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STUDIES ON THE PERMEABILITY OF HUMAN ORAL MUCOSA

III. THE PERMEABILITY OF DRY BUCCAL MUCOSA TO WATER, SODIUM AND POTASSIUM

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The loss of water, sodium and potassium from human buccal mucosa during temporary suspension of salivary secretion has been studied by analysing the content of filter paper discs applied to the mucosa in 12 young persons, 11 with normal mucosa and 1 with bilateral leukoedema. With continuous sampling with a cytological filter interposed between the mucous membrane and the filter paper, the material showed a uniform increase in weight, whilst corresponding samples with direct contact with the mucosa showed a variable weight level with initially increased, but gradually falling values. The increase in weight originated partly from a continuous outward diffusion of water, and partly from local fluid accumulations in the epithelium. The diffusional loss was negatively correlated with the surrounding air humidity and showed significantly higher values than the corresponding loss through palatal epithelium.

The analyses indicated that the local accumulations of fluid in the epithelium were the main reason for the electrolyte content of the samples. The investigation showed no signs of an outward transport of sodium and potassium through the buccal epithelium. The observations are briefly discussed against the background of an equilibrium between the superficial layer of the buccal epithelium and saliva.

The relation between the structure and permeability of stratified squamous epithelium has mainly been studied in epidermis. The intact stratum corneum constitutes an effective barrier, both to water vapour leaving the organism (*Burch & Winsor,* 1946; *Blank,* 1952, 1953; *Mali,* 1956; *Szakall,* 1958) and to the absorption of water from the epidermal surface (*Blank,* 1953; *Blank & Scheuplein,* 1964). Elimination of the stratum corneum results in increased loss of water through the skin (*Blank,* 1953; *Matoltsy, Schragger & Matoltsy,* 1962; *Spruit & Malten,* 1965). This barrier function of the epithelium is re-established quickly and to some extent independently of the formation of a new stratum corneum, as a temporary barrier can be demon-

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strated after a few days (*Matoltsy et al.*, 1962; *Spruit & Malten*, 1965). A similar barrier function in stratum corneum has been demonstrated with respect to the absorption of sodium and potassium from the epidermis (*Tregear*, 1966).

The barrier functions of the corresponding types of oral epithelium have not yet been fully investigated. After drying, keratinized palatal epithelium without visible glandular tissue shows a distinct permeability to water, but not to sodium and potassium (*Kaaber*, 1971b). The permeability of non-cornified epithelium has not yet been studied in human mucosa. In vitro studies on dog tissue (*Kawamura & Takata*, 1960) and corresponding in vivo studies on rabbit mucosa (*Aoyama*, 1968) have demonstrated a definite transport of sodium and potassium through the epithelium. The significance of these observations for the human mucosa is not clear, however, as comparative studies of human and animal skin have shown great differences in ion absorption rates (*Tregear*, 1966). The purpose of the present experiment has been to study the permeability to water, sodium and potassium of human, non-cornified oral mucosa.

MATERIAL AND METHODS

The material comprised 12 adult persons, 7 men and 5 women aged 22—25 years. All subjects had clinically normal oral mucosae, except one woman with moderate bilateral leukoedema of the buccal mucosa. None were smokers. The investigation was carried out on an area of buccal mucosa 10 mm distal to the angle of the mouth, having a smooth surface and no visible gland tissue. In all experiments, both the left and the right cheek were sampled.

The procedure followed the lines laid down by *Kaaber* (1971b). Two series of samples were taken. In one, the samples were weighed before and after tissue contact and their sodium and potassium content determined. In the other, the samples were stained after weighing and their contact surfaces examined for adherent epithelial cells. In the latter series, the loss of water vapour from the samples was investigated in the material from three subjects.

During sampling, salivary secretion was suspended by submucous injection of scopolamine. For the initial sampling series, the subjects received 0.50 ml 0.05% scopolamine nitrate, but on account of the discomfort suffered from the drying up of the mucosae, a reduced dosage of 0.25 ml was afterwards used in several cases. The distribution of the sample series according to the variations in procedure is shown in Table I.

