The History of Anesthesiology

Reprint Series: Volume Twenty-eight

PAIN: Perspectives & Trends

Le Mal de Tête

This suffering French citizen of the mid 1800s is experiencing an unbearable headache. Although the cause is not betrayed, his affliction may relate to any of a number of recurrent vascular syndromes: tic doloreaux or other cranial neuralgias, migraine or tension headache, postherpetic neuralgia or temporomandibular joint syndrome.

From a lithograph by Honoré Daumer (1808–1879), French painter and caricaturist. Reproduced with permission from the Boston Medical Library in the Francis A. Countway Library of Medicine.

PAIN: HISTORICAL PERSPECTIVES AND RECENT TRENDS

Introduction

After the founding in 1938 of the American Board of Anesthesiology, it was hoped that residents in approved training programs, in addition to giving anesthetics, could learn to treat pain. This goal would be accomplished by injection of local anesthetics at the locus of pain. A leading proponent of this concept was E.A. Rovenstine at New York University, Bellevue Medical School who not only practiced the art but also tutored generations of graduate students on how to treat the many painful afflictions, then categorized. However, the catalyst and visionary in this broad area was John J. Bonica of the University of Washington who is today essentially responsible for the multidisciplinary approach to pain therapy as utilized in the burgeoning anesthesia pain clinics.

In seeking to cast light on the problem of pain by reprinting seminal articles of the past, it was not possible to define a specific starting point as has been accomplished with prior subject matter in the anesthesia reprint series. This is because, from the beginnings of communication, the idea of pain has occupied the thoughts of all manner of people, professionals and laity. E. M. Papper in his dissertation on Pain, Suffering and Anesthesia in the Romantic Period nicely illustrates these multicentric origins. Thus we present a selection of reprints of articles which have directed us toward the current era of optimism in pain therapy mainly through discoveries in the neurosciences.

Leroy D. Vandam, M.D. and B. Raymond Fink, M.D.

PAIN: HISTORICAL PERSPECTIVES AND RECENT TRENDS

Selected Papers

1. Ford FR, Wilkins L. Congenital universal insensitiveness to pain. *Bull J Hopkins Hospital* 1938; 63:448–466.

2. Dallenbach KM. Pain. History and present status. *Amer J Psych* 1939; 52:331–347.

3. Gerard RW. The physiology of pain. *Anesthesiology* 1951; 12:1–13.

4. Melzack R, Wall PD. Pain mechanisms: A new theory. *Science* 1965; 150:971–978.

5. Basbaum AI, Fields HL. Endogenous pain control systems. Brainstem spinal pathways and endorphin circuitry. *Ann Rev Neurosci* 1984; 7:309–338.

CONGENITAL UNIVERSAL INSENSITIVENESS TO PAIN

Frank R. Ford, Lawson Wilkins

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CONGENITAL UNIVERSAL INSENSITIVENESS TO PAIN

A Clinical Report of Three Cases in Children with Discussion of the Literature

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The three cases which form the subject of this article were observed at the Harriet Lane Home between the years 1932 and 1937. Since it was only by chance that the peculiar insensitiveness of these children was recognized it is not unlikely that other children among the thousands treated in this clinic may exhibit the same peculiarity. The cases are of such interest that we feel justified in reporting them even though we have obtained no anatomical material and though we cannot offer a satisfactory explanation for the findings.

Case History 1 (Ped. A-4143). *Boy of 9 years who had sustained numerous injuries including fractures of bones, extensive burns and laceration of the cornea which seemed to cause him no pain. No objective evidence of disease of the nervous system on examination. Intelligence quotient 104. Specific reading defect.*

W. S. was born on December 18, 1928, by normal spontaneous delivery. He weighed 8 lbs. at birth and seemed to be healthy. During infancy he gained weight well and there was never any difficulty about feeding. Early development satisfactory. The boy walked and talked normally at the age of 2 years. There were no serious illnesses during infancy or childhood. The parents were healthy. The mother gave birth to a boy 2 years later and then, after another interval of 2 years, to twin boys. These children were quite normal. There was one miscarriage at 3 months.

The parents had noticed when the child was quite young that he did not seem to notice injuries as other children did. The usual falls and blows never caused him to cry or to show signs of pain. As an infant he developed the habit of chewing his fingers. He would bite so hard that the fingers bled and they eventually became scarred and deformed. At the age of 2 years he fell and broke his left fibula; this did not seem to cause him any pain and he continued to walk about. When he was 5 years old, sand was thrown into his left eye and the cornea became ulcerated. He made no complaint of this and it was not until several days later that his mother noticed his eye was inflamed. She took him to an ophthalmologist who washed out the sand. However, the cornea never cleared and vision was impaired. The child was frequently involved in fights with his playmates. While fighting, he would protrude his tongue between his teeth and bite it until it would bleed. The tongue eventually became badly scarred. Frequently the boy would return home dripping with blood from lacerations and injuries due to being struck with stones in a fight. He never cried or complained of pain and would fight boys who were much older and stronger. At the age of 5½ years he was

admitted to a hospital because of a large swelling on the dorsum of the left foot. This was not tender and seemed to cause him no pain, but roentgenograms showed a fracture of the first metatarsal bone with much callus formation. It was learned that several months previously a large rock had been dropped on his foot, but the boy had continued to run about and play as before. In April 1937, when the patient was 8 years old, the mother discovered a large sore over the sacrum which the child had not mentioned. He was taken to a hospital where it was found that he had a deep, ulcerated lesion over the sacrum, measuring 2 by 3 inches, and also extensive, but less severe lesions over both buttocks and the posterior aspects of the thighs which resembled burns. It was learned, on questioning the child, that he had sat upon a hot radiator until the burn had resulted. The lesions were infected and covered with necrotic tissue so they were cleaned with a sharp knife and the wound was scrubbed with alcohol. It is reported that the child showed no sign of pain during this procedure. The wound healed slowly by granulation and left a dense scar. It is of interest that during his stay in the hospital he complained of abdominal pain on one occasion. This was associated with acute pharyngitis and with a fever of 103°F. The next day the pain had ceased, the temperature was lower and the child was convalescent. During this period, roentgenograms of the feet were made which disclosed an old fracture of the first metatarsal bone on the left, and of the second metatarsal of the right foot. It was never determined when the second fracture had occurred, for the child had never mentioned it. There was also atrophy of the left scaphoid bone, the cause of which was not evident. The boy was discharged on July 10, 1937. In October, 1937 he sustained a deep cut just above the left knee which opened the patellar bursa. This became infected and a sinus formed, which opened into the bursa. He was readmitted to the hospital where he was treated until the wound healed. On November 1, 1937, at the age of 9 years, he was admitted to the Harriet Lane Home for study of his apparent analgesia.

Examination revealed that the patient was 47 inches tall, which is about 4 inches below the average height for his age and about the average height of a boy of 7 years. His weight was average for his height. He had a rather "tough," shrewd expression and appeared older than his age. His features were small compared with his cranium and the supraorbital ridges were heavy, the eyes deeply set and closely spaced, and the bridge of the nose well developed. The hands were rather short and stubby, with prominent knuckles. The skin of the hands was rough and thickened but elsewhere was of normal texture. The hair of the scalp was dry and coarse. The dental development was normal for his age and the teeth were normally spaced. The sexual development was normal. Scars were found on almost every part of the body, some linear and some round. Most of these were old, white and atrophic, but there was a recent, reddish scar, 5 by 8 cm., situated over the sacrum and a small red scar over the left iliac crest. There were numerous scars over the hands and fingers, and the skin of the index fingers was so thickened, hard and contracted that the fingers were held in flexion. There was an infected linear cut a short distance above the the left patella which was in process of healing. There was moderate enlargement of the cervical, axillary and inguinal lymph nodes. The tip and edges of the tongue were much scarred. Examination of the heart, lungs and abdomen disclosed no abnormalities. The left foot was sightly smaller than the right and there was a dorsal dislocation of the metatarso-phalangeal joint of the left fifth toe. The spine was straight and the shoulders and hips were level.

Neurological examination revealed that the cranial nerves were quite normal. The musculature was of moderate bulk but firm and strong. There was no disturbance in muscle tone

on passive movement and no suggestion of spasticity. No tremors or other involuntary movements were present. Coordination in the arms and legs was excellent. The station was steady and the gait quite normal. All the tendon reflexes were of about normal amplitude. The plantar response was normal. The abdominal and corneal reflexes were active and equal. The sensory examination revealed astonishingly little. The child was able to appreciate a light touch everywhere over the face, body and extremities. When tactile hairs were employed, the threshold was quite normal. Slight differences in temperature were recognized at once. He could distinguish between the sharp and the dull end of a pin, although he did not wince when the pin was thrust into the skin. Squeezing the testicles and the tendo achilles, with a force that would cause an adult to wince, caused him no apparent distress and no change could be detected in the pulse rate. Pinching the neck caused no dilatation of the pupil. In the same way, pressure on the supraorbital and ulnar nerves caused no particular reaction. Sense of passive movement, of position, of vibration, 2-point sense and stereognosis were all intact.

Opthalmological examination by Dr. Walsh revealed a large opacity of the left cornea. There was also a posterior capsular cataract and dense vitreous opacities causing reduction of vision in the left eye. These changes were all attributed to the old injury.

Psychiatric examination by Dr. Kennedy gave the intelligence quotient as 104. He was right-handed, right-eyed, and right-legged. He was an average scholar and performed third grade school work successfully. It was discovered by Dr. Latshaw that the patient had a specific reading defect, *i.e.* a mild congenital word blindness. There was deficient appreciation of the orientation of words with reversal of the "was" for "saw" type. The reading index was 40, whereas it should have been 100. There were also low scores in auditory discrimination. A personality study by Dr. Conn disclosed no striking trends. The child's behavior was not abnormal in any way. He claimed that he did not like to fight but older boys were always "trying to put him in the hospital." The impression was gained that he was not unduly pugnacious but became involved in fights because his courage and tenacity made him unwilling to submit to older boys. A study of conditioned reflexes by Dr. Horsley Gantt revealed no lack of normal reflexes.

The vasomotor reflexes of the extremities were studied by Dr. James Bordley, who recorded the temperatures of the left hand and foot after immersing the right arm and leg in water at a temperature of 45°C. There was normal vasomotor response. No suggestion of any defect in the vasomotor system could be discovered.

The roentgenographic study of the skeleton showed old fractures with callus formation of the first metatarsal bone of the left foot, the second metatarsal of the right foot, dislocation of the metatarsal-phalangeal joint of the left fifth toe, atrophy of the left scaphoid bone and some destruction of the left cuboid bone. The bones were otherwise normal and osseous development was proper for the patient's age. Upon examination of films taken in other hospitals, it was discovered that the atrophy of the scaphoid bone had developed while the patient was in the hospital between April and August 1937. This bone showed the changes which are described as characteristic of Koehler's disease.

Laboratory Examination: Blood Wassermann negative. Intradermal tuberculin 0.1 mg., negative. Urine negative. RBC 4,690,000 WBC 11,600. Blood Chemistry: NPN 25 mgs. Sugar 109 mgs. Calcium 10.6 mgs. Phosphorus 4.6 mgs. Cholesterol 232 mgs. Spinal Fluid: Pressure 90 mm. water. No cells. Pandy negative. Wassermann negative.

Course in Hospital: The child remained under observation in the hospital for a number

of weeks. He was quite docile and well behaved and showed no tendency to quarrel or fight with the other children with whom he came in contact. He showed no bravado and no evidence of pride in his insensitiveness and apparently did not realize that he was different from other children. After many tests had been made, some of which must have been alarming to the child, he began to protest as if he were afraid that he would be hurt. When it was proposed to pull a carious tooth without anesthesia he refused to submit. One gained the impression that the child was becoming more conscious of pain and more sensitive to it.

Case History 2 (Ped. 62734). *Boy of 8½ years who was apparently quite insensitive to burns and other injuries. Neurological examination negative. Intelligence quotient 76. Various behavior disorders. Bad family background and long history of minor illnesses.*

G. T. W., second child of poor and ignorant parents, was born at full term on May 19, 1929 by normal spontaneous delivery. He was regarded as a healthy baby. During infancy he was undernourished, probably because of inadequate care. At the age of 3 weeks, he was brought to the Harriet Lane Home and has been examined at intervals ever since. During the first 2 years he was treated for undernutrition, rickets, constipation, otitis media, pharyngitis, pinworms and prolapse of the rectum. However, he seemed to develop normally. He walked at 13 months and began to talk at the age of one year.

On February 8, 1932, when the child was nearly 3 years old, it was noticed by one of the staff that he showed numerous scars over his hands, legs and body. The mother stated that many of these scars were due to his having taken hot plates from the stove. He never cried or showed any signs of pain when he burned himself, she claimed. He frequently fell down and was always in fights, but never seemed to notice the injuries he sustained. His father said that the child never cried when whipped or when he struck him with his hand, but would cry if struck with a stick.

Physical examination revealed numerous scars over the body and extremities. These were all small and suggested burns and cuts. There was prolapse of the rectum and excoriations of the anus, due to pinworms. No abnormalities of the heart, lungs or abdominal organs could be discovered.

Neurological examination revealed complete indifference to stimuli that would cause a healthy adult to protest. The child would permit the skin of his chest to be pinched and twisted until ecchymosis resulted and would also allow the examiner to squeeze the tendo achillis with his full strength. Pins could be thrust deeply into the flesh without protest or any sign of pain. This insensitiveness was present over the entire surface of the body, the face and extremities. The child could, however, distinguish between the point and the head of a pin and also between warm and cool test tubes. Tactile sensibility was normal. The cranial nerves were quite normal. Speech was fairly fluent, but the boy stuttered at times. The gait showed a slight limp upon the left leg but there was no weakness, spasticity or ataxia. There were no deformities of the spine or extremities and no atrophy of the muscles. The tendon reflexes were all in order and the plantar and abdominal reflexes were normal.

The psychiatric investigation revealed that the child had always been emotional and used to cry a great deal. He was subject to night terrors and to temper tantrums. He had a violent temper and never played with other children without quarrelling and fighting. He would fight boys older and larger than himself, for his disregard of injuries gave him the advantage. Strangely enough, he was afraid of dogs and would not go into the yard because a big dog was often there. He often wet the bed at night and masturbated at times. At the age of 2 years he had 3 convulsive seizures, during which he is said to have been unconscious, but no

details are available and he had no more seizures. The father had been very backward at school and had never passed beyond the fourth grade. He was subject to temper tantrums and been arrested for beating his mother and his wife. He took delight in quarrels and was frequently in fights. Before his marriage he had been an alcoholic, but had ceased to drink after marriage. He was said to be insanely jealous of his wife, without cause, and frequently threatened her about the attention of other men. Because of this, she was in constant terror of him. The mother, as a child, had been subject to temper tantrums and had had convulsions. At the age of 12 years, she was found to have a mental age of 6 years and was sent to an institution for defective children where she stayed for four years. There were 4 children. John, the oldest, had breath-holding spells as a baby, was subject to tantrums and was always disobedient. The patient was the second child, a year younger than John. Jeannette, the third child, was always undernourished and had numerous illnesses. She often ate paint and things that were unfit for food and at the age of 2 years her bones showed changes which were considered to indicate lead poisoning. The fourth child had been fairly healthy, it is said, but was recently operated upon for bilateral mastoid infection.

Dr. Curt Richer tested the psychogalvanic reaction to pain, employing a pinprick as the stimulus. There was no response even when the child was pricked deeply.

Orthopedic examination was made because of the limp. No explanation could be found. The bones and joints were all normal. Roentgenograms of the pelvis were negative.

Roentgenograms of the chest were negative. The intradermal tuberculin test was negative. Wassermann reaction of the blood serum was negative.

After this time the child's health improved. The pinworms were eliminated and the prolapse of the rectum was treated successfully. His behavior did not improve in the same way, however, and the Department of Public Welfare, which had been helping the family, reported on September 2, 1937 that the child was a problem and had shown a tendency to steal.

The patient was reexamined on November 23, 1937 at the age of 8½ years. His father stated that the child had been going to school and had always made his grades. The patient was then a sturdy, muscular child who made a much better impression than on previous occasions. The limp had disappeared and the child seemed to be in excellent physical condition. There were numerous small, fresh and old scars over the arms, legs, chest, back and face which had resulted from cuts, burns, abrasions and other minor injuries, but no evidences of more severe injuries. The bony structures were well formed and no deformities could be discovered. The cranial nerves were all in order. Motility was unimpaired and the reflexes were all equal and active. The patient could recognize and distinguish all types of cutaneous stimuli, but was indifferent to potentially painful stimuli as before. Psychometric test revealed an intelligence quotient of 76. Roentgenograms of the skull, spine and feet showed no bony abnormalities.

Case History 3 (Ped. A-740). *Girl of 7 years, who was brought to the hospital because of recurrent attacks of pyelitis, was found to be insensitive to potentially painful stimuli over the entire surface of the body. She was not indifferent to pain of visceral origin, however. Neurological examination negative. Mental age, low normal.*

M. L. G. was seen for the first time in the Harriet Lane Home on January 30, 1937. She was then 7 years old. The chief complaint was that of recurrent attacks of abdominal pain with fever, dysuria and vomiting. A second complaint was that the child was prone to injure herself and seemed to be quite indifferent to such injuries. She was always very active and when she began to walk she frequently fell and bruised herself or produced excoriations of

the arms or legs. She always had fresh lesions over the bony prominences of the arms and legs. Her mother noticed that the patient, when still very young, did not cry when injured as the other children did and did not cry, as a rule, when whipped. Her abdominal pains, however, seemed to cause her great distress.

The patient's family were poor and of less than average intelligence. The mother's health was good but the father was never vigorous and had been suspected of having tuberculosis. There had been 7 pregnancies in all, the patient being the product of the fourth. The first child was living and well. The second child was suffering from tuberculosis of the cervical lymph nodes. The third child died at 2 months, of an illness of unknown nature. The fifth and sixth pregnancies were terminated by induced abortions, but the seventh resulted in a healthy child. None of the siblings or relatives are known to have symptoms similar to those of the patient.

The patient was born by normal labor, but was somewhat premature. She was kept in the premature room for some weeks after birth and was not discharged from the hospital until she was 2 months old. At that time her weight was only 6 ½ lbs. For the first 2 years of her life she was undernourished and weak. Her early development was delayed She did not sit up firmly until she was one year old and then not walk until she was 3 years old. She began to talk at the end of the second year, but her speech was imperfect for a time. Her mother claimed that the child was disobedient, destructive and irritable. She cried a great deal and on slight provocation, wet the bed at night and was subject to temper tantrums. There were numerous illnesses. At the age of one year she had pertussis with pneumonia. At 2 years she had measles without nervous complications or sequelae. A few months later she began to have attacks of abdominal pain and fever, which recurred from time to time at irregular intervals, up to the time she was brought to the Harriet Lane Home. The onset of these attacks was abrupt, with severe pain in the lower abdomen which radiated down the thighs. The temperature rose rapidly and there was usually a chill. On several occasions the temperature had reached 104°F. or more. There was usually complaint of headache and frequently the child was delirious for a time. During the attacks there was frequency of urination and incontinence. Several time pus was found in the urine during such attacks. She was studied in several hospitals between the ages of 2 and 7 years and was treated for pyelitis. In October 1936 she entered another hospital, where a diagnosis of hysteria was made. This was apparently based upon the discovery of "analgesia." When she came to the Harriet Lane in January 1937 she was just recovering from one of her attacks.

Examination revealed a sparely nourished and only fairly well developed child of 7 years. She was of normal height for her age but very slender. Her general appearance suggested that she was chronically ill. She was cooperative and did not impress the examiner as mentally deficient. Crusted ulcerations were seen over the malleoli, the elbows, the left heel, right calf, right toe and in the lumbar region. These suggested excoriations and there was no evidence of burns or cuts. There was nothing of significance found in the examination of the head, chest or abdomen. A soft systolic murmur was audible over the heart but the heart was not enlarged. Temperature, pulse and respiration were all normal.

Neurological examination disclosed no abnormality of the cranial nerves. The musculature was slender but no atrophy was discovered. Strength was proportional to muscular development. There was no scoliosis or deformity of the extremities. Muscle tone and coordination were normal. Station steady and gait normal. Speech slightly indistinct but easily comprehensible. The tendon reflexes were all sluggish but all were present and approxi-

mately equal on the two sides. The abdominal reflexes were equal and the plantar reflexes were normal. Tests of sensibility revealed that the child could appreciate light touch, could distinguish between warm and cool test tubes and also between the head and the point of a pin. She showed no sign of pain when pricked deeply with a pin or when the tendo achillis was squeezed with the examiner's full strength. The indifference to such stimuli was most evident in the extremities and least evident in the face and over the scalp. She showed the usual evidence of pain when the ureters were catheterized, but was indifferent to the pain of venipuncture.

The psychogalvanic reflex to pain was tested by Dr. Curt Richter. Pin prick was employed as the stimulus. No response was elicited when the stimulus was applied to the extremities, but a feeble reaction was evident when the face was pricked. The patient reacted when a threat to stick her was made, even though no stimulus was applied.

Psychiatric examination revealed that intelligence was of low normal level, with a quotient at 86. It was concluded that the child was untruthful, disobedient, emotionally unstable, selfish and spoiled, but not of hysterical personality and not definitely mentally deficient.

Laboratory Tests: The urine showed a little albumin and a little pus. RBC 4,500,00. WBC 13,600. Wassermann test on blood serum negative. The spinal fluid contained no cells and no increase in protein. The Wassermann test was also negative. Roentgenograms of the head, spine and feet were all negative. Films of the chest showed a mild non-tuberculous infiltration of the lung bases. Blood Chemistry: NPN 36 mgs. Calcium 9.7 mgs. Phosphorus 5.0 mgs. The ureters were catheterized and cultures were made which showed B. coli. Pyelograms revealed mild hydronephrosis on the right. There was thought to be a stricture of the ureter. Phenolphthalein test gave 68% excretion of the dye in two hours.

Course in Hospital: The child was treated by dilatation of the ureter to relieve the hydronephrosis and ammoniated mercury was applied to the sores on the extremities. The urine culture became negative. The control of the bladder became normal. The sore healed. The child was discharged March 9, 1937.

Interpretation of the Findings: The observations described above indicate that these three children are indifferent to stimuli which ordinarily cause pain. The nature of this peculiarity is not at all clear. All three children can distinguish between the sharp and blunt ends of the pin and can recognize slight differences in the temperature of test tubes. We have not been able to detect any elevation of the threshold of any modality of sensibility. It must be admitted that exact quantitative methods have not been employed, for children are not suitable subjects for such tests. When the tendo achillis is squeezed or some other potentially painful stimulus is applied, these children make no protest and show no sign of pain. When the examiner inquires whether the procedure is painful, they answer indifferently, "No," "Not much," "A little" *etc.* These examinations have been made repeatedly by a number of examiners and the results have always been the same. It might be suggested that these children are analgesic and distinguish between the point and head of a pin by means of their tactile

sensibility. It scarcely seems possible to accept this theory, however, for patients suffering from true analgesia, as in syringomyelia, cannot make such a differentiation. We have, therefore, formed the opinion that these patients do not have analgesia or loss of any type of sensibility and that they are merely *indifferent to pain.* This statement must be qualified by the mention that the little girl seems to be normally sensitive to the pain associated with her attacks of pyelitis and that the first boy is known to have complained of abdominal pain on one occasion. These facts do not necessarily indicate a true dissociation between pain of peripheral and of visceral origin. The abdominal pain may cause the children to complain because it is more intense. In fact, the indifference to pain seems to be merely a relative one in all three cases.

If we are correct in our belief that these children have no true analgesia, we cannot entertain the supposition that they are suffering from any defect in the sensory pathways of the spinal cord or peripheral nerves. We have considered the possibility of syringomyelia and of defects in the spinal cord such as are associated with spina bifida. In such conditions the sensory loss is localized and not universal; there is also thermanesthesia, atrophy of the muscles, changes in the tendon reflexes, deformities of the bones and the so-called trophic changes in the tissues, all of which are absent in our cases. Syringomyelia rarely, if ever, gives rise to symptoms early in childhood and most defects of the spinal cord are associated with spina bifida or spina bifida occulta which are not found in our cases. The rare familial condition termed lumbosacral syringomyelia should be mentioned, for it is associated with atrophy of the bones of the feet. In case 1, there is some atrophy of the bones of one foot, but as this appeared after a severe injury to the foot and was not found in the other foot or in either foot of the two other children we are not inclined to lay much stress upon it.

The indifference to pain can scarcely be due to mental defect, for although the intelligence rating is rather low in cases 2 and 3, in case 1 it is a bit above the average. None of the children are profoundly defective and if we take into consideration the family background and the conditions under which they were brought up, it is evident that their intelligence compares favorably with that of their parents. They impress us as average individuals of an unintelligent stock.

