Acupuncture (derived from the word acus, meaning a sharp point, and punctura, meaning to pierce), is defined as "stimulation, primarily by the use of solid needles, of traditionally and clinically defined points on or below the skin, in an organized fashion for therapeutic and/or preventive purposes" (1). The original acupuncture points (or acupoints) are superficial anatomic loci described in traditional Asian texts. The skin directly over these points is generally lower in transdermal electrical resistance than the skin surrounding them. There is considerable overlap between these traditional acupoints and treatment locations defined in modern physical medicine such as "trigger points," "motor points," or "osteopathic lesions." Acupuncture points are often palpable as either mild depressions or small, and sometimes tender, subcutaneous nodules. In traditional Asian medicine, these points are stimulated either by puncture and manipulation with solid needles or by local heating. Heating is generally accomplished by the burning of dried, powdered Artemisia vulgaris (moxa), referred to as moxibustion. This moxa is either held just above the acupoint by the acupuncturist (indirect moxibustion), attached to a needle penetrating the point, or applied directly to the skin (direct moxibustion). In modern times, new methods of stimulating the acupoints include applications of electric current to needles in the points (electroacupuncture) or skin electrodes over the points, injections into the points, laser-light directed onto the points, or finger-pressure massage of selected points, called acupressure. In addition, many new points and whole new "microsystems" of points have been described on specific body parts on which an entire hunchulus is represented, leading to, for instance, scalp acupuncture, hand acupuncture, and (of particular interest for addiction treatment) ear acupuncture, also known as auricular acupuncture.

Although acupuncture and related acupoint therapies are most commonly known for their analgesic effects, their medical applications are by no means limited to pain treatment. After a careful literature and clinical survey, the World Health Organization (WHO) listed 42 medical problems that are were considered suitable for acupuncture treatment, including the treatment of drug abuse. A smaller group of definite or possible indications for acupuncture were recommended by an National Institutes of Health (NIH) Consensus Panel in 1997 as follows: "Promising results have emerged, for example, showing efficacy of acupuncture in adult postoperative and chemotherapy nausea and vomiting and in postoperative dental pain. There are other situations such as addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofacial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma when acupuncture may be useful as an adjunct treatment or an acceptable..."
alternative or be included in a comprehensive management program" (2). Although a consensus on the clinical efficacy of acupuncture for the treatment of addictions has not yet been achieved in the United States, it has been amply demonstrated that acupuncture is an addiction treatment service now being sought by many potential patients (3). Thus, as with many low-cost alternative-healing practices, acupuncture may serve an important role in social marketing of the entire treatment package, enhancing use and compliance. This is an important potential benefit that is additional to any specific physiologic effect(s) of acupuncture, which is documented in the rest of this chapter.

CLINICAL OBSERVATION

The application of acupuncture in the treatment of opioid addiction originated from a serendipitous observation made by Dr. H. L. Wen in Hong Kong in 1972. The following is a brief description quoted from Dr. Wen’s report on this case:

In early November 1972, a 50-year-old man was admitted to the Neurosurgical Unit of the Kwong Wah Hospital, Tung Wah Group of Hospitals, Kowlong, in Hong Kong, because of brain concussion. He was a known opium addict of 5 years’ duration. While in the ward, he was given tincture of opium to relieve his withdrawal syndrome. After the cerebral concussion had improved, the patient was asked whether he would agree to cingulotomy to relieve his drug abuse problem. He agreed. He was scheduled for surgery on the 9th of November 1972. During the operation for surgery, instead of local anesthesia being injected under the scalp (where the incision was to be made), acupuncture anesthesia (analgesia) was used.

Four needles were inserted into the right hand (IL-4 and SI-3) and in the arm (EH-4 and TB-9), and another two needles were inserted into the right ear (brainstem and Shenmen). Stimulation with an electrical stimulator was carried out for half an hour. At that time, our interest was in discovering whether the patient obtained analgesia in the scalp prior to surgery. During stimulation, 15 to 30 minutes later, the patient voluntarily stated that his withdrawal syndrome had completely cleared up. We examined him and found that he was free of withdrawal syndrome. Operation was canceled and the patient returned to the ward with advice to the nursing staff that doctor should be informed if the patient showed withdrawal symptoms again. At 9:00 P.M. 1 [HKW] was informed that the patient had another withdrawal syndrome. Again, acupuncture and electrical stimulation was carried out in a similar manner, the withdrawal symptoms again disappeared. The next day, we saw two other patients in the orthopedic wards who were both opium abusers. When we explained how we wanted to treat their withdrawal symptoms, both agreed to the procedure. Both responded well to the half hour of acupuncture and electrical stimulation and their withdrawal symptoms stopped.

After the above observation, Dr. Wen and his colleague, Dr. Cheung, at the Kwong Wah Hospital, subsequently reported that, in a study of 40 heroin and opium addicts, acupuncture combined with electrical stimulation was effective in relieving the symptoms of narcotic withdrawal (4).

This method was later adopted in many clinical settings in Western countries, including at Lincoln Hospital in New York City. However, as time and experience accumulated, the body acupuncture points originally used by Wen and Cheung on the arm and hand were gradually omitted, retaining only the ear points for acupuncture in drug abuse treatment (5) and doing without additional electrical stimulation. The protocol developed at Lincoln Hospital by Dr. Michael Smith and his colleagues was subsequently promulgated by the National Acupuncture Detoxification Association (NADA) on a national basis, with formalized training and standards for the application of ear acupuncture in a group setting without the use of electricity. This has been the predominant approach studied by clinical trials and practiced in the United States since then, and is described in more detail later in the Clinical Trials section.

IMPLICATION FROM ANIMAL EXPERIMENTS

The use of acupuncture as a method of anesthesia and/or analgesia for surgery in the People’s Republic of China in the late 1950s raised a great deal of interest among the public and the biomedical community. This led to exploration of the biologic mechanisms underlying the actions of acupuncture. Starting in 1965, the Department of Public Health of the Chinese government sponsored extensive research in this area. The discovery of morphine-like substances (endorphins) in the mammalian brain (6) in 1975 had a great impact on modern concepts of pain and analgesia. It was soon clear that acupuncture (manual needling)-induced analgesia can be blocked by the opioid antagonist naloxone (Narcan), suggesting the involvement of endogenous opioid substances in acupuncture analgesia (7). In animal experiments, manual acupuncture or acupuncture combined with electrical stimulation (electroacupuncture) was shown to accelerate the production and release of endorphins which could then interact with various opioid receptors to relieve or prevent pain (8). It was further clarified that endorphins are a group of peptides possessing a variety of specific characteristics. Among those peptides, β-endorphin and enkephalin are primarily agonists of the μ and δ opioid receptors, whereas dynorphin is the agonist for the κ opioid receptors (9). Interestingly, electrical stimulation of different frequencies can specifically induce the release of different endorphins. For
example, low-frequency (2 to 4 Hz) electroacupuncture stimulates release of the enkephalins that interact with \( \mu \) and \( \delta \) opioid receptors, whereas high-frequency (100 Hz) electroacupuncture can stimulate the release of dynorphin to interact with \( \kappa \) opioid receptors (10). These findings provided a biochemical explanation for traditional practice and suggested that the usefulness of acupuncture might be much broader than pain control.

China had suffered seriously from problems of opiate addiction in the 1800s and early 1900s. This problem was minimized from 1949 to 1951 because of the complete closure of overseas trade involving opioids. However, concurrent with the implementation of the “open door policy” of the 1980s, large amounts of opiates began to be smuggled into border areas and increasing problems were seen with opiates and heroin addiction. In that period, the number of persons abusing or addicted to heroin was estimated to be increasing as much as 10% to 40% per year. Accompanying this, hand in hand with heroin injection, was the problem of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). It was natural to think that if acupuncture can release endogenous opioids in the brain to ease pain, why not make use of it to relieve withdrawal symptoms? This idea was initially tested in morphine-dependent rats. The withdrawal symptoms were significantly reduced by high-frequency (100 Hz) electroacupuncture administered at the hind limbs. This effect was found to be much greater than that induced by low-frequency (2 Hz) stimulation (11). Encouraged by the experimental results, electroacupuncture was applied clinically to heroin-addicted patients to see if it suppressed withdrawal symptoms. The results here were also promising. However, it was soon found that it was not always feasible for patients to attend the clinic to obtain professional treatment one or more times a day, and, as a result, patients often missed many of the recommended number of sessions of acupuncture, with adverse consequences for therapeutic results. Technology for self-administration of the stimulation was developed to see whether it would be possible for patients to treat themselves as many times per day as they might desire, by using electrical acupoint stimulation without a needle, as part of the treatment program for their addiction.

Experimental findings obtained in the rat model had showed that electrical stimulation applied to the surface of the skin could produce analgesic effects similar to that produced by electroacupuncture, as long as the stimulator provided a controlled current (to correct for varying skin resistance in the absence of a penetrating needle electrode) (12). Satisfactory subjective results were obtained for the treatment of heroin withdrawal in humans using the same method of electrical acupoint stimulation via skin electrodes (13). Later it was found that this device was also useful in suppressing the conditioned place preference (CPP) to morphine in the rat (14). This is an animal model of craving for drugs of abuse. Subsequent human studies revealed that this form of stimulation could also inhibit the craving for heroin in addiction patients (see below).

