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Due to the increase in high-quality submissions from psychologists around the world, *Psychological Bulletin* will publish approximately 20% more pages in 1989. Therefore, subscription prices will be $50 for members, $100 for individuals, and $200 for institutions in 1989.

Rayner Appointed Editor of *JEP: Learning, Memory, and Cognition,* 1990–1995

The Publications and Communications Board of the American Psychological Association announces the appointment of Keith Rayner, University of Massachusetts, as editor of the *Journal of Experimental Psychology: Learning, Memory, and Cognition* for a 6-year term beginning in 1990. As of January 1, 1989, manuscripts should be directed to

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Manuscript submission patterns for *JEP: Learning, Memory, and Cognition* make the precise date of completion of the 1989 volume uncertain. The current editor, Henry Roediger, will receive and consider manuscripts until December 31, 1988. Should the 1989 volume be completed before that date, manuscripts will be redirected to Rayner for consideration in the 1990 volume.

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Etiology and Treatment of the Psychological Side Effects Associated With Cancer Chemotherapy: A Critical Review and Discussion

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Cancer patients receiving chemotherapeutic treatments routinely experience a wide range of distressing side effects, including nausea, vomiting, and dysphoria. Such symptoms often compromise patients' quality of life and may lead to the decision to postpone or even reject future, potentially life-saving, treatments. In this article, we discuss the hypotheses that have been offered to explain the development of such symptoms. We also review, in greater detail, the research evidence for the efficacy of five treatments for such symptoms: hypnosis, progressive muscle relaxation training with guided imagery, systematic desensitization, attentional diversion or redirection, and biofeedback. We discuss the implications of this treatment research, paying particular attention to factors associated with treatment outcome, mechanisms of treatment effectiveness, and issues associated with clinical application.

Chemotherapy is the treatment of choice for hundreds of thousands of cancer patients diagnosed each year in the United States (Silverberg & Lubera, 1986). Its frequent use with cancer patients is the result of recent advances in antineoplastic medication; new and more effective medications have increased the life expectancy for many patients and, in some cases, have resulted in remission and cure. Unfortunately, such long-term gain can come at considerable short-term cost to the cancer patient in the form of aversive and debilitating side effects. Among the more common drug-induced side effects are alopecia, stomatitis, immunosuppression, anorexia, nausea, and vomiting. In addition to these pharmacological side effects, chemotherapy patients also experience psychological side effects.

Psychological side effects, which should not necessarily be regarded as abnormal or indicative of psychopathology, are those that cannot be attributed directly to the antineoplastic medications; instead, such symptoms are believed to result from psychological processes (e.g., learning) that occur in the chemotherapy context. These symptoms can occur before chemotherapy (in which case they are referred to as anticipatory side effects) as well as during and after the actual chemotherapy infusion. When they occur after chemotherapy has been administered (and while the drugs remain pharmacologically active within the system), it is practically impossible to distinguish such psychological side effects from their pharmacological counterparts. Unfortunately, there has been much inconsistency in the literature concerning the definition of these symptoms and the terminology used to describe them. For the most part, however, research with humans has focused on three symptoms, namely, nausea, vomiting, and dysphoria. However, it should be noted that considerable animal research and recent human research have also focused on other side effects of cancer treatments, especially learned side effects such as conditioned taste and food aversions (e.g., Bernstein & Borson, 1986; Smith, Blumsack, & Bilek, 1985) and conditioned immunosuppression (e.g., Ader, 1981; Ader & Cohen, 1985). These phenomena may develop through mechanisms that are similar to those that are the focus of this article.

