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FINE STRUCTURE OF THE SMALL INTESTINAL MUCOSA IN INFANTILE MARASMIC MALNUTRITION

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The jejunal mucosa was studied in infantile marasmic malnutrition in the early phase after treatment was begun and before the onset of significant weight gain. In 7 infants light microscopy before recovery showed that the mucosa was normal or mildly abnormal in 4, and moderately abnormal in 3 cases. The electron microscope disclosed abnormalities of the brush border, large autophagosomes and residual bodies, and the deposition of collagen, filaments, and a dense, finely granular material below the basal lamella. Three of the infants were studied again during recovery. Although the histology remained unchanged, electron microscopy revealed improvement of the brush border, disappearance of the autophagosomes, and smaller and fewer residual bodies. The dense material below the basal lamella was absent whereas the fibrillar components remained. It is postulated that the fine structural lesions observed may be due to the derangements in cell metabolism caused by the severe, prolonged restriction of protein and caloric intake.

Marasmus, the most prevalent form of malnutrition in Chile, is frequently associated with gastrointestinal disturbances.[1] The most common and significant of these is diarrhea, a major cause of death from resultant dehydration and abnormalities of acid-base metabolism.[2-3] Malnutrition often precedes the onset of severe diarrheal episodes among infants in underdeveloped countries,[4] and this has been shown to be mainly secondary to colonization of the small intestine by pathogenic bacteria.[5] The gastrointestinal tract of marasmic infants may be prone to infection because of morphologic changes, metabolic disturbances, or local or generalized immunologic defects.[6, 7] Repeated episodes of diarrhea might further aggravate malnutrition and induce deficiencies in brush border enzymes, which could complicate refeeding and recovery of patients.[8-9]

Light microscopic examination among marasmic infants revealed that the mucosa of the small intestine was normal or only slightly damaged.[6] A few children in this study were shown to have moderately severe, nonspecific alterations. Mitotic indices were low, indicating that metabolic disturbances probably existed in the epithelium.[6] The electron microscopic studies reported here were undertaken to extend these histologic observations among children with calorie and protein deprivation. It was hoped that examination of the fine structure of highly differentiated cells with intense and complex metabolic activities might offer clues to the pathogenesis of the gastrointestinal symptomatology encountered in the condition.

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Patients and Methods

Seven marasmic infants with weights at least 40% below that of normal Chilean infants of the same age and sex, and 3 normal infants free of gastrointestinal disease were studied.[10] Four of the malnourished patients were females and 3 were males. At the time of biopsy their ages ranged from 3 to 14 months (table 1). The cause of their malnutrition was prolonged, general underfeeding, with severe restriction in intake of both protein and calories. All had been weaned very early to dilute, half-skimmed milk with or without addition of carbohydrates.

On admission the patients were apathetic and extremely thin, with little or no subcutaneous fat; in some, even Bichat's fat pad had disappeared. Physical examinations and histories revealed none of the stigmata of kwashiorkor (protein-calorie malnutrition)[11-13]: the typical skin and hair changes of that condition were absent, as were signs of edema, ascites, or specific vitamin deficiencies. The livers were not enlarged.

TABLE 1. *Clinical data in 7 marasmic patients*

Patient	Sex	Birth		Conditions on admission					First biopsy		Second biopsy		
		Weight	Length	Age	Weight	Length	Weight, deficit	Length, deficit	Observation period	Weight	Observation period	Weight	Length
		kg	*cm*	*mo*	*kg*	*cm*	%	%	*days*	*kg*	*days*	*kg*	*cm*
F. N.	M	2.700	49	3	3.600	51	43	83	20	3.700			
I. S.	F	3.800	53	6.3	4.100	56	44	89	14	4.200			
J. A.	M	3.380		4	3.360	52	50		20	3.500	121	5.635	60
G. C.	M	2.380	46	14	4.240	54	60	81	9	4.300			
M. G.	F	2.890	49	6	3.250	54	49	86	10	3.300			
J. R.	F	3.800	53	2.3	3.560	55	40	61	6	3.700	73	5.750	61
M. R.	F	3.050	51	6.5	3.140	55	58	73	12	3.200	119	5.220	59

TABLE 2. *Admission laboratory values in 7 marasmic infants*

Patients	Hemoglobin	Hematocrit	Total serum proteins	Serum albumin	Serum carotene	Serum cholesterol
	g/100 ml		*g/100 ml*		*μg/100 ml*	*mg/100 ml*
F. N.	11.3	35	5.6	3.6	58	132
I. S.	11.3	34	6.3	4.1	72	181
J. A.	12.4	35	5.4	3.5	58	152
G. C.	9.3	32	6.7	4.2		126
M. G.	11.7	39	6.0	3.6	158	106
J. R.	10.2	30	5.9	3.4	236	115
M. R.	12.2	34	6.7	3.5	76	124
Normal values	11.6 ± 0.6	33 ± 3	6.5 ± 0.4	3.9 ± 0.4	over 55	146 ± 42

Laboratory tests performed on admission included: serum examinations of fasting blood sugar, protein and serum albumin, carotene, total bilirubin, SGOT, SGPT, blood *p*H, cholesterol, sodium, potassium, chloride, calcium, phosphate, alkaline phosphatase and blood urea nitrogen. Each subject also had a chest radiograph, urinalysis with culture, a search for ova and parasites in three fecal samples, and bidimensional urine chromatograph to determine the pattern of amino acid excretion. All patients 6 months of age or older were tested intradermally with 5 U of tuberculin purified protein derivative. Each patient was weighed daily before the morning feeding. Body length was measured every 15 days using a measuring board.[14]

All infants were hospitalized in closed wards, access to which was restricted to the physicians and nurses. The precautions in the wards were the same as those in a newborn nursery. Before entering the study all patients underwent a period of observation and clinical evaluation that lasted from 6 to 20 days. Infants included in this study were afebrile, did not have diarrhea, and were not receiving any drugs. They were fed a sterilized formula composed of half-skimmed milk (milk provided by the National Health Service, Chile, fat content, 12%) with corn oil added (Mazola, Corn Products of Chile, Llay-Llay, Chile). Boiled water was provided as needed ad lib between feedings.

Patients with severe marasmic malnutrition usually exhibit a characteristic response to refeeding. Their body weights remain stable during an initial period of 1 to several weeks, despite adequate intake of calories and protein. In the ensuing period continuation of the same food intake leads to normal weight gain.[13] In our 7 marasmic patients the first biopsy was taken during the early period when, despite receiving 140 kcal and 3 g of protein per kg per day, their weights remained stable or increased by less than 5 g daily during the week preceding the procedure. Three of these infants were biopsied again 73, 119, and 121 days following the first examination, respectively (table 1). They had been gaining 15 to 25 g of weight daily for at least 3 weeks before the second biopsy.

