CHAPTER 48

Effects of Radiation Therapy and Drugs on Cell Turnover and Taste

Lloyd M. Beidler and James C. Smith

Renewal of Cells of Oral Cavity, 753
Epithelial Penetration, 754
Situations that Result in Taste Changes, 754
  General, 754
  Head and Neck Irradiation, 755
  Chemotherapy, 755
Causes of Taste Changes Associated with Cancer and Cancer Therapy, 756
  Arrest of Turnover, 756

Salivary Glands, 758
Changes in Blood Chemistry, 759
Conditioned Taste Aversions, 759
Oral Epithelium, 760
Conclusions, 760
References, 761

The oral cavity serves both as the locus of taste and as the major entrance of food and fluids to the human body.

Three primary characteristics of oral tissue maintain the integrity of the oral cavity in the face of mechanical, thermal, and chemical insults. First, the epithelium is continually renewed by a layer of proliferating cells at its base. The sensitive cells of taste buds that must be in direct contact with chemicals in the oral cavity are also continually replaced. Second, the tissues that are most insulted while eating, those of the dorsal surface of the tongue and the palate, contain a keratinized layer that serves as a barrier to penetration of most chemicals, particularly those that are hydrophilic. This protects the underlying layer of proliferating cells and sensitive nerve endings from injury. Third, salivary secretion must serve as a vehicle for tastant and food transport and provide agents to fight foreign bacteria and fungi of the oral cavity. This requires adequate flow rate, suitable viscosity, and the presence of over a hundred different salivary proteins to help make this possible.

Renewal of Cells of Oral Cavity

Epithelia Cells

The cells of the stratified squamous epithelium lining most of the oral cavity can be classified into three compartments: the proliferation, the maturation, and the outer functional (1). Cell proliferation occurs primarily at the base of the epithelium, where the cells undergo mitotic division. Their cell cycle is shown diagrammatically in Fig. 1. The exact lengths of times for the various phases vary with both species and location of the epithelium. Diurnal rhythms are well documented and the highest mitotic activity usually occurs between 4:00 and 10:00 a.m. (2).

After cell division, one of the daughter cells migrates upward in the epithelium while maturing. The cell then enters the outer cell layer and finally dies. Thus, cell proliferation and migration serves to renew the total cell population of the epithelium. The time necessary to replace all the cells is referred to as the turnover time. This transit time has been calculated to be 5 to 9 days in the nonkeratinizing epithelium of hu-
but it can be greatly altered by experimental manipulation.

**Epithelial Penetration**

Free lingual nerve endings near the base of the epithelium respond to chemicals that may penetrate after being placed in the oral cavity. This gives rise to many sensations often associated with food. If the epithelium is damaged, as during mucositis, chemical penetration is rapid and pain may become the dominant sensation.

Mistretta (4) studied the passive permeability of the rat tongue epithelium to a variety of radioactive compounds. The speed of penetration of a nonelectrolyte as indicated by the permeability coefficient was found to be directly related to the ether-water partition coefficient (see Fig. 2). Thus, methanol and ethanol penetrate very much faster than lipophobic substances such as glucose and mannitol. The rapid penetration of alcohol suggests that patients undergoing treatment of the oral cavity should refrain from alcohol consumption. The negative aspects of such consumption has often been noted for smokers who develop leukoplakia and later display evidence of cancer.

**SITUATIONS THAT RESULT IN TASTE CHANGES**

**General**

There are many traumatic situations and diseases that alter the sense of taste, but none have had the impact of cancer and its associated therapies. It is estimated that over 400,000 cancer patients in the United States demonstrate damage to the oral cavity each year. Since food intake is primarily a sensory experience, alterations to the oral epithelium, taste buds, or saliva could be detrimental to normal food intake and thus adequate nutrition. To the scientist, taste is a sensory experience associated with the chemical stimulation of taste cells. To the patient, however, taste is a summation of all sensory experiences associated with food intake. In fact, other bodily conditions such as nausea are also said to affect taste. It is the view of the patient that is considered in this chapter.

Irradiation and chemotherapy are the major tools used to treat cancer. They are chosen since they are most effective with tissues that rapidly turnover and have high metabolic activity. Since both cancerous and oral tissue display these characteristics, it is not unexpected that oral complications are associated with head and neck irradiation as well as prolonged chemotherapy. This greatly affects the quality of life of the patient and may lead to a return to those habits such as increased alcohol consumption and smoking that
exaggerate the decreased health of the oral cavity. If the condition is both prolonged and severe, the decrease in food intake may undermine the nutrition that is so needed during the medical treatment.

