ANTICIPATORY NAUSEA AND VOMITING IN CANCER PATIENTS UNDERGOING CHEMOTHERAPY TREATMENT: PREVALENCE, ETIOLOGY, AND BEHAVIORAL INTERVENTIONS

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Patricia L. Dobkin

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ABSTRACT. Nausea and vomiting are common side effects that occur after chemotherapeutic drugs are given to treat cancer. Recent attention has been focused on the occurrence of nausea and vomiting in anticipation of a treatment. Prevalence data from a variety of studies show that approximately 25% of patients receiving chemotherapy treatments for cancer develop anticipatory nausea and vomiting (ANV) by the time of their fourth treatment. A review of studies examining models and variables associated with potential etiology indicates that no single demographic, clinical, or psychologic characteristic appears to be as related to the development of anticipatory side effects as are several characteristics in concert. Specifically, patients under 50 years of age who are treated with potentially emetic chemotherapy and who experience distressing nausea and vomiting after treatment appear to be at risk for the development of anticipatory nausea and vomiting. The development of anticipatory side effects appears to follow a classically conditioned model; no compelling data contradict a view that anticipatory side effects are learned. A review of both case and controlled studies on the biobehavioral treatment of ANV indicates that: (a) while studies on Hypnosis have been methodologically weak, they provide support for continued controlled investigations in children; (b) Progressive Relaxation Training appears effective in controlling posttreatment nausea and vomiting; and (c) Systematic Desensitization appears effective in controlling both anticipatory and posttreatment nausea and vomiting. The review concludes with a brief consideration of several methodologic and practical issues that point to promising directions for future research in the area.

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The most common side effects of chemotherapy drug treatment for cancer are nausea and vomiting. If not adequately controlled, nausea and vomiting can lead to further complications, such as anorexia and metabolite imbalance, along with contributing to a general deterioration of the cancer patient’s psychological and physical condition. Cancer patients may develop as much apprehension and dread about treatment and its side effects as they do about their disease. Many cancer patients treated with chemotherapy drugs request dosage reductions or even terminate potentially curative treatment regimens prematurely due to poorly controlled nausea and vomiting (Holland, 1977; Hoagland, Morrow, Bennett, & Carnrike, 1983). In addition to becoming nauseous and/or vomiting following chemotherapy treatment, a number of patients experience these aversive side effects prior to a treatment session (Morrow, 1981, 1982, 1986a).

Increasing experimental attention is being paid to this phenomenon referred to as anticipatory nausea and vomiting (ANV), for it is a side effect that appears to link psychological, neurological, and physiological systems. In addition, anticipatory side effects may provide an unusual opportunity to study the natural occurrence of what appears to be a form of aversive learning in humans (Burish & Carey, 1986). Here we examine and critique studies on the prevalence, etiology, and treatment of anticipatory nausea and vomiting, with a view toward organizing past research to identify further directions for exploration.

**PREVALENCE OF ANTICIPATORY NAUSEA AND VOMITING**

Since 1979 at least 28 studies (summarized in Table 1) have reported the prevalence of anticipatory nausea and vomiting in adult and pediatric cancer chemotherapy patients. As shown at the bottom of the table, a range of prevalence rates of anticipatory nausea and vomiting have been reported in the different studies. On the lower end of estimates, rates of anticipatory side effects of 18% of 71

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1To appreciate how psychological and biobehavioral effects may influence the physiologic response of nausea and vomiting, it may be helpful to briefly review the physiology of these side effects. The final common pathway for the coordination of the respiratory muscles and other structures involved in the act of vomiting and probably also the sensation of nausea is an area of the dorsolateral reticular formation of the medulla called the vomiting center (Borison & Wang, 1953). There are at least three major inputs to this structure. Although the mechanisms by which nausea and vomiting occur during chemotherapy treatment are not totally characterized (Lazlo, 1983), there is an emerging consensus that at least three major inputs are involved. The first is from the vestibular system. This is thought to be involved in the development and expression of nausea and vomiting due to motion (Reason & Brand, 1975). A second input is the area postrema (Borison, Hawken, Hubbard, & Sirett, 1975). This is an area near the fourth ventricle that is in the unique position of being in contact with both cerebral spinal fluid and blood. It is thought to be that area in which nausea and vomiting due to chemical challenges, such as food poisoning, toxicity, and nausea attributable to chemotherapy drugs takes place. The final large input are cortical areas from the limbic system and the cerebrum. There are fiber tracts from areas in the limbic system associated with the expression of emotion and associated with memory that connect to the vomiting center. This provides a neurologic substrate which makes possible the involvement of psychologic phenomenon in the expression of nausea/vomiting.
TABLE 1. Prevalence of Anticipatory Side Effects in Cancer Chemotherapy Patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number studied</th>
<th>Anticipatory nausea</th>
<th>Anticipatory vomiting</th>
<th>Anticipatory nausea and/or vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrykowski (1987)</td>
<td>78</td>
<td>33%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Andrykowski et al. (1985)</td>
<td>71</td>
<td>37%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Andrykowski et al. (1987)</td>
<td>77</td>
<td>57%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cella et al. (1984)</td>
<td>60</td>
<td>63%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cohen (1982)</td>
<td>149</td>
<td>42%</td>
<td>27%</td>
<td>-</td>
</tr>
<tr>
<td>Dobkin et al. (1985)</td>
<td>125</td>
<td>32%</td>
<td>12%</td>
<td>-</td>
</tr>
<tr>
<td>Dolgan et al. (1986)</td>
<td>80</td>
<td>29%</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>Fdez-Argeuilles et al. (1985)</td>
<td>72</td>
<td>-</td>
<td>-</td>
<td>31%</td>
</tr>
<tr>
<td>Fetting et al. (1983)</td>
<td>123</td>
<td>14%</td>
<td>-</td>
<td>31%</td>
</tr>
<tr>
<td>Jacobsen et al. (1985)</td>
<td>27</td>
<td>57%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ingle et al. (1984)</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>25%</td>
</tr>
<tr>
<td>Love et al. (1983)</td>
<td>126</td>
<td>38%</td>
<td>-</td>
<td>38%</td>
</tr>
<tr>
<td>Morrow (in press)</td>
<td>406</td>
<td>24%</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Morrow et al. (1982)</td>
<td>225</td>
<td>-</td>
<td>-</td>
<td>21%</td>
</tr>
<tr>
<td>Morrow &amp; Dobkin (1985)</td>
<td>736*</td>
<td>26%</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td>Nesse et al. (1980)</td>
<td>18</td>
<td>44%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nerenz et al. (1986)</td>
<td>61</td>
<td>24%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nicholas (1982)</td>
<td>71</td>
<td>-</td>
<td>-</td>
<td>18%</td>
</tr>
<tr>
<td>Nicholas (1983)</td>
<td>50</td>
<td>42%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olafsdottir et al. (1986)</td>
<td>50</td>
<td>40%</td>
<td>14%</td>
<td>-</td>
</tr>
<tr>
<td>Palmer et al. (1980)</td>
<td>24</td>
<td>22%</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Schultz (1980)</td>
<td>68</td>
<td>-</td>
<td>-</td>
<td>31%</td>
</tr>
<tr>
<td>Scogna &amp; Smalley (1979)</td>
<td>41</td>
<td>-</td>
<td>-</td>
<td>37%</td>
</tr>
<tr>
<td>van Komen &amp; Redd (1985)</td>
<td>100</td>
<td>33%</td>
<td>11%</td>
<td>-</td>
</tr>
<tr>
<td>Weddington (1982)</td>
<td>17</td>
<td>53%</td>
<td>12%</td>
<td>-</td>
</tr>
<tr>
<td>Weddington et al. (1984)</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>38%</td>
</tr>
<tr>
<td>Wilcox et al. (1982)</td>
<td>52</td>
<td>-</td>
<td>33%</td>
<td>-</td>
</tr>
<tr>
<td>Wilson (1986)</td>
<td>66</td>
<td>20%</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2,452</td>
<td>18%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>80</td>
<td>33%</td>
<td>12%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>17–736</td>
<td>14–63%</td>
<td>9–27%</td>
<td>18–38%</td>
</tr>
</tbody>
</table>

*These patients were part of a consecutive series; therefore, the patients reported in Morrow (1982) and Morrow (in press) are part of the n = 736 in Morrow & Dobkin (1985).

Patients were reported by Nicholas (1982). A rate of over 50% was reported by Cella, Pratt, and Holland (1984) for 60 patients treated for Hodgkin's Disease.

Several factors have been proposed to account for variation in prevalence rates (see discussions by Andrykowski, 1986; Burish & Carey, 1986; Duigon, 1986; Morrow, 1982, 1984b; Nicholas & Hollandsworth, 1986). These reviews generally point to one or more of the following explanations of variation in prevalence rates of anticipatory nausea: (a) Some researchers have studied anticipatory nausea and vomiting symptoms independently of each other, whereas other researchers combined them and viewed the symptoms as one phenomenon. Often it is not
evident which phenomenon was being reported. (b) Nausea and vomiting side
effects may occur during chemotherapy treatment. While this may represent antici-
patory phenomenon, it is more likely a physiological response since some chemo-
therapy drugs may be reacted to during the time that they are actively given. (c)
Prevalence rates may be influenced by the type of chemotherapy drugs adminis-
tered to cancer patients, since side effects vary across different treatment regi-
ments. (d) The time frame in which ANV symptoms were studied has differed
across studies. For example, Morrow, Arseneau, Asbury, Bennett, and Boros
(1982) assessed patients prior to their fourth chemotherapy cycle whereas Wilcox,
Fetting, Nettesheim, and Abeloff (1982) did so prior to the tenth chemotherapy
cycle. The data currently available support the view that there is a positive
correlation between ANV and the number of chemotherapy treatments (see Fig-
ure 2). (e) A portion of the variation in prevalence rates may be due to measure-
ment artifacts. A variety of self-report measures have been used to assess ANV
across studies (Morrow, 1984b). For example, some studies involved interviewing
patients by asking retrospective questions (e.g., Dobkin, Zeichner, & Dickson-
Parnell, 1985), whereas others used patient-completed logs during and following
treatment (Burish & Carey, 1984).

As a means of approximating how much variation in prevalence rates may be
due to the factors mentioned above, data from a series of 1,480 consecutive
chemotherapy patients reported by Morrow (1986b) can be compared with the
rates cited in Table 1 summarizing data collected on 2,452 patients. By aggregat-
ing the data from Table 1, it appears that the overall prevalence rate of anticipato-
ry nausea is 33%. From Morrow's data, collected on 1,480 patients from a single
cancer center, assessed with the same scale (Morrow Assessment of Nausea and
Emesis), at a standard time (prior to the fourth chemotherapy cycle), it appears
that the overall prevalence rate is 23%. Thus, 10% of the variance may be due to
factors mentioned above.

**Summary and Suggestions for Future Research Directions**

Comparing the results for anticipatory nausea shows that approximately one in
four patients was found to have experienced anticipatory nausea based on a
standard criteria in a series of consecutive patients. A 10% higher figure of
approximately one in three patients found to experience anticipatory nausea was
found for a sample of chemotherapy patients aggregated from different studies,
from a variety of geographic locations, using potentially disparate definitions.
These rates are comparable from a clinical as well as practical standpoint.

