

that there are cytological, hormonal, enzymatic, metabolic, neuromuscular and electrolytic effects of ACTH and cortisone, it is not difficult to understand the far-reaching bodily changes produced. While it is true that these effects appear daily as a part of the body's normal response to stress and the consequent adrenal cortical stimulation, it is rare that they reach the proportions seen with ACTH and adrenal steroid therapy. Fortunately, most diseases that are amenable to ACTH and cortisone therapy respond to doses of the hormones not far in excess of those produced normally by the adrenal in response to the stress of a disease. Actually, however, the adrenal cortical hormone level is often exceeded to some extent in order to provide adequate control of the disease. It is then that complications develop, sometimes unavoidably, because of the large doses of hormone required. As we learn more and more about applying adjunctive agents which will reduce the number and the severity of the complications—viz., potassium chloride for hypotassemic, hypochloremic alkalosis, insulin for hyperglycemia and estrogens for excessive masculinizing effects—it will be possible to extend treatment with ACTH and adrenal steroids to more and more patients without causing complications. However, at present their widespread use without a proper understanding of the physiology of the pituitary-adrenocortical system and the physiology and pharmacology of adrenal steroids is going to continue to lead to complications—some reversible, others permanent and still others fatal. It is hoped that the above discussion of the prevention and diagnosis of the complications of ACTH and cortisone therapy will serve a useful purpose in allowing those afflicted with disease to be treated properly, completely and safely.

DISCUSSION

DR. MARIAN W. ROPES, Boston: In rheumatoid arthritis we had some impressions differing from Dr. Frawley's, particularly in regard to the dangers. I agree entirely that the acute dangers, especially the acute electrolytic disturbances, can be relatively well controlled and that the glycosuria and the hypertension usually disappear very quickly after stopping the treatment. Usually one can prevent the electrolyte disturbances by giving potassium chloride, 4 Gm. a day, and by giving a low sodium diet. However, there remains the possibility of slow, gradual retention of sodium and water. We have already begun to see some difficulties that may be on this basis after three to five months of treatment. One patient recently went acutely into cardiac failure when she contracted what appeared to be a severe virus infection. We had no reason to think she had cardiac disease, and we assume that the failure was due, at least in part, to the slow retention of sodium and water. She lost 8 lb. (3.5 Kg.) in the next few days and has now regained cardiac compensation.

In dealing with psychoses we have been much less fortunate than those at some other places. We think that one cannot pick the patients in whom psychoses are going to develop. We have seen them develop from average or large doses of ACTH and cortisone. Of course, it is true that in some of the patients there had been emotional disturbances of moderate to severe degree, as is not uncommon in many patients with chronic disease, but we think we cannot predict whether an individual will become psychotic. One of the more severe psychoses we have seen occurred in a relatively stable patient. Other workers have reported severe psychoses, some apparently permanent. There are several reported suicides as well as several suicidal attempts.

The other thing that we have seen that worries us a little is decalcification of bones. Dr. Frawley said he hadn't seen osteoporosis. We don't know how to explain the difference. It is true that we deal with diseases that affect the bone, but loss of calcium during administration of these hormones has been shown by all metabolic studies. Several fractures have occurred. To date I think all of them have healed satisfactorily. The two we have seen have healed quickly.

We are also disturbed about the concealing of manifestations of infection in patients receiving these hormones. Surely, as Dr. Frawley said, pneumonia can develop without any symptoms