Head and Neck Irradiation

Patients with head and neck irradiation often complain of marked changes in taste sensations. Deficits in taste sensation resulting from radiotherapy were first described in detail in 1959 by MacCarthy-Leventhal (5). She described a “blindness of the mouth” along with severe taste hallucinations. Many of the subsequent reports of such taste deficits following head and neck irradiation describe in detail elevations in taste threshold values (6–15).

Also described are many reports of suprathreshold changes in taste following head and neck irradiations (16–18). A good example of such changes were reported in a study by Chencharick and Mossman (19) where patients tended to use more sugar as the course of radiotherapy developed but not more salt (see Fig. 3). These decrements in taste perception could result from a variety of causes and are not necessarily the result of alterations in taste cell turnover rate.

Chemotherapy

With chemotherapy there are numerous reports by patients that their sense of taste is changed. One of the most common side effects of vinblastine (a mitotic inhibitor) injections is the loss of taste (20). Taste alteration is one of the most frequent problems reported by patients following neoadjuvant cisplatin, bleomycin, and methotrexate therapy (21). In another study 46% of the patients reported taste changes, and a significantly larger number of these patients also showed the greatest weight loss (22). After combination chemotherapy using bleomycin, actinomycin D, vindesine, and dacarbazine (DTIC) low concentrations of sweet,
sour, salty, and bitter substances were rated as more intense (23).

There have been very few studies of taste changes actually during chemotherapy and shortly thereafter. If the chemotherapy drugs indeed do inhibit turnover of taste cells in clinical patients (as has been clearly shown in rats following vinblastine injections), then it will be necessary to study taste alterations both during and for a few days following each treatment. In one study (24) it was reported that 16 out of 45 patients reported bitter tastes during the treatment. This could result from systemic stimulation of taste receptors by drugs that are passed into the saliva. Sjoden et al. (25) showed that patients undergoing chemotherapy reported abnormal taste and olfactory sensations outside the treatment setting but close in time to the therapy. These studies were directed toward identifying factors that caused nausea and vomiting prior to, during, and after the therapy. Patients who have been treated for psoriasis with oral doses of methotrexate (MTX) report having a sour or metallic taste. One patient who had normal taste acuity before treatment lost sensitivity to all four taste modalities 12 hr later (26). These investigators postulated some central nervous system site of action rather than cell turnover. In other patients they showed that oral administration of folic acid could block the MTX-induced taste loss.

Bartoshuk (27) interviewed patients undergoing chemotherapy and observed a relationship between those who experienced the bitter taste during therapy and the perception of bitterness in saccharin. Since the bitter taste in saccharin is associated with the genetic status for phenylthiocarbamide/6-n-propyliothiouracil (PTC/PROP) tasting, there may lie a predictor for which patients will experience severe nausea associated with chemotherapy. These relationships need to be further explored.

CAUSES OF TASTE CHANGES ASSOCIATED WITH CANCER AND CANCER THERAPY

Arrest of Turnover

In 1965 it was first discovered that cells of the taste bud are continually replaced, with a half-life of about 10 days (3). This was an unusual finding since it was previously thought that cells of a sensory organ are never replaced. Today, it is known that olfactory cells also are continually replaced. Conger and Wells (28) demonstrated a relationship between radiation dose and number of taste buds in humans. Therapeutic radiation to the human tongue decreased taste acuity with a peak in loss of acuity occurring in 2 to 3 weeks and a recovery in 60 to 100 days. The area of the oral cavity stimulated determines the extent of taste loss since taste buds are not uniformly located over the entire area. The soft palate, the circumvallate and foliate papillae on the tongue posterior, and the fungiform papillae spread over the two-thirds portion of the tongue anterior are the three locations of maximum taste bud density. Shielding of as many of these locations as possible would minimize irradiation-induced losses in taste sensitivity and normal food intake.