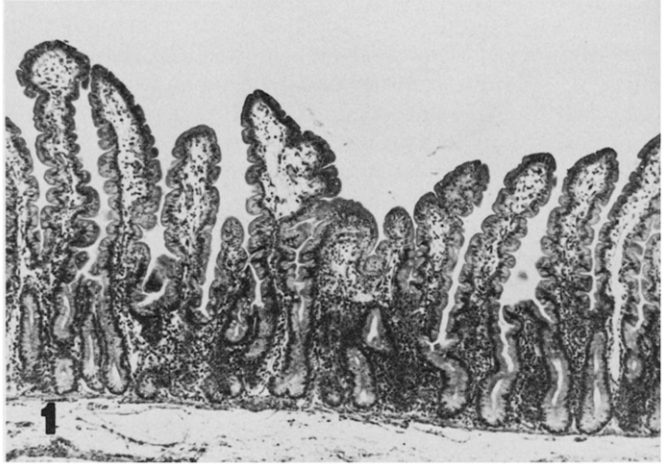


FIG. 1. (M. G.) Normal intestinal mucosa in marasmic infant. The villi are long, thin and with scallopings on the sides. The epithelium is normal and the lamina propria shows a normal cell population. H & E, × 40.

Before biopsy all patients were sedated with pentobarbital after a 4- to 6-hr fast. Samples of mucosa were obtained with a modified multipurpose tube (O. Brunser, personal communication, and reference 15) or with an 8-mm Crosby capsule.[16] The position of the instrument was verified fluoroscopically with an image intensifier. The gonads were protected, and total exposure was limited to 60 sec or less. One sample was fixed for electron microscopy, and the other for light microscopy when the multipurpose tube was used. The piece of tissue retrieved

TABLE 3. *Morphological changes in the intestinal mucosa of marasmic infants*

Patient	Architecture[a]	Thickness (μ)[b] before recovery	Bifurcated microvilli[c]	Short microvilli	Autophago-somes	Residual bodies	Basal deposits	Thickness (μ)[d] during recovery	Large mitochondria
F. N.	N	342	–	+	+	+	+	O	O
I. S.	NSC.	332	+	–	+	+	+	O	O
J. A.	N	401	+	+	+	+	–	457	+
G. C.	NSC.	386	+	+	+	+	+	O	O
M. G.	N	460	+	+	+	–	–	O	O
J. R.	N	346	+	–	–	+	–	409	+
M. R.	NSC.	328	+	+	+	+	+	364	–

[a] N, normal; NSC, non-specific changes.
[b] Mean ± 2 SD = 372 ± 98 μ. Thickness of normal controls: 506 ± 72 μ.[6]
[c] –, absent; +, present.
[d] Mean = 410 μ; O, not examined.

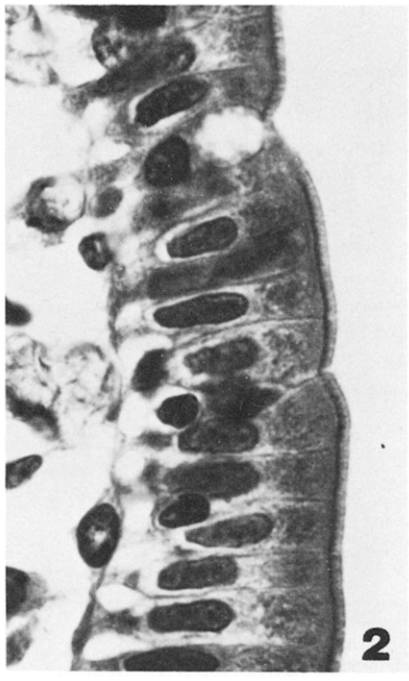


FIG. 2. (M. G.) Higher power view of epithelium from the middle one-third of one of the villi shown in fig. 1. The brush border is normal and the terminal web is clearly visible. Some lymphocytes are present in the interepithelial spaces. H & E × 400.

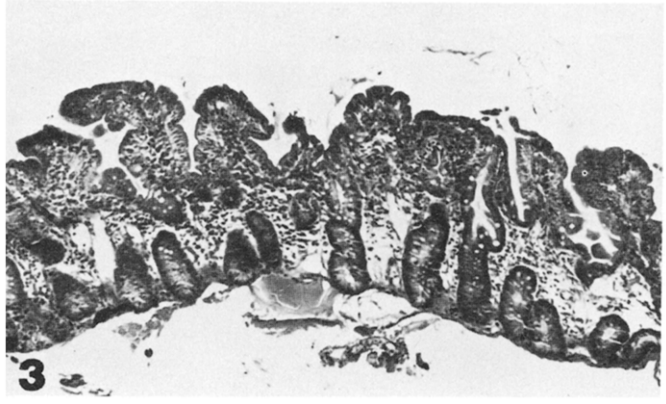


FIG. 3. (I. S.) Biopsy characteristic of the most severe architectural abnormalities found among this group of patients. The villi are shortened and blunted. Shallowness of the biopsy may have contributed to this appearance. H & E × 40.

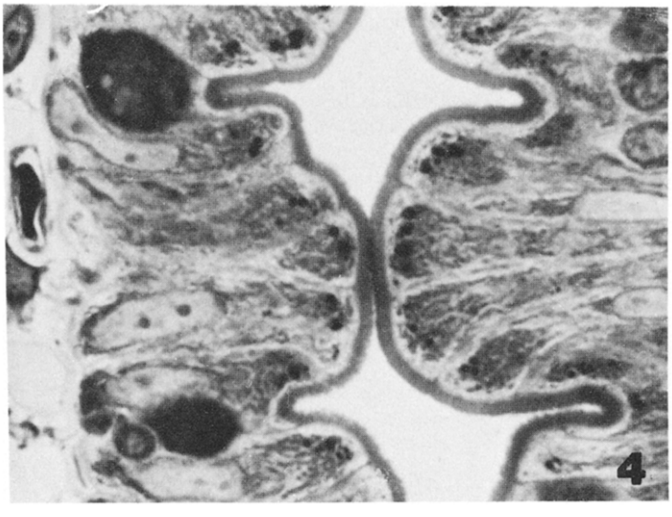


FIG. 4. (G. C.) Higher power of a 1-μ section of Epon-embedded material. Dense bodies of variable size, occasionally up to 2 μ in diameter, are present in almost every cell. All of the other features of the epithelium are normal. Azur II-methylene blue, × 1200.

with the Crosby capsule was divided into two halves for these purposes. Less than 1 min elapsed between actuation of the biopsy mechanism and fixation of the tissue for electron microscopy.

Before fixation, the mucosa was mounted cut side down on Saran monofilament mesh. The tissue was fixed in Bouin's solution, dehydrated, embedded in paraffin, sectioned serially, and stained with hematoxylin and eosin, or with the periodic acid-Schiff reagent for light microscopy. The slides were coded and evaluated blindly. Thickness of the mucosa was measured as reported elsewhere.[6] Tissue prepared for electron microscopy was fixed in bicarbonate-buffered osmium tetroxide[17] for 1 to 3 hr, dehydrated, and embedded in Epon 812.[18] After proper reorientation, the Epon-embedded biopsies were divided and mounted on aluminum rods. One-micron sections obtained with glass knives were stained with Azur II-methylene blue for study by light microscopy.[19] Single, well oriented villi sectioned along their main axes and visible from tip to base were selected and trimmed. Gray sections cut with Du Pont diamond knives on a Reichert Om U2 ultra microtome were collected on Parlodion and carbon-coated grids, stained with

uranyl acetate and lead citrate[20, 21] and studied under a Philips EM-300 electron microscope operated at 60 kv using a 50-μ objective aperture.

