HOW THE DOCTOR'S WORDS AFFECT THE PATIENT'S BRAIN

FABRIZIO BENEDETTI
University of Turin Medical School

Clinicians have long known that context is important in any medical treatment and that the words and attitudes of doctors and nurses can have great impact on the patient. There is now experimental evidence indicating that the medical context influences specific neural systems. The importance of the context is shown by the lesser effectiveness of hidden administrations of analgesics compared with open ones. Because the placebo effect is a context effect, its study has been useful in clarifying this complex issue. There are now several lines of evidence that placebo analgesia is mediated by endogenous opioids and placebo motor improvement by endogenous dopamine. Moreover, a placebo treatment is capable of affecting many brain regions in depressed patients. All these studies, taken together, lead to a neurobiological understanding of the events occurring in the brain during the interaction between the therapist and his or her patient.

EVALUATION & THE HEALTH PROFESSIONS, Vol. 25 No. 4, December 2002 369-386
DOI: 10.1177/0163278702238051

INTRODUCTION

Any medical treatment is carried out within a context. Although this statement seems quite obvious, what is not so obvious is the role played by the context in the effectiveness of the therapy that is being administered or, in other words, what Balint (1955) called the whole atmosphere around the treatment. The context is made up of anything that surrounds the patient under treatment, such as doctors, nurses, hospitals, syringes, pills, machines, and so forth (Di Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001). Certainly, doctors and nurses represent a very important component of the context because they can transmit a lot of information to the patient through their words, attitudes, and behavior. Consider, for example, the following two situations. First, a patient in pain lies in a bed with an intravenous line connected to an infusion pump. Does it make any difference whether the analgesic treatment is started automatically by the infusion machine or by the doctor herself at the bedside? Second, a patient in pain goes to the doctor's office for an analgesic therapy. Does it make any difference whether the doctor gives the patient a painkiller and says "It may work" or "It does work"? These are very common situations in routine medical practice, and certainly most of us do not worry very much about the subtle differences between a machine-initiated and a doctor-initiated therapy in the postoperative phase or between the words "it may" and "it does." Nevertheless, the impact of these different situations on the patient can sometimes be dramatic and can trigger mechanisms that have been little understood and partly neglected. Anything around the patient can potentially contribute to creating these differences and thus to producing either a positive or a negative impact.

Many clinicians have long known this powerful effect of the context and, accordingly, have used the appropriate words and attitudes with their patients. For example, Thomas (1987) found that both positive and negative consultations in general practice have a tremendous impact on patients who present with minor illness. Likewise, Kaplan, Greenfield, and Ware (1989) found that blood pressure, blood sugar, functional status, and overall health status were consistently related to specific aspects of physician-patient communication. Although many other studies have shown that the doctor-patient relationship plays an important role in the outcome of illness (Bass et al., 1986; Gracely, Dubner, Deeter, & Wolskee, 1985; Greenfield, Kaplan, & Ware, 1985;

Starfield et al., 1981; Stewart, 1995; Stewart, McWhinney, & Buck, 1979), the underlying mechanisms are not always clear. For example, a better interaction between the doctor and the patient might lead to a better compliance with the drug regimens (Inui, Yourtee, & Williamson, 1976). However, the symbolic and emotional impact of doctors and other aspects of medical contexts on the patient certainly has a crucial role (Brody, 1988). This is also shown by the fact that diagnostic tests, which have nothing to do with therapy, reduce short-term disability (Sox, Margulies, & Sox, 1981). In addition, it has been shown that psychosocial treatment has positive effects in advanced malignant disease (Spiegel, Bloom, Kraemer, & Gottheil, 1989), although contrasting data exist in this field (Cassileth, Lusk, Miller, Brown, & Miller, 1985).

Whereas all these studies have mainly used a clinical approach, today we are beginning to understand some of the neurobiological mechanisms that take part in the complex events linking context and health outcomes. In other words, there is now experimental evidence that the context has an important influence on the outcome of a medical treatment and that it affects the course of some pathological conditions, such as pain and motor disorders, through the modulation of specific neurochemical systems (for a review, see Benedetti & Amanzio, 1997; Benedetti & Pollo, 2001). The experimental approach to this complex issue has been mainly based on the study of the placebo effect, both in the clinical and in the laboratory setting.

THE PLACEBO EFFECT

According to Brody (2000a), the placebo effect is a change in the body, or the body-mind unit, that occurs as a result of the symbolic significance that one attributes to an event or object in the healing environment. To be more specific, a placebo is an inert substance or, in general, an inert medical treatment and the placebo effect is the response to it. However, it is important to point out that the effect is not due to the inertness of the treatment per se. In fact, an inert medical treatment is administered within a context, and it is the context that plays the crucial role.

