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Radiosensitivity of the Human Parotid Gland (39988)

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The severe xerostomia generally associated with cancerocidal levels of radiotherapy administered to head and neck malignancy patients makes oral health maintenance exceedingly difficult. Meticulous oral hygiene and vigorous fluoride therapy are essential in protecting the teeth from rampant dental caries (1-5) and a saliva substitute can be very helpful in overcoming the soft tissue problems that accompany the xerostomia (6).

These troublesome intraoral problems result from the depression of salivary gland function by the irradiation (7-11). We have previously reported (12) that the rate of unstimulated whole saliva flow decreases progressively during radiotherapy to the point that, after 6 weeks, only 5% of the original flow remains. It has been suggested that the parotid is more radiosensitive than the other salivary glands (13-16) and salivary gland extirpation experiments (17) have indicated that the level of caries developed is in direct proportion to the amount of serous glandular tissue removed. There is thus the indication that the rate of function of the parotid gland may be of critical importance in preserving the teeth of the irradiated patient.

The present study evaluates the resting parotid flow rate response in patients receiving radiotherapy involving the salivary glands.

Materials and methods. Patients were seven white males ranging in age from 42 to 71 years, with primary malignant lesions in the head and neck area. Lesions were located in either the base of the tongue, the soft palate, the hard palate, or the retromolar trigone. The fields were such that the parotid glands were totally within the beam. Prior to the initiation of radiotherapy a series of parotid saliva samples was collected to establish baseline values. Sampling was undertaken at about 7:30 AM with the patients fasting. Patients were seated comfortably in a semi-isolated area and extraneous interferences were not allowed. The patient was instructed not to engage in conversation and to reduce oral excursions to a minimum. Every effort was made to collect, as nearly as possible, the true resting secretion of the parotid gland. A vacuum-maintained sampling device (18) was positioned over the orifice of the parotid duct with an absolute minimum of manipulation and the patient sat quietly over a period of 0.5 hr. Accumulating parotid saliva was collected in a graduated tube and a rate of flow was expressed in milliliters per minute. The device was drained thoroughly after each sampling to assure that any saliva within its confines would be harvested.

The first day's collection for each patient was considered a familiarization procedure and no data were recorded. Three pretreatment control samples were subsequently collected from each of five of the patients and two were obtained from each of the remaining two patients. In each instance, the last baseline sample was collected on the morning of and just prior to the first treatment. Irradiation was administered by parallel opposed fields from a cobalt-60 source and was given at a daily dose level of 225 rads, customarily on a Monday through Thursday schedule each week. Attempts to collect saliva continued throughout the first 4 weeks of therapy and flow rates were recorded for any period in which flow was noted.

Results and discussion. Resting flow rate responses are outlined in Table I. The pretreatment flow rate mean (19 samples from seven subjects) was 0.045 ml/min (SD = 0.023). This is an acceptable baseline figure since in previous work (19) with over 4000 healthy young adult males we found a com-

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TABLE I. RESTING PAROTID FLOW RATE RESPONSES TO RADIOTHERAPY.

Patient identification	Resting parotid flow rate (ml/min)				
	Pretreatment			Number of treatments (225 rads)	
	Number of samples	Mean	SD	1	2
ENC	3	0.057	0.006	0.030	0
DEF	3	0.073	0.028	0.040	0
GRA	3	0.040	0.013	0.010	.005
LAM	2	0.030	0.000	0.001	0
MOR	2	0.070	0.014	0.060	0
PRO	3	0.012	0.004	0.005	0
SCS	3	0.032	0.003	0.012	0

parable mean value of 0.040 ml/min (SD = 0.031).

On the morning after the first radiotherapy treatment (approximately 24 hr after this first treatment) the parotid flow rate mean had decreased to 0.023 ml/min (SD = 0.022). This virtually 50% reduction in resting flow resulted from the administration of only 225 rads. At the next sampling interval, 24 hr later (24 hr after radiotherapy treatment No. 2), there was no trace of flow in six of the seven patients. In the seventh patient a total of 0.15 ml of saliva was collected in the 30-min period; rate of flow was thus only 0.005 ml/min for this patient. There was no quantifiable flow in any of these patients after this time. On occasion the inner surface of the metal collecting cap might appear damp, but not even one drop of saliva was present.

Even though resting flow from the parotids had virtually ceased in these patients, it did not induce immediate complaints associated with intraoral dryness. Clinically, the saliva appeared somewhat thickened and ropy but it was evident that extraparotid sources retained the ability to maintain a relatively adequate degree of moisture in the mouth. This supports previous work on the contribution of the parotids to whole saliva volume. Gore (20) found that the parotids provided slightly more than 50% of the whole saliva output when exogenous stimulants were not employed. Schneyer and Levin (21) noted a 26% contribution in 23 subjects at a very low state of stimulation. Suhara *et al.* (22) studied two subjects and found that the parotids contributed 25% of the resting saliva flow. In 71 subjects, Enfors (23) found that the submandibular glands contribute more than three times as much resting flow as do the parotids. Kerr (24) also found that, under resting conditions, the submandibular glands secrete at a rate about three times that of the parotids. Shannon (25) has reported data from 63 healthy young adult males indicating that the parotid glands contribute an average of 32.9% to the total resting salivary flow. In general, these observations support the clinical finding that extraparotid saliva sources are adequate to maintain a wet state in the mouth even when resting parotid flow has been obliterated.