A different assessment framework for measures of nausea would be of potential
advantage in this area. For example, if selected physiologic parameters were

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Chemotherapy treatment is typically given repeatedly over a number of weeks in episodes
that are called treatment cycles. For example, it is common to be treated with a chemo-
therapy drug once every three weeks for a total of perhaps a dozen cycles. During each of
these treatments, patients spend several hours in the treatment clinic. Chemotherapy
drugs are given through a small needle typically placed in a vein in the back of the hand.
Some drug regimens (especially those that are more toxic) are administered slowly over a
period of more than one hour. Thus, an individual treatment may occupy a significant
portion of the day.
shown to be replicable concomitants of patient reported nausea, they could be used to systematically examine variation in patient report by providing an objective frame of reference (Nicholas & Hollandsworth, 1986; Burish & Carey, 1986; Andrykowski, 1986; Morrow, in press). Some preliminary work has been reported in the motion sickness literature, where physiological measures such as skin pallor have been shown related to motion-induced nausea (Oman, Lichtenberg, & Mooney, 1984). If motion-induced nausea is analogous to chemotherapy drug-induced nausea, then this methodology may be useful. Morrow has modified and refined assessment instruments for the measurement of several physiological parameters associated with nausea (pallor, skin temperature, blood volume pulse, heart rate, and body motion). Preliminary data (Morrow, in press) have shown a physiologic pattern that matches patient report of drug-induced nausea. Over a series of repeated chemotherapy cycles, eight patients have shown an increase in pallor and decrease in skin temperature, blood volume pulse, and body motion that corresponds to self-reported nausea. During vomiting episodes, pallor decreases and skin temperature transiently increases during expulsion, although there is a gradual decrease of up to 4.6°C over ten vomiting episodes.

If these findings are supported by larger scale studies, this framework of physiologic assessment may be applicable to studies not only on the prevalence of anticipatory side effects but also on determinants and the efficacy of treatment. Such an assessment technology could prove useful in studies examining aspects of patients' self-report of both anticipatory and posttreatment nausea.

**ETIOLOGY OF ANTICIPATORY NAUSEA AND VOMITING**

A wide variety of correlates of anticipatory nausea and vomiting have been explored. In this section, studies exploring associations among demographic, clinical and/or psychological variables and ANV are presented and discussed. This is followed by a critique of the four basic models that have been proposed for how ANV develops. The section ends with a detailed examination of how available data support a model of ANV development based on learning principles.

**Univariate Correlates of Anticipatory Nausea and Vomiting**

A number of characteristics have been examined for their possible association to anticipatory side effects. They may be conveniently grouped under the categories of demographic, clinical, and psychological characteristics studied.

**Demographic Variables.** Table 2 summarizes demographic variables examined for a correlation with anticipatory side effects. Several investigators (Cohen, 1982; Fetting et al., 1983; Ingle, Burish, & Wallston, 1984; Morrow, 1982; van Komen & Redd, 1985) have found an association between age (that is, being younger than 50 years old) and experiencing ANV. Only two of the eleven studies investigating gender (Fetting et al., 1983; Wilson, Rahdert, Black, Taylor, & Holloway, 1986) found it to be associated with ANV symptomatology. None of six studies including data on ethnicity (Fetting et al., 1983; Ingle et al., 1984; Morrow, 1982; Weddington, Miller, & Sweet, 1982; van Komen & Redd, 1985) have reported a relationship between race and anticipatory side effects. Education level and socioeconomic and marital status do not appear to be critical factors for the development of ANV symptoms (Fetting et al., 1983; Morrow, 1982; Weddington, Mill-
TABLE 2. Demographic Variables Associated with Anticipatory Nausea and Vomiting

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Gender</th>
<th>Age</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrykowski et al. (1985)</td>
<td>71</td>
<td>—</td>
<td>x</td>
<td>—</td>
</tr>
<tr>
<td>Cohen (1982)</td>
<td>149</td>
<td>x</td>
<td>younger</td>
<td>—</td>
</tr>
<tr>
<td>Dolgan et al. (1985)</td>
<td>80</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Fetting et al. (1983)</td>
<td>123</td>
<td>female</td>
<td>younger</td>
<td>x</td>
</tr>
<tr>
<td>Ingle et al. (1984)</td>
<td>60</td>
<td>x</td>
<td>younger</td>
<td>x</td>
</tr>
<tr>
<td>Love et al. (1982)</td>
<td>126</td>
<td>—</td>
<td>younger</td>
<td>—</td>
</tr>
<tr>
<td>Morrow (1982)</td>
<td>225</td>
<td>x</td>
<td>younger</td>
<td>x</td>
</tr>
<tr>
<td>Nesse et al. (1980)</td>
<td>18</td>
<td>x</td>
<td>x</td>
<td>—</td>
</tr>
<tr>
<td>Schultz (1980)</td>
<td>68</td>
<td>x</td>
<td>x</td>
<td>—</td>
</tr>
<tr>
<td>van Komen &amp; Redd (1985)</td>
<td>100</td>
<td>x</td>
<td>younger</td>
<td>—</td>
</tr>
<tr>
<td>Weddington et al. (1982)</td>
<td>17</td>
<td>x</td>
<td>x</td>
<td>—</td>
</tr>
<tr>
<td>Weddington et al. (1984)</td>
<td>50</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Wilson (1986)</td>
<td>66</td>
<td>female</td>
<td>younger</td>
<td>x</td>
</tr>
</tbody>
</table>

Association found: 2/11 (18%) 7/13 (54%) 0/6 (0%)

Note: x indicates that the factor was investigated and was not found to correlate with ANV.
— indicates that the factor was not investigated.

er, & Sweet, 1982). Overall, with the marked exception of age, there appears to be little association between patient demographic characteristics and the development of anticipatory side effects. It is possible, however, that since younger patients are more likely to receive highly emetic chemotherapy regimens that age, in and of itself, is not a crucial factor.

Clinical Variables. Table 3 summarizes results of clinical variables examined in 14 studies for their association to ANV. Nesse, Carli, Curtis, & Kleinman (1980) reported that cancer patients with anticipatory nausea, when compared to those cancer patients without anticipatory nausea, had been treated for a significantly longer period of time (M = 9.3 months versus M = 4.2 months, respectively). Morrow (1982; 1984c) noted that, compared to patients who did not report ANV symptoms, ANV patients experienced more post-chemotherapy nausea and vomiting, of longer duration and greater severity.

All three studies that examined a potential relationship between how much nausea and vomiting a chemotherapy drug typically caused after treatment (its emetic potential) and ANV reported a significant relationship. Seven out of seven studies, and seven out of nine studies reported a relationship between post-chemotherapy nausea and vomiting, respectively, and ANV symptoms. The neural pathway between the vomiting center (an area in the dorsolateral reticular formation of the medulla) and the vestibular system has been implicated in motion induced nausea and vomiting as well as vomiting from poisons given to animals (Money & Cheung, 1983). Thus, a possible relationship between motion sickness susceptibility and chemotherapy nausea/vomiting has been studied. Using a case control methodology, Morrow has shown that patients who report a susceptibility to motion sickness (compared to patients without a susceptibility) had (a) signifi-
cantly more side effects from chemotherapy drugs (Morrow, 1985); (b) significantly more posttreatment nausea and vomiting (Morrow, 1984f); (c) significantly more anticipatory nausea and vomiting (Morrow, 1984e).

Psychological Variables. Consistent with a view that emotions and cognitions may contribute to the development of ANV (Ahles et al., 1984; Schultz, 1980; van Komen & Redd, 1985), anxiety, depression, hostility, and coping styles in cancer chemotherapy patients have been studied. As shown in Table 4, 10 out of 11 investigations found that state anxiety levels were significantly elevated in patients with ANV compared to patients without ANV. Two out of three investigations found trait anxiety related to ANV.

Love, Nerenz, & Leventhal (1982), using a prospective research design, studied 126 cancer patients being treated with chemotherapy for breast cancer (n=94) and malignant lymphoma (n=32). Patients were interviewed repeatedly during their initial six months of chemotherapy. Thirty-eight percent of the patients

### TABLE 3. Clinical Variables Associated with Anticipatory Nausea and Vomiting

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>No. of Rx</th>
<th>Emetic Potential</th>
<th>Post Rx Nausea</th>
<th>Post Rx Vomiting</th>
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<tbody>
<tr>
<td>Andrykowski et al. (1985)</td>
<td>71</td>
<td>a</td>
<td>—</td>
<td>*</td>
<td>—</td>
</tr>
<tr>
<td>Andrykowski et al. (1987)</td>
<td>77</td>
<td>*</td>
<td>—</td>
<td>*</td>
<td>—</td>
</tr>
<tr>
<td>Cohen (1982)</td>
<td>149</td>
<td>x</td>
<td>—</td>
<td>— b</td>
<td>— b</td>
</tr>
<tr>
<td>Dobkin et al. (1985)</td>
<td>125</td>
<td>—</td>
<td>—</td>
<td>b</td>
<td>—</td>
</tr>
<tr>
<td>Dolgan et al. (1985)</td>
<td>80</td>
<td>x</td>
<td>*</td>
<td>— x</td>
<td></td>
</tr>
<tr>
<td>Fetting et al. (1983)</td>
<td>123</td>
<td>—</td>
<td>—</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Ingle et al. (1984)</td>
<td>58</td>
<td>x</td>
<td>*</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Morrow (1982)</td>
<td>225</td>
<td>—</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Morrow (1984c)</td>
<td>176</td>
<td>—</td>
<td>*</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Nesse et al. (1980)</td>
<td>18</td>
<td>*</td>
<td>—</td>
<td>* *</td>
<td></td>
</tr>
<tr>
<td>Nerenz et al. (1982)</td>
<td>61</td>
<td>—</td>
<td>—</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Nicholas (1983)</td>
<td>71</td>
<td>*</td>
<td>—</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>van Komen &amp; Redd (1985)</td>
<td>100</td>
<td>*</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Weddington et al. (1982)</td>
<td>17</td>
<td>*</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Weddington et al. (1984)</td>
<td>50</td>
<td>*</td>
<td>—</td>
<td>bx</td>
<td></td>
</tr>
<tr>
<td>Wilcox et al. (1982)</td>
<td>52</td>
<td>—</td>
<td>*</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Association found: 7/10 (70%) 3/3 (100%) 9/9 (100%) 5/7 (71%) 7/7 (100%) 7/9 (78%)

Note: x indicates that the factor was studied and was not found to correlate with ANV.
* indicates that the factor was not studied.
* indicates that the factor was found to correlate significantly with ANV.
Rx=chemotherapy regimen; S=severity; D=duration.
* indicates length of infusion.
* indicates frequency (rather than duration).
TABLE 4. Psychological Variables Associated with Anticipatory Nausea and Vomiting