When we talk about the medical context, basically we are talking about the placebo effect. The terms "context effects," "nonspecific

effects," and "placebo effects" can be used, at least in part, interchangeably (Di Blasi et al., 2001). Turner, Deyo, Loeser, Von Korff, and Fordyce (1994) emphasized the importance of placebo effects in pain treatment and stressed that the interaction between caregivers and patients can be extremely influential in the therapeutic outcomes. Likewise, Thomas (1994) pointed out that a placebo effect can also be produced by a consultation in which no treatment is given. Thus, the classic concept of the placebo as a phenomenon whereby patients are made to feel better after receiving an inert treatment is too restrictive. The broader term "context effect" is advisable to clarify that it is the context that influences the specific treatment (Di Blasi et al., 2001).

Although one of the simplest and most controllable contexts, at least from an experimental viewpoint, is represented by words (verbal context), there are plenty of contextual factors that contribute to the placebo response: visual, auditory, olfactory, tactile, and the like—or, in other words, any clue that leads to the knowledge that a medical treatment is being performed (Benedetti & Amanzio, 1997; Benedetti & Pollo, 2001). A positive context can produce the reduction of a symptom (placebo effect), and a negative context can produce its increase (nocebo effect). Most of these aspects of the placebo effect have been reviewed in detail recently (Guess, Kleinman, Kusek, & Engel, 2002; Harrington, 1997; White, Tursky, & Schwartz, 1985).

DOCTOR-INITIATED VERSUS MACHINE-INITIATED THERAPY

The importance of the doctor-patient interaction is shown by the emotional impact that the anesthetist has on his or her patient (Egbert, Battit, Turndorf, & Beecher, 1963; Egbert, Battit, Welch, & Bartlett, 1964). Egbert et al. (1964) found a reduction in postoperative pain in those patients who had been informed about the course of their postoperative pain and encouraged to overcome it. Moreover, the requirement of narcotics for these patients was much lower as compared to a control group. These studies are important because they compare the outcomes of an analgesic treatment following the anesthetist's visit with those following no visit at all, thus emphasizing the important role of the doctor-patient interaction in the global experience of pain.

In more recent years, a similar approach has been used in more controlled conditions. To eliminate the context around a medical treatment, the patient was made completely unaware that a medical therapy was being carried out. To do this, drugs were administered through hidden infusions by machines (Amanzio, Pollo, Maggi, & Benedetti, 2001; Gracely, Dubner, Wolskee, & Deeter, 1983; Levine & Gordon, 1984; Levine, Gordon, Smith, & Fields, 1981). It is possible to perform a hidden infusion of a drug by means of a computer-controlled infusion pump that is preprogrammed to deliver the drug at the desired time. The crucial point here is that the patient does not know that any drug is being injected. This hidden procedure is relatively easy to carry out in the postoperative phase, in which the patient recovers from surgery and is prepared with several intravenous lines for antibiotic therapy, blood transfusion, rehydrating infusion, and the like. The computer-controlled infusion pump can deliver a painkiller automatically, without any doctor or nurse in the room, leaving the patient completely unaware that an analgesic treatment has been started.

In postoperative pain following the extraction of the third molar, Levine et al. (1981) and Levine and Gordon (1984) found that a hidden injection of a 6- to 8-mg dose of morphine corresponds to an open injection of saline solution in full view of the patient (placebo). In other words, telling the patient that a painkiller is being injected (when it is actually a saline solution) is as potent as 6 mg to 8 mg of morphine. Only by increasing the hidden morphine dose to 12 mg was an analgesic effect stronger than the placebo observed. These authors concluded that an open injection of morphine in full view of the patient, which represents usual medical practice, is more effective than a hidden one because in the latter, the placebo component is absent.

A careful analysis of the differences between open and hidden injections in the postoperative setting has been recently performed by my group (Amanzio et al., 2001). We analyzed the effects of four widely used painkillers (buprenorphine, tramadol, ketorolac, and metamizol) that were administered with either open or hidden injections. The open injection was carried out by a doctor at the bedside, who told the patient that the injection was a powerful analgesic and that the pain was going to subside in a few minutes. By contrast, the hidden injection of the same analgesic dose was performed by an automatic infusion machine that started the painkilling infusion without any doctor or nurse in the room. Thus, these patients were completely

unaware that an analgesic therapy had been started. In one analysis, we found that the analgesic dose needed to reduce the pain by 50% (AD_{50}) was much higher with hidden infusions than with open ones for all four painkillers, indicating that a hidden administration is less effective than an open one. In another analysis, we found that the time course of postsurgical pain was significantly different between open and hidden injections. In fact, during the first hour after the injection, pain ratings were much higher with a hidden injection than with an open one.

