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CHANGES IN THE LIVER AND PANCREAS IN KWASHIORKOR WITH REFERENCE TO THE ROLE OF ANTECEDENT INFECTIONS AND INFESTATIONS

NEVIN S. SCRIMSHAW, Ph.D., M.D., CARLOS TEJADA, M.D., GUILLERMO ARROYAVE, Ph.D., AND MOISÉS BÉHAR, M.D.

From the Institute of Nutrition of Central America and Panama, Guatemala City, Guatemala

Children developing kwashiorkor have dietary intakes which are simultaneously deficient in the amount and quality of protein and in the porportion of protein to the caloric intake.[1-3] Not only does dietary treatment with milk alone bring about the prompt improvement of major signs and symptoms, but also vitamin-free casein or even mixtures of synthetic amino acids will have this effect.[4, 5]

It is noteworthy, however, that even in areas in which kwashiorkor is prevalent, only relatively few of the children consuming deficient diets develop acute clinical kwashiorkor. Of course this variation in individual resistance to stress, whether metabolic or infectious, is characteristic of all diseases. But careful examination of the medical histories of children with kwashiorkor, in some areas at least, has revealed that a very large proportion of the children admitted to the hospital with kwashoirkor have a history of diarrheal disease or other apparently acute infectious process occurring a few days or weeks before the onset of the edema and other clinical signs.[3, 6] This had quite naturally led to efforts to determine the role of infection in precipitating kwashiorkor in children who might not otherwise have developed the clinical syndrome. Of 88 cases which have been studied in detail by the Institute of Nutrition of Central America and Panama, 66 per cent had episodes in their medical history which were suggestive of diarrhea of infectious origin and a few had other acute infections.

By chance one of the children who had recovered from kwashiorkor developed diarrhea while on a metabolic balance period with milk. In a previous balance the child had shown a nitrogen retention of 240 mg. per kg. per day, a total of 27.1 per cent of the quantity ingested.[7] During one day of mild diarrhea this dropped to −6 mg. per kg. per day, which was −1 per cent of the nitrogen consumed. During the succeeding four days, when the stools were loose but frank diarrhea was no longer present, the daily nitrogen retention averaged 28 mg. per kg., or 4.6 per cent of the total consumed. Only after the stools had again become normal did the amount retained rise to 150 mg. per kg. per day, or 33.1 per cent of the total nitrogen intake. While these data involve only one case and the protein intake varied from one period to another, they are extremely suggestive. One cannot avoid speculating on the duration and severity of the period of negative nitrogen retention and the magnitude of the total nitrogen loss which might have occurred if the diarrhea had been of the severe and extended type so common among Central American children. Furthermore, it is a common observation that the recovery of children with kwashiorkor is retarded as long as the diarrhea persists.

It would also be desirable to know whether only intestinal infections have this sort of effect or whether childhood diseases and other systematic infections affect nitrogen retention in a similar manner. We have recently obtained some evidence on this point. Two children on metabolic trials with various diets showed marked decreases in nitrogen retention during fever associated with the prodromal and early acute phase of measles. The actual retention changes were from 12 per cent to −4 per cent and from 15 per cent to 0 per cent. Platt[8] also cites published reports of the adverse effects on nitrogen metabolism of acute infections[9, 10] and even convalescence from infections.[11]

Another approach to the problem is to determine the prevalence of major enteric

pathogens in those populations from which most cases of kwashiorkor come. For the past two years a group of 12 villages selected to represent the major geographic and cultural variations among Guatemalan rural populations in which kwashiorkor is prevalent have been visited every two months and all available children up to 12 years of age are examined by rectal swab for Salmonella and Shigella. The results indicate that approximately 7.5 per cent of all apparently well children in rurual communities harbor Shigella and 0.6 per cent, Salmonella.[12]

More pertinent is the evidence that clinical diarrhea is common in populations of this type. In two towns in the Guatemalan highlands, trained field workers visited each family every two weeks during a period of

