caecum produced exactly the same kind of pain as that felt by these patients in attacks of appendicitis. Pulling on the mesentery of the appendix, pinching it, or heating it gives pain in the region of the umbilicus (Lennander, 120; Kinsella, 107; and personal communication from Professor Pilcher; Mitchell, however, reported reference to the epigastrium). Lennander's conclusions were drawn from such observations, by which he was convinced that contraction of the gut, however powerful, might be painless, while strain upon parietal structures—such as would become effective as a greater length of gut became involved—would be painful. His observations that strong contraction of the bowel does not necessarily cause pain agreed with the previous experience of Bier (10). Wilms (243, 244), who otherwise largely

agreed with Lennander, emphasised the mesentery itself as the source of pain impulses in intestinal colic because he found it to be sensitive.

These questions of the effect of strains on gut wall and mesentery have been investigated in more detail in animals. Kappis (96) used dogs prepared by preliminary operation under anaesthetics but fully conscious at the stage of testing. He found that distension of a piece of bowel between two clamps is painful (i.e., gives the reactions of pain), although tug on the base of the mesentery could be excluded; but the distension stretched the mesentery at its attachment to the bowel, and it was to this that he attributed the pain. He also caused the bowel to contract firmly but painlessly by injecting barium chloride into its wall; Meyer (160), using cats, extended this work. He painted barium chloride on the wall of the gut, a procedure which yields a hard contraction. He found that maximal contraction so induced gives no pain, unless a long stretch of bowel is involved, and concluded that pain then comes from mesenteric stretching. If the two limbs of a loop of bowel were stitched together, the mesentery lying guarded between them, barium contraction then produced no pain. There was no indication of pain if separate lengths of bowel were thrown into contraction, provided that short lengths of uncontracted bowel intervened, although the total length of the contracted pieces might together exceed that of a single piece, the contraction of which produced pain. But if the short intervening stretches were also thrown into contraction, the evidences of pain appeared. This experiment would appear to show that the length of bowel involved is important from its increasing power to affect the mesentery rather than from the heaping up of numerous impulses to form a stronger intrinsic stimulus. Meyer also used an ingenious instrument which allowed him to stretch tightly a short piece of bowel, with or without the corresponding mesenteric attachment, and obtained evidence of pain only in the former circumstance. Breslauer (16) followed with experiments along much the same lines; he demonstrated that blowing up a length of gut does strain the mesentery and concluded with Meyer that this is painful but that stretching the bowel wall is not. He also confirmed Meyer in finding that contraction induced by painting barium chloride

on the gut is painless. There are many observations upon man in which balloons have been introduced and distended under pressure within various parts of the alimentary tract (see p. 144; and Payne and Poulton, 179). For the most part, such a procedure produces a sense of fullness or discomfort rather than of pain. These observations have the advantage that, being made on man, the subjective phenomenon can be described; the observations suffer from the disadvantage that it is far less possible to be sure of the structures placed under tension than in the case of the animal experiment. The experiments of Meyer with those of Breslauer offer, when taken in conjunction with Lennander's work, strong evidence against the pain stimulus arising ordinarily either directly out of the contraction process or directly out of tension in the walls of the gut. Here, too, it may be added that, in my observations with Kellgren (140) on animals, we were unable to elicit reflex muscular contractions of the abdominal wall either by stretching the gut or by throwing short lengths of it into contraction, though such reflexes were obtainable from the mesentery.

That pain impulses may arise in the gut wall is not conclusively disproved; but it seems from the evidence more probable that in colic they come usually from supporting structures and especially from the mesentery itself. If they ever come from the gut wall, then the adequacy of the stimulus arises more probably from a spatial than from a temporal summation.

Chapter XV

PRINCIPLES IN THE CLINICAL USE OF PAIN

In passing to a brief exposition of the principles underlying the application of experimental methods to patients suffering from spontaneous pains, it should be made clear that I have not in mind so much their application as a routine in diagnosis—though here, too, the same principles are already showing increasing value—but rather their use in investigating persons chosen because they are observant and are sufficiently interested in tests of the kind to give close attention and to help in attempts to solve the mechanisms of pain.

