Renal Lesions in Kwashiorkor

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THERE IS general agreement over many of the pathologic changes seen in the disease known as kwashiorkor. The importance of the changes in the digestive glands, liver, skin, and other organs is appreciated, and there is agreement over many of the biochemical changes which are a feature of this disease.[1] There is growing evidence that a dietary deficiency of protein is a basic factor in the etiology,[2] although the play of other and quite different types of factor may also be important.[3] It has not yet been possible to show that a specific amino acid deficiency is responsible.[4] If protein deficiency is the basic etiologic factor, then it is to be presumed that there will be lesions, although not necessarily important lesions, in all the organs and tissues of the body. There is not, however, any agreement as to the existence of a renal lesion in kwashiorkor.

CLINICAL EVIDENCE OF RENAL DISEASE

The frequency and the severity of the edema in kwashiorkor has often roused suspicions of the existence of renal disease, and, in some minds, these have been confirmed by the finding in particular cases of a slight but constant albuminuria. But while there are reports of albuminuria as a frequent finding in cases of kwashiorkor in some countries, in others it is not reported or it is denied.

In Uganda, albuminuria is very common in children with kwashiorkor, but there are usually no red blood corpuscles, leukocytes, or casts in the urine. Evidence of urinary infection is rarely seen. The albuminuria is slight in amount, it does not correlate with the severity of the disease, it does not usually disappear on treatment, and it is, of course, not present in every case. Similar findings are recorded from West Africa,[5,6] from India,[7] and from South Africa.[8] In Mexico albuminuria is rarely seen, but in occasional cases it is present, sometimes with evidence of more severe renal lesions,[9] and similar findings are recorded from Guatemala.[10] de Silva[11] reported fever and albuminuria in 66 per cent of his cases in Ceylon. But, on the other hand, Gillan[12] denied its presence in his Kenya cases, and its presence in Indian children is denied by Achar[13] and by Gopalan and Ramalingaswami.[14]

Clinical observations would, therefore, appear to show that albuminuria is an inconstant feature of kwashiorkor. It may be due, not to kwashiorkor itself, but to some associated condition, for the age at which children get kwashiorkor is also the age at which, at least in the tropics, they are also coping with malaria, respiratory disease, and parasitic invasions. Not merely may albuminuria in kwashiorkor be epiphenomenal but also of little importance, were it not that even a slight drain of protein from a severely protein-depleted organism may be important.

PATHOLOGIC CHANGES IN THE KIDNEY IN KWASHIORKOR

Pathologic changes in the kidney have been little studied. The most interesting reports were those of Smith[15] in Lagos, West Africa. These were made before the importance of kwashiorkor in tropical pediatrics had been generally recognized. They were incidental to Smith's main purpose, which was to determine from post-mortem investigations the causes of child mortality in Lagos. In 500 autopsies he recognized 14 cases of what we would now term kwashiorkor, with intense fatty changes in the liver. All showed fatty changes in the convoluted tubule cells of the kidney. He considered that these findings supported the theory that poisoning by cyanogenetic glucosides might be an etiologic factor, and thus he sought in his other cases for evidence of albuminuria

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and fatty change. Albuminuria was found in 86 per cent of 208 cases where bladder urine was available. Fat changes were present in the cells of the convoluted tubules of the kidney in 32 per cent of 350 cases, and in the liver in 58 per cent of the 500 cases. The fat was in the periphery of the lobule in 173 out of the 290 cases positive for fat; in the remainder it was centrolobular or diffuse. It is, therefore, reasonable to suppose that kwashiorkor was present, even if unsuspected, in a great many of Smith's cases.

The presence of a considerable degree of fatty change in the convoluted tubule cells of the kidney has been found a constant lesion in kwashiorkor in Uganda. It may be slight in some cases but very marked in others, with occasional evidence of cytolysis. The nuclei are often pyknotic. The glomeruli are often congested but hemorrhages have not been seen. Exactly similar changes have been recorded from Dakar by Houssiaux.[16] Such changes do not seem to have attracted much attention elsewhere. de Silva[11] records that no renal lesions are seen in his cases. But it is not certain from the various reports if some degree of fatty change in the cells of the convoluted tubules has been regarded as a lesion.