In the same study (Amanzio et al., 2001), we also investigated the difference between open and hidden injections in the laboratory setting by using the experimental model of ischemic arm pain in healthy volunteers. Just as in the clinical setting, we found that a hidden injection of the non-opioid painkiller ketorolac was less effective than an open one. Most interesting, in these controlled experimental conditions, we added a 10-mg dose of the opiate antagonist naloxone to an open injection of ketorolac and found that the effect was as reduced as with a hidden injection of ketorolac. As will be explained in detail below, this indicates that an open injection in full view of the patient activates the endogenous opioid systems that enhance the effects of the injected painkiller. It is fundamental to remember that ketorolac is a non-opioid drug, thus it does not bind to opioid receptors. It is the words the doctor uses at the bedside or, more generally, the medical context that makes the difference and activates the endogenous opioid systems.

The importance of these findings is twofold. First, by eliminating the context (i.e., the component that produces the patient's perception of the administration of the agent) by means of a hidden administration of a medical treatment, a reduction of the effectiveness of the treatment itself occurs. Second, the effects of the context can be blocked either psychologically by means of a hidden administration or pharmacologically through the opiate antagonist naloxone, thus indicating that the context affects the endogenous opioid systems.

"IT MAY WORK" VERSUS "IT DOES WORK"

Although the previous section shows the importance of the context and the effects of its absence, even more subtle differences exist. For

example, can the uncertainty of the doctor's words and attitudes affect the outcome of a medical treatment? Does it make any difference whether we tell the patients "This painkiller may work" or "Rest assured, this painkiller does work"?

Thomas (1987) conducted either positive or negative general practice consultations in patients with different kinds of pain, cough, giddiness, nasal congestion, and tiredness. In the positive consultations, the patients were given a firm diagnosis and therapeutic assurance. If no prescription was to be given, they were told that they required none, and if a prescription was to be given, they were told that the therapy would certainly make them better. In the negative consultations, no firm assurance was given. For example, if no prescription was to be given, the following statement was made: "I cannot be certain what your problem is, therefore, I will give you no treatment." Conversely, if a prescription was to be given, the patients were told, "I am not sure that the treatment I am going to give you will have an effect." The treatment was a placebo (thiamine hydrochloride). Two weeks after consultation there was a significant difference in recovery between the positive and negative groups but not between the treated and untreated groups, thus indicating that the words the doctor used were crucial for recovery.

Another study by Kirsch and Weixel (1988), albeit outside the clinical setting, shows that different verbal contexts produce different outcomes. In this study, coffee and decaffeinated coffee were administered following different verbal instructions. In one case, they were given according to the usual double-blind design (i.e., subjects knew either the active substance or a placebo was being administered), and in the other case, decaffeinated coffee was deceptively presented as real coffee. Kirsch and Weixel found that the placebo response was stronger following the deceptive administration than the double-blind paradigm. They concluded that this was due to the fact that the double-blind administration induces less certain expectations about the outcome.

In light of the importance of these subtle differences in the doctor's interaction, my colleagues and I conducted a similar study in the clinical setting to investigate the differences between the double-blind and the deceptive paradigm (Pollo et al., 2001). We treated several postoperative patients with buprenorphine, on request, for 3 consecutive days and with a basal infusion of saline solution. However, the symbolic

meaning of this saline basal infusion varied in three different groups of patients. The first group was told nothing (natural history or no-treatment group), the second was told that the infusion could be either a potent analgesic or a placebo (classic double-blind administration), and the third group was told that the infusion was a potent painkiller (deceptive administration). The placebo effect of the saline basal infusion was measured by recording the doses of buprenorphine requested over the 3-day treatment. It is important to stress once again that the double-blind group received uncertain verbal instructions ("It can be either a placebo or a painkiller. Thus, we are not certain that the pain will subside."), whereas the deceptive administration group received certain instructions ("It is a painkiller. Thus, pain will subside soon."). We found a decrease in buprenorphine intake with the double-blind administration and even more with the deceptive administration of the saline basal infusion. The reduction of buprenorphine requests in the double-blind group was as large as 20.8% compared with the natural history group, and the reduction in the deceptive administration group was even larger, reaching 33.8%. It is important to note that the time course of pain was the same in the three groups over the 3-day period of treatment. Thus, the same analgesic effect was obtained with different doses of buprenorphine.

The above studies teach us that the uncertainty of verbal instructions and attitudes leads to different results. Thus, as Thomas (1987) said, there is a point in being positive. Subtle differences in the verbal context around the patient may have a significant impact on the therapeutic outcome.

THE APPROPRIATE WORDS ACTIVATE THE ENDOGENOUS OPIOID SYSTEMS

To analyze the effects of the context on the patient, we need to eliminate the specific action of a medical treatment (e.g., a drug). In other words, it is necessary to reproduce a context that is similar in all respects to that of a real drug administration without, however, the specific action of the drug itself. To do this, a classic placebo procedure is used in which a dummy treatment is given. The patient does not know that a dummy therapy is being administered. He or she believes that an effective treatment has been started. In this way, we can study

the effects of the context on the patient's brain. The experimental investigation of these effects is paying off in both the clinical and the laboratory setting.