It has long been manifest that a history of pain, as it is related with the full circumstances in which pain is felt by an observant subject, may be itself diagnostic of a given disease or of disturbance of given tissue. Time will show this method to possess a longer reach than has been suspected; but, before its full worth can be attained, descriptions of pain must be made more accurate.

It must be obvious to anyone who has given thought to the matter that most descriptions of pains—as these are supplied to us by those who suffer from such pains in words purely of their own choice—fail to convey sufficiently precise ideas of the sensations experienced and therefore do not adequately identify the pains. One reason for inaccuracy and inadequacy of description is the difficulty of calling up exact memories of what has been felt some time previously. It is certain that the closer the description is to the event the more accurate it becomes, and that the description is most accurate when given at the time pain occurs and deliberately revised at the time the pain recurs. Another reason is the difficulty of finding right words of description and apposite illustrations; to do this requires observational and didactic skill in a degree which few possess.

In Chapter III, I have already outlined views of the form descriptions of pain should take and have pointed particularly to the weakness of present usage, which permits observations of pain to be recorded mainly in terms of some agency imagined by the subject of pain to be capable of causing it. Such descriptions, while very imperfect, are also often misleading. To be complete, a description of pain experienced must at least comprise a statement of severity, of kind or quality, of locality, of relation to time, and of the precise circumstances in which it is felt.

Severity

The general level of a pain's severity is recognised to possess some clinical value. It is true that severe pain often indicates a grave disorder; few spontaneous pains can be described as agonising, and most of these are known to be derived from the viscera. But the general rule has very definite limitations, for severe pain, as in intestinal colic or in dysmenorrhoea, may be a passing event and of relatively trivial concern; and it is well known that minor degrees of pain are often provoked by very serious diseases. It is widely believed that the intensity of pain in patients can be evaluated by those possessing intimate knowledge and sound judgement of human types and motives; but it is clear that, in very many individual instances, intensity cannot be gauged accurately either from the patient's account of it or from associated reactions. For these reasons, it is very doubtful if there is much or even anything to be gained by further studies of pain severity or by attempting to set up standards of severity with which spontaneous pain can be compared. That is not to say that studies of pain threshold may not be serviceable (see 77).

Quality

The quality of pain arising from many tissues and organs of the body has been discussed at length in Chapters III and XI. It has been concluded that superficial or skin pain stands by itself; this is derived exclusively from skin, from certain mucous membranes, from the nervous apparatus which supplies these structures, and from nothing else. Once pain is properly identified as having this particular quality, which, when experienced

continuously, is called in common parlance "burning", its origin from the structures named is certain; such pain is not derived from muscle or other deep-lying structure.

Pain clearly recognised as having the quality of that elicited by squeezing the webs of the fingers always comes from deep structures. The point emphasised is that, for purposes of investigation and ultimately for diagnosis, the quality of pain derived from the limbs should be described under such terms as "skin" and "web" pains, or their equivalents "superficial" and "deep" pains. These are descriptive terms of quality which can be used by the experienced with accuracy and to convey essential information.

Localisation

The source of pain may be localised by patients with precision, or the general region from which it comes may be indicated clearly. The value of such localisation, in pointing to the seat of mischief, is universally recognised. It should be remembered that accuracy in describing locality in which pain has been felt begins to decline from the moment pain ceases and that the most valuable statements are to be obtained while the pain is actually present. It is also fully to be appreciated that, whereas pain arising from skin is localised with almost negligible error, the pain arising from deep-lying organs may be referred remotely. The usual and often remote reference of pains from deep-lying somatic structures and the strong resemblances between such reference and those arising in the course of visceral disease are not usually recognised. They have been dealt with in Chapter XI. Appreciation of the references that occur from muscles of limbs and body wall is especially important if confusion is to be avoided. When pain has a segmental distribution, it is to be assumed that it may arise from any deep structure innervated in that segment. This is not to say that all these possible sources are equally likely; experience will provide knowledge of relative frequency, which will guide judgement as to the probable source. Though pain distributed in the territories of the last cervical and upper dorsal nerves may have its source in muscles of the back or of the chest wall, it is usually derived from the heart.