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Hostility</th>
<th>Coping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahles et al. (1984)</td>
<td>9</td>
<td>* (state)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Altmaier et al. (1982)</td>
<td>9</td>
<td>* (state)</td>
<td>-</td>
<td>x</td>
<td>o</td>
</tr>
<tr>
<td>Andrykowski et al. (1985)</td>
<td>71</td>
<td>* (state)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Andrykowski et al. (1987)</td>
<td>77</td>
<td>+ (state)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cohen (1982)</td>
<td>31</td>
<td>* (state)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>x (trait)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Houts et al. (1982)</td>
<td>90</td>
<td>* (state)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ingle et al. (1984)</td>
<td>58</td>
<td>* (state)</td>
<td>x</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Nerenz et al. (1986)</td>
<td>18</td>
<td>* (state)</td>
<td>-</td>
<td>-</td>
<td>**</td>
</tr>
<tr>
<td>Shultz (1980)</td>
<td>68</td>
<td>* (state/trait)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>van Komen &amp; Redd (1985)</td>
<td>100</td>
<td>* (trait)</td>
<td>-</td>
<td>*</td>
<td>-</td>
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<tr>
<td>Wilson (1986)</td>
<td>66</td>
<td>+</td>
<td>+</td>
<td>x</td>
<td>-</td>
</tr>
</tbody>
</table>

Summary

Total 509 10/11 (state) 2/4 1/3 1/3

2/3 (trait)

Note: * indicates that there was no difference between ANV and non-ANV patients
- indicates that the factor was not investigated
* indicates that the measure was significantly elevated in ANV patients
o indicates that the measure was depressed in ANV patients
** indicates that "more attempts to cope" were made
+ indicates that conflicting results were found between measures
++ indicates that anxiety was significantly elevated only in late-onset of ANV patients

developed ANV, with patients who experienced anxiety during injections significantly more likely to develop anticipatory nausea than non-anxious patients. Interestingly, the association between anxiety and anticipatory nausea was not statistically significant during the first two chemotherapy cycles but became significant by the sixth cycle. Andrykowski et al. (1987) also reported that the relationship between anxiety and ANV should be qualified according to the treatment time frame. To determine if there were different patterns of infusion-related state anxiety and posttreatment nausea prior to AN onset, AN patients were divided into early (i.e., prior to chemotherapy cycle number 7) and late (i.e., following chemotherapy cycle number 7) onset groups. According to this distinction, anxiety appeared to contribute to the development of AN only for patients who were in the late onset group. A simple, direct relationship between anxiety and ANV development has not been found.

Depression was found to be significantly elevated in ANV patients in two out of four studies, whereas hostility and coping styles were not found to be consistently different in ANV patients. Altmaier, Ross, & Moore (1982) reported that patients with ANV exhibited a coping style which was “inhibitive rather than facilitative in nature.” In contrast, Ingle et al. (1984) found a greater number of “attempts to cope with chemotherapy and a higher level of hostility in patients with ANV compared to patients without ANV. Hostility and coping styles are, however,
difficult hypothetical constructs to operationalize; it is, therefore, possible that these divergent findings reflect measurement variance rather than actual differences in responses.

**Summary.** Methodological differences in research designs used and assessment techniques employed render firm comparisons among these investigations difficult. In addition, the retrospective nature of studies examining the possible association between single variables and the development of anticipatory side effects limit the conclusions that can be reached from these data.

### Multivariate Correlates of Anticipatory Side Effects

Several recent studies have built on some of the earlier promising univariate findings and used multivariate procedures to examine potential joint or interactive relationships among variables that might be associated with the development of anticipatory side effects.

Morrow (1982) reported results from a two-group discriminant analysis on 225 cancer patients. Overall, an 80% accurate classification was achieved with 42% of patients experiencing ANV and 91% of patients not experiencing ANV, correctly classified based on a combination of age, severity, and duration of postchemotherapy nausea and vomiting. Cohen (1982) reported that the frequency of vomiting during/after chemotherapy sessions and age (younger than 50 years-old) accounted for 32% of the variance in the occurrence of anticipatory nausea. Similar patterns were observed in analyses involving anticipatory vomiting. In a follow-up study (Cohen, 1982) involving 14 patients with ANV, five variables—nausea, anxiety, noxious sensations, frequency of post-chemotherapy vomiting, and age—accounted for 88% of the variance for anticipatory nausea. Four variables—nausea, frequency of vomiting during/after chemotherapy, anxiety and age—accounted for 65% of the variance in anticipatory vomiting. Since complete data were obtained from only 14 patients, these results require cautious interpretation.

In a study of 58 adult cancer patients, Ingle et al. (1984) used a three-group (“conditioned, may be conditioned, and not conditioned”) discriminant analysis involving seven variables in order to determine the best set of “predictors” for patients with ANV. These authors reported an overall assignment rate of 71% to the three groups based on: age (younger than 50 years old), postchemotherapy nausea and vomiting, anxiety, and “coping effect.”

Dolgan, Katz, McGinty, & Seigel (1985), in a study of 80 pediatric (mean age of nine years-old) cancer patients, identified five variables which accounted for 23% of the variance in group membership; these were: postchemotherapy nausea and vomiting, emetic potential of chemotherapy regimen, administration of the drug cyclophosphamide, time since diagnosis, and parental anxiety.

van Komen and Redd (1985), in an investigation of 59 cancer patients, administered the Millon Behavioral Health Inventory (Millon, Green, & Meagher, 1979) and the Spielberger State-Trait Anxiety Inventory (Spielberger, Gorsuch, and Lushene, 1968) in order to examine potential personality factors hypothesized to be associated with ANV symptomatology. The most important discriminator variables found were: social alienation, future despair (depression), and gastrointestinal susceptibility. Trait anxiety was also shown to be higher in
patients with ANV compared to patients without ANV. Interestingly, patients who received chemotherapy in a group setting were more likely to experience ANV compared to patients who were treated on an individual basis.

Andrykowski, Redd, and Hatfield (1985) studied 26 patients who displayed anticipatory side effects and 45 who did not. While seven variables entered into a hierarchical regression accounted for about half (47%) of the variance in group membership, posttreatment nausea alone accounted for about one quarter (24%). State anxiety and length of time it took to give the chemotherapy drug were the only two other variables giving a significant increment in explained variance.

A recent study (Morrow, 1984c) provided support for a view that clinically relevant characteristics are associated with anticipatory side effects. One hundred seventy-six consecutive ambulatory patients with histologically confirmed cancer who were being treated at three geographically separate hospitals at the University of Rochester Cancer Center were studied at the time of their fourth chemotherapy treatment. Patients found to experience anticipatory nausea and vomiting were significantly more likely to have four or more of the following characteristics compared to patients who did not report anticipatory side effects: (a) age (less than 50 years); (b) the experience of nausea and/or vomiting after their last chemotherapy treatment; (c) describe nausea after the last treatment as "moderate, severe, or intolerable"; (d) describe vomiting after the last treatment as "moderate, severe, or intolerable"; (e) report the side effect "warm or hot all over" after their last treatment; (f) susceptibility to motion sickness; (g) experience "sweating after their last treatment"; and (h) experience "generalized weakness after their last chemotherapy treatment."

These results were recently replicated in a prospective study (Morrow, submitted for publication). Five hundred thirty consecutive cancer patients were asked the previously reported eight questions following their first chemotherapy treatment. The outcome measure was whether or not they had developed anticipatory nausea/vomiting by the time of their fourth chemotherapy treatment. Those patients who had four or more of the eight characteristics were predicted to develop anticipatory side effects. Those with three or less were predicted not to. A significant association was found between these characteristics and subsequent development of anticipatory side effects for 345 patients entered into the study and followed through their fourth chemotherapy treatment. This finding provides a reasonably robust test of the importance of the eight characteristics in the development of the anticipatory side effects.

Several of these factors were implicated in univariate investigations. The fact that there are consistent findings regarding patient and treatment characteristics that contribute to the development of anticipatory side effects, irrespective of patient sample and definition used, point to the stability of these factors.

Summary and Suggestions for Future Research Directions. Definitional differences may account for some of the variation in correlates of ANV found. For example, most studies have set up criterion groups of those who have developed the symptoms and those who have not, and then examined potential correlates based on those criterion.

At least one study has used a three-group criterion of those patients who were "conditioned," "may be conditioned," and "not conditioned" based on the MANE (Ingle, Burish, & Wallston, 1984). A multiple regression model yielded no clear
Anticipatory Nausea and Vomiting

Correlates of the intermediate, “may be conditioned,” group. The study found that those subjects who fell in a “conditioned” group were significantly younger and experienced greater severity of posttreatment nausea and vomiting and were generally more anxious than patients who did not. These findings are consistent with previous investigations outlined in Table 2 through 4.

Thus, while a variety of research methodologies involving a variety of samples from populations that may have varied on a number of clinical characteristics, a reasonable consistency of results has been shown. While they have differed in sample, assessment, and analysis, the more recent multivariate studies support an emerging consensus on which factors contribute to the development of anticipatory side effects. At least three summary contentions are supported by the data. First, ANV is multiply determined in that no single demographic, clinical, or psychological characteristic appears to be as related to ANV development as are several characteristics in concert. Second, a subset (usually no more than three or four) of any larger set of characteristics accounts for as much variance in group membership (has ANV versus does not have ANV) as the larger set. And third, patients under 50 years of age who are treated with potentially emetic chemotherapy and who experience distressing postchemotherapy nausea and vomiting appear to be at risk for the development of an anticipatory response.

There has been a general increase in the methodologic sophistication of studies investigating ANV correlates; however, improvements can still be made. Early studies were basically correlational in nature. More recent studies have focused on multivariate methods; regression models have been used primarily. While an improvement over simple univariate studies, multivariate methodology introduces difficulties and potential pitfalls of its own. There are potential problems of validity in analyzing large numbers of variables with a small data set. The stability of multivariate statistical procedures such as regression-based statistical models depends on the number of observations available for each of the variables being examined (or, rather, parameters being estimated) (Cohen & Cohen, 1975). A generally accepted lower bound is on the order of ten subjects for each variable entered in a regression equation (Chatterjee & Price, 1977; Lewis-Beck, 1980). Few previous studies have met even this minimal standard.

Several suggestions for improvements in studies designed to explore etiology may be made. The first of these is that little is likely to be learned from one-shot assessment studies. Longitudinal designs assessing the development of the side effects over time are preferred. While methodologically more sophisticated, such longitudinal studies unfortunately involve practical difficulties in attrition and compliance. For example, attrition rates on the order of 25–50% may be expected for studies that follow patients even through four chemotherapy cycles (Morrow, 1984d). Part of the attrition is due to medical complications. A sizable percentage of patients treated on chemotherapy also have their drug treatment changed or modified prior to their fourth or fifth chemotherapy cycle. Such changes in pharmacologic agents may have a pronounced effect on studies examining potential etiology of side effect development.

Models of Etiology

Theories of how anticipatory nausea/vomiting develops take either a physiologic or psychologic view. The physiologic view is that anticipatory symptoms may be
produced by brain metastasis or local cancer involvement of the gastrointestinal tract (Chang, 1981). This potential explanation is not consistent with at least two findings. The first is that metastatic spread of cancer to the brain or the gastrointestinal tract is significantly less evident than the greater than 25% prevalence of anticipatory side effects. Second, in a series of randomized clinical trials, we (and collaborating oncologists) carefully screened for any clinical evidence of metastatic spread and found no association between metastatic disease and ANV (Morrow, 1981; 1982; 1984c; 1984d).