An important step in understanding the neurobiological mechanisms of the placebo effect was made when Levine, Gordon, and Fields (1978) showed that placebo analgesia is mediated by endogenous opioids. These pioneering findings have been confirmed by other studies (Benedetti, 1996; Grevert, Albert, & Goldstein, 1983; Levine & Gordon, 1984). Today, we know that placebo analgesia has both opioid and non-opioid components, depending on the procedure used to induce the placebo response (Amanzio & Benedetti, 1999). In fact, by using the experimental ischemic arm pain model, it was found that if the placebo response is induced by means of strong expectation cues, it can be blocked by the opioid antagonist naloxone, whereas if the expectation cues are eliminated, it proves to be naloxone-insensitive. The crucial point here is that the expectation cues were induced by means of different verbal instructions. In a first experiment, the non-opioid analgesic ketorolac was given for 2 consecutive days and replaced with saline solution on the third day by telling the subjects that it was the same analgesic as the previous days (expectation cues of analgesia). In these conditions, naloxone partially blocked placebo analgesia. In a second experiment, the same procedure was used, but the subjects were told that the saline solution was an antibiotic (elimination of the expectations of analgesia). In these conditions, naloxone did not block placebo analgesia. Thus, depending on the verbal context, either opioid or non-opioid components can be involved.

Highly specific placebo responses can also be obtained in specific parts of the body (Benedetti, Arduino, & Amanzio, 1999a; Montgomery & Kirsch, 1997; Price et al., 1999). For example, it was found that specific verbal instructions can be aimed at directing the subject's attention to specific body parts. In fact, if four noxious stimuli are applied to the hands and feet and a placebo cream is applied to one hand only, pain is reduced only on the hand where the placebo cream had been applied. Because this highly specific effect is blocked by naloxone, these findings suggest that the placebo-activated endogenous opioid systems have a precise and somatotopic organization (Benedetti et al., 1999a).

Another line of research suggesting an important role for endogenous opioids in placebo analgesia comes from cholecystokinin (CCK) antagonists. In fact, on the basis of the anti-opioid action of CCK (Benedetti, 1997), it was found that CCK antagonists are capable of potentiating the placebo analgesic effect (Benedetti, 1996; Benedetti, Amanzio, & Maggi, 1995). Thus, the placebo analgesic response appears to result from a balance between endogenous opioids and endogenous CCK. It is also worth remembering that the placebo-activated endogenous opioids act not only on pain mechanisms, inducing analgesia, but also on the respiratory centers, inducing respiratory depression, a typical side effect of opioids (Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999b; Benedetti et al., 1998).

Two additional studies confirm the role of endogenous opioids in placebo analgesia. The first study was performed by Lipman et al. (1990) involving chronic pain patients. These authors found that those patients who responded to a placebo administration showed higher concentrations of peak B endorphin in the cerebrospinal fluid compared with those patients who did not respond to the placebo. The second and very recent study (Petrovic, Kalso, Petersson, & Ingvar, 2002) used positron emission tomography to analyze the brain regions that are affected by both placebo analgesia and the rapidly acting opioid agonist remifentanil. In both cases, the regional cerebral blood flow changed in the very same areas in the anterior cingulate cortex and in the brain stem. This anatomical similarity between placebo analgesia and remifentanil analgesia suggests that placebos activate the same opioid receptors to which remifentanil binds.

It is important to emphasize that in all these studies on placebo analgesia, the verbal context plays a crucial role. In fact, the typical placebo procedure used in the studies described above is characterized by the appropriate verbal instructions, which make the subjects believe that an analgesic treatment is being performed. Although it is not known exactly the mechanisms through which the context affects the endogenous opioid systems (see below), researchers can now assert that at least some types of placebo procedures activate the endogenous opioid systems.

THE RIGHT CONTEXT TRIGGERS THE RELEASE OF ENDOGENOUS DOPAMINE

The release of endogenous substances by placebos is a phenomenon that is not confined to the field of pain but that is also present in motor disorders such as Parkinson's disease. The verbal context is here represented by verbal instructions about motor improvement. As occurs with pain, patients are given an inert substance (placebo) and are told that it is an anti-Parkinsonian drug producing an improvement in their motor performance. It has been shown that Parkinsonian patients respond to placebos quite well (Goetz, Leurgans, Raman, & Stebbins, 2000; Shetty, Friedman, Kieburtz, Marshall, & Oakes, 1999). A recent study shows that placebos activate endogenous dopamine in the nigrostriatal pathway of Parkinsonian patients—in the very same circuit that is damaged in Parkinson's disease (de la Fuente-Fernández et al., 2001). In particular, by using positron emission tomography to assess the competition between endogenous dopamine and [^{11}C]raclopride for D_2/D_3 receptors, a method that allows identification of endogenous dopamine release, this study shows that placebos trigger the release of dopamine in the striatum, in both the caudate nucleus and the putamen.