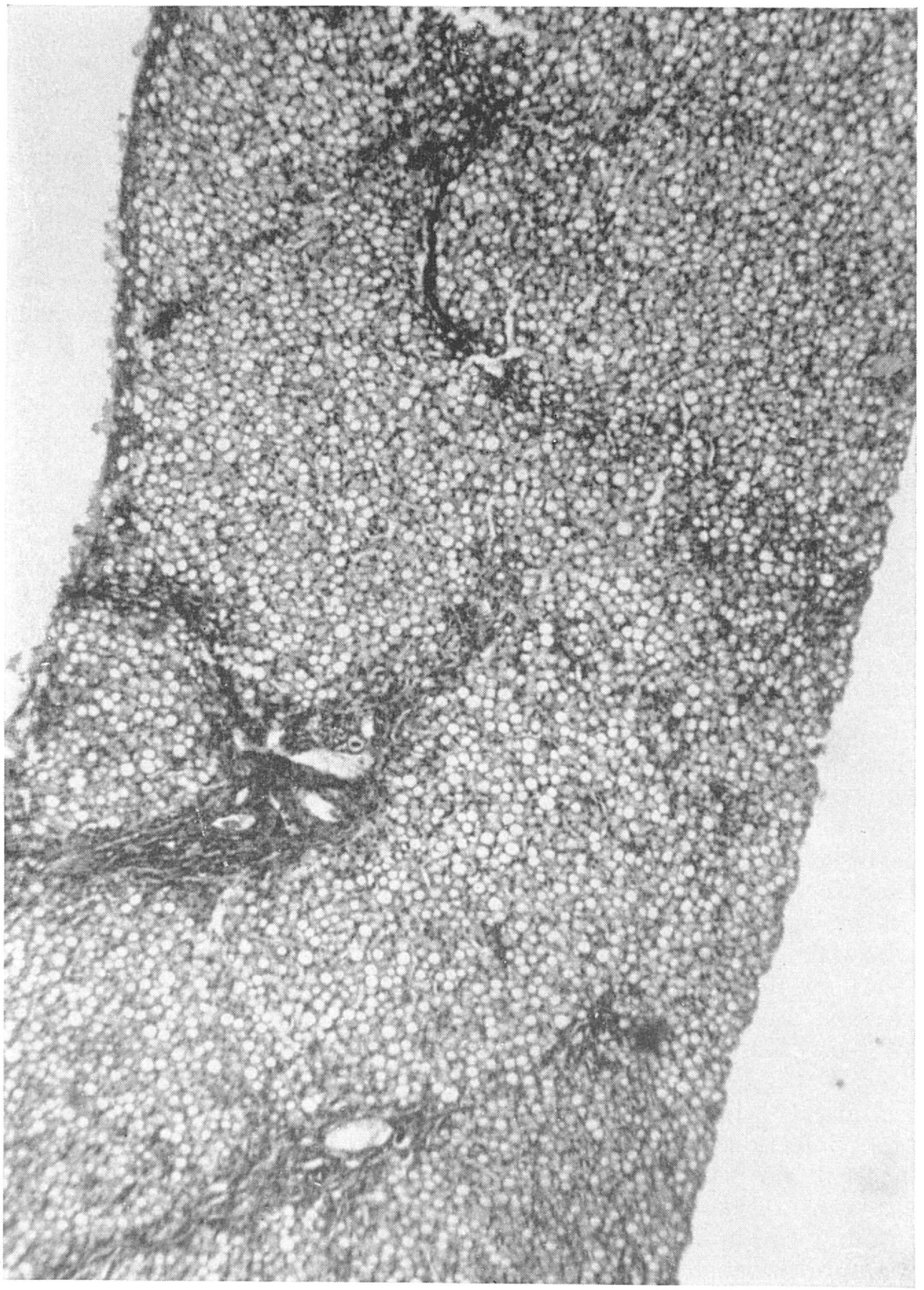

FIG. 1. Liver from a child with kwashiorkor. Fat fills each hepatic cell and gives to the liver a honeycomb appearance (H & E, × 30).

12 months to learn of the occurrence of diarrhea in children. The percentage of children under 5 years of age having clinical diarrhea at any given time was 5 per cent, and 23 per cent of the children in this age group in the villages had three or more episodes during the year. Furthermore, a single episode of diarrhea frequently lasted for two weeks or more. In a few cases it has been possible to follow the same child through one or more episodes of chronic diarrhea and to observe the subsequent development of