The results of this study support the widely held concept that a marked depression in salivary flow results when the salivary glands are exposed to radiation. It provides additional information, however, in that the flow rate contribution of the parotid gland to whole saliva flow is almost completely eliminated after only two irradiation treatments of 225 rads each. Our previous work with whole saliva indicated a 60% loss in flow after 1 full week of treatment and steadily decreasing residual flow rates of 29, 24, 19, 9, and 5%, after 2, 3, 4, 5, and 6 weeks of treatment, respectively (12). It is apparent that most of the oral fluid being produced in postradiotherapy patients is derived from mucous glandular components and that the parotid contribution is negligible.

It has been known for many years that salivary gland changes transpire within a short time following irradiation. It was pointed out in 1911 (26) that swelling occurs within a few hours, and in 1912 Ceresole (27) observed that this swelling began

after about 5 hr and peaked at about 10 hr after treatment. Kashima *et al.* (28) studied surgical specimens from 22 patients that had been irradiated. Ten irradiated parotid glands were examined microscopically and all exhibited acute inflammatory and degenerative changes. The discrete outlines of the acini were barely discernible and the serous cells had large irregular basilar vacuoles that seemed to rupture cells and cleave them free from the basement membrane. Fourteen submandibular glands were similarly examined and the serous acini showed all of the degenerative changes described for the parotid glands. In sharp contrast, little if any discernible microscopic change was present in mucous cells. It was concluded that the primary damage from irradiation was in the serous cells, that this brings about the release of amylase to produce the characteristically observed hyperamylasemia, and that this degeneration brings about the marked inflammatory cell infiltration found in these glands. It was also noted that prompt and near-total cessation of salivary gland secretion occurred early in the postirradiation period. Silverman and Chierici (13) and Rubin and Doku (16) also stated that serous acini are more sensitive to irradiation than mucous-producing components, but no supporting data were provided.

Eneroth *et al.* (14) collected resting parotid saliva from the eight glands of four patients undergoing radiotherapy. The mean rate of flow decreased from 57 mg/min (SD = 85) to 12 mg/min (SD = 22) after administration of 550–700 rads. For a group of 11 parotid glands they found that the flow fell to less than 60 mg (1 drop) per 10-min collection period after a 550- to 700-rad dose. Four other glands required 1000–4200 rads to reach this low level of function. They also reported that in seven parotid glands the flow was practically extinguished by this 550- to 700-rad dose, while three others required a much higher dosage. This same group of investigators (15) reported resting parotid flow rate responses for four additional patients receiving 200 rads per day. For three of the four patients, the flow rate fell to less than 60 mg/10 min after 600 rads. The fourth patient required 2600 rads to reach this low level.

It is thus clear that the human parotid gland is exquisitely sensitive to radiation and that the response is rapid and virtually complete. A single dose of 225 rads reduced the rate of resting parotid flow by one-half and a second dose of the same magnitude induced the virtual elimination of the remaining flow. It is evident that these changes are not rapidly reversible since these collections were made 24 hr after the radiation was administered. This deprivation of flow from serous elements explains the ropy, sticky, viscous nature of the residual oral fluid that is generally seen in these patients.

A further complicating consideration is that, if animal caries studies can be extrapolated to the human, this serous deprivation may specifically accelerate caries development. Cheyne (17) removed salivary glands selectively from rats and placed the animals on cariogenic or control diets. The operated animals with totally removed serous components showed a very high incidence of caries. Removing other combinations of glands produced an increased level of caries but it was much less marked. It was concluded that the animals developed caries in direct proportion to the amount of serous gland elements that was removed.

Summary. Resting parotid flow rate response to irradiation was evaluated in seven patients. The mean for pretreatment flow was 0.045 ml/min (SD = 0.023). Twenty-four hours after the first treatment (225 rads) this mean had decreased to 0.023 ml/min (SD = 0.022), and after the second treatment the mean was only 0.001 ml/min (SD = 0.002). Six of the seven patients exhibited no flow at all after 450 rads administered over 2 days, and the seventh flowed at a rate of only 0.005 ml/min. There was no detectable resting parotid flow from these patients after this time. These results confirm that the human parotid gland is highly sensitive to irradiation and suggest that virtually all of the oral fluid generated by the irradiated patient, even very early in the course of treatment, originates in glands other than the parotid.

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