ceiving short-term treatment with neuroleptics, the amount of this dopamine metabolite decreases after a few weeks of drug treatment (*16*). The clinical effects of the neuroleptics, like the biochemical effects, vary with the duration of drug treatment. Extrapyramidal side effects often occur with short-term drug treatment. After several weeks of drug administration, the extrapyramidal symptoms usually disappear, and the antipsychotic effects become evident. Tolerance to the antipsychotic effects of the drugs does not occur. The adaptive changes in the striatum may be related to the loss of extrapyramidal symptoms or the emergence of the therapeutic effects of neuroleptics, or both. The data presented here provide an example of the remarkable propensity of neurotransmitter systems to return to the baseline state after provocation by pharmacological or environmental stimuli. Such adaptation may represent a tolerance phenomenon or may actually be involved in the onset of the desired therapeutic effects (*17*). Dopaminergic areas in the mesolimbic system and the cortex are also of interest, because these brain regions are known to function as mediators of emotional response. These areas may play an important role in the expression of the antipsychotic effects of the neuroleptics. Our study reemphasizes the complexity of the adaptive mechanisms of neuronal systems and the potential significance of these regulatory changes with regard to the therapeutic efficacy of antipsychotic drugs.

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Pain Relief by Electrical Stimulation of the Central Gray Matter in Humans and Its Reversal by Naloxone

Abstract. *Relief of intractable pain was produced in six human patients by stimulation of electrodes permanently implanted in the periventricular and periaqueductal gray matter. The level of stimulation sufficient to induce pain relief seems not to alter the acute pain threshold. Indiscriminate repetitive stimulation produced tolerance to both stimulation-produced pain relief and the analgesic action of narcotic medication; this process could be reversed by abstinence from stimulation. Stimulation-produced relief of pain was reversed by naloxone in five out of six patients. These results suggest that satisfactory alleviation of persistent pain in humans may be obtained by electronic stimulation.*

After the initial report by Reynolds (*1*), potent analgesic effects produced by electrical stimulation of discrete areas of medial diencephalon and the brainstem have been demonstrated in the cat (*2*) and monkey (*3*) as well as the rat (*4*). Richardson and Akil (*5*) reported that permanent clinical pain states, in addition to normal pain perception, can be blocked by electrical stimulation of the periventricular and periaqueductal gray matter in humans. We now report the application of the above findings in six human patients suffering from intractable pain (*6*). Electrical stimulation by permanently implanted brain electrodes was chosen as the method of pain alleviation for these patients because of the inability of narcotic analgesics at reasonable dose levels to suppress their constant pain, the widespread and diffuse nature of this pain, and the serious side effects that can occur when conventional neurosurgical lesions in the pain pathways are made as a way to manage such diffused pain.

In all six patients the anatomical target selected for stimulation was at the level of the posterior commissure on the anterior-posterior axis and the ventral-dorsal axis, and 2 to 3 mm lateral from the medial wall of the posterior third ventricle. The electrodes (*7*, *8*) were implanted stereotactically, with the use of anatomical and electrical stimulation-response parameters (*5*). Electrode location was also verified by intraoperative x-ray. Initially, the electrodes were externalized to permit temporary trial stimulation for 1 to 2 weeks. In all patients, self-mediated electrical stimulation began a few days following electrode implantation. Short (0.2 to 0.3 msec) bipolar square pulses, 10 to 20 hertz in frequency, were delivered from a battery-operated stimulator. After successful trial stimulation over a period of 1 to 2 weeks, the electrodes were internalized and connected to a radio-frequency-coupled receiver. The external generator was specifically designed to produce a time-modulated

Table 1. Clinical results with implanted electrodes.