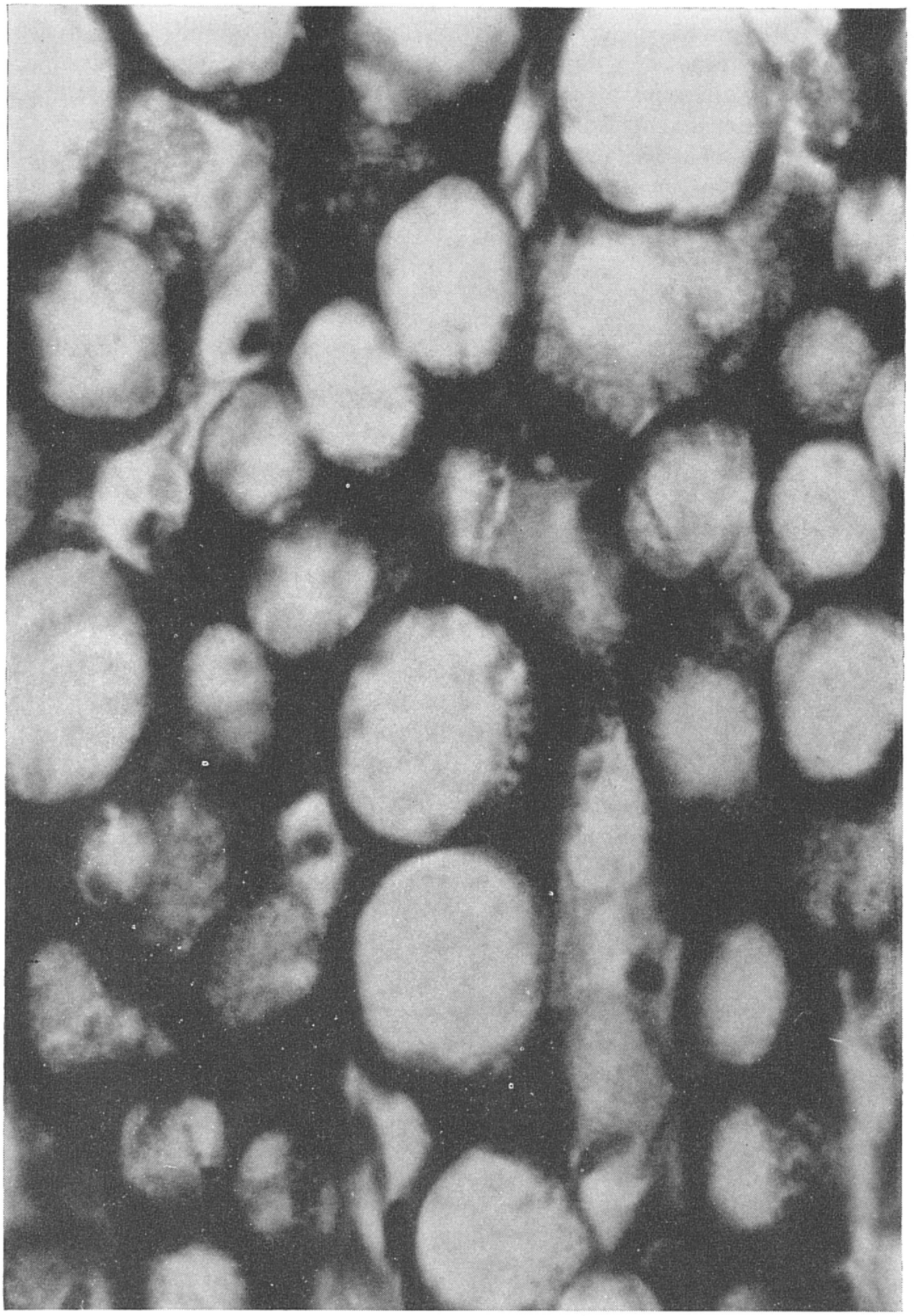

FIG. 2. Liver from a child with kwashiorkor. The cytoplasm of the hepatic cell is forced to the periphery and glycogen is diminished (PAS, × 400).

clinical kwashiorkor. Obviously, more longitudinal studies of this nature are badly needed.

Workers in India[13] have shown a marked decrease in nitrogen excretion in the feces after treatment of persons for heavy infestations of ascaris. There is little additional evidence, however, to link the high prevalence of intestinal parasitism in cases of kwashiorkor with the etiopathogenesis of the syndrome since parasitic infestation is no more common in these cases than in the general population from which they come. This statement also applies to the occurrence of eosinophils in the liver and portal spaces in approximately one-third of kwashiorkor cases coming to autopsy in Central America. Of 18 children admitted with kwashiorkor who did not appear to have intestinal parasites, only 1 showed similar eosinophilia.

Pathologic Changes in the Liver

The livers of children dying with acute kwashiorkor are yellow and friable, and the normal lobulation is obscured. Histologically, fat fills each cell and gives the liver a honeycomb appearance (fig. 1). The nucleus and remaining cytoplasm are forced to