Results

Marasmus

The clinical data of the 7 patients selected for this study as typical examples of the most severe, pure form of marasmic malnutrition are detailed in table 1. Their weights varied between 40 and 60% of the ideal for a comparable Chilean population of the same age and sex.[10] Their lengths were from 60 to 89% of what they might have attained had they thrived normally. Values for fasting blood sugar, total bilirubin, blood urea nitrogen, blood *p*H, and serum levels of cholesterol, sodium, potassium, chloride, calcium, phosphate, alkaline phosphatase, GOT, GPT, and carotene were within normal levels for all the infants. No ova or parasites were detected in the stools. The urinalyses were normal in all cases, and the cultures did not grow any pathogens. No abnormalities in the urinary patterns of amino acids were detected. All had normal chest X-rays, and those tested had negative response to injections of 5 U of purified protein derivative. As previously reported for similar patients by our group and by other investigators, hemoglobin concentrations, total serum proteins, and

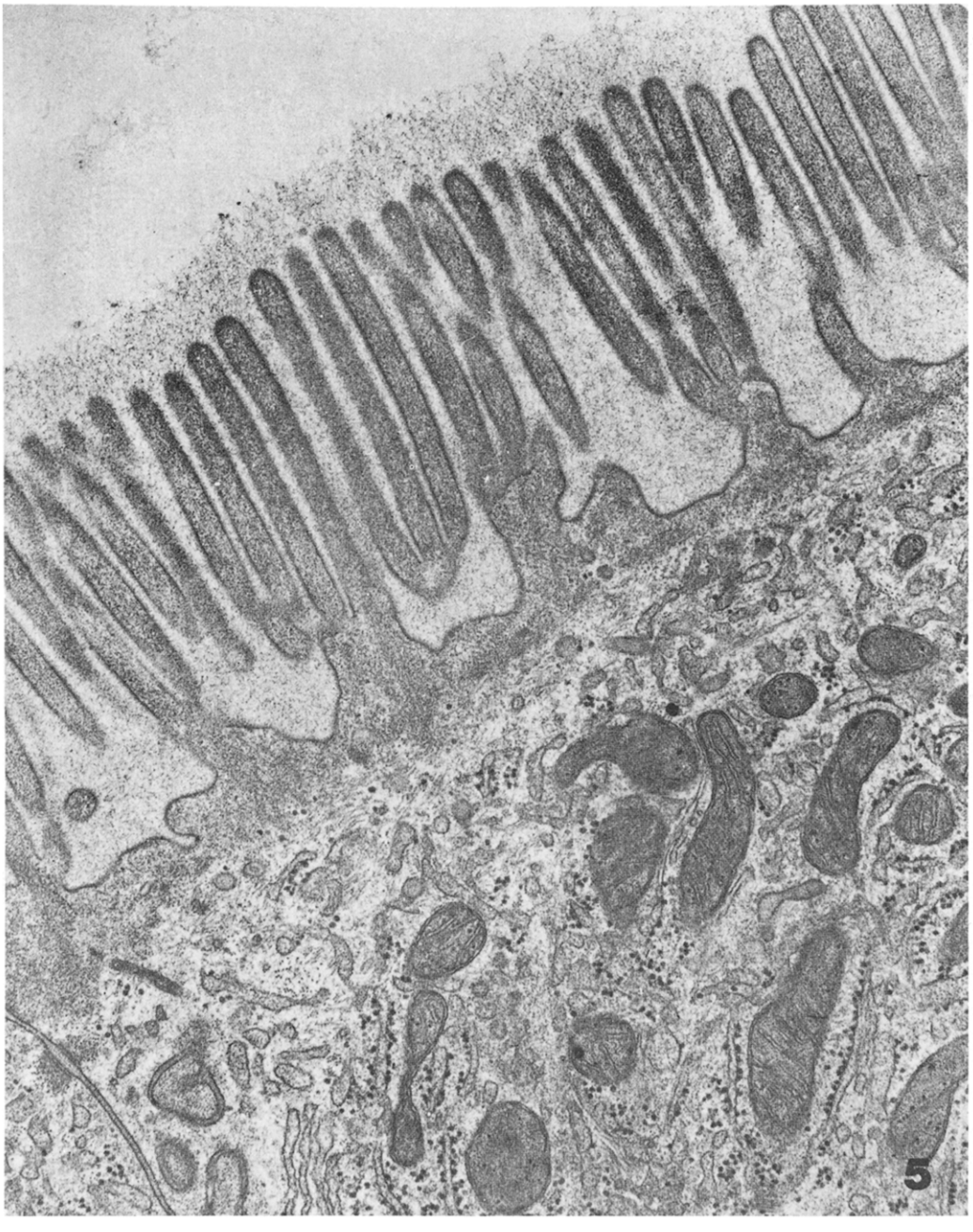


FIG. 5. (G. C.) Brush border composed of groups of two or three microvilli sharing a common base of implantation and separated by rather straight stretches of plasma membrane. × 35,000.

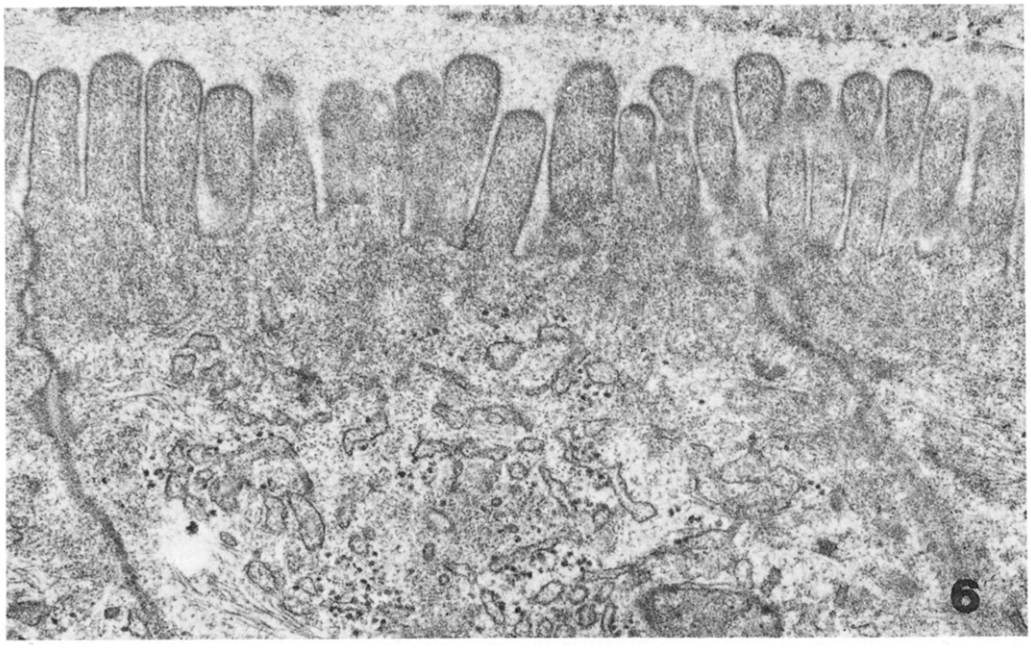


FIG. 6. (M.R.) Short microvilli, measuring about 0.6 μ in length, some probably bifurcated, in the upper one-third of a villus. × 39,000.