Conger (8) noted changes in human taste sensitivity within the first 2 days of irradiation. Since the cell population of taste buds are not very much affected within this short time interval, these changes cannot be attributed to cell death. He suggested that damage

![Graph showing changes in taste and salt sensitivity during radiotherapy.](image-url)
to the microvilli of taste cells, which react directly with tastants, may be altered in this early time period. Perceptible changes in taste function were noted with irradiation doses of 2.4 to 4.0. Grays and acuity approaches nil at accumulated doses of 30 Gy. Partial recovery is noted 20 to 60 days after termination of a 3.0-Gy dose and full recovery within 60 to 120 days (14). However, taste disorders may persist for at least 5 years in 50% of irradiated patients given doses of 50 to 65 Gy (12). There appears to be great individual differences in the taste cell response to irradiation. The degree of taste loss does not appear to be correlated to amount of salivary flow. In fact, salivary dysfunction appears to be much more sensitive to irradiation than taste loss. Figure 4 suggests a 50% salivary dysfunction with about a 9-Gy accumulated dose whereas a 50% taste loss occurs after a 28-Gy accumulated dose (Fig. 5). This difference in sensitivity cannot be accounted for on the basis of magnitude of cell turnover rate or the percentage of cells in metaphase at any given time.

Chemotherapy utilizes chemicals that interfere with mitotic activity and thus destroys proliferating cells. This tends to select cancer cells for elimination, in contrast to normal cells of lower mitotic activity. However, taste cells possess a life span just slightly greater than many other cells of the oral cavity. Thus, taste cells are also destroyed during chemotherapy. Laboratory experiments with the mitotic inhibitor vinblastine sulfate show that water intake of rats declines to about one-third normal value within 2 days of treatment and then returns to normal levels about 6 days later (29). It has been shown in our laboratory (unpublished data) that food intake is also markedly reduced following vinblastine injection and does not return to normal levels until 8 days postinjection. The reductions in food and water intake are probably a general consequence of alterations in many bodily functions and not necessarily due to taste alone. However, preference for both sucrose and saccharine solutions gradually declines following vinblastine injection, reaching the lowest level 8 days later (Fig. 6). This is followed by a rapid return to normal preference levels. This change in preference for the sweetened solutions may well reflect some aspect of the reduction in taste cell turnover. There could be alternative explanations, however, since we have also shown that it is easy to condition a taste aversion by pairing the saccharin solution close in time with the vinblastine injection (see the later section on conditioned taste aversions).

The complexity of the sensory foundation for the eating symptoms given by anorectic cancer patients was studied by Trant et al. (30). They were as follows:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste of food</td>
<td>54%</td>
</tr>
<tr>
<td>Early satiety</td>
<td>46%</td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
</tr>
<tr>
<td>Pain</td>
<td>27%</td>
</tr>
<tr>
<td>Constant fullness</td>
<td>15%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>15%</td>
</tr>
<tr>
<td>Bitter taste in mouth</td>
<td>12%</td>
</tr>
<tr>
<td>Dryness of mouth</td>
<td>8%</td>
</tr>
</tbody>
</table>

Although taste of food was the largest complaint, it was only cited 54% of the time. However, 43% of these taste complaints were due to tastelessness of the foods. Both nausea and satiety also played a large role in eating behavior.

It is not clear, however, that these reports of alterations in taste perception result from changes in taste receptors as related in the preceding. They may relate to olfactory changes, deficits in the salivary system, changes in blood chemistry, hedonic changes, learned food aversions, or other causes. Furthermore, the ap-
parent changes in taste perception may result from the cancer itself or from the associated therapy. If the cancer is localized in the oral cavity, many of the problems regarding taste are evident. Cancers located elsewhere have been reported to cause taste changes, but the evidence is strong that these changes are hedonic and not the result of taste receptor problems (27,30–32). Many of the reports of taste changes in cancer patients have focused on changes in taste detection thresholds, i.e., what is the minimum concentration of a taste compound that is perceived by the patient. Bartoshuk (27) said that these threshold changes “have limited relevance for real-world taste.” She measured both detection threshold and suprathreshold taste function in a patient with neck cancer. The detection threshold returned to normal in 2 months following treatment, but the suprathreshold functions did not return to normal.

Salivary Glands

Since the turnover rate of salivary gland cells is quite low, one would not expect much damage by X-ray irradiation. However, loss of salivary flow is a common problem experienced by patients undergoing either irradiation or chemotherapy treatment. Experimental studies with rats show loss of gland weight, changes in salivary protein composition, decrease in flow rate, and cellular degeneration. The acinar cells are the most sensitive cells of the salivary gland. The parotid gland is more radiosensitive than the submandibular or sublingual gland.