At least four different psychologic viewpoints have been proposed to explain how psychological processes may cause anticipatory side effects. These hypotheses range from a psychodynamic conceptualization to a learning paradigm involving classical conditioning.

Psychodynamic Model. Chang (1981) has proposed a psychodynamic origin of anticipatory side effects. According to this view, nausea and vomiting "are not always direct side effects of chemotherapy, but rather may be surfacing manifestations of underlying psychological readjustment problems associated with life-threatening illness" (p. 707). Chang further suggests that these side effects may be caused by "psychological mechanisms, including anger, anxiety, and frustration" (p. 707). This theory has received no direct empirical support (Redd, Burish, & Andrykowski, 1985; Morrow & Dobkin, in press), although the data regarding elevated levels of anxiety in patients with ANV may be interpreted to support the theory, albeit indirectly.

Coping Model. If having cancer is conceptualized as being in a health crisis, then it follows that cancer patients are subjected to multiple stressors that call for effective coping strategies. Altmaier et al. (1982) suggested that patients who develop ANV may be deficient in their ability to adjust to, or cope with, the physical and emotional challenges associated with their chemotherapy treatments. The fact that patients with ANV tend to be anxious about treatment supports this hypothesis. High levels of anxiety may be seen as a failure to cope effectively.

Altmaier et al. (1982) reported that patients with ANV demonstrated significantly less desire and ability to cope than patients without ANV. Although this appears to support their hypothesis, their method of assessing coping has never been validated or replicated. Ingle et al. (1984) also investigated the relationship between coping styles and ANV symptomology. They found a "high correlation" between the ANV score and "coping effort," indicating that the "more conditioned" a patient was, the more ways s/he had tried to cope with having cancer. These apparently contradictory results may be reconciled if one accepts the notion that the patients in Ingle et al.'s study made more attempts to cope because their initial trials had failed (i.e., been inadequate/deficient). Yet, since Ingle et al.'s methodology was also problematic, these findings are preliminary, at best.

These two studies approached the area of coping in a very broad and general

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3Ingle et al. (1984) administered the Horowitz Coping Inventory (Horowitz & Wilner, 1980) as a means of assessing coping styles. Reportedly, the nurse investigator observed that many subjects experienced difficulty in understanding statements on the coping inventory. Thus, the validity of the instrument has yet to be established.
manner. Perhaps by narrowing the focus and organizing one's thoughts around a model of coping we could gain insight into its contribution to the development of ANV. Gil (1984), for example, proposed a model of coping which recognizes a three-way interaction between physical and psychological demands of the medical situation and the coping resources of the individual. These, in turn, are broken down into three channels of responses: overt behavioral, physiological, and cognitive. Thus, patients may differ on any of these factors and thereby respond quite differently. In the context of the cancer chemotherapy setting, the physical and psychological demands might include the administration of potentially toxic chemicals, symptoms of the disease itself, concern about prognosis, fear of injections, etc. As for coping resources, this constitutes an area replete with individual variation. Examples of coping resources are: overt behavioral control (e.g., seeking information), cognitive control (e.g., using a cognitive strategy such as restructuring), and physiological control (e.g., deep breathing techniques). These control responses may be used adaptively to reduce the individual's arousal and thereby reduce the individual's awareness or interpretation of the demands of the situation.

The main point to be retained from Gil's model is that coping is multidimensional and that individuals may vary on any one or combination of the factors involved. It is likely that little is known about how cancer patients cope with their disease and its treatment because the methodology used to investigate this phenomenon thus far has failed to address the complexity adequately.

Anxiety Model. Several investigators have speculated that anxiety may be involved in the development of anticipatory side effects. Houts, Morrow, Lipton, Harvey, and Simmons (1984) have proposed four potential ways that anxiety might relate to anticipatory side effects: (a) anticipatory nausea causes pretreatment anxiety; (b) pretreatment anxiety causes anticipatory nausea; (c) anticipatory nausea and pretreatment anxiety are both caused by posttreatment nausea; and (d) pretreatment anxiety facilitates the conditioning process of anticipatory side effects. There are some data that lend partial support to each of the four potential explanations.

However, in order to examine separately each of the potentially competing hypotheses, experiments would have to be designed that would isolate a particular portion of the chemotherapy treatment. This, unfortunately, is not possible in a clinical setting since chemotherapy is given in repeated cycles. Andrykowski et al. (1985) recently provided evidence that elevated levels of state anxiety may precede the initial occurrence of anticipatory symptoms. These authors caution, however, that the relationship between anxiety and anticipatory side effects may not be a strictly causal one. Their data also support a view that the anxiety may be heightened following a particular chemotherapy treatment and that, in turn, the increased anxiety may increase posttreatment nausea/vomiting which, in turn, may increase susceptibility to conditioning on the next chemotherapy cycle. This circular process may facilitate and promote a conditioning process rather than serve as a direct cause itself. Thus, the explanation that anxiety is involved in some form in the conditioning of side effects is the most plausible of the four. It is likely that some degree of anxiety facilitates the conditioning process by alerting or sensitizing the patient in much the same way that somebody who is mildly anxious may be quite prone to suddenly notice and become concerned over a
physical sensation such as irregular heart beats that had probably been present for a period of time.

**Learned Etiology Model**

The development of anticipatory side effects closely follows the principles of learning. While potential differences between them are often complex and controversial, there are basically two principal models of learning: operant and classical.

An operant model suggests that behavior develops and continues because it is reinforced. Such a view of the development of anticipatory side effects would state that the patient received some reward for nausea and vomiting behavior. While it is certainly the case that nausea and vomiting side effects are attended to by treating staff and others, it stretches credibility that someone would continue these behaviors for the rather meager reinforcement being provided. The high prevalence of ANV casts further doubt on the validity of this potential explanation.

A classical conditioning explanation of how ANV might develop is outlined below. The conditioning process proposed involves the elements in the top part of the model of Figure 1 which was modified from Burish and Carey (1984). An unconditioned response (posttreatment nausea and vomiting) which follows an unconditioned stimulus (the chemotherapy drugs administered) in the context of potentially conditionable stimuli (sensations, thoughts, images of the clinic and/or nurse) will, after a number of repeated trials (chemotherapy treatments), give rise to a conditioned stimulus (such as the chemotherapy nurse) eliciting a conditioned response of anticipatory nausea and vomiting. A number of indirect lines of evidence support such an etiology.

**The First Few Chemotherapy Treatments**

<table>
<thead>
<tr>
<th>Conditioned Stimulus</th>
<th>No Response</th>
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<tr>
<td>(nurse)</td>
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</table>

<table>
<thead>
<tr>
<th>Unconditioned Stimulus</th>
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<tbody>
<tr>
<td>(chemotherapy drugs)</td>
<td>(nausea, vomiting)</td>
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</table>

**After Several Chemotherapy Treatments**

<table>
<thead>
<tr>
<th>Conditioned Stimulus</th>
<th>Conditioned Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(nurse)</td>
<td>(nausea, vomiting)</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Conditioning Model of how Anticipatory Side Effects Develop.
Parameters of Classical Conditioning Which Support the View that ANV is Learned: Course of Development. Anticipatory nausea and vomiting develops only after a number of administrations of chemotherapeutic agents have been given (Morrow et al., 1982; Love et al., 1982). Clinical reports, along with clinical studies (Wilcox et al., 1982), support the notion that anticipatory nausea and vomiting is virtually never seen before a number of administrations of chemotherapeutic agents have been given. The percent of patients who develop anticipatory nausea and vomiting increases with the number of courses of chemotherapy given (Morrow, 1982; Morrow & Dobkin, in press; Olafsdottir, Sjoden, & Westling, 1986). Figure 2 combines data from several studies and suggests that the development of anticipatory symptoms is a function of the number of treatment cycles administered. This observation is consistent with the development of a learned response where the strength of that response increases with the number of conditioning trials given. In a clinical situation, each administration of chemotherapy agents would correspond to a conditioning trial.

Stimulus Generalization. The learning phenomenon of stimulus generalization, where a response may be elicited by a stimulus similar to the original conditioned stimulus, fits the available clinical data. Patients' anticipatory side effects may be elicited by an increasing constellation for stimuli and situations as treatment continues. It is not uncommon, for example, for patients to report nausea when they see the clinic nurse who administers their drugs, and then report, after a few more chemotherapy treatments, that the sight of any clinic nurse elicits nausea (Redd & Andrykowski, 1982).
Correspondence Between Unconditioned and Conditioned Responses. Several investigations have shown a relationship between the occurrence of posttreatment nausea/vomiting and the likelihood of an individual patient developing anticipatory nausea and vomiting. There has not been a study that reported the presence of anticipatory nausea/vomiting in the absence of posttreatment nausea/vomiting. The fact that the anticipatory nausea and vomiting so closely resemble the posttreatment nausea and vomiting fits a traditional Pavlovian or classical conditioning model, in which the posttreatment nausea and vomiting is an unconditioned response and the anticipatory nausea and vomiting is a conditioned response.

Intensity of Unconditioned Response. The intensity of an unconditioned response has been shown to affect the development of a conditioned response (Dragoin, 1971; Nachman & Ashe, 1973). When applied to ANV, this finding from classical conditioning would hypothesize that the severity of posttreatment nausea/vomiting (intensity of unconditioned response) would be related to the development of anticipatory nausea/vomiting (the conditioned response). All eight studies (summarized in Table 3) that have examined severity of posttreatment nausea/vomiting have found it significantly associated with the development of ANV; the greater the severity of posttreatment nausea/vomiting, the higher the incidence of anticipatory nausea/vomiting.

Higher-Order Conditioning. Aspects of ANV development are consistent with the process of higher-order (also termed second-order) conditioning. Through higher-order conditioning, neutral stimuli can come to elicit a conditioned response by being paired with a conditioned stimulus (CS\textsubscript{1}). A more exact definition would be that a neutral stimulus, when paired with CS\textsubscript{1}, can come to elicit a CR even though it has never been paired directly with the UCS (Konorski, 1948; Rescorla, 1973, 1978, 1979). Typically, a higher-order conditioned stimulus (CS\textsubscript{2}) does not elicit as great a magnitude or frequency of CR's as does the CS\textsubscript{1} (Rizley & Rescorla, 1972). This finding fits well with the data concerning cancer chemotherapy patients, as a patient approaches the treatment center, the intensity of ANV tends to increase (Nicholas, 1982; Olafsdottir et al., 1986). According to this process, the increased intensity of ANV would be the result of the patient coming into contact with successively strong (i.e., more conditioned) CS's as the distance from the CS\textsubscript{1} decreases.

Higher-order conditioning would proceed through this association of stimuli with the CS\textsubscript{1} which, in some manner, predict the occurrence of this stimulus. Specifically, these stimuli could be an oncology nurse or doctor, clinic odors, sights or sounds of the treatment room, or a myriad of other stimuli that are predictive of chemotherapy. As these stimuli come to be associated with chemotherapy, other stimuli such as the hospital parking lot which predict their occurrence would begin to be conditioned. Thus, over time, an association among these stimuli is formed for which ANV is the overt behavioral manifestation.

