Quantitative Studies on Small Lymphocyte Disposition in Epithelial Cells

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ONE of the most important medical problems remaining to be resolved is the function of migratory lymphocytes in the healthy individual, and what these cells actually do during disease.[1] Normally such cells, as we see them in the peripheral blood, constitute 0.5–1.0% of the total lymphoid tissue mass. Taken with their precursors and counterparts in the lymphoid organs and peripheral connective tissues, they constitute a total mass estimated to be 1.0–2.0% of total body weight [2,3]—a mass roughly equivalent to the parenchymal cell mass of the liver. Because of the large mass but relatively small cell size, lymphocytes are probably the most common nucleated cells in the body. Some suggest that they form a reserve of stem cells which, when stimulated, undergo direct transformation into antibody-producing cells or into other types of blood cells.[4–7] Others have suggested they constitute a very labile pool of nutritious substances (trephones), which are reutilized to enhance growth in other cells.[8–12]

In support of the latter concept of lymphocyte function, it has been observed that small lymphocytes normally migrate into the epithelia, including that of the esophagus, intestine, trachea, various glands and their ducts, uterus, oviduct, vagina, ureter and bladder, the tongue, lip, epididymis, and epidermis.[13–14] Moreover, it has been noted that the small lymphocytes enter the individual epithelial cells [10,14] and are found to undergo degenerative changes there.[14] As the numbers involved and the nature of the degenerative changes deserve further study, it is our purpose (1) to present differential counts indicating how many lymphocytes are normally found, and how many show degenerative changes within epithelial cells of selected human tissues; (2) to describe the degenerative changes undergone by these intraepithelial lymphocytes as they appear under the light microscope; and (3) to comment on the significance of our observations.

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Material and Methods of Study

While it is possible to count lymphocytes and nuclear fragments within most of the aforementioned epithelial tissues, within histiocytes of hematopoietic tissues, and within neoplastic cells, specially selected for this study were the mucosal cells of the human jejunum, bronchus, and uterus. These tissues were selected primarily because of their relatively rapid rates of cell renewal under normal conditions* and, secondarily, because of their relative availability in our surgical pathology department.

Surgical specimens obtained by means of Rubin tube biopsy, pulmonary lobectomy, and cervical dilatation and uterine curettage were fixed immediately in 10% neutral buffered formalin or in 2.0% glutaraldehyde, embedded in paraffin, cut in 5-μ sections, and stained with hematoxylin and eosin. Only histologically normal tissue sections were chosen for counting, sections showing any evidence of inflammation, neoplasia, or necrosis being discarded. In Table 1 are given the clinical diagnoses in patients whose tissue sections were chosen for study.

Under oil immersion and at a magnification of 1000 times, 1000 successively encountered mucosal cells were counted in each tissue section. Counts were made only in areas where the mucosal cells could be seen in entire profile with clear attachment to basement membranes. Tangentially cut cells were passed over. Within each 1000 mucosal cells thus counted, the number of intracellular lymphocytes was counted at the same time. These lymphocytes were subdivided into three categories: (1) intact—resembling the majority of the small lymphocytes in the blood, blood-forming organs, and connective tissues (Fig. 1 and 2); (2) ballooning—showing relatively intact nuclear structure, but appreciable swelling of cytoplasm with loss of cytoplasmic markings (Fig. 1, 3, and 4); and (3) degenerate—showing varying stages of nuclear pyknosis and chromatolysis, with or without cytoplasmic ballooning (Fig. 1, 2, 4, 5, 7, and 8).

Observations

In the jejunal mucosa 75 ± 6 intracellular small lymphocytes were found per each one thousand mucosal cells successively encountered (Table 1). Lymphocytes obviously between mucosal cells were not counted. Of the intracellular lymphocytes 45% appeared intact, 11% showed cytoplasmic ballooning, and 44% appeared degenerate. The majority of the lymphocytes were located between the basement membrane and the nuclei of the mucosal cells, as noted previously by Eberth,[17] Andrew and Sosa,[14] and Kelsall and Crabb,[10] who found that 96.4% of the intracellular lymphocytes were located in this region. In counting the mucosal cells from one villus to the next, we included the cells in the crypts of Lieberkuhn, but it seemed that intracellular lymphocytes were more numerous toward the midportions and tips of the villi. The biopsy specimens were obtained after an overnight fast from individuals in whom malabsorption was suspected but not found.