The salivary glands are susceptible to damage by head and neck irradiation. If severe, this may lead to complete lack of salivary flow. Saliva is a complex fluid containing a large number of proteins, a buffering system and a solvent with a viscosity appropriate for adequate sensory function. A number of the proteins act as fungicides and bacteriicides that help control the ecology of the oral cavity. Saliva may contain high concentrations of such important proteins as nerve growth factor, epidermal growth factor, renin, somatostatin, etc., whose functions in saliva are still unknown. Thus, absence of adequate volumes of saliva is very detrimental to the oral cavity, taste function, and food intake and may pose a serious health hazard.

The parotid glands of rats irradiated with a 20-Gy dose of X-rays show microscopic and degenerative changes within 1 day (33). Pyknotic nuclei averaged between 4 and 13% after 1 day but declined rapidly within 3 days. Secretory function also declined with flow rate being halved within 3 days after irradiation. Oral mucositis was severe and food consumption dropped so that body weight declined 42% within a week. Seventy-five percent of all animals died within 10 days postirradiation. This study demonstrates the severe consequence of oral mucositis and loss of normal salivary function! It is interesting to note that if the parotid salivary glands is irradiated with a 20-Gy dose, then excised and acini cultured in vitro, they quickly recover and show normal function. The reason for this difference between in vivo and in vitro is not clear. Perhaps malnutrition of irradiated animals plays a large role in loss of glandular recovery. On the other hand, damage to the blood supply may account for some of the observed decrements in salivary function after irradiation.

Irradiation of salivary glands of humans show similar decreases in function. The salivary flow rate declines rapidly and exponentially with increasing X-ray
doses (34). The rate also declines linearly with the proportional radiation damage (see Fig. 7). A maximal accumulative dose of 40 to 65 Gy results in a 50% complication rate after 5 years, whereas 50% taste loss occurs after 50 to 66 Gy during the same period (34). The parotid and submandibular glands produce most (50 to 75%) of the saliva in man with the parotid being the larger contributor during stimulation.

The quality and quantity of saliva is much more complex than simple measurement of flow rate would indicate. Alteration of function of one of the parotid glands has a definite effect on the other. Similarly, interference with the function of the sublingual-submandibular complex affects the function of the parotid glands. Whole saliva contains a complex mixture of over 100 different proteins. Many of these proteins are primarily manufactured by only one kind of salivary gland. For example, both epidermal growth factor and nerve growth factor are supplied by the submandibular and not the parotid salivary gland. Many of these proteins play an important role in the health of the oral cavity. It is particularly true of immunoglobulin A (IgA), lactoferrin, proline-rich proteins, etc.

A relationship between saliva and taste has been proposed in the past (35–38). Recently more direct roles of saliva have been discovered; for example, neonatal removal of the sublingual gland in the rat changes the response of taste receptors to salt as well as the animal's ingestive behavior (39). In addition, a specific protein has been found in saliva that is similar to one previously discovered in the olfactory mucus. This is thought to play a role in carrying the chemical stimulus to the sensory chemoreceptors (40).

Almost all attention has centered upon the relationship between saliva from the major salivary glands and taste. However, the majority of taste buds are located in the circumvallate and foliate papillae. These papillae are supplied by their own salivary glands; namely, the von Ebner glands. These minor glands manufacture amylase, nerve growth factor, epidermal growth factor, etc., as do some of the major salivary glands (41), as well as an unusual lipase not found in the other salivary glands (42). The salivary glands of the lips are a primary source of IgA (43). Thus, the minor salivary glands do play an important role in the oral cavity.

The decline in salivary flow rate reduces tannant solubilization, diminishes lubrication, and decreases the joy of eating. Since relative taste loss and increased pain sensitivity due to mucositis occurs at the same time, food is no longer pleasurable. Thus, the patient eats less and becomes undernourished at the very time the salivary gland is in most need of nourishment during irradiation or chemotherapy. Although the common complaint is that food does not taste good, many of the preceding additional factors are also important and the sensory involvement is not limited to taste alone. Many, but not all, of these patients may recover their taste and joy of food several months after irradiation is terminated.