Data are presented in the following sections on the role of acupuncture and related techniques in treating both withdrawal from, and craving for, drugs of abuse, especially cocaine and possibly heroin, as well as other substances of abuse, such as alcohol. Results obtained in animal experiments are presented as a method of exploring acupuncture’s potential mechanisms of action.

**ACUPUNCTURE AND RELATED TECHNIQUES**

**Manual Needling**

As discussed in the previous paragraphs, classical acupuncture involves the piercing of the skin by a sharp metallic needle and manipulation by up-and-down and twisting or twirling movements. The traditional purpose of these movements is supposedly to stimulate the underlying anatomic conceptual structures described as meridians or channels (jing) and their branches (luo). The meridians may represent networks of connective tissue and nerves or may be merely allegorical and/or functional entities that serve as mnemonic aids to point locations. The correct placement of the needle at the acupoint and the optimal manipulation are generally characterized by feedback from the patient concerning a subjective feeling called de-qi. This sensation, reported by patients to include heaviness, soreness, numbness, and sense of swelling, occasionally also involves the trembling of the local muscle. In the meantime, the operator of the needle (the acupuncturist) often has a feeling resembling that experienced during fishing when a fish is nibbling at or swallowing the bait. This is likely the result of the rhythmic contraction of muscle fibers surrounding the needle. With this approach, the tip of the needle is felt to go deep into the tissue and believed to stimulate the structures to induce maximal de-qi, experienced by both patient and acupuncturist. The shortcoming of this method, especially for research purposes, is that it is empirical and subjective in nature, difficult to describe precisely, and by no means easy to replicate by others. According to the traditional acupuncturist, it takes years to really master the particular modes of manual stimulation.

**Electroacupuncture**

It has been made clear that the analgesic effect induced by acupuncture can be completely blocked by a local procaine injection deep into the acupoint, but not by its subcutaneous injection, suggesting that the signal of acupuncture originates mainly from nervous tissues (or tissues susceptible to procaine blockade) located in deep structures rather than in the superficial layer of the skin (15). Using single nerve fiber recording technique to record the afferent
impulses of the nerve innervating the site of stimulation, it was found that the nerve fibers responsible for transmission of acupuncture signals belong to the group II (Aδ) fibers (16). Strong twisting and up-and-down movements of the needle produces a firing as high as 50 to 80, but no more than 100, spikes per second. Because the analgesic effect induced by manual needling can be totally abolished by local nerve blockade (15) or nerve transection, a neural mechanism is strongly implicated. It is thus rational to use electrical stimulation administered via the metallic needles in lieu of its mechanical movement. This has been called electroacupuncture. The advantage of the electroacupuncture is that the frequency, amplitude, and pulse width of the electrical stimulation can be determined precisely and objectively. Consequently, it can be replicated by other acupuncturists or experimenters without difficulty. Moreover, the procedure of inserting the needle at a precise skin location, as well as changing the direction and the depth of the needle to an optimal status, can still be performed by an experienced acupuncturist to achieve a maximal de-qi for confirmation of placement. It is only at the end of the placement procedure that the needles are connected to the electrical stimulator in place of further manual stimulation. This is exactly the procedure described by Dr. Wen in his first report, that is, “acupuncture and electrical stimulation” (4). Having said that, it should be mentioned that because electroacupuncture should optimally be given daily, or even on an as-needed basis, several times per day in the period of detoxification, which may be difficult for outpatients who are at a distance away from the clinic. A procedure that can be operated by the patient at home under the supervision of the physician might be a desirable alternative to daily treatment in the clinic or inpatient care.

In addition, because drug-addiction patients, especially those using injection routes of administration, have a high incidence of blood-borne viral infections, it may be more convenient for invasive procedures to be replaced by non-invasive methods that do not produce sharp biohazardous waste.

Han’s Acupoint Nerve Stimulator

An alternative to use of the electroacupuncture (insertion of a needle through the skin to deliver electrical stimulation for the underlying tissue) is to use a transcutaneous route of electrical administration. However, because the skin has a very high impedance, which is more than 10 times that of the muscle tissue, it is necessary to use a constant current output device to assure a regular level of stimulation without being affected by the degree of moisture of the skin surface or the change of blood flow rate within the skin. Because the tip of the needle goes several millimeters or even centimeters below the skin, the placement of the skin electrodes should ensure the maximal stimulation of the deep structures underlying the acupoint. For example, to stimulate the Hegu point (coded as Large Intestine 4 [LI-4]) located in the thenar muscle of the hand, the correct placement of the skin electrodes should be on the dorsal side and the other on the palm side of the point, so that the current is forced to pass through the thenar muscle with little deviation.

Regarding the frequency of stimulation, it is commonly accepted that conventional transcutaneous electric nerve stimulation (TENS) is based on the gate-control theory (17) that high-frequency (e.g., 100 Hz) low-intensity stimulation is preferable to activate the large-caliber nerve fibers in order to suppress the pain mediated by the unmyelinated small-caliber fibers. On the other hand, “acupuncture-like” stimulation is characterized by low-frequency (e.g., 2 Hz), high-intensity stimulation. The current approach attempts to combine TENS-like and acupuncture-like stimulation to create what is hoped to be an optimal mode of stimulation to maximize the release of both classes of endorphins. A device that possesses these features was designed and named Han’s Acupoint Nerve Stimulator (HANS), and used in a series of animal and clinical experiments, the details of which follow.

**OPIOID DETOXIFICATION**

**Experimental Studies**

Systemic studies reveal that the mechanism of acupuncture analgesia is attributed mainly to the increased release of endogenous opioid peptides in the central nervous system (CNS) (8). A rational extrapolation is that the activation of endogenous opioid systems by acupuncture should be useful to ease opiate withdrawal symptoms.

It has been reported that transauricular electrostimulation suppressed the naloxone-induced morphine withdrawal syndrome in mice (18) and in rats (19). Auriacombe et al. (20) demonstrated that TENS with an intermittent high-frequency current effectively attenuated the abstinence syndrome of the rat after abrupt cessation of morphine administration. The mechanisms of action remained obscure. Based on our previous findings that low-frequency electroacupuncture (e.g., 2 Hz) accelerated the release of β-endorphin and enkephalin in the CNS, whereas high-frequency electroacupuncture (e.g., 100 Hz) accelerated the release of dynorphin (10,21) in the spinal cord, we tested the effect of electroacupuncture in a naloxone-precipitated morphine withdrawal model of the rat. The original perspective was that 2 Hz would be more effective than 100 Hz in suppressing withdrawal syndrome, if the effect of electroacupuncture is to accelerate the release of morphine-like opioid peptides (enkephalin and endorphin) to replace morphine, thus ameliorating abstinence syndrome. To our surprise, the results showed that 2-Hz electroacupuncture was only marginally effective in reducing withdrawal in 2 of 5 signs, whereas 100 Hz electroacupuncture produced a dramatic suppression of all 5 withdrawal signs. In other words, 100-Hz
electroacupuncture was far more effective than 2-Hz electroacupuncture in suppressing withdrawal syndrome (11).

This outcome can be explained in three ways. First, the experimental design was that naloxone was given immediately after the electroacupuncture, therefore the effect of electroacupuncture itself may be partially blocked by naloxone. One may expect that if 2-Hz electroacupuncture is used to treat spontaneous withdrawal rather than naloxone-precipitated withdrawal, the therapeutic effect might be more prominent. This was verified in the human studies cited in the Human Observations section. Second, compared with 2 Hz, the effect of 100-Hz electroacupuncture is less likely to be affected by naloxone at this dose, because 100-Hz electroacupuncture effect is mediated by dynorphin, which is a K opioid agonist and is relatively resistant to naloxone blockade (ID$_{50}$ = 10 mg/kg) (22). Third, dynorphin suppresses the withdrawal syndrome in heroin-dependent humans (23) and in morphine-dependent monkeys (24), and the site of action is in the spinal cord (25).

To explore the possible involvement of dynorphin and K opioid receptor in the effect of 100-Hz electroacupuncture for modulating withdrawal syndrome in rats, Cui et al. (26) used rats made dependent on morphine. These rats were then given spinal intrathecal administration of a K opioid receptor agonist U-50488 or its antagonist nor-binaltorphimine dihydrochloride (nor-BNI). Naloxone (0.5 mg/kg) was then administered to precipitate withdrawal syndrome. U-50488 produced a dose-dependent suppression, whereas nor-BNI elicited a dose-dependent augmentation of naloxone-precipitated withdrawal. The latter result implies that an endogenous K agonist, most probably dynorphin, exerts a tonic suppressive effect on morphine withdrawal syndrome at the spinal level.

Withdrawal syndromes have multiple manifestations. One of the cardiovascular manifestations of the withdrawal syndrome is an increase in heart rate. In a mouse model of morphine dependence induced by multiple injections of increasing doses of morphine for 8 days, the heart rate and blood pressure were measured by tail cuff method (27,28). Morphine abstinence resulted in a 20% increase of the heart rate without affecting the blood pressure. Electroacupuncture of 100 Hz or 15 Hz was very effective in bringing down the heart rate to approach normal level; 2 Hz produced only a mild effect.