Dobkin et al. (1985) asked patients to indicate the location where anticipatory symptoms occurred; sixteen patients identified their home, three reported becoming ill while traveling to the clinic, five identified the clinic, and three reported other locations. In the interview, the cancer patients described the cues occurring just prior to the anticipatory response. Sixteen patients reported thinking about the chemotherapy and four reported visual cues (e.g., visualizing needle inser-
Anticipatory Nausea and Vomiting 533

tions), while four others reported olfactory cues (e.g., smell of clinic). None of the patients reported gustatory cues. Similar cues were reported by Olafsdottir et al. (1986). Andrykowski (1985) also reported that tastes and odors, both during patients' initial two chemotherapy infusions and during the two infusions preceding their initial report of ANV, were unrelated to subsequent development of ANV. Thus, the cognitive conditioning model appears to be a viable one.

Summary and Suggestions for Future Research Directions. The case for a conditioned response developed above provides circumstantial support for a learned etiology of anticipatory side effects. There are no carefully controlled studies that demonstrate conclusively that the anticipatory nausea and vomiting seen prior to chemotherapy treatment are unequivocally a result of learning. Such a finding would, of necessity, involve the experimental, deliberate development of anticipatory nausea and vomiting within a conditioning paradigm. While of scientific interests, such a study would not be ethically feasible. Clinical studies carried out "in the field" (e.g., oncology wards) may not permit the experimental precision afforded in carefully controlled laboratory settings. Nonetheless, while there are no objective scientific data from which to state conclusively that ANV are the result of learning, a number of converging lines of indirect evidence strongly support such a view. None of them singly may be viewed as either necessary or sufficient; however, taken together, they provide reasonably strong support for viewing anticipatory nausea and vomiting as a learned phenomenon. To date, there are no compelling data which contradict this viewpoint.

While prevailing data fit the learning theory-based model presented above, at least two characteristics of ANV development do not fit as comfortably within a classical conditioning framework as they might with a different model of learning: the relatively long interval between the US (presentation of chemotherapy drugs) and UR (posttreatment nausea/vomiting), and the intermittent nature of the CR.

In classical conditioning, the US-UR interval is typically on the order of seconds or possibly minutes. A common finding is that the shorter the interval, the more pronounced the conditioning. The US-UR interval in the chemotherapy treatment context is typically on the order of hours as opposed to seconds or minutes. There is some evidence (Garcia, Ervin, & Kocllinger, 1966; Rusiniak, Palmerino, Rice, Forthman, & Garcia, 1982) that conditioning involving the gastrointestinal system (such as would be present in nausea and vomiting) can occur with CS-US intervals of up to 75 minutes and has been shown to occur in special circumstances with a delay up to eight or nine hours. The fact that learning can take place with this longer CS-US interval suggests that anticipatory side effect development may also be consistent with a learned taste-aversion model (Robertson & Garcia, 1985, 1986) as well as the cognitive model of classical conditioning examined by Rescorla (1978).

The conditioned response of anticipatory nausea and vomiting may not be present prior to each chemotherapy treatment. While no hard data exist, it is a clinical observation that sometimes the patient will show anticipatory side effects prior to one chemotherapy treatment, not show the CR again for one or more treatments, and then show the anticipatory side effect again. This is somewhat at variance with a classical conditioning model in that after CS-UCS pairings a response (CR) is observed each time the CS occurs while the UCS is still being
paired with CS. One potential explanation for the intermittent nature of this CR may be that the CS might not be present prior to each chemotherapy treatment. For example, if the nurse has become part of the CS, the patient may not be treated by the same chemotherapy nurse at each administration of the drug. The patient may also travel a different route to the clinic or have a different constellation of sensations present. There are no firm data at present to support or refute this possibility.

The development of ANV may provide a common set of observable phenomena in humans with which to discuss and contrast various learning theories. While detailed examination of these is beyond both the scope and intent of this review, an example might illustrate how ANV might be useful.

The relatively long US-UR interval has been mentioned as a possible contrast between a classical conditioning model and learned taste-aversion explanation. The learned taste-aversion model would further predict that the organism (patient) does not have to be aware of the UR (nausea) for conditioning to occur. The theory would thus predict that chemotherapy patients who were medicated below the threshold of conscious awareness could nonetheless develop ANV without awareness of having experienced postchemotherapy nausea (Garcia, personal communication, 5 Dec 1986). Given that a state of altered awareness seems often to be clinically present in several antiemetic drugs such as high dose Lorazepam (Laszlo, 1985), a relevant experiment might be feasible.

It would be important to keep in mind, however, that the vast majority of research in the area of both classical conditioning and food aversion learning has involved laboratory animals and/or reasonably trivial responses such as eye blinks. Among the more problematic “leaps of faith” needed to extend and apply findings from this body of research are the fact that a rat cannot vomit (thereby causing problems in indirect measurement) and the fact that the original work commonly mentioned as showing a relationship between “anxiety” and “conditionability” involved eye blinks and an effect size so small that dozens of trials were needed to show any effect.

Nonetheless, it may be possible for ANV to fit together clinical treatment and studies on learning theory. The challenge is to devise experiments that can coexist within a medical delivery system.

Causal modeling approaches based on sophisticated statistical modeling procedures such as LISREL (Joreskog & Sorbom, 1981) are being used more often in theory building and confirmation. They might, at first glance, seem applicable to a study of models of ANV development. A major problem, however, is that LISREL-type analyses typically require that each hypothesized construct (like anxiety) be measured by two or more different assessment instruments or approaches (or both). A longitudinal assessment is also important in sorting out directionality (or causality) of effects (for example, changes in anxiety must precede changes in anticipatory nausea if anxiety causes anticipatory nausea).

Sample sizes of several hundred are often recommended. Given the logistics of repeated psychological measurement in an ongoing medical treatment setting with marked attrition and compliance problems, it is unlikely definitive data could be gathered.

**BEHAVIORAL TREATMENT OF SIDE EFFECTS**

Both anticipatory and posttreatment nausea and vomiting are not completely
Anticipatory Nausea and Vomiting

controlled by antiemetic medicines (Laszlo, 1983; Morrow, 1982, 1984d; Morrow, Loughner, & Bennett, 1984). Three principal interventions (Hypnosis, Progressive Relaxation Training, and Systematic Desensitization) have been investigated for their effectiveness in controlling nausea and vomiting. Table 5 summarizes selected aspects of case studies and controlled investigations of these interventions.

**Hypnosis**

Hypnosis has been defined as a state of intensified attention and receptiveness and an increased responsiveness to an idea or set of ideas (Erickson, 1959). Six case histories of hypnotherapy with cancer patients have reported positive therapeutic results (e.g., Dempster, Balson, & Whalen, 1976; Ellenberg, Kellerman, Dash, Higgins, & Zeltzer, 1980; LaBaw, Holton, Tewell, & Eccles, 1975; Margolis, 1983; Olness, 1981; Zeltzer, Kellerman, Ellenberg, & Dash, 1983). The majority of these investigations have been carried out with a pediatric population probably since children are more readily hypnotized than adults (Olness, 1981). This may be also because children often experience undesirable side effects from antiemetic drugs and thus some antiemetics are not used with children (Cotanch, Hockenberry, & Herman, 1985).

LaBaw et al. (1975) studied 27 children and adolescents, aged 4–20 years, who were treated with self-hypnosis over a two-year period (the exact number of treatment sessions per patient was not specified). “Progressive Body Relaxation” was employed as an inductive technique which was followed by “psychic imagery” of fantasied idyllic scenes common in the patient’s experience. Dependent measures included patients’ self-report and therapist observations. Results indicated that “varying degrees of success” were obtained where “success” was defined as improved sleep, increased caloric intake and retention, increased fluid intake, and greater tolerance for therapeutic procedures. In general, few objective data were collected from these case studies. The “hypnotic” intervention was not standardized and sometimes not described. These methodological limitations preclude definitive conclusions.

Three controlled studies have examined hypnotherapy. Redd, Andresen, and Minagawa (1982) treated six patients experiencing ANV with hypnosis in a multiple baseline design. During treatment, each patient was individually instructed in focusing attention, achieving deep muscle relaxation, and imagining pleasant scenes. Training sessions were audiotaped and patients were instructed to practice the treatment daily. Due to unforeseen events, the hypnotic intervention was temporarily interrupted for several of the patients. At this time, the symptoms that had been apparently controlled by hypnosis reappeared, suggesting that the intervention was involved in the initial positive effects. Given the small sample size, these findings require replication before conclusions can be drawn.

Cotanch et al. (1985) also combined relaxation training with hypnosis in a study of 12 pediatric inpatients (aged 10–18 years), who were referred by oncologists for treatment since they were experiencing troublesome chemotherapy-related nausea and vomiting. The children were randomly assigned to an experimental group (n=6) or a control group (n=6) who received standard care. On the day of chemotherapy, the children in the experimental group were trained by a therapist in self-hypnosis. Both groups were followed through two consecutive chemotherapy cycles. Child self-report and nurse observations were obtained on
<table>
<thead>
<tr>
<th>Case studies</th>
<th>Design</th>
<th>Demographic/Clinical data</th>
<th>Protocol</th>
<th>Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>La Baw et al. (1975)</td>
<td>Serial case studies</td>
<td>Gender: Mixed (about 50-50)</td>
<td>Unspecified number of Tx (Treatment)</td>
<td>Pt self-report</td>
<td>Varying degrees of &quot;success&quot; reported (&quot;Success&quot; defined as: improved sleep, increase caloric intake and retention, increase fluid intake, and greater tolerance for therapeutic procedures.)</td>
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<tr>
<td></td>
<td></td>
<td>Age: 4-20</td>
<td></td>
<td>Therapist observations</td>
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<td></td>
<td></td>
<td>Status: Not reported</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Gender: F</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Age: 21</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Status: Stage IV</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Dx: Hodgkins disease</td>
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<td></td>
<td></td>
<td>Unspecified Pt self-report</td>
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<td>Varying degrees of &quot;success&quot; reported</td>
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<td>number of Tx (Treatment)</td>
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<td></td>
<td></td>
<td>Therapist observations</td>
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<td></td>
<td></td>
<td>&quot;Success&quot; defined as: improved sleep, increase caloric intake and retention, increase fluid intake, and greater tolerance for therapeutic procedures.</td>
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<tr>
<td>Dempster et al. (1976)</td>
<td>Case study</td>
<td>Gender: F</td>
<td>Unspecified number of Tx</td>
<td>Pt self-report</td>
<td>ANV extinguished</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: 21</td>
<td></td>
<td></td>
<td>Reduction in duration of PCN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Status: Stage IV</td>
<td></td>
<td></td>
<td>Increases in &quot;quality of life&quot;</td>
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<tr>
<td></td>
<td></td>
<td>Dx: Hodgkins disease</td>
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<td></td>
<td></td>
<td>Unspecified Pt self-report</td>
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<tr>
<td></td>
<td></td>
<td>number of Tx</td>
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<td></td>
<td></td>
<td>Therapist observations</td>
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<td></td>
<td></td>
<td>&quot;Success&quot; defined as: improved sleep, increase caloric intake and retention, increase fluid intake, and greater tolerance for therapeutic procedures.</td>
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<tr>
<td>Dash (1980)</td>
<td>4 Pts referred</td>
<td>Gender: 2 F; 2 M</td>
<td>1-4 Tx</td>
<td>No objective data</td>
<td>Anecdotal reports of improvement</td>
</tr>
<tr>
<td></td>
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<td>Age: 7-13 (X = 11)</td>
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<td>Status: Not reported</td>
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<tr>
<td></td>
<td></td>
<td>Dx: Leukemia</td>
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<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
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<tr>
<td></td>
<td></td>
<td>Hodgkins disease</td>
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<td>Hodgkins disease</td>
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<td></td>
<td>Ewing's sarcoma</td>
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<tr>
<td>Ellenberg et al. (1980)</td>
<td>1 Pt referred</td>
<td>Gender: F</td>
<td>1 BL (baseline)</td>
<td>Self-report of anxiety, pain, anorexia, nausea (N), vomiting (V)</td>
<td>Reduction of PCN frequency (but Rx also reduced)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: 12</td>
<td></td>
<td>Nurse observations</td>
<td>Reduction of pain and anxiety associated with medical procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Status: Inpt</td>
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<tr>
<td></td>
<td></td>
<td>Dx: Leukemia</td>
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<tr>
<td>Olness (1981)</td>
<td>25 Consecutive referrals</td>
<td>Gender: Not reported</td>
<td>No BL</td>
<td>Self-report of pain, NV</td>
<td>Reduction in pain, NV for 10 pts</td>
</tr>
<tr>
<td></td>
<td>Serial case studies</td>
<td>Age: 3-18</td>
<td>4-7 Tx (+optimal group)</td>
<td>Nurse observations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Status: Inpt</td>
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</tbody>
</table>
Redd et al. (1982) 6 Single subject Multiple baseline (ABAB design) Pts referred for ANV Gender: All F Age: 24-54 Status: Not reported Dx: Lung 1 Hematologic 1 Breast 4 7-14 BL 5-7 Tx Pt self-report of N Nurse observations of V Decreased NV during all Rx sessions for all pts Elimination of ANV