Table I

Distribution of material according to variations in experimental procedure

Dose of scopolamine		Type of experiment: Weight/electrolyte determinations, Without filter: Number of series	Without filter: Number of samples	With filter: Number of series	With filter: Number of samples	Weight/cytological determinations, Without filter: Number of series	Without filter: Number of samples	With filter: Number of series	With filter: Number of samples
0.25 mg	♂	7	34	8	39	4	16	4	16
	♀	5	24	6	29	—	—	—	—
	Total	12	58	14	68	4	16	4	16
0.13 mg	♂	3	15	3	15	2	8	2	8
	♀	1	5	1	5	4	16	4	16
	Total	4	20	4	20	6	24	6	24

30 minutes after the injection, samples were taken from the surface of the clean, dry mucous surface over a 120 or 150 minute period. For sampling, circular discs of cleaned, electrolyte-free filter paper (Frisenette type 644—25)* with a diameter of 6.3 mm were employed. The disc was placed on the mucous membrane under an air- and watertight sampling chamber for a contact period of 30 minutes (Fig. 1). With the right cheek, the filter paper was in direct contact with the mucosa, whilst with the left cheek, a similar disc of porous cellulose ester (Millipore MF-filter type 11302)** with a pore diameter of 5 μ was interposed between the filter paper and the tissue. During sampling, a number of discs, both of filter paper and of membrane filter, served as controls. The temperature and humidity of the air in the room was continuously registered.

For the weight and electrolyte determinations, closed polyethylene bottles were employed to contain the discs before and after tissue contact. Weighing was carried out 30—45 minutes before and after tissue contact with a microbalance (Mettler M5) at an air humidity of 60—65% and an air temperature of 21$\pm$2°C, to confine the variation to $\pm$ 10 micrograms (*Kaaber*, 1971a). Sodium and potassium content was determined after at least 20 hours' elution of the sample in 600 μl 15 mmol LiCl solution in the closed container. A flame photometer (IL model 143) was employed with lithium chloride as

* A.G. Frisenette & Sons, Farum, Denmark.
** Millipore Corp. Bedford, Mass. U.S.A.

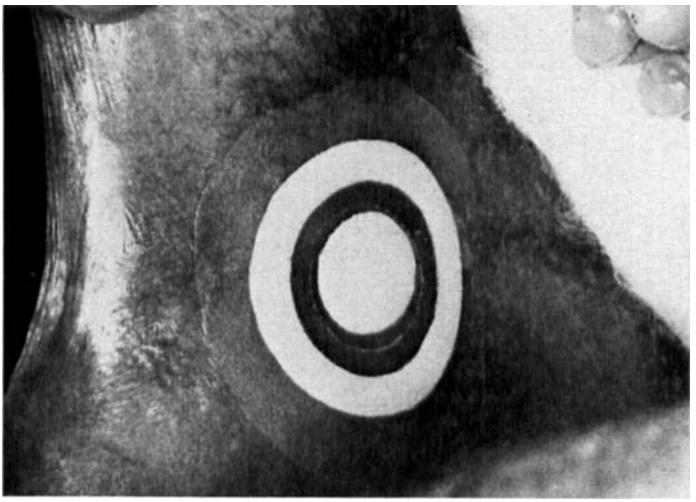

Fig. 1. Location of sampling area on the buccal mucosa and type of sampling chamber employed.

internal standard. The instrument was adjusted to a standard of 10 mmol Na and K/l, diluted 1:200. After adjustment, the reading range was increased from 10 to 40. The sensitivity of the quantitative determination was 30 ± 15 nanograms for both sodium and potassium (*Kaaber*, 1971b).

The cytological examination was performed on samples fixed after the second weighing with a drop of albumenglycerine, stained with haematoxylin-eosin, and mounted with the contact side up in Eukitt.* The content of nucleated cells was determined in dark field with reflected light at 250 times magnification, using a deuble count.

The water content of these samples was determined by opening the weighing bottle after the second weighing and regular weight control of the open bottle until its weight level was constant, when the bottle was closed and allowed to stand for 30 minutes bofore a third weighing was performed.

The statistical analysis employed parameters calculated by conventional methods. Parameter values with a significant deviation at a 5 %, a 1 % or a 0.1% level are indicated in the tables with 1, 2 or 3 asterisks respectively. Corresponding data were analysed with Student's t-test. Variance was analysed with Snedecor's F-test. Covariation between coordinate variables was investigated by means of a correlation and regression analysis. All calculations were performed on an electronic computer.

* O. Kindler AG, Freiburg, W. Germany.

Table II.

