Postoperative analgesia with the oral compounds utilized was good, no significant differences being shown between the two preparations. Side-effects were minimal and acceptable, and it is evident that patients can be changed to this type of oral analgesia within 12 - 24 hours of the operative procedure. Smoking does not appear to produce any serious side-effects, either deleterious or beneficial.

The objective of effective management of postoperative pain should be to provide optimal pain relief with minimal danger, side-effects and adverse reactions. Currently there does not appear to be an analgesic agent or technique which offers clearly superior advantages over all others so that it can be recommended unequivocally.

Dr S. G. Reinach of the Institute for Biostatistics of the South African Medical Research Council, Johannesburg, performed the statistical analyses. We should like to thank our many colleagues for allowing this study to be performed on patients in their care, in particular Dr C. J. T. Craig. Thanks are also due to the Chief Medical Superintendent of Groote Schuur Hospital, Dr H.-Reeve Sanders, for permission to publish.

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Low plasma pyridoxal-5′-phosphate levels in children with the nephrotic syndrome

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Summary

Of 35 children with the nephrotic syndrome in relapse, 88% were found to have low circulating plasma pyridoxal-5′-phosphate (PLP) levels. Remission of the syndrome was associated with spontaneous normalization of plasma PLP levels in 23 such children. A significant ($P < 0{,}001$) positive correlation ($r = 0{,}81$) was found between plasma albumin and PLP levels and a significant ($P < 0{,}001$) negative correlation ($r = -0{,}66$) between plasma PLP and serum cholesterol levels. The low plasma PLP levels may be due to enhanced urinary excretion of albumin-bound PLP in view of the severe proteinuria which characterizes the nephrotic syndrome.

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The active co-enzyme form of vitamin B_6, pyridoxal-5′-phosphate (PLP), is considered to be a good index of vitamin B_6 nutriture,[1-3] and on this basis biochemical deficiencies have been reported in a variety of clinical conditions.[1-7] In particular, biochemical vitamin B_6 deficiency has been documented in chronic renal failure[8,9] with enhanced degradation of PLP proposed as the underlying mechanism.[10,11] Similar explanations have been proposed for the deficiency documented in patients with liver disease.[6,12,13]

Although some extensive work has been done on the requirements of vitamins in chronic renal failure, and in haemodialysed patients in particular,[14] the vitamin requirements in other renal conditions such as the nephrotic or nephritic syndromes are unknown. We report on vitamin B_6 nutrition in children with the nephrotic syndrome.

Patients and methods

Forty-eight children who had either previously had or at the time of the study were suffering from active nephrotic syndrome were studied. The criteria used for inclusion in the study were: (*i*) heavy proteinuria (> 2 g/m^2/d); (*ii*) hypoalbuminaemia (< 30 g/l); and (*iii*) hypercholesterolaemia.

Nine of these children were studied in both relapse and remission (no proteinuria), 26 were studied in relapse and 13 in remission alone, giving a total of 35 studied in relapse and 22 in remission. There were 29 boys and 19 girls. Six of the children were white and 42 of various ethnic origin; their ages

varied from 1½ years to 15½ years with a mean age of 7 years (median 6 years 11 months).

As part of their assessment renal needle-biopsy specimens were taken under direct fluoroscopy from 38 children. In 1 case consent for the biopsy procedure was refused. The histological classification was as follows: 12 cases of membranous nephropathy (all hepatitis B-associated), 4 mesangiocapillary glomerulonephritis, 3 endocapillary glomerulonephritis, 15 varying degrees of mesangial proliferative glomerulonephritis with or without mesangial matrix thickening, 1 focal segmental glomerulosclerosis, and 3 minimal-change disease (MCD). The remaining children who did not undergo renal biopsy procedures were presumed to have MCD because of their previous or subsequent satisfactory response to corticosteroids. There were therefore 11 cases of MCD. Children with MCD tended to have selective proteinuria whereas those with other histological findings had non-selective proteinuria.

Treatment was essentially supportive in those children requiring hospitalization during the study (27 patients). This included a high-protein (4 g/kg), low-salt diet as well as intravenous 20% low-salt human albumin and diuretics as necessary. No vitamin supplements were administered before or during the study period. Four children who had initially been studied in relapse were studied in remission after steroid therapy. No cytostatic agents were used during the study. Mild prerenal uraemia was evident in several children in the acute nephrotic phase. Supportive therapy in those children studied as outpatients could not be monitored.

Forty-one healthy children with normal renal function attending follow-up outpatient clinics served as controls; there were 24 boys and 17 girls and none had proteinuria. Three children were white and 38 were of various ethnic origins, their ages ranged from 6 months to 15 years 10 months with a mean of 9 years 6 months (median 9 years 8 months). None of these children was on vitamin supplementation before or during the study.