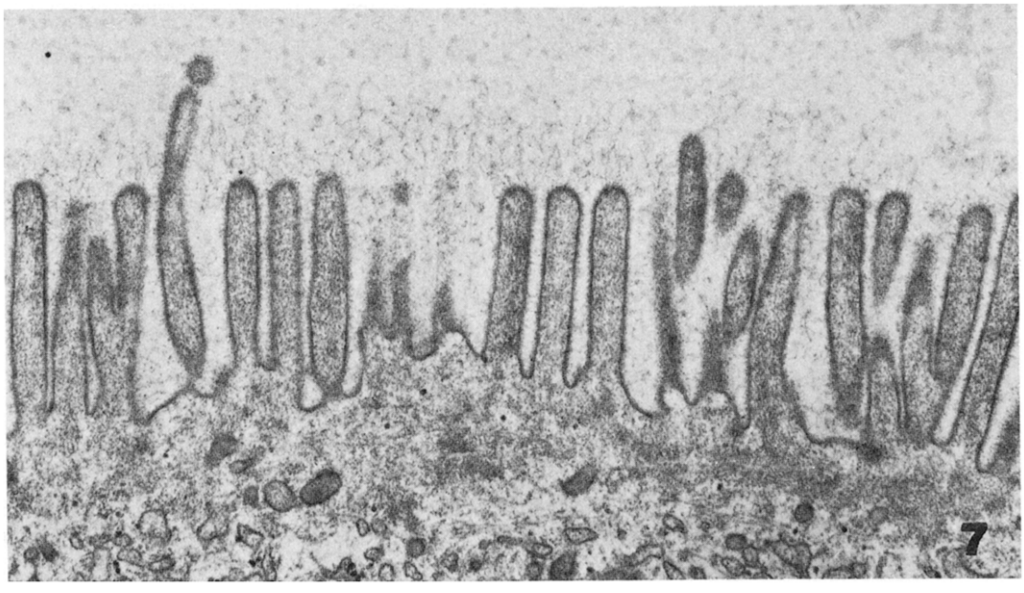


FIG. 7. (F. N.) Sparse microvilli in epithelial cell at the middle one-third of a villus. Some are bifurcated. Their length is variable and some are devoid of glycocalix. × 35,000.

serum albumins were either normal or only slightly lowered (table 2).[1, 12, 13, 22-24]

Light microscopy. During the period in which the 7 marasmic infants showed no weight increase, the mucosae of only 4 were either normal or showed only minimal, nonspecific changes (fig. 1) (table 3). The villi were long and slender and covered by normal epithelial cells with well defined brush borders (fig. 2). Their nuclei were generally located at the same level. Isolated goblet cells were present along the sides of the villi. Among the epithelial cells there were single, scattered lymphocytes. The crypts of Lieberkühn were normal. Normal Paneth cells were located at the bottom of every crypt. The cellularity of the lamina propria was within normal limits.

In 3 patients there were moderate nonspecific changes of the mucosa with some shortening and broadening of the villi, the shapes of which were not as regular as in the first group (fig. 3) (table 3). The crypts of Lieberkühn were slightly elongated. Epithelial height was decreased in some areas, and the cytoplasm was more basophilic than in normal controls. The arrangement of the nuclei was somewhat irregular, and the brush border was thinner. An increased number of lymphocytes and plasma cells was present in the lamina propria.

Stained with periodic acid-Schiff the brush borders,

basement membranes, and contents of the goblet cells gave a positive reaction. Also a few positive granules were observed in some cells of the lamina propria, probably macrophages. The thickness of the mucosa in the 7 malnourished patients varied from 328 to 460 microns (table 3) (mean ± SD = 372 ± 98 μ). All osmium-fixed, Epon-embedded mucosal specimens taken from marasmic infants before the onset of weight gain demonstrated from one to three dark-staining granules of variable size in the supranuclear cytoplasm of almost every epithelial cell, even of those at the bases of the villi. Some measured up to 1.5 μ or greater in diameter (fig. 4). The basement membrane was moderately thickened in the vicinity of the tips of the villi of the three most altered mucosae.

Electron microscopy. The brush border of numerous epithelial cells lining the middle and upper thirds of the villi was made up of groups of three or four microvilli sharing a common base implanted on the cell surface by a short stalk (fig. 5). Separating each stalk from its neighbor was a stretch of plasma membrane from which pinocytotic vesicles sometimes originated. In the upper third of the villus the microvilli were shorter, thicker, and slightly more irregular (fig. 6). A single, very long microvillus occasionally stood out among its neighbors (fig. 7) and was generally devoid of glycocalix. A normal terminal web was present below the brush border and extended laterally towards the zonula adhaerens of the junctional complex (fig. 5). Other cell organelles were of normal appearance (fig. 8).

In the supranuclear cytoplasm of some cells there were large autophagosomes up to 2 μ in diameter. These bodies were limited by a single or double membrane and contained a portion of dense, rather tightly packed cytoplasm, including a few cisternae of the endoplasmic reticulum, ribosomes, and mitochondria. The latter showed degenerative changes of variable intensity: swelling, loss of matriceal density, and rupture of membranes with dispersion of the contents (fig. 9, *a* and *b*). Residual bodies were found in almost every cell. They were more frequent than the autophagosomes and also measured up to 2 μ in diameter. They were limited by a single membrane and their content was finely granular, with some areas of increased density, or they displayed tubular or crystalline-like arrangements (fig. 10, *a* and *b*). The association of myelinoid material, membranes,