Symptoms such as nausea, vomiting, and dysphoria are not only frequent among cancer chemotherapy patients but can also be extremely stressful. In addition to the physical and affective distress they cause, many patients are embarrassed by their display of symptoms (e.g., anticipatory vomiting), and others even fear for their sanity. In fact, some patients eventually discontinue chemotherapy, abandoning the hope for remission and cure rather than suffer from such symptoms (Wilcox, Fetting, Nettesheim, & Abeloff, 1982). It has been suggested that still other patients will turn to ineffective and expensive "quack" treatments rather than tolerate the paradoxical worsening quality of life that chemotherapy can bring. Consequently, oncologists (e.g., Laszlo & Lucas, 1981), oncology nurses (e.g., Oberst, 1978), and cancer patients themselves (e.g., Cohn, 1982) have all implored researchers to identify an effective treatment for the side effects associated with cancer chemotherapy.

Pharmacological agents (e.g., prochlorperazine, delta-9-tetrahydrocannabinol) have been used to control the psychological responses to chemotherapy, but standard antiemetics have been found largely ineffective for this type of symptom (Laszlo, 1983;

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Morrow, Arseneau, Asbury, Bennett, & Boros, 1982). In addition, there is evidence that these medications can actually worsen the symptomatology under some conditions (Zeltzer, LeBaron, & Zeltzer, 1984a). Moreover, even when antiemetics provide some relief, they often have side effects of their own (e.g., sedation, dystonic reactions) or administration demands (e.g., the need for inpatient hospitalization) that limit their acceptance or usefulness among some patients. The ineffectiveness, the paradoxical worsening of symptoms, and the practical limitations of pharmacological agents have all prompted researchers to consider psychological treatments as an alternative method of controlling such symptoms.

In recent years, research on the etiology and treatment of anticipatory and exacerbatory side effects of cancer chemotherapy has burgeoned and has attracted researchers from several health-care disciplines. This increasingly widespread interest is based on at least two primary factors. First, from a theoretical point of view, the psychological side effects of cancer chemotherapy present an unusual opportunity to study the natural development of reactions to repeated aversive treatment within a clinical population. As we shall see, these reactions share some commonalities with other aversive responses but also appear to have some notable differences. Second, from a clinical point of view, these side effects are quite prevalent and can be aversive and debilitating. As a result, they represent an important clinical problem.

The primary purpose of this article is to review the research evidence on the etiology and treatment of the most common psychological side effects associated with cancer chemotherapy, namely, nausea, vomiting, and dysphoria. We begin with an overview and evaluation of the etiological formulations that have been proffered to explain the development of such symptoms. After this discussion of etiology, we review and critique the treatment literature, focusing on investigations that provide quantitative outcome data. We discuss the implications of this research, paying particular attention to patient factors associated with outcome, hypothesized mechanisms by which the treatments may exert their impact, and clinical issues in the application of such interventions.

Etiology of Psychological Side Effects Associated With Cancer Chemotherapy

Psychological side effects are believed to be relatively common. For example, prevalence data obtained from prospective, longitudinal studies indicate that approximately 45% of adult cancer patients experience nausea, vomiting, or both in the 24 hr preceding their chemotherapy (Burish & Carey, 1986). Although precise estimates of the prevalence of postchemotherapy psychological side effects in adults are not available, they are believed to be even more common (Burish & Carey, 1986).

Several causal explanations have been offered to explain the development of psychological side effects. One hypothesis is that these symptoms "may be surfacing manifestations of underlying psychological readjustment problems, associated with life-threatening illness" (Chang, 1981, p. 707). This view suggests that nonpharmacological symptoms represent the negative affect that patients harbor toward their chemotherapy treatments. To date, no data are available to support this assertion. A second hypothesis is that patients may display such symptoms in order to gain attention and sympathy. Inconsistent with this hypothesis, however, is the observation that the punishing side effects of chemotherapy far outweigh any secondary gains that may be realized by cancer patients; moreover, there are no data to support the notion that removal of attention can reduce nonpharmacological symptoms. A third hypothesis is that the observed symptoms may "be produced by brain metastasis or local cancer involvement of the gastrointestinal tract" (Chang, 1981, p. 707). Although this explanation may be accurate for a few patients, it has been ruled out as an explanation for most patients (e.g., Morrow, 1982).