Hysteria, of course, deserves serious consideration, but there are certain features of these cases which are not easily reconciled with hysteria. It has often been pointed out that hysterical anesthesia is the product of suggestion and that it is most frequently the product of the examination. The hys-

terical patient insists upon giving incorrect answers during the examination. In our cases, the children name all stimuli correctly and seem to be unconscious of any abnormality of sensibility. Hysterical anesthesia is apt to appear and disappear from time to time and to be associated with other hysterical manifestations, but in our cases the condition is not associated with other symptoms and has apparently been present without modification during the patients' entire lives. Although types of hysteria may occur very early, the writers have never seen hysterical anesthesia at the age of 2 years.

Certain psychoanalysts have claimed that insensitiveness to pain may be the expression of a sado-masochistic personality and as such may be associated with strong criminal trends. Numerous cases are on record of murderers who not only took great delight in torturing their victims but inflicted serious mutilations upon themselves for their pleasure. The tendency of all these children to become embroiled in fights and of the first child to bite his tongue and fingers might be taken to point to some such mental condition. However, these children all live in neighborhoods in which fights are common, and we have gained the impression that they do not fight more than other children of the same class. We do not believe that they enjoy pain or seek injuries; they are merely indifferent to pain. Psychiatric study, moreover, has revealed no trends indicating sadism or masochism in any case although it must be admitted that the analytic technique has not been employed.

We have formed the impression that these children exhibit a peculiar indifference to pain but that they are not really analgesic. We are not inclined to attribute this condition to hysteria or to masochism. This indifference to pain is apparently of congenital origin, for in all three cases the child's peculiar reaction to injuries was discovered before the age of three years. Similar cases have been described before and several of these are presented briefly below.

Résumé of Similar Cases Described in Medical Literature: A small number of cases may be found in medical journals which seem to be more or less identical with the cases reported above. Dearborn has recently given a brief description of the case of a man of 54 years who claimed that he had never experienced pain at any time during his life, with the single exception of a few dull headaches. At one time this man made a living on the vaudeville stage by allowing spectators to push pins into his body. He also put on an exhibition in which large spikes were driven into his palms so as to crucify him. The patient recounted numerous episodes which served to illustrate his insensitiveness to various injuries, some of which occurred in

childhood. He could not recall ever having had any abdominal pain or visceral pain of any type. Neurological examination is said to have revealed only minor and insignificant signs. The author considered hysteria but rejected this diagnosis, since the patients personality was not that of an hysteric. In the discussion following the presentation of this case, Schilder stated that he had seen a case of the same type and that the patient's mother presented the same peculiarity. Both of Schilder's patients were able to appreciate pain but were indifferent to it. Critchley mentions briefly the case of a young man whose physician had noticed his disregard of such painful experiences as the lancing of a whitlow, and had requested a neurological consultation. The patient appreciated the pain of a pin prick but said, "It is nothing very much." The history revealed that he had never been sensitive to pain. Weir Mitchell described the case of a personal friend who rose to become an eminent jurist. He died at the age of 56 years and had never felt pain very keenly. On one occasion his finger was crushed and to get rid of it he had bitten off the end. He had undergone several operations, including the removal of bilateral cataracts and the lancing of a spreading abscess in the palm of the hand, without anesthesia and without a sign or complaint of pain. None of these patients exhibited any other evidence of disease of the nervous system and all of them could appreciate pain, although they were indifferent to it. No criminal trends are mentioned in any of these histories.

Discussion of the Nature of this Condition: In an interesting article entitled "Some Aspects of Pain," McDonald Critchley calls attention to the well known fact that individuals vary widely in their sensitiveness to pain and that even the same individual may react differently under different circumstances. He mentions our unconsciousness of injuries which occur in states of anger and excitement as in fighting and even in competitive sports, the increased sensitiveness to pain in psychoneurotic subjects and in those given to introspection. The apparent insensitiveness to pain in certain types of hysteria, in subjects in hypnotic trances, and the extraordinary stoicism of religious martyrs should also be mentioned in this connection. Critchley refers to cases of insanity in which the subject may produce terrible mutilations upon himself such as avulsion of the eyeballs or burning of the hands. Cases reported by Goodhart and by Conn and attributed to epidemic encephalitis are mentioned. In the former, the patient tore out both eyeballs with her fingers and, in the latter, the patient broke all her fingers and tore off one ear. Neither of them evinced any sign of pain, although both were able to appreciate all the usual stimuli employed in the examination of sensibility. Reference might be made also to the case of a young woman

who crawled headfirst into a great furnace in an effort to commit suicide and was so terribly burned that she died a few hours later. Before her death she was able to answer questions but could not explain her unnatural act.

It is evident, therefore, that under certain circumstances subjects who have no analgesia may be quite insensitive to injuries which under other circumstances would give rise to intense pain. Unquestionably a number of theoretical interpretations of these observations might be offered, but to us the simplest hypothesis is the assumption that there are two factors in our normal response to noxious stimuli: (1) Pain as a crude sensation. (2) The reaction to pain which under normal circumstances is associated with appropriate emotional elements including fear. If the latter is minimized in any way we may become quite indifferent to the former. The writers have formed the impression that in our cases it is the second element, the reaction to pain, which is deficient. The failure of these children to show any psychogalvanic reaction[1] to pain would be quite consistent with this hypothesis.

Since the condition seems to be of congenital origin, it is natural to consider the possibility of a congenital defect of the nervous system and to speculate about its possible location. Since a defect in the peripheral nerves or in the spinothalamic tracts would cause analgesia and not the condition which we find in these children, it would seem logical to seek the defect in either the optic thalamus or in the cerebral cortex. We may say at once that we can reach no satisfactory conclusions, but certain hypotheses may be mentioned which have a bearing on the problem.

According to the teaching of Henry Head, the cerebral cortex is not essential for the appreciation of pain, for the thalamus is capable of subserving such crude sensations. Head's theory is based upon the study of cases of cortical anesthesia and of the thalamic syndrome. When the sensory cortex is destroyed, the patient can always appreciate pain and reacts normally to painful stimuli. In the thalamic syndrome, the patient often exhibits some elevation of the threshold for pain, but once the stimuli are appreciated, the patient experiences an intensely disagreeable feeling which cannot be precisely described. Head terms this the thalamic "over-reaction" and explains it as follows: The lesion in this syndrome is so situated as to sever the corticothalamic fibers and thus releases the "essential organ" of the thalamus from the control of the cerebral cortex. When pain stimuli

[1] This reaction cannot be discussed fully here. Suffice it to say that painful stimuli cause in normal subjects an imperceptible sweating over the hands, which seems to be a part of an emotional reaction. Sweating diminishes the resistance of the skin to electric currents and this change in resistance can be measured by a string galvanometer. Thus, the skin resistance becomes the measure of emotional reactions.

enter the thalamus thus released, it reacts excessively and the resulting sensations are clothed with an excessive feeling tone with the production of pain of a peculiarly excruciating character. If we accept Head's hypothesis, may we not conceive of a defect in the "essential organ" of the thalamus which would deprive pain of its disagreeable affective significance? That is, if we regard the thalamic syndrome as the expression of excessive activity of the thalamus, may not our cases be a result of deficient activity of the same organ? It must be admitted that Head did not mention such a possibility and may have believed that destruction of the "essential organ" of the thalamus would cause analgesia. This is, of course, all vague speculation based upon an unproved hypothesis.

Schilder and Stengel describe several cases in which universal insensitiveness to pain was found in association with unilateral lesions in the cortex of the left cerebral hemisphere chiefly in the region of the supramarginal gyrus. Three postmortem examinations were made. The authors state that the patients were not inattentive, and speak of the condition as "asymbolia for pain." Such a hypothetical condition would be a form of agnosia, a disorder of the same order as aphasia. In the agnosias, the difficulty lies not in the appreciation of the sensory stimuli but in the interpretation and understanding of the sensations. The mild congenital word blindness which the first patient exhibited might be taken to favor the idea of a lesion in the region of the supramarginal and angular gyri, for lesions in this region in adults give rise to word blindness, or alexia. The significance of Schilder's observations is not entirely clear, for patients suffering from aphasia are not the most suitable subjects for the examination of sensibility, but if we should accept his conclusions that cortical mechanisms lying in the left hemisphere are essential for the normal reaction to pain, we might consider the possibility that deficient development of such mechanisms might result in the interesting picture presented by the children who are the subjects of this paper.

In conclusion we must admit that we cannot offer any entirely satisfactory interpretation of the condition described above. Sensitiveness to pain among normal subjects is subject to striking variation, but in these children the indifference to noxious stimuli seems to exceed any reasonable limit of the normal. We are inclined to believe that we are dealing with a congenital defect of development involving in a selective manner the neural mechanisms concerned in our reaction to pain and comparable perhaps to color blindness, congenital word deafness and congenital word blindness, which are also regarded as selective defects of development. The site of the disor-

der in the nervous system is uncertain. Our ability to correlate the anatomical condition of the nervous system with its functional reactions is still imperfect and were the brains of these children available for study we would not feel confident that anatomical changes would be demonstrable.

SUMMARY

(1) Three cases are reported of children between the ages of 7 and 8 years in which there was congenital indifference to potentially painful stimuli leading in one case to severe burns, multiple fractures and other serious injuries.

(2) Except for the disregard of pain we have been able to demonstrate no other evidence of disease or defect of the nervous system.

(3) Various reasons are given to support our belief that these children do not have true analgesia but present a defective reaction to the crude sensation of pain which makes that sensation a matter of indifference.

(4) A small number of cases of a similar nature found in medical literature are mentioned.

(5) We are inclined to believe that these cases represent a congenitally defective development in the sensory system which involves selectively the pain mechanisms and is comparable to congenital color blindness and similar conditions.

The writers wish to thank Dr. Edwards A. Park for his permission to report these cases and the various members of the hospital staff who were kind enough to aid in the numerous special examinations. We are also much indebted to Dr. A. J. Alexander of the Union Memorial Hospital who permitted us to examine the first patient while on his service and allowed us to remove the patient to the Harriet Lane Home for further study.

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PAIN: HISTORY AND PRESENT STATUS

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PAIN: HISTORY AND PRESENT STATUS

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The doctrine of the five senses, which is common sense today, is ascribed to Aristotle, although it is probable that it was also common sense in his day and generation. However that may be, the doctrine descends to us from antiquity, and its does not include, nor does it make any provision for, a sense of pain. Though Aristotle states that touch, the fifth of the senses enumerated by him, "discriminates several sense-qualities,"[1] pain is explicitly not one of them; for he, like Plato before him, places pain with pleasure among the passions of the soul.

It is not surprising that the Ancients should have set pain apart from the senses, or that they should have considered it as the antithesis of pleasure. Unlike sight, hearing, smell, taste, and touch, pain does not possess an obvious sense-organ; nor is it restricted to any part of or locus in the body, but rather pervades the whole. Moreover, it is not a quality of external objects as the qualities of the five senses were supposed to be; and it does seem to be inherently unpleasant, as most pains (probably more than 99% of them—indeed, a recent writer, Fröbes,[2] says *all*) may thus be characterized. Once pain, identified with unpleasantness, is set in opposition to pleasure, it transcends the limitations of the sensory field and extends into the other fields of mental life.

These considerations, together with the dominant influence of Aristotle's pronouncements upon subsequent philosophical and scientific thought, long delayed the recognition of pain as a sensory quality. The affective classification of pain and the doctrine of the five senses prevailed until

* Presidential address of the Eastern Psychological Association, given at Bryn Mawr College, March 31, 1939.

[1] Aristotle, *Treatise on the Principles of Life*, Eng. trans., W. A. Hammond, 1902, bk. ii, chap. 6; bk. iii, chap. 1.

[2] Joseph Fröbes, *Lehrbuch der experimentellen Psychologie*, 1, 1923, 149.

comparatively recent times. All through the intervening years, however, some intrepid souls have considered and variously answered the question tacitly raised by Aristotle regarding touch: "Is it a bundle or group of many special senses?" Since pain was turned into a special sense as a result of the attempts to analyze touch, it may be profitable as well as interesting to review the answers that have been given to that question.

Aristotle's commentators were divided. Themistius [317-387] adopted the view that touch was a plurality of senses.[3] He held, though he did not specify, that there were as many separate senses in touch as there were different tactile qualities. Alexander, in the 2nd century, Simplicius, in the 6th, and Philoponus, in the 7th, were, however, of the contrary opinion,[4] and, since the 'master' had not definitely spoken, but had merely mooted the point, the contrary opinion that touch was a single sense prevailed for their day and generation.

The question was raised again in the 11th Century by the Schoolmen. Themistius' doctrine, that touch was a plurality of senses,[5] was adopted by Avicenna [980-1038] and Averroes [1126-1198] among the Arabian Schoolmen, and by Appollinaris [12th century], Albertus Magnus [1193-1280], Aegidius [1247-1316], Jandunus [d. 1328], and Marcellus [14th century] among the Latin Schoolmen. They were not, however, in agreement regarding the kind or the number of senses into which it was to be divided. Avicenna, like Themistius, divided it into as many senses as there were tactile qualities. He did not, however, specify their number, though he did distinguish two from touch proper; namely, the sense of pain from a wound and the sense of titillation.[6] Averroes, his compatriot, accepted titillation; but he disagreed regarding pain, and added hunger and thirst.[7] Aegidius increased the number of senses by two: one for temperature (hot and cold) and the other for humidity (dry and moist).[8]

Among the more modern philosophers, Cardano [1501-1576] divided touch into four senses: one for the tactile qualities of hot, cold, wet, and dry; a second for light and heavy; a third for pleasure and pain; and a fourth for titillation.[9] These were denied by Scaliger [1484-1558] who himself distinguished sexual appetite as a sixth sense. Francis Bacon[10] [1561-1626] distinguished sex and so also did Voltaire[11] [1694-1778] and Buffon[12] [1707-1788]. Locke [1632-1704] added hunger and thirst;[13] and Kant, [1724-1804] a vital sense (*sensus vagus*) into which he placed heat, cold, shudder, quake, thrill, hunger and thirst.[14]

Beginning in the 2nd century A.D., the physicians and scientists also tried their hand at analyzing touch. Galen [131-200] thought that in addition to touch proper there was a sense of heat and cold.[15] Pechlini, in 1691, divided the fifth sense into touch, cold, and heat.[16] In the 18th century, Erasmus Darwin, [1731-1802]—who

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[3] Cited by William Hamilton, *Lectures on Metaphysics and Logic,* edited by H. L. Mansel and John Veitch, 2, 1870, 155.

[4] *Idem.* [5] *Idem.* [6] *Idem.*

[7] *Ibid.,* 156. [8] *Ibid.,* 155 f. [9] *Ibid.,* 156.

[10] *Idem.* [11] *Idem.* [12] *Idem.*

[13] *Idem.* [14] *Idem.* [15] *Idem.*

[16] J. N. Pechlini, *Observationum physico-medicarum libri tres,* 3, 1691, 410; quoted from Torsten Thunberg, Physiologie der Druck-, Temperatur- und Schmerzempfindungen, in W. Nagel's *Handbuch der Physiologie des Menschen,* 3, 1904, 648.

had the misfortune to be the grandfather of Charles Darwin, since otherwise he would have been great in his own right—added seven senses to the traditional five: the sense of heat, of muscular extension, of hunger, of thirst, of suffocation, of sexual appetite, and of lactiferousness.[17]

In support of his statement that "nature has provided us with a set of nerves for the perception of heat,"[18] Erasmus Darwin cites an interesting observation made on a patient by one of his relatives, Dr. R. W. Darwin. This patient, as a result of fever and violent cramps in his legs, had lost sensitivity to touch in one of his feet. "Though pricked with a pin in five or six places," Darwin reports, "the patient declared he did not feel it in the least, nor was he sensible of a very smart pinch. I then held a red hot poker at some distance, and brought it gradually nearer, till it came within three inches, when he asserted that he felt it quite distinctly. I suppose some violent irritation of the nerves of touch had caused the cramps, and had left them paralytic; while the nerves of heat, having suffered no increase of stimulus, retained their irritability."[19]

Some of Darwin's observations regarding the other senses that he proposed are also worthy of quotation. In reference to the sense of extension, he writes: "the whole set of muscles, whether they are hollow ones, as the heart arteries and intestines, or longitudinal ones attached to bones, . . . may be considered as one organ of sense, and the various attitudes of the body, as ideas belonging to this organ."[20] The sense of hunger, he writes, "is most probably perceived by those numerous ramifications of nerves that are seen about the upper opening of the stomach;" and thirst "by the nerves about the fauces and top of the gula."[21]

At the end of the section on the organs of sense, Darwin adds that "there are many more senses than have been here mentioned . . . which have not acquired the name of senses."[22] Pain, however, was not one of these, for he regarded pain and pleasure as central effects of sensorial motions. Pain results, he says, "whenever the sensorial motions are stronger than usual. . . . A great excess of light . . . of pressure or distension . . . of heat . . . of cold produces pain."[23] He thus anticipates the intensive theory of pain that was introduced several generations later.

About a decade after Darwin, Bell [1774-1842] posited,[24] without reference to earlier writers, a sixth sense—a sense of movement—in addition to the traditional five. This new sense, whose organs are the muscles of the body, was, he believed, "the most important of all . . . for it is by a sense of motion that we know many of the qualities of outward things, as their distance, shape, resistance, and weight[25] . . . hardness, softness, figure, extension, and motion."[26]

Bell also writes of hunger and thirst as sensations. "We are," he states, "solicited to take food by the uneasy sensation of hunger," which is "the effect of the attrition of the sensible coats of the stomach upon each other by the peristaltic motion of the stomach and compression of the viscera."[27] "Thirst is a sensation seated in the

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[17] Erasmus Darwin, *Zoonomia*, 1, 1794, 76-90, sec. xiv.
[18] *Ibid.*, 86. [19] *Ibid.*, 87. [20] *Ibid.*, 87.
[21] *Ibid.*, 89. [22] *Ibid.*, 90. [23] *Ibid.*, 90.
[24] Charles Bell, *Anatomy of the Human Body*, 3, 1803, 224-372; John and Charles Bell, *The Anatomy and Physiology of the Human Body*, 5th Amer. ed., revised by Charles Bell, 2, 1827, 154-290, esp. 158, 290.
[25] John and Charles Bell, *op. cit.*, 158.
[26] *Ibid.*, 290.
[27] *Ibid.*, 326.

tongue, fauces, esophagus, and stomach. It depends on the state of the secretions which bedew these parts and arises either from a deficiency of secretion or from an unusual acrid state of it."[28] He took no account of either of them, however, in his classification of the senses; nor did he specifically mention pain.

Approximately 100 years ago, in 1840, Johannes Müller [1801-1858] presented his theory of the specific energies of nerves. Though this theory was anticipated by Bell, as has frequently been pointd out, it was independently formulated by Müller and its scientific significance was not recognized until Müller had published it. In accordance with the traditional doctrine of the senses, Müller posited five kinds of sensory nerves.[29] The fifth class, the nerves of feeling (*Gefühlsnerven*), yielded, he believed, a number of different sensations: tickle, itch, shudder, pleasure, pain, fatigue, suffocation, warmth, cold, touch, and movement. He did not, however, posit different nerve-specificities for those qualities but attempted to account for them by differences in their mode of arousal and in the state of the organism at the time of their arousal. There is, therefore, as far as the analysis and classification of the senses are concerned, little in Müller beyond Aristotle. Müller is, nevertheless, important to us for two reasons: first, because his doctrine of nerve-specificity effectively destroyed, in the realm of scientific thought at least, the point of view, against which the philosophers have inveighed since Descartes and Locke, that sensory nerves conduct to the brain properties or incorporeal copies of the objects perceived. He showed definitely that that was not the case, as different objects produce the same effect with the same nerves, and the same object produces very different effects with different nerves. He is important to us, secondly, because his doctrine provided a sanction for analysis and a systematic basis for classification. If a given nerve, however affected, gives rise to a sense quality that depends upon the specific character of that nerve, may it not be then that the various nerves giving rise to different qualities of touch or feeling have different specificities? The question raised by Aristotle has now obtained systematic significance.

Before Müller, there was no unifying doctrine to shape analysis nor any accepted principle of classification. The efforts of the various inquirers who have been mentioned were without lasting significance. Their individual insights were merely eddies in the current of thought. The gains made by them were not consolidated. Every author wrote, against the background of the traditional doctrine of the five senses, as if he were pro-

[28] *Ibid.*, 327.
[29] Johannes Müller, *Handbuch der Physiologie des Menschen*, 2, 1840, 249-502.

posing something new. Lapses of centuries and differences in language may in part account for the lack of continuity, but even Bell, Darwin's contemporary in England, wrote of the 'muscle sense' as if he were discussing something new. He gave no indication of knowing Darwin's work.

The testimony of the ages proved ineffectual in refuting the Aristotelian doctrine of the senses. Negative evidence usually is ineffectual. Doctrines pass from the scientific stage, not because they have been discredited but because they have been superseded—pushed off the stage and replaced by others. What had been lacking all along to consolidate the gains as they were being made was a positive principle; and Müller, though he himself, as we have seen, accepted the traditional doctrine of the five senses, gave us such a principle. His work may consequently be reckoned as the dividing line between the ancient and the modern history of the psychology of the senses.

Under the impetus of the Müllerian doctrine, scientific thought was tremendously quickened. The principle of the dependence of qualitative difference upon specific nerves, though denied by some,[30] was immediately extended by others to the different sense departments, and Müller's "sense of feeling," which is of particular interest to us, was divided into several senses.

For example, in 1844, Natanson divided the sense of feeling into touch, temperature, and resistance.[31] Weber, in 1846, divided it into touch and common sensibility (*Gemeingefühl*).[32] Touch was restricted by Weber to the skin; and common sensibility, which stems from Kant's "*sensus vagus*," was defined to include all the qualities common to the skin and the other organs and tissues of the body. These two classes were then further divided. "Touch," he wrote, "provides us with two kinds of sensations which are peculiar to it, pressure sensations (*Druckempfindungen*) and temperature sensations (*Temperaturempfindungen*); at the same time the organ of touch and its nerves are so constituted that the same sensations may be differentiated from one another when they are aroused at two different places on the skin. We may, therefore, distinguish the sense of locality, the sense of pressure, and the sense of temperature."[33] These senses were restricted to the skin because he had failed to elicit them from the internal organs and deep tissues exposed in operations and wounds.

The sensations of common sensibility (*Gemeingefühlsempfindungen*) were even

[30] Cf. R. H. Lotze, *Allgemeine Pathologie und Therapie,* 1842, 164; also A. W. Volkmann, Von der specifischen Reizbarkeit der Nerven, in Rudolph Wagner's *Handwörterbuch der Physiologie,* 2, 1844, 521-526.

[31] — Natanson, Analyse der Funktionen des Nervensystems, *Arch. f. physiol. Heilkunde,* 3, 1844, 515-535, esp. 517 f.

[32] E. H. Weber, Der Tastsinn und das Gemeingefühl, in Rudolph Wagner's *Handwörterbuch der Physiologie,* 3, 1846, 481-588. Reprinted separately as *Die Lehre von Tastsinne und Gemeingefühl,* 1851.

[33] *Op. cit.,* 511.

more varied in kind. They derive, as he thought, from all parts of the body possessing nerves (the bones, cartilage, tendons, enamel of the teeth, nails, hair, and epidermis being the exceptions); and are characterized by the fact that "we cannot relate them to outer objects."[34] From internal stimuli (such as chemical and nutritive changes in muscles, organs, and blood) derive fatigue, hunger, thirst, nausea, feelings of well-being and of sickness, etc. From external stimuli and the movement of muscles derive pain, sensations of movement, shudder, tickle, itch, sting, etc. The category of *Gemeingefühl* is Weber's scrap basket into which he cast a miscellany of sensory remnants. It is, as Henle [1809-1885] wrote of it, "the sum, the unsorted chaos of sensations from all the sensitive parts of the body, which leads to the consciousness of self."[35]

Common sensibility, as Weber believed, was finest in the muscles and skin, and pain was its most marked characteristic. Like Darwin, Romberg, Henle, and Volkmann before him,[36] he anticipated the intensive theory of pain, as he wrote that pain "is aroused in all organs of sense by external stimuli which are so strong that they affect not only the ends of the nerves, but also their trunks."[37]

From Weber on down to the present, numerous analyses of the sense of touch have been made and numerous classifications proposed. In all of them, *Gemeingefühl*—or *coenaesthesis*, as Weber also called it—has played an important though varying rôle, serving ever as the classificatory term for the residue of unsorted sensations and feelings.

The divers classifications are, however, no longer of concern to us. The principle of analysis having been accepted, we may now turn to our special interest, pain, and follow its rapid unraveling—and snarling—from the skein of theory.

Several investigators, as we have seen, anticpated the intensive theory of pain. It was first explicitly formulated, however, by Erb, in 1874,[38] who held that pain was not a sensation specific in kind, but one of high degree. Every sensory stimulus, he maintained, was capable of producing pain if it reached sufficient intensity. This theory, as we shall see, was accepted and supported by many writers.