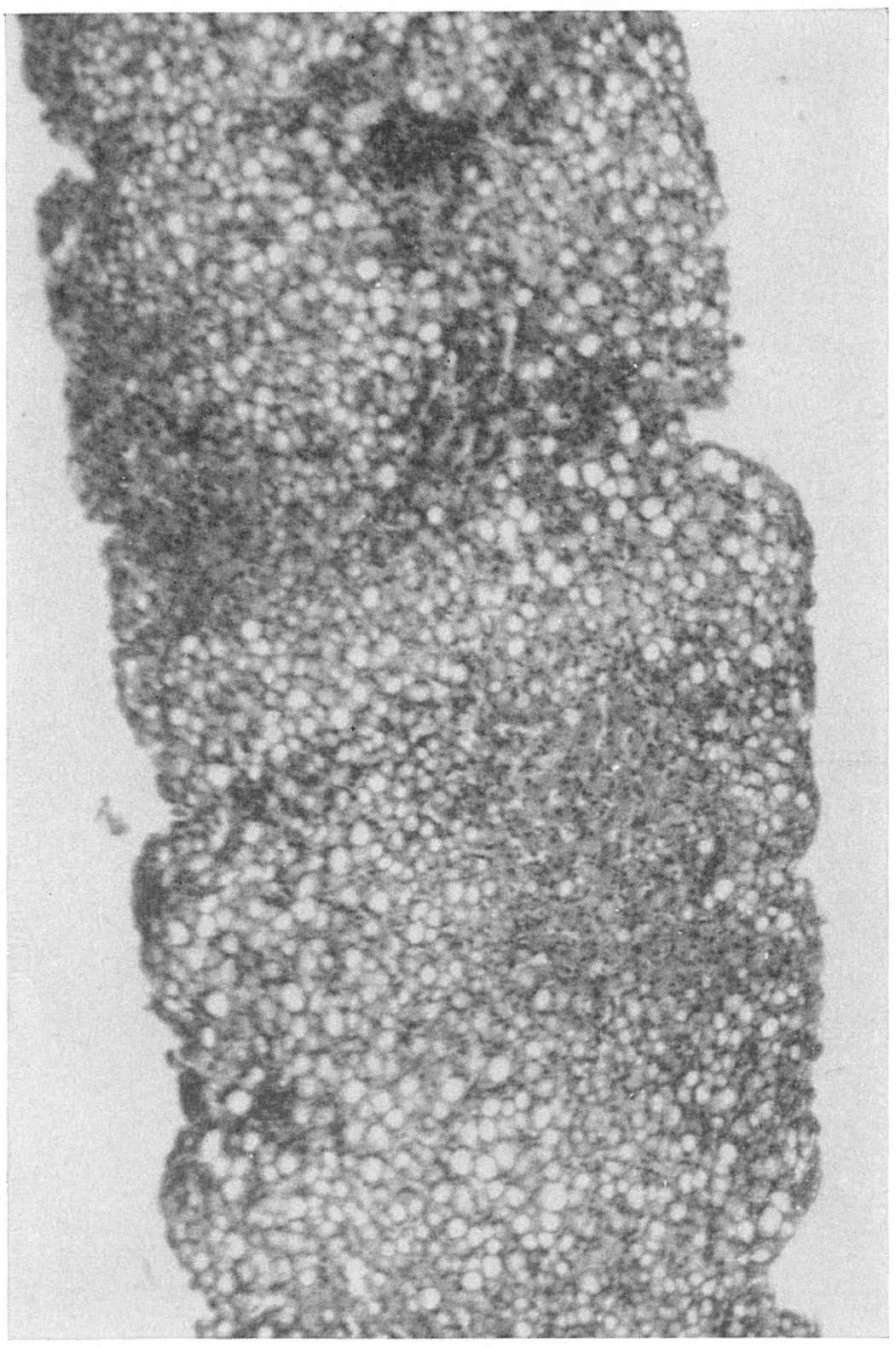

FIG. 3. Liver from a child partially recovered from kwashiorkor. The fat has disappeared from the central portion of the hepatic lobules (H & E, × 30).

the periphery of the cells and glycogen is diminished (fig. 2).

Liver biopsies in Central America[14] as well as Africa[15, 16] show that the fat is first laid down in the periphery of the lobule and with continuing deficiency becomes distributed throughout the whole lobule. With adequate treatment fat disappears in the reverse order in which it is laid down (fig. 3), although 15 to 30 days may be required for all of it to disappear even with good treatment. Concomitant infections seem to make the deposition of the fat less regular and to retard its disappearance.[15]

Deposits of hemosiderin in the Kupffer cells and macrophages of the portal spaces of the liver have been observed in approximately 35 per cent of the kwashiorkor cases biopsied by us (fig. 4). In no case, however, have they proved sufficient to justify the diagnosis of siderosis or hemochromatosis. In general, the deposition of iron in Central American cases is much less than that reported by African authors.[17, 18] Deposits of iron were found in 64 per cent of the livers showing excessive fat at the time of admission, whereas only 32 per cent still had evidence of slight iron deposits by the time the