The protocol for the study was approved by the Ethics Committee of the University of Stellenbosch. Informed consent in respect of the extra 5 ml of blood drawn by venepuncture over and above that required for the children's evaluation was obtained from their parents. Plasma albumin levels were determined by protein electrophoresis and serum cholesterol and creatinine levels by the Technicon sequential multiple analyser computer system. Plasma PLP was determined by the tyrosine apodecarboxylase method.[15] Serial determinations of PLP, albumin, cholesterol and creatinine levels were determined whenever possible (necessary), in which case the average of such determinations was taken both in relapse and in remission or in the control group. The analysis of variance was used for the statistical evaluation of all the results obtained.

Results

The mean plasma albumin concentration (± SE) (Fig. 1) in children with the nephrotic syndrome (18,2 ± 1,1 g/l) was significantly ($P < 0{,}001$) lower than in normal controls (41,4 ± 0,5 g/l) and children in remission (38,5 ± 1,0 g/l). The mean plasma albumin concentration was also significantly lower ($P < 0{,}05$) in children in remission than in normal controls. Similarly, the mean plasma PLP concentration (Fig. 2) was significantly ($P < 0{,}001$) lower in children with the nephrotic syndrome (3,9 ± 0,3 ng/ml) than in normal controls (10,8 ± 1,0 ng/ml) and children in remission (11,5 ± 0,7 ng/ml). The difference in mean plasma PLP in normal controls and children in remission was not significant. Thus a significant ($P < 0{,}001$) positive correlation ($r = 0{,}81$) existed between plasma albumin and PLP levels in these patients (Fig. 3). As expected, the mean serum cholesterol concentration (10,3 ± 0,7 mmol/l)

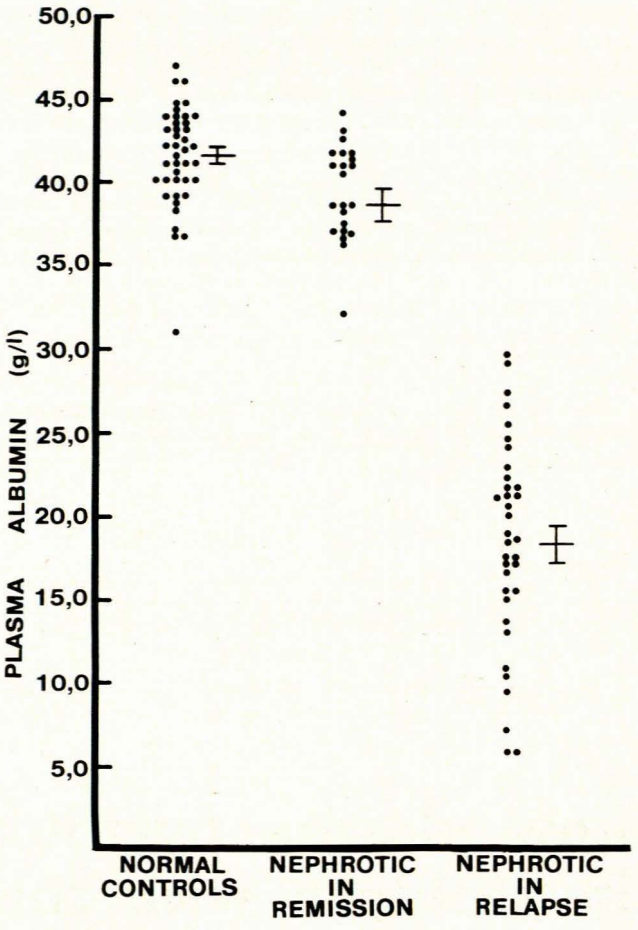

Fig. 1. Mean plasma albumin concentration in normal controls and children with the nephrotic syndrome in remission and relapse.

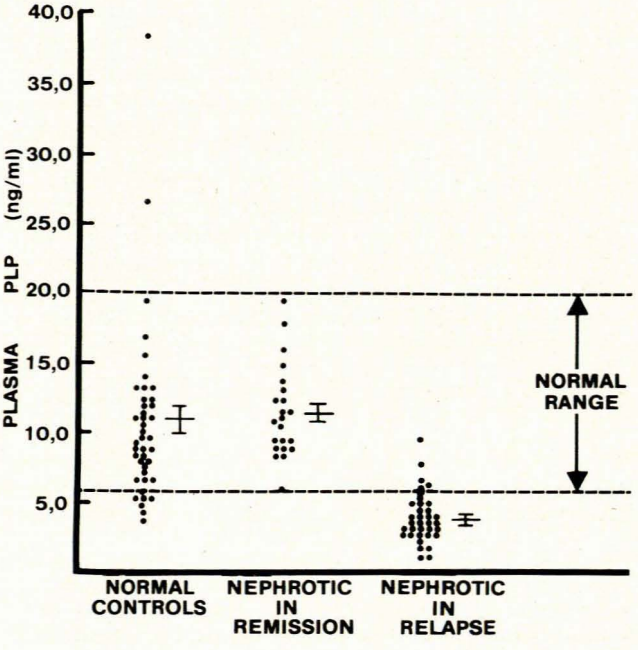

Fig. 2. Plasma PLP levels in normal controls and children with the nephrotic syndrome in remission and relapse.