The theory that pain was a separate and distinct sense, first suggested by Avicenna in the 11th century, was intimated for a second time by Lotze in 1852.[39] It was first definitely formulated, however, by Schiff in 1858, following his analgesic experiments on animals.[40] Noting the

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[34] *Ibid.*, 495.
[35] Henle, *Allgemeine Anatomie*, 1841, 728; quoted from Weber, *op. cit.*, 563.
[36] Volkmann, *op. cit.*, 520.
[37] Weber, *op. cit.*, 495.
[38] Erb, *Krankheiten der peripherischen cerebrospinalen Nerven*, 1874. Quoted from G. W. A. Luckey, Some recent studies of pain, this JOURNAL, 7, 1895, 109.
[39] R. H. Lotze, *Medicinische Psychologie*, 1872, 247.
[40] Schiff, *Lehrbuch der Physiologie*, 1, 1858, 228. (Cf. O. Funke, Der Tastsinn und die Gemeingefühle, in L. Hermann's *Handbuch der Physiologie der Sinnesorgane*, 3, (2), 1879, 297.

effects of various incisions in the spinal cord, he found that pain and touch were independent. When he cut thrugh the gray matter, pain could not be aroused below the level of the incision while touch was left intact; when he cut through the white matter, but not the gray, touch was lost but pain remained. The results of these vivisections were immediately corroborated by clinical evidence, as physicians reported numerous pathological cases of diseased or injured spinal cords with similar sensory defects.[41] Cases of tabes dorsalis with a marked differentiation in the time of arousal of touch and pain—the pressure from the jab of a needle preceding the pain by several seconds—were also placed in evidence.

This theory of pain, which may be designated as the sensory theory, was reaffirmed by Funke in 1879 after a thorough examination of the evidence pro and con.[42] It did not, however, come to full bloom until after the classical experiments of Blix and Goldscheider in the early '80s. Blix,[43] in 1882, and Goldscheider,[44] in 1884,—in experiments undertaken to extend the Müllerian doctrine of specific nerve-energies to touch —independently discovered in the skin separate spots for warmth, cold, pressure, and pain, which—no matter how stimulated—yielded, if stimulated, their own specific quality. These results were accepted by many as conclusive evidence for the theory that pain is a separate department of sense.

The intensive theory and the sensory theory stood in opposition to one another, and they both stood in opposition to the traditional pleasure-pain theory which represented pain as an affective *quale*. In the decade between 1886-1896, these different opinions clashed and a three-cornered controversy ensued, the like of which has never before, nor since, appeared in the scientific literature. The proponents of the contending views had to defend themselves from two directions and at the same time lead a divided attack. The controversy was intense; no quarter was asked and

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[41] Cf. O. Funke, *op. cit.*, 299.

[42] Funke, *op. cit.*, 289-309.

[43] Magnus Blix, Experimentelle Beiträge zur Losung der Frage über die specifische Energie der Hautnerven, *Zsch. f. Biol.*, 20, 1884, 141 ff., 160 ff. This was a translation of a paper read in Sweden in November 1882 and first published in *Upsala läkareförен. förhandl.* 18, 1883, 87 ff.

[44] Alfred Goldscheider, Die specifische Energie der Temperaturnerven, *Monatshft. f. prak. Derm.*, 3, 1884, 198-208, 225-241; Die specifische Energie der Gefühlsnerven der Haut, *ibid.*, 283; Die specifischen Functionen der Nerven der Haut, *Proc. 8th Internat. Cong. Kopenhagen*, 3, 1884, 25-27, also *Vtjsch. f. Derm., Wien*, 11, 1884, 313-316; Nachtrag zu den Mittheilungen über die specifischen Energieen der Hautnerven, *Monatshft. f. prac. Derm.*, 4, 1885, 5; Ueber Wärme-, Kälte- und Druckpunkte, *Verhandl. d. Physiol. Gesellsch., Berlin*, 1885, 000. All of these studies may be found in Goldscheider's *Gesammelte Abhandlungen*, 1, 1898, 53-107.

none given. Writers were dogmatic and caustic, offering the apology that this manner "made for brevity and explicitness of exposition."[45]

The traditional point of view, that pain was an affective *quale,* was supported by the philosophers and by psychologists of philosophical bent: notably by Hurwicz, Lehmann, and Wundt in Germany; by Bain, Bradley, Spencer, Sully, Stout, and Ward in England; and by Baldwin, Dewey, James, and Marshall in America. Of all of these, the American, Henry Rutgers Marshall, was the most active and articulate. He wrote one book and numerous articles in behalf of the theory[46] and though, as it turned out, he fought a losing battle, he fought determinedly and vigorously. The "weight of authority" was with him, as he himself pointed out; but that proved of slight advantage as the authorities were widely divided among themselves. There was not *one* pleasure-pain theory but many; indeed, there were almost as many different theories as there were writers on the subject; and, as a rule, the theories proposed were satisfactory only to the men proposing them. Concerted effort and the maintenance of a common front were, under those conditions, impossible. It was almost a case, among the pleasure-pain theorists, of every man for himself. Though Marshall did yeoman's service in behalf of the traditional point of view, the particular theory that he advocated was as unsatisfactory to most of the members of his own camp as it was to his opponents in the other two camps. The internecine quarrels among the pleasure-pain theorists probably did more to advance the theories of the opposition than all their criticisms did to check them.

The situation was very different in the opposing camps. The intensive and sensory theories were supported by physiologists and by younger psychologists with psychophysical interests. These men were untrammeled by tradition; they put their trust in experiment and observation, and followed where their results led, even though this meant, as it frequently did, change of allegiance. For example, when Blix discovered the pain spots in 1882, he was inclined to believe that pain was specific; but by 1885 later experiments moved him to conclude that it was not. "There

[45] Herbert Nichols, The origin of pleasure and pain, *Philos. Rev.,* 1, 1892, 404.

[46] H. R. Marshall, The classification of pleasure and pain, *Mind,* 14, 1889, 511-536; The physical basis of pleasure and pain, *ibid.,* 16, 1891, 327-354, 470-497; Pleasure-pain and sensation, *Philos. Rev.,* 1, 1892, 625-648; *Pain, Pleasure, and Aesthetics,* 1894, 1-364; Pleasure-pain, *Mind,* 19, 1894, 533-535; Are there special nerves for pain?, *J. Nerv. & Ment. Dis.,* 21, 1894, 71-84; Pleasure and pain, *Proc. Amer. Psychol. Ass.,* 1894, 24; Pleasure-pain and emotion, *Psychol. Rev.,* 2, 1895, 57-64; Emotion versus pleasure-pain, *ibid.,* 166-168; *Mind,* 4, 1895, 180-194; Physical pain, *Psychol. Rev.,* 329-347.

are," he writes in his second study, "three specific kinds of nerve apparatus in the skin, one for warmth, one for cold, and one for pressure. No specific organs for the sense of pain have been proved to be in the skin."[47] Goldscheider also shifted front. At first he did not believe that pain was specific; but by 1885, just when Blix was shifting in the other direction, he came to the conclusion that the evidence did speak in favor of specificity.[48] He held to that view until about 1891,[49] when he shifted once more—this time to the theory, which he fully developed in 1894,[50] that pain was mediated by the tactile nerves and resulted from an intensive summation of their excitations. He turned to that theory because of an experiment of Naunyn's,[51] in 1889, in which pain was aroused through the summation of weak stimuli rapidly applied. Naunyn found, in cases of tabes dorsalis, that a mechanical stimulus (a hair for example) that was below the threshold for touch or pain, when applied repeatedly from 60-600 times a second, yielded in a few seconds (from 6-20) a pain which soon became unbearable. Since he obtained similar results with other stimuli (electrical for example), he concluded that pain was the result of summation. This conclusion and Goldscheider's extension of it must be counted as variants of the intensive theory. According to that theory as originally formulated, pain arises from the intense stimulation of any sensory organ. Bright lights, loud sounds, strong smells and tastes, severe pressures, and extremes of temperature, all, it was thought, arouse pain if they are intense enough. The ultimate extension of this doctrine is exemplified in the writings of Külpe and Titchener. Külpe wrote in his *Grundriss* in 1893: "pain has been held to be a special quality of cutaneous sensation, and pain nerves put alongside of the nerves subserving heat, cold, and pressure. The hypothesis has found its chief support among physiologists. We cannot accept it, as it stands: for pain is produced in all cases where the stimulation of a sensory nerve passes a certain limit of intensity."[52] Titchener wrote in the first edition of his *Outline* in 1896:

[47] Blix, *op. cit.*, *Zsch. f. Biol.*, 21, 1885, 160 ff.

[48] Goldscheider, Neue Thatsachen über die Hautsinnesnerven, *Arch. f. Anat. u. Physiol.*, 1885, Physiol. Abth., Suppl. Bd., 1885, 1-110 (*Gesammelte Abhandlungen*, 1, 1898, 197 ff.).

[49] Goldscheider, Ueber die Summation von Hautreizen, *Arch. f. Physiol.*, 1891, 164-169 (*Gesammelte Abhandlungen*, 1, 1898, 397-432).

[50] Goldscheider, *Ueber den Schmerz in physiologischer und klinischer Hinsicht*, 1894, 1-66.

[51] B. Naunyn, Ueber die Auslösung von Schmerzempfindung durch Summation sich zeitlich folgender sensibler Erregungen, *Arch. f. exper. Pathol. u. Pharm.*, 25, 1889, 272-305.

[52] Oswald Külpe, *Outlines of Psychology*, 1893; Eng. trans., E. B. Titchener, 1905, 90.

"excessive stimulation of any sense-organ, or direct injury to any sensory nerve, occasions the common sensation of pain."[53]

The sensory theory, that pain is a sensation mediated by specific nerves, found its chief support, as Külpe remarked, among the physiologists. Blix and Goldscheider were among the pioneers holding this view. Though they later shifted position, as we have seen, their places were taken by others—notable among whom was Max von Frey. This theory, it should also be noted, received almost unanimously the support of the clinicians, the most prominent among them being S. Wier Mitchell,[54] in America, and Henry Head,[55] in England. Psychologists were long in joining this camp. The first and for a time the only psychologist to uphold this point of view was Herbert Nichols[56]—a former student of G. Stanley Hall and a man who had come to psychology with training in engineering and sixteen years of successful service with the Pennsylvania Railroad.[57] Unprejudiced and not indoctrinated with psychological lore, he was possessed of sufficient self-confidence to espouse and to take a leading rôle in a minority movement. He opined, that "the prejudice of science . . . ran in favor of specific end-organs,"[58] and, as it turned out, he was right; for, when Head published his clinical observations[59] and Von Frey his experimental conclusions[60] correlating warmth with Ruffini cylinders, cold with Krause end-bulbs, pressure with hair follicles and Meissner corpuscles, and pain with free nerve endings,[61] psychologists moved over to the sensory view almost in a body. Here was something definite to teach, and textbooks changed over night. For example: Titchener, who had written in 1896 from the point of view of the intensive theory, wrote in his *Primer* in 1898 "of the sensation of pain,"[62] and placed it alongside

[53] E. B. Titchener, *An Outline of Psychology*, 1896, 65.

[54] S. W. Mitchell, Precision in the treatment of chronic diseases, *Med. Rec.*, 42, 1892, 721-726; Post-hemiplegic pain, *Med. News*, 62, 1893, 421-423, Wrong reference of sensations of pain, *ibid.*, 66, 1895, 281 f.

[55] Henry Head, On disturbances of sensation with especial reference to the pain of visceral disease, *Brain*, 16, 1893, 1-133; 17, 1894, 339-480; 19, 1896, 153-276.

[56] Herbert Nichols, The origin of pleasure and pain, *Philos. Rev.*, 1, 1892, 402-432, 518-534; Pain nerves, *Psychol. Rev.*, 2, 1895, 487-490; The feelings, *Philos. Rev.*, 4, 1895, 506-530; Pain nerves, *Psychol. Rev.*, 3, 1896, 309-313.

[57] K. M. Dallenbach, Herbert Nichols: 1852-1936, this JOURNAL, 49, 1936, 320-321.

[58] Nichols, Pain nerves, *Psychol. Rev.* 3, 1896, 311.

[59] Head, *opp. citt.*

[60] Max von Frey, *Die Gefühle und ihr Verhältnis zu den Empfindungen*, 1894, 1-24; Beiträge zur Physiologie des Schmerzsinnes, *Ber. ü. d. Verhandl. d. k. sächs. Ges. d. Wiss. z. Leipzig*, math.-phys, Kl., 46, 1894, 185-196, 288-296; Beiträge zur Sinnesphysiologie der Haut, *ibid.*, 47, 1895, 166-184; 48, 1896. 462-468; Untersuchungen über die Sinnesfunctionen der menschlichen Haut: I. Druckempfindungen und Schmerz, *ibid.*, 49, 1897, 169-266.

[61] *Op. cit., ibid.*, 47, 1895, 181-184.

[62] Titchener, *A Primer of Psychology*, 1898, 45.

of the sensations of pressure, heat and cold; and in his *Instructor's Manual* he said: "investigation of the cutaneous sensations has moved so rapidly during the past five years that there is no adequate account of them to be found in the textbooks."[63]

Evidence for the sensory theory extant in 1896 was derived from many sources.

(1) A large share was drawn from pathology, as clinical evidence indicated that the skin possessed four distinct forms of sensibility: warmth, cold, pressure, and pain; and that any one or any combination of them may be lost or impaired without involving the others.

(2) Experiments with intense stimuli also showed that pain was specific; for, contrary to the views of the intensive theorists, excessive stimulation of the special senses does not yield pain when the effect is limited to the organ concerned. For example: if the retina is stimulated, however intensely, it yields not pain but light. If proximal regions are stimulated simultaneously, pain results, but only because those extra-retinal regions are themselves capable of yielding pain. As with vision so also with audition, smell and taste. Excessive stimulation of any of the special senses does not yield pain unless the effects involve tissues that are themselves supplied with pain nerves. Even the warm and cold spots were found to be specific. No matter how excessive their stimulation—whether they are prodded with a probe, pricked with a needle, or burned with a red hot wire—they yield, when stimulation is restricted to the proper area, not pain, but their own specific quality.

(3) The long latent period, the comparatively slow rise of pain after stimulation, which is exaggerated in cases of tabes dorsales, was set in evidence of specificity.

(4) So also were the results obtained with anesthetics. Under light chloroform anesthesis, the patient is sensitive to the slightest touch, but to pain he is totally insensitive. Again, if an ice pack is applied to the elbow, pressure, warm, and cold, and finally pain lapse from the lower arm in that order. Similar results were obtained with cocaine and menthol. These findings, that pain disappears under the influence of anesthetics while the other senses remain and that it remains while the other senses disappear, spoke for specificity.

(5) Mapping the distribution of pain spots on the body with punctiform stimulation and graded esthesiometers.

(6) Liminal determinations of pain in different areas.

(7) The uniqueness of certain areas in yielding pain alone (*e.g.* the cornea of the eye) and the insensitivity of certain other areas (*e.g.* Kiesow's area, the mucous membrane of the cheek opposite the second lower molar).

The evidence for the sensory theory in hand in 1896 was impressive. It convinced many, but it did not place the theory in the realm of fact. There were still many unsolved problems. Outstanding among them were: (1) the definite identification of the pain-receptors; (2) the establishment of the peripheral pathways; (3) the localization of the cerebral centers; (4) the interpretation of the non-adaptability of pain; and (5) the explanation of its unique relationship with unpleasantness.

[63] Titchener, *Experimental Psychology: I. Qualitative Experiments: ii. Instructor's Manual,* 1901, 81.

Solutions of these problems were, to be sure, proposed in the '90s, but none were final. For example, Von Frey thought that the free nerve-endings were the organs of pain; but, his direct experimental evidence being meager, he relied upon circumstantial evidence. The free endings are the only nerve structures widely scattered throughout the body and existing in sufficient profusion in the skin to correlate with the numerous pain-spots localized upon the surface. Again, the non-adaptability of pain was explained biologically. Pain is deleterious; adaptation would be of anti-survival value, as organisms that become adapted to pain would, in the long run, not survive; hence pain is non-adaptable. A false explanation, to be sure, but one that satisfied the exigencies of the occasion.[64]

The sensory theory was widely accepted. When Sherrington[65] in Schäfer's *Textbook* and Thunberg[66] in Nagel's *Handbuch* wrote of pain as a specific sensation coördinate with the other cutaneous sensations, the theory was 'in,' and it was presented and taught in most textbooks of physiology and psychology as established fact. The other theories were eclipsed. The traditional pleasure-pain theory underwent a complete reorganization. After vain attempts to discover nerves of pleasure—Nichols, for example, searched for them throughout the body and finally decided that they must be in the organs of sex and alimentation, the two systems vitally concerned with the preservation of the species[67]—the theory was placed in a new perspective. Pain was removed as a term in the dichotomy, unpleasantness was substituted, and the dichotomy was changed to one of pleasantness-unpleasantness and then relegated to the affective sphere where it would no longer be of concern to those chiefly interested in sensation.

The intensive theory in its more general form was definitely disproved. Pain positively is not a common sense-quality that is aroused by excessive stimulation in all sensory nerves. The pains of dazzling lights, of shrill tones and intense noises, of pungent tastes and smells, of extremes of cold and heat, are mediated by the co-excitation of other nerves than those of the specific senses. So much we may accept as established fact.

Goldscheider's modification of the intensive theory was, however, un-

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[64] Cf. also G. W. A. Luckey, Some recent studies of pain, this JOURNAL, 7, 1895, 108-123; W. von Tschisch, Der Schmerz, *Zsch. f. Psychol.*, 26, 1901, 14-32.

[65] C. S. Sherrington, Cutaneous sensations, in E. A. Schäfer's *Textbook of Physiology*, 2, 1900, 920-1001.

[66] Torsten Thunberg, Physiologie der Druck-, Temperatur- und Schmerzempfindungen, in W. Nagel's *Handbuch der Physiologie des Menschen*, 3, 1905, 647-733.

[67] Nichols, *op. cit.*, *Philos. Rev.*, 1, 1892, 414.

touched by these considerations. It was, nevertheless, at the textbook level at least, completely ignored; it was put in the discard along with the general form of the intensive theory with which it was incorrectly identified. At the frontiers of research, on the other hand, the theory was very much alive. There it took its place as a theory contending on equal footing with Von Frey's; and many have been the studies undertaken to decide between them!

Goldscheider partly prejudiced the issue by his adherence to the term *Gemeingefühl,* which is the context into which he set his theory. It is, nevertheless, clear from his treatment that he, like Von Frey, regards pain as a specific sensation subserved by a special class of nerves. From there on, however, their theories diverge. Goldscheider holds that pain is mediated by the tactile nerves and that it results from the summation of their excitations in the gray substance of the spinal cord. Von Frey, as we have seen, holds that pain is unique, that it is a separate modality subserved by discrete receptoral structures—the free nerve-endings. In writing of these theories, Kiesow says: "the differences between them goes so deep that a reconciliation is hardly conceivable . . . if one view is correct, the other must necessarily be false. Consequently, we cannot expect the conflict to end until one of the views attains general recognition and so flict to end until one of the views attains general recognition and so vanquishes the other."[68] But how to set the experimental stage so that the contending theories could meet? That question was long in answering.

As we have seen, pain, for biological reasons, was not supposed to show adaptation.[69] This point of view was held for many years. It was not until comparatively recent times (1919) that Straus and Uhlmann discovered in the Cornell laboratory that pain *did* show the phenomenon of adaptation.[70] One of the outstanding problems regarding pain, *i.e.* the explanation of its none-adaptability, was solved, and pain, as far as adaptation is concerned, stepped into line with the other cutaneous senses. All that is required for its adaptation is a relatively constant, unvarying stimulus—the very conditions necessary for adaptation in all the other departments of sense. When this result was obtained, the reason that pain had heretofore been regarded as non-adaptable immediately became clear. The stimulus-conditions in injuries, tooth-aches, and headaches are constantly varying.

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[68] Friedrich Kiesow, The problem of the condition of arousal of the pure sensation of cutaneous pain, *J. Gen. Psychol.,* 1, 1928, 199-212.

[69] Titchener (A Textbook of Psychology, 1909, 154) says, in 1909, that "the pain sense does not appear to show the phenomenon of adaptation;" and Fröbes (*op. cit.,* 151) in 1923, writes, "der Schmerz zeigt keine Adaptation," although numerous experiments had by then been reported showing the contrary.

[70] H. H. Straus and F. R. Uhlmann, Adaptation of superficial pain, this JOURNAL, 30, 1919, 422-424.

Straus and Uhlmann were content to rest their study at that point, but the experiment, as it turned out, was destined to play a larger rôle. As an *experimentum crucis,* it led to a decision between Von Frey's and Goldscheider's theories. If Von Frey's sensory theory were correct, pain should, in the course of its adaptation, simply become progressively weaker and disappear without undergoing any qualitative change. If Goldscheider's theory, on the other hand, were correct, then, as pain becomes less intensive through adaptation, it should also undergo a qualitative change, *i.e.* it should change into pressure. Goldscheider,[71] accepting the logic of the adaptation-experiment, claimed that the excitation of the pain-spots arose and disappeared through subpainful experiences ("die Erregung der Schmerzpunkte unterschmerzlich beginnt und unterschmerzlich aufhört").[72] He found, in his studies of its adaptation, that pain not only became weaker under continuous stimulation but also that it underwent a qualitative change, *i.e.* before completely adapting and disappearing, it passed into a subpainful sensation (*unterschmerzliche Empfindung*) of contact (*Berührung*) or pressure (*Druck*).

In an experiment on pain[73] in 1922, Von Frey tested Goldscheider's subpainful sensations. In order to avoid the concomitant pressures that are aroused when an object is brought to bear upon the skin, Von Frey elicited pain by focusing the sun's rays upon the skin by means of a hand lens. Because he was able to obtain pure pressureless pains by this as well as by other means, he concluded that Goldscheider's summation theory was untenable.

In refutation, Goldscheider, in 1926, pointed out that Von Frey had used strong stimuli, and that the course of experience, under those circumstances, is telescoped and the subpainful pressures are obscured by the intense pains.[74] He laid down two necessary conditions for the subpainful pressures: first, the pain should not be intense; and secondly, it should be produced slowly, not quickly or suddenly. His conclusion was that "the doctrine of specific peripheral nerves of pain is unwarranted."[75] So the situation was back again to where it was before! Opinion set against opinion, and observation against observation.

In 1931, Wells and Hoisington reported a phenomenological study of pain-adaptation which, they thought, settled the controversy by reconciling the disparate points of view.[76] They found that the end-quality in the course of pain-adaptation

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[71] Goldscheider, *Das Schmerzproblem,* 1920, 20, 71-73.
[72] *Op. cit.,* 20.
[73] Von Frey, Versuche über schmerzerregende Reize, *Zsch. f. Biol.,* 76, 1922, 1-24.
[74] Goldscheider, Beiträge zur Physiologie der Gemeingefühle, *Zsch. f. Sinnesphysiol.,* 57, 1926, 1-14.
[75] *Ibid.,* 14.

"is neither a weak pain (Von Frey) nor a pressure (Goldscheider), but a non-pressury 'bright contact.'"[77] Upon the basis of this finding, they suggested that the difference between Von Frey and Goldscheider was principally terminological. Though recognizing that "interpretation and comparison of qualitative terms is always dangerous," they, nevertheless, ventured the opinion that Von Frey's "weak pains" and Goldscheider's "subpainful pressures," which those investigators obtained just before complete adaptation was reached, corresponded to their own "bright contacts." If such is the case—"if Von Frey's insistence that isolated pain spots give nothing but pain is . . . due to a confusion of 'weak pain' with non-painful 'bright contact'," and "if Goldscheider's contention that isolated pain spots give 'pressure' is the result of a failure to differentiate between true pressure and the non-pressury contact-like experience"—then, they conclude, "the controversy will be settled." Yes, settled by the elimination of Von Frey! For Von Frey to admit "that the final phase of pain subsidence is not really painful"—as Wells and Hoisington would have him do—would be for him to accept Goldscheider's theory. Wells and Hoisington reconcile the controversy by corroborating Goldscheider!

It was at this point that I undertook, in coöperation with several of my students, a series of studies on the problem. The first study (with Burns) was performed, following Goldscheider, with needle esthesiometers.[78] We found, in confirmation of Goldscheider, that pain was replaced by pressure in every instance before complete adaptation was secured. The normal and typical course of adaptation was "a gradual subsidence from a maximal pain through pressure to indifference."[79] At which point or points in the curve, however, was complete adaptation attained? When pain disappeared and pressure emerged? Or only when pressure disappeared? Or have we here two cases of complete adaptation: one of pain, and another of pressure? Our answers to these questions will depend upon our point of view, but it should be recalled that our stimuli—needle esthesiometers—were applied at superliminal pressure values; they were, therefore, capable of eliciting pressure as well as pain. The pressures reported after the subsidence of pain may very well be nothing more or less than the residual effect of our own stimuli. The only way of deciding the matter was to arouse pain with stimuli, like radiant heat, that do not give rise simultaneously to pressure.

We therefore devised, in the second study (with Stone),[80] a thermo-esthesiometer that yielded pain in conformity with the strict conditions laid down by Goldscheider for the observation of his subpainful pressures.