Margolis (1983) 6 Pt referred Serial case studies Gender: 3 F; 3M Age: 27-54 (X =39) Tx varied across pts Dx: Lymphoma 1 Lung 1 GYN 3 Pancreas 1 Male BL No BL Self-report of N, V, insomnia, pain Reduction in suffering (No objective data)

Zeltzer et al. (1983) 12 Pt referred Serial case studies Gender: 5F; 7M Age: X =14.2 1-3 Tx Dx: Hodgkins 4 Hematologic 2 GYN 1 Brain 3 Other 2 Not reported 1 FU (6 m) Pt self-report of V Anxiety (25 % of pts rejected Tx) 73% reduced—PCV frequency Health Locus of Control Reduction in trait anxiety Illness Impact (No changes in health locus of control, impact of illness, self-esteem) Self-esteem

Zeltzer et al. (1984) 19 Time series design Stratified (age & severity) Random assignment: (1) Hypnosis (n=9) (2) Supportive Counseling (n=10) Gender: Not reported Age: 6-17 (X =11.3) Status: Not reported Dx: Hematologic 14 Lymphoma 3 Bone 5 2 BL 2 Tx FU (n=9) Pt self-report of N “bother” Parent report Both groups: Reduction in NV, and “bother” (continued)
<table>
<thead>
<tr>
<th>N</th>
<th>Design</th>
<th>Demographic/Clinical data</th>
<th>Protocol</th>
<th>Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case studies</strong></td>
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<td></td>
</tr>
<tr>
<td>Burish &amp; Lyles (1979)</td>
<td>Pt referred</td>
<td>Gender: F Age: 30 Status: Outpatient Dx: Lymphoma</td>
<td>1 BL</td>
<td>Anxiety, depression</td>
<td>Nausea reduced during Tx Pulse rate (PR) Negative affect reduced during Tx</td>
</tr>
<tr>
<td>Cotanch (1983)</td>
<td>Pts referred</td>
<td>Gender: 5 F; 7 M Age: 17-49 (( \bar{x} = 34 )) Status: Outpt 4 Inpt 8 Dx: Melanoma 3 Soft cell 5 Adenocystic 1 Breast 1 Testicular 2</td>
<td>1 BL 1 Tx (audiotape) 6 FU</td>
<td>Anxiety, depression, PR, BP</td>
<td>N/V Anxiety All patients — reduced PCNV N/V All patients — increased caloric intake, — decrease in pulse rate (Anxiety — reductions suggested)</td>
</tr>
<tr>
<td>Scott et al. (1983)</td>
<td>“Convenience” sample</td>
<td>Gender: All F Age: 42-67 Status: Stage III or IV/Inpts Dx: Ovarian</td>
<td>No BL 2 Tx</td>
<td>Observations of emesis Diarrhea</td>
<td>Reduction in duration, frequency, and intensity of emesis; in diarrhea Improved pt perception of experience Pt “perception of the experience”</td>
</tr>
</tbody>
</table>
Controlled studies

Burish & Lyles (1981)
16 Pt referred
Stratified according to Dx and Rx
Random assignment to:
(1) PRT
(2) Control
Gender: 14 F; 2 M
Age: Not reported
Status: Outpt
Dx: Mixed
1 BL
2 Tx (written instructions only)
2 FU
Anxiety, depression
PR, BP, N/V
Nurse observations

Lyles et al. (1982)
50 Pt referred
Stratified according to Dx and Rx
Random assignment to:
(1) PRT
(2) Attention - control
(3) NTC
Gender: 31 F; 19 M
Age: 14
Status: Outpt
Dx: Breast 14
Lung 10
Ovarian 10
Testicular 5
Lymphoma 5
Hodgkins 3
Other 3
3 Tx
1 FU
Anxiety, depression
PR, BP, N/V
Nurse observations

Burish et al. (1985)
24 "Select" sample*
Stratified according to Dx and Rx
Random assignment to:
(1) PRT
(2) NRC
Gender: 19 F, 5 M
Age: 23-69
Status: Outpt
Dx: Breast 9
Lung 4
Ovarian 10
Hodgkins 1
No BL*
6 Tx
Anxiety, depression
PR, BP, N/V
Nurse observations

Carry & Burish (1985)
45 Stratified according to Dx and Rx
Random assignment to:
(1) Professional
(2) Volunteer
(3) Audiotape
(4) NATC
Gender: 25 F, 20 M
Age: 25-73
Status: Not reported
Dx: Breast 9
GYN 10
Hematologic 10
Lung 9
Other 7
1 BL
3 Tx
1 FU
Anxiety, depression
PR, BP
Nurse observations

PRT group:
During and post-Rx—less distress and nausea
Post-Rx—reduction of PR and BP
(No changes in vomiting)

PRT group:
During Rx—reduction in anxiety and N
Post-Rx—reduction in PR and BP
nausea—less severe, shorter duration

NATC group:
ANV did not develop in PRT pts
ANV developed in “majority”

Pts treated by professional experienced less distress than did pts treated by volunteers or with audiotape

(continued)


| N  | Design                                      | Gender: 28 F; 32 M | Age: 17–68 | Status: Not reported | Dx: Breast 11 | Hematologic 17 | Melanoma 10 | Testicular 11 | Other 11 | Protocol: 1 BL | Measures: Anxiety | Respiratory rate | NV | Caloric count | Skin fold | Body weight | Results: Lower BP, PR, RR, V and anxiety (trait) | Increased cardiac intake | (Data for NTC not reported) |
|----|---------------------------------------------|--------------------|-------------|----------------------|----------------|----------------|-------------|--------------|---------|----------------|---------------------|------------------|---|--------------|-----------|------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|

**TABLE 5. Continued**

**SYSTEMATIC DESENSITIZATION**

<table>
<thead>
<tr>
<th><strong>Case studies</strong></th>
<th>1 Pt referred</th>
<th>Gender: M</th>
<th>Age: 28</th>
<th>Status: Outpt (No FU due to Rx change)</th>
<th>Dx: Lymphoma</th>
<th>Protocol: No BL</th>
<th>Measures: Pt self-report of distress, NV, ANV, self-control</th>
<th>Results: Elimination of ANV Reduction in severity of PCN Increase sense of self-control Results generalization to hosp. environment</th>
</tr>
</thead>
</table>

**Controlled studies**

| 37 Pt referred | Gender: 25 F; 12 M | Age: 18–67 (X = 43) | Status: Not reported | Dx: Breast 8, Lung 8, GYN/Genital 8, Hematologic 4, Other 9 | Protocol: 1 BL | Measures: Pt self-report NV, and Anxiety | Results: Less severe PCN for 2 Tx groups (SD sooner than PRT) | Decrease in duration of PCN for SD Decrease in frequency of PCV for SD Decrease in anxiety for both Tx groups |
Morrow & Morrell (1982) 60 Consecutive pts (with ANV) Gender: 49 F: 18 M 2 BL. Random assignment to:
(1) SD Age: 19-76 2 Tx
(2) Counseling Status: Outpt 2 FU
(3) NTC Dx: Breast 29

Dobkin & Morrow (1985) 40 Consecutive pts Gender: 26 F: 8 M 1 BL. Random assignment to:
(1) SD Age: \(\bar{X} = 52.2\) 2 Tx
(2) NTC Status: Out- and Inpt 3 FU
Dx: Breast 15

Morrow (in press) 92* Consecutive pts (with ANV) Gender: 56% F; 33% M 2 BL. Group assignment to:
(1) SD Age: Median > 50 yrs 2 Tx
(2) PRT Status: Inpt 2 FU
(3) Counseling Dx: Mixed – maj. = breast
(4) NTC

*Some overlap with patients from Morrow and Morrell (1982)

OTHER

Burish et al. (1981) 1 Single subject Gender: F 3 BL
Multiple baseline Age: 44 4 Tx (EMG biofeedback)
Status: Not reported Anxiety Reduced BP, PR, EMG levels
Dx: Adenocarcinoma

(continued)
<table>
<thead>
<tr>
<th>N</th>
<th>Design</th>
<th>Demographic/Clinical data</th>
<th>Protocol</th>
<th>Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moore &amp; Altmaier</td>
<td>Gender: 6 F; 3 M</td>
<td>6. Tx (stress inoculation; including PRT)</td>
<td>Structured interview Anxiety</td>
<td>Reduction in anxiety</td>
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<tr>
<td></td>
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<td>Status: Outpt</td>
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<tr>
<td></td>
<td></td>
<td>Dx: Breast 4</td>
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<td>Sarcomas 3</td>
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<td></td>
<td>Other 2</td>
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<tr>
<td></td>
<td>LeBaron &amp; Zeltzer</td>
<td>Gender: Not reported</td>
<td>2-3 BL</td>
<td>Pt self-report N, V “bother”, “disruption”</td>
<td>Reduced N/V, bother, and disruption of activities</td>
</tr>
<tr>
<td>8</td>
<td>(1984)</td>
<td>Age: 10–17 (X = 12)</td>
<td>2-3 Tx (distraction)</td>
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<tr>
<td></td>
<td>Single subject</td>
<td>Status: Not reported</td>
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<td></td>
<td>Multiple baseline</td>
<td>Dx: Hematologic 6</td>
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<td></td>
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<td>Bone 2</td>
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<td>Kolko &amp; Rickard-</td>
<td>Gender: M</td>
<td>3-5 BL</td>
<td>Pt self-report of anxiety, distress, and chemo-related symptoms</td>
<td>Reduction in ANV and severity of PCNV</td>
</tr>
<tr>
<td>3</td>
<td>Figueroa (1985)</td>
<td>Age: 11–17</td>
<td>3 Tx (video game – distraction)</td>
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<td></td>
<td>Serial single case</td>
<td>Status: Outpt</td>
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<tr>
<td></td>
<td>Multiple baseline (ABAB)</td>
<td>Dx: Hematologic</td>
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the parameters of nausea and vomiting (intensity, severity, frequency) and on the amount of oral intake 24 hours postchemotherapy. Data were collected by staff nurses and research assistants who were unaware which group the child was assigned to. In the experimental group, there was a significant reduction in nausea and vomiting both in terms of intensity and severity, and a significant increase in oral intake. These changes were not evident in the control group. Although this study is suggestive regarding the effectiveness of hypnotherapy, the results could be explained in terms of an attention effect. The children in the experimental group received “extra” attention from a therapist whereas the children in the control group did not. While these findings are suggestive, they require replication with an attention-placebo group to rule out this alternative hypothesis.