Mean weight changes in sampling materials after contact with human buccal mucosa

Dosage of scopolamine		Filter paper				Membrane filter			
		Samples			Blinds	Samples	Blinds		
		Without membrane filter	With membrane filter	t					t
0.25 mg	N	74	84		157	18	39		
	range	364—1102	398—744		÷20—+61	46—470	19—+82		
				2.67***					7.52***
	$\bar{x}$	557.61	515.19		+11.14	171.44	14.25		
	S.E.	127.38	66.15		+10.04	129.90	15.23		
0.13 mg	N	48	48		86	10	21		
	range	322—1311	311—695		÷11—+68	60—164	0—82		
				2.34*(*)					10.16***
	$\bar{x}$	490.11	434.34		6.02	103.90	7.71		
	S.E.	149.31	74.91		12.40	39.81	12.91		
	t	2.71**	6.47***		3.50***	1.59	1.67		

RESULTS

The weight changes in the samples after tissue contact are shown in Table II. Filter paper and cellulose ester discs both showed a significant increase in weight in relation to the corresponding controls. The highest values were obtained after injection of 0.25 mg scopolamine. The values showed distinct differences according to whether a cytological filter had been used. The variation in weight level during the entire sampling period is shown in Table III. When a filter was used, uniform mean values were obtained, whereas samples obtained by direct contact with the mucosa showed a distinct increase in weight in the two first, but not the following periods. This difference was especially pronounced after high scopolamine dosage (Table III A), but less pronounced after low scopolamine dosage (Table III B). The individual variations in the weight level in series with high scopolamine dosage are shown in Fig. 2. With direct tissue contact, several series showed considerable variation in the form of an initially high, but gradually falling level, whilst others showed a more uniform weight level throughout the series. Table IV shows the relation between the relative air humidity during the experiment and the weight level in samples taken with a membrane filter

Table III.

Weight increase in filter paper discs after contact with human buccal mucosa

A. Sampling with strong scopolamine-effect

Sampling procedure		Mean weight changes after 30 minutes contact Values in micrograms First period	Second period	Third period	Fourth period	Fifth period
	N	16	16	16	16	10
no	$\bar{x}$	648.06	578.75	545.25	496.25	497.00
filter	S.E.	189.86	122.57	71.85	72.06	53.39
	N	18	18	18	18	12
with	$\bar{x}$	513.27	505.39	532.27	500.00	529.91
filter	S.E.	74.62	64.22	74.33	61.69	48.64
Value of t		2.7843**	2.2223*	0.5167	0.1635	1.0692

B. Sampling with reduced scopolamine effect

	N	12	12	12	11	4
no	$\bar{x}$	587.75	485.83	435.50	456.00	467.75
filter	S.E.	236.00	121.02	95.89	83.88	37.45
	N	12	12	11	10	4
with	$\bar{x}$	477.08	444.41	403.90	398.20	450.00
filter	S.E.	92.22	68.70	66.16	57.51	31.22
Value of t		1.5121	1.0313	0.9393	1.8141	0.7280

during suspended secretion with a high scopolamine dosage. The samples exhibited a lowering of the mean value with increasing air humidity.

The electrolyte content of the same sample series as in Fig. 2 is shown in Fig. 3. With direct contact with the mucous membrane, nearly all the series showed an initially high, thereafter rapidly falling potassium content, whilst this tendency was less pronounced for the sodium content of the samples (Fig. 3 A). The use of a membrane filter caused a strong reduction in the electrolyte content and less marked quantitative variation during sampling (Fig. 3 B). The relation between the sodium and potassium content in the entire material according to the sampling procedure is shown in Table V. Most subjects showed a clear agreement in the ratios for the two cheeks. Only four subjects (ASL, FHv, IB and partly AC) exhibited marked differences. A correlation analysis of the corresponding ratio values showed a high positive correlation, r: + 0.76***, Fig. 4.