An intriguing finding was that the therapeutic effect of electroacupuncture was achieved only when the stimulation intensity was kept at a low level (1 mA). The effect of electroacupuncture disappeared when the intensity was increased to 2 to 3 mA. This is probably a result of the stressful effect produced in mice by high-intensity stimulation that activates the sympathetic system, thus antagonizing the calming effect of electroacupuncture. Subsequent studies revealed that the intensity tolerated by the mouse is indeed smaller than that for the rat. For example, to induce an analgesic effect, the optimal intensity is 0.5 to 1.5 mA for mice (29), in contrast to 1 to 3 mA for rats (30).

To summarize, for the purpose of opioid detoxification in rats and mice, it is preferable to use electroacupuncture of higher frequency and lower intensity, which may have some implication for its application in humans.

**Human Observations**

To observe the effect of HANS on the withdrawal syndromes in heroin addiction, HANS was used once a day for 30 minutes for a period of 10 days in a drug-addiction treatment center (13). Aside from the subjective answer to a standard questionnaire, two objective parameters were measured, that is, heart rate and body weight.

**Single Treatment**

To observe the immediate effect of HANS on the heart rate of patients in withdrawal from heroin, the two pairs of output leads of the HANS were connected to four acupuncture points in the upper extremities. One pair of skin electrodes was placed on the Hegu point (LI-4, at the dorsum of the hand on the thenar eminence) and the other at the palmar side on Laogou (P-8, opposite to LI-4), to complete an electric circuit. Another pair of electrodes were placed on Neiguan (P-6, located at the palmar side of the forearm, 2 inches proximal to the palmar groove, between the tendons of the palmaris longus and flexor carpi radialis) and Waiguan (TE-5, on the dorsal surface of the forearm opposite the P-6 point, to complete a circuit. A "dense-and-disperse" mode of stimulation was administered, in which 2-Hz stimulation alternated automatically with 100-Hz stimulation, each lasting for 3 seconds. This mode of stimulation releases all four kinds of opioid peptides in the central nervous system (CNS) (10), hopefully producing a maximal opioidergic effect. The control group received the same treatment of placing the skin electrodes on site, except that the electrodes were disconnected from the electronic circuitry. The average heart rate of the patients in opioid withdrawal was 109 beats per minute before treatment. The dense-and-disperse mode stimulation for 30 minutes reduced the heart rate in a significant extent, as shown in Figure 49.1. Suppression of the tachycardia occurred within the first 5 to 10 minutes. Heart rate continued to fall through the 20th minute, and leveled at 90 beats per minute for the last 10 minutes. This change is statistically significant, although the effect is short lasting. The full effect remained for only 20 minutes after the stimulation; thereafter, heart rate began returning to its original level (31).

**Multiple Treatments**

To observe the cumulative effect of multiple daily treatments with HANS, 117 heroin-addiction patients were
randomly divided into 4 groups. Three groups received HANS of 2 Hz (constant frequency), 100 Hz (constant frequency), or 2/100 Hz (2 Hz alternating with 100 Hz, or "dense-and-disperse mode") respectively. The control group received mock stimulation, where the skin electrodes were placed on site and connected to the stimulator with blinking signals, yet the electric circuitry was disconnected. The treatment was for 30 minutes a day and was given for 10 consecutive days. Heart rate was measured with an electrocardiogram before and immediately after the HANS stimulation. Figure 49.2 shows the results. Taking the 2-Hz group as an example, in the first day of observation, the heart rate averaged 110 beats per minute, which dropped to 90 beats per minute immediately after the HANS treatment ($p < 0.01$). In the second day, the heart rate averaged 102 beats per minute, and then dropped to 91 beats per minute after the treatment ($p < 0.01$). This trend continued for days 3 and 4. On day 5, no significant difference was found in heart rate before and after the treatment ($p < 0.01$). This suggesting that the heart rate had returned to "normal" range (13).

Comparing the effects among the three HANS groups, the 100-Hz group produced a slightly better result than that of 2 Hz. In the 2/100-Hz group, the after-HANS heart rate reached an even lower level (72 beats per minute). Additionally, the heart rate of the 2/100-Hz group returned to "normal" range on day 4, 1 day earlier than the fixed frequency groups (day 5). In the control group ($n = 30$) receiving mock HANS, heart rate did not come down to a level of 100 beats per minute until 8 days after the treatment. The results suggest that repeated daily electroacupuncture treatment is effective in reducing the tachycardia of heroin withdrawal, with an effective order of dense-and-disperse $> 100$ Hz $> 2$ Hz.

Another objective parameter for measuring the severity of heroin withdrawal is body weight. The heroin addicted subjects recruited in this study were aged 17–35, their average body weight was only 49–51 kg. In the control group receiving mock HANS, body weight showed a reduction of 1 kg at the end of the first week, probably due to the presence of withdrawal distress. In the HANS treated groups, a significant increase of body weight developed after 4 days of treatment, and continued to increase thereafter. A net increase of 5 kg was recorded in the HANS groups compared with the control group at the end of 10 day observation period. This increase of body weight (approximately 10%) is apparently due to the reduction of the withdrawal syndrome and an increase of food and water intake in the HANS-treated groups. It is interesting to find that while the dense-and-disperse mode is significantly better than the fixed frequency groups in ameliorating the tachycardia, no significant difference was observed among the three HANS groups in terms of body weight changes, suggesting that the mechanisms of action underlying heart rate- and body weight-modulation may not be identical (13).
In clinical practice with Chinese inpatients, opiate withdrawal symptoms have been significantly reduced, but not totally abolished by the HANS treatment, especially in those who had a history of heroin abuse for more than 5 years. To obtain a quantitative estimate of the effect of HANS, the following protocol was established (32): (a) HANS was used several times a day, with a maximum of four times a day on days 1 and 2, then two to three times a day on days 3 to 7, and twice a day on days 8 to 14. (b) A four-channel HANS device was used instead of two-channel device. The acupoints used were Hegu/Laogong for left (or right) hand, Neiguan/Waiguan for right (or left) arm, and Xingjian/Sanyinjiao (LV-2/SP-6) for left leg, as well as for right leg. (c) The intensity of stimulation was 5 to 7 mA for the first day (5 to 6 mA being the threshold value [T]), 1.5 to 2.0 T for the second day, and 2.5 to 3.0 T for the third day and thereafter. (d) Buprenorphine (Buprenex) i.m. was used as a supplement to HANS when the patient experienced a certain degree of withdrawal distress. Patients were allowed to ask for buprenorphine as much as they liked, and medication was administered on request. The purpose of this arrangement was to maintain a comfortable detoxification procedure with minimal withdrawal discomfort. In a study to quantify the role of HANS in a combined HANS/buprenorphine treatment, 28 heroin addiction patients were randomly divided into 2 groups, receiving buprenorphine only, or HANS plus buprenorphine. The results are shown in Figure 49.3A. In the buprenorphine-only group, the total dose requested in 14 days averaged 12.91 ± 1.34 mg (X ± SEM [standard error of mean]), whereas the total dosage requested by the HANS-plus-buprenorphine group averaged only 1.01 ± 0.09 mg, which was consumed only in the first 5 days. In other words, the total amount of buprenorphine used in the HANS group was only 7.8% of that needed in the pure buprenorphine group. This can be taken as a quantitative estimate of the effect of HANS for opioid detoxification. Compared with the relatively mild and short-lasting therapeutic effect observed in the first day treatment (see Fig. 49.1), the marked symptomatic improvement of the 14-day multiple treatment regime (Fig. 49.3) is apparently a result of an accumulation of the therapeutic effect produced by repetitive treatments. These results of short-term withdrawal are described primarily to illustrate the physiologic effects of the acupoint stimulation. Because short-term withdrawal does not have significant effects on the long-term course of addiction, these results are not described as a measure of true clinical or therapeutic benefits.

**Fig. 49.3.** Influence of 2/100Hz electric stimulation (HANS) on the requirement of buprenorphine (BPN) (A) or methadone (B) for heroin detoxification. °° P<0.01 compared with the corresponding control group. (Modified from Wu LZ, Cui CL, Han JS. Treatment on heroin addicts by 4-channel Han's Acupoint Nerve Stimulator (HANS). J Beijing Med Univ 1999;31:239-242, and Wu LZ, Cui CL, Han JS. Reduction of methadone dosage and relief of depression and anxiety by 2/100 Hz TENS for heroin detoxification. Chin J Drug Depend 2001;10:124-126, respectively, with permission.)
Similar observations were made in another group of heroin-addicted subjects using a methadone reduction protocol as control group and HANS (2/100 Hz) plus methadone as the experimental group (33). Figure 49.3B depicts the results. The total dose of methadone used in the control group averaged 202 ± 15 mg (X ± SEM), whereas in the HANS-plus-methadone group the total dose of methadone was only 50.5 ± 8.2 mg, showing a reduction of 75% (p<0.001).

A bonus effect of HANS treatment is on the injection mark syndrome (32). At the end of the 14-day detoxification period, the injection marks on the skin were significantly reduced in the HANS-plus-buprenorphine group as compared with the buprenorphine-only group. Among the five indicators, such as the venous collapse, fibrotic thickening of the venous wall, thrombosis, bluish streak, and scarred mainliners, the first two indicators showed the most striking difference. Although a minor finding, the disappearance of the injection marks made the patients very happy, because was a symbol indicating the beginning of a new and normal life. The mechanisms underlying these structural changes remain unclear. A plausible hypothesis is that an improvement of the microcirculation as a result of the decrease of the peripheral sympathetic tone is responsible for the facilitation of tissue repair as well as the production of the “warm feeling” (13) experienced by the patient during the HANS treatment.