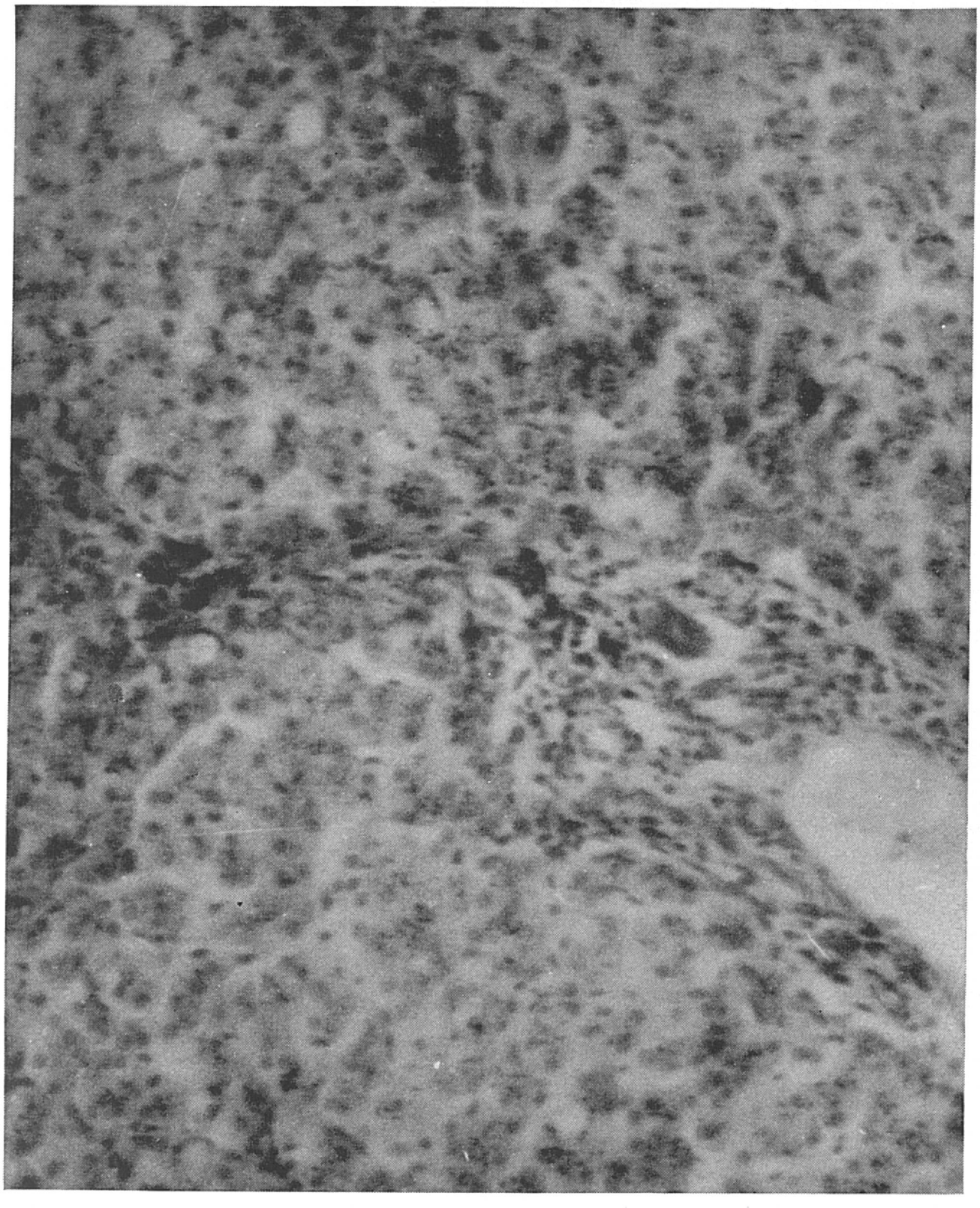

FIG. 4. Liver from a child with kwashiorkor. Iron deposits in form of hemosiderin are observed in the hepatic as well as in Kupffer cells and histiocytes of the portal tract (iron stain, × 200).

fat had disappeared with treatment. This suggests that during treatment hitherto unused iron is mobilized for the synthesis of hemoglobin as protein becomes available for this purpose.

Since cirrhosis of the liver has not been encountered in over 100 biopsies from children being treated for kwashiorkor nor in over 300 autopsies of children dying in the principal charity hospital of Guatemala, we agree with Van der Sar[19] and with Brock[20] that protein malnutrition alone does not cause hepatic cirrhosis in children. Primary cancer of the liver is also rare; only 6 cases have been encountered in over 1000 autopsies in Guatemala.

Most of the children with kwashiorkor studied in Central America at autopsy or through biopsy specimens show some degree of reticulin fiber proliferation in the liver[21] (fig. 5). However, no correlations between reticulin fiber proliferation and the severity of the malnutrition, the duration of the disease process, the age of the child, or even repeated admissions could be found in our material.