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[76] E. F. Wells and L. B. Hoisington, Pain adaptation: A contribution to the Von Frey-Goldscheider controversy, *J. Gen. Psychol.*, 5, 1931, 352-366.

[77] *Ibid.*, 364.

[78] Maryland Burns and K. M. Dallenbach, The adaptation of cutaneous pain, this JOURNAL, 45, 1933, 111-117.

[79] *Ibid.*, 115.

[80] L. J. Stone and K. M. Dallenbach, Adaptation to the pain of radiant heat, *ibid.*, 46, 1934, 229-242.

Goldscheider said that there should be no telescoping of experiences and, as the typical reports of our observers showed, there was none. Warmth, the first quality elicited, passed slowly through intensive gradations to heat; this, in turn, passed through intensive gradations to weak pain which grew in turn in intensity, remained constant at a high degree for a short time, and then gradually declined, and disappeared into heat, which in turn subsided into warmth. Pressure was noticeable by its absence. This result might lend support to a new theory that pain is a summation of warmth; but we preferred the explanation that the accompaniments of pain, whether pressure or warmth, are functions of the type of stimuli employed. Since a pressure stimulus yields residual pressure on its way to complete adaptation, and a warmth stimulus residual warmth, we hazarded the opinion that a cold stimulus would yield residual cold—and thus set the problem for our third study.

This study (with Edes) yielded the expected results.[81] A dry-ice stimulator elicited pain without telescoping the experience. From slowly increasing degrees of cool and cold, pain emerged gradually, grew in intensity, remained at a high degree for a time, and then gradually disappeared, subsiding into decreasing degrees of cold and cool. At no time during the course of adaptation to the cold stimulus was pressure reported by our observers.

Did our observers, in the two studies with temperature, miss Goldscheider's pressures? Were those pressures so weak that they escaped notice? We think not. Our *Os* were highly trained in cutaneous observation; it is hardly possible that all of them would have failed all the time to report those qualities if they occurred, particularly as our experimental conditions fulfilled all the requirements that Goldscheider laid down and should, therefore, have been highly favorable for their observation.

All the pain-adaptation studies reveal, as residual effects, the qualities that are inherent in the stimuli. A pressure stimulus yields residual pressure; a warmth stimulus, residual warmth; and a cold stimulus, residual cold. Surely, these experiments justify us in concluding with Von Frey that the nerves of pain are separate and distinct from the tactile nerves, and that Goldscheider's summation theory is untenable. This conclusion is corroborated by experiments during the past decade in the field of neurophysiology, demonstrating that pain is subserved by specific nerve fibers.[82]

[81] Barbara Edes and K. M. Dallenbach, The adaptation of pain aroused by cold, *ibid.*, 48, 1936, 307-315.

[82] E. D. Adrian, *The Mechanism of Nervous Action*, 1932, 42-60.
H. S. Gasser and J. Erlanger, The rôle of fiber size in the establishment of a nerve block by pressure or cocaine, *Amer. J. Physiol.*, 88, 1929, 581-591.

Though the investigators disagree among themselves regarding details, they agree in general that separate nerve fibers subserve the function of pain.[83] Further support for this point of view is provided by the experiments in sensory chronaxy which demonstrate significant and reliable differences in the chronaxies and in the strength-duration curves of pressure and pain.[84] Thus we see that Nichols was right when he opined that the prejudice of science ran in favor of specificity.

Of the five outstanding problems at the turn of the century, I have touched upon two. One of these, as we have seen, has definitely been solved. The discovery that pain was adaptable removed the explanation of its non-adaptability from the list of problems. The other, the establishment of the pathways of pain, is well on the way to solution, if, indeed, it is not settled now. Of the three problems that I neglected, only one is nearer solution now than it was a third of a century ago. The identification of the pain-receptors is bound up with the establishment of the structural pathways, but the evidence for the free nerve-ending is only a little more convincing now than it was when Von Frey formulated his theory. The other two problems, the localization of the cerebral centers, and the explanation of pain's unique relationship with unpleasantness, are practically untouched. We still are, as Waterston recently observed, "entirely ignorant of any 'cortical area' associated with pain perception, nor do we know whether such an area exists or whether the thalamus alone . . . is sufficient for the pain sensation."[85]

The uneven advance since the turn of the century characterizes the history of the subject from the beginning.

P. Heinbecker and G. H. Bishop, The mechanism of painful sensations, *Proc. Ass. Res. Nerv. & Ment. Dis.*, 15, 1935, 226-238.

P. Heinbecker, G. H. Bishop, and J. O'Leary, Fibers in mixed nerves and their dorsal roots responsible for pain, *Proc. Soc. Exp. Biol. & Med.*, 29, 1932, 928-938; Analysis of sensation in terms of the nerve impulse, *Arch. Neurol. & Psychiat.*, 31, 1934, 34-53.

S. W. Ranson, Cutaneous sensory fibers and sensory conduction, *Arch. Neurol. & Psychiat.*, 26, 1913, 1122 f. 1 Cutaneous sensation, *Science*, 78, 1933, 397 f.

S. W. Ranson and H. K. Davenport, Sensory unmyelinated fibers in the spinal nerves, *Amer. J. Anat.*, 48, 1931, 331-353.

David Waterston, Observation on sensation: The sensory functions of the skin for touch and pain, *J. Physiol.*, 77, 1933, 251-257; On pain, *Lancet*, 224, 1933, 943-946; Pain and the mechanism of its production, *Brit. Med. J.*, (no. 3857), 1934, 1087-1089.

[83] The outstanding exceptions are Heinbecker, Bishop, and O'Leary (*opp. citt.*). These authors report results which agree with Goldscheider's theory.

[84] Cf. W. S. Neff and K. M. Dallenbach, The chronaxy of pressure and pain, this JOURNAL, 48, 1936, 632-637, and the references cited by them.

[85] Waterston, *op. cit.*, *Lancet*, 224, 1933, 943.

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THE PHYSIOLOGY OF PAIN: ABNORMAL NEURON STATES IN CAUSALGIA AND RELATED PHENOMENA

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THE PHYSIOLOGY OF PAIN: ABNORMAL NEURON STATES IN CAUSALGIA AND RELATED PHENOMENA *

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THE physiology of pain is too broad for this brief analysis; by pointing toward the problem of causalgia, however, the most significant aspects of the larger subject may come into focus. It is encouraging that purely physiologic considerations have led to an interpretation very close to that reached by Livingston (1) from clinical experience.

In the space available, one must necessarily omit much highly relevant material. On the problem of the periphery in pain mechanisms, for example, I can merely state some facts that seem established. There are two types of nerve fibers that carry pain messages centrally: the more rapid delta fibers, about one third of the A elevation and conducting about 20 m. per second, and the very slow, nonmedullated C fibers, perhaps four times as numerous as the A group and conducting only 2 m. per second (2). The latter are particularly concerned with the burning pain associated with causalgia and are often called protopathic. Each pain fiber has a peripheral branching network of its own which may serve an area of several square centimeters, and the separate terminal fibers may interlace; but they do not form a continuum with each other, as had been thought. The separate twigs of one fiber, or of more than one, may interact in the periphery under certain conditions, as in antidromic effects, H substance release, spreading hyperalgesia or, in one fiber, even in normal function (3). The autonomic system can be involved in pain, both on the efferent and afferent side, even though only 10 to 20 per cent of C fibers are related to the sympa-

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thetic. Pain impulses can run up afferent fibers that are clearly in the autonomic system; stimulation of sympathetic ganglia can cause pain (4) and the autonomic can carry pain past a cord transection (5, 6). Vasomotor and other autonomic afferent fibers have been explored extensively, and such peripheral effects as dilation or constriction, excessive pulse pressure, liberation of H substance, tissue edema, and pressure of a scar on a nerve have been invoked in the genesis of causalgia. None of these is critical, however, and it is well to remember that compression blocks A fibers before C and cocaine blocks C before A, and that, although anoxia lowers the threshold of pain fibers and may give spontaneous firing, these are normally insensitive to pressure (2, 7, 8).

The phenomenon of cross talk, or artificial synapse, can occur between fibers that have become oversensitive to the electrical fields of their neighbors (9, 10). This breakdown of the law of isolated conduction so that sympathetic efferent impulses excite somatic afferents (11) does not, however, seem an adequate basis for causalgia. It does not account for the greater frequency with high lesions or stretch (12), nor for the persistence or recurrence after high nerve section or sympathectomy or even amputation, nor, for that matter, the rarity of causalgia after nerve trunk injury. Indeed, I would like to discard the whole problem of the periphery because, in my judgment, no matter how necessary it may be in the initiation of causalgic phenomena, it has become secondary and unimportant by the time one is dealing with a really developed causalgia. The most direct evidence of this is that, when such pain has persisted for a sufficient time, no peripheral operation relieves it. The disturbance somehow has moved into the central nervous system.

A second important phase of the problem that I shall merely allude to concerns the actual coming into consciousness of pain, whether in the thalamus or cortex or elsewhere. Considerable evidence, accumulated particularly in recent years, suggests that pain consciousness has more to do with the cortex than had usually been believed, even though not predominantly there. Pain has occurred with focal epilepsy and been abolished by local excision of a bit of cortex (13). Similarly, phantom limb pain has been relieved by cortical operation (14). Stimulation of the postcentral gyrus, in turn, has evoked pain awareness (15). It remains true for the most part, however, that cortical manipulation is not related to pain; indeed, bilateral pain seemed normal in a patient with an entire hemisphere missing (and corresponding thalamic degeneration) (4), as pain may be absent with a presumably normal cortex (16). Leukotomy, even unilateral leukotomy, seems able to relieve the "inconvenience" and unpleasant affect of pain, but this seems less the result of decreased sensation than of decreased attention to the sensation (17). Again, this cannot be the region that demands really critical analysis, since a double tractotomy eliminates the pain in all

but the most prolonged and delayed cases, in which the whole pathologic process has moved cephalad. Rather, some abnormal pattern of nerve impulses reaches the upper part of the nervous system, and just where is now unimportant, which gives rise in consciousness to this horrible type of suffering. We must focus, then, in our physiologic analysis, on some kind of maintained disturbance in the spinal cord.

Briefly, the outstanding phenomena of causalgic type pain are as follows. It is a slow, burning, poorly localized and irradiating pain, easily provoked by peripheral stimulation (at or above normal thresholds) or by central facilitation (especially by emotional states), with a peculiarly unpleasant quality and associated with such severe affective reactions that the personality may be strikingly altered. Particularly, it tends to increase in time and to spread in space. It has a devastating ability to leak around any kind of surgical block interposed in its path. The pain exhibits the tendency, seen in the course of evolution of the nervous system itself, of progressive centralization and cephalization of its site. Central pain is common only when pathologic change involves the grey matter proper (18). We have, then, this basic problem of a maintained, abnormal, dynamic state of the cord neurons. It is the nature and mechanism of production of this state to which attention is now directed.

First, what is the essential change? A view almost seventy years old (19), which has received reinforcement from observers at regular intervals since (20, 1), is that the fundamental abnormality is some sort of overactivity, perhaps an increased subliminal fringe, that the cells (21, 12, 1) develop. I have called this a "physiological inflammation" (22) of the neurons of the cord, some abnormal hyperactive state of the neurons associated with the bombardment of these neurons by excessive impulses. The evidence for an interpretation in terms of overactivity is convincing, even dramatic. The relevant findings can be summarized under the headings of reinforcement and of block.

First, the pain is exacerbated by a variety of peripheral or central stimuli. The existence of peripheral trigger points, able to provoke an agonizing bout of the pain, is well known. The gentlest stimulus of skin or muscle, even light in the eye (12; compare the augmentation of auditory impulses by visual activity, 23) may suffice. Recent laboratory work (24, 25, 26) has shown that trigger zones, associated with chronic skeletal or visceral lesions, often can be demonstrated objectively in terms of areas of lowered threshold or skin resistance, increased blood flow and the like. Injection of a fraction of a milliliter of irritant hypertonic salt solution into the spinous ligaments at the appropriate segmental level can bring about, in patients who had had a renal colic, cardiac angina or other visceral pain syndrome, a recrudescence of the typical pain picture in each case (27). The irritation, so to speak, created trigger points. Conversely, others report that injection of cocaine into a trigger zone in the pectoral region can relieve an

anginal attack (28, 29) or that injection of the interscapular skin can initiate crisis and resolution in lobar pneumonia (30).

Central reinforcement is probable in the increased pain with emotion, although in certain cases a peripheral factor, as increased muscle tension (31), may be involved. Menstrual pain, from uterine contractions, is enhanced by the increased muscle tone induced by apprehension (32), but purely central effects probably contribute. Certainly, the reaction to pain, even to a pain stimulus subthreshold to perception, is exaggerated by fear (31; not found in recent studies, 33). Central reinforcement and irradiation are, in fact, of very general occurrence. Even the spread of deep pain from one cooled finger to adjacent ones is entirely central, since it occurs when the nerves from the adjacent fingers are blocked (31).

The second main line of evidence, for some kind of overactivity owing to maintained overstimulation, is that early interruption of afferent impulses by transient nerve block often relieves the pain permanently. The clinical efficacy of single or repeated nerve block is too well accepted to require discussion, but some specific experiments deserve mention. On the basis of clues from other studies, referred pain to filled teeth was examined (34). Symmetrical cavities on the two sides of the mouth were filled, using equal technical skill, but, on one side, maximal care was exerted to protect the patients' sensibilities while, on the other, all analgesia was eschewed and the handling was a bit rough. In all of thirty odd cases the subject developed, in the roughly handled tooth, a severe referred pain from mechanical stimulation of the maxillary antrum. This never appeared on the control side. Such pain patterns remained indefinitely, unchanged over many months, with no further manipulation. A single procaine block of the roughly handled tooth, however, although worn off in a few hours, permanently abolished the referred pain. Here, then, is strong evidence that an initial excessive afferent barrage had set up in the central nervous system a modified functional state, continuously reinforced by a steady but not particularly excessive train of impulses from the periphery, and that temporary interruption of the peripheral reinforcement sufficed to allow this central abnormality to subside. After the inflammation had subsided, the normal flow of impulses neither reinforced nor reestablished it.

This evidence by a maintained overexcitatory state in the cord is easily supplemented by other types of experimentation. A source of irritation, a *locus resistentiae minoris,* was produced in patients with anginal pain by injecting a vesicant into the skin on the right chest (35). In time the irritation completely disappeared, leaving no local signs; nevertheless in subsequent anginal attacks the pain, previously limited to the left side, now regularly radiated in addition to this particular region on the right side. Even more dramatic evidence of an enduring central change was obtained by injecting turpentine into the

paw of a cat (36). This produced severe pain, limping, flexion and the other phenomena of attending a severe local irritation; in time the symptoms had completely vanished, the cat was running around entirely normally, and there was no reason to suspect that any residue remained. Nevertheless, when the animal was then decerebrated by an intercollicular section, the decerebrate rigidity that resulted was not symmetrical. The posture of the hind legs was exactly that seen in the flexion reflex produced by severe painful stimulation of the nerve from one leg; the previously injected leg was kept in strong flexion, the other in crossed extension. There is even a claim (37) of unilateral histologic changes in the cord of such an animal. Finally, placing aluminum cream in the motor cortex of a monkey, even if excised after four days, can lead to focal epilepsy three months later (38). Comparable injection of this agent into the lower cord of the cat has generated a spreading causalgia-like hyperalgesia well ahead of the initial point of injection (39). Some kind of maintained overactivity of central neurons is present and continuously reinforced, at least at first, by the arrival of impulses from the periphery.

Yet there exists another, equally impressive, body of evidence which points in exactly the reverse direction. This leads to an interpretation of causalgia, not as a result of overdriving but as a result of loss of impulses, as defective rather than excessive innervation. This general conception also has a long history, at least from the studies of Holmes on the dissociation of epicritic and protopathic sensation and the view that the former, perhaps by way of the cerebrum, holds in check diencephalic responses to the latter (20). That cortex can inhibit hypothalamus (40) and thalamus (41) is established, but reverse relations also exist (42) and, in any event, these cephalic relations are not disturbed in causalgia. A related suggestion (43), however, has been offered specifically to account for causalgic pain. A peripheral stimulus normally leads to two sets of ascending cord impulses; the fast, epicritic-like messages reach a thalamic relay in time to inhibit there the slow pain impulses, which are thus largely kept from the cerebrum and consciousness. This interesting view is at least partly right, for electrophysiologic work (44) has demonstrated such fast and slow ascending paths. Unfortunately, in these experiments the fast impulses condition the brain stem centers positively and enable the slow ones to pass upward more easily; but this need not be the action in all such systems, for inhibitory conditioning is also well known (e.g. 45). Considerable clinical experience is in harmony with such a view. In pruritus ani (46) for example, section of the anterolateral columns, in which travel the "protopathic" pain tracts, tends to relieve the symptoms, while a more dorsal section, destroying the touch-pressure fibers, far from relieving pain, exacerbates the whole pain syndrome.

Further evidence of interaction between sensory modalities comes from studies on peripheral nerves. A pressure cuff on the arm leads,

after about a half hour inflation, to a fairly abrupt loss of fast pain sensation from the lower arm and to loss of touch and temperature shortly before or after this (47). At that time the slow pain is suddenly exaggerated and acquires the peculiar burning, unpleasant, suffering-producing quality of causalgic pain. The obvious interpretation is that, when the larger fibers fail (and experimentally they do block first under pressure or asphyxia, 2), the small pain fiber impulses, no longer modulated in the cord, carry up and into consciousness the excessive and distorted awareness of pain. Perhaps the mere absence of other sensory modalities leads the cortex to overestimate those which do arrive (48). There are some difficulties with this interpretation, but they can be passed by since recent work makes even this dichotomy perhaps unnecessary.

Careful physiologic assay of sensations from a given skin area followed by excision and histologic mapping of nerve endings has yielded important information, especially following damage to the cutaneous nerve (49). A critical finding dealt with a reinnervated skin area, part of which showed normal pain sensation while another part exhibited typical causalgic pain. Only normal pain fibers were found in both regions and their terminal nets also appeared entirely normal. In the region with undisturbed pain sensation, however, several pain fibers were present with their interdigitated terminal nets, while in the causalgic area only a single fiber and terminal supplied the innervation of a given skin region. Causalgic pain, then, is here attributed to the activity of single pain units, unmodulated by other pain units normally excited by the same stimulus. Even the cuff experiments might be the result of block of some slow pain fibers rather than of the faster fibers; and, indeed, causalgic pain has been found in a skin area which possessed touch sensibility (50).

A case has been reported (51) which is almost diagrammatic of the view that causalgic pain results from the simple loss of normal innervation. Following injury, three nerves in the arm regenerated so as to innervate the same bit of skin. Sensation from that bit was normal. After procaine block of one of the nerve branches, pain sensations became more unpleasant; after block of two, pain became completely causalgic in type; after block of all, anesthesia was complete. Here, then, is an example of progressive whittling down of the pain innervation by physiologic means, with a parallel appearance of excessive and abnormal pain experience. Another illustrative case (52) is cited. A man who had had a limb amputated twenty-nine years earlier was operated on (for some irrelevant condition) under spinal block anesthesia. During the time that the nerves were blocked and afferent impulses were prevented from reaching the cord, and only during that time, he complained of terrific causalgic pain in the phantom limb. No such sensation had been experienced previously. (I am grateful to several anesthesiologists who have informed me of entirely comparable, and

previously inexplicable, experiences from their own practice. It has also been called to my attention, by Dr. H. Davis, that tinnitus may be greatly reduced when ordinary sounds are present.)

I present a final point on the greater incidence of causalgia with nerve injury that is violent or close to the central system than under other conditions of injury. Such peripheral injury is commonly associated with the actual degeneration of neurons. Sensory neurons degenerate more easily than motor, and some four times as many of the small neurons of the spinal ganglia are lost as of the large ones (53). There is even significant transneuronal degeneration in Clarke's column (54). Thus, in cases of high, violent nerve damage there is almost certainly a considerable component of actual anatomic degeneration in the cord, with especial loss of the neurons serving slow pain (12). This is just the situation for producing causalgic pain.

Here, then, are two sets of evidence, each extremely convincing, one tracing causalgia to an initial overactivity and the other to an underactivity. Fortunately, these are not irreconcilable in terms of physiologic mechanisms; they are, in fact, quite in harmony with reasonable interpretations. We must account for an abnormal state of spinal neurons, set up by a combination of excessive activity of some afferent neurons and deficient activity of others, a state which exhibits first centralization and then cephalization and one which tends to increment in time and spread in space. The disturbance is not uniquely related to any particular anatomically defined neurons, but is a pattern involving neuron groups and able to shift its locus and so the actual units implicated.

Such a situation is by no means unique to causalgic pain. If the affective sign is reversed from unpleasant to pleasant, we would have a good description of the neurologic and psychologic consequences of stimulation of the external genitalia. The phenomena of motion sickness, from labyrinthine stimulation, seem comparable. In all there are marked summation, irradiation, prepotency, a vague and prevasive quality with a nonetheless intense affect and great susceptibility to both reinforcement and suppression by peripheral or central activity. On the motor side, epilepsy comes strongly to mind as a related phenomenon, and many of the attributes of neurosis are strikingly similar. Indeed, such cases as the following, for a description of which I am indebted to Dr. H. Jasper, supply a wide bridge between epilepsy and overt neurosis. A man had his first epileptic attack on seeing an object taken from a dog. Attacks recurred only on renewal of such an experience; but, over years, the precipitating situation became more generalized, to seeing anything taken from anyone, until observing a checkgirl receive a customer's coat led to a full-blown episode. Also, the regular habit-forming action of analgesic drugs, and the ability of a leukotomy to relieve, if not pain, at least the pain's mattering, and to eliminate narcotic withdrawal symptoms (17) are impressive (a decor-

ticate addicted dog can, however, die on abrupt withdrawal of drug, 33); but such considerations lead further into the unknown.

That a certain type of neuron activity may depend on continued presence of impulses in some impinging nerve fibers and absence of impulses in others is well known. Even the alpha rhythm of brain waves depends on the arrival of some thalamic impulses but is disrupted by others associated with vision. An even sharper example was encountered in a regular rhythm in the optic thalamus of the cat (55). This rhythm, like the human alpha, is abolished by bright illumination of the eyes; but it fades away in an hour or two in complete darkness, when the continuous gentle reinforcement supplied by diffuse illumination is withdrawn. The physiologic mechanisms now require attention.

There could be, of course, the sort of chemical and morphologic mnemonic traces in synapses, often assigned to one type of memory, which would lower thresholds of an internuncial pool and increase the subliminal fringe. Or interneurons could be captured by certain arcs, when these are driven more than competing ones (56). Doubtless such mechanisms could be elaborated to fit the phenomena, but they seem less promising than others. Reverberating circuits are more interesting, indeed they are currently being invoked to account for much of neural physiology. The possibility that one neuron activates a second, this a third, and so on until the last one reactivates the first, leading to a trapped impulse running around and around in neuron circles (57), is theoretically most attractive. It could explain the present phenomena: a single input starts some neuron chain reverberating; additional impulses coming in out of phase or in other positions would tend to disrupt, but continued impulses in the appropriate channels would tend to reinforce and maintain it. Such reverberating nets could constitute the maintained abnormal dynamic state of the cord neurons. There are difficulties that could be met by subsidiary assumptions, but it is well to remember that even the existence of circuits so functioning remains at present an hypothesis. To my knowledge, they have not been actually demonstrated.

I am inclined to still another view, suggested to me by experiments we performed in an entirely different connection. It does not necessitate any neuron circuit; it requires merely that groups of neurons (perhaps considerable masses of neurons) become locked together in their spontaneous rhythms. The electrical rhythm in neurons, including the brain waves or alpha rhythm in many if not all cases, is a true autochthonous beat. The rhythm becomes larger and more regular in a few neurons removed from the frog's brain and examined *in vitro;* the nerve cells continue to beat electrically just as the heart does (58). Unless large numbers of those neurons are locked in step together, are beating in synchrony, the whole mass of them would give no electrical record, for, being out of phase, their positive and negative changes would counteract each other to give a neutral background. But they

are locked together—they are synchronized, and in varying degrees of goodness. The mechanism of synchronization we think we understand (59, 60); it depends on electric currents that flow through the intercellular fluids between neurons, not on nerve impulses running from cell to cell.