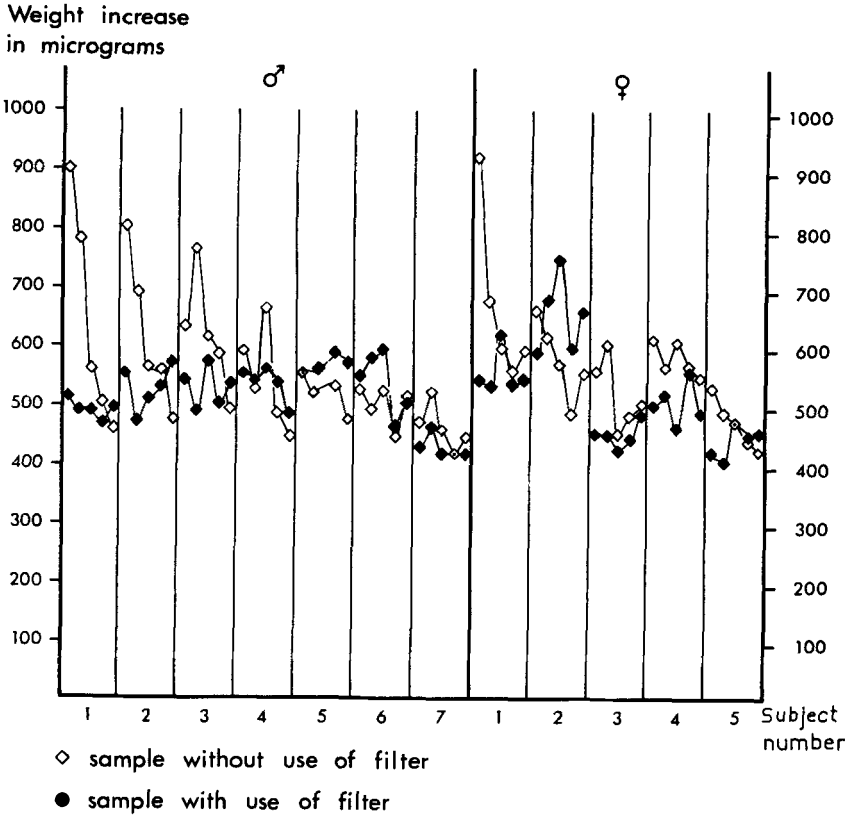

Fig. 2. Weight increase in filter paper discs during consecutive sampling from the same area of buccal mucosa after dosage with 0.25 mg scopolamine nitrate.

The cytological tests revealed a constant presence of nucleated epithelial cells. The greatest numbers were found on membrane filters, varying from about 4.000 to 12.000, Fig. 5. In almost all samples taken by direct tissue contact, the cell count was highest in the first sample, whereas it seemed to vary at random when membrane filters were used (Fig. 6). The use of a membrane filter caused a reduction in the total cell count of 50 %.

Changes in the weight level after evaporation of filter paper and membrane discs containing cells are shown in Table VI. After an evaporation period of 150 minutes, the individual samples exhibited a uniformly low weight level, irrespective of the cell count.

Table VII shows the relation between the weight increase, the content of sodium and potassium and the number of epithelial cells in samples from

Table IV.

Relation between relative humidity of air and weight changes in samples from buccal mucosa in persons with suspended salivary secretion

Relative humidity in % (mean values)	Number of series	Weight changes in micrograms		t
30—35	5	N	25	2.68**
		$\bar{x}$	563.76	
		S.E.	73.60	
40	5	N	25	2.53*(*)
		$\bar{x}$	520.16	
		S.E.	34.32	
45—50	5	N	22	
		$\bar{x}$	487.22	
		S.E.	53.60	
55—60	5	N	12	2.02(*)
		$\bar{x}$	453.42	
		S.E.	42.34	

Table V.

Mean values for the ratio of sodium to potassium in sample series from buccal mucosal surface

Electrolyte content in nanograms

A. Single series

Person	Sex	Date	Samples without use of filter	Samples with use of filter
JKi	♂	1/5 70	0.67 ± 0.11	0.96 ± 0.18
FHv	»	14/5 70	0.79 ± 0.20	1.47 ± 0.75
FL	»	19/5 70	0.56 ± 0.12	0.80 ± 0.14
ASL	»	10/6 70	1.24 ± 0.33	0.64 ± 0.17
LCl	♀	11/3 70	0.31 ± 0.11	0.36 ± 0.19
IB	»	11/5 70	0.99 ± 0.18	2.80 ± 1.32
BSJ	»	29/6 70	0.47 ± 0.11	0.24 ± 0.04
UJ	»	30/6 70	0.78 ± 0.18	0.58 ± 0.11

B. Repeated series

TFM	♂	10/3 70	1.55 ± 0.33	2.55 ± 1.61
»	»	21/4 70	3.10 ± 1.33	3.48 ± 1.20
PBL	♂	14/4 70	0.66 ± 0.14	0.46 ± 0.12
»	»	22/4 70	0.84 ± 0.31	0.99 ± 0.31
AC	♂	8/4 70	0.51 ● 0.16	0.64 ± 0.27
»	»	23/6 70	1.34 ± 1.01	0.70 ± 0.33
IL	♀	30/4 70	0.62 ± 0.05	0.58 ± 0.11
»	»	28/5 70	0.44 ± 0.08	0.37 ± 0.19

