SUMMARY AND CONCLUSIONS

In this thesis we describe the results of studies on sickle cell nephropathy, performed in Curaçao.

In the late sixties disturbances in renal concentrating capacity and in renal acidification have been demonstrated in sickle cell disease. Afterwards the results of the microradioangiographic studies of Statius van Eps et al offered more insight in the aetiology of these functional abnormalities. While in the kidney of normal subjects in the pyramids parallel, longitudinal bundles of vasa recta can be observed (introduction figure 1, page 2), the number of vasa recta in the kidneys of homozygote sickle cell anaemia (SCA)-patients are almost reduced to zero (figures 3 and 4, page 4 and 5). The few that are present are spiral, dilated and end bluntly, suggesting obliteration.

Since we observed elevated serum phosphate concentrations during our studies on sickle cell nephropathy we investigated the renal handling of phosphate in SCA. In chapter 1 we describe an increased proximal tubular phosphate reabsorption per litre of glomerular filtrate (TmP/GFR) in patients with this disorder. There were no known causes for such an increased TmP/GFR in SCA. Moreover, we could demonstrate a normal response in phosphate excretion after parathyroid hormone injection in two SCA-patients. During an Ellsworth Howard test (1), in which 200 units U.S.P. of parathyroid extract were given intravenously to the fasting patients, we found a six- to ten-fold increase in phosphate excretion and a four- to six-fold rise in sodium excretion. TmP/GFR sharply fell from 1.84 to 0.90 mmol/l and from 1.94 to 0.77 mmol/l, respectively. We conclude that the renal tubule in sickle cell nephropathy is not insensitive to parathyroid hormone. This increased proximal tubular reabsorptive activity is considered to be a particular characteristic of sickle cell nephropathy.

In chapter 2 we evaluate another aspect of the proximal tubule. In this part of the nephron reabsorption and catabolism occur of beta-2-microglobulin, a low molecular weight protein which is filtered by the glomerulus. We found an increased tubular uptake of beta-2-microglobulin and a positive correlation between the reabsorption of beta-2-microglobulin and the reabsorption of phosphate. These findings offer additional proof of a supernormal proximal tubular reabsorption in SCA. Moreover, in this part of the nephron not only reabsorptive but also secretory processes are elevated, since secretion of para-aminohippurate, urate and creatinine have been found increased.

Sickle cell nephropathy therefore is a quite particular model for the evaluation of intrarenal haemodynamic balance, since there are medullary abnormalities, both functional and anatomical, with supernormal proximal tubular function and, in addition - especially in younger patients - a supernormal glomerular filtration rate (GFR) and effective renal plasma flow (ERPF).

In chapter 3 we discuss the possible role of renal prostaglandins in sickle cell nephropathy. Since we were unable to measure prostaglandin concentrations in a reliable manner and since it is known that studying the effects of indomethacin on renal function can give indirect information about the role of renal prostaglandins we evaluated the effects of indomethacin in sickle cell nephropathy.
Chapter 4 describes the effects of indomethacin administration on renal haemodynamics. It was found that after indomethacin administration GFR and ERPF decrease more in SCA-patients as compared to control persons. We conclude that renal prostaglandins are of importance in maintaining a (super-)normal GFR and ERPF in sickle cell nephropathy. These findings also favour the hypothesis that prostaglandin synthesis is increased in sickle cell nephropathy. In this chapter special emphasis has been given to the urea handling before and after indomethacin. Fractional urea excretion in the control situation was found increased in the SCA-patients but could be corrected by giving indomethacin. We suggest that this is due to effects of indomethacin on renal medullary sodium and urea transport.

We therefore subsequently evaluated the influence of indomethacin on renal water and salt handling during water loading and water deprivation in normal persons and SCA-patients (chapter 5). Indomethacin was found to promote sodium chloride reabsorption in the ascending limb of the loop of Henle. As a consequence thereof urea diffusion into the medulla was enhanced and in the water deprived (vasopressin stimulated) control persons maximum urinary osmolality rose. In the SCA-patients however, sodium chloride reabsorption in the ascending limb normally will be insufficient, due to the vascular abnormalities in the medulla and the supposed increased renal prostaglandin synthesis. Since prostaglandins decrease sodium reabsorption in this part of the nephron, urea reabsorption in SCA also will be insufficient and fractional urea excretion will be increased. After indomethacin administration sodium chloride reabsorption in the thick ascending limb in SCA also improved and more urea could be reabsorbed. Urinary osmolality however, did not increase in SCA patients, although these patients showed a similar decrease in diuresis as the control persons. This inability to increase urinary osmolality is probably due to a defect in the trapping of solute in the medulla with solute washout. As a consequence thereof serum urea concentration rose after indomethacin (Chapter 4, figure 1, pag. 33).