One can demonstrate this in the case of large alga cells, Nitella, which show a similar electrical beat. When several of these are

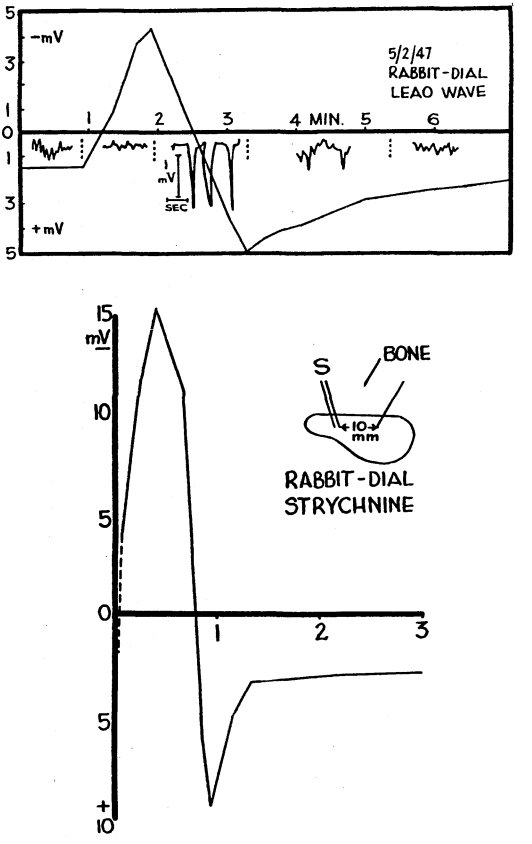

FIG. 1.

dumped on the bottom of a dish, not touching each other, at first each one beats at its own rhythm; soon a couple close together have somehow come into phase and are beating in synchrony. Their joint, and so more powerful, electrical field "captures" additional cells farther away, until finally all the cells in the dish are beating in unison. The more cells that beat together, the harder it is to break it up (61). Discharges from the cut end of a peripheral nerve similarly are at first independent in each fiber; after a while, especially if thresholds are low-

ered chemically, the fibers are firing together, and large waves of impulses ascend the nerve (62, 63). The same thing is true in the retina. The whole retina gives rhythmic beats with diffuse uniform illumination, whereas patterned illumination, which introduces extra impulses irregularly, breaks up the rhythm (64). The alpha rhythm of the human brain is comparably disrupted by light.

Evidence will not be developed here for the importance of steady potentials (D. C. fields), and currents in a volume conductor, for the functioning of neural masses. Such currents can give wave propagation across anatomic discontinuity, such potentials do exist and are considerable, and deliberately altering the potentials can start or stop neuron rhythms (65, 66). Figure 1 shows the striking D.C. potential changes in the mammalian brain associated with strychnine action and with the spread of cortical "suppression." (These records were first presented by my colleague, Dr. B. Libet, (67); they have not previously been published.) The more complete the interlocking of beating neurons, the more difficult it is to disrupt such hypersynchronization—by high potassium, for example, or by applied currents. The same is probably true for incoming out-of-phase impulses.

Thus, I suggest that in the cord, under causalgic conditions, a hypersynchronization, a firmer locking together of a larger than normal number of neurons, has occurred to form a pulsating pool, and that this synchronization has become exaggerated by virtue of the lack of disturbing impulses to disrupt the synchrony and by reinforcement with those specific pain afferents that are feeding in to lock the neurons (just as cortical neurons become locked in their beat by a flickering light). Such a pulsing pool could recruit additional units, could move along in the grey matter, could be maintained by impulses different from and feebler than those needed to initiate it, could discharge excessive and abnormally patterned volleys to the higher centers. In short, such a hypersynchronization could be the physiologic inflammation that would account for the phenomena discussed in this paper.

If this view is correct in principle, it would be worth seeking abnormal electric rhythms and perhaps D.C. potentials in the cords of patients who have causalgia—or of animals rendered causalgic (39). It would also be interesting to attempt to terminate causalgia by disrupting the neuron beat with applied currents, as electroshock is used on the brain. Whether or not such more remote possibilities work out, these physiologic considerations lead to obvious therapeutic suggestions. If the abnormality in the cord neurons is the result of excess activity in pain fibers and subnormal activity in other fibers, then the treatment should be to block the pain fibers combined with stimulation of the normal input. It is most impressive that physiology thus accurately predicts what clinical experience has found; nor is this "wishful explaining," for I was initially quite skeptical of the importance of a normal input. I agree with Dr. Livingston: block pain fibers as need

be, and then superimpose stimuli of the normal afferent systems. Cord depressants, which would tend to unlock the cells, might be therapeutically advantageous, but high potassium would affect the heart too early. Electrotherapy should be explored with caution.

Finally, our knowledge of the nervous system has advanced enormously in the last half century, and the picture of its activity has changed dramatically from that of a static telephone system to that of a far more complex, flexible, mobile, dynamic instrument (22). This change has come about in good part because neurophysiologists have had to consider new phenomena, discovered in many cases in the clinic and by clinical workers, which demanded scientific analysis and interpretation. Such phenomena force the experimentalist and the scientific theoretician into broader and more useful and certainly truer views of the real mechanisms of the nervous system. The clinician who observes carefully and allows himself to think about the meaning of his observations will do a great service to medical science by supplying the experimentalist with valuable stimuli. This is nowhere better illustrated than by the clinical contributions in the field of pain.

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PAIN MECHANISMS: A NEW THEORY

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Pain Mechanisms: A New Theory

A gate control system modulates sensory input from the skin before it evokes pain perception and response.

Ronald Melzack and Patrick D. Wall

The nature of pain has been the ıbject of bitter controversy since the ırn of the century (*1*). There are ırrently two opposing theories of ain: (i) specificity theory, which olds that pain is a specific modality ke vision or hearing, "with its own ɔntral and peripheral apparatus" (*2*), nd (ii) pattern theory, which mainıins that the nerve impulse pattern ɔr pain is produced by intense stimuıtion of nonspecific receptors since here are no specific fibers and no ɔecific endings" (*3*). Both theories deve from earlier concepts proposed by on Frey (*4*) and Goldscheider (*5*) ı 1894, and historically they are held ɔ be mutually exclusive. Since it is ur purpose here to propose a new ıeory of pain mechanisms, we shall ate explicitly at the outset where we gree and disagree with specificity and attern theories.

pecificity Theory

Specificity theory proposes that a ıosaic of specific pain receptors in ody tissue projects to a pain center ı the brain. It maintains that free erve endings are pain receptors (*4*) nd generate pain impulses that are arried by A-delta and C fibers in eripheral nerves (*6*) and by the latral spinothalamic tract in the spinal ɔrd (*2*) to a pain center in the ıalamus (*7*). Despite its apparent mplicity, the theory contains an exlicit statement of physiological specialization and an implicit psychological assumption (*8, 9*). Consider the proposition that the skin contains "pain receptors." To say that a receptor responds only to intense, noxious stimulation of the skin is a physiological statement of fact; it says that the receptor is specialized to respond to a particular kind of stimulus. To call a receptor a "pain receptor," however, is a psychological assumption: it implies a direct connection from the receptor to a brain center where pain is felt (Fig. 1), so that stimulation of the receptor must always elicit pain and only the sensation of pain. This distinction between physiological specialization and psychological assumption also applies to peripheral fibers and central projection systems (*9*).

The facts of physiological specialization provide the power of specificity theory. Its psychological assumption is its weakness. As in all psychological theories, there is implicit in specificity theory the conception of a nervous system; and the model is that of a fixed, direct-line communication system from the skin to the brain. This facet of specificity theory, which imputes a direct, invariant relationship between stimulus and sensation, is examined here in the light of the clinical, psychological, and physiological evidence concerning pain.

Clinical evidence. The pathological pain states of causalgia (a severe burning pain that may result from a partial lesion of a peripheral nerve), phantom limb pain (which may occur after amputation of a limb), and the peripheral neuralgias (which may occur after peripheral nerve infections or degenerative diseases) provide a dramatic refutation of the concept of a fixed, direct-line nervous system. Four features of these syndromes plague patient, physician, and theorist (*8, 10*).

1) Surgical lesions of the peripheral and central nervous system have been singularly unsuccessful in abolishing these pains permanently, although the lesions have been made at almost every level (Fig. 2). Even after such operations, pain can often still be elicited by stimulation below the level of section and may be more severe than before the operation (*8, 10*).

2) Gentle touch, vibration, and other nonnoxious stimuli (*8, 10*) can trigger excruciating pain, and sometimes pain occurs spontaneously for long periods without any apparent stimulus. The fact that the thresholds to these stimuli are raised rather than lowered in causalgia and the neuralgias (*10*), together with the fact that referred pain can often be triggered by mild stimulation of normal skin (*8*), makes it unlikely that the pains can be explained by postulating pathologically hypersensitive "pain receptors."

3) The pains and new "trigger zones" may spread unpredictably to unrelated parts of the body where no pathology exists (*8, 11*).

4) Pain from hyperalgesic skin areas often occurs after long delays, and continues long after removal of the stimulus (*10*). Gentle rubbing, repeated pin pricks, or the application of a warm test tube may produce sudden, severe pain after delays as long as 35 seconds. Such delays cannot be attributed simply to conduction in slowly conducting fibers; rather, they imply a remarkable temporal and spatial summation of inputs in the production of these pain states (*8, 10*).

Psychological evidence. The psychological evidence fails to support the assumption of a one-to-one relation-

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ship between pain perception and intensity of the stimulus. Instead, the evidence suggests that the amount and quality of perceived pain are determined by many psychological variables (*12*) in addition to the sensory input. For example, Beecher (*13*) has observed that most American soldiers wounded at the Anzio beachhead "entirely denied pain from their extensive wounds or had so little that they did not want any medication to relieve it" (*13*, p. 165), presumably because they were overjoyed at having escaped alive from the battlefield (*13*). If the men had felt pain, even pain sensation devoid of negative affect, they would, it is reasonable to assume, have reported it, just as lobotomized patients (*14*) report that they still have pain but it does not bother them. Instead, these men "entirely denied pain." Similarly, Pavlov's (*15, 16*) dogs that received electric shocks, burns, or cuts, followed consistently by the presentation of food, eventually responded to these stimuli as signals for food and failed to show "even the tiniest and most subtle" (*15*, p. 30) signs of pain. If these dogs felt pain sensation, then it must have been nonpainful pain (*17*), or the dogs were out to fool Pavlov and simply refused to reveal that they were feeling pain. Both possibilities, of course, are absurd. The inescapable conclusion from these observations is that intense noxious stimulation can be prevented from producing pain, or may be modified to provide the signal for eating behavior.

Psychophysical studies (*18*) that find a mathematical relationship between stimulus intensity and pain intensity are often cited (*2, 13, 18, 19*) as supporting evidence for the assumption that pain is a primary sensation subserved by a direct communication system from skin receptor to pain center. A simple psychophysical function, however, does not necessarily reflect equally simple neural mechanisms. Beecher's (*13*) and Pavlov's (*15*) observations show that activities in the central nervous system may intervene between stimulus and sensation which may invalidate any simple psychophysical "law." The use of laboratory conditions that prevent such activities from ever coming into play reduces the functions of the nervous system to those of a fixed-gain transmission line. It is under these conditions that psychophysical functions prevail.

Physiological evidence. There is convincing physiological evidence that specialization exists within the somesthetic system (*9*), but none to show that stimulation of one type of receptor, fiber, or spinal pathway elicits sensations only in a single psychological modality. In the search for peripheral fibers that respond exclusively to high-intensity stimulation, Hunt and McIntyre (*20*) found only seven out of 421 myelinated A fibers, and Maruhashi *et al.* (*21*) found 13 out of several hundred. Douglas and Ritchie (*22*) failed to find any high-threshold C fibers, while Iggo (*23*) found a few. These data suggest that a small number of specialized fibers may exist that respond only to intense stimulation, but this does not mean that they are "pain fibers"—that they must always produce pain, and only pain, when they are stimulated. It is more likely that they represent the extreme of a continuous distribution of receptor-fiber thresholds rather than a special category (*24*).

Similarly, there is evidence that central-nervous-system pathways have specialized functions that play a role in pain mechanisms. Surgical lesions of the lateral spinothalamic tract (*2*) or portions of the thalamus (*25*) may, on occasion, abolish pain of pathological origin. But the fact that these areas carry signals related to pain does not mean that they comprise a specific pain system. The lesions have multiple effects. They reduce the total number of responding neurons; they change the temporal and spatial relationships among all ascending systems; and they affect the descending feedback that controls transmission from peripheral fibers to dorsal horn cells.

The nature of the specialization of central cells remains elusive despite the large number of single-cell studies. Cells in the dorsal horns (*24, 26*) and the trigeminal nucleus (*27*) respond to a wide range of stimuli and respond to each with a characteristic firing pattern. Central cells that respond exclusively to noxious stimuli have also been reported (*28, 29*). Of particular interest is Poggio and Mountcastle's (*28*) study of such cells in the posterior thalamus in anesthetized monkeys. Yet Casey (*30*), who has recently confirmed that posterior thalamic cells respond exclusively to noxious stimuli in the drowsy or sleeping monkey, found that the same cells also signaled information in response to gentle tactile stimulation when the animal was awake. Even if some central cells should be shown unequivocally to respond exclusively to noxious stimuli, their specialized properties still do not make them "pain cells." It is more likely that these cells represent the extreme of a broad distribution of cell thresholds to peripheral nerve firing, and that they occupy only a small area within the total multidimensional space that defines the specialized physiological properties of cells (*9*). There is no evidence to suggest that they are more important for pain perception and response than all the remaining somesthetic cells that signal characteristic firing patterns about multiple properties of the stimulus, including noxious intensity. The view that only the cells that respond exclusively to noxious stimuli subserve pain and that the outputs of all other cells are no more than background noise is purely a psychological assumption and has no factual basis. Physiological specialization is a fact that can be retained without acceptance of the psychological assumption that pain is determined entirely by impulses in a straight-through transmission system from the skin to a pain center in the brain.

Fig. 1. Descartes' (*76*) concept of the pain pathway. He writes: "If for example fire (*A*) comes near the foot (*B*), the minute particles of this fire, which as you know move with great velocity, have the power to set in motion the spot of the skin of the foot which they touch, and by this means pulling upon the delicate thread *CC*, which is attached to the spot of the skin, they open up at the same instant the pore, *d.e.*, against which the delicate thread ends, just as by pulling at one end of a rope one makes to strike at the same instant a bell which hangs at the other end."

Pattern Theory

As a reaction against the psychological assumption in specificity theory, new theories have been proposed which can be grouped under the general heading of "pattern theory." Goldscheider (*5*), initially one of the champions of von Frey's theory, was the first to propose that stimulus intensity and central summation are the critical determinants of pain. Two kinds of theories have emerged from Goldscheider's concept; both recognize the concept of patterning of the input, which we believe (*9*) to be essential for any adequate theory of pain, but one kind ignores the facts of physiological specialization, while the other utilizes them in proposing mechanisms of central summation.

The pattern theory of Weddell (*31*) and Sinclair (*3*) is based on the earlier suggestion, by Nafe (*17*), that all cutaneous qualities are produced by spatiotemporal patterns of nerve impulses rather than by separate modality-specific transmission routes. The theory proposes that all fiber endings (apart from those that innervate hair cells) are alike, so that the pattern for pain is produced by intense stimulation of nonspecific receptors. The physiological evidence, however, reveals (*9*) a high degree of receptor-fiber specialization. The pattern theory proposed by Weddell and Sinclair, then, fails as a satisfactory theory of pain because it ignores the facts of physiological specialization. It is more reasonable to assume that the specialized physiological properties of each receptor-fiber unit—such as response ranges, adaptation rates, and thresholds to different stimulus intensities—play an important role in determining the characteristics of the temporal patterns that are generated when a stimulus is applied to the skin (*9*).

Other theories have been proposed, within the framework of Goldscheider's concept, which stress central summation mechanisms rather than excessive peripheral stimulation. Livingston (*8*) was perhaps the first to suggest specific neural mechanisms to account for the remarkable summation phenomena in clinical pain syndromes. He proposed that intense, pathological stimulation of the body sets up reverberating circuits in spinal interneuncial pools, or evokes spinal cord activities such as those reflected by the "dorsal root reflex" (*32*), that can then be triggered by normally nonnoxious inputs and generate abnormal volleys that are interpreted centrally as pain. Conceptually similar mechanisms were proposed by Hebb (*33*) and Gerard (*34*), who suggested that hypersynchronized firing in central cells provides the signal for pain.

Related to theories of central summation is the theory that a specialized input-controlling system normally prevents summation from occurring, and that destruction of this system leads to pathological pain states. Basically, this theory proposes the existence of a rapidly conducting fiber system which

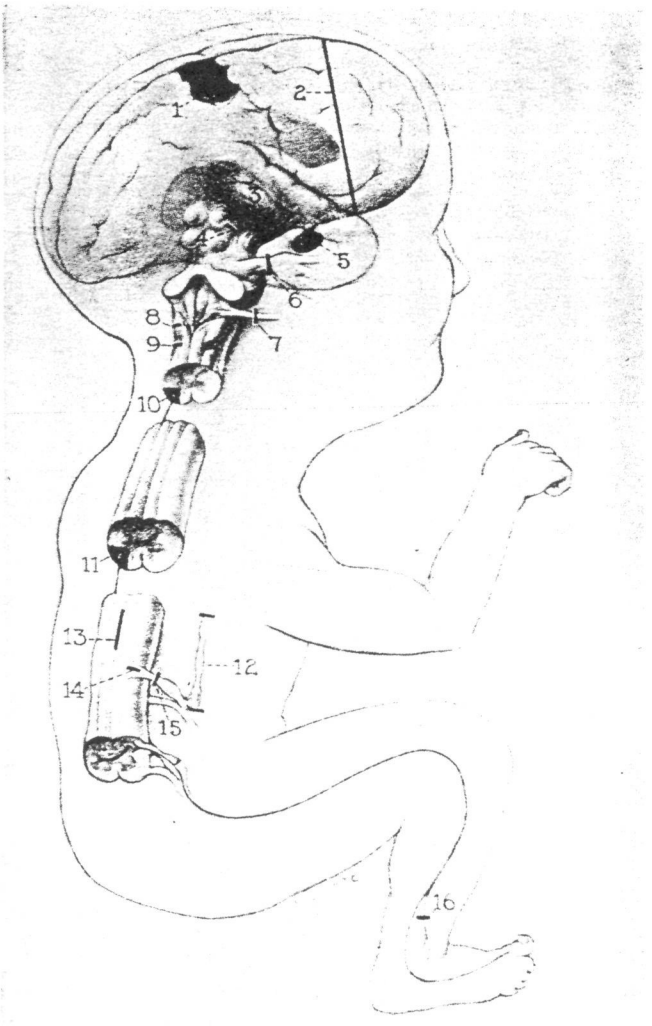

Fig. 2. MacCarty and Drake's (*77*) schematic diagram illustrating various surgical procedures designed to alleviate pain: 1, gyrectomy; 2, prefrontal lobotomy; 3, thalamotomy; 4, mesencephalic tractotomy; 5, hypophysectomy; 6, fifth-nerve rhizotomy; 7, ninth-nerve neurectomy; 8, medullary tractotomy; 9, trigeminal tractotomy; 10, cervical chordotomy; 11, thoracic chordotomy; 12, sympathectomy; 13, myelotomy; 14, Lissauer tractotomy; 15, posterior rhizotomy; 16, neurectomy.

inhibits synaptic transmission in a more slowly conducting system that carries the signal for pain. These two systems are identified as the epicritic and protopathic (*7*), fast and slow (*35*), phylogenetically new and old (*36*), and myelinated and unmyelinated (*10*) fiber systems. Under pathological conditions, the slow system establishes dominance over the fast, and the result is protopathic sensation (*7*), slow pain (*35*), diffuse burning pain (*36*), or hyperalgesia (*10*). It is important to note the transition from specificity theory (*7, 35, 36*) to the pattern concept: Noordenbos (*10*) does not associate psychological quality with each system but attributes to the rapidly conducting system the ability to modify the input pattern transmitted in the slowly conducting, multisynaptic system.

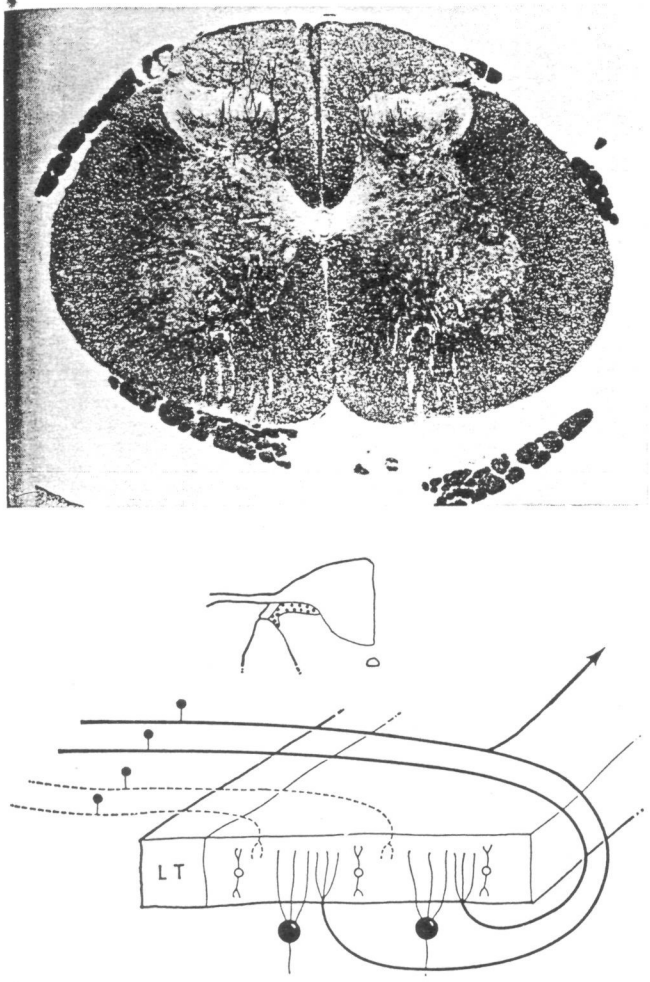

Fig. 3. (Top) A histological section of the cat spinal cord (lumbar region). (Middle) Cross section of the dorsal quadrant. The stippled region is the substantia gelatinosa. (Bottom) Main components of the cutaneous afferent system in the upper dorsal horn. The large-diameter cutaneous peripheral fibers are represented by thick lines running from the dorsal root and terminating in the region of the substantia gelatinosa; one of these, as shown, sends a branch toward the brain in the dorsal column. The finer peripheral fibers are represented by dashed lines running directly into the substantia gelatinosa. The large cells, on which cutaneous afferent nerves terminate, are shown as large black spheres with their dendrites extending into the substantia gelatinosa and their axons projecting deeper into the dorsal horn. The open circles represent the cells of the substantia gelatinosa. The axons (not shown) of these cells connect them to one another and also run in the Lissauer tract (*LT*) to distant parts of the substantia gelatinosa. From Wall (*37*)]

The concepts of central summation and input control have shown remarkable power in their ability to explain many of the clinical phenomena of pain. The various specific theoretical mechanisms that have been proposed, however, fail to comprise a satisfactory general theory of pain. They lack unity, and no single theory so far proposed is capable of integrating the diverse theoretical mechanisms. More important, these mechanisms have not received any substantial experimental verification. We believe that recent physiological evidence on spinal mechanisms, together with the evidence demonstrating central control over afferent input, provides the basis for a new theory of pain mechanisms that is consistent with the concepts of physiological specialization as well as with those of central summation and input control.

Gate Control Theory of Pain

Stimulation of the skin evokes nerve impulses that are transmitted to three spinal cord systems (Fig. 3): the cells of the substantia gelatinosa in the dorsal horn, the dorsal-column fibers that project toward the brain, and the first central transmission (T) cells in the dorsal horn. We propose that (i) the substantia gelatinosa functions as a gate control system that modulates the afferent patterns before they influence the T cells; (ii) the afferent patterns in the dorsal column system act, in part at least, as a central control trigger which activates selective brain processes that influence the modulating properties of the gate control system; and (iii) the T cells activate neural mechanisms which comprise the action system responsible for response and perception. Our theory proposes that pain phenomena are determined by interactions among these three systems.

Gate control system. The substantia gelatinosa consists of small, densely packed cells that form a functional unit extending the length of the spinal

cord. The cells connect with one another by short fibers and by the longer fibers of Lissauer's tract (*37, 38*), but do not project outside the substantia gelatinosa. Recent evidence (*39*) suggests that the substantia gelatinosa acts as a gate control system that modulates the synaptic transmission of nerve impulses from peripheral fibers to central cells.

Figure 4 shows the factors involved in the transmission of impulses from peripheral nerve to T cells in the cord. Recent studies (*39–41*) have shown that volleys of nerve impulses in large fibers are extremely effective initially in activating the T cells but that their later effect is reduced by a negative feedback mechanism. In contrast, volleys in small fibers activate a positive feedback mechanism which exaggerates the effect of arriving impulses. Experiments (*37, 39, 41*) have shown that these feedback effects are mediated by cells in the substantia gelatinosa. Activity in these cells modulates the membrane potential of the afferent fiber terminals and thereby determines the excitatory effect of arriving impulses. Although there is evidence, so far, for only presynaptic control, there may also be undetected postsynaptic control mechanisms that contribute to the observed input-output functions.