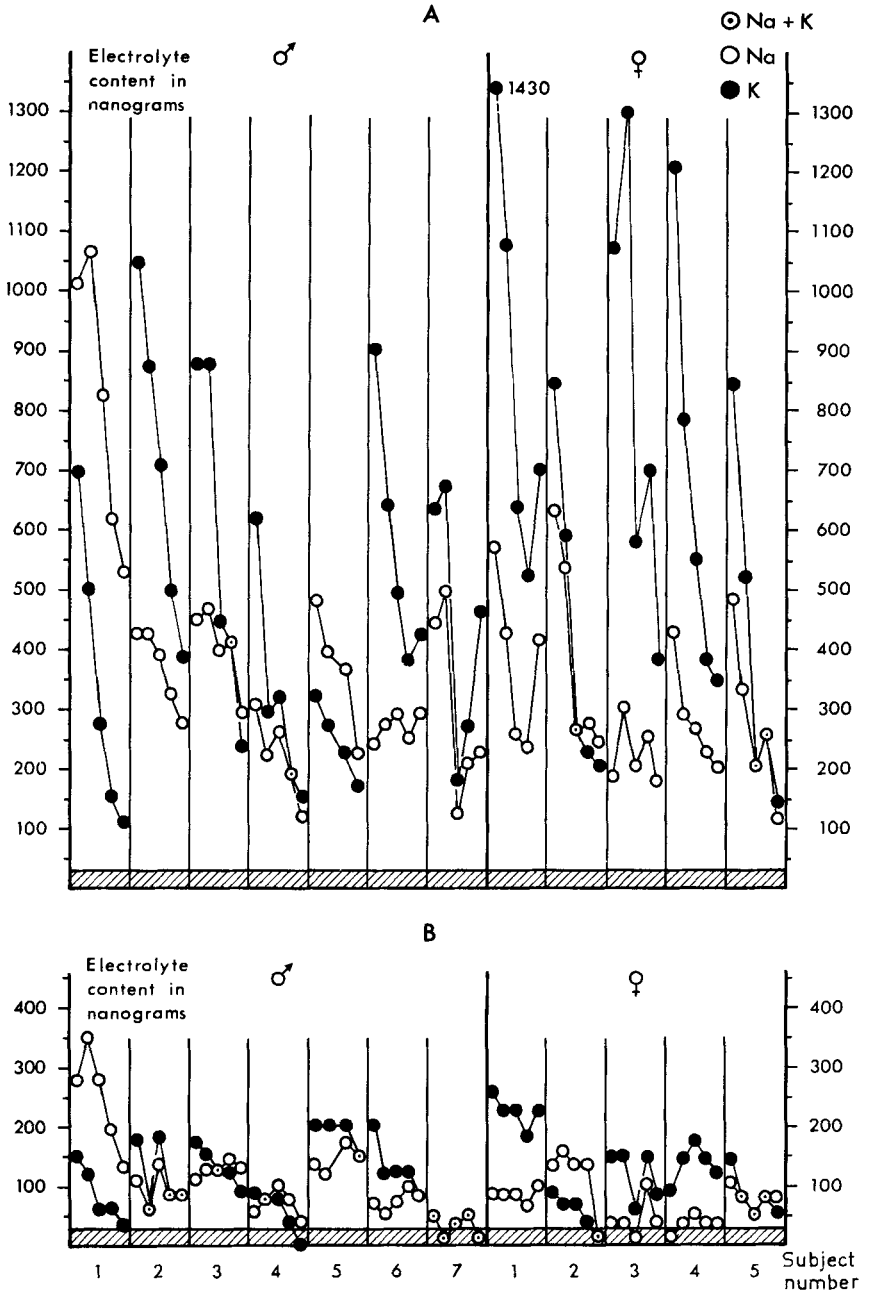

Fig. 3. Sodium and potassium content of the samples in Fig. 2.
A: Samples obtained without use of membrane filter.
B: Samples obtained with use of membrane filter.

Table VI.

Evaporative changes in weight increase of samples from the surface of human buccal mucosa

Sampling material		Weight increase after sampling (values in micrograms) Before evaporation	After evaporation for 150 min.
Filter paper without membrane filter (N:12)	range	329—1255	40—120
	$\bar{x}$	556.58	63.58
	S.E.	244.83	23.09
Filter paper with membrane filter (N:12)	range	308—647	25—80
	$\bar{x}$	434.33	56.50
	S.E.	93.65	17.86
Membrane filter (N:3)	range	88—165	25—40
	$\bar{x}$	121.33	33.67
	S.E.	39.53	7.78

the same subjects for each sampling procedure. With sampling by direct tissue contact, the material showed a clear positive correlation between the variables investigated, whilst when membrane filters were employed, corresponding correlations were found only between the sodium and the potassium content and between the sodium content and weight level.

Table VII.