In using localisation, it is necessary to be familiar with the segmental distribution of deep pain (see Fig. 20).

Duration; Time-Intensity Curve

Obviously, a pain's duration throws important light on its mechanism and shows the interference to be a transient event or to be long continued and stable.

A feature to which too little attention has been given is what may be called the time-intensity curve of pain (137). It is important both because it is usually capable of accurate description and because it has a number of very significant associations.

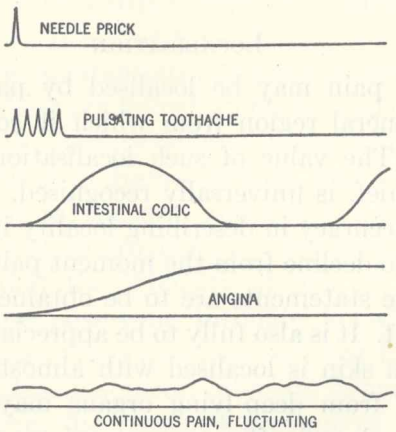

Fig. 26. A diagram illustrating time-intensity curves of various well-known pains, namely, needle prick, pulsating toothache, intestinal colic, angina, and continuous fluctuating pain.

The curve portrays the manner in which pain starts, the rapidity of its culmination, the duration and smoothness at its height, and the manner of its decline. Pain may come and go in a flash, as when the skin of the face is pricked; it may be felt in rhythmic pulses, as in inflammation of dental pulp or in pulsating headache; it may be experienced as longer and less rhythmic phases, as in intestinal colic; it may rise to a plateau and last with little fluctuation for a long time before diminishing and vanishing, as in cases of burnt skin or in the attack of angina pectoris; it may be continuous but fluctuating in intensity, as in aches that come from the musculature of the limbs (Fig. 26). All such variations

possess exact significances, if we can but discover them. It will be obvious from the examples given that often the time-intensity curve, if it does not identify the organ or tissue, provides very important clues to the manner in which the pain is produced.

Circumstances in Which Pain Develops

If a finger is caught between two stones and is crushed, the lesion giving rise to pain does not remain for a moment in doubt. Here there is a manifest relation between cause and effect. Similarly, if overdistension of the bladder is allowed to occur or if indigestible food is swallowed, pain arising therefrom will readily be ascribed to its appropriate and ultimate cause. If pain in the chest develops on walking and if this reaction is repeated uniformly, the subject will recognise that exercise provokes pain; but, unaided, he will not recognise that it is derived from the heart. The circumstances in which pain develops form most important, often conclusive, evidence of the meaning of pain from the standpoint of disease when we have the requisite knowledge.

In reviewing the description of pain as presented in this chapter and book, it may be said that the cause of pain is rarely known, immediately and with certainty, unless such pain is provoked at the surface of the body. Deep pains cannot be distinguished from each other by their quality; the localisation has neither the constancy nor the individuality enabling us to regard it as specific. We have seen how closely both in quality and in segmental distribution deep somatic and visceral pain may resemble each other. Localisation of deep pain in general apprises us with certainty only of the side and the segment or segments from which pain comes. In the syndrome of deep pain, wall tenderness, and muscular rigidity, there is nothing conclusively stamping the syndrome as originating in visceral disease. In the case of these deep pains, it is only when we combine localisation with time-intensity, or localisation with the circumstances in which pain appears, that we begin to reach reliable conclusions. The time-intensity curve and the circumstances in which pain develops bring consideration of the activities of the suspected organs under suspicion, the pain coming with the movement of a joint, with visible or audible movement of the bowel, or with

extra work thrown upon the heart. These considerations serve to emphasise the danger, from the standpoint of accurate diagnosis, of placing reliance on a single feature of the pain and the importance of marshalling the essential features of the pain syndrome as a whole.

