1. RATIONALE

One of the problems facing the clinical application of vitamin D research in man has been the intensely biochemical roots from which this knowledge has grown. Many concepts, which are the currency of clinical endocrinology in other areas, are only recently being considered in the vitamin D area. In order to demonstrate the point I will instance some endocrinological investigations which would be considered basic in the assessment of an individual with either deficient or excessive production of glucocorticoids by the adrenal cortex. In the former case no assessment would be complete without a short (1 hr) or long (3 day) stimulation of plasma cortisol levels using the natural stimulator adrenocorticotrophic hormone or the synthetic partial sequence polypeptide (Tetracosactrin). In the case of possible excessive production the simplest investigation would be an overnight test of suppressing plasma cortisol with a pharmacological amount of a synthetic glucocorticoid. This would be followed as necessary by a more prolonged suppression test with increasing doses of the same synthetic steroid. These investigations are aimed not only at demonstrating the abnormality but also at elucidating the primary site of the dysfunction. While the regulation of synthesis and mode of action of this hormonal system is widely accepted as a model of 1,25-(OH)₂D control and function, where are the equivalent investigations for the vitamin D - endocrine system? One must concede that the regulatory mechanisms may be more complex in this system and that such investigation in the glucocorticoid system may not be necessary at the extremes of absent or excessive production particularly where other clinical information indicates the most likely primary pathology and dictates the course of action. I would suggest that similar exclusions, e.g. hypoparathyroidism, advanced renal failure and end organ resistance,
exist for the vitamin D endocrine system and have occupied almost all of our attention to the present. Now that we have started to examine more subtle abnormalities, the inadequacies of a single isolated plasma or serum 1,25-dihydroxyvitamin D (1,25-(OH)₂D) level becomes glaringly apparent. The point can be demonstrated with reference to early renal failure, osteoporosis and idiopathic hypercalciuria but other examples abound.

1.1 Stress testing in early renal failure

A role of 1,25-(OH)₂D deficiency in renal bone disease has been accepted given the facts that the kidney is the major source of production of 1,25-(OH)₂D and that this synthetic ability is grossly impaired in advanced renal failure. It is clearly important to determine the stage during the deterioration of renal function at which renal 1,25-(OH)₂D production becomes limiting. The initial data on this question, provided by Slatopolsky and coworkers (1), indicated that in patients with mild renal failure (creatinine clearance 50 ± 3.7 ml/min) and elevated PTH levels the circulating levels of 1,25-(OH)₂D were not decreased but in fact were slightly elevated (44 ± 3.7 pg/ml cf 34 ± 1.5 pg/ml for normal controls). As these workers pointed out these data suggest that 1,25-(OH)₂D production per gm of functioning kidney must be greatly increased; an effect, which can be explained most easily as due to secondary hyperparathyroidism. The question which arises from these data is whether or not renal 1-hydroxylase activity is maximally stimulated. If the 1-hydroxylase is maximally stimulated it may not be capable of further response and may even be responding inadequately given the prevailing pathophysiological stress e.g. hypocalcemia. If the latter is the case then an effective deficiency of 1,25-(OH)₂D exists, even in the face of a "normal" plasma 1,25-(OH)₂D level. Such a situation must eventually arise at some stage between normal renal function and advanced renal failure (Figure 1). Under this situation, where the homeostatic response to a calcium stress is limited, a case could be made for physiological replacement with 1,25-(OH)₂D₃. Determination of the appropriate stage of renal disease, at which to consider such an approach in any individual, could be based on the response to a stress test designed to maximise the plasma 1,25-(OH)₂D level. This is an area, where a stimulation test could be most useful.