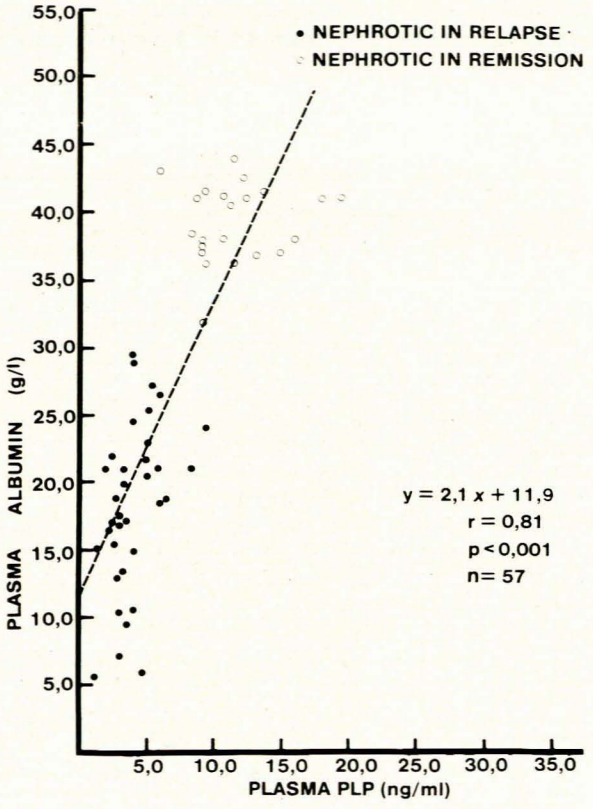

Fig. 3. Correlation between plasma albumin and PLP levels in children with the nephrotic syndrome in relapse and remission.

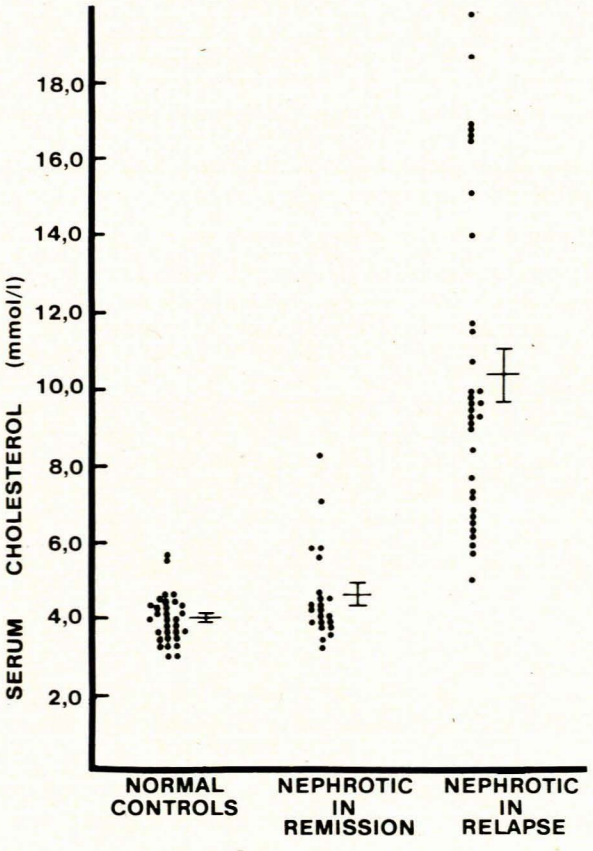

Fig. 4. Serum cholesterol concentration in normal controls and children with the nephrotic syndrome in remission and relapse.