Zeltzer, LeBaron, and Zeltzer (in press) compared hypnotherapy to supportive counseling and suggested that nonspecific therapy effects, such as demand characteristics and/or attention, may contribute to treatment changes found. In their study, 19 children, aged 16–17 years, were randomly assigned to a hypnotherapy or a supportive counseling group. Children in both groups reported reductions in nausea and vomiting and rated chemotherapy as “less noxious” following intervention. There were, however, no statistically or clinically significant differences in outcome found between the two approaches.

Overall, it appears that studies using hypnosis for ANV control have shown that this intervention may be beneficial for children. Less evidence is available demonstrating its usefulness for adults. In order to establish the effectiveness of hypnotherapy for cancer chemotherapy patients, studies with larger sample sizes in which patients are randomly assigned to treatment or appropriate control groups are needed.

**Progressive Relaxation Training**

Progressive Relaxation Training (PRT) is a behavioral technique which involves learning how to relax by actively tensing and relaxing muscle groups in a progressive manner. Typically, an individual is taught deep muscle relaxation by a therapist, a training audiotape is made, and the individual is requested to practice PRT at home in order to acquire the skill. Four case studies and five controlled investigations of PRT have been reported thus far. Results from case studies (Burish & Lyles, 1979; Cotanch, 1983; Weddington, Blindt, & McCracken, 1983) have suggested that PRT can benefit cancer patients by reducing side effects, such as postchemotherapy nausea and vomiting, and negative states such as depression and anxiety.

Lyles, Burish, Krozely, and Oldham (1982) studied cancer patients experiencing anxiety, depression, nausea, and vomiting; 50 patients were randomly assigned to one of three treatment conditions: (a) relaxation training with guided imagery; (b) therapist control, in which a therapist spent an equal amount of time with the patients as in condition (a); and, (c) no-treatment control. Patients who received PRT were found to be less anxious and nauseated both during and following their chemotherapy treatment sessions compared to the patients in the two other groups. Additionally, patients in the PRT group evidenced less physiological arousal (pulse rates) and were less depressed following chemotherapy. The positive treatment effects found in the PRT condition, but not in the therapist
attention-control condition, suggest that the improvements were not simply the result of "nonspecific" treatment factors.

These results were supported by Cotanch (1983) in a study in which 43 cancer patients were randomly assigned to one of three conditions: (1) PRT, provided by audiotape; (2) tape control, in which patients listened to soothing music and were requested to focus on positive thoughts; and (3) no-treatment control. Patients took part in one baseline session and "varying numbers" of training sessions. Cotanch reported that 67% of the patients in the PRT conditions showed increases in postchemotherapy nausea and vomiting (PCNV), whereas 85% of the patients in the two control groups showed increased in PCNV. This 18% difference between the groups suggests that PRT can be helpful even with a minimal amount of therapist contact.

In the first reported PRT prevention study, Burish, Carey, Krozely, and Greco (1987) investigated whether PRT could be used to prevent or at least ameliorate chemotherapy side effects through early intervention. Thirty two cancer patients about to start their first course of emetogenic chemotherapy were randomized to either a PRT group or a no-treatment control group. PRT sessions were held prior to the initiation of chemotherapy and during the first five chemotherapy treatments. Patients in the PRT group reported feeling less nauseated during and following chemotherapy. Additionally, these patients reported fewer occurrences of vomiting and lower physiological arousal (e.g., heart rate and blood pressure) compared to the patients in the control group. PRT also resulted in less dysphoria and a progressive reduction in PCNV symptoms as treatment with chemotherapy continued over time. Reportedly, by the fifth session only 10% of the PRT patients experienced PCN whereas 54% of the control patients experienced PCN. These findings are both impressive and encouraging.

Overall, the data regarding the use of PRT with cancer chemotherapy patients show that this type of intervention can be effective in reducing side effects which are present during and after cancer chemotherapy sessions. Since nausea symptoms occurring before a treatment session were not assessed in the early work carried out by Burish and his associates (Burish, personal communication), any potential impact PRT has on ANV symptoms defined strictly as pretreatment remains uninvestigated. Given the relationship between postchemotherapy side effects, and the subsequent development of ANV, using this technique before the initial chemotherapy treatment could potentially block the conditioning process and thereby prevent its occurrence.

**Systematic Desensitization**

Systematic Desensitization (SD) is a well-developed, standardized behavioral technique which has been shown to be useful in altering maladaptive learned responses such as phobias (Wolpe, 1983). In SD, patients are first taught a response incompatible with the maladaptive response they presently have to particular stimuli. This alternative response is then paired in imagination with the original stimuli so as to countercondition the maladaptive response.

At the University of Rochester Cancer Center, ANV patients have been taught a modified version of Progressive Muscle Relaxation as a competing response to the maladaptive response of anticipatory nausea/vomiting. During the Systematic
Desensitization treatment, patients imagine scenes from a hierarchy of events related to chemotherapy treatment (such as driving to the cancer center) while remaining deeply relaxed. In this way, treatment stimuli become associated with relaxation so that when the patient encounters stimuli (such as the clinic nurse), they respond with relaxation rather than nausea and vomiting.

Two case studies and four controlled investigations of SD have been reported (Dobkin, 1987; Hailey & White, 1983; Hoffman, 1983; Meyer, 1982; Morrow, 1986; Morrow & Morrell, 1982). Morrow and Morrell (1982), in a study designed to examine the antiemetic efficacy of SD for the control of ANV, randomly assigned 60 patients with ANV to one of three groups: (a) SD; (b) counseling, based on a Rogerian, client-centered approach; and (c) no-treatment control. It was found that only patients in the SD group showed a significant reduction in the frequency, severity, and duration of ANV. The efficacy of SD appeared unrelated to antiemetic medications used by the patients. Additionally, patients in the SD group reported no greater expectation for improvement than did the patients in the counseling group. Thus, apparently, nonspecific therapy effects (e.g., attention) were not responsible for the reported positive effects.

In a follow-up study, Morrow (1986) compared the effectiveness of SD to (a) relaxation only, (b) counseling, and (c) no-treatment control in order to examine the essential treatment components in the SD procedure. Relative to the other three groups, patients treated with SD reported a significant decrease in the severity and duration of anticipatory nausea from baseline to follow-up sessions. SD and relaxation patients had a significantly greater decrease in the duration and severity of posttreatment nausea compared to patients who were in the other two groups. These results were independent of patients' ratings of their expectations for success or the credibility of the experimenter. Results support a view that both the cognitive stimulus hierarchy and relaxation response are necessary components for the successful treatment of ANV.

In another investigation, Dobkin (1985) examined the possibility of reducing, retarding, or preventing the development of both post- and anticipatory side effects in new-to-chemotherapy cancer patients. Forty consecutive patients were randomly assigned to either a SD or Waiting-List Control group. SD was administered in two separate one-hour sessions prior to the second chemotherapy cycle. A repeated measures design was employed with one baseline and three follow-up periods; dependent measures included: postchemotherapy nausea and vomiting, anticipatory nausea and vomiting, anxiety (trait at baseline, state at all periods), and tension level postchemotherapy.

Preliminary results showed a downward trend for the SD patients' PCNV side effects, in that nausea and vomiting were less frequent, severe, and of shorter duration as chemotherapy progressed. In contrast, there was an upward trend for the control group patients' PCNV side effects in that nausea and vomiting were more frequent, severe, and of longer duration as chemotherapy progressed. In addition, the control patients reported higher levels of tension following chemotherapy compared to SD patients. These preliminary findings suggest that introduction of SD early in treatment can reduce and retard the development of conditioned side effects resulting from chemotherapy in cancer patients.

In summary, consistent findings regarding the effectiveness of SD have been reported in both case and controlled studies. Although the majority of the SD
investigations have been carried out in one research center, two case studies and one controlled investigation (Meyer, 1982) in other geographical locations have replicated these promising results.

Other Behavioral Interventions

Five studies have used behavioral interventions other than the three discussed above. Moore and Altmaier (1981) reported a pilot study of nine cancer patients (6 female, 3 males; mean age=47 years) who were treated with Stress Inoculation Training (the six-session treatment “package” consisted of Cognitive Behavior Modification combined with PRT and Education). Prior to the intervention, patients were interviewed and completed the Multiple Affect Adjective Checklist (MAACL: Zuckerman, Lubin, Vogel, & Valerius, 1964) which is designed to measure anxiety, depression, and hostility. Five of the nine patients exhibited ANV prior to treatment. Since the authors discontinued monitoring the patients at the last training session (i.e., no follow-up data), it is impossible to determine the effectiveness of this approach. Three patients did report, however, that they felt less anxious prior to treatment having learned effective coping skills.

Burish, Shartner, and Lyles (1981) treated a 44-year-old female cancer patient with EMG biofeedback combined with relaxation in order to help control anticipatory and posttreatment symptoms. Baseline measures of affect (anxiety, depression, and hostility, MAACL: Zuckerman et al., 1964), muscle tension, pulse rate, and blood pressure were taken. Following ten training sessions, the patient was able to reduce her physiological arousal levels (as measured by EMG, pulse rate, and blood pressure) and reported feeling less nauseated. These changes were maintained during three follow-up periods. There were no reported improvements in affect. These results, which are similar to those found for PRT, suggest that EMG Biofeedback may be another means of teaching relaxation to cancer patients.

Three studies, LeBaron and Zeltzer (1984), Kolko and Rickard-Figueroa (1985), and Redd, Jacobsen, Die-Trill, Dermatis, McEvoy, and Holland (1987) have investigated interventions based on cognitive diversion techniques. The former study involved directing adolescents’ attention away from the administration of chemotherapy by having them play games and be actively engaged with a therapist (modified relaxation training was also included in some cases). The latter two studies involved the use of video games to distract pediatric and adolescent patients.

LeBaron and Zeltzer (1984) reported a decrease in postchemotherapy nausea, vomiting, and “bother” during the intervention, along with fewer disruptions of activities following treatment. These improvements were maintained at follow-up (time period not reported). The investigators concluded that “since a repeated measures design found no symptom reductions prior to intervention, it can be assumed that some aspects of the intervention itself were responsible for the reductions found, rather than attention or expectations related to assessment alone” (p. 180). This conclusion seems premature given a sample size of n=8, no control groups, and no theoretical rationale of how distraction alone could reduce chemotherapy-related side effects.