Effects of indomethacin on renal salt and water handling are also illustrated in chapter 7. Administration of indomethacin to normal persons induced sodium retention accompanied by water retention and led to a rise in body weight. In SCA-patients sodium retention was neither followed by water retention nor by a rise in body weight, but by an increase in serum urea and osmolality. These findings taken together are proof of a defect in trapping of solute due to the 'washout' of the medulla in sickle cell nephropathy. They also illustrate the role of urea in the renal concentrating mechanism, as proposed by Kokko and Rector (2). It is moreover demonstrated in chapter 5 that the normal diluting capacity in SCA deteriorated during indomethacin administration. This lead us to suggest that the normal diluting capacity of SCA-patients is due to the renal prostaglandins. This might have important clinical implications since these patients in periods of crises often are treated with fluid replacements and analgesics. When prostaglandin-synthesis inhibiting analgesics are used a dilutional hyponatraemia might develop.

We describe in chapter 5 that indomethacin induced a distinct phosphaturia in both control persons and SCA-patients. When in this study TmP/GFR was estimated before administration of indomethacin (Table I), TmP/GFR in the control subjects was found similar in both the water loaded and the water deprived situation (1.29 and 1.16 mmol/l, respectively). In the SCA-patients however, the already increased TmP/GFR during water-loading (1.48 in SCA compared to 1.29 mmol/l in control subjects) rose even further to an exorbitant high value of 1.99 mmol/l during water-deprivation. Although the patients
undergoing a diluting test were not the same as those undergoing a concentrating test and although the groups were too small for statistical evaluation, these findings do suggest that the proximal tubular reabsorptive activity in SCA is maximally stimulated during water depletion. This is further demonstrated in a patient described in chapter 7 (figure 3 and 4, page 60 and 61), who showed a decrease in TmP/GFR when water intake was increased from 2 l to 1 l per day. In chapter 1 we suggested that the increased phosphate reabsorption in SCA is due to homeostatic readjustments to structural and functional abnormalities in the renal medulla. Our findings now indeed offer evidence that the increased proximal tubular phosphate reabsorption is a consequence of the defect in renal medullary function with a tendency for water deficit and moreover, that renal prostaglandins play a role in the resetting of the proximal tubular activity to a higher level. This results in an adequate water and sodium homeostasis in SCA.

In chapter 6 we describe the results of studies on the influence of indomethacin on renal acidification in normal persons and SCA-patients. Titratable acid excretion increased in both groups, probably as a consequence of the phosphaturia. Ammonium excretion however, decreased after indomethacin administration in the SCA-patients while it did not change in the control persons. We argue therefore that indomethacin has a particular influence on ammoniagenesis and we suggest that ammonium excretion in untreated SCA-patients is normal thanks to the function of renal prostaglandins.

Finally, in chapter 7 we discuss the consequences which our observations on the proximal tubular function and the role of renal prostaglandins in sickle cell nephropathy have for the interpretation of the renal handling of sodium in these patients. In SCA we observed a normal sodium conserving capacity during salt depletion combined with moderate water restriction. In this situation serum sodium and osmolality remained normal. This is in contrast with the findings of Goossens et al of an insufficient sodium conservation with hyponatraemia during salt restriction (3). Their patient however, did receive sufficient amounts of water. We conclude that SCA-patients have on the one hand a tendency to sodium loss in the ascending limb of Henle's loop during diuresis, while on the other hand sodium, once reabsorbed into the medulla (as in antidiuresis) is transported into the systemic circulation. This explains the rise in serum sodium and osmolality observed during salt loading combined with moderate water restriction. It should be noticed that hyponatraemia could develop both due to a sodium loss and, when prostaglandin synthesis inhibiting drugs are used, due to a dilutional phenomenon.

It is evident that measurements of prostaglandins and vasopressin levels in SCA-patients are warranted.