INTRODUCTION

Until recently, human investigation was the only means to study the pathogenesis of VDRR. In 1976 the discovery of a mouse model by Eicher et al facilitated the study of this disease. After five years, a substantial amount of data has accumulated, which will be summarized here.

THE SITE OF THE RENAL DEFECT

Although a defect in phosphate (Pi) transport is suspected in the intestine and bone cell, the excessive excretion of urinary Pi is probably the basis for the hypophosphatemia and the resulting symptoms.

The micropuncture studies (Giasson et al, 1977 and Cowgill et al, 1979) performed in rachitic mice, reported a major defect of Pi transport in the proximal convoluted tubule (PCT). In contrast, water and therefore Na transport, were found to be normal.

A defect in Pi transport in the PCT may result from either a curtailed inward transport through the luminal membrane or the basolateral membrane, or from a backflux of the electrolyte into the tubular lumen. As a consequence of these various possibilities, the defect may or may not modify the intracellular Pi content.

Eicher et al (1976) measured the inorganic and organic phosphorus content in cortex homogenates and found no difference between normal and rachitic mice. However, Drezner et al (1981) measured ATP as a probe of intracellular phosphate depletion and found
this metabolite to be significantly decreased in diseased mice. The uptake of $^{32}\text{Pi}$ and its release by kidney slices are normal (Tenenhouse et al, 1978) suggesting a normal Pi movement through the basolateral membrane. In contrast, Pi transport studies through brush border membrane vesicle preparations clearly indicate a defect in rachitic mice, thus explaining the low ATP intracellular concentration.

Are the regulatory mechanisms of Pi transport preserved in VDRR? The finding of a brush border membrane defect does not establish its primary or secondary nature. However, it is plausible that a primary defect would curtail the normal response of this membrane to the physiological regulatory mechanisms.

Several studies (Tenenhouse and Scrivener 1979, Mulbauer et al 1980, and Insogna et al 1981) indicate that the mechanisms of Pi saving in a phosphate depletion situation is intact in VDRR. Not only does the fractional excretion of Pi fall from 57% to 1.4% but also the $T_m$ value increases in the same manner as in normal animals, but at lower levels. As in normal mice the information is transmitted to the brush border which reproduces in vitro the increased Pi uptake observed in vivo, following a low Pi diet.

In VDRR man the tubular response to exogenous PTH is curtailed. It has been proposed that the brush border membrane possesses two types of Pi transport, one of which, sensitive to PTH is absent in VDRR. This is probably not the case, since according to Cowgill et al (1979) and our laboratory (unpublished data), VDRR mice respond normally to parathyroidectomy by increasing Pi reabsorption in the same way as normal mice.

PLASMA PTH AND NUCLEOTIDE METABOLISM IN VDRR

The PTH level has been repeatedly measured in man and mice. In man, the results are contradictory; levels were found to be either normal or slightly increased (Arnaud et al 1971, Lewy et al 1972, and Reitz and Weinstein, 1973). In mice, Eicher et al (1976) and Cowgill et al (1979) reported normal or low normal levels. In any case, the hyperphosphaturia is not related to hyperparathyroidism.

Aside from the observations of a normal or almost normal PTH plasma level, and a well preserved response to parathyroidectomy, an abnormal nucleotide metabolism has been consistently reported in this disease. The absolute urinary excretion of cAMP was found to be high by Tenenhouse et al (1978) and by Meyer et al (1980b). However, the tissue adenylate cyclase response to PTH is significantly decreased (Cowgill et al, 1979). In a microdissection study (Brunette et al, 1979) we found that this defect was localized in the proximal convoluted tubule (PCT). In the distal convoluted tubule the adenylate cyclase response to PTH is normal but the