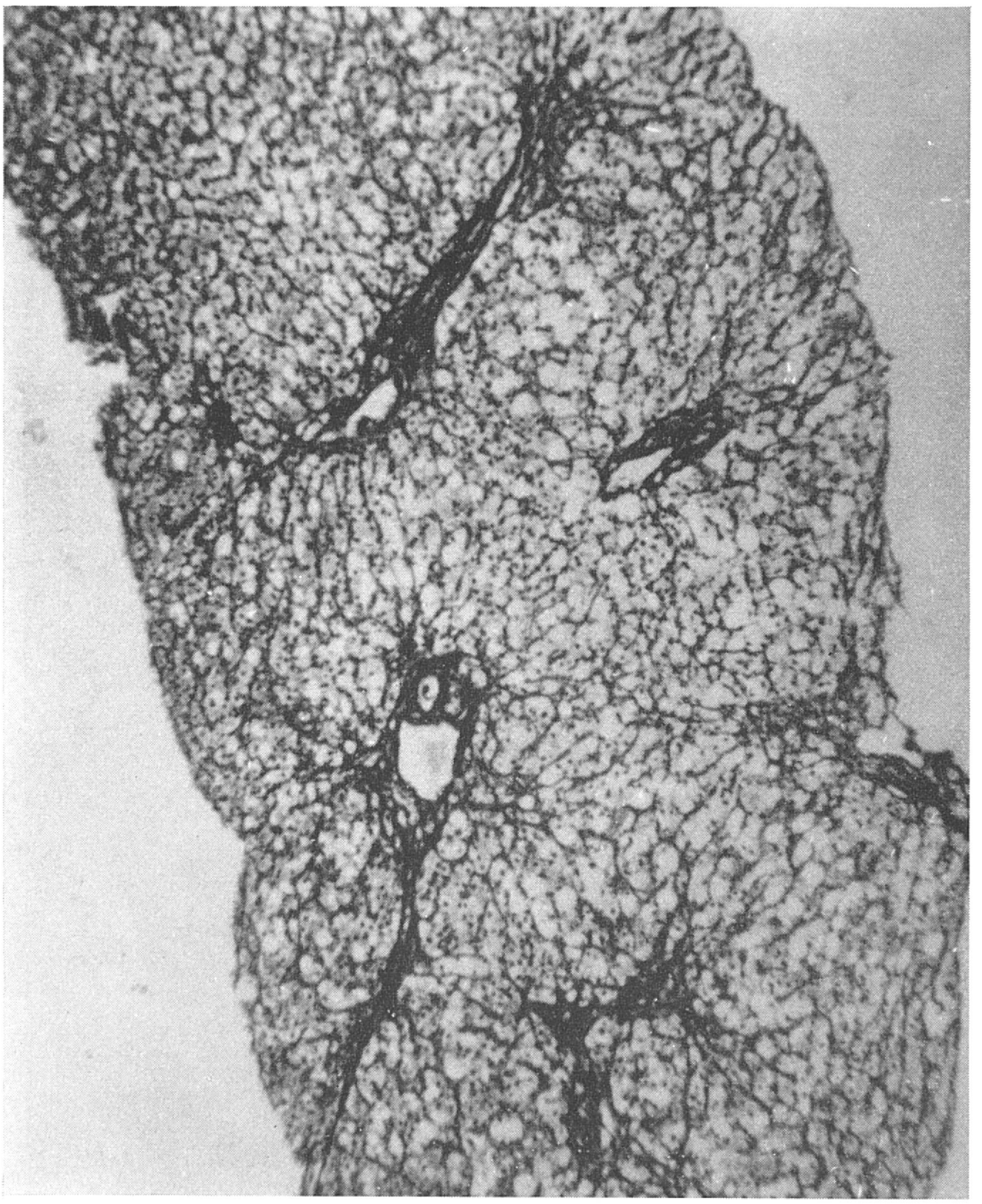

FIG. 5. Liver from a child with kwashiorkor. There is mild proliferation of reticulin fiber coming out from the portal tracts (Laidlaw reticulin fiber stain, × 30).

Pathologic Changes in the Pancreas

The histologic examination of the pancreas of untreated cases shows a marked atrophy characterized by a diminished size of the acini, which show no evidence of central lumen. The cytoplasm of the acinar cells is reduced and compact, their nuclei are pycnotic and secretory granules have disappeared (fig. 6).

In approximately 10 per cent of cases there is a proliferation of reticulin fibers which occasionally amounts to a severe diffuse pancreatic fibrosis (fig. 7). With treatment, the pancreatic acini regenerate rap-

