Kaliopenic Nephropathy

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THE PURPOSE of this paper is to marshal presently available evidence that chronic hypokalemia, always associated with a significant deficit of body potassium (kaliopenia), results in characteristic anatomic and functional lesions of the renal tubules. Our own interest in this fascinating lesion has been heightened by the demonstration that it exists in the newly described clinical syndrome called primary aldosteronism.[1-5] Since in the latter condition chronic hypokalemia occurs in man via a mechanism which is unique, and different from previously recognized causes of potassium depletion, demonstration of the typical pathologic and functional lesions of the renal tubules seems finally to relate the condition to lack of the potassium ion.

In 1919 Jaffe and Sternberg,[6] reporting upon a large series of cases of chronic dysentery which had come to autopsy, noted that 25 per cent showed a specific lesion of the renal tubules. They described it as a "vacuolar degeneration" with ballooning of many of the epithelial cells, particularly those of the proximal convoluted tubules. The vacuoles did not take up stains for either fat or glycogen. The glomeruli and arterioles appeared to be spared. That the tubular changes could be "due to disturbed absorption of nutritional substances from the intestinal tract" was one of the possibilities seriously considered.

Clinically, little more was heard about this interesting lesion until 1940 when Ch'in and Hu[7] described it again in autopsy material from cases of bacillary dysentery. In 1947[8] and again in 1950,[9-12] papers appeared associating these tubular changes to chronic intestinal disease, but only Perkins *et al.*[12] related the lesion to a deficiency of potassium. Since then, the relationship of "clear cell nephrosis" or "vacuolar nephropathy" to the state of potassium deficiency associated with chronic intestinal disease has gradually become appreciated.[13-16]

In the meanwhile, tubular lesions practically identical with those described above had been produced by Schrader and associates[17] in long-term experiments in rats fed a potassium-deficient diet. This was confirmed five years later by Durlacker, Darrow and Winternitz,[18] who noted, too, a significant increase in both dry and wet weights of the kidneys after rats had been on a diet deficient in potassium for four weeks. From this same laboratory[19] came the report that renal tubular lesions indistinguishable from those produced by a potassium-deficient diet are observed in rats given repeated injections of desoxycorticosterone (DOC); and that supplementary potassium chloride prevents the DOC-induced tubular vacuolar nephropathy. Although mild polyuria occurred in the rats on potassium-deficient diets (this is true in dogs, too[20]), urinary volume was increased greatly in the rats treated with DOC over long periods of time. In the latter groups the serum sodium was elevated. Thirst, therefore, may have been responsible in part, at least, for increasing total urinary volume in the DOC experiments.

Ragan *et al.*[21] induced severe polyuria and polydipsia in dogs by administration of DOC (25 mg intramuscularly daily for six weeks). The serum sodium was elevated and the "diabetes insipidus-like" symptoms were greatly accentuated by the addition of sodium to the diet. The urinary specific gravity had fallen and was found to be poorly responsive to administered pitressin. Upon cessation of DOC, polydipsia ceased quickly (as the serum

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sodium came to normal), but it required seven days for the specific gravity to return to baseline values. These workers pointed out the distinct differences between true diabetes insipidus and the syndrome induced by excessive activity of DOC. Ferrebee and coworkers[22] continued these experiments and observed that urinary potassium increased on the very first day that DOC was given; and that excessive losses of potassium in the urine continued even after the development of hypokalemia, which appeared within 10 days (DOC—25 mg intramuscularly daily).

Primary aldosteronism, the spontaneously occurring counterpart in man of the DOC experiments referred to above, is now an established clinical entity;[1-5,23-26] and the morphologic renal tubular lesion observed in this condition[3,5] is characteristic of that found in other states of chronic hypokalemia of diverse etiology (Fig. 1).