Changes in Blood Chemistry

Changes in perceived taste by cancer patients could also be due to changes in blood chemistry. Bradley (44) has shown experimentally that some chemicals injected intravascularly stimulate the taste cells. In clinical tests, chemicals injected into the blood were often used to measure arm-to-tongue circulation time. It is not surprising that some patients complain about bitter tastes during a chemotherapy treatment and many patients report both bitter and metallic tastes long after the treatment is completed.

Conditioned Taste Aversions

When studying decrements in taste sensation associated with radiotherapy and chemotherapy drugs, it is important to be aware of the fact that these decrements are quite possibly the result of a learning process. Learned taste (or food) aversions can occur as a result of ionizing radiation exposure (45). Succharin-flavored water, a normally preferred taste solution by rats, was presented simultaneously with a sublethal exposure to gamma rays. Several days after this pairing of the taste of saccharin with the irradiation, the rats avoided the normally preferred solution in subsequent preference tests. Animals that received only gamma exposure, i.e., no saccharin was paired with the irradiation, showed a strong preference for the sweetened solution in subsequent tests. One could in-

![Flow rate](chart)

**FIG. 7.** Salivary dysfunction as indicated by flow rate decreases linearly with proportional radiation damage. (Redrawn from Makkonen and Nordman, ref. 69.)
fer that an animal experiencing nausea or another repugnant sensation due to irradiation exposure associates it with the ingestion of a novel food or liquid and therefore avoids its further ingestion. Smith and Morris (46) reported that a taste aversion could be conditioned by pairing saccharin ingestion with injections of physostigmine. In the years that followed, both radiation- and drug-induced conditioned taste aversions were subsequently demonstrated under a variety of conditions and with a broad number of drugs [see Barker et al. (47) and Riley and Tuck (48) for comprehensive reviews]. Taste aversions seem to be easier to condition when novel tastants are used rather than familiar ones.

A learned taste aversion can be readily conditioned in laboratory rats using the chemotherapy drug, vinblastine. In unpublished research in our laboratory, we have shown that a single presentation of saccharin solution for 10 min followed by a vinblastine injection results in a subsequent saccharine taste aversion that lasts for at least 2 weeks. Rats given a saccharin pairing with a control saline injection show no aversion to the saccharin over the same time period (see Fig. 8).

It has also been shown that taste aversions in rats can be conditioned with radiation exposure when the saccharin taste is presented by intravascular injection rather than directly into the oral cavity (49). Thus, bitter chemotherapeutic drugs injected into the vascular system might also produce a taste aversion in humans.

Based on this literature demonstrating learned taste aversions with animals, it is not at all surprising that similar aversions have been conditioned with human radiotherapy and chemotherapy patients. Bernstein first reported (50) a demonstration of learned taste aversions in children receiving chemotherapy. Children that received a distinctive tasting ice cream prior to chemotherapy avoided this flavor in subsequent tests. This study was followed by a series of investigations where she demonstrated similar aversions in human adults (51–54). Other investigations have also shown that taste aversions are readily learned in chemotherapy patients (53–58). As in the previous studies with rats, it was found that novel tastants paired with chemotherapy resulted in stronger taste aversions than the aversions to familiar foods (58). Learned taste aversions to fruit juices have also been conditioned in radiotherapy patients (59–61). A way to avoid the formation of taste aversions in cancer patients would be to intentionally pair a “scapegoat” food with the therapy, conditioning an aversion to this unimportant food source (62). It was successfully demonstrated with children patients. It should be noted that learned taste aversions are probably the rule, rather than the exception, in cancer patients. The fact that intravascular "tastes" have been conditioned in rats has strong implications for learned aversions in chemotherapy patients. The intensity and longevity of these learned aversions as related to the appetite problems in cancer patients needs to be more fully explored.

**Oral Epithelium**

The oral epithelium is well designed to absorb the insults that accompany the intake of hot coffee, cold ice cream, tough and hard food, etc. Yet the sensitivities of thermal and tactile receptors of the tongue remain high. This beautiful balance is disrupted if the epithelium is defaced and substances taken into the mouth can easily penetrate toward the base of the epithelium. Stomatitis, the inflammation of the mucous membrane of the mouth, presents an excellent mode of entrance for foreign chemicals, bacteria, viruses, etc., into the base of the epithelium and eventually into the vascular system (62). The associated pain disrupts the normal appreciation of food taken into the mouth, and both the pattern and amount of consumption can change. If severe, inadequate nutrition results. In addition, many of the habits associated with normal dental and oral hygiene will be disrupted, which leads to further deterioration of both teeth and the mucous membranes.