Peking University Clinical Bases
Treatment Protocol

The following protocol is based on the clinical practice evolved over the past 10 years at Peking University Drug Abuse Treatment Clinical Bases (PUCB):

1. Patients with drug addiction are admitted for inpatient treatment once their status has been verified by physical examination and urine toxicology and informed consent is obtained.

2. No drug whatsoever, including narcotics and nonnarcotics, can be brought into the PUCB from the outside.

3. The principle of electrically stimulated acupuncture treatment (to make full use of the resources existing in the central nervous system to counter the pathophysiologic changes produced by drug abuse) is explained to the patient. Although this is a nonpharmacologic treatment, enough pharmacologic supplements will be available, if needed, to avoid any excessive withdrawal symptoms.

4. HANS is immediately administered to the patient upon admission. A four-channel device is used, with the four electrical leads connected to four pairs of skin electrodes placed at four pairs of acupoints: Hegu and Laogong on the left (or right) hand; Neiguan and Waiguan on the right (or left) arm; and Xingjian (LV-2) and Sanyinjiao (Sp-6) on the left and the right legs.

5. Unless otherwise stated, the frequency is put at the dense-and-disperse mode, that is, 2 Hz alternating with 100 Hz at 3-second intervals. The pulse width changed automatically with the frequency, that is, 0.2 ms pulse width for 100-Hz stimulation and 0.6 ms for the 2-Hz stimulation.

6. The intensity of the electric stimulation is determined according to the sensitivity of the subject to the stimulation. In the first treatment when the patient is not familiar with the electrical stimulation, a threshold (T) intensity (5 to 6 mA) is preferable. When patients become familiar with the stimulation, they usually prefer to have higher intensity in order to strengthen the relief experienced from withdrawal symptoms. The stimulation intensity can then be increased to twice threshold (2T or 10 to 12 mA), or even greater, so long as the patient feels comfortable. Rhythmic contraction of the local muscle is often observed. One treatment session lasts for 30 minutes. The electric output is automatically cut off at the end of that period.

7. HANS treatment is given for no more than four times a day in days 1 and 2 of drug abstinence. Thereafter it is administered three times a day for the first week, and then twice a day for the second week. Irrespective of how many times a day HANS treatment is given, a session before going to bed is always administered with the intention of ensuring a good night’s sleep.

8. Buprenorphine (32) or methadone (33) can be used as supplement when the patient feels excessive degrees of withdrawal distress. The dose for the first 2 days is 30 to 40 mg for methadone or 2 to 3 mg for buprenorphine. It should then be gradually reduced according to the individual’s requirements. Opioid supplementation usually lasts for 2 to 7 days. Compared with the purely pharmacologic regimen, the HANS-treated patients report an easier time in becoming drug free.

9. Patients that are coaddicted to sedatives or other drugs of abuse often ask for the relevant drugs. These requests are usually not fulfilled. The standard treatment regime usually takes care of all the related symptoms (see “Lincoln Hospital Protocol” below).

10. Close contact between doctor and patient and communication between patients are highly encouraged.

11. Detoxification is usually completed in 14 days. However, the patient is welcome to stay longer in the treatment center for consolidation of the therapeutic effect. In that case, HANS can be given once or twice a day for another 2 weeks.

Lincoln Hospital Protocol

Acupuncture treatment for drug and alcohol problems was originally introduced in 1974 at Lincoln Hospital (LH), a city-owned facility in the South Bronx of New York
City for the treatment of drug and alcohol problems. The Substance Abuse Division at LH is a state-licensed treatment program that has provided more than 500,000 acupuncture treatments in the past 20 years. Initially, in 1974, LH used Dr. H. L. Wen's method, applying electrical stimulation to the lung point in the ear. At that time acupuncture was used as an adjunctive treatment for prolonged withdrawal symptoms after a 10-day detoxification cycle. Subsequently twice daily acupuncture was used concurrently with tapering methadone doses. Reduction in opiate withdrawal symptoms and higher retention rates were reported (34).

It was serendipitously discovered that electrical stimulation was not necessary to produce symptomatic relief. Instead, simple manual needling was found to produce a more prolonged effect. Patients using acupuncture only one time a day still experienced a suppression of their withdrawal symptoms. Gradually the acupuncture protocol was expanded by adding the "Shen Men" (spirit gate), an ear point that is well known for producing relaxation. Other points were tried on the basis of lower skin resistance, pain sensitivity, and clinical indications during a several-year developmental process. Dr. Smith of LH added the "sympathetic," "kidney," and "liver" points to create a basic five-point formula. Over time, patients receiving ear needling reported continuing benefits from use of this protocol and were allowed to continue to attend LH for acupuncture on a "drop-in" basis, often continuing to attend several times per week for months or even years. Patients received frequent (on-site) urine testing for drugs, and were given their results in an immediate and nonjudgmental fashion. Although they came to LH for acupuncture, patients often took advantage of a variety of treatment services that were available there. Over time, although still called "acu-detox, the program included as-needed "aftercare" to such a large degree that it came to resemble more of an ongoing or maintenance program than a detoxification program. This was seen as a good thing, because patients in the literature were making it clearer that length of stay in any modality of treatment was a key predictor of better outcomes (35).

The standard formula seemed to be equally helpful for different drugs of abuse and at different stages of treatment (36). Patients responded better when acupuncture treatment was administered quickly without a self-conscious, diagnostic prelude. A group setting enhanced the acupuncture effect. A group size of fewer than six members seemed to diminish symptom relief and retention significantly. Patients receiving acupuncture in an individual setting were often self-conscious and easily distracted. These problems are more evident in the management of new patients. In general acupuncture treatment, sessions usually last for 20 to 25 minutes. Because chemical dependency patients seemed more resistant and dysfunctional, their length of treatment session in the acupuncture group setting was prolonged to 30 to 45 minutes, for a fuller effect to be reported.

The atmosphere of the treatment room should be adjusted to fit varying clinical circumstances. Programs with a significant number of new intakes or socially isolated patients should use a well-lighted room and allow a moderate amount of conversation to minimize alienation and encourage social bonding. On the other hand, programs with relatively fixed clientele who relate to each other frequently in other group settings should dim the lights and not allow any conversation to minimize distracting cross talk. Background music is often used in the latter circumstance. Dr. Smith developed an herbal formula known as "sleep mix," which can be used for the treatment of conventional stress and insomnia, as well as for providing an adjunctive support in addiction treatment settings. Although acupuncture was originally seen as a potential alternative to methadone maintenance, it has never shown comparable long-term efficacy against heroin addiction and is now seen as a potential adjunctive to opioid maintenance, perhaps assisting with cocaine or stimulant problems in methadone patients, or in other settings, to facilitate psychosocial treatment for addictions which do not have pharmacologic therapeutics available. While various numbers and combinations of ear points have been used, an important and interesting commonality to all of them is that many points are claimed to represent (37-39). The LH protocol was codified by NADA, which established training standards (including an emphasis on the clean-needle technique) for "acu-detox technicians" who, depending on specific state regulations, were sometimes addiction counselors without other acupuncture training. This model became especially popular in the drug court setting, where, paradoxically, methadone (a lifesaving treatment with well-established efficacy), is often seen as controversial, whereas acupuncture is accepted as very much a standard treatment. Some of the earliest U.S. trials came from an early drug court setting in Dade County, Florida, where acupuncture seemed to facilitate compliance with a drug-free treatment program (40). The same LH/NADA ear acupuncture protocol was adopted by a number of "detox programs in the Boston area, where fewer subsequent detoxification readmissions where required by patients who attended programs incorporating acupuncture (41). This result held, suggesting that the risk of relapse was lower in patients with access to acupuncture, even when statistical adjustments were made.
between groups for clinical severity and other risk factors for relapse.

PREVENTION OF RELAPSE TO OPIOID ABUSE

Drug addiction is a chronic and recurrent condition. A high rate of relapse after prolonged drug-free periods characterizes the behavior of experienced abusers of heroin and other addictive drugs. Compared with physical dependence and withdrawal syndromes, addiction and relapse to opioids is an issue more difficult to deal with. It is typical that once addicted to heroin, the craving for heroin lasts a lifetime. It is the protracted patient's withdrawal syndromes (negative reinforcement) and the craving for drugs (positive reinforcement) that are the behavioral engines driving the patient to drug relapse. According to statistics from different sources, the relapse rate is no less than 95% and can be as high as 99%. If one confesses that for most patients craving will last their whole life, then long-acting opioid (methadone, levo-alpha-acetylmethadol [LAAM], or buprenorphine) maintenance is the principal choice to prevent relapse to heroin for most patients. Alternately, for some patients, especially those with strong resources for social support (or actual environmental control), one may try to find other ways to substantially reduce craving so that the occasional patient may become drug free for the rest of the patient's life. A radical change in the environment is often one of the most successful contributors to such efforts. The following sections explore whether acupuncture helps to reduce craving and postpone or prevent the relapse.

