CHAPTER V

CONCLUSION

In these experiments it has been shown clearly that pharmacologic doses of glucocorticoid (prednisolone) had adverse effects on adrenocortical functions in 3 groups of the patients studied,i.e. nephrotic syndrome, rheumatic heart diseases and rheumatoid arthritis. These alterations in adrenocortical functions were interpreted by the change in the circadian rhythm of normal diurnal variation as well as the suppression of plasma cortisol levels and decreased 24 hour urinary 17-OHCS excretion which reflects the total cortisol production indirectly. The disturbed adrenocortical functions are influenced by the dose, duration and method of administration. These suppressed adrenocortical functions have been shown to be directly correlated to the dose and duration of steroid administration. However the method of steroid administration also plays an important role of adrenocortical suppression. This has been demonstrated in the patients with nephrotic syndrome who received different therapeutic regimen between every day schedule and every other day schedule. With the same doses of prednisolone (interpreted as mg/kg/day) and the same duration of therapy, those who received the oral prednisolone every day disclosed the more serious adverse effects on the adrenocortical function. The longer period of resting state (days interval without taking prednisolone) showed the less suppressive effects on the adrenocortical function.

and plasma cortisol levels were higher in patients receiving alternate-day therapy than in those receiving daily steroid treatment.

This is obviously the advantage of the alternate-day schedule over that of the every day schedule because of less suppressive effect on adrenal function. On the "off-day" when corticosteroids are not given, normal or low levels of cortisol maintain the stimulus to corticotrophin-releasing factor and production of adrenocorticotrophic hormone. Hypothalamo-pituitary-adrenal mechanisms are greater sensitive to low levels of plasma cortisol in patients receiving every other day steroids than daily therapy. (Fleisher,1967;Ackerman and Nolan, 1968)

Prolonged high-dosage steroid therapy is recognized as the treatment of choice in the management of childhood nephrosis. Such therapy is accompanied not only by suppression of the endogenous pituitary adrenal axis, but also by cessation of growth, convulsion, osteoporosis, gastrointestinal bleeding. Because of the short periods of observation in the present study, growth suppression was not evaluated. The advantages of every other day steroid therapy are its less severe side effects than those expected from identical amounts of corticosteroids administered in daily doses. (Soyka and Saxena, 1965; Soyka, 1967., Harter et al., 1963)

Patients with rheumatic heart disease

From Tables 1 and 4 it was shown that in patients receiving oral prednisolone of different doses, the mean values of plasma cortisol levels in the morning and in the afternoon were significantly lower ($p<0.001$) than those in normal subjects. In the group receiving oral prednisolone 3 times of physiologic dosage these levels were significantly higher ($p<0.001$) than those found in the group receiving 7.5 times, the 7.5 times higher ($p>0.05$) than those found in patients receiving 10 times, the 10 times significantly higher ($p<0.001$) than those found in patients receiving 12.5 times, the 12.5 times significantly higher ($p<0.005$) than those found in patients receiving 15 times.

From Tables 6 and 9 it was shown that in patients receiving oral prednisolone of different doses, the mean values of 24 hour urinary 17-OHCS excretions were significantly lower ($p<0.001$) than that in the normal subjects. In the group receiving oral prednisolone 3 times of physiologic dosage the excretion was significantly higher ($p<0.025$) than that found in the group receiving 7.5 times, the 7.5 times significantly higher ($p<0.005$) than that found in patients receiving 10 times, the 10 times significantly higher ($p<0.025$) than that found in patients receiving 12.5 times, but the 12,5 times not significantly higher ($p>0.05$) than that found in patients receiving 15 times.

From Tables 6 and 9 it was shown that in patients receiving oral prednisolone of different doses, the mean values of 24 hour urinary 17-KS excretions were significantly lower ($p<0.001$) than that in the normal subjects. In the group receiving oral prednisolone 3 times of physiologic dosage the excretion was significantly higher ($p<0.001$) than that found in the group receiving 7.5 times, the 7.5 times significantly higher ($p<0.001$) than that found in patients receiving 10 times, the 10 times significantly higher ($p<0.01$) than that found in patients receiving 12.5 times, the 12.5 times significantly higher ($p<0.025$) than that found in patients receiving 15 times.