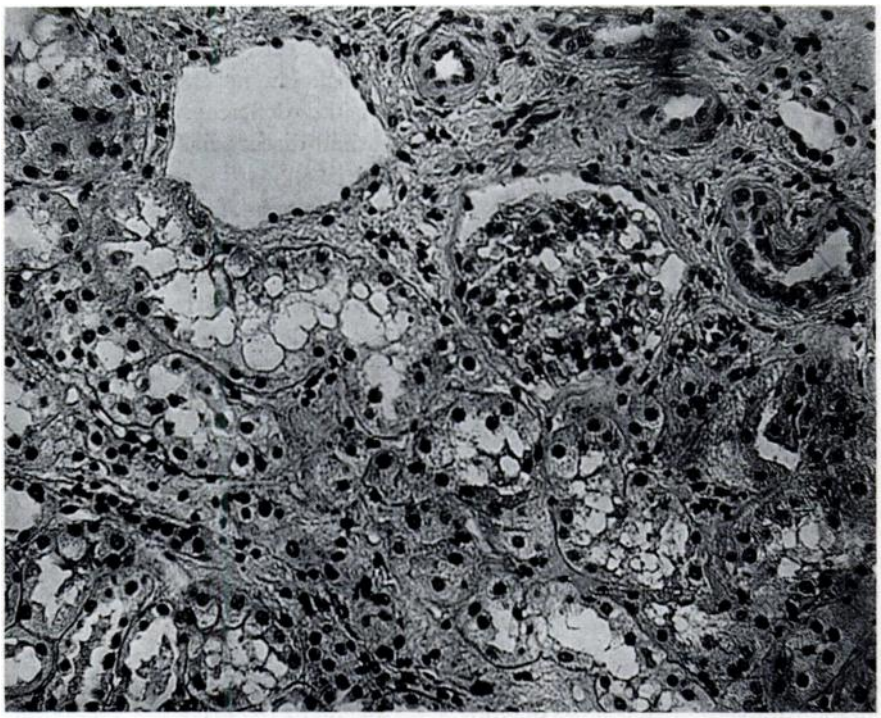

Fig. 1. Renal biopsy specimen from a case of primary aldosteronism subsequently cured by removal of an aldosterone-secreting adrenal cortical adenoma. Note the tubular vacuolar nephropathy. The vacuoles do not contain glycogen or fat.

The functional status of the kidneys in primary aldosteronism is of great interest. Apart from a much more intense polydipsia and polyuria (due in part to the accompanying hypernatremia) than is observed in potassium depletion due to other causes, the alterations of function in both situations are very similar.[14] In the original reports describing primary aldosteronism[1-3] the following points regarding renal function were emphasized: (a) the existence of great polyuria and polydipsia; (b) hyposthenuria unresponsive to pitressin; (c) impairment of tubular capacity to reabsorb water greatly out of proportion to other defects in renal function; (d) persistently alkaline urine; (e) persistently high U/P (urine/plasma) ratios for potassium in the face of severe hypokalemia.*

Much more detailed studies of renal function in three proved cases of primary aldosteronism have been reported recently by

* This is a specific effect of aldosterone upon tubular function and does not occur in other states of chronic hypokalemia. An exception to this statement is the increased clearance for potassium in renal tubular acidosis, but this situation is very different from the renal disturbance observed in primary aldosteronism.

Dustan, Corcoran, and Farrell.[27] Their findings are precisely as those listed above, but in addition, they have been able to characterize the mechanism of the hyposthenuria. It was found that the tubular capacity to reabsorb free water (T^c H_2O) is mildly but persistently negative in primary aldosteronism and that this is not affected by pitressin. On the other hand, T^c H_2O in true diabetes insipidus is strongly negative without pitressin, but becomes *normally positive* upon administration of pitressin. It was pointed out that the defect in water reabsorption is similar to that seen in DOC-induced "diabetes insipidus" in dogs and rats, as well as to that observed in dogs made chronically hypokalemic by potassium-deficient diets.

Thus, studies in humans with primary aldosteronism show (a) the same tubular lesion morphologically that has been observed after death in people who had been depleted of potassium by chronic intestinal disease, and (b) the same histologic lesion which is seen in animals fed a diet deficient in potassium, or fed an adequate diet but given large doses of desoxycorticosterone. Essentially the same disturbances of renal function, too, are observed under these various conditions. Obviously, the common denominator is chronic deficiency of potassium.

To what extent is this renal tubular vacuolar nephropathy in man reversible both from the anatomic and functional points of view? It is somewhat disconcerting that so few studies are available in man with which one can document his answers to these questions. Nevertheless, we believe that they can be answered with reasonable assurance.

REVERSIBILITY OF THE RENAL ANATOMIC LESION IN MAN

The only study applicable to this question is that reported recently by Relman and Schwartz.[28] Renal biopsy specimens obtained from two patients severely depleted of potassium because of chronic diarrhea showed the characteristic tubular vacuolar nephropathy. Repeated biopsies obtained after partial repletion of potassium (and before significant functional improvement had occurred) showed evidence of healing of the tubular lesion. More studies of this type are needed.

