

Pretreatment Nausea in Cancer Chemotherapy: A Conditioned Response?*

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Many patients receiving cancer chemotherapy become nauseated as they anticipate their treatments. We studied this phenomenon in eighteen cancer chemotherapy patients. The eight patients who reported pretreatment nausea had more extensive disease than the other patients and had received twice as much chemotherapy. In most cases pretreatment nausea developed only after a number of months of treatment. Nausea was usually precipitated by the odor of the clinic and similar odors elsewhere also caused nausea. Patients continued to experience nausea during follow-up visits after treatment was completed. This syndrome of pretreatment nausea can be understood as a classically conditioned response. Clinical recommendations can be made on this basis.

INTRODUCTION

Many cancer chemotherapy drugs cause nausea and vomiting beginning 1 to 2 hr after injection and persisting for 2 to 24 hr (1). A number of patients with lymphoma mentioned, in the course of a seminar, that they experienced nausea as they entered the clinic before any treatment was given. Clinic staff interpreted this phenomenon as "hysteria," "anxiety," or as a "conditioned response." The only pertinent reference we found said that pretreatment nausea "attested to the disgust with which these patients view their treatment" (2). For these reasons we investigated the frequency and correlates of pretreatment nausea in a chemotherapy clinic population.

METHODS

Patients

Eighteen outpatients with lymphoma were selected without knowledge of their history of treatment or side effects. Each patient had received MOPP therapy for Hodgkin's disease or CHOP therapy for non-Hodgkin's lymphoma (3). No patient was severely debilitated.

Each patient was interviewed by a physician who completed rating scales on multiple aspects of the illness, treatments, and side effects. Standardized questions regarding other nausea inducing situations, such as motion sickness, were also recorded on quantitative scales. Tape recordings made with the patient's permission were later reviewed to verify details.

Case Histories

Case 1. A 23 year-old man had severe nausea and vomiting which began 1 hr after each mustard injection and persisted for 4 hr, but he had no pretreatment symptoms until his third month of treatment. From then on, he became nauseated as soon as he walked in the clinic building and noticed its "chemical odor." A month later, the odor of isopropyl alcohol, which was used to prepare the injection site, also began to make him nauseated. He

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would often open alcohol swabs in his work, but now he began doing it at an arms length to avoid the odor. When he returned to the clinic for routine follow-up visits, he experienced the same nausea though he knew he would not receive treatment. This symptom gradually disappeared and was absent by the fourth follow-up visit.

Case 2. A 52-year-old woman had received 16 months of MOPP treatment. She had no symptoms before her first treatment session but she had severe nausea and vomiting for 12 hr after each injection. During each subsequent treatment she became nauseated and vomited as soon as she entered the clinic and noticed its odor. Her father's car had a characteristic odor from rustproofing treatments and from his cigars. She often vomited in the car on the way home and subsequently the odor of the car made her nauseated.

Case 3. A 20-year-old woman had no pretreatment symptoms when first interviewed after 2 months of MOPP treatment. Six months later, during a second interview, she said she had become "hypersensitive to the smell of the clinic." She now became nauseated as she approached and entered the building. This nausea has persisted for her most recent visits which have been for follow-up only. The clinic building did have a distinctive odor, but it was not nauseating except for patients.

RESULTS

Eight of the eighteen patients were rated as having "moderate" or "severe" nausea prior to receiving treatment injections. Two of these patients had vomited immediately as an injection was being given, and one reported vomiting shortly after walking in the door during each clinic visit. Table 1 shows the characteristics of each group.

Demographically and diagnostically the groups were similar, but the patients with pretreatment nausea were three times more likely to have Stage IV disease (4) and had received twice as much chemotherapy as the other patients. They also had more extensive and more severe vomiting after their three most recent treatments. Of the ten patients in the study who had 6 or more months of treatment, eight experienced pretreatment nausea.