Patient No.	Age (years)	Sex	Etiology of pain	Location of pain	Side of implant	Extent of pain relief central gray matter stimulation	Duration of use
1	39	M	Carcinoma of larynx	Right neck; throat; shoulder	Left	Complete	3 months; died
2	54	M	Carcinoma of rectum	Bilateral hip; right lower quadrant of abdomen	Bilateral	Complete with right electrode; nil by left electrode	5 months; died
3	51	F	Carcinoma of colon	Bilateral back; right leg	Bilateral	Complete with either electrode	18 months
4	60	M	Diabetic neuropathy	Bilateral leg; perineum	Left	Complete	7 months; died
5	46	F	Sacral cordoma	Right hip and leg; sacrum	Bilateral	Complete with left electrode; nil with right electrode	7 months
6	27	F	Facial anesthesia dolorosa	Right face	Left	Partial*	

*The second electrode implanted in the left posterior ventral medial nucleus of the thalamus gave more complete relief of pain and was internalized (*9*).

stimulus (ramp current). The stimulus envelope progresses linearly for 30 seconds from 0.5 volt to the desired voltage and then repeats; the stimulus pulse is biphasic, with a variable pulse duration lasting up to 1.2 msec (*8*).

During the trial period, as well as after internalization of the electrodes, electrical stimulation of the brain was evaluated for each case in regard to its effect on (i) the patient's original pain, by the patient's subjective "pain estimate" based on a 0 to 10 scale (*9*), intake of analgesic medication, and general life style; (ii) the response to acute pain tested by either the Hardy-Wolf-Goodell dolorimeter (*10*) or pin-prick stimulation (or both); (iii) possible associated alterations in neurological or autonomic function (for example, blood pressure, respiration, heart rate, and electrocardiogram); and (iv) the voltage threshold necessary to produce pain relief. Because of reports (*11*) on the antagonist action of naloxone on stimulation-produced analgesia in animals, all patients were given intravenously administered naloxone to test this drug's effect on stimulation-produced analgesia as previously described (*12*). In all patients, naloxone was also given during the period when the stimulator was not in operation.

The clinical results are summarized in Table 1. Over a range of 3 to 6 volts stimulation, five patients reported total relief and one reported partial relief from intractable pain, with a latent period of 5 to 10 minutes. Those who reported total relief from their pain gave a "pain estimate" of 0 to 1 on the 0 to 10 scale and completely eliminated their intake of analgesic drugs. In the absence of brain stimulation an average pain level of 6 to 8 (*9*) was usually reported, even with an intake of intramuscular morphine amounting to 15 mg every 2 hours. One patient (case 6) who experienced partial relief after stimulation reported reduction of her facial pain from a 6 to 7 level to a 2 to 3 rating; she occasionally required additional nonopiate analgesics.

In addition to effective control of pain in the absence of opiate analgesics, all patients noted marked enhancement of their general feelings of well-being, increased appetite, and an ability to sleep better without sleep medication. All patients also reported that the pain relief they experienced allowed them greater ease in general physical activities than had been the case prior to electrode implantation.

There was no associated alteration in neurological or autonomic function during the electrical stimulation at levels that were sufficient to produce pain relief. Higher voltage or higher frequency stimulation often induced oscillopsia, ocular fluttering, nystagmus, nausea, peculiar sensations in the epigastrium, chest, and face, and a generalized impression of feeling "hot" (*13*).

Since the voltage threshold sufficient to award pain relief did not of itself produce any other characteristic sensations, it was easy to test the placebo effect of brain stimulation in a coded manner by providing a stimulus generator with a dead battery to the patient. In all patients, this placebo "stimulation" had no pain-relieving effect.

The first three patients were allowed to utilize the stimulation almost continuously. Within 4 to 5 weeks, the efficacy of pain control by electrical stimulation rapidly diminished, despite our efforts to increase the voltage and pulse duration to the maximum tolerance level. It was of interest that patients also developed considerable tolerance for narcotic medication. Larger quantities of intramuscular morphine or hydromorphone were needed for pain control than were required prior to initiation of brain stimulation. However, after electrical stimulation had been discontinued for a few weeks, the demand for narcotic medication dropped precipitously. Brain stimulation once again began to afford pain relief. We therefore instructed the patients to use the stimulation not more than 1 to 2 hours at a time and to wait at least 3 or 4 hours between periods of stimulation. This scheduled stimulation pattern eliminated both the development of tolerance to stimulation and the cross-tolerance to narcotic medication, phenomena which had previously been demonstrated in rats by Mayer and Hayes (*14*). Usually 30 minutes of stimulation afforded 3 to 4 hours of pain relief.