Experimental Studies in the Rat

There are several animal models (42) that can be used to study the problem of craving and relapse to drugs of abuse (the central issue in addictive disorders). Conditioned place preference (CPP) is one of the frequently used models (43). In a two-chamber or three-chamber experimental apparatus, the drug (unconditioned stimulus) is injected in the animal in one of the chambers. Thus it becomes associated with the environmental stimuli unique to that chamber (color of the surroundings, texture of the floor, etc.). After repeated training, the rat will choose to stay longer on the drug-associated side than in a chamber associated with normal saline injection or no injection. The ratio between the time spent in the drug-associated side and the saline-associated side can be taken as an index for the degree of craving. The CPP model is regarded as a relatively pure measure of addiction (as opposed to physical dependence) because the preference for the drug-associated compartment can be demonstrated when the animal is in the undrugged condition and free of withdrawal symptoms. Using this model, experiments were conducted to test whether acupuncture suppresses the expression of the CPP.

Wang et al. (14) (Fig. 49.4) were among the first to explore the effect of electroacupuncture on morphine CPP in the rat. A two-chamber apparatus was used. CPP was established by morphine injection at 4 mg/kg dose and the rats were trained for 10 days. The rats were then given electroacupuncture at 2 Hz, 100 Hz, or 2/100 Hz (dense-and-disperse mode) for 30 minutes, with intensity increasing stepwise from 1 mA to 2 mA to 3 mA within 30 minutes. Twelve hours after the end of electroacupuncture session, when the rats completely recovered from the manipulation of electroacupuncture procedure, they were put into the testing phase of CPP. CPP was significantly suppressed by electroacupuncture of 2 Hz and 2/100 Hz, but not of 100 Hz. Because the procedure of electroacupuncture consists of keeping the rat in the holder, the insertion of the stainless steel needles into the hind leg points (Zusanli...
and Sanyinjiao at both hind legs) and the administration of electrical stimulation, three control groups of rats received one of the following: (a) restraining in the holder for 30 minutes, (b) holder restraining plus needle insertion without electrical stimulation, or (c) intermittent electrical stimulation on the feet (foot shock). None of the three control groups showed any suppression of the CPP. Interestingly, electroacupuncture of 100 Hz was without effect, although the manipulation was exactly the same as for the 2-Hz group except for the difference in stimulation frequency. The results suggest that it is the low-frequency component of the electroacupuncture that suppressed the morphine CPP. Because the effect of electroacupuncture can be completely reversed by the opioid receptor antagonist naloxone at a small dose of 1 mg/kg, which is sufficient to block the opioid μ and δ, but not the κ, receptors, it seems evident that the effect of electroacupuncture is mediated by endogenously released μ- and δ-opioid agonists, most likely endorphins and enkephalins, to ease "craving" for exogenous opioids (in this case, the morphine). Another issue deserving attention is that the effect of electroacupuncture can still be revealed 12 hours after the episode of electroacupuncture, suggesting that this effect lasts longer than acupuncture-induced analgesia (which usually disappears within 60 minutes after the end of stimulation). Thus, a sensitization of the endogenous opioid circuits might be implied, which would readily release more opioids after electroacupuncture stimulation, resulting in a relatively long-lasting effect.

In practical life, craving and relapse can be easily induced by stress or by a very small dose of opioids. This phenomenon can be reproduced in animals using the CPP model. Wang et al. (44) reported that morphine-induced CPP disappeared after a 9-day extinction period. The extinguished CPP could be easily reinstated by foot shock stress, or by a small dose of morphine or amphetamine. Again, the reinstated CPP could be reversed by 2-Hz or 2/100-Hz electroacupuncture in a naloxone-preventable manner (45). It is worth mentioning that while both drug priming and foot shock stress can reactivate morphine CPP, the underlying mechanisms may be different. The drug-priming-induced reactivation can be totally blocked by the destruction of the mesolimbic dopamine system, including the ventral tegmental area (VTA) and the shell part of the nucleus accumbens, while the foot-shock-induced reactivation of CPP depends on the integrity of the central nucleus of the amygdala (46). Consequently, the mechanisms of electroacupuncture suppression of morphine CPP may involve a variety of neural pathways.

For simplicity and clarity of analysis, previous studies observed only the effects produced by a single session of electroacupuncture. However, in clinical practice, acupuncture or HANS is delivered daily in consecutive days or even several times a day. To mimic the clinical situation, animal experiments were designed using (a) electroacupuncture once a day for 3 consecutive days, (b) a 50% lower current intensity, and (c) a three-chamber device instead of a two-chamber device. The results showed that not only 2-Hz electroacupuncture, but also 100-Hz electroacupuncture is effective in suppressing morphine CPP (47). It seems plausible that by optimizing the parameters of electroacupuncture, its utility for the suppression of craving might be further improved.

Effect of HANS on Opiate Craving in Humans

To obtain a quantitative estimate of possible suppression of craving in response to acupuncture or related techniques, we used a visual analogue scale (VAS) to represent the degree of craving in a group of heroin-addicted patients who had completed the process of detoxification more than 1 month previously. A scale of 10 (10 cm in length) was used in the standard VAS, with VAS = 0 as having absolutely no craving and VAS = 10 as having the most severe craving imaginable. The experimenter can read the scale to the precision of 0.1 unit. The results from subjects with an initial VAS score of less than 2.0 were discarded. A total of 117 subjects were recruited, and were randomly and evenly assigned into 4 groups. Three groups received HANS treatment, each with a different frequency, 2 Hz, 100 Hz, or 2/100 Hz. Self-sticking skin electrodes were placed on four acupoints: Hegu and Laogong (palmar side of the Hegu point) in the left (or right) hand to complete a circuit, and Neiguan and Weiguan in the right (or left) arm to complete a circuit. The intensity was increased from the threshold level of the first day by two or three threshold values in the following days. The fourth group was processed as in the previous groups except that the intensity was minimal (15 Hz, threshold stimulation for 3 minutes, and then switched to 1 mA thereafter) to serve as a mock HANS control. There was a very slow decline of the VAS in the mock HANS control group. A dramatic decline of the degree of craving was observed in the groups receiving 2-Hz and 2/100-Hz electric stimulation, but not in the group receiving 100-Hz stimulation. In summary, the results observed in humans coincided with the findings obtained in the rat: low-frequency HANS is more effective than high-frequency HANS at reducing the craving for opiates (45) (Fig. 49.5). Interestingly, low-frequency electroacupuncture results in neural input to the CNS more like that of traditional acupuncture than does high-frequency electroacupuncture.

Drug Free for 1 Year as a Standard for Successful Prevention of Relapse

Heroin addiction is characterized by a high rate of relapse even after a long abstinence (for patients not in opioid-maintenance therapy). While the relapse rate after 3 months of being drug free is usually more than 50%, the relapse rate in 6 months can be as high as 95% to 99%. The hedonic concept holds that the fear of withdrawal
symptoms and the craving for extreme pleasure constitute the two-wheel drive for relapse to drug-taking. Without taking special measures, the chance of complete drug abstinence for a period of 1 year is minimal. Consequently, we accept 1 year as a criterion of successful prevention of relapse. At least five factors determine the chance for success: (a) strong personal desire and determination to be rid of the drug; (b) warm and strong support from the family; (c) understanding from social relations; (d) having a job, even a part time job; and (e) having continuous care from the treatment center, including pharmacologic and non-pharmacologic and psychological interventions. Because methadone treatment has not been generally available in China, and based on the findings shown in the previous study concerning the effect of HANS on opiate craving, we encouraged the detoxified-addiction patients to take with them 1 unit of portable HANS when they are discharged from the detoxification center to ameliorate the protracted withdrawal syndrome and to suppress the craving induced by environmental cues. It is strongly recommended to the patient to have at least one session (30 minutes) before going to bed to facilitate sleep. It is also suggested that they use the device anytime there is a strong drug cue or a significant craving. The anticraving effect is usually reported to appear within 20 minutes.

Although there is a whole host of factors affecting the success of HANS in the prevention of relapse over 1 year, the most important one seems to be the effectiveness of the treatment system in taking care of the overall medical and psychological needs of the patient. In south China's Hainan province, a local rehabilitation center under the auspices of the Peking University Neuroscience Research Institute was established. The staff make friends and keep in close contact with all the drug-addiction patients discharged from the detoxification center. These patients can get HANS treatment from the rehabilitation center for free and ad lib. As an alternative, they can buy a unit of the device at an affordable cost and apply HANS at home under the staff's continuing supervision. A followup study was conducted on a group of 56 patients who used HANS at home. Using monthly urine test as criterion, the relapse rates at third, sixth, ninth, and twelfth months were 50.0%, 71.4%, 80.4%, and 83.9%, respectively. Those showing negative urine tests for 12 or 24 consecutive months were given a naloxone test (0.4 mg subcutaneously \( \times \) 2 at 15-minute intervals) to further confirm their heroin-free status. Compared with the 97% relapse rate at 6 months and more than 99% relapse rate at 1 year in the majority of reports on heroin addiction (without methadone maintenance), an 83.9% relapse rate (16% success rate) at 1 year is encouraging. Similar studies were performed in treatment centers located in south China's Guangdong province. In Shanghai and in Tianjin, the 1-year success rate was between 2% and 10%, depending on the degree of followup medical care offered to the patients.