Relations between electrolyte content, weight increase, and cell counts in corresponding samples from buccal mucosal surface

Variables	Samples without filter Number of samples	Coefficient of correlation	Samples with filter Number of samples	Coefficient of correlation
Na/K	40	0.7419***	40	0.5372***
Na/weight	40	0.6266***	40	0.6749***
K weight	40	0.7268***	40	0.0750
cells/weight	40	0.7599***	40	0.1184
Na/cells	40	0.4795**(*)	40	0.0039
K/cells	40	0.5045***	40	0.1583

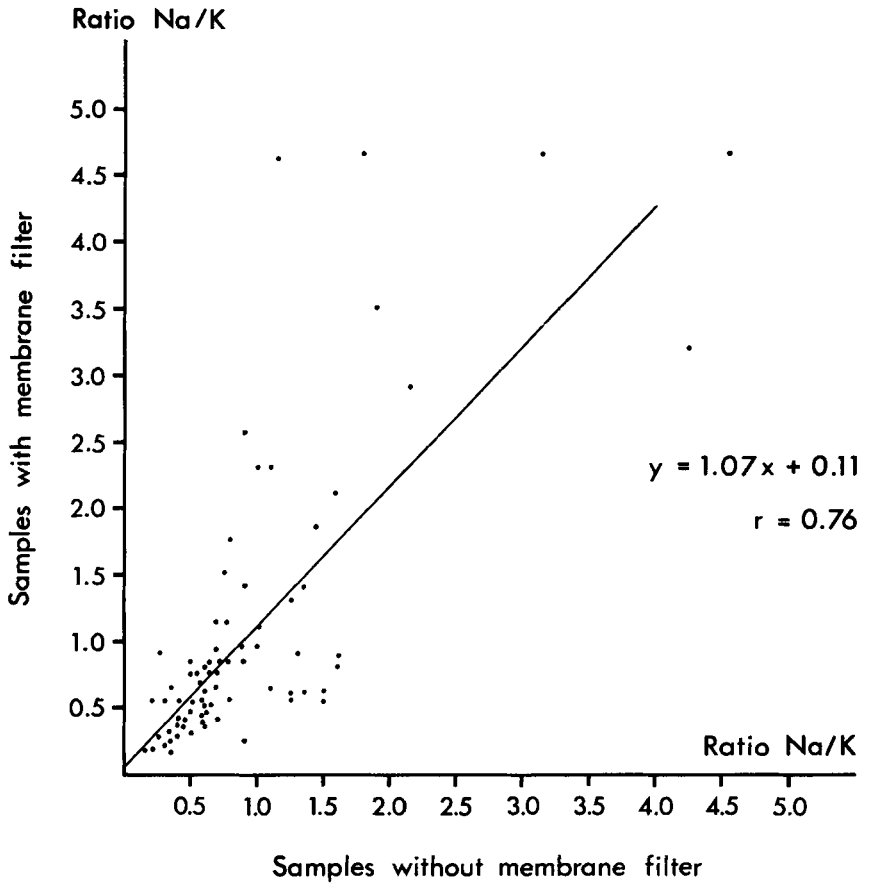

Fig. 4. Scattergram of the relation between the sodium and potassium content in corresponding samples obtained from the two analogous areas on the buccal mucosa.

DISCUSSION

The permeability of buccal mucosa to water. The present material was obtained at the same time as, and largely from the same persons and with the same technique as the corresponding material from the palatal mucosa (*Kaaber*, 1971b). A comparison of the weight increase in the samples from the two areas showed that the material from the buccal mucosa differed by having a consistently higher weight level, both for samples of filter paper and membrane filter, a differing weight level according to the sampling procedure, and an increased variation in spite of the uniform values of the control samples. The weight increase of the samples was due primarily to absorption

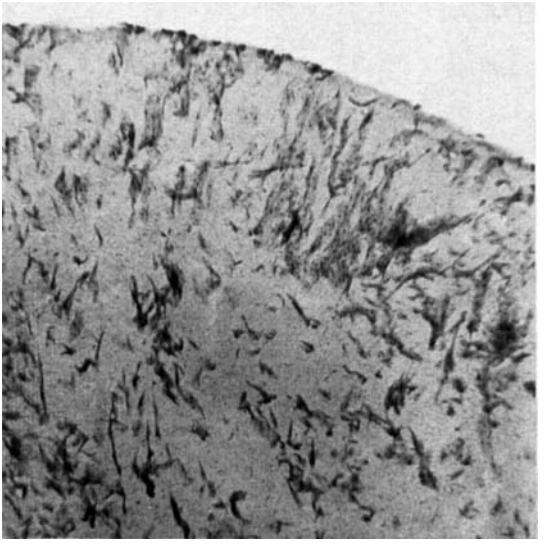

Fig. 5. Clusters of nucleated epithelial cells on the surface of a membrane filter after 150 minutes of contact with human buccal mucosa. Haematoxylin-Eosin, × 100.