In contrast with the first three hypotheses, which are speculative and lack empirical support, the fourth hypothesis has been supported by the research literature. This hypothesis holds that nonpharmacological or psychological side effects develop through an associative learning process. According to the most widely accepted conditioning viewpoint, after one or more pairings, an association is established between the pharmacological side effects (the unconditioned responses; UCRs) caused by the chemotherapy (the unconditioned stimulus; UCS) and various stimuli (e.g., sights, smells, thoughts; the conditioned stimuli; CSs) associated with the chemotherapy setting. As a result of repeated associations, the CSs begin to elicit nausea, vomiting, and dysphoria (the conditioned responses; CRs), even in the absence of the UCS. Two variations of the conditioning model have also been suggested. The first, proposed by Leventhal, Easterling, Nerenz, and Love (1988), is that postchemotherapy nausea and vomiting might occasionally serve as the UCS, with responses to this nausea and vomiting (e.g., anxiety and secondary nausea occurring later in time) being the UCRs. These UCRs then become conditioned to various stimuli in the chemotherapy environment and thereby take the form of CRs. Thus, in this first variation of the conditioning model, the morphology of the CS and CR is similar to that of the original model, but the UCS and UCR are not. The second variation was suggested by Garcia y Robertson and Garcia (1985), who believe that conditioned responses to cancer chemotherapy may develop through a process that closely resembles taste aversion learning. Although the published literature on conditioned responses to cancer chemotherapy has been based almost exclusively on the first model of conditioning, it should be noted that these two variations do provide viable conceptualizations of alternative, though not necessarily mutually exclusive, processes.

There are several sources of data that converge to support the hypothesis that associative learning is the primary phenomenon underlying the etiology of psychological symptoms. In no case were the data generated by experimental research that was designed deliberately to induce conditioned nausea and vomiting in cancer chemotherapy patients through controlled experimental manipulations, a procedure that would be ethically unacceptable. Rather, the data are based on analogous phenomena or experimental outcomes that consistently, logically, or exclusively point to associative learning as the most reasonable explanation. At least four sources of supporting data can be identified.

First, the symptoms that are displayed by chemotherapy pa-

tients have several topographical similarities to those of laboratory animals that ingest a gastrotoxic substance or that are irradiated while eating a certain food. The animals subsequently avoid that substance or food during future feedings, a phenomenon referred to as learned taste aversion (for an extended discussion of the similarities of conditioned nausea and vomiting in cancer patients and learned taste aversions, see Garcia y Robertson & Garcia, 1985). The symptoms have been shown to result from a learning process that is associative in nature, although it deviates, as does the conditioned response of chemotherapy patients, from the traditional classical conditioning paradigm in some interesting respects (e.g., the symptoms often develop after only one or a few associations and despite the fact that there may be several hours between the UCS and UCR). Another example of documented animal conditioning that bears even closer resemblance to the chemotherapy situation was demonstrated by Collins and Tatum (1925) and Pavlov (1927). These investigators showed that dogs repeatedly injected with an emetic drug developed conditioned vomiting in response to stimuli associated with the injection.

Second, several human studies provide data that support an associative learning explanation. For example, I. L. Bernstein and her colleagues (e.g., I. L. Bernstein, 1978; I. L. Bernstein & Webster, 1980) demonstrated experimentally that taste aversions can develop in chemotherapy patients as a result of the emetic properties of the infused drugs. For example, in one study the investigators assigned pediatric cancer patients receiving emetogenic chemotherapy agents to one of two groups: to an experimental group that received a novel-flavored ice cream shortly before their scheduled drug treatment or to a control group that did not receive the ice cream. A second control group of patients receiving nonemetic chemotherapy drugs was also included. After 2 or more weeks, patients in all groups were offered either some of the novel-flavored ice cream or an opportunity to play with a game. Patients in the two control groups overwhelmingly chose the ice cream; patients in the experimental group showed an aversion to the ice cream, generally preferring the game. Similar results were subsequently demonstrated in adult cancer patients (see I. L. Bernstein & Webster, 1985, for a review).