In addition, by assessing the stimulus-response curve of the subthalamic nucleus in Parkinsonian patients by means of intracranial electrodes, we showed that different verbal contexts (verbal suggestions of either bad or good motor performance) alter the motor responses following the stimulation of the subthalamic nucleus (Pollo et al., 2002). All these data, taken together, indicate that a placebo procedure with its verbal context is capable of inducing the release of endogenous substances in very specific brain regions, such as the brain stem in analgesia (Petrovic et al., 2002) or the striatum in Parkinson's disease (de la Fuente-Fernández et al., 2001).

THE RIGHT WORDS AFFECT BRAIN ACTIVITY OF DEPRESSED PATIENTS

Very recently, the neurobiology of the placebo effect has also been studied in depression. Depressed patients who received a placebo treatment showed both electrical and metabolic changes in the brain.

In the first case, placebos induced electroencephalographic changes (cordance) in the prefrontal cortex of patients with major depression, particularly in the right hemisphere (Leuchter, Cook, Witte, Morgan, & Abrams, 2002). In the second case, changes in brain glucose metabolism were measured by using positron emission tomography in subjects with unipolar depression. Placebo response was associated with metabolic increases in the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate and metabolic decreases in the subgenual cingulate, para-hippocampus, and thalamus (Mayberg et al., 2002). Interestingly, these regions were also affected by the selective serotonin reuptake inhibitor fluoxetine, thus suggesting a role for serotonin in the placebo response.

THE APPROPRIATE WORDS YIELD A NOCEBO EFFECT

If the context is opposite to that producing the placebo effect, a nocebo response can be elicited. In fact, whereas the verbal instructions to induce a placebo response are represented by a hopeful and trust-inducing stimulus, the verbal context that elicits a nocebo response is represented by a fearful and stressful stimulus (Benedetti & Amanzio, 1997; Hahn, 1985, 1997). The nocebo effect has been investigated less than the placebo effect, and very little is known about its neurobiological mechanisms, although it is common, distressing, and costly (Barsky, Saintfort, Rogers, & Borus, 2002).

In a study performed by my group (Benedetti, Amanzio, Casadio, Oliaro, & Maggi, 1997), we obtained some results that are not easy to interpret. In postoperative patients who reported mild pain, we induced a nocebo effect by injecting an inert substance (saline solution) and telling them that pain was going to increase in a few minutes. We observed a straightforward nocebo effect that was blocked by adding a CCK antagonist, proglumide (0.5 mg to 5 mg), to the saline solution. This indicates that the nocebo hyperalgesia of these patients was mediated, at least in part, by CCK. However, the effects of proglumide were not antagonized by naloxone, even at high doses (10 mg), showing that endogenous opioids were not involved. Because CCK plays a role in anxiety and the nocebo procedure itself is anxiogenic, we interpreted these results by suggesting that proglumide acts on a CCK-dependent increase of anxiety during the nocebo procedure.

Therefore, although further research is needed to confirm these findings in the nocebo effect, CCK seems to play a pivotal role in both the placebo (see above) (Benedetti, 1996; Benedetti et al., 1995) and nocebo effect (Benedetti et al., 1997). The knowledge of these mechanisms is particularly important in light of the model suggested by Hahn (1985). In fact, in his anthropological analysis on the sociocultural creation of sickness and healing, Hahn proposes a model of the placebo-nocebo phenomenon, in which positive-hopeful beliefs and expectations produce therapeutic effects, whereas negative-fearful beliefs and expectations produce pathological outcomes. As stated by Hahn (1985), beliefs and expectancies sicken, kill, and heal. Needless to say, expectations are largely generated from the context (Hahn, 1997).

TOWARD A NEUROBIOLOGY OF THE DOCTOR-PATIENT INTERACTION

As pointed out by Rowbotham (2001), the placebo analgesic response is a physiological phenomenon and not imagined pain and plain malingering. The interaction between therapists and their patients triggers physiological mechanisms that have so far been neglected. Although we now know that the context can induce the release of endogenous opioids and dopamine and the modulation of endogenous CCKergic systems, we have not yet understood how it acts. For example, cognitive factors could be involved, such as expectancies (Kirsch, 1999). In this sense, the term "meaning response" in place of "placebo response" has been emphasized (Moerman, 2002; Moerman & Jonas, 2002). Conversely, a mechanism of classical conditioning could play a crucial role without any involvement of expectancies, meanings, and symbols (Ader, 1997). Both cognitive and conditioning mechanisms are probably important in different situations (Amanzio & Benedetti, 1999), and these mechanisms are not mutually exclusive. Further research is needed to clarify this point.