of fluid, cytological contamination of samples having little effect on the weight level (Table VI). The strong increase in weight during the two first sampling periods with direct tissue contact compared with the uniform weight level with a membrane filter (Table III) showed that the fluid content of the samples originated from two sources. One was a continuous and steady diffusion of fluid through the epithelium and the other local accumulations of fluid in the epithelium. The extent of this accumulation varied considerably in the material. It was especially marked in the mucous membrane with leukoedema (Fig. 2, ♀—1), but was also present in samples from several persons with clinically normal mucosa (Fig. 2, ♂—1, ♂—2, ♂—3 and to some extent ♀—5). The corresponding weight values from the cytological series (Fig. 6) indicated that this accumulation of fluid in the mucosa was characteristic of the persons. The increased variation in the material taken with a membrane filter, compared with the corresponding values from human palatal mucosa (*Kaaber,* 1971b), was probably due to an interaction of various factors. The water content remaining in the filters (Table II and VI) represented one. Another factor was the connection between the rate of the water loss and the humidity of the air during sampling (Table IV). A comparison between the values in Table IV and the analogous values obtained from non-glandular palatal mucosa (Table III) demonstrated a consistent increase of 53—57% for the values from the buccal mucosa. This increase

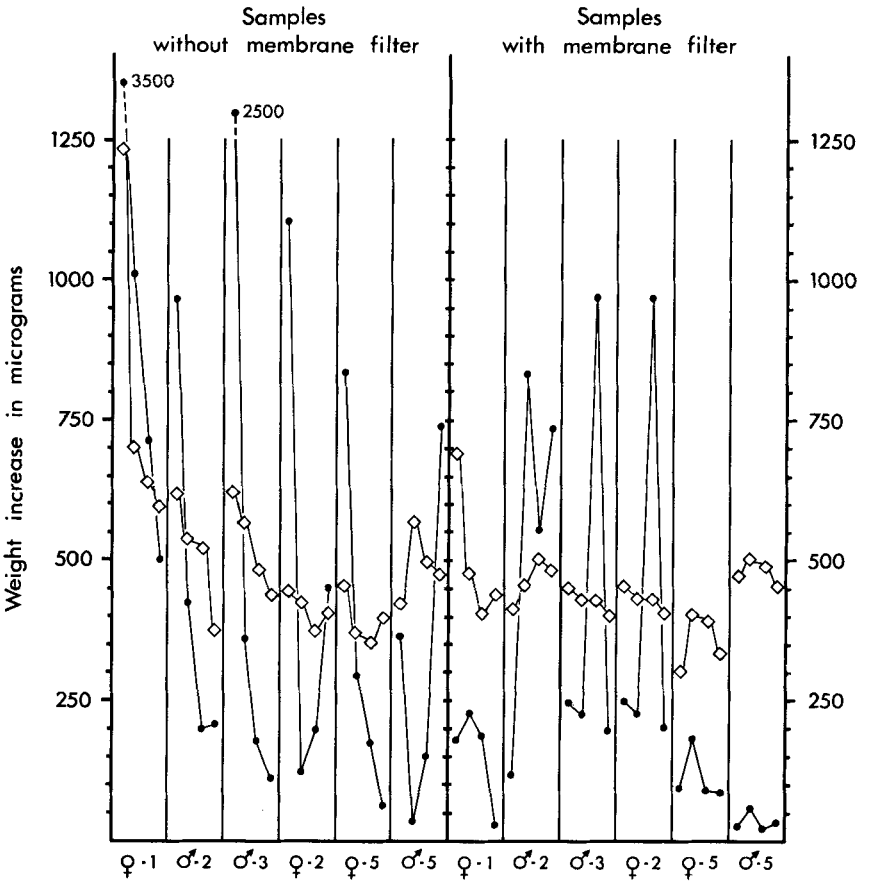

Fig. 6. Relation between the weight increase in samples of filter paper discs and the number of nucleated epithelial cells on the sample surface.

was significant, $p < 0.001$. The strong parallellity between the values from both areas indicated that the diffusion of water through dry buccal epithelium was a linear function of the humidity of the surrounding air, as in the palatal epithelium. Furthermore, the reduced level of the values from the palatal mucosa demonstrated the local significance of the stratum corneum as a diffusion barrier.