REVERSIBILITY OF THE RENAL FUNCTIONAL LESION IN MAN

Carefully performed studies in normal men with induced depletion of potassium are few.[29–34] These studies, together with observations made upon (a) patients recovering from primary aldosteronism (after removal of the adrenal tumor[4,5,27]), and (b) patients being treated with potassium for chronic kaliopenia due to diarrhea,[14,28,35] make it clear that a major degree of recovery of impaired renal function can be attained in most instances. That kaliopenic nephropathy may not be completely reversible and that it may lead to progressive renal disease has been shown recently by Fourman, McCance, and Parker in experiments upon rats.[36]

From the data available to date one can state that recovery of renal function following removal of an adrenal aldosteronoma proceeds in the following temporal order:

(1) Abrupt decrease in potassium clearance.[4,5,24,27] This rapid return of efficient renal conservation of potassium indicates that the capacity of the tubules to reabsorb potassium has remained intact despite the presence of the tubular hydropic vacuolization. This is true, too, in kaliopenia due to diarrhea in which efficient renal conservation of potassium is maintained.[28] The difference in the two conditions before treatment is due, of course, to the presence in one of them of the hormonal effect on the tubule of an excessive amount of aldosterone. This must be kept in mind when one attempts to interpret the findings in such excellent studies as those of Earle and associates,[37] Wyngaarden *et al.*,[38] and Evans and Milne[39] on cases which are now regarded, in retrospect, as examples of primary aldosteronism. In fact, this has now been proved in the case reported by Evans and Milne.[39] An aldosterone-secreting adrenal cortical tumor has been removed surgically from this patient.[40]

(2) Relief of intense polyuria and polydipsia.[4] This parallels the disappearance of hypernatremia and occurs long before there is any change in concentrating ability or in pitressin

responsiveness. Thus, it appears that much of the polyuria is secondary to polydipsia.

(3) Return of the capacity to produce an acid urine.[4,27]

(4) Disappearance of proteinuria.[4,27]

(5) When initially depressed, renal plasma flow and glomerular filtration rates return to normal slowly.[27]

(6) Return of tubular capacity to reabsorb free water[27] with gradual return of the concentrating ability.[4,27]

In the nephropathy associated with diarrheal depletion of body potassium, practically complete reversal to normal of the abnormal renal functions (depressed clearances of inulin, endogenous creatinine, and *p*-aminohippurate; hyposthenuria unresponsive to pitressin; and proteinuria) can occur after the potassium deficit has been relieved.[14,28,41] Although alkalinity of the urine is not evident here as it is in primary aldosteronism, recent studies[34] indicate that under conditions of simple depletion of potassium the ability to produce a maximum concentration gradient of hydrogen ion between urine and plasma is impaired; and that this capacity is restored by administration of potassium. Many weeks may be required before normal tubular capacity to reabsorb water is restored.[14] The possibility exists that in some cases sufficient renal damage occurs in the course of a period of kaliopenia to render return of adequate function impossible.[36]

We believe that one is justified now in speaking of *kaliopenic nephropathy* as an established entity[28] with characteristic clinical and pathologic features. The functional and pathologic lesions may be completely reversible early, but it is likely that chronicity and intensity of kaliopenia are important factors with respect to the degree of functional and anatomic recovery that is possible. Why kaliopenia produces a vacuolar nephropathy in which the major morphologic lesion is found in the cells of the proximal convoluted tubules must await more information regarding such phenomena as the relationships between potassium and tubular enzymatic activities,[41-43] and the effects of hormones upon specific cells[44] in the potassium-deficient state.

Finally, it should be pointed out that degenerative vacuolar lesions of the renal tubular epithelium, similar in many respects to those seen in kaliopenic nephropathy, have been observed under other circumstances. This is not to de-emphasize the importance of kaliopenia, but to suggest that studies of the metabolism of potassium, both general and tubular, may prove fruitful in the other circumstances. The situations which produce a tubular lesion not unlike that observed in kaliopenic nephropathy are "sucrose nephrosis,"[45-48] neomycin nephropathy,[49] and diethylene glycol poisoning.[50]

SUMMARY

Kaliopenic nephropathy must be recognized as an established clinical and pathologic entity. It can be induced experimentally by diets deficient in potassium. It is reproducible by repeated administration of large doses of desoxycorticosterone and preventable when supplementary potassium is given in such desoxycorticosterone experiments.

In man, the syndrome is observed most frequently in the potassium-deficient state associated with chronic intestinal disease. It is also present in primary aldosteronism, the renal manifestations of which are analagous to DOC-induced "diabetes insipidus" in animals.

A decreased tubular capacity to reabsorb water, not influenced by administered pitressin, is the most distinctive functional abnormality encountered in kaliopenic nephropathy. While other renal functions, too, may be impaired, hyposthenuria is disproportionately severe. Histologically, the lesion is limited to tubular cells and is characterized by diffuse hydropic vacuolarization. This anatomic lesion is observed in chronic hypokalemia in man whether the latter is produced by long-standing diarrhea on the one hand, or by an aldosterone-secreting cortical tumor on the other.

In most instances both the functional and anatomic abnormalities appear to be slowly reparable after replacement of the potassium deficit. It is likely, however, that in some cases so much damage has occurred during chronic kaliopenia that functional recovery is impossible.

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