* On the basis of mitotic indexes, the turnover time of jejunal mucosal cells is estimated to be 1.4 days in rats, 1.8 days in mice, and less than a week in humans.[15-16] In rats the turnover time of respiratory mucosal cells is estimated to be 47.6 days.[15] In menstruating women the endometrial mucosal cells are normally renewed at least once a month.

Table 1. Intracellular Lymphocytes per 1000 Mucosal Cells

Diagnoses	Intracellular lymphocytes			
	Intact	Ballooning	Degenerate	Total
		*Jejunum**		
Malabsorption	22	12	33	67
Malabsorption	27	7	30	64
Pancreatic insufficiency	24	7	36	67
Nontropical sprue	31	7	35	73
Nontropical sprue	34	8	35	77
Malabsorption	32	9	33	74
Malabsorption	32	7	35	74
Irritable bowel	33	7	40	80
Malabsorption	42	10	35	87
Pancreatic insufficiency	36	8	31	75
Pancreatic insufficiency	40	9	28	77
Malabsorption	34	8	26	68
Malabsorption	34	10	35	79
Malabsorption	38	7	30	75
Pancreatic insufficiency	41	11	32	84
Malabsorption	40	7	27	74
Range	22–42	7–12	26–40	64–87
Arithmetic mean	33.75	8.38	32.56	74.69
Per cent	45	11	44	100
Standard deviation	5.67	1.63	3.60	6.01
		Bronchus		
Tuberculosis	23	7	14	44
Fibrosis	18	11	17	46
Fibrosis	16	12	14	42
Bronchogenic carcinoma	21	7	20	48
Giant cell carcinoma	22	8	18	48
Bronchogenic carcinoma	25	7	21	53
Squamous cell carcinoma	24	4	19	47
Coin lesion—hamartoma	27	3	22	52
Coin lesion—granuloma	20	6	19	45
Range	16–27	3–12	14–21	42–53
Arithmetic mean	21.77	7.22	18.22	47.22
Per cent	46	15	39	100
Standard deviation	3.26	2.74	2.66	3.36
		Endometrial tissue		
Proliferative	14	5	16	35
Secretory	16	9	12	37
Secretory	9	5	12	26
Secretory	11	4	23	38
Early secretory	11	4	12	27
Secretory	16	8	25	49
Secretory & proliferative	10	4	11	25
Proliferative	18	8	15	41
Range	9–18	4–9	11–23	25–49
Arithmetic mean	13.12	5.88	15.75	34.75
Per cent	38	17	45	100
Standard deviation	3.10	1.96	5.04	7.82

Statistical evaluations were performed by computer.

* In patients whose jejunal mucosa was studied, such diagnoses were suspected, but the patients proved to be normal.

(In freshly sacrificed, healthy guinea pigs, one of us has found that intracellular small lymphocyte counts range from 60 to 120 per 1000 successively encountered jejunal mucosa cells.[18] Some of these animals had been starved for 4 days, and others were feeding freely. Other investigators, studying lizards and toads, have found that the number of intracellular leukocytes appears greater in the fasting state than during the postprandial state.[19])

In bronchi lined by a single layer of columnar epithelium, 47 ± 3 small lymphocytes were found in an intracellular position per 1000 mucosal cells successively encountered (Table 1). Of these lymphocytes, 46% appeared intact, 15% showed cytoplasmic ballooning, and 39% appeared degenerate. Again, the majority of lymphocytes were located in the basal portion of the mucosal cells. The bronchi studied were considered to be histologically normal and were removed from sites as remote as possible from the areas of inflammation or neoplasia for which the lung lobes were resected.

In the endometrium, 35 ± 8 intracellular small lymphocytes were found per 1000 mucosal cells successively encountered (Table 1). Of these lymphocytes, 38% appeared intact, 17% showed cytoplasmic ballooning, and 45% showed degenerative nuclear changes. The distribution of intracellular lymphocytes seemed roughly equal within the superficial and glandular endometrial cells. Again, the majority of lymphocytes appeared basal in location. Although it was noted that the endometrial stroma is normally infiltrated with lymphocytes and that some of these appear to show degenerative nuclear changes similar to those described above (Fig. 3), no attempt was made to assess the percentage of small lymphocytes showing such changes. The endometrial specimens were obtained near the end of the cycle from healthy young women being studied for fertility problems or for functional uterine bleeding. Although some of the specimens were classified as proliferative and some as secretory, no significant difference in intracellular lymphocyte counts was noted in the two phases of the menstrual cycle. However, the number sampled and the time of sampling were not appropriate to ascertain whether there is a significant difference.