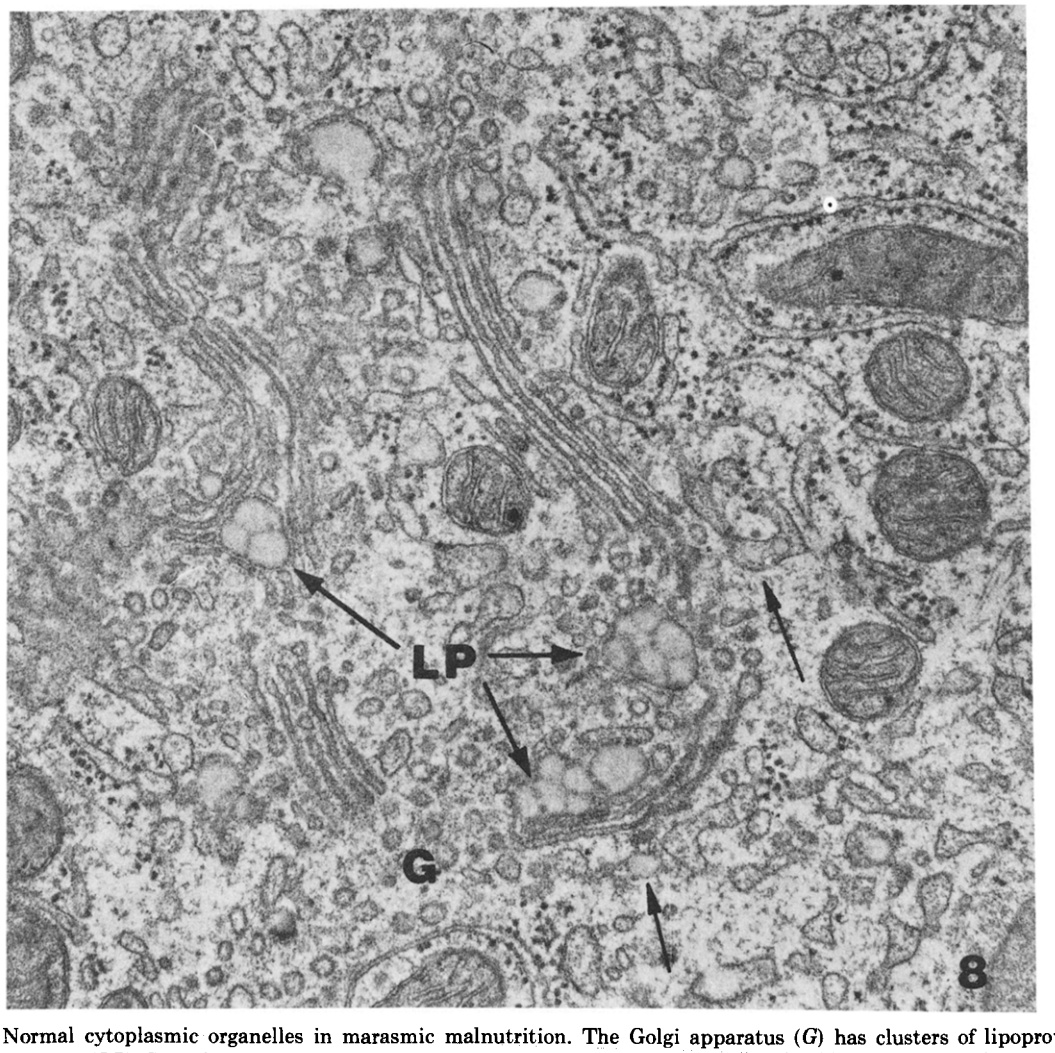


FIG. 8. (J. R.) Normal cytoplasmic organelles in marasmic malnutrition. The Golgi apparatus (*G*) has clusters of lipoprotein particles in relation to its maturing face(*LP*). Some lipoprotein particles are also present in cisternae of the smooth endoplasmic reticulum (*arrows*). × 40,000.

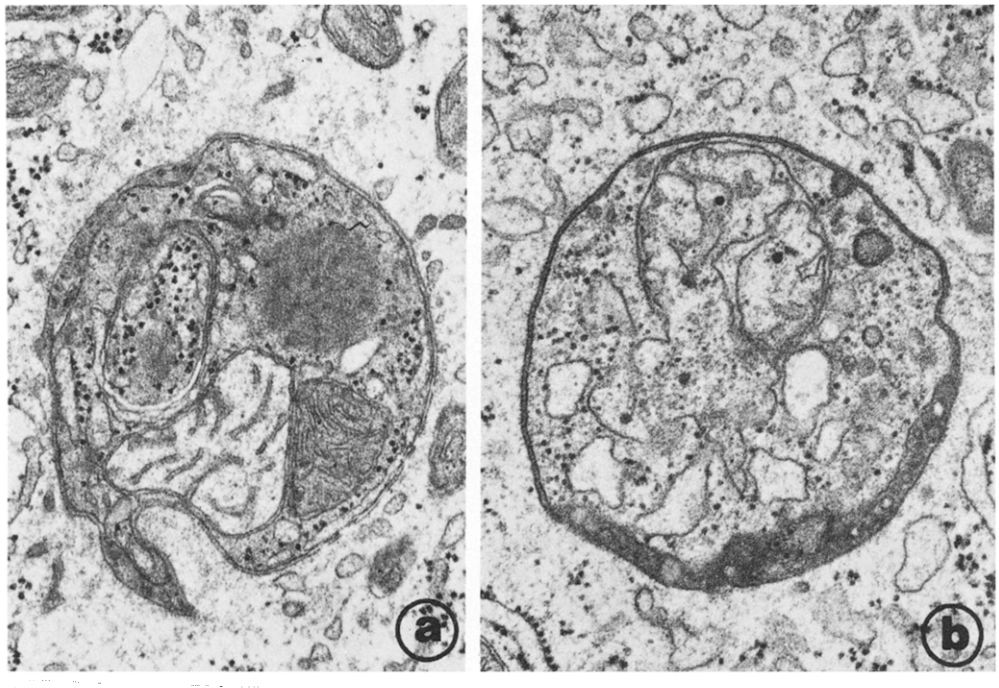


FIG. 9. (F. N.; J. A.) Large autophagosomes, measuring up to 1.8 μ in diameter, in the apical cytoplasm of epithelial cells from the middle one-third of villi. The condensation of the sequestered cytoplasm as well as the progressive degradation of the structures enclosed is evident. × 34,000.

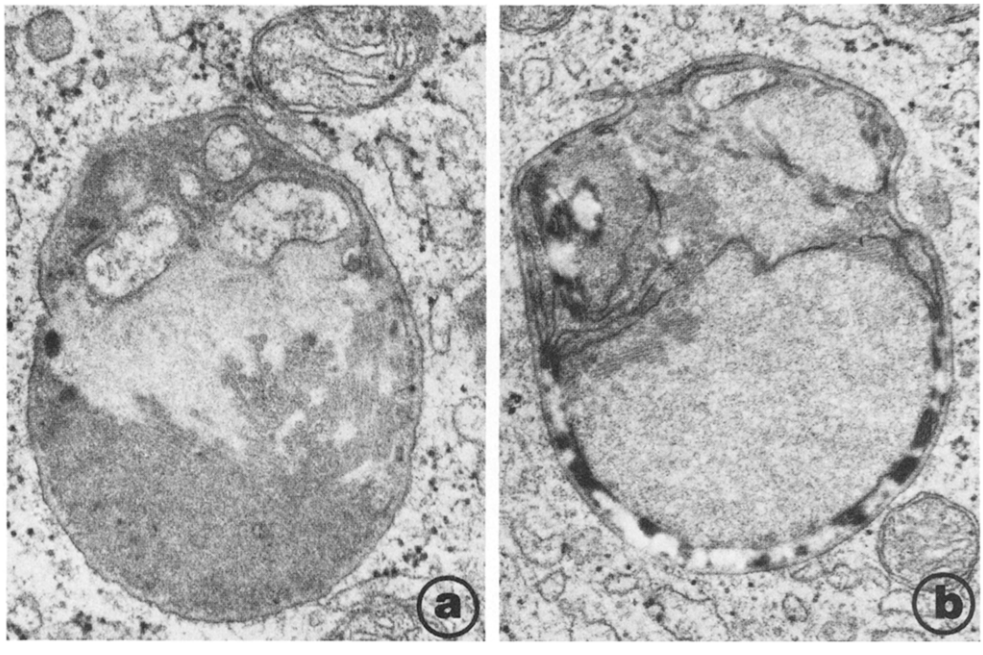


FIG. 10. (G. C.; M. R.) Residual bodies measuring up to 1.5 μ in diameter. Their structures vary and some are quite complex. Crystalline-like arrangements of the contents, whorls of microtubules, and complex arrays of microtubules and membranes are evident. × 45,000.

and tubules gave some of these bodies a very complex structure (fig. 10*a*).