**COCAINE ABUSE**

Cocaine addiction is one of the most important challenges for acupuncture treatment of substance abuse for two reasons. First, the incidence of cocaine addiction has surpassed that of heroin in the whole world (13.4 vs. 9.2 million [48]). Second, there is no effective pharmacologic treatment available for cocaine addiction.

Compared with heroin addiction, cocaine addiction shows much less withdrawal syndrome on abstinence, yet more prominent and longer-lasting craving, serving as one of the most important cues leading to its relapse. Therefore the most important issue is whether acupuncture can have an effect in treatment on the prevention of cocaine craving. Data obtained from animal experiments is discussed first, followed by a discussion of the clinical trials.

**Experimental Studies**

In the last three decades, the self-administration technique has commonly been used to assess the degree of psychic dependence to cocaine in rats, that is, to mimic the degree of craving in humans. In recent years, CPP has also been used for this purpose. Drug-induced CPP is thought to mimic the cue-elicited conditioning that motivates drug-seeking behavior. The establishment of cocaine-induced CPP depends on the dose and route of administration, as well as the number of conditioning sessions used. Using an 8-day conditioning paradigm and the dose of cocaine at 1 mg/kg (intraperitoneally) and higher, Ren et al. (49) studied the expression of cocaine-induced CPP in rats, which maintained as long as 4 weeks at weekly
checking, or 13 days at daily checking schedule. High-frequency electroacupuncture (100 Hz) applied at hind leg points for 30 minutes was found to significantly reduce the CPP, whereas low-frequency (2 Hz) electroacupuncture was without effect (Fig. 49.6A). The procedure of electroacupuncture might involve at least three stress factors: restraining, needling, and electric shocking. These possibilities have individually been ruled out by control studies. The results suggest that it is the specific parameter of electroacupuncture rather than a nonspecific stressful condition that played an important role in modulating cocaine CPP.

Electroacupuncture of identified frequencies mobilizes different kinds of endogenous opioid peptides. The attenuation of cocaine CPP by 100-Hz electroacupuncture may involve a $\kappa$-opioid mechanism. Indeed, the effect of 100 Hz can be blocked by the opioid antagonist naloxone only at a high dose of 10 mg/kg. This dose is sufficient to antagonize all three subtypes of opioid receptors, including $\kappa$. On the other hand, the lower doses (1 and 5 mg/kg) that are only able to inactivate $\mu$- and $\delta$-opioid receptors could not block the effect of electroacupuncture (Fig. 49.6B).

It is worth noting that (a) the effect of electroacupuncture can be detected 10 to 24 hours, but not 5 hours, after the termination of electroacupuncture, suggesting that this could be an effect involving a cascade of reactions, probably through transcriptional regulation. (b) Naloxone injected 20 minutes prior to electroacupuncture can block the effect of electroacupuncture as detected 24 hours post-electroacupuncture, suggesting that the role of naloxone is to block the initiation of the electroacupuncture effect. (c) The effect of electroacupuncture on suppressing cocaine CPP can be blocked by a specific $\kappa$ opioid receptor antagonist administered into the nucleus accumbens, but not into the amygdala, suggesting that nucleus accumbens is one of the sites of action for endogenous opioid peptide, most probably dynorphin, to suppress cocaine CPP. (d) Injection of $\kappa$ receptor agonist into the nucleus accumbens suppresses CPP in a dose-dependent manner (50). Together this suggests that cocaine-induced CPP can be suppressed by electroacupuncture in a frequency-dependent manner, being effective at 100 Hz, but not at 2 Hz. The effect of 100 Hz electroacupuncture can be reversed by naloxone at 10 mg/kg but not with lower doses, suggesting the involvement of a $\kappa$-opioid mechanism in mediating electroacupuncture effect. This was verified using highly specific $\kappa$ agonist and antagonist, and the site of action was targeted to the nucleus accumbens. These results may suggest a role for 100-Hz electroacupuncture or HANS to reduce cocaine craving and to prevent

FIG. 49.6. A: Effect of electroacupuncture of different frequencies on CPP expression induced by 5 mg/kg of cocaine B: Naloxone reversal of the CPP-attenuating effect of 100 Hz electroacupuncture. (Modified from Ren YH, Wang B, Luo F, et al. Peripheral electric stimulation attenuates the expression of cocaine-induced place preference in rats. *Brain Res* 2002;957:129–135, with permission.)
relapse. Clinical trials of this approach are certainly indicated.

Clinical Trials

Ear acupuncture is often used for the treatment of cocaine addiction in the United States, using the same four to five ear points bilaterally originally developed at Lincoln Hospital for use against opioid addiction and promulgated by NADA for general use in addiction programs. In a series of 226 cases of users of cocaine or crack cocaine who had more than 20 visits to the Lincoln Hospital treatment center, 149 (65%) had more than 80% negative urine tests during the entire treatment involvement. Of the remaining patients, 39 (17%) had at least 80% negative urine test during the 2 weeks prior to data collection. While there is no control group, the success rate by itself was felt to be quite encouraging (36). The Yale group (51) studied 32 cocaine-dependent, methadone-maintained patients who received an 8-week course of auricular acupuncture for the treatment of cocaine dependence. Fifty percent completed treatment; 88% of study completers attained abstinence, defined as providing cocaine-free urine samples for the last 2 weeks of the study, yielding an overall abstinence rate of 44%. Post hoc comparisons to pharmacotherapy with desipramine (Norpramin), amantadine (Symmetrel) and placebo revealed a higher abstinence rate for acupuncture (44%) than for amantadine (15%) or placebo (13%), but not significantly higher than for desipramine (26%). Avants et al. (52) obtained similar results in a moderately sized randomized (n = 82) trial. Longitudinal analysis of the urine data for the intent-to-treat sample showed that patients assigned to acupuncture were significantly more likely to provide cocaine-negative urine samples relative to both the relaxation control (odds ratio: 3.41) and the needle-insertion control (odds ratio: 2.40). These findings suggested that acupuncture was effective for the treatment of cocaine dependence under the conditions at the site under study.

Encouraged by the aforementioned results, a randomized, controlled, single-blind, multisite large-scale clinical trial was conducted from 1996 to 1999. The results were published in the Journal of the American Medical Association in 2002 (53). This study included 620 cocaine-dependent adult patients, 420 of whom used cocaine only and 208 of whom used both cocaine and opiates and were receiving methadone maintenance. Patients were randomly assigned to receive auricular acupuncture (four needles schedule), a needle-insertion control (four needles inserted into the helix of the ear), or a relaxation control. Treatments were offered five times weekly for 8 weeks. Main outcome measures were cocaine use during treatment and at the 3- and 6-month followup based on urine toxicology screen and retention in treatment. Analysis of urine samples showed a significant overall reduction in cocaine use but no differences by treatment condition, nor any difference in the rate of treatment retention. The conclusion is that within the clinical context of this study, acupuncture was not more effective than a needle insertion or relaxation control in reducing cocaine use. The authors concluded that the results do not support the use of acupuncture as a stand-alone treatment for cocaine addiction, yet it may play an ancillary role for the treatment of cocaine addiction. This conclusion is apparently in contrast to that derived from the animal experiments, as well as results from the preceding pilot study. Consideration of important differences between the conditions under which acupuncture demonstrated efficacy in the pilot and then failed to do so in the larger study leads to implications for the clinical conditions under which acupuncture may be most useful. Because of changes in available resources, it seems that the psychosocial and rehabilitative services made available for patients during the second study was fairly minimal, while in the first, the services had been considerable (54). Also, of particular methodologic importance, patients in the first trial were not paid, and those in the second were. This is, of course, quite different from the situation found in clinical practice. Although paying subjects is a common practice in clinical research, it could obviously create inferential problems when studying a therapy who's major effects may interact with or actually depend on patient motivation, especially when outcomes are so dependent on patient behavior. If acupuncture's major benefit lies in motivating patients to keep returning to the clinic, then paying subjects to participate in and complete the study could have easily eliminated most of the study's potential for showing such a difference between the groups.

Finally, in the planning of future large trials of acupoint therapy for cocaine addiction, attention should also be directed to the results obtained in rat experiments showing that 100-Hz, rather than 2-Hz, stimulation can suppress the cocaine-induced CPP. Recalling that this high-frequency, dynorphinergic (primarily δ-receptor activating) stimulation is quite different from the more closely related low-frequency or manual (primarily μ- and δ-receptor activating) stimulation, it may be important to include 100-Hz electroacupuncture (and possibly body electroacupuncture or HANS) stimulation in future American trials of acupoint therapy for the treatment of cocaine addiction.