All patients were tested with pin-prick stimulation for acute pain sensation during brain stimulation. Only patient 5 reported a diminished sensitivity to pin-prick stimulation; this returned to normal 5 to 10 minutes after cessation of stimulation. This effect was repeatedly observed by several independent observers. Patient 3 also reported a similar diminished sensitivity to pain during pin-prick stimulation of her lower extremities, although this analgesic effect occurred only at a higher voltage that induced unpleasant ocular fluttering.

Patients 1, 2, and 3 were tested with the Hardy-Wolf-Goodell dolorimeter on face, limbs, and trunk (*10*) during brain stimulation. Despite the generalized relief from the original cancer-induced pain felt by all three patients, only patient 3 showed a 28 percent (230 mcal/cm^2 baseline to 320 mcal/cm^2 during brain stimulation) increase in pain threshold in the lower extremities during higher voltage brain stimulation, as described above.

Upon intravenous administration of naloxone, all patients except one (patient 6) reported the total reversal of pain relief produced by brain stimulation. The

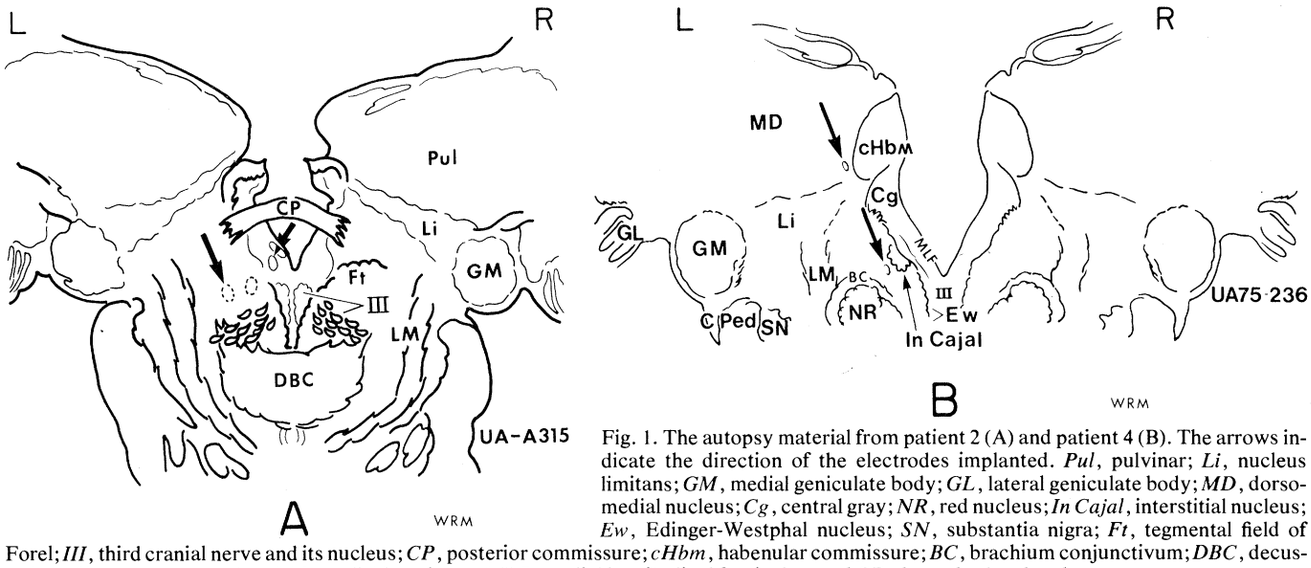

Fig. 1. The autopsy material from patient 2 (A) and patient 4 (B). The arrows indicate the direction of the electrodes implanted. *Pul*, pulvinar; *Li*, nucleus limitans; *GM*, medial geniculate body; *GL*, lateral geniculate body; *MD*, dorsomedial nucleus; *Cg*, central gray; *NR*, red nucleus; *In Cajal*, interstitial nucleus; *Ew*, Edinger-Westphal nucleus; *SN*, substantia nigra; *Ft*, tegmental field of Forel; *III*, third cranial nerve and its nucleus; *CP*, posterior commissure; *cHbm*, habenular commissure; *BC*, brachium conjunctivum; *DBC*, decussation of brachia conjunctiva; *LM*, medial lemniscus; *MLF*, medial longitudinal fasciculus; and *CPed*, cerebral peduncle.

dose of naloxone required for complete blockage of stimulation-induced pain relief varied from 0.2 mg to 1 mg, depending on the individual patient.