Single lymphocytes were often present between epithelial cells. The epithelium rested on a normal basal lamella with openings through which absorbed material was probably being discharged into the lamina propria. Other openings were seen in relation to the migration of lymphocytes through this structure. Subjacent to the basal lamella, a layer was present in many cases composed of collagen fibers, filaments of about 140 Å in diameter, and dense, finely granular or fibrillar material. This layer was more abundant in the three mucosae with nonspecific changes. It was thin and loose at the base of the villus and increased in density and thickness toward the apex, where it sometimes masked the basal lamella (fig. 11). The collagen fibers, which formed rather thick bundles appeared by contrast as negative images. Fat droplets were sometimes embedded in this complex

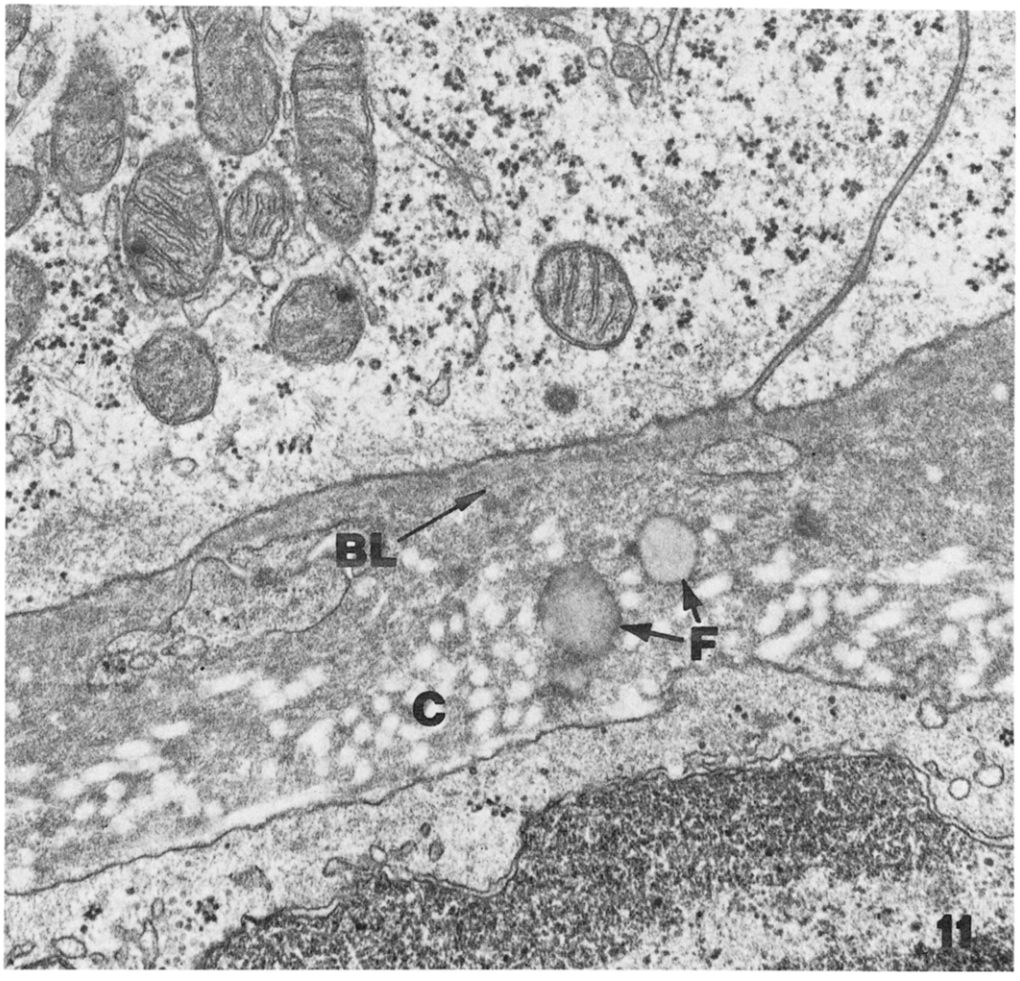


FIG. 11. (F. N.) Base of epithelium in the upper one-third of a villus. The basal lamella (*BL*) is normal but obscured by deposits of dense, finely granular material. Embedded in this material there are collagen fibers (*C*) and some fat droplets (*F*). × 36,000.

structure (fig. 11). The crypt epithelium was similar to that of the controls except that a few autophagosomes and residual bodies were present in some cells close to the junction with the villi.

The lamina propria was populated by plasma cells, lymphocytes, a few granulocytes that were mainly eosinophiles, and an occasional macrophage.

The morphologic findings in the 7 marasmic patients are summarized in table 3.

Recovery

Light microscopy. The thickness of the mucosa increased in all the patients studied: in J. A. from 401 to 451 μ, in J. R. from 346 to 409 μ, and in M. R. from 328 to 364 μ (table 3).

Of the 3 patients studied after the onset of weight gain, the mucosa was normal in 2 and exhibited nonspecific changes although of somewhat lesser severity than at admission in the 3rd. These findings represented no fundamental architectural differences from the previous biopsies taken from the same infants. However, the dense bodies in the supranuclear cytoplasm were somewhat less frequent during recovery from malnutrition.

Electron microscopy. The brush border was either normal or presented only minimal disturbances, i.e., slight irregularities in implantation and a moderate degree of shortening of the microvilli. Autophagosomes were seldom found, and residual bodies were less frequent than in the previous group. Their fine structure remained similar to that observed before recovery. Numerous multivesicular bodies were found in the supranuclear cytoplasm of many cells. The other organelles were normal. However, in two of the cases, the mitochondria in the basal cytoplasm were enlarged and showed an increased number of cristae in some of the cells (fig. 12). The basal lamella was normal. The complex layer beneath the basal lamella was composed of abundant collagen fibers and thin filaments. In some areas it looked as though the collagen had increased. On the other hand, the dense, finely granular material was either absent or scant (fig. 13, *a* and *b*).

Controls

The biopsies from the control infants were considered to be normal by light and electron microscopy. The thickness of the mucosa was within the normal range,