Administration of corticosteroids inhibits the release of corticotrophin through the so-called feedback system, and this provides a ready explanation for the low plasma cortisol levels observed in steroid-treated patients.

The results of the present study showed that with higher doses of the steroid therapy the pituitary-adrenal axis was greater suppressed than with the lower doses. The results are not in agreement with those studies by Shuster and Williams (1961) who found that small doses of corticosteroids did not suppress secretion of cortisol by the adrenal. The reason for this difference could be because the patients in this present study were children whose pituitary-adrenal axis were more sensitive than those of patients reported by Shuster and Williams, or the lowest dose in this study

was higher than that in their study. High-dose prednisolone had been shown to suppress hypothalamo-pituitary-adrenal function principally at hypothalamic or pituitary level. (Wilson et al., 1976) The degree of adrenal impairment was related to the dose of steroid administered. (Landon et al.,1965)

Glucocorticoids might impair steroidogenesis directly at the adrenal level or indirectly by an effect on the hypothalamus or pituitary. There is evidence on the basis of in vitro and in vivo studies in animals, that exogenous corticosteroids may impair functions by a direct action on the adrenal (Birmingham and Kurlents, 1958; Peron et al., 1960; Black et al., 1961) Bennett (1954) reported that the atrophy and depression of function of the adrenal cortex which may be induced by cortisone are a consequence of suppression of endogenous production of corticotrophin by the pituitary gland, rather than of a direct effect of cortisone on the adrenal cortex.

Patients with rheumatoid arthritis

From Tables 1 and 5 it was shown that in patients receiving oral prednisolone for various durations of therapy, the mean values of plasma cortisol levels in the morning and in the afternoon were significantly lower ($p<0.001$) than those in normal subjects. In the group receiving oral prednisolone for 5 months, the mean levels were significantly higher ($p<0.05$) than that in the group receiving the drug for 9 months, and the value in the latter group was significantly

higher ($p<0.05$) than that in the group receiving the drug for 12 months.

From Tables 6 and 10 it was shown that in patients receiving oral prednisolone for various durations of therapy, the mean values of 24 hour urinary 17-OHCS excretions were significantly lower ($p<0.001$) than those in normal subjects. In the group receiving oral prednisolone for 5 months the excretion was significantly higher ($p<0.05$) than that in the group receiving the drug for 9 months, and value in the latter group was significantly higher ($p<0.005$) than that in the group receiving the drug for 12 months.

From Tables 6 and 10 it was shown that in patients receiving oral prednisolone for various durations of therapy, the mean values of 24 hour urinary 17-KS excretions were significantly lower ($p<0.001$) than that in the normal subjects. In the group receiving oral prednisolone for 5 months the excretion was not significantly higher ($p>0.05$) than that in the group receiving the drug for 9 months, and the value in the latter group was significantly higher ($p<0.005$) than that in the group receiving the drug for 12 months.

During prolonged corticosteroid treatment, the diminution in endogenous ACTH output and the resulting decrease in adrenal stimulation lead to marked hypoplasia of the adrenal glands. The results in the present study showed that with longer duration of therapy the pituitary-adrenal axis was greater suppressed than with shorter term therapy. This result agrees with Naysmith et al. (1976) who found

that long-term, continuous corticosteroid therapy was associated with suppression of the hypothalamo-pituitary adrenal axis and prolonged steroid therapy even with maintenance doses would impair adrenal function (Engleman et al., 1953, Larzelere et al., 1959) The degree of adrenal impairment was related to the duration of glucocorticoid therapy. (Landon et al .1965)

It has been known for many years that prolonged administration of corticosteroids can cause atrophy of the adrenal glands. (Fraser et al., 1952; Lewis et al., 1953) and that the severity of the atrophy is proportional to the duration of administration (Salassa et al., 1953; Bennett, 1954) and dosage of therapy. This atrophy is characterized by a decrease in weight of the gland as compaired to the normal weight and a narrowing of the cortex with loss of lipid content of cells both in the zona glomerulosa and in the zona fasciculata.

Adrenal atrophy may lessen the body's ability to withstand trauma and stress. Fraser et al. (1952) found that the patient who underwent major surgery after receiving cortisone for a period of eight months died of immediate postoperative shock. Postmortem examination showed marked bilateral adrenal atrophy, suggesting adrenal insufficiency.