**Conclusions**

It can be seen from the preceding discussion that the alterations in taste sensitivity reported by cancer patients are likely due to multiple causes. These could differ markedly depending upon the location and type of malignancy, the course of radiation or chemother-
apy, and the psychologic state of the patient. The following suggestions could help to reduce taste changes and losses and possible subsequent diminishing of appetite.

**Taste, Food Intake, and Nutrition: Suggestions for Their Improvement**

1. Psychologic trauma occurs even before treatment begins and thus interest in eating declines. Patient should be told what to expect during treatment. It is important that the patient understands when to expect improvement in his or her conditions as a function of time. Acute and chronic effects are listed in Table 1. A state of hope is very important.

2. Tolerance dose, fractionation pattern, and target volume must be selected with attention to minimum damage to salivary and taste organs when using radiation. Selective shieldings of parotid glands as well as some of the taste buds are most important.

3. Mucositis appears early during irradiation treatment but also declines sooner than taste dysfunction. Bland foods with neutral pH are best tolerated. Milk is a good food source under these conditions. Alcohol should be forbidden.

4. Severe xerostomia can be of long duration and should be avoided if possible. The parotid glands are the major source of salivary production during periods of sensory stimulation. Artificial saliva should be suggested to patients, but it is of limited use. Since severity of xerostomia is directly related to total radiation dose and to volume of salivary gland irradiated, adequate attention should be given to both. Treatment with oral pilocarpine could be considered (63-66).

5. Since candidiasis often follows chemotherapy and contributes to poor oral hygiene, it should be adequately treated.

6. Poor oral hygiene before treatment increases the risk of tissue damage and eventual tooth decay. Consultation with a dentist before treatment is most beneficial.

7. Acute radiation enteritis after small or large bowel irradiation as well as the use of chemotherapy often leads to taste aversion. However, the probability of taste aversion can be decreased:

   a. The patient should avoid eating 4 hr before and after chemotherapy or bowel irradiation.

   b. The patient should intentionally ingest a novel tasting but nutritionally unimportant food (scapegoat tastant) shortly before irradiation or chemotherapy.

   c. The patient should be informed of the possibility of creating a food aversion during treatment. This knowledge may decrease the possibility of such a conditioning.

8. Patients should be encouraged to eat many small meals throughout the day rather than only three per day.

9. It is of utmost importance that the physician providing the primary care is in close communication with others involved (dentist, oncologist, radiologist, etc.) and communicates all objectives. In particular, the radiologist must be aware of the need for adequate taste and salivary function.

10. A recent National Cancer Institute monograph (67) on oral complications of cancer therapies should be examined for current approaches.

**ACKNOWLEDGMENTS**

This work was supported by National Institutes of Health Grants Ag 04932, Ag 06841, and NS 20320.

**REFERENCES**


---

**TABLE 1. Summary of effects of radiation therapy**

<table>
<thead>
<tr>
<th>Region</th>
<th>Acute effects</th>
<th>Chronic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Nausea, vomiting</td>
<td>—</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Mucositis, sore mouth and throat, dysphagia, odynophagia, dry mouth (xerostomia), loss of taste (hypo-agesia), dysgeusia, dysosmia, anorexia</td>
<td>Xerostomia, loss of taste, dental caries, ulcer, osteoradionecrosis, trismus</td>
</tr>
<tr>
<td>Thorax</td>
<td>Dysphagia</td>
<td>Fibrosis, stenosis, perforation, fistula</td>
</tr>
<tr>
<td>Abdomen and pelvis</td>
<td>Anorexia, nausea, vomiting, diarrhea, acute enteritis, acute colitis, choleretic enteropathy</td>
<td>Diarrhea, maldigestion, malabsorption, chronic enteritis, chronic colitis: ulcer, stricture, obstruction, diarrhea, perforation, fistula</td>
</tr>
</tbody>
</table>

From Thiel et al., ref. 70.


32. Settle RG, Quinn MR, Brand JA. Gustatory evaluation of cancer patients: preliminary results. In: J Van Eijis, MS See-