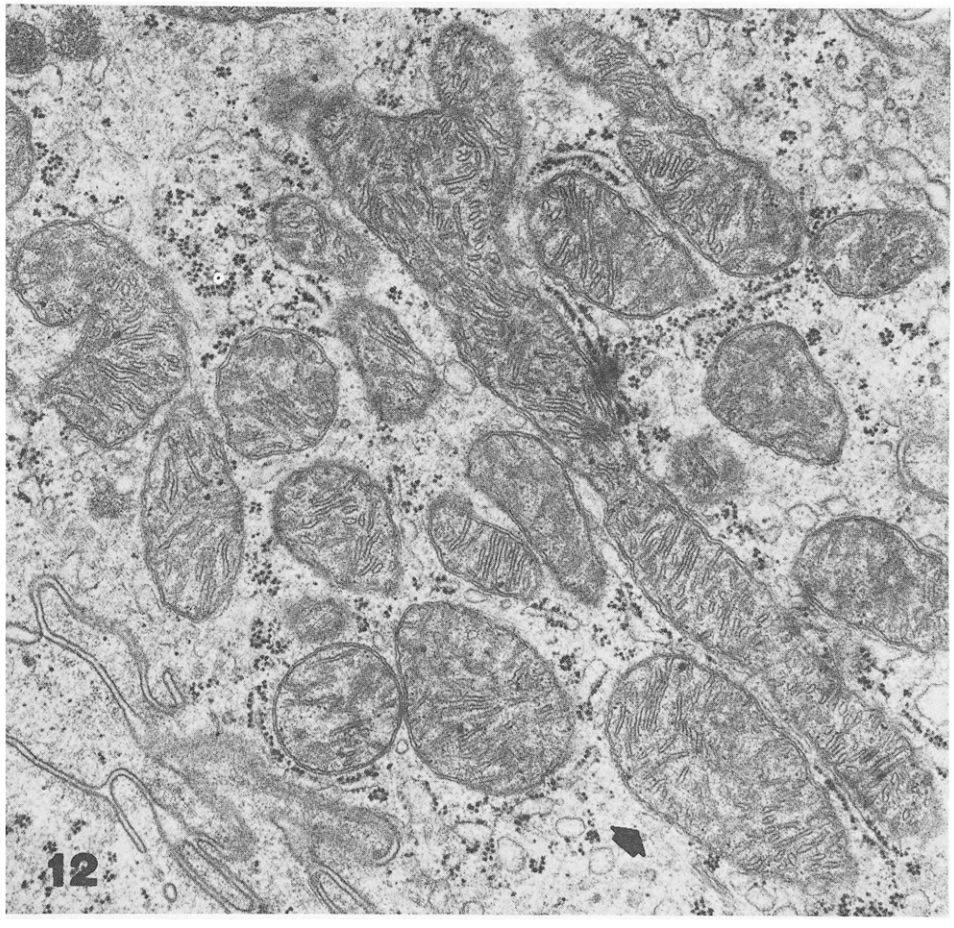


FIG. 12. (J. A.) Large mitochondria in the basal cytoplasm of an epithelial cell from the middle third of a villus during recovery from marasmic malnutrition. The long mitochondrion measures at least 4.8 μ in length while that at the lower right angle (*arrow*) measures at least 0.75 μ in diameter. Their cristae are arranged irregularly and the density of the matrix is normal. × 26,000.

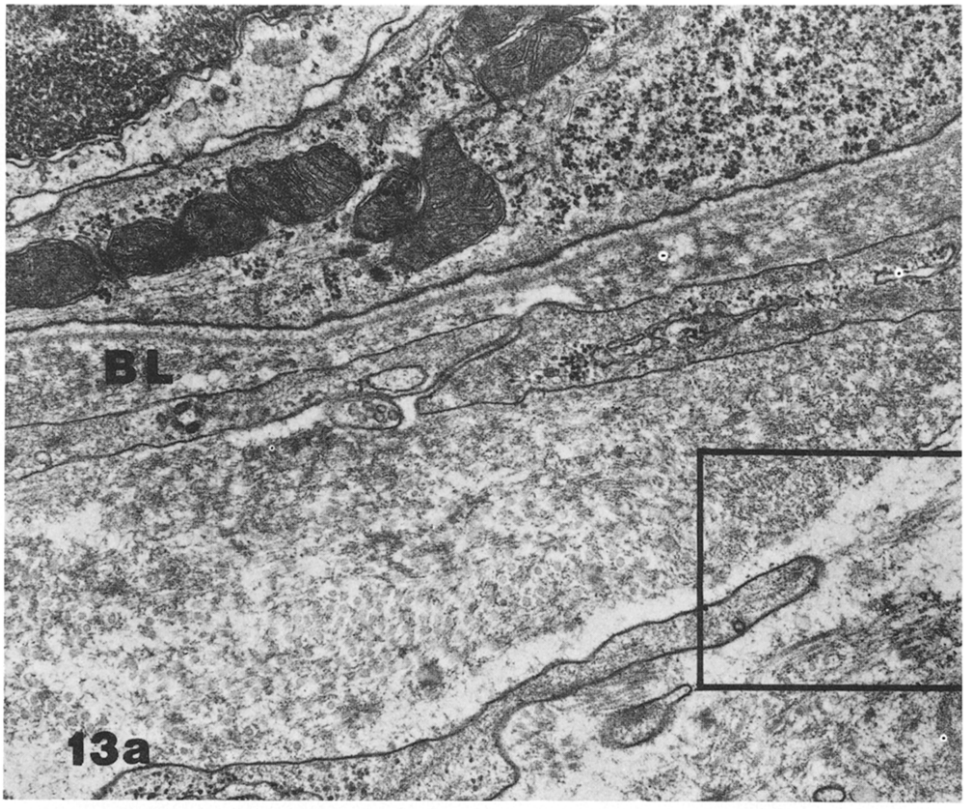
i.e., 506 ± 72 μ.[6] The fine structural changes seen in the marasmic patients were absent. In the cells at the tip of the villi the microvilli were shorter and an occasional one was bifurcated. Multivesicular bodies were frequent, and some small residual bodies were seen. These measured 0.1 to 0.2 μ in diameter. Autophagosomes were exceptional; they were present in cells at the apex of the villi and consisted mainly of a single mitochondrion surrounded by a thin layer of cytoplasm and enclosed by a membrane.

Discussion

Marasmus is the predominant form of infantile malnutrition in Chile.[13] Kwashiorkor (protein-calorie malnutrition) has been effectively eradicated by the massive programs of free milk distribution established years ago by the National Health Service. Marasmus begins very early in life, because a great majority of infants are weaned early and are fed dilute skim milk formulae.[11, 25] As a consequence, it is not unusual to encounter patients whose weights are even less than at birth.

The edema, skin, hair, and mucosal changes characteristic of kwashiorkor are absent in marasmus. Children with the latter condition display almost complete disappearance of subcutaneous fat, and they do not have hepatomegaly nor fatty livers.[11, 12, 22-24] Serum concentrations of hemoglobin, total protein, and of albumin are characteristically normal or only minimally depressed.[23-26]

Kwashiorkor is a relatively acute disease in which the patient improves or dies within weeks of onset of the symptoms. Marasmic infants survive for long periods of time on minimal intakes of calories and protein.[13] It has been postulated that their survival is due to adaptive mechanisms mediated by the hypophysis and probably regulated by the hypothalamus.[11, 27-29] These mechanisms may reduce the requirements of nutrients to minimal levels. Following institution of normal food intake, recovery is delayed, presumably because of the time required for the endocrine glands and peripheral tissues to return to normal levels of metabolic activity.[13, 29] While the infants remain malnourished, and during the phase in which their weights remain more or less stable despite treatment, many succumb to intercurrent diseases.[3] Therefore, factors other than malnutrition may intervene to some extent in the genesis of morphologic and functional changes. Among these, enteric infection by bacteria or viruses occurring prior to admission may be of importance.[30] It was this problem