In all the sections studied we were impressed, first, by the spectrum of degenerative changes present in the intracellular lymphocytes. In progressive order the changes were as follows:

1. The appearance of vacuoles or clear areas in the thin rim of basophilic cytoplasm surrounding seemingly intact small lymphocyte nuclei (Fig. 1)

2. Loss of cytoplasmic basophilia, loss of visible cytoplasmic struc-

ture, and swelling of cytoplasm extending as a clear halo about the nucleus (Fig. 1, 3, and 4)

3. Increasing swelling and clearing of cytoplasm such that the cell outline appeared two or three times normal diameter, but with a relatively small, central nucleus (Fig. 2 and 3)

4. In conjunction with Changes 2 and 3, variable chromatin condensation, increased affinity for the basic stain, and wrinkling of the nucleus (Fig. 2 and 5)

5. Fragmentation of the nucleus with decreasing basophilia and dispersion of the fragments (Fig. 2, 4, 7, and 8)

6. Loss of cytoplasmic outline and advanced, almost imperceptible fading away of all recognizable nuclear and cytoplasmic structures into the background cytoplasm of the mucosal cells (Fig. 2, 7, and 8)

Lymphocyte nuclei around which no cytoplasmic rim could be seen (despite adjustment of focal plane) were frequent, and presented problems in classification. Such nuclei appeared to undergo the degenerative changes outlined in Points 4–6 above, and were classified accordingly.

Second, we were impressed by the close physical proximity between degenerating intracellular lymphocytes and the nuclei of the mucosal cells (Fig. 1–5). Very few lymphocytes were found in the apical cytoplasm, and few of these showed degenerative changes. Most were found either between the nuclei of the mucosal cells and the basement membrane, or alongside the nuclei. When cytoplasmic ballooning was prominent, the adjacent nuclei of the mucosal cells were often sharply indented (Fig. 3). When advanced nuclear degeneration was prominent, the nuclear remains were close to the nuclei of the mucosal cells. No nuclear fragments were identified at the apical surface of the mucosal cells—a finding mitigating against the extrusion of degenerating nuclear material.

Third, at a frequency of less than one per thousand successively encountered mucosal cells, polymorphonuclear leukocytes were found, apparently within the mucosal cells of the various mucosae studied (Fig. 6). The polymorphonuclears appeared to undergo degenerative changes similar to those of the intracellular lymphocytes, and appeared to do so in a similar intracellular location. Where cytoplasmic morphology was recognizable, the polymorphonuclears appeared to be neutrophils. While eosinophils usually appeared to outnumber neutrophils in the lamina propria of the jejunum, no eosinophils were recognized in the jejunal mucosa.

Finally, no mitotic figures were observed in what we interpreted to be intracellular lymphocytes.

Discussion

Studies of mitotic indexes indicate that the lymphoid organs produce astronomical numbers of small lymphocytes.[2,3,15] Some of the latter and/or their precursors appear to undergo degenerative changes, are ingested by histiocytes, and appear as the tingible bodies in the germinal centers.[20,21] During stress, extraordinarily large numbers of small lymphocytes undergo lysis, and disintegrate in the thymus and in the follicles of other lymphoid organs.[16,22,23] Under normal conditions sufficient numbers of intact small lymphocytes leave the lymphoid organs via the efferent lymphatics to replace the lymphocyte population in the blood two to twelve times daily (depending on the species).[2,5] Comparative cell counts in peripheral, intermediate, and central lymph suggest that most of the lymphocytes entering the bloodstream are newly formed in the lymphoid organs [2] and, therefore, presumably short-lived.[3,15,24] On the other hand, isotopic [24-26] and chromosome marker [27] studies suggest that many small lymphocytes have a prolonged life span and recirculate from lymph to blood, and back to lymph. Some argue that the latter studies can be interpreted to be indicative of prolonged recirculation and quantitative reutilization of labeled nucleotides, or marked DNA, instead of a prolonged life span and recirculation of intact cells.[28-30] At any rate, if the great numbers of small lymphocytes produced in lymphoid organs have a finite life span, whether it be a few hours or hundreds of days, it still remains to be determined what happens to them (or their disintegration products), both within and outside the lymphoid organs.