We propose that three features of the afferent input are significant for pain: (i) the ongoing activity which precedes the stimulus, (ii) the stimulus-evoked activity, and (iii) the relative balance of activity in large versus small fibers. The spinal cord is continually bombarded by incoming nerve impulses even in the absence of obvious stimulation. This ongoing activity is carried predominantly by small myelinated and unmyelinated fibers, which tend to be tonically active and to adapt slowly, and it holds the gate in a relatively open position. When a stimulus is applied to the skin, it produces an increase in the number of active receptor-fiber units as information about the stimulus is transmitted toward the brain. Since many of the larger fibers are inactive in the absence of stimulus change, stimulation will produce a disproportionate relative increase in large-fiber over small-fiber activity. Thus, if a gentle pressure stimulus is applied suddenly to the skin, the afferent volley contains large-fiber impulses which not only fire the T cells but also partially close the presynaptic gate, thereby shortening the barrage generated by the T cells.

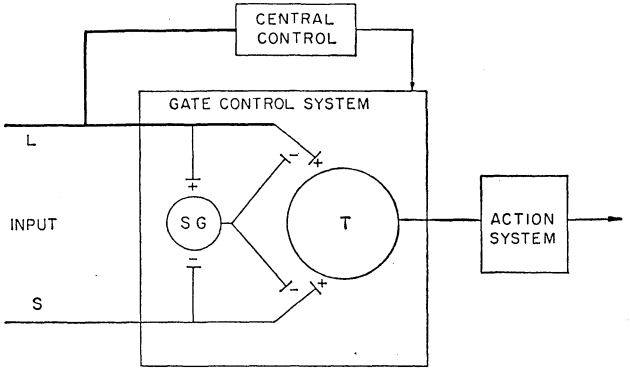

Fig. 4. Schematic diagram of the gate control theory of pain mechanisms: *L*, the large-diameter fibers; *S*, the small-diameter fibers. The fibers project to the substantia gelatinosa (*SG*) and first central transmission (*T*) cells. The inhibitory effect exerted by *SG* on the afferent fiber terminals is increased by activity in *L* fibers and decreased by activity in *S* fibers. The central control trigger is represented by a line running from the large-fiber system to the central control mechanisms; these mechanisms, in turn, project back to the gate control system. The T cells project to the entry cells of the action system. +, Excitation; −, inhibition (see text).

If the stimulus intensity is increased, more receptor-fiber units are recruited and the firing frequency of active units is increased (*9, 24*). The resultant positive and negative effects of the large-fiber and small-fiber inputs tend to counteract each other, and therefore the output of the T cells rises slowly. If stimulation is prolonged, the large fibers begin to adapt, producing a relative increase in small-fiber activity. As a result, the gate is opened further, and the output of the T cells rises more steeply. If the large-fiber steady background activity is artificially raised at this time by vibration or scratching (a maneuver that overcomes the tendency of the large fibers to adapt), the output of the cells decreases.

Thus, the effects of the stimulus-evoked barrage are determined by (i) the total number of active fibers and the frequencies of nerve impulses that they transmit, and (ii) the balance of activity in large and small fibers. Consequently, the output of the T cells may differ from the total input that converges on them from the peripheral fibers. Although the total number of afferent impulses is a relevant stimulus parameter, the impulses have different effects depending on the specialized functions of the fibers that carry them. Furthermore, anatomical specialization also determines the location and the extent of the central terminations of the fibers (*24, 41, 42*).

There are two reasons for believing that pain results after prolonged monitoring of the afferent input by central cells. First, threshold for shock on one arm is raised by a shock delivered as long as 100 milliseconds later to the other arm (*43*). Second, in pathological pain states, delays of pain sensation as long as 35 seconds after stimulation cannot be attributed to slow conduction in afferent pathways (*10*). We suggest, then, that there is temporal and spatial summation or integration of the arriving barrage by the T cells. The signal which triggers the action system responsible for pain experience and response occurs when the output of the T cells reaches or exceeds a critical level. This critical level of firing, as we have seen, is determined by the afferent barrage that actually impinges on the T cells and has already undergone modulation by substantia gelatinosa activity. We presume that the action system requires a definite time period for integrating the total input from the T cells. Small, fast variations of the temporal pattern produced by the T cells might be ineffective, and the smoothed envelope of the frequency of impulses—which contains information on the rate of rise and fall, the duration, and the amplitude of firing—would be the effective stimulus that initiates the appropriate sequence of activities in the cells that comprise the action system.

Central control trigger. It is now firmly established (*44*) that stimula-

tion of the brain activates descending efferent fibers (*45*) which can influence afferent conduction at the earliest synaptic levels of the somesthetic system. Thus it is possible for central nervous system activities subserving attention, emotion, and memories of prior experience to exert control over the sensory input. There is evidence (*44*) to suggest that these central influences are mediated through the gate control system.

The manner in which the appropriate central activities are triggered into action presents a problem. While some central activities, such as anxiety or excitement, may open or close the gate for all inputs at any site on the body, others obviously involve selective, localized gate activity. Men wounded in battle may feel little pain from the wound but may complain bitterly about an inept vein puncture (*13*). Dogs that repeatedly receive food immediately after the skin is shocked, burned, or cut soon respond to these stimuli as signals for food and salivate, without showing any signs of pain, yet howl as normal dogs would when the stimuli are applied to other sites on the body (*16*). The signals, then, must be identified, evaluated in terms of prior conditioning, localized, and inhibited *before* the action system is activated. We propose, therefore, that there exists in the nervous system a mechanism, which we shall call the central control trigger, that activates the particular, selective brain processes that exert control over the sensory input (Fig. 4). There are two known systems that could fulfill such a function, and one or both may play a role.

The first is the dorsal column–medial lemniscus system. The largest and most rapidly conducting A fibers which enter the spinal cord send short branches to the substantia gelatinosa, and long central branches directly to the dorsal column nuclei. Fibers from these nuclei form the medial lemniscus, which provides a direct route to the thalamus and thence to the somatosensory cortex. The striking characteristics of this system are that information is transmitted rapidly from the skin to the cortex, that separation of signals evoked by different stimulus properties and precise somatotopic localization are both maintained throughout the system (*46*), and that conduction is relatively unaffected by anesthetic drugs (*47*). Traditionally, the dorsal column system is supposed to carry two-point discrimination, roughness discrimination, spatial localization, tactile threshold, and vibration (*48*). Complex discrimination and localization, however, are not a modality; they represent decisions based on an analysis of the input. Indeed, the traditional view is questionable in the light of Cook and Browder's (*49*) observation that surgical section of the dorsal columns produced no permanent change in two-point discrimination in seven patients.

The second candidate for the role of central control trigger is the dorsolateral path (*50*), which originates in the dorsal horn and projects, after relay in the lateral cervical nucleus, to the brain stem and thalamus. This system has small, well-defined receptive fields (*51*) and is extremely fast; in spite of having one additional relay, it precedes the dorsal column–medial lemniscus volley in the race to the cortex (*52*).

Both these systems, then, could fulfill the functions of the central control trigger. They carry precise information about the nature and location of the stimulus, and they conduct so rapidly that they may not only set the receptivity of cortical neurons for subsequent afferent volleys but may, by way of central-control efferent fibers, also act on the gate control system. Part, at least, of their function, then, could be to activate selective brain processes that influence information which is still arriving over slowly conducting fibers or is being transmitted up more slowly conducting pathways.

Action system. Pain is generally considered to be the sensory adjunct of an imperative protective reflex (*53*). Pain, however, does not consist of a single ring of the appropriate central bell, but is an ongoing process. We propose, then, that once the integrated firing-level of T cells exceeds a critical preset level, the firing triggers a sequence of responses by the action system.

Sudden, unexpected damage to the skin is followed by (i) a startle response; (ii) a flexion reflex; (iii) postural readjustment; (iv) vocalization; (v) orientation of the head and eyes to examine the damaged area; (vi) autonomic responses; (vii) evocation of past experience in similar situations and prediction of the consequences of the stimulation; (viii) many other patterns of behavior aimed at diminishing the sensory and affective components of the whole experience such as rubbing the damaged area, avoidance behavior, and so forth.

The perceptual awareness that accompanies these events changes in quality and intensity during all this activity. This total complex sequence is hidden in the simple phrases "pain response" and "pain sensation." The multiplicity of reactions demands some concept of central mechanisms which is at least capable of accounting for sequential patterns of activity that would allow the complex behavior and experience characteristic of pain.

The concept of a "pain center" in the brain is totally inadequate to account for the sequences of behavior and experience. Indeed, the concept is pure fiction, unless virtually the whole brain is considered to be the "pain center," because the thalamus (*7, 25*), the limbic system (*54*), the hypothalamus (*55*), the brain-stem reticular formation (*56*), the parietal cortex (*57*), and the frontal cortex (*14*) are all implicated in pain perception. Other brain areas are obviously involved in the emotional and motor features of the behavior sequence. The idea of a "terminal center" in the brain which is exclusively responsible for pain sensation and response therefore becomes meaningless.

We propose, instead, that the triggering of the action system by the T cells marks the beginning of the sequence of activities that occur when the body sustains damage. The divergence of afferent fibers going to the dorsal horns and the dorsal column nuclei marks only the first stage of the process of selection and abstraction of information. The stimulation of a single tooth results in the eventual activation of no less than five distinct brain-stem pathways (*58*). Two of these pathways project to cortical somatosensory areas I and II (*59*), while the remainder activate the thalamic reticular formation and the limbic system (*60*), so that the input has access to neural systems involved in affective (*54*) as well as sensory activities. It is presumed that interactions occur among all these systems as the organism interacts with the environment.

We believe that the interactions between the gate control system and the action system described above may occur at successive synapses at any level of the central nervous system in the course of filtering of the sensory input.

Similarly, the influence of central activities on the sensory input may take place at a series of levels. The gate control system may be set and reset a number of times as the temporal and spatial patterning of the input is analyzed and acted on by the brain.

Adequacy of the Theory

The concept of interacting gate control and action systems can account for the hyperalgesia, spontaneous pain, and long delays after stimulation characteristic of pathological pain syndromes. The state of hyperalgesia would require two conditions: (i) enough conducting peripheral axons to generate an input that can activate the action system (if, as in the case of leprosy, all components of the peripheral nerve are equally affected, there is a gradual onset of anesthesia), and (ii) a marked loss of the large peripheral nerve fibers, which may occur after traumatic peripheral-nerve lesions or in some of the neuropathies (*61*), such as post-herpetic neuralgia (*10*). Since most of the larger fibers are destroyed, the normal presynaptic inhibition of the input by the gate control system does not occur. Thus, the input arriving over the remaining myelinated and unmyelinated fibers is transmitted through the unchecked, open gate produced by the C-fiber input.

Spatial summation would easily occur under such conditions. Any nerve impulses, no matter how they were generated, which converge on the central cells would contribute to the output of these cells. These mechanisms may account for the fact that non-noxious stimuli, such as gentle pressure, can trigger severe pain in patients suffering causalgia, phantom limb pain, and the neuralgias. The well-known enhancement of pain in these patients during emotional disturbance and sexual excitement (*62*) might be due to increased sensory firing [as a result of an increased sympathetic outflow (*63, 64*)] which is unchecked by presynaptic inhibition. Conversely, the absence of small fibers in the dorsal roots in a patient with congenital insensitivity to pain (*65*) suggests that the mechanisms for facilitation and summation necessary for pain may be absent.

Spontaneous pain can also be explained by these mechanisms. The smaller fibers show considerable spontaneous activity, which would have the effect of keeping the gate open. Low-level, random, ongoing activity would then be transmitted relatively unchecked (because of the predominant loss of A fibers), and summation could occur, producing spontaneous pain in the absence of stimulation. This is a possible mechanism for the pains of anesthesia dolorosa and the "spontaneous" pains which develop after peripheral-nerve and dorsal-root lesions. Because the total number of peripheral fibers is reduced, it may take considerable time for the T cells to reach the firing level necessary to trigger pain responses, so perception and response are delayed. This same mechanism can also account for post-ischemic pressure-block hyperesthesia and for the delays in sensation of as much as 10 seconds which occur when the large peripheral fibers fail to conduct (*66*).

We propose that the A-fiber input normally acts to prevent summation from occurring. This would account for Adrian's (*67*) failure to obtain pain responses in the frog from high-frequency air blasts which fired peripheral nerves close to their maximum firing rate, in an experiment meant to refute the view that summation of the effects of noxious stimuli is important for pain. It is now clear that the air blasts would tend to fire a high proportion of the low-threshold A fibers, which would exert presynaptic inhibition on the input by way of the gate control system; thus the impulses would be prevented from reaching the T cells where summation might occur. The double effect of an arriving volley is well illustrated by the effects of vibration on pain and itch. Vibration activates fibers of all diameters, but activates a larger proportion of A fibers, since they tend to adapt during constant stimulation, whereas C-fiber firing is maintained. Vibration therefore sets the gate in a more closed position. However, the same impulses which set the gate also bombard the T cell and therefore summate with the inputs from noxious stimulation. It is observed behaviorally (*26, 68*) that vibration reduces low-intensity, but enhances high-intensity, pain and itch. Similar mechanisms may account for the fact that amputees sometimes obtain relief from phantom limb pain by tapping the stump gently with a rubber mallet (*69*), whereas heavier pressure aggravates the pain (*8*).

The phenomena of referred pain, spread of pain, and trigger points at some distance from the original site of body damage also point toward summation mechanisms, which can be understood in terms of the model. The T cell has a restricted receptive field which dominates its "normal activities." In addition, there is a widespread, diffuse, monosynaptic input to the cell, which is revealed by electrical stimulation of distant afferents (*41*). We suggest that this diffuse input is normally inhibited by presynaptic gate mechanisms, but may trigger firing in the cell if the input is sufficiently intense or if there is a change in gate activity. Because the cell remains dominated by its receptive field, anesthesia of the area to which the pain is referred, from which only spontaneous impulses are originating, is sufficient to reduce the bombardment of the cell below the threshold level for pain. The gate can also be opened by activities in distant body areas, since the substantia gelatinosa at any level receives inputs from both sides of the body and (by way of Lissauer's tract) from the substantia gelatinosa in neighboring body segments. Mechanisms such as these may explain the observations that stimulation of trigger points on the chest and arms may trigger anginal pain (*70*), or that pressing other body areas, such as the back of the head, may trigger pain in the phantom limb (*11*).

The sensory mechanisms alone fail to account for the fact that nerve lesions do not always produce pain and that, when they do, the pain is usually not continuous. We propose that the presence or absence of pain is determined by the balance between the sensory and the central inputs to the gate control system. In addition to the sensory influences on the gate control system, there is a tonic input to the system from higher levels of the central nervous system which exerts an inhibitory effect on the sensory input (*44, 71*). Thus, any lesion that impairs the normal downflow of impulses to the gate control system would open the gate. Central nervous system lesions associated with hyperalgesia and spontaneous pain (*7*) could have this effect. On the other hand, any central nervous system condition that increases the flow of descending impulses would tend to close the gate. Increased central firing due to denervation supersensitivity (*72*) might be one of these conditions. A peripheral nerve lesion, then,

would have the *direct* effect of opening the gate, and the *indirect* effect, by increasing central firing and thereby increasing the tonic descending influences on the gate control system, of closing the gate. The balance between sensory facilitation and central inhibition of the input after peripheral-nerve lesion would account for the variability of pain even in cases of severe lesion.

The model suggests that psychological factors such as past experience, attention, and emotion influence pain response and perception by acting on the gate control system. The degree of central control, however, would be determined, in part at least, by the temporal-spatial properties of the input patterns. Some of the most unbearable pains, such as cardiac pain, rise so rapidly in intensity that the patient is unable to achieve any control over them. On the other hand, more slowly rising temporal patterns are susceptible to central control and may allow the patient to "think about something else" or use other stratagems to keep the pain under control (*73*).

The therapeutic implications of the model are twofold. First, it suggests that control of pain may be achieved by selectively influencing the large, rapidly conducting fibers. The gate may be closed by decreasing the small-fiber input and also by enhancing the large-fiber input. Thus, Livingston (*74*) found that causalgia could be effectively cured by therapy such as bathing the limb in gently moving water, followed by massage, which would increase the input in the large-fiber system. Similarly, Trent (*75*) reports a case of pain of central nervous system origin which could be brought under control when the patient tapped his fingers on a hard surface. Conversely, any manipulation that cuts down the sensory input lessens the opportunity for summation and pain, within the functional limits set by the opposing roles of the large- and small-fiber systems. Second, the model suggests that a better understanding of the pharmacology and physiology of the substantia gelatinosa may lead to new ways of controlling pain. The resistance of the substantia gelatinosa to nerve-cell stains suggests that its chemistry differs from that of other neural tissue. Drugs affecting excitation or inhibition of substantia gelatinosa activity may be of particular importance in future attempts to control pain.

The model suggests that the action system responsible for pain perception and response is triggered after the cutaneous sensory input has been modulated by both sensory feedback mechanisms and the influences of the central nervous system. We propose that the abstraction of information at the first synapse may mark only the beginning of a continuing selection and filtering of the input. Perception and response involve classification of the multitude of patterns of nerve impulses arriving from the skin and are functions of the capacity of the brain to select and to abstract from all the information it receives from the somesthetic system as a whole (*7–9*). A "modality" class such as "pain," which is a linguistic label for a rich variety of experiences and responses, represents just such an abstraction from the information that is sequentially reexamined over long periods by the entire somesthetic system.

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ENDOGENOUS PAIN CONTROL SYSTEMS:

BRAINSTEM SPINAL PATHWAYS AND ENDORPHIN CIRCUITRY

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ENDOGENOUS PAIN CONTROL SYSTEMS: Brainstem Spinal Pathways and Endorphin Circuitry

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INTRODUCTION

In 1978, we published two reviews on pain control mechanisms in the central nervous system. One concentrated on brainstem control of spinal nociceptive neurons (Fields & Basbaum 1978). The other focused on those pain control systems which use endogenous opioid compounds and presumably mediate the analgesic action of exogenous opiate analgesics (Basbaum & Fields 1978). Since those reviews were published, information in both areas has grown rapidly. For example, it is now known that there are at least three families of endogenous opioid peptides (endorphins), each having a different precursor and a differential distribution in the CNS. In addition, knowledge of the immunohistochemistry and pharmacology of the brainstem and spinal neurons involved in pain transmission and modulation has expanded. Finally, much more is known about the circuitry underlying both the transmission and control of pain. These new observations make revisions necessary in the mechanisms proposed to account for the analgesic action of exogenous opiates and electrical brain stimulation. In this paper we review the new information, concentrating on those studies that necessitate changes in the original model.[1]

[1]Abbreviations: BAM, bovine adrenal medulla; CSF, cerebrospinal fluid; DLF, dorsal part of the lateral funiculus; GABA, gamma aminobutyric acid; MSH, melanocyte stimulating hormone; NRM, n. raphe magnus; PAG, periaqueductal gray; pCPA, parachlorophenylalanine; POMC, proopiomelanocortin; Pro A, Proenkephalin A; Rgc, n. reticularis gigantocellularis; Rgcα, n. reticularis gigantocellularis, pars alpha; Rmc, n. reticularis magnocellularis; Rpg, n. reticularis paragigantocellularis; Rpgl, n. reticularis paragigantocellularis lateralis; RVM, rostral ventral medulla; SG, substantia gelatinosa; SIA, stress-induced analgesia; SP, Substance P; SPA, stimulation-produced analgesia; TRH, thyrotropin releasing hormone; VIP, vasoactive intestinal polypeptide; II_i, inner layer of the substantia gelatinosa; II_o, outer layer of the substantia gelatinosa; 5HT, 5-hydroxytryptamine, serotonin.

THE PREVIOUS MODEL OF BULBOSPINAL CONTROL

The original model outlined a three-tiered pain control system (Basbaum & Fields 1978). Its major components included the midbrain periaqueductal gray (PAG), several nuclei of the rostral ventral medulla (RVM), specifically the midline nucleus raphe magnus (NRM) and adjacent reticular nuclei, and the spinal dorsal horn. We proposed the following. The analgesic action of opiates given systemically, or via intracerebral injection into the PAG, results from activation of excitatory connections between the PAG and the raphe. Raphe neurons, in turn, project, via a pathway in the dorsal part of the lateral funiculus (DLF) of the spinal cord (Basbaum et al 1978, Basbaum & Fields 1979) to the region of nociceptors in the spinal dorsal horn, and its trigeminal equivalent, the nucleus caudalis. These raphe-spinal neurons selectively inhibit dorsal horn nociceptive neurons, including interneurons (Fields et al 1977) and a population of rostrally projecting spinothalamic and spinoreticular neurons (Willis et al 1977).

The original model proposed major endorphin links at the level of the PAG and spinal cord. The PAG contains both high affinity opiate binding sites (Atweh & Kuhar 1977b) and significant levels of endogenous opioid peptides (Hökfelt et al 1977, Moss et al 1983). More important, injection of the specific opiate antagonist, naloxone, into the PAG (Tsou & Jang 1964, Yeung & Rudy 1978) or the third ventricle (Yeung & Rudy 1980) reverses the analgesic action of systemic opiates, and microinjection of opiates into the PAG generates analgesia that is reversed by lesions of the spinal dorsolateral funiculus (Murfin et al 1976). Thus, exogenous opiates "substitute" for the endogenous opioid peptide, thereby activating pain control circuits that originate in the PAG. A second endorphin component in this descending pain control model is in the spinal dorsal horn. This region also has high levels of immunoreactive enkephalin (Hökfelt et al 1977, Glazer & Basbaum 1981) and opiate binding sites (Atweh & Kuhar 1977b, LaMotte et al 1976). Furthermore, there is now evidence that descending serotonergic raphe-spinal axons exert their antinociceptive effects, in part, via synapses with opioid peptide-containing neurons of the dorsal horn. First, intrathecal injection of naloxone can antagonize the analgesic action of raphe stimulation (Zorman et al 1982); second, using a method to localize tritiated serotonin and immunoreactive enkephalin simultaneously at the ultrastructural level, we demonstrated that the terminals of descending 5HT axons are presynaptic to enkephalin-containing neurons of the spinal dorsal horn (Basbaum et al 1982, Glazer et al 1981, 1983b).

In addition to 5HT and enkephalin links, the original model included descending catecholamine systems, thought to originate in the dorsolateral pons, and a pharmacologically undefined descending system originating in the nucleus reticularis magnocellularis (Rmc) located lateral to the raphe. As de-

scribed below, additional bulbospinal systems have now been identified and the contribution of the catecholamines is known to be more complicated than originally proposed.

Although exogenous opiates or electrical brain stimulation can activate this endorphin-mediated pain control system, the factors that naturally activate the system are poorly understood. Taking into account the evidence that "pain inhibits pain" (Melzack 1975) and the consistent observations that noxious stimuli activate raphe spinal neurons (Anderson et al 1977, Guilbaud et al 1980), we proposed that pain, itself, is a critical factor that reliably activates these pain control circuits. It is now clear that a variety of behavioral contingencies affect the operation of this system. These we describe below.

THE ENDORPHINS

Information about the endorphins was limited when our earlier reviews were written. Although leucine and methionine enkephalin and β-endorphin had been isolated from brain and pituitary, respectively, their precursors were unknown. Recently, attention has focused on another class of endorphins, specifically dynorphin and related opioid peptides (Goldstein et al 1979, 1981). Thus, the enkephalins, dynorphin and β-endorphin, represent three distinct families of endogenous opioid peptides (Hollt 1983) (Table 1). Each class is cleaved from a different precursor and each has a distinct anatomical distribution. Our discussion of the endorphins highlights those aspects relevant to pain control. (See also Akil et al 1984, this volume.)

β-Endorphin

β-endorphin, ACTH, and three copies of melanocyte-stimulating hormone (MSH) are derived from a common precursor molecule, proopiomelanocortin (POMC) (Mains et al 1977, Roberts & Herbert 1977). Unlike the enkephalins and dynorphin, which are widely distributed in the brain, POMC-neurons are concentrated in the basal hypothalamus (Bloom et al 1978). Axons of these cells course caudally along the wall of the third ventricle, toward the midbrain PAG and locus coeruleus. The possibility has been raised that stimulation-produced analgesia from electrodes placed in the midbrain PAG, rather than arising from activation of cell somata within the PAG, results from activation of the axons of β-endorphin neurons that pass through the PAG. This possibility has not been ruled out; however, the fact that glutamate injection in the PAG (which would not activate axons of passage) can generate analgesia (Behbehani & Fields 1979) indicates that local cells can activate the system. On the other hand, increases in cerebrospinal fluid (CSF) β-endorphin after brain stimulation in humans are consistent with a contribution of this peptide to pain control (Akil et al 1978, Hosobuchi et al 1979). That the CSF levels reflect changes

TABLE 1 Amino acid sequences of major endogenous opioid peptides

Leucine-enkephalin	Try-gly-gly-phe-leu-oH
Methionine-enkephalin	Try-gly-gly-phe-met-oH
β-Endorphin	Try-gly-gly-phe-met-thr-ser-glu-lys-ser-gln-thr-pro-leu-val-thr-leu-phe-lys-asn-ala-ile-val-lys-asn-ala-his-lys-gly-gln-oH
Dynorphin A	Try-gly-gly-phe-leu-arg-arg-ile-arg-pro-lys-leu-lys-try-asp-asn-gln-oH
Dynorphin B	Try-gly-gly-phe-leu-arg-arg-gln-phe-lys-val-thr
α-Neoendorphin	Try-gly-gly-phe-leu-arg-lys-try-pro-lys

resulting from the "stress" of surgery must, however, also be considered (R. H. Gracely and R. Dubner, personal communication).