The permeability of buccal mucosa to sodium and potassium. The positive correlation in Table VI between the electrolyte and fluid content and the cell counts after direct tissue contact showed that the absorbed fluid accumulations and the cytological contamination were two important factors governing the transfer of electrolytes to the samples. The marked reduction in the

electrolyte content of samples after the use of a membrane filter (Fig. 3) was, however, not accompanied by a corresponding reduction in the number of epithelial cells (Fig. 5). This indicated that the local fluid accumulations in the epithelium were the most important cause of the electrolyte content of the samples. The close agreement between the Na:K ratios in corresponding samples from the two cheeks and the position of the regression line in Fig. 5 indicated that the small amounts of sodium and potassium in those samples which were taken with a membrane filter, in which the increase in weight was primarily due to diffused water, must be regarded as contamination effect, caused during the outward-directed flow of water through the fluid-containing areas of the epithelium. The not inconsiderable number of electrolyte-free samples (Fig. 3 B) emphasized that the non-cornified buccal epithelium acted as an effective barrier against the loss of sodium and potassium from the subepithelial area, apparently as effective as the cornified palatal epithelium (*Kaaber*, 1971b).

The equilibrium between buccal epithelium and saliva. The apparent impermeability of the buccal epithelium to sodium and potassium implied that the electrolyte-containing fluid accumulations in the epithelium originated from the saliva. Their modest size was a clear expression of the presence of an equilibrium between the epithelium and the surrounding saliva. This equilibrium has hitherto not been studied to any extent, in contrast to that between the hard dental tissue and the saliva (cf. *Brudevold, Steadman & Smith*, 1960; *Brudevold & Söremark*, 1967).

The positive correlation between the amount of fluid and cells in samples taken with direct contact with the mucous membrane (Table VII), and the rapidly decreasing weight level with this procedure (Table III) made it likely that these accumulations of fluid were mainly localised extracellularly in the upper epithelial layers. The great amounts of fluid and cells in the samples from the subject with leukoedema supported this. In this condition, the buccal epithelium is characterized by an increased parakeratosis resulting from incomplete desquamation of the superficial epithelial layers (*Sandstead & Love*, 1953; *Archard, Carlson & Stanley*, 1968). The large individual variation in the occurrence of these accumulations with sampling from normal mucosa was more difficult to evaluate. Both light microscopic and electron microscopic studies of normal buccal epithelium (*Zelickson & Hartmann*, 1962; *Hashimoto, di Bella & Shklar*, 1966; *Silverman*, 1967) have established the presence only of small intercellular spaces in the surface layers. Electron microscopic investigations of gingival epithelium seem to show, however, that the width of these spaces varies according to the buffers and fixation media employed (*Schroeder & Theilade*, 1966). The risk of

shrinkage artefacts in histological studies therefore gives rise to considerable uncertainty in evaluation of the physiological structure of the epithelium. Histological studies of frozen sections of gingival epithelium, where this uncertainty is reduced, seem to support the supposition that the saliva has some influence on the surface structure of the epithelium. With this technique a distinct demarcation zone is seen in the epithelium, with distinct differences in cell morphology and permeability reaction in the superficial cell layers (*Schilli*, 1968). Similar histological studies of buccal epithelium are therefore called for to locate the corresponding inductive changes in this type of oral epithelium.

Table V showed that the sodium: potassium ratio with repeated sampling from the same mucosal area was apparently relatively constant in most of the persons. In spite of the absence of similar analyses from the saliva layer on the mucosal surface, it was natural to expect uniform values for the Na:K ratio in the saliva layer and the fluid accumulations in the superficial layers of the epithelium. Earlier observations of unstimulated mixed saliva in a corresponding age group (*Hungerland, Quenzlein & Weber*, 1955) have shown that the ratio between the two electrolytes has a mean value of 0.13. The values in Table V showed in relation to this figure a generally higher sodium content, probably determined by changes in the local content of the mixed saliva. Correspondingly increased sodium concentrations, compared with the content of unstimulated parotid saliva, have been demonstrated on the surface of buccal mucosa (*Wiesmann, Boat & di Sant'Agnese*, 1970). A thorough discussion of the present observations is excluded, however, on account of the imperfect knowledge of the electrolyte content of the secretion from the small mucous salivary glands and their effect on the regional composition of mixed saliva. Systematic study of the secretion from these glands is therefore important for the further study of the equilibrium between the saliva and oral mucosa.

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