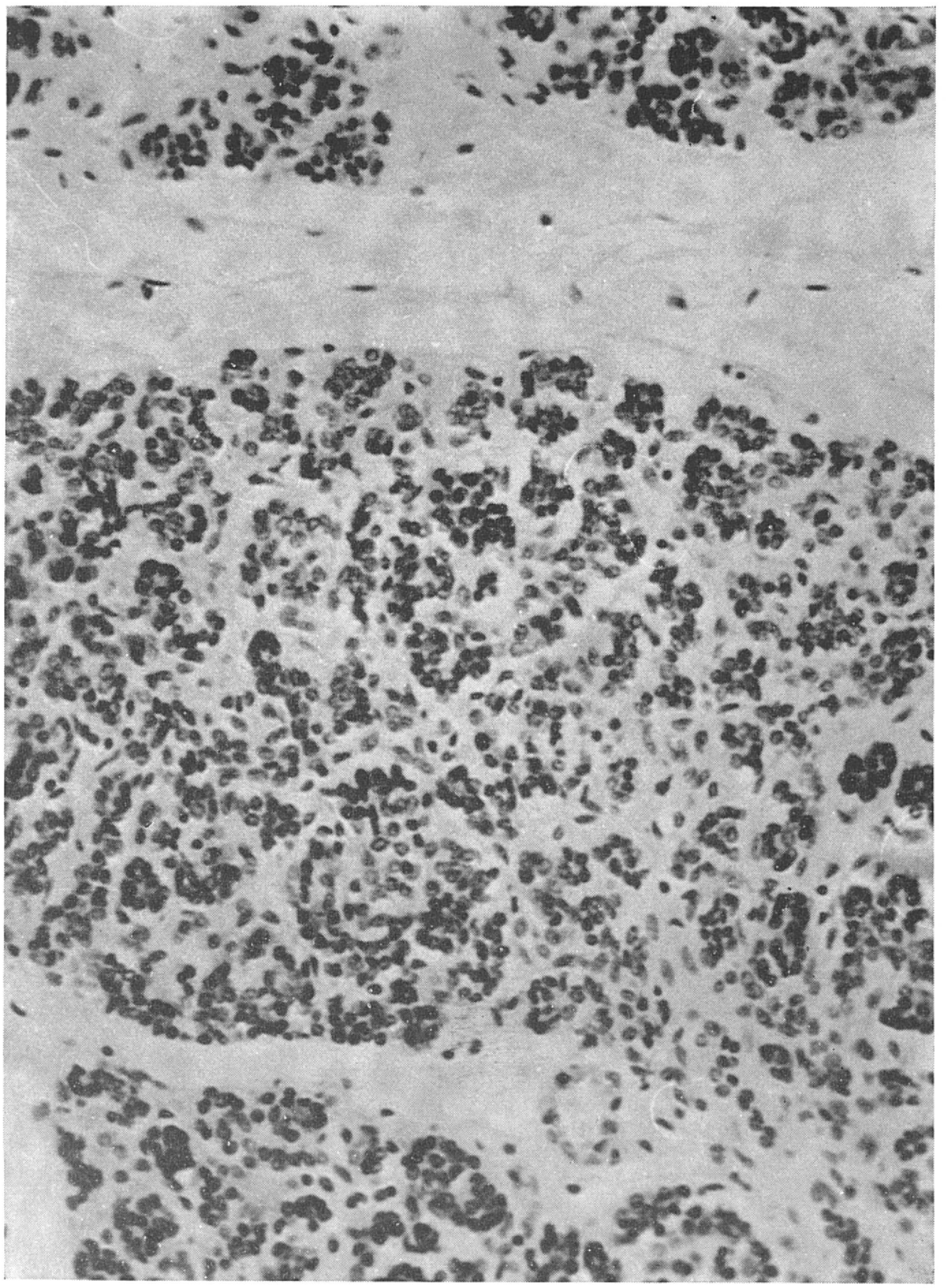

FIG. 6. Pancreas from a child with kwashiorkor. There is marked atrophy of the pancreatic acini without any evidence of luminal arrangement. The cytoplasm of the cells is markedly reduced and the nuclei are pycnotic (H & E, × 200).