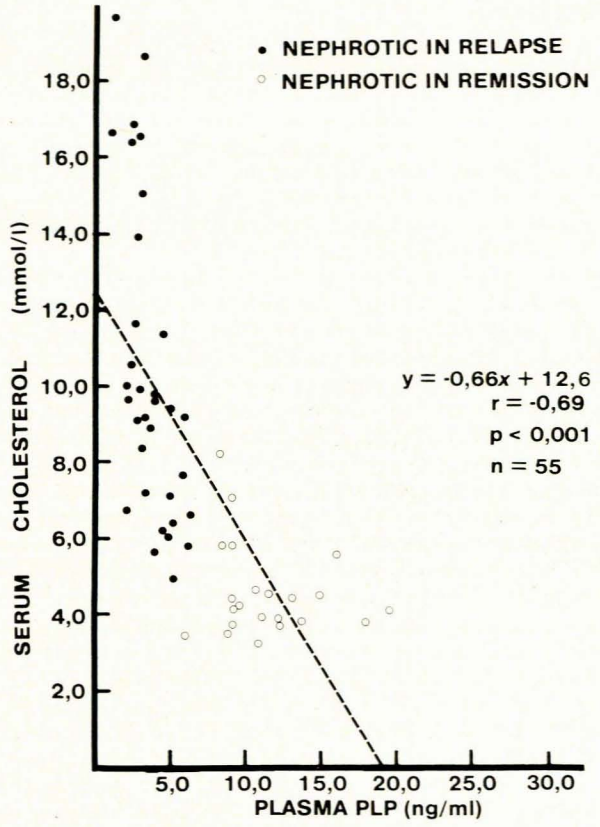

Fig. 5. Correlation between serum cholesterol and plasma PLP levels in children with the nephrotic syndrome in relapse and remission.

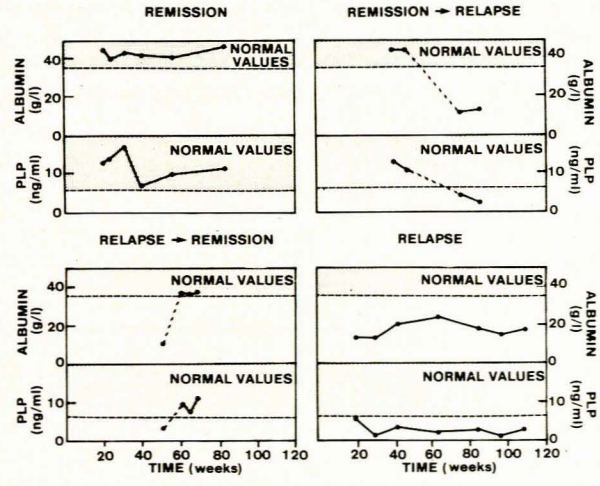

Fig. 6. Sequential plasma albumin and PLP levels in 4 typical patients during the course of their illness.

was significantly ($P < 0,001$) higher in the patients in relapse than in normal controls (4,0 ± 0,18 mmol/l) and children in remission (4,5 ± 0,3 mmol/l) (Fig. 4). Furthermore, a significant ($P < 0,001$) negative correlation ($r = -0,69$) existed between serum cholesterol and plasma PLP levels (Fig. 5). Sequential determinations of plasma albumin and PLP levels during the course of the illness in 4 typical patients are presented in Fig. 6.

Discussion

Our findings have shown for the first time that, regardless of the aetiology of the nephrotic syndrome, 88% of patients in relapse have low circulating plasma levels of PLP. A positive significant correlation was obtained between plasma levels of PLP and albumin and a negative one between plasma PLP and serum cholesterol levels. Remission of the syndrome was associated with spontaneous normalization of plasma PLP levels in all the patients studied.

The underlying mechanism of the low plasma PLP levels is not at present clear. PLP, the main circulating vitamer in blood, is known to be 'almost totally' bound to albumin.[3] The nephrotic syndrome is characterized by massive proteinuria, either selective (mainly albumin) or non-selective (albumin + other proteins), generally depending on whether the nephrotic syndrome is due to MCD or not. It would therefore appear that increased urinary excretion of PLP in the albumin-bound form may be responsible for the low PLP levels documented in our patients. This postulate would be consistent with the spontaneous normalization of plasma PLP levels upon remission. The importance of proteinuria is further substantiated by the normal plasma PLP levels in the children in remission, in whom the plasma albumin level was significantly lower than that of normal controls, which may be due to the fact that the patients were sampled too early in remission. A similar mechanism has been proposed for other protein-bound materials, such as calcium and vitamin D and its vitamers,[16] which are reported to be low in patients with the nephrotic syndrome. Alternatively, and in view of the documented malabsorption of certain nutrients[17] such as Ca^{2+} in patients with the nephrotic syndrome, the absorption of vitamin B_6 may be impaired in these patients.

Although plasma PLP is considered to be a reliable index of vitamin B_6 nutrition,[18] it is not clear whether the low plasma PLP levels reported in the present study indicate vitamin B_6 deficiency in these patients, particularly in view of the hypoalbuminaemia and proteinuria which characterize the nephrotic syndrome. However, in view of the important role of vitamin B_6 in intermediary metabolism, prophylactic administration of vitamin B_6 supplements in the management of these patients would appear to be desirable.

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