It seems quite certain that many small lymphocytes disappear within the hematopoietic tissues, wherein the cell turnover rates are among the highest in the body.[15] While many lymphocytes are obviously digested by histiocytes in these tissues, this does not necessarily prove that others do not transform directly into other types of blood cells. As it is generally believed that the parenchymal cells of nonhematopoietic tissues are renewed by homoplastic replication of similar cells, rather than by heteroplastic transformation of lymphocytes,[15,16] the problem of lymphocyte disposition is, perhaps, easier to study here.

Pertinent to the problem of intraepithelial lymphocyte disposition and, also, in support of the trephocyte concept of small lymphocyte function is that Carrel,[31] almost 50 years ago, showed that blood lymphocytes enhance the growth of other types of cells in tissue culture. Kelsall and Crabb [9,10] have reviewed the literature and presented observations to indicate that the small lymphocytes which migrate from lymphoid organs are admirably adapted to transport valuable nutrients, especially DNA, to enhance the growth and replication of other types of

cells. Fichtelius and Diderholm,[32] Bryant,[33] and Craddock, Rytoma, and Nakai [34] have shown that isotope-labeled DNA from transfused lymphocytes is quantitatively incorporated into cells of actively regenerating tissues, such as fibroblasts in healing wounds and proliferating hepatic cells after partial hepatectomy. It is known that small lymphocytes are actively motile within other tissues, and that they are capable of invading other cells by a process which has been called emperipolesis.* [35] Quite recently this motility and invasive capacity have been forcefully demonstrated in a movie sponsored by the American Cancer Society, entitled, "The Embattled Cell." Our microscopic observations indicate that significant numbers of small lymphocytes not only invade other cells, but also disintegrate there under normal conditions. As they disintegrate, they must, in accordance with the laws of conservation of mass and energy, give up their substance to be incorporated within the protoplasm of the other cells, or be excreted from thence. Because of the potential size and complexity of molecules involved, both the manner of incorporation and the mode of excretion merit further study.

While it is possible to estimate how many small lymphocytes normally terminate their existence by giving up their substance within other cells, such an estimate would have little meaning without further knowledge of how long it takes a lymphocyte to disintegrate within another cell, the total number of epithelial and other types of cells wherein the lymphocytes normally disintegrate, and how many lymphocytes are merely observed in the process of passing through.[2,36] Because the migratory lymphocytes are small cells, poor in cytoplasm, but relatively rich in nucleoplasm,[8-10,16] irrespective of what the total number turns out to be, it seems reasonable to suspect that the total contribution of protoplasm will be small—but the contribution of nucleoplasm containing the cellular DNA will prove to be large in terms of biological significance.

Summary

Although lymphocytes are probably the commonest nucleated cells in the body of the healthy individual, and astronomical numbers migrate from the lymphoid organs daily, their function remains to be clarified, both during health and during disease. Pursuant to observations that small lymphocytes invade other cells in a variety of tissues, we have studied the lymphocytes in mucosal cells of normal human jejunum, bronchus, and uterus. In biopsies from these tissues (respectively) 75 ± 6, 47 ± 3, and 35 ± 8 intracellular small lymphocytes were found per 1000 mucosal cells successively encountered. These lymphocytes were usually located between the nuclei and the basal attachment of

* Greek translation: "inside round about wandering."

the mucosal cells. More than half the intracellular lymphocytes showed degenerative changes varying from cytoplasmic swelling, nuclear pyknosis, and chromatolysis to almost complete effacement of all lymphocytic structures within the mucosal cells. Our data support the concept that small lymphocytes normally function as trephocytes within such mucosal cells, and give some indication of how many are terminating their existence there at a given time in relatively healthy humans.

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[*Illustrations follow*]

Legends for Figures

All sections were stained with hematoxylin and eosin.

Fig. 1 *(top).* Jejunum. Five intracellular lymphocytes are located between the nuclei and the basement membrane of the mucosal cells. Two *(A* and *B)* are intact; one *(C)* has an intact nucleus but early ballooning of inferior cytoplasmic rim. A fourth *(D)* also has an intact nucleus but more advanced ballooning of cytoplasm. The fifth *(E)* is degenerate with nuclear pyknosis and advanced cytoplasmic ballooning. × 1700.