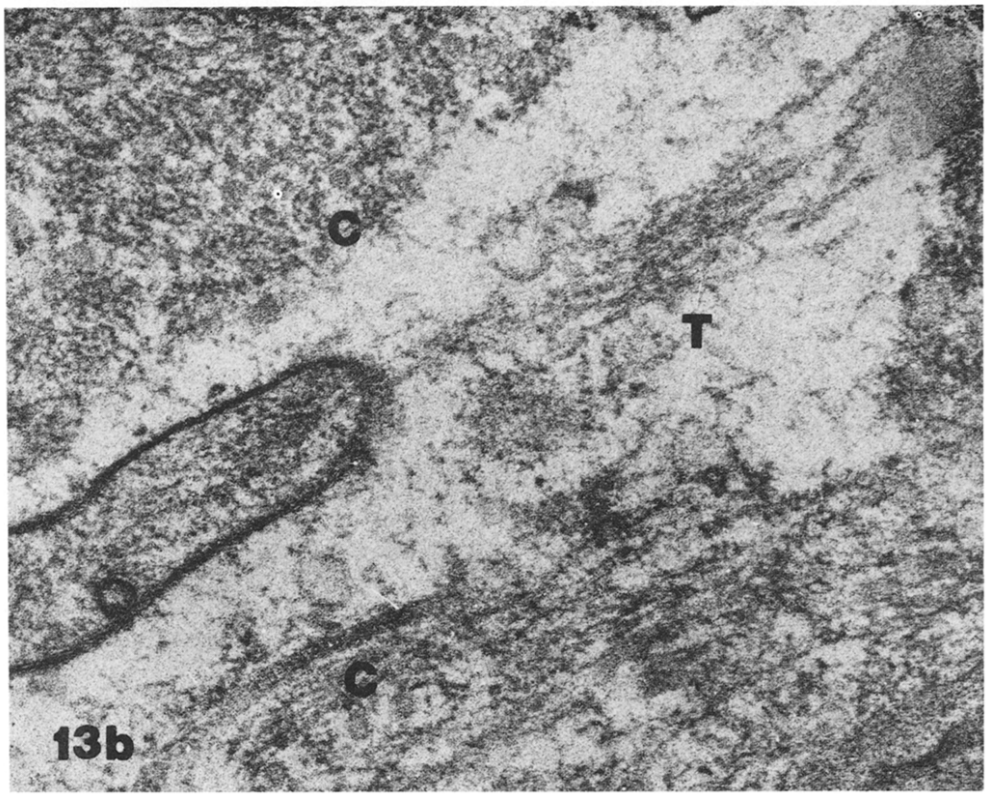


FIG. 13. *a* (J. R.) Base of epithelium from the middle one-third of a villus in a marasmic patient during recovery. The basal lamella (*BL*) is normal. Beneath it there are thin filaments approximately 140 Å in diameter, and large numbers of collagen fibers sectioned transversally and longitudinally. × 25,000. *b*, higher magnification of the area enclosed in fig. 13*a*. The collagen fibers (*C*) and the thin filaments (*T*) are shown more clearly. The moderately dense, homogeneous mass in the *right upper corner* is probably fat. × 81,000.

that initially led to our light microscopy studies of the structure of the small intestine during marasmus.[6] These are supplemented by the current observations with the electron microscope.

The 7 patients reported here were selected because they represented marasmic malnutrition in as pure a form as could be found, and because they fulfilled all the diagnostic criteria for this condition. It is possible that the adequate amount of calories and protein and the clean environment provided for about 1 week prior to the biopsy may have induced some modifications in the small intestinal milieu, and that this in turn may have been reflected in the mucosal morphology. The solution to this problem would have required that the biopsies were obtained under "field" conditions, in an unselected malnourished population. This, however, would have necessitated examination of a large number of infants, exposing them unnecessarily to irradiation. It would have been costly and inefficient and might have introduced a selection bias.

The histology of the intestinal mucosa in these patients was similar to that reported earlier.[6] It is apparent, however, that even when the mucosa looked normal after processing by conventional histological techniques, the higher resolution obtained by fixation in osmium, embedding in Epon, and sectioning at 1 μ revealed definite changes. The larger bodies, seen in practically every cell with the latter technique, were identified as autophagosomes and residual bodies by electron microscopy. Their presence in the epithelial cells at the opening of the crypts and at the base of the villi suggests that the effects of marasmus on these cells occurred very early in their life span, probably in the crypts of Lieberkühn.

Light microscopy also disclosed thickening of the basement membrane in the distal portions of the villi, resembling that seen in celiac sprue and in tropical sprue.[31, 32]

With the electron microscope the brush border of the epithelial cells was damaged. In normal controls it consists of tightly packed microvilli of similar thickness and length which are only moderately shortened in a few cells at the very apex of the villus.[33] The branched, shortened, and sparse microvilli seen in the marasmic infants whose weights were stable, probably represented another manifestation of deranged metabolic processes which resulted from prolonged restriction of food. A possible parallel may be cited: when protein synthesis is blocked in chicken by chemical inhibitors the brush borders of the intestinal epithelium exhibit changes similar to those here described.[34] It may be presumed that because it is a very complex structure with a high protein content and a high turnover rate, the brush border in certain species may be particularly vulnerable to low protein availability.[35] Moreover, the activity of the disaccharidases is reported to be decreased in these animals.[34] This may parallel the low levels of lactase and sucrase that have been demonstrated in marasmic infants by González et al.[8] and by Berkel et al.[36]

Portions of the cytoplasm of the epithelial cells become segregated in large autophagosomes. The organelles enclosed with the autophagosomes undergo morphological changes due to anoxia, lack of substrate, and degradation by lysosomal enzymes.[37-41] As a consequence of these processes some of the structures are broken down, the resultant material may become available for cell metabolism.[38] Autophagosomes have been reported in the epithelium of the small intestine following radiation damage and administration of folate antagonists leading to sublethal injury.[42-44] They have been demonstrated in the rat liver and intestine during partial or total starvation[44-46] and have been shown to disappear when normal food intake was restored.[47] A similar degree of injury may have occurred in the small intestinal epithelium as a consequence of marasmus as demonstrated by our finding of large autophagosomes in our patients. Some of the structures enclosed in the autophagosomes cannot be digested, so that voluminous and complex residual bodies result.[38, 39, 41]

Collagen is frequently found in the lamina propria of normal subjects in the form of isolated fibers. In addition, occasional fibrils about 140 Å in diameter may be seen. In the marasmic infants described here one encounters much denser deposits of collagen. Accumulation of collagen in increased amounts also occurs in a disease characterized by severe malabsorption as described by Schein and by Hourihane which does not appear to bear any relationship to marasmus.[48, 49] Dense collagen accumulations below the basal lamella have also been described in celiac sprue[50] and in tropical sprue.[51]

In addition to the dense collagen our patients showed accumulations of an unidentified finely granular material below the basal lamella of the epithelium. This material increases in amount from the base to the tip of the villus. Deposits with the same appearance have been described in celiac sprue[50] and in tropical sprue.[51] In other organs such as the kidney, the thyroid, and the bronchial tree, deposits with similar morphological characteristics appear in conditions whose common denominator is the occurrence of antigen-antibody reactions in the vicinity of the epithelium.[52-55]

As the patients recovered, the fine structure of the intestinal mucosa tended to revert toward normal. The microvilli showed a more regular implantation and increased in length. Autophagosomes were infrequent, and the number and size of residual bodies were reduced. Although the collagen fibers and the thin filaments persisted in amounts comparable to those observed before recovery, the dense, finely granular material disappeared almost completely. With the light microscope the architecture of the small intestinal mucosa did not change dramatically in the only patient who had nonspecific changes, and that was studied again after 120 days of adequate diet. It is not known whether a more prolonged period of optimal feeding would have lead to the return to normalcy. Another point that awaits elucidation is the potential role of this previous episode of marasmus on other forms of pathology that may affect the small intestinal mucosa of these patients later in life.

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