Today, we can rely on modern diagnostic tools and many effective pharmacological and surgical treatments. Thus, it would be a mistake to believe that placebos and bedside manners heal everything. A recent meta-analysis study teaches us that the placebo effect is sometimes small or even completely absent (Hróbjartsson & Gøtzsche,

2001), a concept that we have long known. However, it should be recognized that the humane aspect of care and the importance of the doctor at the bedside are often neglected in the treatment of many symptoms, such as pain and motor disorders, which respond to placebos quite well. The recent neurobiological approach to the placebo effect described throughout this article alerts us to the fact that specific neurochemical mechanisms are triggered by the doctor-patient relationship. Of course, this relationship is a very complex one and cannot be simplified in a few words. Plenty of factors are involved (Benedetti & Amanzio, 1997; Di Blasi et al., 2001) and these are very difficult to identify. For example, a hidden injection of a drug (Amanzio et al., 2001) can eliminate only some aspects of the context (e.g., the presence of the doctor), but it cannot eliminate the hospital environment, the beliefs of the patients, the room layout, and so forth. This is only the very beginning of a true neurobiology of the therapist-patient relationship, and much research still needs to be done to identify all the contextual factors that affect the patient's brain. The understanding of these mechanisms may have important clinical and social implications (Brody, 2000b), for example, in medical practice, psychotherapy, and various unconventional medical and nonmedical approaches.

It is interesting to note that the primary reason for lawsuits in the United States is not medical injury itself but the failure of communication between doctors and their patients. Patients sue their physician when they feel that he or she did not care or did not inform them adequately (Levinson, 1994). Beckman, Markakis, Suchman, and Frankel (1994) identified four types of communication problems: deserting the patient, devaluing patients' views, delivering information poorly, and failing to understand patients' perspectives. Thus, the same communication skills that are capable of reducing the risk of malpractice lead to what has been seen throughout this article—better therapeutic outcomes. Perhaps patients simply need to be better looked after and contacted more often for optimum benefit (Wohrl & Hemmer, 2001) so that we can harness these endogenous mechanisms. In this sense, a better doctor-patient interaction and a few more words from the doctor to his patient could enhance the efficacy of different methods of pain control as well as other therapeutic interventions (Chaput de Saintonge & Herxheimer, 1994; Thomas, 1994; Price, 2001). One must also bear in mind that the word "doctor" can be replaced with the more general term "healer" to make it clear that the

"shaman factor" is always present in any medical treatment (Thong, 1995). In other words, the placebo effect and the mechanisms underlying the healer-patient relationship act irrespective of whether the therapeutic approach comes from conventional or unconventional treatments. What counts, at least for some symptoms, is the context and the interaction of patients with their healers, be they doctors, psychologists, or shamans.

REFERENCES

Ader, R. (1997). The role of conditioning in pharmacotherapy. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 138-165). Cambridge, MA: Harvard University Press.

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *Journal of Neuroscience*, *19*, 484-494.

Amanzio, M., Pollo, A., Maggi, G., & Benedetti, F. (2001). Response variability to analgesics: A role for nonspecific activation of endogenous opioids. *Pain*, *90*, 205-215.

Balint, M. (1955). The doctor, his patient, and the illness. *Lancet*, *1*, 683-688.

Barsky, A. J., Saintfort, R., Rogers, M. P., & Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *Journal of the American Medical Association* (*JAMA*), *287*, 622-627.

Bass, M. J., Buck, C., Turner, L., Dickie, G., Pratt, G., & Robinson, H. C. (1986). The physician's actions and the outcome of illness in family practice. *Journal of Family Practice*, *23*, 43-47.

Beckman, H. B., Markakis, K. M., Suchman, A. L., & Frankel, R. M. (1994). The doctor-patient relationship and malpractice: Lessons from plaintiff depositions. *Archives of Internal Medicine*, *154*, 1365-1370.

Benedetti, F. (1996). The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain*, *64*, 535-543.

Benedetti, F. (1997). Cholecystokinin type-A and type-B receptors and their modulation of opioid analgesia. *News in Physiological Sciences*, *12*, 263-268.

Benedetti, F., & Amanzio, M. (1997). The neurobiology of placebo: From endogenous opioids to cholecystokinin. *Progress in Neurobiology*, *52*, 109-125.

Benedetti, F., Amanzio, M., Baldi, S., Casadio, C., Cavallo, A., Mancuso, M., et al. (1998). The specific effects of prior opioid exposure on placebo analgesia and placebo respiratory depression. *Pain*, *75*, 313-319.

Benedetti, F., Amanzio, M., Baldi, S., Casadio, C., & Maggi, G. (1999b). Inducing placebo respiratory depressant responses in humans via opioid receptors. *European Journal of Neuroscience*, *11*, 625-631.