ALCOHOLISM

Acupuncture was considered quite promising for the treatment of alcohol addiction in the 1980s. Two consecutive papers were published providing clearly positive results in this regard (55,56). The orthodox ear points suggested in the LH/NADA protocol were used, and points 3 to 5 mm apart were used as nonspecific points for control. The subject size was 54 and 80, respectively, and the observation period was 6 months. The results obtained were in favor of acupuncture treatment, as manifested in the reduced need
for alcohol, fewer drinking episodes, fewer subsequent admissions requiring detoxification, less desire to drink, and more people to complete the acupuncture program. However, this result could not be replicated by Worner et al. (57) in the United States (56 cases) or by Sapir-Weise et al. (58) in Sweden (72 cases). In a recent randomized, placebo-controlled study of auricular acupuncture, Bullock et al. (59) conducted a large-scale clinical trial that included 503 cases. The unique feature of the design of the study for the patient grouping was that, aside from the "specific" ear acupuncture group, "nonspecific" ear acupuncture group, and the conventional treatment group, a fourth group was set using symptom-based acupuncture where the acupuncturists were not constrained to the four ear points stipulated in the other acupuncture treatment group, and point prescription could be changed on a day-to-day basis according to the patients' discomfort. The patients were given six treatments per week for as long as 3 weeks to maximize the therapeutic effects. The outcome, however, was quite different from the original hypothesis. All four groups showed a significant improvement. There were few differences associated with treatment assignment, and there were no treatment differences on alcohol use measures, although 49% of subjects reported that acupuncture reduced their desire for alcohol. These authors concluded that ear acupuncture did not make a significant contribution over and above that achieved by conventional treatment alone in the reduction of alcohol use.

Lots of data show that the euphoric effect of alcohol is mediated by endogenous opioid peptides (60) and the opioid antagonist naltrexone has been used to assist cognitive-behavioral therapy for alcoholics (61). Therefore, modulation of the endogenous opioid system should be considered as one of the approaches for the treatment of alcohol craving and reward in alcoholic patients. Yoshimoto et al. (62) reported that rats subject to repeated restriction stress consume more alcohol than the control animals. Electroacupuncture at hind limb points zusani (ST-36) significantly reduced the alcohol-seeking behavior, whereas the lumbar point Shenshu (BL-23) was not effective. The effect of electroacupuncture stimulation at ST-36 was accompanied by an increase in dopamine level in the striatum, compared with that produced by electroacupuncture at BL-23. These findings provide new information for understanding alcohol-drinking behavior and for treating human alcoholics.

**TECHNICAL COMMENTS ON USING ACUPUNCTURE IN THE TREATMENT OF ADDICTION**

Because of the conflicting opinions regarding the efficacy of acupuncture for the treatment of substance abuse, the National Institute on Drug Abuse (NIDA) sponsored a technical review on October 23, 1991, to discuss this issue in an attempt to propose directions for future studies. A summary of the report was published in the *Journal of Substance Abuse Treatment* in 1993 (5). The review pointed out four major problems that required a solution: the nonstandard terminology used to describe it, the wide range of procedures that have been called acupuncture, the lack of a clear mechanism to explain the purported benefits of acupuncture treatment, and the lack of systematic clinical research in this area. Ten years have passed since the publication of the report. In that time, terminology has become somewhat more standardized, but not completely and clinical trials have begun to focus on a limited number of procedures, guided more by popularity than any particularly rational or planned approach. Perhaps the furthest progress has been made in the area of acupuncture's mechanisms. With a new wealth of biochemical data and neuroanatomic imaging, it is no longer essential to postulate traditional paradigms such as yin and yang in order to approach the topic of acupuncture. However, the millennia of clinical experience encoded in the allegorical imagery of elements and meridians and functional concepts, such as the triple burner, may still have much to offer on the empiric clinical level. It may be useful to admit that we will never see the superego or id on an x-ray or under the microscope, or measure either on a meter or a blood test, and the same may be true for chi. Most of the important problems seem to remain, although many issues have become clearer than before for both research and practice.

**Ear Acupuncture Versus Body Acupuncture**

From an historical point of view, the 14 meridians or channels considered by ancient Chinese physicians as the linkage for acupuncture points, serving as the channel for the flow of "Qi", are distributed over the body rather than on the ear. Dr. H. L. Wen of the Kwong Wah Hospital of Hong Kong, the pioneer of the acupuncture treatment for drug addiction, used four needles in the hand and arm, plus two needles in the ear (4). These needles were manipulated to induce de-qi sensation and then connected to an electronic stimulator for further stimulation lasting for 30 minutes. In states that require fully licensed acupuncturists or physicians to administer ear needles to begin with, these operators may wish to consider the addition of body points or even additional treatment for other symptoms or complaints while the patient is being treated, concurrently with the NADA ear protocol. In states that have created the category of mid-level "acu-detox technicians" allowed only to administer the ear protocol, this would not be possible unless the fully licensed practitioner were called in. While training or certification to pierce the skin is not required for the use of a TENS or HANS device, a knowledge of the location of the relevant points is still required, as is the ability to communicate the finding of these points for patients who will be self-administering electrical acupoint.
stimulation. Whichever methods of point stimulation are chosen, it is vital to keep in mind that engagement of the patient with an adequate program and frequently revisited visits by the patient are just as, if not more, important than the acupuncture stimulation itself. While clinical trial data are still somewhat equivocal on acupuncture and are not yet helpful in selecting one modality or protocol over another, it is still clear that increasing the length and frequency of clinical engagement with an otherwise adequate treatment program will improve the long-term outcome of patients being treated for addictive disorders. To the degree that acupuncture or other safe and low-cost alternative therapies will accomplish this, their benefits in incremental use and compliance may be enough to make them worthwhile for programs that wish to take advantage of current positive public perceptions. Having said this, such programs should feel obligated to follow the results of new research as it emerges. An upcoming Treatment Improvement Protocol (TIP) from the Center for Substance Abuse Treatment will include the clinical trial data to date, and current plans include the dissemination of further new trial data, especially U.S. trials, as they emerge.

**Needle Staying Versus Manual Needling**

According to traditional acupuncture practice, a needle inserted into the acupoint can be further processed in at least different three ways: (a) left in situ undisturbed for a period of time, which is defined as “needle staying;” (b) manually twisted to obtain maximal *de-qi* sensation; or (c) heated at the shaft of the needle to intensify the therapeutic effect. It is clear that needle staying is the most modest of the three procedures. Moreover, the efficacy of needle staying depends on the site of needle insertion. The ear comprises skin that is covering cartilage, which is quite sensitive to mechanical stimulation and may produce continuous input during the staying of the needle. The situation will be dramatically different if the needle is inserted into soft tissues. In our pilot experiment performed in human volunteers, it was evident that merely leaving the needle in the Hegu (LI-4) point for 30 minutes in the control group produced little change in the pain threshold of the skin (15). When a needle is inserted in most body points, to induce a marked elevation of the pain threshold one has to twist or otherwise stimulate it. Early in 1973, a research group at Jiangsu College of New Medicine in Nanjin, China, showed that insertion of a needle in the ear point Shenmen (single point) with manipulation for 60 minutes produced a gradual increase of the pain threshold of the skin over the body (chest and abdomen) as measured by the potassium iontophoresis method. It reached a plateau in 30 minutes and remained there for the duration of the study. The pain threshold went down when the needle was left in situ un-manipulated, and went up again when the needle was manipulated for another 50 minutes (Fig. 49.7). The results suggest that manipulation of the needle produces much stronger physiologic effects than does needle staying, at least when pain modulation is measured.

**Acupuncture and Electroacupuncture Versus Transcutaneous Electric Stimulation**

A series of studies showed that the manipulation of the needle triggers a train of nerve impulses transmitted along the afferent nerve fibers to the CNS. The physiologic effects produced by acupuncture (e.g., the antinociceptive effect) can be readily blocked by the injection of local anesthetics deep into the point (15), or along the nerve trunk. If nerve activation accounts for the transmission of the acupuncture signals, then similar effects should be induced whether similar nerve impulses are generated by manipulation of a needle, or directly by electrical impulses through the needles inserted into the point, or even by electrodes on the surface of the skin over the point, that force a current to pass through the same underlying tissue and produce a feeling of *de-qi*. In an experiment performed in the rat, the analgesic effects induced by electroacupuncture (via needles) and by transcutaneous stimulation (via skin electrodes) were compared. No significant difference was found between the two approaches in the efficacy of inducing an analgesic effect (12). It is interesting to note that a similar mechanism seems to underlie the two analgesic effects. Thus, no matter the electrical stimulation is delivered via needles or skin electrodes, opioid antagonist naloxone at 2 mg/kg dose produced a complete reversal of 2-Hz stimulation-produced analgesia, a partial reversal of 15-Hz stimulation-produced analgesia, and no reversal on 100-Hz stimulation-produced analgesia (12). In a human

![FIG. 49.7. Influence of manual needling at ear acupoint Shenmen (n = 16) or Shenmen plus lung (n = 18) on pain threshold of the skin over the chest and abdomen in humans. (Modified from Research Group of Ear Acupuncture, Jiangsu College of New Medicine. The effect of ear acupuncture on the pain threshold of the skin at thoracic and abdominal region. In: Theoretical study on acupuncture anesthesia. Shanghai People’s Press, Shanghai, China 1973:27-32, with permission.)](image-url)
study, the analgesic effect induced by manual needling was compared to that induced by transcutaneous electric stimulation at the Hegu (LI-4) point. The results indicated that they are essentially the same, if not identical (64). It should also be mentioned that this and other clear evidence of neuronal mediation of the analgesic effects of acupuncture, while not necessarily excluding the meridian model or the existence of chi, certainly demonstrates that this model (or allegory) of meridians and chi is not required for an explanation of acupuncture’s effects.