Third, there have been reports of cancer chemotherapy patients becoming conditioned to antiemetic treatments. In these situations, the antiemetic was apparently given each time the patient became nauseated or was vomiting; as a result, it became associated with nausea and vomiting and later was able to elicit, on its own, nausea and vomiting. For example, Kutz, Borysenko, Come, and Benson (1980) reported the case of a patient with neurofibrosarcoma who smoked marijuana to alleviate severe nausea and vomiting. After chemotherapy was discontinued, the smell of marijuana in social situations elicited nausea and vomiting. In another case reported by the same authors, the marijuana was administered in brownies and cookies. For a year after the chemotherapy was discontinued, the taste or sight of these foods produced nausea. Similar conditioning to antiemetics has been reported by other investigators (e.g., Morrow et al., 1982).

Fourth, research has shown that factors related to the development of conditioned symptoms in cancer chemotherapy patients conform to the principles of associative learning. For example, Andrykowski et al. (in press) and Andrykowski, Redd, and Hatfield (1985) conducted two longitudinal studies of the development of anticipatory nausea in cancer chemotherapy patients. In these investigations, which together involved the study of over 150 patients, the authors found that anticipatory nausea never occurred without the prior occurrence of postchemotherapy nausea, that is, consistent with the principles of associative learning, the presence of a UCR was necessary for the acquisition of a CR. Moreover, after a careful analysis of other factors that contributed to the development of anticipatory symptoms, the authors concluded that, consistent with an associative learning model, "all of the factors that reliably predicted the development of AN [anticipatory nausea] were either directly or indirectly linked to the magnitude" of the unconditioned symptoms (Andrykowski et al., in press, p. 11). As has been noted elsewhere (Burish & Carey, 1986), other descriptive data on the development and nature of conditioned responses in cancer chemotherapy patients also consistently conform, in prospective as well as retrospective studies, to the principles of associative learning.

In addition to supporting the conditioning model, the available data suggest that several factors can serve to mediate or potentiate the learning process and thereby produce considerable variation in symptom development. These individual difference factors may arise independently of, but nonetheless contribute to, the development of conditioned responses.

One major individual difference may be proneness to nausea and vomiting. Research has suggested that patients who have a history of motion sickness or of experiencing nausea and vomiting to various foods or situations (e.g., pregnancy) are more likely to report posttreatment and anticipatory nausea and vomiting in response to cancer chemotherapy (Jacobsen et al., 1988; Morrow, 1985). Morrow (1985) has suggested that there is a neurological basis for this relationship. The experience of nausea and vomiting is thought to result from activation of the "vomiting center," located in the lateral reticular formation of the medulla oblongata (Borison & McCarthy, 1983). The vomiting center has four major inputs, including one from the vestibular system, which is thought to play a role in motion sickness. It has been suggested that in addition to affecting the other major inputs, chemotherapy may affect the vestibular system, which in patients with a susceptibility to motion sickness may lead to additional stimulation of the vomiting center and therefore an increased likelihood of nausea and vomiting (Morrow, 1985). Redd and his colleagues (Jacobsen et al., 1988; Andrykowski et al., in press) have suggested that there may be constitutional differences in cancer patients' susceptibility to gastrointestinal distress, including that due to chemotherapy. Patients with a greater constitutional vulnerability to gastrointestinal distress may be more likely to respond to chemotherapy with high levels of posttreatment nausea and vomiting, which in turn increases the likelihood that they will develop conditioned nausea and vomiting, in comparison with patients without this diathesis. In summary, the data suggest that patients with a past history of nausea and vomiting resulting from motion sickness, certain foods, or other experiences are more likely to develop

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