Benedetti, F., Amanzio, M., Casadio, C., Oliaro, A., & Maggi, G. (1997). Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. *Pain*, *71*, 135-140.

Benedetti, F., Amanzio, M., & Maggi, G. (1995). Potentiation of placebo analgesia by proglumide. *Lancet*, *346*, 1231.

Benedetti, F., Arduino, C., & Amanzio, M. (1999a). Somatotopic activation of opioid systems by target-directed expectations of analgesia. *Journal of Neuroscience*, *19*, 3639-3648.

Benedetti, F., & Pollo, A. (2001). The pharmacology of placebos. *International Journal of Pain Medicine and Palliative Care*, *1*, 42-48.

Brody, H. (1988). The symbolic power of the modern personal physician: The placebo response under challenge. *Journal of Drug Issues*, *29*, 149-161.

Brody, H. (2000a). *The placebo response*. New York: HarperCollins.

Brody, H. (2000b). The placebo response: Recent research and implications for family medicine. *Journal of Family Practice*, *49*, 649-654.

Cassileth, B. R., Lusk, E. J., Miller, D. S., Brown, L. L., & Miller, C. (1985). Psychosocial correlates of survival in advanced malignant disease? *New England Journal of Medicine*, *312*, 1551-1555.

Chaput de Saintonge, D. M., & Herxheimer, A. (1994). Harnessing placebo effects in health care. *Lancet*, *344*, 995-998.

de la Fuente-Fernández, R., Ruth, T. J., Sossi, V., Schulzer, M., Calne, D. B., & Stoessl, A. J. (2001). Expectation and dopamine release: Mechanism of the placebo effect in Parkinson's disease. *Science*, *293*, 1164-1166.

Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., & Kleijnen, J. (2001). Influence of context effects on health outcomes: A systematic review. *Lancet*, *357*, 757-762.

Egbert, L. D., Battit, G. E., Turndorf, H., & Beecher, H. K. (1963). The value of the preoperative visit by an anesthetist. *JAMA*, *185*, 553-555.

Egbert, L. D., Battit, G. E., Welch, C. E., & Bartlett, M. K. (1964). Reduction of postoperative pain by encouragement and instruction of patients. *New England Journal of Medicine*, *270*, 825-827.

Goetz, C. G., Leurgans, S., Raman, R., & Stebbins, G. T. (2000). Objective changes in motor function during placebo treatment in Parkinson's disease. *Neurology*, *54*, 710-714.

Gracely, R. H., Dubner, R., Deeter, W. R., & Wolskee, P. J. (1985). Clinicians' expectations influence placebo analgesia. *Lancet*, *1*, 43.

Gracely, R. H., Dubner, R., Wolskee, P. J., & Deeter, W. R. (1983). Placebo and naloxone can alter postsurgical pain by separate mechanisms. *Nature*, *306*, 264-265.

Greenfield, S., Kaplan, S., & Ware, J. E. (1985). Expanding patient involvement in care. *Annals of Internal Medicine*, *102*, 520-528.

Grevert, P., Albert, L. H., & Goldstein, A. (1983). Partial antagonism of placebo analgesia by naloxone. *Pain*, *16*, 129-143.

Guess, H. A., Kleinman, A., Kusek, J. W., & Engel, L. W. (Eds.). (2002). *The science of the placebo: Toward an interdisciplinary research agenda*. London: British Medical Journal Books.

Hahn, R. A. (1985). A sociocultural model of illness and healing. In L. White, B. Tursky, & G. E. Schwartz (Eds.), *Placebo: Theory, research, and mechanisms* (pp. 167-195). New York: Guilford.

Hahn, R. A. (1997). The nocebo phenomenon: Scope and foundations. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 56-76). Cambridge, MA: Harvard University Press.

Harrington, A. (Ed.). (1997). *The placebo effect: An interdisciplinary exploration*. Cambridge, MA: Harvard University Press.

Hróbjartsson, A., & Gøtzsche, P. C. (2001). Is the placebo powerless? *New England Journal of Medicine*, *344*, 1594-1602.

Inui, T. S., Yourtee, E. L., & Williamson, J. W. (1976). Improved outcomes in hypertension after physician tutorials. *Annals of Internal Medicine*, *84*, 646-651.

Kaplan, S. H., Greenfield, S., & Ware, J. E., Jr. (1989). Assessing the effects of physician-patient interactions on the outcomes of chronic disease. *Medical Care*, *27*(Suppl. 3), S110-S127.

Kirsch, I. (Ed.). (1999). *How expectancies shape experience*. Washington, DC: American Psychological Association.

Kirsch, I., & Weixel, L. J. (1988). Double-blind versus deceptive administration of a placebo. *Behavioral Neuroscience*, *102*, 319-323.

Leuchter, A. F., Cook, I. A., Witte, E. A., Morgan, M., & Abrams, M. (2002). Changes in brain function of depressed subjects during treatment with placebo. *American Journal of Psychiatry*, *159*, 122-129.