In the past, blood-borne virus and anecdotal reports of bacterial infections have been associated with acupuncture (65). Woo et al. recently reported four cases encountered with acupuncture in a 2-year period with relatively alcohol-resistant mycobacteria infection at acupuncture-point-specific locations (66). The risk of acupuncture-mediated infection is minimized by strict adherence to the instructions for single use only, which are included in the packaging of all FDA-approved acupuncture needles. For those still concerned, use of skin electrodes rather than needles will reduce this risk from minimal to zero.

**Opioid- Versus Nonopioid Mechanisms**

The mechanism of acupuncture or electroacupuncture relies, at least partly, on the frequency-dependent release of opioid peptides in the CNS (67). For example, high-frequency (100 Hz) stimulation is more efficacious than low-frequency (2 Hz) stimulation in reducing opiate withdrawal syndrome through activation of the dynorphin system mediated by the α-opioid receptors, whereas the low-frequency stimulation is more efficacious than high-frequency stimulation in reducing opiate craving by the activation of endorphin/enkephalin system mediated by µ- and δ-opioid receptors. In contrast to opiate addiction, effects on cocaine addiction may work through a slightly different mechanism, such that the CPP for cocaine in the rat, a rodent model of cocaine craving, can be suppressed only by 100-Hz, but not 2-Hz, stimulation (49).

Aside from the opioid systems, electroacupuncture also activates nonopioid systems of the brain, including the norepinephrine system (68) and the serotonin (5-HT) system (69) of the CNS. Activation of these monoaminergic pathways may also help to ameliorate the withdrawal syndrome, although it has not been elucidated whether there is also a frequency dependence in this context.

**How Frequently Should Acupuncture Be Used for the Treatment of Drug Abuse?**

In an inpatient setting, it is clear that both electroacupuncture and HANS works to suppress opiate-withdrawal syndrome even if it is administered only once (for 30 minutes) a day (13). However, for the best results, it is recommended to use it three to four times a day for the first 5 days, followed by a reduction to twice a day for another 5 days, and then once a day for the rest of the time for a total of 2 weeks. Too frequent an application results in the decrease of the therapeutic effect because of the development of tolerance (70). For the treatment of protracted withdrawal syndromes in the period of rehabilitation, once or twice a day is sufficient. The session applied immediately before sleep is critical for the treatment schedule, because this will facilitate a good sleep (13). It is noticeable that in the rat experiment, the effect of electroacupuncture in suppressing CPP induced by morphine or cocaine bears with a long latency of 10 hours and a long aftereffect of at least 24 hours (14, 49). This may serve as a mechanism for the cumulative effect observed in the treatment of drug abuse with acupuncture.

**Design Considerations**

Acupuncture, as a procedure (or group of related procedures), is far more difficult to subject to a traditional double-blind clinical trial than is a drug. In this respect, clinical trials of acupuncture should be compared with trials for different types of psychotherapy or for surgical procedures, rather than drug trials. Considerable methodologic progress has been made in recent years, that will make better randomized trials possible and should help answer the many questions yet unanswered about acupuncture’s efficacy.

**Mock Needle**

To design a study where mock acupuncture is administered is by no means an easy task, because needling by itself will produce a vague sensation. In fact no one can tell how far from an acupoint would needling become ineffective. So the determination of a "sham point" has no scientific basis. The invention of a mock needle seems to provide a solution to this question. The design of the mock needle is such that the needle looks like penetrating the skin, but it actually withdraws into a hollow space, leaving a touch sensation on the skin to mimic the de-qi sensation (71). This is a single-blind design, because the acupuncturist knows the difference between the conventional needle and the mock needle.

**Frequency Specificity Design**

Another design involves insertion of the needle to the real acupoint, but electrical stimulation at two different frequencies is used, which might induce a qualitatively different result. For example, it happens that 2 Hz and 2/100 Hz stimulations are effective in producing a suppression of the opiate craving, whereas 100-Hz stimulation is ineffective (see Fig. 49.5). In contrast, cocaine-induced CPP can be suppressed by 100-Hz, but not 2-Hz, electroacupuncture (49).
Intensity Specificity Design

To use electroacupuncture or TENS at different intensities is another choice. For example, using a constant current device, the threshold intensity for a 4 × 4-cm skin pad is 5 to 6 mA for most subjects. A desirable intensity is two times threshold, that is, 10 to 12 mA. By using the two different levels of intensity it can be expected that the higher intensity group would produce a more prominent effect, and that relapse would occur more often in the lower intensity group.

Outcome Measure

Urinalysis is an objective and essential measure. Three times per week during the detoxification period and once or twice a month during the rehabilitation period are reasonable design. It should be continued for as long as 1 year to obtain a 1-year abstinence record.

PSYCHOSOCIAL PERSPECTIVES

Dr. Michael Smith made an important statement (36) when he wrote that “it is essential to understand acupuncture’s psychological and social mechanisms of action to use this modality effectively. Acupuncture has an impact on the patient’s thoughts and feelings that is different from conventional pharmacological treatments.”

Seeking Help from Outside or from Within

Conventional treatment efforts tend to focus on assessment of past activities and planning for the future. However, the past leaves nothing to the addicts but pain. As for the future, they feel hopeless because they lose confidence to themselves. What is important to them is the present: Can you solve my problem without my taking drugs? Acupuncture allows treatment staff to respond to one of the patient’s immediate needs without using addictive drugs. That is, to meet the patient in present-time reality, validating their needs and providing substantial relief. The nonverbal, present-time aspects of the treatment make it easy to respond to a patient in whatever stage of crisis or denial that may exist. Additionally, and unlike talk therapy, acupuncture will not challenge the patient cognitively or emotionally. Acupuncture provides a way for patients to feel they are being helped by a health professional without being threatened or confronted. Having acupuncture in a group setting, and seeing fellow patients being similarly helped, may reinforce this message. This and other nonverbal interactions in the group acupuncture setting may be responsible for the observation from Lincoln Hospital that patients respond much better to acupuncture in the group setting.

One difference between pharmacologic treatment and acupuncture treatment is that the former relies more on external help whereas the latter builds up one’s self-confidence. Addicts may well feel hopeless about their future, even for those who really want to quit drugs. They perceive themselves as being unable to change from within: “once an addict, always an addict.” They seek external help to provide hospitalization and medication. The help can be pills or injections. Taking medications, for example, methadone or buprenorphine, may help to relieve their withdrawal syndrome, but does not improve their confidence, because they know that they will rely on the medication just as they relied on their drug of abuse. In contrast, acupuncture can be explained to reprogram their brain function, and thereby restore their ability to live a normal life. It is the patient’s common feeling that after the first treatment, they often have a very good sleep that night, which has not been experienced for a very long period of time. The confidence and loyalty for this nonpharmacologic treatment becomes increasingly evident, and the compliance to acupuncture is built up quickly. Once a comfortable day-to-day support is established, we can approach past and future issues with a better alliance with the patient.

Group Setting or Single Treatment

According to Dr. Smith, a group setting may be more suitable for addiction patients to interact with others as compared to one-to-one conversation between the doctor and the patient. “We describe acupuncture as a foundation for psychosocial rehabilitation,” stated Dr. Smith. In their practice, acupuncture for substance abuse is provided in a group setting, with a group being no fewer than six patients. “This encouraging and balancing group experience becomes a critically important basis for the entire process of substance abuse treatment.”

Unexpected Physiologic Changes that Help to Build Psychological Confidence

In the treatment of opiate addiction, two unexpected changes in the body function help the patient to build their confidence. One is the disappearance of injection marks and the other is the recovery of the depressed sexual function. In an incidental case, the patient treated with HANS supplemented with a small dose of buprenorphine reported that his injection marks in the forearm disappeared and the veins reappeared at the end of the 14-day detoxification period. That was recognized as a strong indication by the existence of fibrotic thickening of the blood vessel wall, thrombosis, bluish streak, scared mainliners, and venous collapse. Statistical analysis revealed that these changes were significantly less frequently revealed in the control group using only buprenorphine for detoxification (32). Another observation was on the sexual function as
revealed by standard questionnaire. The sexual function of the 32 male patients was seriously depressed at their enrollment to the treatment center, and was markedly recovered (to 80% of the normal level) at the end of 1 month of treatment with HANS supplemented with small amount of buprenorphine, but not in the group using the full dose of buprenorphine (it remained at a level equivalent to 20% to 25% of the normal level of sexual function) (72). These changes provided the patient with positive psychological impact and confidence, and would certainly be helpful in the establishment of a normal life, thus delaying the occurrence of the relapse to drugs.

The friendship established between the patient and the staff in residential treatment can, and should be continued when the patients are discharged from the treatment center. The transfer from the treatment center to the home is a very critical period, especially for persons leaving prison. They are confronted with a bleak uncaring world. Their own feelings of inadequacy frequently become so overwhelming that a return to prior drug use may occur within hours of release. It is in this sense that family help, social caring, and medical instruction should be intimately organized from the first day of returning home, and acupuncture provides a unique chance to let the patient feel that there is something to rely on.

Acupuncture is an emerging treatment for drug abuse. This new approach is different from that of pharmacologic treatment. From a technical point of view, there is plenty of room for improvement and definitive evidence of efficacy remains to be shown. Many patients and providers remain convinced that it has something to add to the treatment package. The complicated network underlying drug abuse can be unraveled only through combined physiologic, neurobiologic, and psychological endeavors, and acupuncture can play a role at least as one of the tools in a comprehensive approach.

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