Whether pituitary β-endorphin plays any role in descending pain control remains a mystery. While it is possible that pituitary β-endorphin can enter the brain via retrograde flow in the portal system, this has not been demonstrated. Systemically administered β-endorphin has been recovered in spinal CSF (Houghten et al 1980); however, the quantities were exceedingly low and probably insufficient to have significant biological effects. Moreover, since 96% of intermediate lobe β-endorphin is acetylated and thus inactive as an analgesic, it is even more difficult to assess its contribution. On the other hand, the report that hypophysectomy can interfere with certain forms of stress-generated analgesia (see below) indicates that pituitary endorphins may contribute to pain control.

Finally, recent studies have demonstrated interactions between the different peptides derived from POMC. Antagonism between ACTH and β-endorphin is the most frequently reported interaction. Thus, for example, intraventricular (Smock & Fields 1980) or intrathecal (Belcher et al 1982) microinjection of ACTH can antagonize morphine or β-endorphin induced analgesia. Intraventricular injection of ACTH, however, has been reported to generate analgesia (Walker et al 1981). These data indicate that cosynthesis and release of β-endorphin and ACTH may interact physiologically at CNS synapses. Furthermore, the action of ACTH in the cord raises the possibility that CSF β-endorphin and ACTH, released by hypothalamic neurons, may reach the cord via the CSF and influence spinal nociceptors directly.

Enkephalin and Dynorphin

The discovery of the enkephalin precursor molecule Pro-enkephalin A (ProENK A) has generated renewed focus on the first opioid peptides that were described. ProENK A was originally isolated from the adrenal medulla (Kimura et al 1980), but is also found in brain. Probable cleavage products of the ProENK A molecule include six copies of met-enkephalin and one copy of

leu-enkephalin (Comb et al 1982, Gubler et al 1982). Two of the met-enkephalin sequences are extended and include the octapeptide, met-enkephalin-arg-gly-leu, and the heptapeptide, met-enkephalin-arg-phe. Other larger cleavage products have also been identified. That the enkephalins and the dynorphin-related peptides are different was unequivocally established with the identification of the prodynorphin molecule, from which dynorphin and two other peptides with *N*-terminal leucine enkephalin residues, alpha-neo-endorphin and dynorphin-B, are cleaved (Kakidani et al 1982).

The possible functional significance of the different enkephalin fragments to pain control has been recently demonstrated by Hollt et al (1982). They found that while the short enkephalin-containing cleavage products of ProENK A are very weak or inactive as analgesics, significant analgesia is produced by intracerebral injection of the larger products isolated from bovine adrenal medulla, BAM 12 and 22, and Peptides E and F. In fact, on a molar basis, these ProENK A derived peptides are somewhat more potent than morphine, but still significantly less potent than β-endorphin. In contrast to the larger ProENK A cleavage products and β-endorphin, intracerebral injection of prodynorphin-cleavage peptides had no analgesic effect. On the other hand, other studies indicate an analgesic effect of spinally administered dynorphin (see below).

The majority, if not all, of studies that have examined the distribution of immunoreactive enkephalin (leu or met) did not examine for cross-reactivity of antibodies with the prodynorphin peptides (for review see Miller 1981). It is thus possible that much of what was described is actually dynorphin or alpha-neo-endorphin. Fortunately, using antibodies directed against those sequences of proENK A and prodynorphin that differ, it is now possible to stain selectively for immunoreactive enkephalin and dynorphin (Watson et al 1982, Weber et al 1982). The distribution of the two compounds is similar. However, in some areas significant differences are found. For example, the substantia nigra has very high levels of dynorphin and very low enkephalin; the opposite is found in the interpeduncular nucleus (a gift of Dr. E. Weber).

We have also used selective antisera to examine the distribution of dynorphin and enkephalin (Basbaum et al 1983a). One antibody was directed against the met-enk-arg-gly-leu peptide of the proENK A molecule; it has no cross-reactivity with any of the prodynorphin peptides. To define dynorphin-like immunoreactivity, we used an antiserum directed against the prodyn C-terminal leu-enk-containing peptide, i.e. Dynorphin B. This antiserum does not cross-react with proENK A products. We focused our attention on "pain" related areas.

In agreement with previous studies we found significant overlap of immunoreactive enkephalin and dynorphin; however, there are some important differences. Both enkephalin- and dynorphin-positive cells and terminals are found in the PAG. In general, however, the dynorphin-positive cells are

located more ventrally. Since β-endorphin terminals are also found in the PAG, these data indicate that the endorphin link in the periaqueductal gray could result from release of any, or all, of the opioid peptides found there.

Analysis of immunoreactive dyn and enk in the rostral medulla also proved interesting. We had previously reported that some 5HT-containing neurons in the raphe magnus, pallidus, and adjacent nucleus reticularis paragigantocellularis lateralis (Rpgl) also contain immunoreactive enk (Glazer et al 1981). In the present study, we examined serial three-micron frozen sections of the medulla of the rat, for dynorphin, enkephalin, and 5HT. We found that not only are there 5HT/enkephalin neurons, but there are separate 5HT/dynorphin neurons. In general, there are more enkephalin than dynorphin immunoreactive neurons in the medulla. While the majority of cells stain for one or the other opioid peptide, in some raphe and neurons, dynorphin and enkephalin coexist. We also found coexistence of dynorphin and enkephalin in some dorsal horn neurons (Mulcahy & Basbaum 1983).

That the different endorphins might have different physiological actions vis-à-vis pain was suggested by our studies in the spinal dorsal horn and its brainstem homolog, the trigeminal nucleus caudalis (Glazer & Basbaum 1981). We found that the densest concentration of immunoreactive enkephalin is in laminae I (the marginal zone), II (the substantia gelatinosa), and in the region of lamina V. Enkephalin-labelled cells are located in both the marginal zone and in the substantia gelatinosa. The distribution of immunoreactive dynorphin, however, is much more limited; the staining is concentrated in the marginal zone. Overall the dynorphin terminal staining is much less than enkephalin, even in colchicine-treated animals; however, the number of immunoreactive cells in the marginal layer far exceeds the enkephalin-positive neurons recorded in an adjacent section.

There is general agreement that intracerebral injection of dynorphin does not produce analgesia. In fact, studies indicate that intracerebral dynorphin can antagonize morphine analgesia (Tulunay et al 1981). Several laboratories, however, report that intrathecal dynorphin generates a prolonged analgesia (Han & Xie 1982, Piercey et al 1982), particularly with tests using noxious heat. We have also found that both dynorphin and α-neoendorphin generate prolonged analgesia when administered intrathecally (Basbaum et al 1983a). A brief paralysis is often produced but it is dissociable from the analgesia. While naloxone did not reverse the analgesia once it was established, pretreatment with naloxone could prevent it, indicating that an opiate receptor is involved.

These data indicate that several endorphins are involved in the descending control of spinal neurons. It is possible that the descending axons contact enkephalin and/or dynorphin neurons. Moreover, different postsynaptic elements may be acted upon by the two putative opioid transmitters. Given its restricted terminal distribution, dynorphin might predominantly influence the

projection neurons of the marginal zone, while both projection neurons and interneurons (of the substantia gelatinosa) may be inhibited by enkephalin.

THE COMPONENTS OF AN ENDOGENOUS PAIN CONTROL SYSTEM

The Periaqueductal Gray

The periaqueductal gray was the first region to be implicated in pain modulation (Reynolds 1969, Mayer et al 1971). Although more rostral sites are usually stimulated in humans, there is evidence that the analgesia elicited from these sites is transmitted via the periaqueductal gray (Rhodes 1979). Whether the periaqueductal gray is functionally homogeneous is controversial. Analgesia can be generated from all regions of the PAG; however, several workers have reported that the ventrolateral region is the most effective (Gebhart & Toleikis 1978). Other investigators, however, emphasize that the midline raphe dorsalis (a specialized midbrain region located within the ventral PAG) is the most effective site for stimulation-produced analgesia (SPA) (Oliveras et al 1979).

The fact that microinjection of opiates into (Murfin et al 1976) or electrical stimulation of (Basbaum et al 1977) the PAG generates analgesia (via a pathway in the DLF) and inhibits the firing of dorsal horn neurons (Liebeskind et al 1973) is consistent with the view that opiate analgesia and stimulation-produced analgesia operate via a common neural mechanism (Mayer & Liebeskind 1974, Mayer & Price 1976). The anatomical substrate for opiate and stimulation-produced analgesia may, however, not be completely identical. Some studies found differences in the PAG loci most effective for stimulation-produced and opiate analgesia (Gebhart 1982).

Although its importance to analgesia mechanisms is unquestioned, the intrinsic circuitry of the PAG is largely unknown. Hamilton (1973) characterized three major cytoarchitectural subdivisions of the PAG and implied that they represented functional subdivisions. Other studies could not distinguish these regions, either with Golgi techniques or on the basis of the afferent and efferent connections of the PAG (Mantyh 1982a,b, 1983). Despite this lack of agreement on cytoarchitecture, immunohistochemical studies of the PAG clearly demonstrate its chemical heterogeneity. For example, in the caudal PAG, enkephalin cells and terminals are concentrated ventrolaterally, but their distribution shifts dorsally in the rostral midbrain (Moss et al 1983). As described above, dynorphin cells have a different location. The distribution of immunoreactive Substance P cells is similar to that of enkephalin; however, the terminal fields of the two peptides are not identical (Moss & Basbaum 1983b). In marked contrast is the distribution of immunoreactive vasoactive intestinal polypeptide (VIP), a peptide which, by PAG microinjection, generates a profound, naloxone-insensitive analgesia (Sullivan & Pert 1981). VIP cells are

concentrated just ventral to the aqueduct, along the rostral caudal extent of the PAG. Although the raphe dorsalis contains a variety of peptidergic neurons, including enkephalin, that are also found within the PAG (Moss et al 1981), its dense concentration of 5HT-containing neurons readily distinguishes it from the rest of the PAG.

When we proposed our original model, information about inputs to the PAG was sparce. Recent studies have demonstrated that the PAG is pivotally located to transmit cortical and diencephalic inputs to the lower brainstem. Retrograde transport studies have established that the PAG receives significant inputs from the frontal and insular cortex, the amygdala, and the hypothalamus (Beitz 1982b, Mantyh 1983). Because endorphin-mediated analgesia can be conditioned (see below), it is likely that cognitive factors can activate these analgesia systems. Whether the cortical inputs to the PAG are a route by which these cognitive inputs exert their influence is unknown, but they do provide a possible anatomical substrate.

The brainstem inputs to the PAG are also diverse. The majority derive from the nucleus cuneiformis, the pontine reticular formation, and from the locus coeruleus. Taken together with the known direct spinal input to the PAG (Mehler 1962), the former two regions provide a probable relay for the nociceptive input that activates PAG neurons (see Gebhart 1982). The locus coeruleus projection is of interest since it may contribute to the known norepinephrine antagonism of opiate and stimulation-produced analgesia (Akil & Liebeskind 1975).

Details of the PAG connections to the rostral medulla have been demonstrated by both anterograde and retrograde (Mantyh 1983) tracing methods (Gallagher & Pert 1978, Abols & Basbaum 1981). Of particular interest are the studies of Beitz (1982a,c), who examined the PAG-medullary connections with combined retrograde tracing methods and immunocytochemistry. His studies established that both 5HT and neurotensin neurons of the midbrain project to the medulla. Substance P and enkephalin neurons of the PAG did not. This is consistent with the idea that the latter are interneurons that modulate neurotensinergic projection neurons (see PAG circuitry below).

The Rostral Medulla

CYTOARCHITECTURE, CYTOCHEMISTRY, AND PHARMACOLOGY The rostral medulla, particularly its ventral aspect (RVM), is the major source of axons projecting via the DLF to the spinal cord (Basbaum & Fields 1979, Martin et al 1978, Liechnitz et al 1978), and thus it is a critical link in the descending contral exerted from the PAG. Medullary cells of origin of DLF axons are found in the NRM, and in the adjacent reticular formation; all are located ventral to nucleus reticularis gigantocellularis (Rgc) (Figure 1). In the rat and cat, neurons of at least three different regions, in addition to the raphe, contribute axons to the

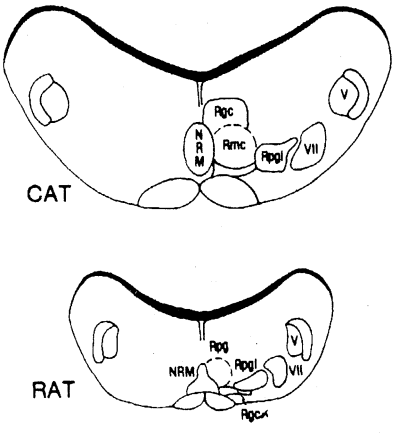

Figure 1 Schematic illustration of the major subnuclei of the rostral medulla of the cat and rat. As indicated in the text, each of these regions contributes to descending control; however, the different regions can be distinguished on cytoarchitectural and cytochemical grounds.

DLF: the n. reticularis paragigantocellularis (Rpg), the n. reticularis gigantocellularis pars α (Rgcα), located ventral to the Rpg, and, more laterally, the n. reticularis paragigantocellularis lateralis (Rpgl). The nucleus reticularis magnocellularis (Rmc) of the cat occupies roughly the region corresponding to the rat Rpg. There is evidence that cells throughout the NRM, Rmc, Rgcα, and Rpgl are involved in pain modulation. All receive projections from the PAG (Beitz 1982c, Mantyh 1983), all send axons to the spinal cord via the DLF, and all produce "analgesia" when electrically stimulated at low intensities (Zorman et al 1981). Finally, in order to block completely the effect of midbrain stimulation, NRM, Rgcα and Rpgl must be simultaneously interrupted, either by lesions (Prieto et al 1983) or by injection of local anesthetic (Sandkuhler et al 1982).

Despite the anatomical and functional similarities, there is evidence that the neighboring regions of the RVM differ. First, the cells of Rpgl and Rgcα are morphologically distinct from those of NRM and Rmc/Rpg; the former are predominantly fusiform, the latter are larger and multipolar. Rmc and Rpgl receive significant afferent projections from the spinal cord (Abols & Basbaum 1981) and project to the cord via both DLF and ventral funiculi (Basbaum et al 1978). In contrast, NRM projects to the cord only via the DLF and receives no direct connections from the spinal cord.

Cytochemical studies also support a parcellation of the region. Thus, NRM, Rgcα, and Rpgl all have significant numbers of 5HT-containing cells (Dahlstrom & Fuxe 1964); Rmc/Rpg does not (Wiklund et al 1982). Although double labeling techniques indicate that many of the 5HT-containing cells in NRM and Rpgl project to the spinal cord (Bowker et al 1981a,b), it has been reported that 5HT-cells in the NRM of the rat do not project to the spinal cord via the DLF (Johannessen et al 1981). This is surprising since the superficial dorsal horn receives its medullary input via axons in the DLF (Basbaum et al 1978) and

since 5HT levels in superficial dorsal horn drop after NRM lesions (Oliveras et al 1977).

Although our original model concentrated on the 5HT component in the control of spinal nociceptive neurons (with the exception of the pharmacologically undefined projection from the Rmc), much new information is now available concerning the chemical heterogeneity of neurons of the RVM. For example, many peptidergic neurons have been demonstrated in the NRM, in Rgcα, and in Rpgl. These include enkephalin, Substance P, somatostatin, and thyrotopin-releasing hormone-containing (TRH) neurons. Although some of these neurons are probably local interneurons, double labeling studies have established that many peptidergic neurons of the medulla project to the spinal cord (Hökfelt et al 1979, Bowker et al 1981a).

Perhaps the most significant finding of the past five years and one which has direct bearing on pain control mechanisms is the coexistence of two putative transmitters in a single neuron (Hökfelt et al 1980). It was first demonstrated that in some cells of the NRM, the Rgcα, and the Rpgl, serotonin and Substance P coexist (Hökfelt et al 1978). Our own studies established that 5HT and enkephalin coexist, particularly in neurons of the Rpgl (Glazer et al 1981). A later study revealed neurons in which three putative transmitters—5HT, SP, and TRH—are colocalized (Johansson et al 1981). That the bulbospinal axons (as well as the cell body) contain multiple transmitters was confirmed using the neurotoxin, 5,7-dihydroxytryptamine. This toxin destroys the 5HT terminals in the spinal cord and concomitantly reduces the level of Substance P (Hökfelt et al 1978, Gilbert et al 1982).

The biological significance of transmitter coexistence is only beginning to be examined, but already several intriguing possibilities can be envisioned. For example, it is generally assumed that 5HT inhibits dorsal horn nociceptors; however, it is not known whether the bulbospinal Substance P-containing terminal excites or inhibits spinal neurons. Nor is it known whether the same terminal releases both 5HT and Substance P. A given terminal could have mixed effects, depending on the amount and nature of the transmitter released, and upon on the distribution of postsynaptic receptors. In our description of circuitry (Figure 2), we have considered the possibility that different bulbospinal terminals release 5HT or Substance P. This raises the possibility that NRM neurons produce both inhibitory and excitatory effects at the spinal level. In fact, in animals depleted of 5HT with parachlorophenylalanine (pCPA), raphe stimulation excites dorsal horn nociceptive neurons (Rivot et al 1980). This could result from an unmasking of excitatory effects of Substance P.

In addition to the anatomical heterogeneity of the RVM, there is evidence in rat, albeit controversial, for significant pharmacological differences among its subdivisions. Rpg has been reported to be exquisitely sensitive to opiate

microinjection (Akaike et al 1978)—perhaps two orders of magnitude more sensitive than NRM or the PAG. Thus, nanograms doses of morphine injected into the Rpg produces potent behavioral analgesia. Using different methods to assess analgesia, however, Dickenson et al (1979) reported that NRM is the most sensitive site. A third group, using still another method to assess analgesia, agreed that the more lateral sites (Rpg and Rpgl) are most sensitive, although not by orders of magnitude (Azami et al 1982).

Another approach to the analysis of pharmacological differences between classes of spinally projecting RVM neurons is to activate them in the medulla and attempt to block their action at the level of the spinal cord, using specific transmitter antagonists. For example, using medullary microstimulation, Zorman et al (1982) showed that stimulation-produced analgesia from RVM could be antagonized by lumbar intrathecal naloxone. Using a similar approach, bulbospinal 5HT and norepinephrine axons have been implicated. The analgesia elicited from the lateral Rpg is blocked by α-adrenergic antagonists (Kuraishi et al 1979), whereas that elicited from NRM is blocked by serotonergic antagonists (Satoh et al 1980).

In summary, there are several chemically distinct classes of neurons in RVM, each of which may be at the origin of a parallel bulbospinal control system. The descending systems, though parallel, are unlikely to be entirely redundant. As pointed out by previous investigators (Casey 1971, Gebhart 1982), this region of the brainstem, classically considered to be part of the reticular formation, is far from homogeneous; different subpopulations of neurons contribute to diverse functions. Whether each of these chemically distinct classes of neuron has a different physiological role is an important question.

AFFERENT CONNECTIONS The major afferent connections of the RVM originate in the PAG and the adjacent midbrain nucleus cuneiformis. Because early studies found minimal direct spinal projections from the PAG, the RVM was considered a necessary "relay" between the PAG and the spinal cord. A recent study, however, using very sensitive retrograde tracers, revealed a far more extensive direct PAG-spinal projection (Mantyh & Peschanski 1982). This direct connection may contribute to pain control by influencing neurons of the spinal dorsal horn; however, since simultaneous interruption of the NRM and Rpgl counteracts the effects of PAG stimulation, the medullary link is essential. This concept is strengthened by the observation that activation of PAG by electrical stimulation (Fields & Anderson 1978, Oleson et al 1978), opiate microinjection (Behbehani & Pomeroy 1978), or glutamate injection (Behbehani & Fields 1979) has a predominantly excitatory effect on NRM and Rmc/Rpg neurons. More recently, the introduction of immunocytochemical

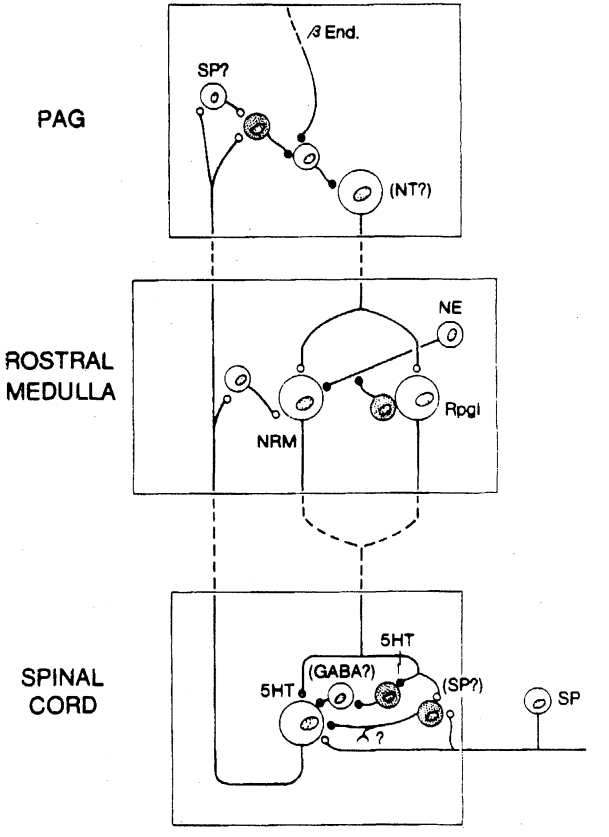

Figure 2 This figure illustrates proposed midbrain (PAG), medullary, and spinal circuitry related to the control of spinal nociceptive neurons. *Unfilled "boutons"* indicate release of an excitatory transmitter, *filled "boutons"* indicate an inhibitory input. In the PAG, the output neuron is depicted as an excitatory neurotensinergic (NT) neuron (Beitz 1982c) that activates cells of the NRM and of the lateral Rpgl of the rostral medulla. An endogenous opioid peptide neuron (*stippled*) in the PAG is presumed to inhibit an inhibitory interneuron that, in turn, controls the PAG output neuron. Input to the opioid interneuron may derive from ascending nociceptive pathways, via a local Substance P-containing (SP) neuron. Inputs from β-endorphin cells of the hypothalamus may also contribute to the opioid link in the PAG. It is not known whether all of the endorphin subtypes act in a similar fashion in the PAG.

At the level of the rostral ventral medulla, we have indicated that there is an inhibitory norepinephrine (NE) input to bulbospinal raphe neurons. We have also included the possibility that local opioid neurons presynaptically control the NE input to raphe-spinal axons. Although not illustrated, it is possible that the noradrenergic neurons that control raphe-spinal neurons are the same as those which exert a direct bulbospinal control. There are a variety of other peptides that must eventually be included in this diagram, but because there is little information as to their local connectivity or possible function in analgesia, these have been omitted.

The greatest complexity is at the level of the dorsal horn. We have only included a few of the synaptic interactions that may be relevant to nociceptive control. While there are numerous other

techniques has made it possible to differentiate the chemical nature of the inputs to the RVM. We will highlight a few that appear relevant to pain control circuitry.

Enkephalin Because microinjection of minute quantities of morphine into RVM generates analgesia, the analysis of opioid peptide inputs is particularly important (Akaike et al 1978, Dickenson et al 1979). Combined retrograde tracing and immunocytochemical double labeling studies in the rat demonstrated several brainstem sources of the enkephalin-like immunoreactivity in or adjacent to the NRM (Beitz 1982a). These include the midbrain nucleus cuneiformis, the nucleus of the solitary tract, and the dorsal parabrachial nucleus of the pons. A smaller enkephalin input originates in the laterally located medullary A5 noradrenergic cell group.

Identifying the extrinsic source of enkephalin inputs is, of course, complicated by the presence of enkephalin neurons within the NRM itself, and particularly by the observation that in some RVM neurons, enkephalin and 5HT coexist. Moreover, the afferent connections originating from dynorphin cells have not been studied; it is likely that these also exist. It is thus possible that the exquisite sensitivity of the RVM to opiate microinjection reflects an extensive, convergent input from both enk- and dyn-containing neurons.