Fig. 2 *(bottom).* Jejunum. In the center *(arrow)* is a degenerate lymphocyte with chromatolysis and advanced cytoplasmic ballooning. To the right is an intact lymphocyte in the apical cytoplasm *(small arrow).* × 1700.

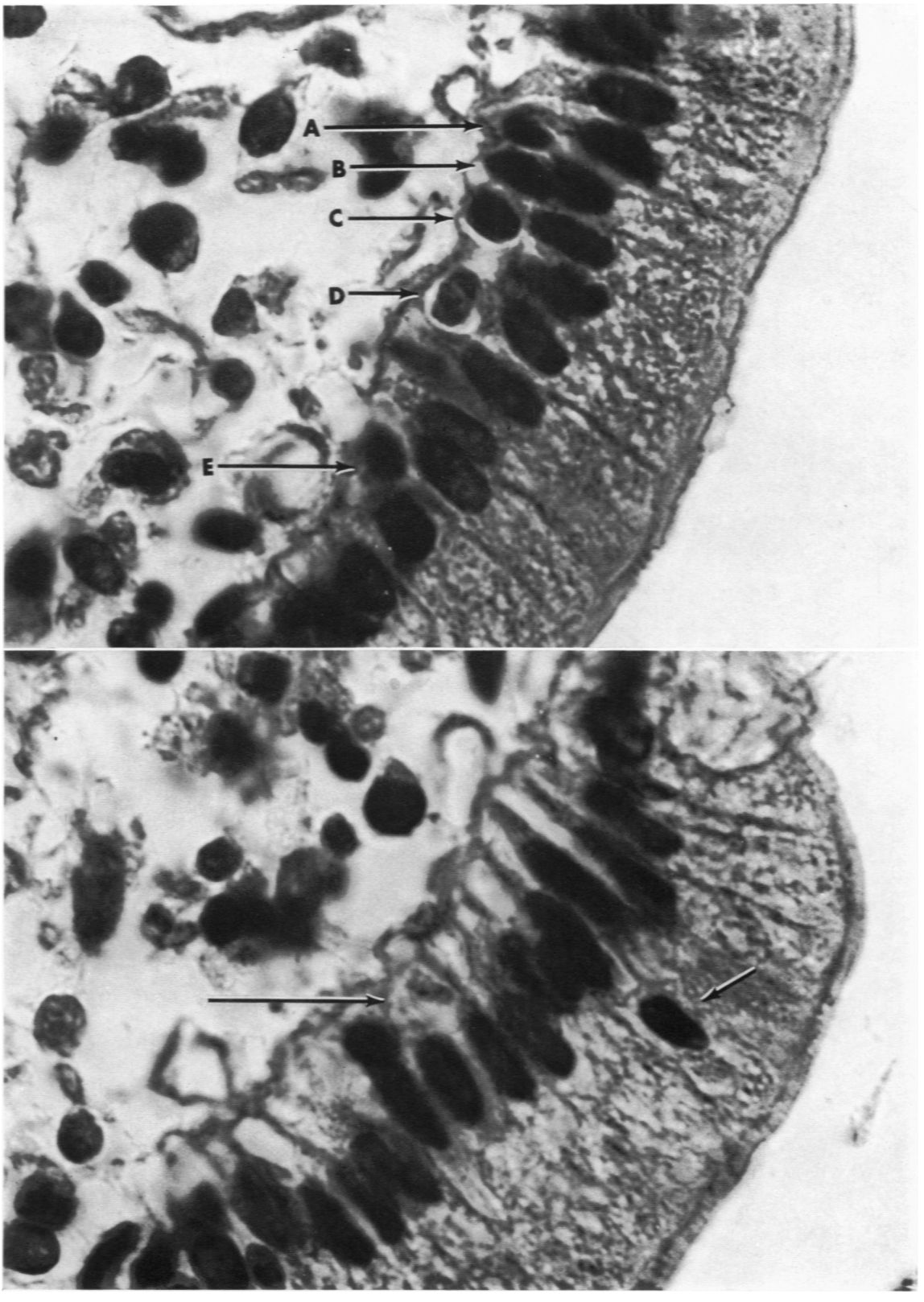
A
B
C
D
E

Fig. 3 *(top).* Endometrial gland. In the center is a basally located lymphocyte with early nuclear pyknosis and advanced cytoplasmic ballooning *(arrow).* In the adjacent stroma *(small arrow)* a small nuclear fragment (? from a lymphocyte) undergoes lysis. × 1700.