Patient 6 reported no reversal of stimulation-induced pain relief by 1.0 mg of intravenous naloxone, although she did report peculiar paresthesia at the right corner of her mouth, lasting for 20 minutes after administration of the drug. This was a part of the area rendered anesthetic by a previous trigeminal rhizotomy. Failure to observe the antagonist action of naloxone in this case may be due to an insufficient dose of the drug, although we did not follow up on this observation because of the perioral paresthesia induced by drug administration.

This atypical result, and the patient's report of partial relief from right facial anesthesia dolorosa by periventricular gray stimulation, may be explained by the fact that the patient's pain problem is one of deafferentation pain. The mechanism responsible for her pain, and its central transmission, may be quite different from that associated with pain of peripheral origin (*8, 15*). As was described previously, her dysesthetic pain was totally relieved by stimulation of the left posterior ventralis medialis nucleus of the thalamus (*8*).

When naloxone alone was given without concomitant brain stimulation, five patients reported no effect of naloxone itself on their degree of pain, with the exception of patient 1, who reported intense exacerbation of his throat pain for 45 minutes. To our knowledge, he had not received any narcotic medication for at least 24 hours prior to the administration of naloxone. A cursory sensory examination did not disclose any gross alteration in his sensory threshold, but careful dolorimeter evaluation of this patient was not carried out.

It is not clear whether the apparent alteration in the pain responsiveness of patient 1 is the counterpart of the phenomenon of pain-threshold lowering observed in rats by Jacobs *et al.* (*16*) or whether it is due to the acute withdrawal phenomenon often observed in people habituated to narcotics. No other patients reported similar experiences, even though some were known to have taken heavy narcotic medication for considerably long periods of time. Further evaluation of other patients in chronic pain states with naloxone testing may provide an answer to this question.

Since our patients did not obtain pain relief merely by implantation of the electrodes in the absence of stimulation, and since maintenance of pain relief requires that electrical stimulation be repeated at regular intervals, we do not believe that the mechanism of pain relief in our study is due to mechanical destruction of the area by electrode insertion or to any edema that may have resulted. In addition, no histological changes were observed in the brains of the deceased patients (patients 2 and 4) (Fig. 1). It might be reasonably suggested, however, that stimulation-produced pain relief results from either a functional lesion of this area (medial thalamic nuclei or mesencephalic loci) or the temporary disruption of the pain message at this level. The only evidence available in humans to contradict such an assumption is the data obtained by naloxone testing, and the cross-tolerance phenomenon observed between stimulation-produced pain relief and narcotic-induced analgesia. These results support the previous contention (*4, 17*) that focal electrical stimulation of the brain and morphine activate common mechanisms to produce analgesia, although our data do not provide any direct evidence concerning the mechanism by which tolerance develops.

In view of the demonstration of specific opiate binding sites (*18*) and the discovery of the endogenous substances enkephalin and the endorphins, which have morphine-like activity (*19*), our findings may further support the view that there is a neural system in the brain which utilizes such substances to produce pain relief. It may be that activation of this system can be brought about either pharmacologically, through direct receptor stimulation, or electrically by inducing release of the endogenous substance (*20*).

The specificity of the anatomical location for stimulation-produced analgesia in animals is observed in humans also as shown for patients 2 and 4. In patient 2, the more laterally located left electrode did not afford pain relief upon electrical stimulation of the area (Fig. 1). In patient 5, stimulation from the electrode on the right side had no effect on the pain while stimulation on the opposite side produced complete pain relief. Postoperative x-ray examination revealed that the right electrode appeared to be placed a few millimeters lateral to the intended target point.