Levine, J. D., & Gordon, N. C. (1984). Influence of the method of drug administration on analgesic response. *Nature*, *312*, 755-756.

Levine, J. D., Gordon, N. C., & Fields, H. L. (1978). The mechanisms of placebo analgesia. *Lancet*, *2*, 654-657.

Levine, J. D., Gordon, N. C., Smith, R., & Fields, H. L. (1981). Analgesic responses to morphine and placebo in individuals with postoperative pain. *Pain*, *10*, 379-389.

Levinson, W. (1994). Physician-patient communication: A key to malpractice prevention. *JAMA*, *272*, 1619-1620.

Lipman, J. J., Miller, B. E., Mays, K. S., Miller, M. N. North, W. C., & Byrne, W. L. (1990). Peak B endorphin concentration in cerebrospinal fluid: Reduced in chronic pain patients and increased during the placebo response. *Psychopharmacology*, *102*, 112-116.

Mayberg, H. S., Silva, A. J., Brannan, S. K., Tekell, J. L., Mahurin, R. K., McGinnis, S., et al. (2002). The functional neuroanatomy of the placebo effect. *American Journal of Psychiatry*, *159*, 728-737.

Moerman, D. E. (2002). Meaningful dimensions of medical care. In H. A. Guess, A. Kleinman, J. W. Kusek, & L. W. Engel (Eds.), *The science of the placebo: Toward an interdisciplinary research agenda*. London: BMJ Books.

Moerman, D. E., & Jonas, W. B. (2002). Deconstructing the placebo effect and finding the meaning response. *Annals of Internal Medicine*, *136*, 471-476.

Montgomery, G. H., & Kirsch, I. (1997). Classical conditioning and the placebo effect. *Pain*, *72*, 107-113.

Petrovic, P., Kalso, E., Petersson, K. M., & Ingvar, M. (2002). Placebo and opioid analgesia—Imaging a shared neuronal network. *Science*, *295*, 1737-1740.

Pollo, A., Amanzio, M., Arslanian, A., Casadio, C., Maggi, G., & Benedetti, F. (2001). Response expectancies in placebo analgesia and their clinical relevance. *Pain*, *93*, 77-84.

Pollo, A., Torre, E., Lopiano, L., Rizzone, M., Lanotte, M., Cavanna, et al. (2002). Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. *NeuroReport, 13*, 1383-1386.

Price, D. D., Milling, L. S., Kirsch, I., Duff, A., Montgomery, G. H., & Nicholls, S. S. (1999). An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain*, *83*, 147-156.

Price, D. D. (2001). Assessing placebo effects without placebo groups: An untapped possibility? *Pain*, *90*, 201-203.

Rowbotham, D. J. (2001). Endogenous opioids, placebo response, and pain. *Lancet*, *357*, 1901-1902.

Shetty, N., Friedman, J. H., Kieburtz, K., Marshall, F. J., & Oakes, D. (1999). The placebo response in Parkinson's disease. Parkinson study group. *Clinical Neuropharmacology*, *22*, 207-212.

Sox, H. C., Margulies, I., & Sox, C. H. (1981). Psychologically mediated effects of diagnostic tests. *Annals of Internal Medicine*, *95*, 680-685.

Spiegel, D., Bloom, J. R., Kraemer, H. C., & Gottheil, E. (1989). Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet*, *2*, 888-891.

Starfield, B., Wray, C., Hess, K., Gross, R., Birk, P. S., & D'Lugoff, B. C. (1981). The influence of patient-practitioner agreement on outcome of care. *American Journal of Public Health*, *71*, 127-132.

Stewart, M. A. (1995). Effective physician-patient communication and health outcomes: A review. *Canadian Medical Association Journal*, *152*, 1423-1433.

Stewart, M. A., McWhinney, I. R., & Buck, C. W. (1979). The doctor-patient relationship and its effect upon outcome. *Journal of Royal College of General Practice*, *29*, 77-82.

Thomas, K. B. (1987). General practice consultations: Is there any point in being positive? *British Medical Journal*, *294*, 1200-1202.

Thomas, K. B. (1994). The placebo in general practice. *Lancet*, *344*, 1066-1067.

Thong, Y. H. (1995). The shaman factor. *World Health Forum*, *16*, 238-240.

Turner, J. A., Deyo, R. A., Loeser, J. D., Von Korff, M., & Fordyce, W. E. (1994). The importance of placebo effects in pain treatment and research. *JAMA*, *271*, 1609-1614.

White, L., Tursky, B., & Schwartz, G. E. (Eds.). (1985). *Placebo: Theory, research, and mechanisms*. New York: Guilford.

Wohrl, S., & Hemmer, W. (2001). Placebos and pain management. *Lancet*, *358*, 1101-1102.