In addition, in Uganda, certain other changes in the kidneys have been noted, hyalinization of the glomeruli, sclerosis of glomeruli, and swelling of the cells lining Bowman's capsule. The significance of these changes is, however, obscure; they occur in children and adults without kwashiorkor and are probably due to unrelated conditions.[2]

It would appear then that the only changes in the kidney which might be due to kwashiorkor are fatty changes in the cells of the convoluted tubules, sometimes accompanied by congestion of the glomeruli. The significance of these changes is obscure. The renal changes of choline deficiency in weanling animals are associated with similar but much more marked lesions, and Arends and Nieweg[17] have described lesions in the kidneys of infants which they cautiously suggest may be the results of choline deficiency. There is, however, in kwashiorkor no evidence of choline deficiency, though there is clear evidence of some breakdown in the metabolism of fat. Indeed Schwartz and Dean[18] have suggested that inability to metabolize fat may be a cardinal sign of kwashiorkor. They find a large rise in the amount of fat circulating in the blood soon after treatment has begun and believe that it represents mobilization of fat. Some of this fat might come from the kidney and, by analogy with the changes in the liver, it might be postulated that some enzymic deficiency in the tubule cells is responsible for the failure of the metabolism of fat in these cells. The cause of the fat accumulation in the tubule cells remains obscure, but it does seem to be the renal lesion in kwashiorkor. The importance of this lesion in the individual case is not known, nor are its possible long-term effects on the individual. The work of Hartroft and Best[19] has shown that severe choline deficiency lesions of the kidneys of weanling animals can profoundly affect the individual in later life. Whether the kidney lesions of kwashiorkor could be severe enough to exert such effects is an open question.

EFFECTS ON RENAL FUNCTION

It is not possible to say if the presence of such a kidney lesion has any particular effect on the renal function of a patient with kwashiorkor, for little attention has been paid to renal function in this disorder. When it is, it will be difficult to distinguish between the effects of renal lesions and the effects of changes outside the kidney. Thus, the blood urea is usually low in cases of kwashiorkor in Uganda, but after treatment with a high protein diet, the blood urea will rise rapidly to levels as high as 90 mg/100 ml. These levels are not associated with any evidence of renal failure and soon revert to normal even if a high protein diet continues to be given. This effect is, therefore, probably not due to a renal lesion although it is obvious that the normal mechanism for controlling the blood urea is in abeyance. In some cases of kwashiorkor, very high levels of blood urea may be found in dying patients, again without evidence of uremia.[2] The only evidence of renal impairment so far recorded is that phenolsulfonphthalein clearance is reduced in kwashiorkor.[20] Jayasekera *et al.*[21] reported a reduction in the total nitrogen excretion and in

the excretion of creatine, but the excretion of creatinine was normal.

It is known that there are anomalies in the handling of water in patients with kwashiorkor. When edema is severe, the urine volume is low[22] and the existence of a marked oliguria was stressed by Gopalan.[23] The edema of a kwashiorkor child is lost by diuresis. The existing evidence[23,24] suggested that diuresis is inhibited by some circulating factor which, it has been very tentatively suggested, might be the pituitary antidiuretic factor. The circulating antidiuretic factor in the blood is at a high level in cases of severe kwashiorkor and falls with improvement after treatment. The cause of this is at present uncertain, but this anomaly of water handling may be more concerned with the liver rather than the kidney.

It is well known that liver function tests in kwashiorkor show that, despite the heavy infiltration of the liver with fat, there is comparatively little functional inefficiency. We might, therefore, suppose that fatty lesions in the renal tubule cells might not lead to any great reduction in their efficiency.

CONCLUSIONS

The renal lesion in kwashiorkor consists of fatty changes in the cells of the convoluted tubules. This seems, in Uganda, to be a constant finding. Other changes that have been reported are inconstant, and their importance is uncertain.

There is little evidence to suggest any marked degree of renal damage in kwashiorkor. Functional tests will probably show little deviation from the normal. Pre-renal lesions will probably prove more important than renal lesions.

ADDENDUM

Professor J. H. Heller, of the Department of Pharmacology of the University of Bristol, England, visited Uganda for a brief period to study some aspects of kwashiorkor, with the aid of the Medical Research Council of Great Britain. In the short time at his disposal he was not able to complete his full program, but he has generously allowed me to quote some of his findings which are "reasonably clear."

"(1) Plasma concentrations of sodium and potassium, in infants with pronounced edema but not with diarrhea, before and after treatment, were not significantly different, suggesting that changes in the plasma electrolyte level are not intrinsic features of kwashiorkor.

(2) Infants with untreated kwashiorkor seemed unable to concentrate or dilute their urine to the same degree as white infants of the same age group. After administration of a standard dose of water, the percentage of the water load excreted was lower than in European controls (in England).

(3) White children of an age group similar to that of the children with kwashiorkor concentrate and dilute their urine as well as adults, but do not (as adults do) excrete a volume of urine equal to that of the test dose within three hours.

(4) Small amounts of protein in the urine were found in 7 out of 16 infants. Four of these children with proteinuria were re-examined after treatment. Protein could no longer be detected in the urine.

(5) Capillary permeability tests were done on a small number of edematous and non-edematous children, but no significant difference was found.

(6) Antidiuretic activity in the plasma of blood obtained by internal jugular puncture ranged from values equivalent to less than 15 to 100 μU vasopressin per ml plasma. High values were found even when the infants were losing edema fluid under treatment."

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