Kolko and Rickard-Figueroa (1985) used a multiple-baseline (ABAB) design (Kazdin, 1982) with three pediatric oncology patients (all male, aged 11, 16, and
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17 years). Anticipatory “distress,” PCNV and state anxiety (State-Trait Anxiety Inventory, Spielberger, Gorsuch, & Lushene, 1968) measures were taken. A Modified-Procedure Behavioral Rating Scale (Katz, Kellerman, & Siegel, 1980) was used to gather observational data five minutes prior to chemotherapy. Introduction of video games concurrent with administration of chemotherapy was associated with reduction of self-reported and observer-reported anticipatory symptoms (not ANV) as well as postchemotherapy distress. These improvements were reversed when the return-to-baseline phase was initiated. Symptoms decreased again when the video game procedure was reintroduced in two of the three cases (the third case could not be evaluated due to admission of the patient just before the final condition).

Kolko and Rickard-Figueroa’s study addressed the relaxation versus distraction issue regarding the therapeutic mechanisms underlying behavior therapy. Although the results imply that distraction may effectively reduce symptomatology, ANV and PCNV side effects per se were not reduced; only “distress” levels were altered.

Redd et al. (1987) conducted two experiments, one of which employed an ABAB design, to evaluate the effect of video game playing in pediatric oncology patients with anticipatory nausea and anxiety. In the first experiment, patients were alternately assigned to either the experimental group or to the control condition. In the second experiment, patients from the first experiment were carried over and exposed to an ABAB design presentation of the video games. Unlike Kolko and Rickard-Figueroa’s (1985) study, the ABAB presentation took place within the same chemotherapy session, that is, after a no-video-game baseline assessment (A), patients played video games for 10 minutes (B), followed immediately by a 10-minute no-video-game period (A), and then a second 10-minute video game period (B). Nausea and anxiety were assessed using a 10 cm Visual Analogue Scale; pulse rate and blood pressure measures were taken to assess physiological indices. Results indicated that anticipatory nausea but not anxiety decreased significantly following video game playing in both studies. Reportedly, pulse rates and systolic/diastolic blood pressure rates were variable, with one measure (systolic blood pressure) showing a significant increase from the previous no-game level following the second exposure to video games within the session. The authors interpreted these findings as support for the hypothesis that cognitive distraction, and not relaxation, is the critical component of the intervention. Redd et al.’s (1987) findings complement Kolko and Rickard-Figueroa’s investigation quite well; however, a few methodological flaws need to be rectified before conclusions can be drawn. First, consecutive patients should be randomly assigned to groups. Second, an attention-control group should be included. Third, follow-up measures, both subsequent to chemotherapy for at least three days and following several chemotherapy cycles, need to be documented in order to evaluate treatment effects. Moreover, larger sample sizes should be employed.

**Mechanisms of Actions**

Several hypotheses attempting to explain how and why behavior therapy is effective for cancer patients have been proposed. These explanations range from simple placebo effects to theories involving the conditioning process discussed in the previous section.
Intuitively, "nonspecific factors" such as attention received from a therapist, demand characteristics, patient expectation for success, or other "placebo" effects may seem involved in the effectiveness of behavior therapy with cancer patients. While nonspecific treatment effects may contribute to the improvements reported, several studies have demonstrated that other treatment components are necessary for behavior therapy to be effective. For instance, Morrow (1982) found that expectations for success and demand characteristics did not distinguish patients receiving Systematic Desensitization from patients in counseling and no-treatment control groups. In support of these findings, Burish and his colleagues (1982) presented data from a credible attention-control group suggesting that specific behavioral techniques, not the nonspecific factors involved in the intervention, were responsible for treatment efficacy.

A second hypothesis proposed to explain the underlying mechanisms of behavior therapy is that these techniques distract the patients sufficiently to divert their attention away from the chemotherapy treatments such that conditioning no longer occurs. In other words, by removing the conditioned stimuli, one would prevent the occurrence of the CR (i.e., ANV). Although appealing, this explanation is unlikely. Most oncology clinics are equipped with televisions and patients are often accompanied by friends or relatives; these stimuli have failed to diminish the side effects experienced by cancer patients. Also, studies including control groups have demonstrated that behavior therapy is more effective than attention-diverting alternative procedures. Finally, although hypnotherapy and PRT use guided imagery to divert the patients' attention away from the aversive chemotherapy experience, SD focuses attention on these stimuli. The cognitive hierarchy employed involves scenes which depict going to the chemotherapy clinic.

A third hypothesis proposed to explain the effectiveness of behavior therapy is that these techniques change the patients' self-perceived sense of control over their disease process. According to this view, the patients' psychological state improves and their subjective experience of helplessness diminishes. Although appealing, this hypothesis has no empirical data to support it. In fact, Morrow and Morrell (1982) noted that reductions in ANV were not accompanied by change in locus of control as measured by Wallston, Wallston, and DeVellis' (1978) Health Locus of Control Scale.

Burish and Carey (1984) note that one common element of the various behavioral interventions is the induction of the relaxed state. Progressive Relaxation Training has been shown to reduce anxiety and physiological arousal and, therefore, may be responsible for the reduction in chemotherapy aversiveness. Redd and Andrykowski (1982) suggest that deep muscular relaxation may directly inhibit muscular contractions that generally precede vomiting, thereby eliminating this response.

Data from the Morrow (1986a) study suggest that relaxation itself is a necessary but not sufficient treatment component for reducing anticipatory nausea/vomiting. The data suggests that counterconditioning is a necessary element in the treatment package. As was previously discussed, ANV symptoms are thought to be learned, maladaptive responses which are associated with chemotherapy treatment effects. Using Systematic Desensitization (which involves both relaxation and cognitive elements) to break the associative bond affords the patient the opportunity to learn a new, adaptive response. Relaxation training does, however, appear to provide symptom relief during and following the administration of chemotherapy.
FUTURE RESEARCH DIRECTIONS

Methodology

Several points can be made regarding the methodology of future investigations of chemotherapy side effects. First, these symptoms are best described using a prospective, longitudinal research design. A “one-shot” study gives a flat picture of multidimensional experience. The process of being treated for cancer requires a repeated-measures design. Second, adequate sample sizes and appropriate control groups are essential. Treatments should be described in sufficient detail so that comparisons across studies can be made. It would be helpful if findings from these investigations were reported in terms of both clinical and statistical significance (Morrow, 1980, 1982a, 1984b, 1984d, 1986). Finally, a more critical selection of instruments is needed for the assessment of cancer patients. Questionnaires developed on a psychiatric or college student population are frequently used with cancer patients. Due to both illness and treatment factors, these instruments may be inappropriate for a medical population (cf. Morrow, 1980; Dobkin & Morrow, 1986).

Treatment Comparison Studies

Four studies have compared different interventions for the treatment of cancer patients’ side effects (Meyer, 1982; Morrow, 1986; Morrow & Morrell, 1982; Zeltzer et al., 1984). Three of these compared Systematic Desensitization to other techniques and one compared Hypnosis to Supportive Counseling. Since different modalities may be beneficial for particular side effects (e.g., Hypnosis for pain management, or Systematic Desensitization for ANV), this is an important area yet to be explored. Results from comparative studies may also clarify the underlying mechanisms of the intervention strategies.

Maintenance and Generalization of Treatment Effects

Behavior therapy has been shown to be the “treatment of choice” for numerous disorders (e.g., phobias, enuresis, sexual dysfunction, obesity), yet a recurrent problem is the maintenance and generalization of treatment effects. Burish and his colleagues have consistently reported a reduction of positive treatment effects when the therapist is no longer present to direct the patient in PRT. Redd et al. (1982) showed, through the use of a multiple baseline treatment design, that when Hypnosis was not used, symptoms recurred. These findings were replicated by Kolk and Rickard-Figueroa (1985) and Redd et al. (1987). A lack of generalization of treatment effects comes as no surprise when one considers the poor track record of long-term maintenance of behavioral change for many different problem areas (e.g., alcoholism, smoking, weight management). Future research needs to be directed at developing “built-in” relapse prevention strategies so that the benefits gained can be maintained.

Treatment Exportation

There are too few psychologists working with oncology patients to assist all who could benefit from their interventions. For this reason, it is important to explore
the “exportability” of biobehavioral treatments. That is, can behavior therapy be administered without the presence of a psychologist?

Morrow (1984a) examined the possibility of reducing the necessary professional time required to administer SD by comparing a live presentation to an audiotaped presentation to the relaxation component of the SD procedure. In the live presentation condition, individual instruction in PRT was provided to the patient; the session was tape-recorded and given to the patient for subsequent home practice. In the audiotaped presentation condition, the patient was provided with a prerecorded audiotape which instructed the patient in PRT methods. All patients were requested to practice PRT daily. Surprisingly, 4 of 5 patients in the audiotaped presentation condition spontaneously reported that listening to the audiotape triggered a nausea response. None of the five patients in the live presentation condition reported this phenomenon. When interpreted within a conditioning paradigm, the voice on the tape, a novel stimulus, may have been incorporated in a stimulus configuration which was able to elicit the conditioned nausea response. In contrast, during the live presentation there was a wider range of novel, potentially conditionable stimuli present (e.g., the objects in the room, smells, etc.) such that no single stimulus was easily incorporated into the hierarchy of stimuli which triggered a conditioned response.

Redd, Rosenberger, and Hendler (1983) also found that patients listening to self-hypnosis audiotapes complained that listening to the tapes made them feel nauseous. Redd et al. (1983) also speculated that the therapist’s voice became a conditioned stimulus, eliciting nausea.

Considering the fact that using audiotapes alone does not seem to work, an alternative approach may be to instruct other health professionals in the administration of behavior therapy. Thus, an important research direction involves answering the questions: Can biobehavioral techniques be taught to health professionals and still be as effective? and Will patients perceive physicians and nurses as being as credible as a psychologist in the use of these procedures? Preliminary results suggest that the answers to these questions are yes (Morrow & Dobkin, 1987).

Carey (1985), however, found that patients trained in progressive relaxation by psychologists experienced less distress than did patients who were treated either by a trained volunteer (women from the community) or an audiotaped presentation of the treatment procedure. These results support Morrow’s (1984a) and Redd et al.’s (1983) conclusions concerning audiotape interventions and also suggest that a health professional may be required to administer the treatment. Patients seem to be more likely to respond to a health professional’s rather than a volunteer’s efforts to intervene in their cancer treatment. Clearly, more work is warranted in this area in order to maximize the number of cancer chemotherapy patients who may benefit from biobehavioral interventions.

Past and current studies show clearly the promise of fruitful and productive further research in understanding the development and treatment of anticipatory side effects from chemotherapy treatment. ANV continues to be as challenging an area to study as it is relevant and worthwhile; potentially useful a model for addressing important theoretical issues as it is a model for studying aspects of behavioral interventions. It is as useful an area for interdisciplinary research collaboration as it is for treatment and patient care collaboration, as good an area for teaching students the frustrations and fruits of research with medically ill patients.
patients as it is for continually reminding their supervisor of the same points; and it is as personally rewarding an area of study as it remains professionally challenging.

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