Other potentially related factors were each reported by one of our patients at

TABLE 1. Characteristics of Patients with and without Pretreatment Nausea

	Patients with No Pretreatment Nausea	Patients with Pretreatment Nausea
N	10	8
Race	all Caucasian	all Caucasian
Sex	6M/4F	5M/3F
Age (mean years)	32.4	26.1
Diagnosis	9 Hodgkin's disease 1 lymphosarcoma	7 Hodgkin's disease 1 histiocytic lymphoma
Treatment	9 MOPP 1 CHOP	7 MOPP 1 CHOP
Months of chemotherapy (mean)	4.2	9.3 p<0.01
Number of medication injections (mean)	7.9	15.9 p<0.01
% of patients with Stage IV disease	20	62.5
Severity of posttreatment vomiting a	2.4	3.3 p<0.01

a Scale: 1 = none, 2 = mild, 3 = moderate, 4 severe, 5 very severe.

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most: feeding problems during infancy, peptic ulcer, irritable colon, hyperemesis gravidarum, and an especially sensitive sense of smell or taste. Table 2 shows the frequency of more common potentially related factors. One patient in each group reported anxiety-induced diarrhea, but no patient reported anxiety-induced nausea before starting treatment. Patients with pretreatment nausea were found to be no more susceptible than the other patients to nausea and vomiting in other situations.

DISCUSSION

The nausea and vomiting experienced by some patients in anticipation of cancer chemotherapy injections is often dismissed as "nerves" or is simply not recognized. Patients are embarrassed to mention these symptoms for fear they will be thought to be psychologically abnormal. Our results suggest that pretreatment nausea is a common phenomenon that occurs in most patients who have received more than 6 months of chemotherapy. It exhibits a regular pattern: onset is gradual, the nausea is usually precipitated by similar stimuli encountered elsewhere,

and, when patients return to the clinic for posttreatment follow-up, they experience nausea during the first few visits.

This pattern suggests that the pretreatment nausea is a classically conditioned response. The nausea is analogous to the conditioned salivation of a dog when it hears a bell that has been repeatedly paired with food. Previously neutral clinic stimuli gain the capacity to elicit nausea after repeatedly being paired with medication-induced nausea and vomiting. They continue to elicit nausea during the first few nontreatment follow-up visits. With repeated exposures to clinic stimuli in the absence of the unconditioned stimulus (medication-induced nausea and vomiting), the conditioned response of nausea is gradually extinguished.

In most classical conditioning the interval between the conditioned stimulus and the unconditioned stimulus is a few minutes at most, but conditioning of the gastrointestinal system appears to be an exception. Poison bait shyness in rats is the best studied example (5). An everyday example is well-known to anyone who has been made nauseated by smelling an alcoholic beverage whose previous imtemperate consumption caused illness.

TABLE 2. Comparison of Possible Associated Factors in Patients with and without Pretreatment Nausea

	Patients with No Pretreatment Nausea (N=10)	Patients with Pretreatment Nausea (N=8)
History of:		
Nausea caused by watching someone vomit	3	2
Vomiting caused by watching someone vomit	3	0
Motion sickness	3	2
Nausea from narcotics	2	1
Cigarette smoking	1	3
Alcohol use	4	1
Marijuana use	2	2
Antiemetics relieving post-R, vomiting	5	0

A recent controlled study of leukemic children showed that they developed a conditioned taste aversion to a specially flavored ice cream after it was paired with chemotherapy treatments (6).

Alternate explanations need to be considered. Clinically, we could not identify any diagnosable psychopathology that might explain the syndrome. Anxiety itself can, of course, cause nausea in some people and a number of our patients reported being very anxious as they entered the clinic. Yet no patient reported previous experiences of nausea in response to anxiety. In addition, the anxiety level was high during the first few visits to the clinic, but pretreatment nausea developed slowly over a period of months in all cases but one. Finally, the anxiety hypothesis cannot explain the generalization of the response to stimuli away from the clinic and the continued presence of the nausea during follow-up visits. The concept of

conversion reaction also fails to explain pretreatment nausea, because of the consistent nature of the syndrome in most patients and the lack of evidence for a symbolically expressed unconscious conflict.

The probable explanation of pretreatment nausea as a conditioned response makes it possible for physicians to relieve their patients of much unnecessary worry by simply explaining the phenomenon. The development of the syndrome itself may be slowed by minimizing the presence of distinctive odors in chemotherapy clinics. Finally, the interpretation of pretreatment nausea as a conditioned response raises the possibility that learning theory may help to clarify other similarly confusing clinical phenomena.

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