Fig. 4 *(bottom).* Endometrial gland, showing several degenerating lymphocytes in the basal cytoplasm of the endometrial mucosa cells. In focus *(arrow)* is a degenerate lymphocyte with chromatolysis, nuclear fragmentation, and advanced cytoplasmic ballooning. × 1700.

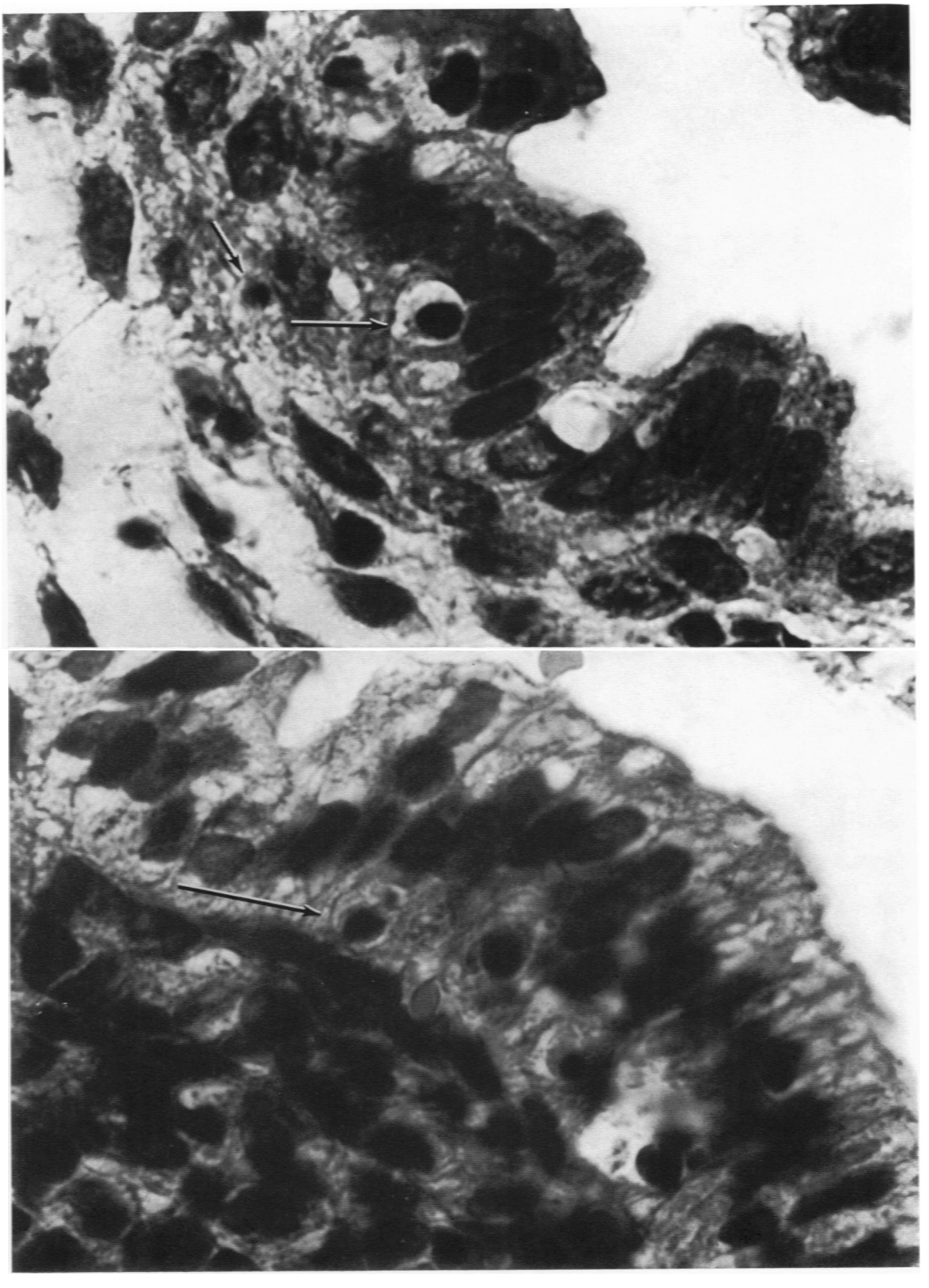

Fig. 5 *(top)*. Surface endometrium. In the basal cytoplasm *(arrow)* is a degenerate lymphocyte with early nuclear pyknosis and practically no surrounding cytoplasm. × 1700.