The "field of analgesia" reported for animals (*4, 21*) has not been observed in our study, with the exception of the pain threshold alteration seen in patient 3. Electrodes were placed contralateral to the side of the patient's original pain or

bilaterally placed if the pain were bilateral or midline in location; however, in all cases unilateral stimulation of the central gray matter afforded generalized pain relief.

Despite the fact that all six patients received partial to total relief from their intractable persistent pain by brain stimulation, only two patients reported alteration in acute pain threshold as tested by pin-prick stimulation or graded thermal energy. In contrast to these results in humans, stimulation-produced analgesia in animals is obviously accompanied by a marked elevation of the pain threshold, varying in magnitude according to the area tested (*2–4*).

At present we do not understand how the afferent mechanism involved in persistent pain differs from that operating in cases of acute pain. It is quite possible that the actual afferent input signal of persistent pain is far less intense than that of acute pain, but that its persistence in duration causes the suffering. For such low amplitude input, the success of stimulation-produced pain relief does not require an alteration in the threshold to acute pain. It is also true that the electrical energy applied to the human central gray matter in this study is far less than that previously applied to animals (*2–5, 8*). Our observation with patient 3 that the threshold to dolorimetry testing was elevated only at the higher voltage supports this view.

Two of our six patients who are still living have been using the stimulator as their sole means of pain control for more than 12 months.

Obviously, many more studies must be conducted before the knowledge already accumulated on the subject of stimulation-produced analgesia in animals can be applied to the benefit of human suffering. However, our results provide evidence for the potential usefulness of brain stimulation as a nondestructive method for controlling intractable persisting pain in humans.

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6. All procedures, risks, benefits, and alternative treatments pertaining to this research were explained to all patients participating in this study, and each of them signed a written informed consent form.
7. The multicontact platinum-iridium electrodes used in this study are manufactured by Medtronic Inc., Minneapolis, Minn. The electrode is a highly flexible cable composed of seven intertwined, separately insulated platinum strands. Each of these strands terminates in a separate contact region 2 mm apart on the cable axis. The contact region is formed by wrapping an insulation-free strand end several times around the cable shaft. Shaft diameter is approximately 0.3 mm. Approximate contact dimensions are diameter, 0.5 mm; length, 0.5 mm; and effective surface area, 1.5 mm^2.
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Electrically Coupled, Photosensitive Neurons Control Swimming in a Jellyfish

Abstract. *Central neurons in* Polyorchis *(Hydromedusae) were impaled with microelectrodes, and conventional resting potentials were obtained. The waveform of action potentials recorded concurrently with swimming events shows evidence of electrotonic coupling between these neurons, which are also directly photosensitive and receive excitatory synaptic input from other conduction systems.*

Considerable advances in our knowledge of coelenterate conduction systems and pacemaker interactions have been made in recent years (*1*), but, with few exceptions (*2–4*), all of our information has come from extracellular recordings. It is known that both nerves and epithelia can provide pathways for behavioral responses, but, since nerves frequently run among epithelial cells, it is often difficult to determine whether a conduction system is nervous or epithelial. Because of their small size, coelenterate cells are hard to record from with microelectrodes; in only one instance (*4*) has it been possible to show, by intracellular recording, that a particular axon is the pathway for a physiologically defined conduction system. As the lowest animals equipped with nerves, the coelenterates can provide important insights into the organization and evolution of nervous systems generally, but the lack of information on neuronal activity at the cellular level has reduced the significance of much of the coelenterate work for neurobiologists as a whole.

This report gives the first results from our work on a coelenterate preparation in which central neurons can be regularly impaled with microelectrodes (*5*). The species is the hydromedusan jellyfish *Polyorchis penicillatus* Eschscholtz. The neurons lie in the inner nerve ring, a bundle of neurons that runs around the margin of the bell near the base of the velum.

Studies on other hydromedusae [for example (*6, 7*)] indicate that the swimming pulse (SP) system, which generates and transmits the impulses for swimming, is located at the margin of the bell, probably in the inner nerve ring. A second conduction system, which uses pathways in one or both of the marginal nerve rings (*6, 7*), is the marginal pulse (MP) system, which coordinates tentacle