Neurotensin Although the literature on the contribution of neurotensin (NT) to pain control mechanisms is limited, there is evidence that it is relevant (Clineschmidt et al 1979). Intracisternal neurotensin produces profound analgesia (Kalivas et al 1982), possibly by direct activation of raphe-spinal inhibitory neurons. Thus, studies showing that neurotensin immunoreactive cells of the PAG project to the RVM are particularly important (Beitz 1982c). Other neurotensin inputs to the RVM derive from the dorsolateral pons and from the ventrolateral medulla, in the region corresponding to the chain of catecholamine cells groups, A1 to 5.

peptidergic elements that have been defined, there is presently little information about their synaptic relationships. In this diagram the bulbospinal serotonin (5HT) axons are shown to inhibit the projection neurons via two circuits. The simpler is a direct postsynaptic inhibition. Another illustrated possibility is that 5HT exerts its effect through as inhibitory opioid interneuron. As described in the text, it is likely that this latter arrangement (for which there is anatomical evidence) would require a further, interposed, inhibitory interneuron, analogous to the arrangement proposed in the PAG. Based on studies in the hippocampus (Nicoll et al 1980) and given the high concentration of GABA in the superficial dorsal horn, GABAergic interneurons may be involved. Alternatively, the bulbospinal axons may excite the inhibitory endorphin interneurons by releasing its cotransmitter Substance P. The opioid interneuron may, as anatomical studies indicate, directly control the projection neurons, or as biochemical studies indicate, presynaptically control nociceptive primary afferent inputs, some of which may contain Substance P.

Norepinephrine In our original model, we proposed a bulbospinal norepinephrine (NE) pathway synergistic with the inhibitory serotonergic projection that controls spinal nociceptive neurons. (For a recent review see Basbaum et al 1983b.) The norepinephrine inhibits spinal neurons has been confirmed in several studies (Belcher et al 1978, Headley et al 1978); however, the origin of the descending norepinephrine input is still unclear. To complicate matters, recent studies indicate that norepinephrine neurons in the brainstem inhibit the descending 5HT system. For example, microinjection of the norepinephrine antagonist, phentolamine, into the NRM produces a hypoalgesia, which is blocked by intrathecal methysergide (Hammond et al 1980). These data suggest that there is a tonic norepinephrine-mediated inhibition of the bulbospinal 5HT pain-modulatory neurons of the NRM. The observation that iontophoresis of norepinephrine inhibits the firing of raphe-spinal neurons supports this hypothesis (Behbehani et al 1981).

Unfortunately, the connections of norepinephrine neurons within the brainstem are still unclear. Although the origin of the input of norepinephrine to the NRM is not known, it is likely that it derives, in part, from the A3 and A5 norepinephrine cell groups of the lateral medulla (Takagi et al 1981). The contribution of the locus coeruleus is apparently limited (Moss & Basbaum 1979).

Acetylcholine Iontophoresis of acetylcholine excites NRM neurons (Behbehani 1982); more important, injection of carbachol, an acetylcholine mimetic, into the NRM generates analgesia (Brodie & Proudfit 1982). It is important to establish the origin of this input of acetylcholine. Histochemical studies that combine retrograde tracers with markers of choline-acetyltransferase may provide the answer.

SUMMARY The evidence reviewed above indicates that no one chemical marker will be sufficient to define the location and pharmacology of those neuronal populations which control the firing of NRM neurons. Our original model emphasized the excitatory inputs from the midbrain PAG. There is now evidence for multiple brainstem inputs, some of which are excitatory, others inhibitory. Just as the thalamus is no longer considered a simple relay between receptor and cortex, so the raphe and adjacent reticular formation are not mere relays between the PAG and cord. These medullary neurons receive input from nociceptive afferents and integrate it with inputs from more rostral structures. This integration establishes the level of control that the bulbospinal neurons exert on the transmission of nociceptive messages at the spinal cord.

Spinal Dorsal Horn

Because the descending inhibitory effects are exerted on spinal cord neurons it is important to review briefly some recent observations on the anatomy and

physiology of dorsal horn neurons. Ultrastructural examination of physiologically identified and intracellularly filled primary afferent axons and dorsal horn neurons have provided particularly valuable new data. The general anatomical (Rexed 1954) and physiological (Wall 1967) laminar schema of the dorsal horn is still accepted, but some modifications are required, particularly in the substantia gelatinosa (SG), lamina II. (For reviews see Cervero & Iggo 1980, Dubner & Bennett 1983). The substantia gelatinosa can be divided into an outer (IIo) and inner (IIi) layer. The former receives inputs from small diameter high threshold primary afferent fibers (Light & Perl 1979) and contains neurons physiologically similar to those in the marginal zone, lamina I. That is, IIo neurons respond to both noxious and non-noxious inputs (Light et al 1979, Bennett et al 1980). It has been hypothesized (Gobel 1979) and there is evidence that neurons in lamina IIo relay nociceptive inputs from primary afferents to marginal neurons (Price et al 1979). The latter hypothesis is particularly relevant because it raises the possibility that the bulbospinal inhibition of marginal neurons could be indirect, i.e. by inhibition of these putative relay interneurons in IIo. Neurons in IIi, in contrast, receive inputs from small diameter, low threshold mechanoreceptors and contain neurons predominantly responsive to non-noxious inputs. IIi may contain interneurons involved in the segmental, inhibitory control exerted by non-noxious peripheral stimuli.

Based on Golgi studies, the majority of neurons of the substantia gelatinosa can be assigned to either one of two distinct morphological types, the stalk or islet cell (Gobel 1978). Immunohistochemical studies, however, reveal greater complexity. Several peptides have been identified in "islet" cells (Glazer & Basbaum 1981, Hunt et al 1981, Bennett et al 1982, Seybold & Elde 1982). In fact, the list of peptides contained in SG neurons continues to grow and includes Substance P, enkephalin, dynorphin, neurotensin, cholecystokinin, and avian pancreatic polypeptide (Gibson et al 1981, Hunt et al 1981). There is also a large population of GABAergic neurons, some of which may control primary afferents presynaptically (Barber et al 1978, Basbaum et al 1981). The functional properties of these chemically distinct neurons have yet to be established. Which are excitatory and which inhibitory? Which elements receive direct input from nociceptive primary afferents which are contacted by bulbospinal axons? These questions will require anatomical and chemical marking of physiologically identified elements in the superficial dorsal horn.

CIRCUITRY

When our original model was proposed, the relevant synaptic circuitry in the PAG, RVM, and cord was largely unknown. With the advent of EM immunohistochemical analysis, however, much new information is available. In this section we propose to provide further details regarding the circuits that have

been defined and discuss the evidence for additional circuits relevant to nociceptive control (Figure 2).

The Periaqueductal Gray

In general, opiate actions on target neurons are inhibitory (Nicoll et al 1980). Thus, the direct action of opiates on the postsynaptic neuron that they contact in the periaqueductal gray is probably inhibition. Since excitation of the PAG output neuron is required to initiate descending control, it follows that morphine, or the endogenous opioid equivalent, does not directly act upon the PAG output neuron. Given that the vast majority of enkephalin-immunoreactive terminals in the PAG are presynaptic to dendrites (Moss & Basbaum 1983a), we propose that endogenous opioid peptides (either enkephalin, dynorphin, β-endorphin, or all three) activate PAG output neurons by inhibiting an inhibitory interneuron. A similar model has been proposed to account for the opiate excitatory effects on hippocampal pyramidal cells (Nicoll et al 1980). In that case, the intervening inhibitory interneuron is probably GABAergic.

In addition to morphine and the endogenous opiates, the nonopioid peptide, Substance P, produces a naloxone-reversible analgesia when injected into the PAG (Fredricksen et al 1978, Mohrland & Gebhart 1979). Antibodies to met-enkephalin also antagonize Substance P analgesia (Naranjo et al 1982). Although there are large numbers of enkephalin cells in the ventrolateral PAG and dorsal raphe (Moss et al 1981, 1983), Substance P cells are not common (Moss et al 1983). In contrast, there is a high concentration of Substance P terminals in these regions and thus enkephalin neurons probably receive a significant Substance P input. These observations indicate that Substance P acts upon local opioid peptide neurons. Figure 2 illustrates one simple circuit through which endogenous opioid peptides or exogenous morphine activate the descending control. Based on Beitz' recent studies, we have indicated the possibility that the PAG-raphe connection, in part, involves neurotensin neurons. It is clearly important to identify the proposed inhibitory interneuron that we hypothesize receives the opioid peptide input.

Rostral Ventral Medulla

Based on our anatomical demonstration of bulbospinal pathways that course in the DLF and terminate in the spinal dorsal horn, we originally proposed at least two descending control systems, one originating in the midline raphe, the second in the adjacent Rpg/Rmc. As described above, a third system has been characterized, namely that deriving from the Rpgl. Although it is not clear whether these systems are activated in parallel, their effects appear comparable (Zorman et al 1981).

Figure 2 illustrates possible medullary circuitry. Local injection of opiates into the RVM generates analgesia. Following the same line of reasoning we

used for the PAG, it follows that the bulbospinal projection neurons are disinhibited by local opioid-containing interneurons. As discussed above, there is an inhibitory catecholamine effect on raphe spinal neurons. Because precedence for presynaptic opiate control of catecholamines release has been described (Llorens et al 1978), we propose that an opioid peptide interneuron (either enkephalin or dynorphin) presynaptically inhibits an inhibitory catecholamine input to raphe-spinal axons. Opiates, therefore, would act, at least partially, by disinhibiting the RVM output neuron.

Some of the cells exerting this opioid peptide control in RVM may be in the Rpgl, a region that contains both enkephalin and dynorphin immunoreactive neurons (Basbaum et al 1983a, Watson et al 1982). The Rpgl also contains many neurons in which opioid peptides coexist with 5HT. Such an arrangement might account both for the analgesic action of Rpgl stimulation and for the observation that a lesion of this area disrupts opiate analgesia (Azami et al 1982).

The Spinal Dorsal Horn

In contrast to the PAG and RVM, where the net effect of opiates is apparently activation of descending projection neurons, at the spinal level it is inhibition of the nociceptor that is required. Thus, direct postsynaptic inhibition of the nociceptive projection neurons by opioid peptides is one obvious mechanism of opiate action. The demonstration that enkephalin-immunoreactive terminals contact spinothalamic tract neurons (Ruda 1982) is consistent with such a direct postysynaptic inhibition.

In addition to these postsynaptic actions, there is considerable evidence for an opioid-mediated presynaptic control of primary afferents. Thus, primary afferents are laden with opiate binding sites (LaMotte et al 1976, Atweh & Kuhar 1977a, Hiller et al 1978, Fields et al 1980) and are sensitive to opiates both in vivo (Carstens et al 1979) and in vitro (Hentall & Fields 1983). Inhibition of Substance P release by opiates has also been demonstrated (Jessel & Iversen 1977, Mudge et al 1979, Yaksh et al 1980). Unfortunately, ultrastructural studies of immunoreactive enkephalin terminals in the dorsal horn reveals that they are exclusively presynaptic to dendritic or somatic profiles (Hunt et al 1980, Aronin et al 1981, Sumal et al 1982, Glazer & Basbaum 1983a). As yet there is no anatomical substrate for presynaptic control of primary afferents by enkephalin. However, numerous associations between enkephalin terminals and primary afferents are found; conceivably the control of primary afferents is exerted via a "nonsynaptic" action, in a manner similar to that described for peptides released into the vicinity of the target cell in the bullfrog sympathetic ganglia (Jan & Jan 1982). Another possibility is that other, as yet unstudied, endogenous opioid peptides, e.g. the prodynorphin products, provide presynaptic control of the primary afferents.

Since intrathecal naloxone antagonizes the analgesic action of IVth ventricle morphine injection (Levine et al 1982c), NRM stimulation (Zorman et al 1982), and forepaw shock (Watkins et al 1982a,b), it follows that there is an opiate link between the bulbospinal axons and the spinal nociceptors. We had originally proposed a 5HT-enkephalin synapse in the cord (Basbaum & Fields 1978) and, in fact, have recently demonstrated this connection anatomically (Basbaum et al 1982, Glazer & Basbaum 1983b). Since 5HT is generally inhibitory to dorsal horn neurons, this synaptic arrangement raised a paradox. Inhibition of the enkephalin neurons by 5HT should disinhibit the spinal nociceptor. Conceivably another inhibitory interneuron, possibly GABAergic, is interposed between the opioid peptide neurons and the nociceptor. It is, of course, possible that 5HT neither excites nor inhibits enkephalin neurons, but modulates other inputs to them (for example, see Davies & Roberts 1981). As described above, it is also possible that the Substance P that coexists in many 5HT-containing raphe neurons is the source of an excitatory input to spinal opioid neurons. Figure 2 also illustrates the segmental inputs that activate opioid-mediated inhibition of pain.

PHYSIOLOGICAL ACTIVATION OF ANALGESIA-PRODUCING NEURAL NETWORKS (STRESS-INDUCED ANALGESIA?)

While it is of interest to analyze the anatomy and physiology of endorphin-related pain-control systems, the most important questions concern their normal function. As described in our previous review, noxious peripheral stimuli are the most consistent way to excite cat RVM neurons, including those that project to the spinal cord (Anderson et al 1977). This observation has been confirmed in rats (Guilbaud et al 1980). Since activation of NRM neurons generates analgesia (Oliveras et al 1975), noxious stimuli should produce analgesia. In fact, stimuli that clearly activate nociceptive primary afferents in awake rats are very effective in producing analgesia.

On the other hand, a variety of environmental stimuli, not all of which are obviously pain-producing, may also have an analgesic effect (Hayes et al 1978, Mayer and Watkins 1981). For example, restraint (Amir & Amit 1978, Bhattachary et al 1978) and hypoglycemia (Bodnar et al 1979a,b) consistently produce analgesia. Not all analgesia-producing environmental perturbations are stressful; nevertheless, the analysis of physiological activation of the endorphin-mediated analgesia system has generally emphasized "stressful stimuli."

Comprehensive treatment of "stress-induced analgesia" research is beyond the scope of this review; however, it is important to discuss some of the concepts and problems that have evolved from these studies. The most com-

mon method used to elicit stress-induced analgesia (SIA) is to stimulate somatic structures electrically, typically the foot or tail. Because footshock (Watkins & Mayer 1982, Watkins et al 1982b) or tailshock (Woolf et al 1980) can inhibit nociceptor-induced withdrawal reflexes in spinalized rats, where stress is clearly not a factor, perhaps nociceptor-induced analgesia is a more appropriate description of this phenomenon. If this segmental mechanism contributes to footshock-induced analgesia in the intact animal, can footshock analgesia be considered stress-induced? One is clearly faced with a serious semantic question, specifically, "What is stress?" It may not be useful to group all phenomena that have been labeled stress-induced analgesia.

Regardless of what makes a stimulus "stressful," there is general agreement that footshock in the noxious range produces analgesia. The mechanism of this effect is complex and apparently varies with the location of the stimulus, its duration, and whether the animal can escape from it or control it (Mayer & Watkins 1981, Lewis et al 1980). For example, Lewis et al (1983) showed that both brief (three minute) and prolonged (20 minute) inescapable foot shock (3 mA, 50 Hz sine waves) elicit hypoalgesia of a similar magnitude, but that only the hypoalgesia secondary to prolonged footshock was blocked by naloxone and showed cross-tolerance with morphine. Furthermore, the analgesia to prolonged foot shock was attenuated by adrenalectomy or adrenal denervation (Lewis et al 1982). Watkins et al (1982a) reported that much briefer stimuli can produce naloxone-reversible analgesia (90 sec, 60 Hz, 1.6 mA) but only when the shock is restricted to the forepaws. When all four paws are on the grid, the analgesia is not blocked by naloxone. Only the forepaw induced shock-analgesia was abolished by a lesion of the DLF or the RVM (Watkins & Mayer 1982). The hindpaw shock analgesia effect survives T2 cord transection; thus its basis is largely intraspinal. Finally, since the forepaw analgesic effect persists after either adrenalectomy or hypophysectomy (Watkins et al 1982c), the pituitary-adrenal axis was ruled out in this form of stress analgesia. Apparently the footshock analgesia induction used by Watkins & Mayer differs from the prolonged shock approach of Lewis et al 1980.

Under certain conditions, restraining an animal is sufficient to produce a naloxone-reversible hypoalgesia (Amir & Amit 1978). Since restricting the shock to the forepaws requires restraining the rats by suspending them, it may be that restraint (alone or with footshock) is the relevant stressor. Other nonspecific effects of the shock may also contribute to the analgesia. For example, an elevation of blood pressure has been reported to produce analgesia in rats (Dworkin et al 1979, Zamir & Segal 1979 and may be associated with hypoalgesia in man (Zamir & Shuber 1980); this effect is reversed by naloxone (Zamir et al 1980). Furthermore, Maixner et al (1982) reported that spontaneously hypertensive rats are relatively hypoalgesic and that the hypoalgesia can be blocked by naloxone (without changing blood pressure), by lowering the

blood pressure with ganglionic blockers, or by cutting the right vagal trunk. Conceivably many of the so-called stress-induced analgesias are secondary to concomitant changes in blood pressure.

Another interesting feature of shock-induced analgesia is the factor of controllability. Maier and colleagues (1982) showed that in identically shocked rats, those that cannot control (escape from) tailshock, develop potent, naloxone-reversible analgesia (Grau et al 1981, Maier et al 1982). This analgesia apparently depends on the rats' learning that they cannot control the shock. Moreover, the effect can be reinstated 24 hours later, by brief shocks that would otherwise not cause analgesia.

It has also been reported that naloxone-sensitive analgesia can be produced by innocuous stimuli under conditions in which such stimuli serve as cues that a noxious stimulus is about to occur (Bolles & Fanselow 1982). Thus, rats repeatedly exposed to aversive shock become hypoalgesic when placed in the same experimental situation, without further shock (Chance et al 1978). It has been proposed that it is fear that causes the analgesia observed in this situation.

In summary, various environmental factors, not all of which are painful, can activate endorphin-mediated analgesia-producing networks in the central nervous system. Pain-producing stimuli can activate this system either directly by activating ascending nociceptive pathways (e.g. spinoreticular or spinothalamic tracts) or indirectly via stress, conditioning, or hypertension. Other stressors, such as restraint and hypoglycemia, may activate similar systems, yet bypass peripheral and central nociceptive pathways. The mechanisms for these phenomena are as yet unknown. Part of the confusion in the field results from the fact that no two workers are studying the system in precisely the same way, so conflicting results may be due to methodological differences. Alternatively, each laboratory may have uncovered separate pain control mechanisms.

The observation that pain, especially when severe enough to be accompanied by "stress," activates an opioid-mediated analgesia system, leads to the prediction that, in man, interruption of analgesia networks would exacerbate preexisting pain. As pointed out in our previous review, the opiate antagonist naloxone does produce hyperalgesia in patients with postoperative pain (Lasagna 1965, Levine et al 1978b). In a subsequent study we showed that the naloxone effect is dose-dependent (Levine et al 1979) and, curiously, that at low doses naloxone (0.4 and 2 mg) tends to produce hypoalgesia. An analgesic effect of low-dose naloxone has also been reported in arthritic rats (Kayser & Guilbaud 1981). The patients in our clinical studies were pretreated with diazepam (5–10 mg i.v.) and had their surgery carried out under nitrous oxide (N_2O) and local block with xylocaine. Thus, the naloxone effect could have resulted from antagonism of the N_2O or diazepam. However, in our experimental model, naloxone has no hyperalgesic effect in patients in whom N_2O was used as the postoperative analgesic (Levine et al 1982a). Fur-

thermore, Gracely et al (1979) have shown naloxone hyperalgesia in patients who had neither N_2O nor diazepam for their postoperative dental pain. It thus is well established that there is a naloxone-sensitive analgesia demonstrable in postoperative patients.

It is not clear, however, what triggers the naloxone-sensitive analgesia or whether it is seen in all patients. It is possible that the pain and stress of surgery are sufficient to release endogenous opioid peptides. Consistent with this hypothesis, we demonstrated that patients reporting higher initial pain (using the visual analog scale) are more likely to have a subsequent reduction in pain (Levine et al 1982b). Furthermore, there appears to be a threshold level of pain that must be crossed before the appearance of a subsequent reduction of pain.

In all of these studies, patients receiving naloxone were compared to patients receiving placebo, under double-blind conditions. Because our preliminary data had indicated that in the absence of treatment, the pain in the model we used increases steadily, it was conceivable that placebo administration was a major factor in generating the analgesic effect. In subsequent work we defined placebo-responders as those patients whose pain either decreased or was unchanged (i.e. did not show the normal increase) following placebo administration. About 35% of our patients fell into this category. We found that the entire naloxone effect could be accounted for by those patients falling into the placebo-responder category and concluded that release of endogenous opioid peptides contributes to the analgesic effect of placebo administration (Levine et al 1978a).

Our experimental design did not permit us to rule out the possibility that the pain reduction following placebo administration was a coincidence, i.e. it would have occurred whether or not a placebo was given. To establish with certainty that a placebo effect had occurred, we should have included a no-treatment group in the protocol. Using such a design, Gracely et al (1982) found naloxone hyperalgesia in patients with dental postoperative pain who had not received a placebo. They showed that a significant placebo effect persists, despite naloxone treatment. On the other hand, Grevert et al (1983), who also used a no-treatment control group, reported a significant, albeit incomplete reversal of placebo analgesia with naloxone.

It thus appears that our original conclusion that placebo analgesia is completely reversed by naloxone does not apply to all situations. Under certain conditions, placeboes do trigger an opioid-mediated analgesia system. However, there is an additional nonopioid component to their action. To some extent, the very concept of a placebo effect is an oversimplification. By extrapolating from the animal studies it is clear that the triggering of pain modulating systems depends on severity of pain, anxiety, blood pressure, and conditioning or expectation of relief. When these factors are completely understood and taken into account by physicians, the placebo may no longer be a useful concept.

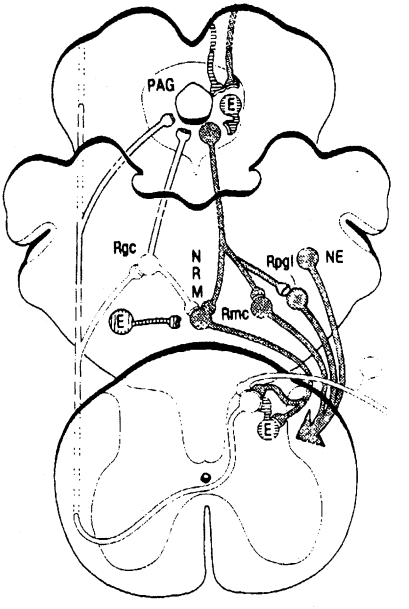

Figure 3 Schematic illustration of the major components of a descending system that contributes to the analgesic action of opiates and of electrical brain stimulation. The basic structure of the original model (Basbaum & Fields 1978) is retained. Highlighted in *stippling* are the connection between the projection neurons of the periaqueductal gray (PAG) and various subregions of the rostral ventral medulla [the nucleus raphe magnus (NRM), the nucleus reticularis magnocellularis (Rmc), and the nucleus reticularis paragigantocellularis lateralis (Rpgl)]. The latter project via the dorsolateral funiculus to the spinal dorsal horn, where they inhibit nociceptive neurons. As indicated in Figure 2, the inhibitory action at the cord may be via direct postsynaptic inhibition, or via an opioid peptide containing endorphin interneuron (indicated by *stripes* and "E"). There are other endorphin links illustrated at the level of the PAG and the rostral medulla; however, their connections are not indicated. Inputs to the PAG (one of which is a hypothalamic β-endorphin pathway) are also illustrated as is the noradrenergic (NE) contribution to bulbospinal control. The NE interactions with the other bulbospinal neurons are better illustrated in Figure 2.

Finally, ascending components of this system are indicated by the *unfilled symbols*. These include afferent inputs (some of which are Substance-P-containing; see Figure 2), projection neurons of the dorsal horn, and their collaterals into the medulla and PAG. The ascending input to the PAG and raphe nuclei is presumed to derive, in part, from collaterals of neurons of the nucleus reticularis gigantocellularis (Rgc).

CONCLUSION

Progress in the field of pain modulation has been rapid and multifaceted. Through a combination of physiological, anatomical, behavioral, and pharmacological approaches there is now much more detailed knowledge of the circuitry involved in pain modulation and the behavioral contingencies that activate pain modulating circuits. Figure 3 illustrates a revised model that incorporates several of the new observations. One of the most significant

advances has been the description of multiple, pharmacologically distinct bulbospinal control systems. In addition, although our previous model discussed several enkephalin links, the revised model is more general, in that it implicates three opioid peptide (E) links. These may involve enkephalin or dynorphin neurons. We have also indicated that cortical and diencephalic sites provide significant inputs to the PAG. An important element of this is the β-endorphin from the hypothalamus.

Major questions remain. We do not know how opiates activate output neurons, or how noradrenergic neurons fit into the activation process. What is the functional consequence of coexistence of neurotransmitters/neuromodulators in a single neuron? Is there descending presynaptic control of primary afferents? Do 5HT and norepinephrine terminals interact at the level of the spinal cord? How do the various endogenous opioid peptides interact? Is there an opiate receptor specific for analgesia?

Despite these questions, it does seem clear that pain modulation is a behaviorally significant physiological process, using a discrete CNS network involving release of opioid peptides, biogenic amines, and other transmitters in its operation. With the tools of single cell neurophysiology, ultrastructural immunocytochemistry, and behavioral pharmacology these systems are beginning to yield their secrets.