Fig. 6 *(bottom)*. Surface endometrium. In the basal cytoplasm *(arrow)* is a degenerate polymorphonuclear leukocyte with nuclear pyknosis, chromatolysis, and minimal cytoplasmic ballooning. × 1700.

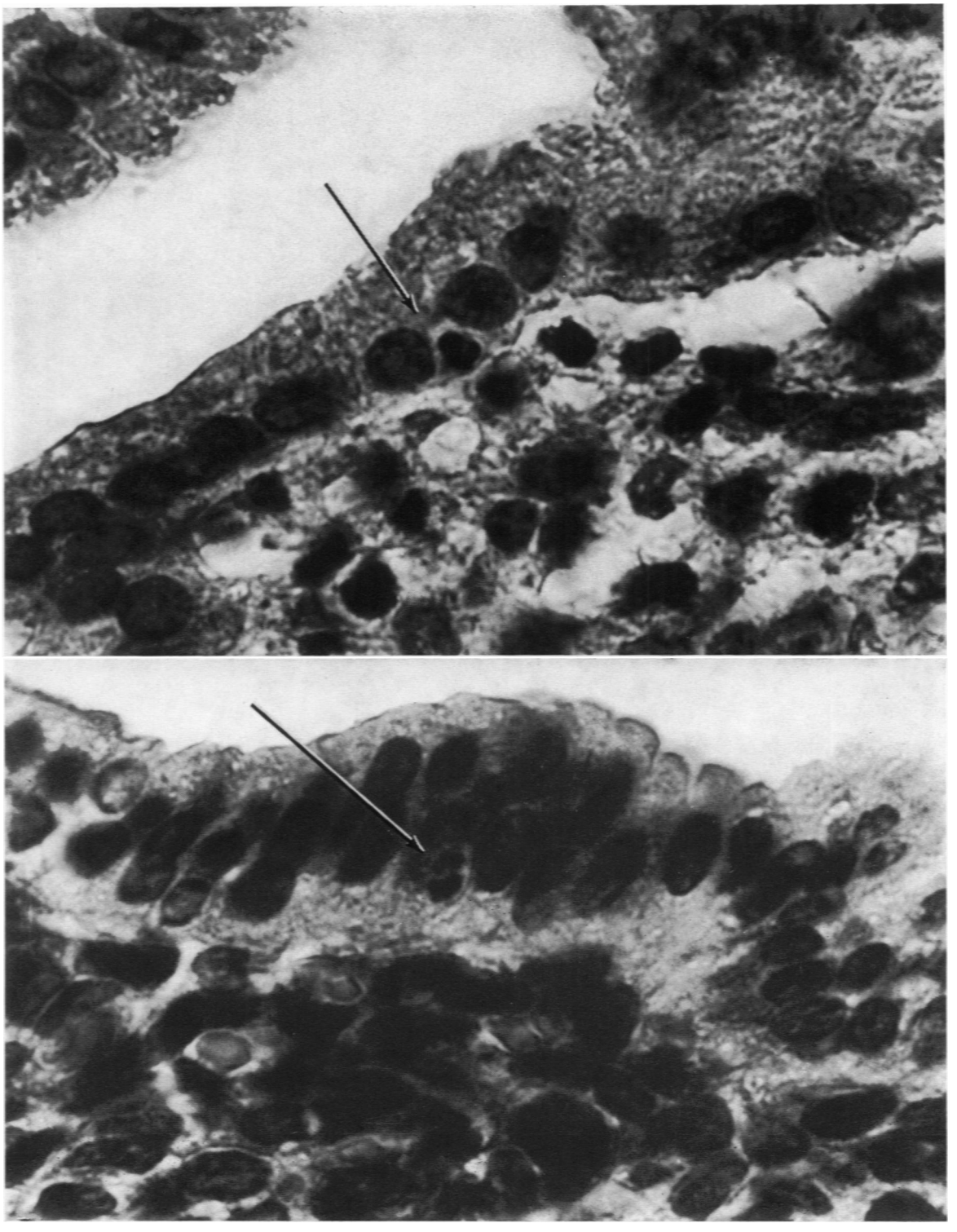

Fig. 7 *(top)* **and 8** *(bottom).* Jejunum. Intracellular lymphocytes in advanced stages of degeneration in the basal cytoplasm of mucosal cells *(arrows).* × 1700.