Duplication of Pain

Descriptions of pain taken from the inexperienced are necessarily inaccurate, just as descriptions of colour by a child are inaccurate. To acquire accuracy, experience must be obtained. The power to distinguish between "skin" and "web" pain can be cultivated in all subjects without difficulty by provoking these pains: the pains can be elicited by pinching a tiny fold of skin or by firmly squeezing the web; the difference is conspicuous. This is a simple distinction between two qualities. Observant subjects can, I think, be brought to differentiate between pain arising from muscle and from web by repeatedly inducing pain from the appropriate structures and focusing attention upon it. But, in this instance, the difference is probably not one of quality. In muscular as in aponeurotic pain, there are little fluctuations; web pain, as also tendon pain, is smoother.

In attempting to investigate spontaneous pain, accuracy is more assured if a pain recognised as identical in quality is deliberately induced in the subject. And the test is more reliable if it is carried out upon a region symmetrically placed to that in which the spontaneous pain occurs, preferably while the latter is being experienced, for the more certainly can the subject then state that these two pains are alike. The origin of headache from muscle or aponeurosis attached to the occiput can be determined through inducing such pain in quiescent periods by the irritation of corresponding structures.

In these attempts to duplicate pain, we may pass from the simple to the more complex, from a test which attempts to differentiate superficial from deep pain to one in which not only quality is taken into account but location, time-intensity, and so forth. It should be manifest that the more exactly the various characteristics are taken into consideration in testing, the more closely will the spontaneous pain be simulated and the nearer shall we approach to an understanding of the mechanism of this

pain. Very suggestive evidence is presented that spontaneous pain comes from a given structure or organ when pain of exactly the same quality and distribution can be provoked readily from that structure. Thus, when pain down the back of the leg—such pain as is commonly called "sciatica"—can be reproduced precisely by finding a tender place in, and deliberately stimulating, the erector spinae muscles of the lumbar region, it is possible if not probable that the spontaneous pain is arising from these muscles. But the tests may take us even farther. A patient complains that an area of skin on the dorsum of a foot is red, tender to light friction, and gives continuous "burning" pain when the foot becomes warm or hangs down; a pain of precisely similar character and location and similarly provoked by warmth or the dependent posture follows after burning the dorsum of the other foot with ultraviolet light or by heat; thus, we are brought to know that the complaints of this patient are all adequately explained by a condition of the skin comparable to the inflammatory condition produced experimentally (Lewis, 131, 139). Again, a man suffers from what is described as "cramp-like" pain in the calf of his left leg, a pain which occurs when he walks a hundred yards and continues for a time when he rests; it is accompanied by tenderness of the calf. A pain identical in all respects and associated with similar local tenderness can be provoked in the man's right leg when he is made to walk a hundred yards after the circulation to this leg has been arrested. We are taught that all the phenomena displayed are reproduced from the muscles of a healthy limb worked in the absence of circulation, and we are content to ascribe the symptoms solely to an obstruction of the man's artery, which we find (Lewis, Pickering, and Rothschild, 145). These two examples illustrate the full application of the principle, for they not only illustrate the discovery by the experimental method of the structures from which pain is derived, but they throw a great deal of light upon the mechanism of syndromes, which in these particular instances have been called "erythromelalgia" and "intermittent claudication", respectively. The tests, as they proceed in detail (see Chaps. V and VIII), become an exploration of mechanism. The most informing statement concerning spontaneous pain is that it can be reproduced exactly by a closely defined experimental

procedure. This method of studying pain by reproducing it or by investigating experimentally the precise circumstances in which pain arises is still far from exhausted. I may point to two further examples as notable illustrations of the method of my laboratory, namely, Pickering's pioneering work on headache (183) and Wayne and Laplace's investigation (237) of angina of effort.

Anaesthetising or Breaking Sensory Nerve Channels

There are other and valuable methods, recently used, of tracing pain to its source.

Where the source of pain is suspected to be somatic, the structures of the segment are searched for point or points of tenderness. If such are found, it is often possible, by pressure on these, to provoke pain similar to that of which complaint is made; it is also possible, in many cases, to abolish the pain by infiltrating the tender structure with local anaesthetic. To illustrate, successes of this kind have been numerous where pain, coming from erector spinae muscles or lumbar fasciae, has been referred to remote parts of the leg (Kellgren, 102).

A second means is the so-called paravertebral injection, given both to relieve pain and to determine the segments involved. It has been considered sufficiently in Chapter XIII.

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