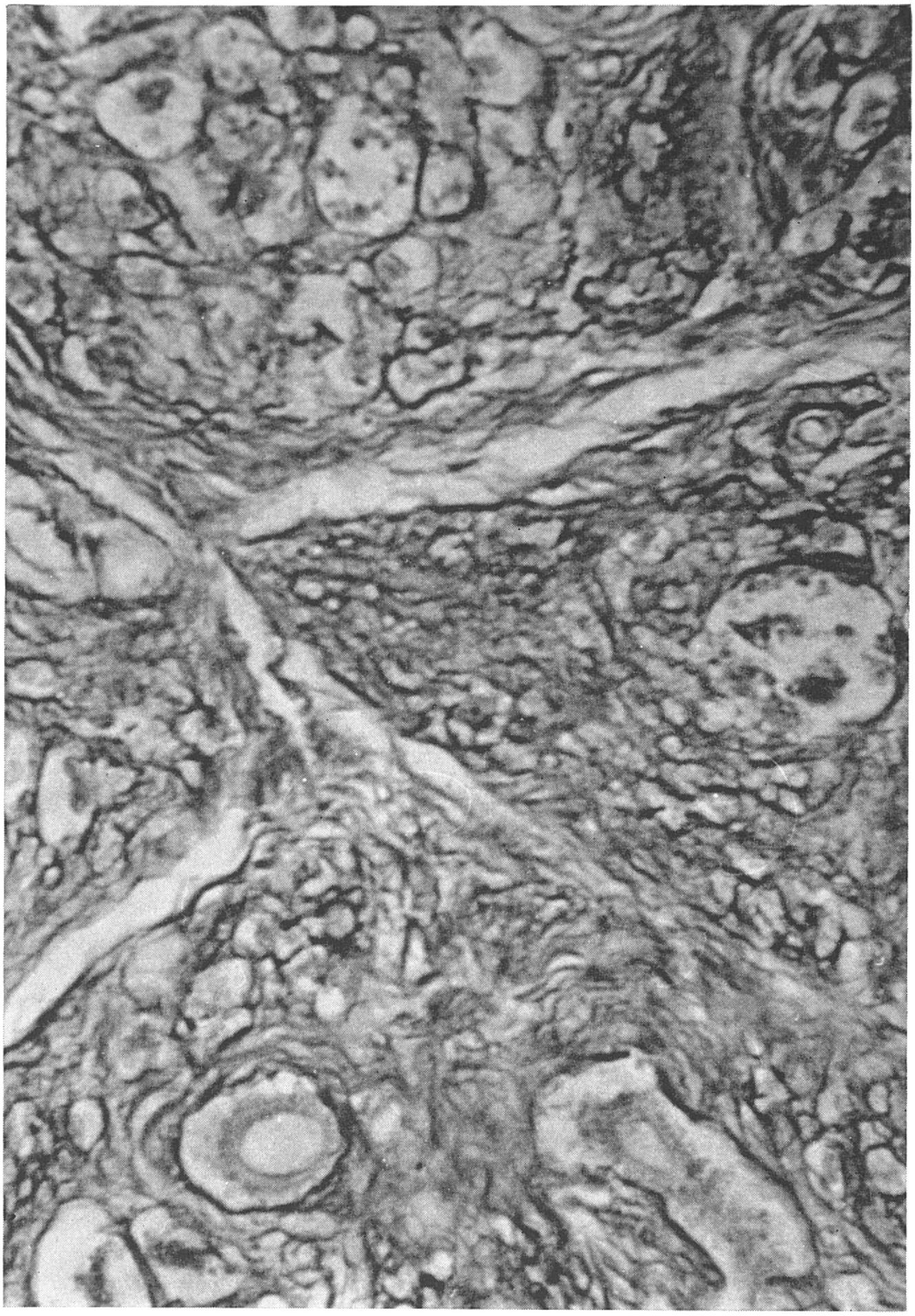

FIG. 7. Pancreas from a child with kwashiorkor; an unusual case with marked reticulin fiber proliferation and formation of collagen (Laidlaw reticulin fiber stain, × 200).

idly, there is an increase in the relative amount of cytoplasm of the acinar cells, and there is evidence of secretory activity. This results in some cases in a hyperplasia, which is macroscopically evident by the increase in size of the organ. The interstitial fibrosis is irreversible and remains as an unfortunate consequence of severe protein malnutrition in some children. It is recognized that these pancreatic changes, although occurring consistently in kwashiorkor, can also be observed in children with marasmus and other forms of malnutrition as well as in some patients with cirrhosis of the liver.

Biochemical Changes Related to the Liver and Pancreas

The drastic decrease in the activity of duodenal enzymes and their rapid return to normal with dietary treatment have been described by several investigators.[22-24] Even when measured in the blood serum, the enzymes amylase, lipase, and esterase, which have their sole or principal origin in the pancreas, reveal altered pancreatic physiology by their lowered activity. Serum amylase is particularly affected, and successful initial recovery is always accompanied by its prompt increase.[14, 25]

The results of the vitamin A absorption tests carried out in kwashiorkor appear to be closely associated with these alterations in enzymatic activity. We have found that on admission, children suffering from the syndrome were unable to absorb a significant amount of vitamin A, even when 75,000 μg. of its palmitate were administered to the fasting patient, followed by a test meal.[26, 27] Following only five days of milk therapy, however, the absorption of this fat-soluble factor had returned to normal as indicated by this procedure, thus paralleling the rapid return of duodenal enzyme activity.[22]

Studies of chemical changes in the liver of children suffering from kwashiorkor have also contributed to a better understanding of the abnormal metabolic pathways in the syndrome. The pioneering investigations of liver enzyme activity in kwashiorkor by Waterlow and Patrick[28] will be summarized later in this symposium. However, it is of interest to mention our own similar results in Central America. Measurements were made of the activities of xanthine, D-amino acid and glycolic acid oxidases, reduced diphosphopyridine nucleotide dehydrogenase, malic dehydrogenase, transaminase, riboflavin, total oxidized pyridine nucleotides, cholesterol, lipid, and protein in liver biopsy specimens.[29] The results of particular interest were an increase in lipid, a decrease in protein, and very reduced activities of xanthine oxidase and D-amino acid oxidase in relation to protein. The other enzymes and metabolites studied appeared unchanged and did not significantly increase relative to liver protein during treatment. All these changes were reversed with appropriate dietary therapy, and levels of all substances measured in the livers of recovered kwashiorkor patients were comparable in magnitude to those of autopsy samples of livers from 5 control children.

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Dr. Carlos Tejada
Instituto de Nutricion de
Centro America and Panama
Carretera Roosevelt, Guatemala

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