A.C.T.H. IN NEPHROSIS

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During the past two years 16 cases of nephrosis have been treated with cortisone and/or A.C.T.H. (adrenocorticotrophin) at this hospital. The results of cortisone treatment have been reported previously (Arneil and Wilson, 1952) and corresponding findings for A.C.T.H. are now given and the value of the two hormones compared. The criteria used when including a patient in this investigation and the methods of study have been described in the previous paper. A.C.T.H. was given for a period of 12 days, the daily dose varying from 40 to 80 mg. intramuscularly with 2 to 3 g. of potassium chloride orally. The effect of such treatment on the oedema, albuminuria, serum proteins, plasma cholesterol levels and other biochemical tests are discussed below. Nine patients were treated with A.C.T.H. and were given 15 courses in all; second and third courses are designated (2) and (3) throughout the text.

Effects of A.C.T.H. on Oedema

Variations in oedema were judged by alterations in the weight of the child. During the first six days of A.C.T.H. therapy the weight rose appreciably on 12 occasions but in the last six days five patients lost

weight and each of these five subsequently had a marked diuresis. No patient who continued to gain weight until the end of A.C.T.H. treatment subsequently had a diuresis. Within 12 days of stopping A.C.T.H. treatment, the main fluid loss occurred: at times this was extensive and in one case amounted to almost 11 kg. More detailed information will be found in Table 1 which shows the average weights of patients during a series of six-day periods. In E.B. and D. McG. the gross oedema recurred after nine and 114 days respectively; in neither D.M., J.N. nor E.B. (2) had it returned after six months.

Effects of A.C.T.H. on Albuminuria

On 14 of the 15 occasions the albuminuria increased during treatment but diminished in all cases within six days after hormone treatment had ceased. The diminution in albuminuria was unassociated with diuresis on seven occasions. Three patients in whom diuresis started during therapy had a marked lessening of albuminuria towards the end of treatment. In P. McD., from whom collection of urine was achieved frequently, the total daily output of albumin doubled when A.C.T.H. was

TABLE 1
EFFECT OF A.C.T.H. ON OEDEMA AS SHOWN BY ALTERING BODY WEIGHT

	Average Weight for Period (Kg.)							Diuresis	Relapse
	1-6 Days before A.C.T.H.	1-6 Days of A.C.T.H.	7-12 Days of A.C.T.H.	1-6 Days after A.C.T.H.	6-12 Days after A.C.T.H.	12-18 Days after A.C.T.H.	18-24 Days after A.C.T.H.		
D.M.	14.0	15.9	15.1	11.4	—	—	11.8	—	0
J.N.	31.5	32.9	32.2	22.0	21.5	21.8	—	—	0
E.B.	35.3	34.8	32.1	28.8	30.6	34.0	38.2	—	—
E.B. (2)	34.0	35.0	36.0 (32.6)	28.1	27.0	28.0	29.7	—	0
D. McG.	17.4	17.3	16.4	13.6	12.4	12.6	13.0	—	—
D. McG. (2)	16.6	17.0	18.3	19.3	18.9	19.6	19.4	0	—
E.M.	17.9	18.5	18.1	18.8	16.8	17.2	16.8	0	—
E.M. (2)	16.8	17.8	18.4	16.5	17.0	16.8	16.6	0	—
E.M. (3)	19.1	19.8	19.9	20.5	21.5	20.7	—	0	—
P. McD.	17.3	17.6	17.8	17.6	17.5	17.6	—	0	—
P. McD. (2)	18.5	18.6	18.2	18.4	18.5	18.7	—	0	—
C.I.	30.6	30.7	31.1	31.3	31.8	32.9	—	0	—
C.I. (2)	33.2	34.8	35.7	35.0	32.7	—	—	0	—
H.D.	19.8	21.0	22.5	24.5	26.6	27.1	27.3	0	—
A.R.	17.9	16.7	16.5	16.4	16.6	16.6	16.8	0	—

* A.C.T.H. therapy continued a further nine days; average weight for extra period in brackets.

TABLE 2
EFFECTS OF A.C.T.H. ON SERUM PROTEINS

	Total Serum Proteins (g. per 100 ml.)			Albumin (g. per 100 ml.)			Globulin (α and β) (g. per 100 ml.)			Diuresis	Relapse
	Before A.C.T.H.	At End of A.C.T.H.	16 Days after A.C.T.H.	Before A.C.T.H.	At End of A.C.T.H.	16 Days after A.C.T.H.	Before A.C.T.H.	At End of A.C.T.H.	16 Days after A.C.T.H.		
D.M.	4.09	4.71	6.59	0.91	1.21	5.06	3.18	3.50	1.53	—	0
J.N.	3.06	3.65	4.30	0.28	1.13	1.36	2.78	2.53	2.94	—	0
E.B.	3.69	4.14	3.51	0.48	0.45	0.28	3.21	3.69	3.23	—	—
E.B. (2)	3.84	5.78	7.49	0.13	2.72	2.90	3.70	3.06	4.59	—	0
D. McG.	4.50	4.34	5.96	0.75	0.44	3.96	3.75	3.90	2.00	—	—
D. McG. (2)	4.29	4.07	—	0.93	0.75	—	3.34	3.32	—	0	—
E.M.	3.92	4.99	4.06	0.67	0.48	0.57	3.25	4.51	3.49	0	—
E.M. (2)	4.06	5.70	—	0.57	1.66	—	3.49	4.03	—	0	—
E.M. (3)	—	4.65	—	—	0.61	—	—	4.04	—	0	—
P. McD.	5.41	6.14	5.45	2.92	2.52	2.64	2.49	3.62	2.81	0	—
P. McD. (2)	5.45	7.67	5.88	2.64	4.06	3.20	2.81	3.61	2.68	0	—
C.I.	3.85	4.10	4.01	0.92	0.50	0.64	2.93	3.60	3.44	0	—
C.I. (2)	4.01	5.21	5.71	0.64	0.55	0.70	3.39	4.67	5.01	0	—
H.D.	3.76	4.12	4.26	0.58	0.30	1.20	3.18	3.82	3.06	0	—
A.R.	5.02	5.71	5.18	1.39	1.27	2.71	3.63	4.44	2.37	0	—

given and fell to one-half of the original quantity when treatment was stopped. In E.B. (2) this trend was more marked; the daily albumin output, which before A.C.T.H. was given had varied from 2 to 4 g., rose to 4 to 9 g. during treatment, then, although A.C.T.H. treatment continued, fell to 1 g. or less per day for a period of a week. This fall in albuminuria was therefore absolute and not due to dilution of the urine, nor could it be explained by a lowering of the plasma albumin level which had in fact altered little during this period. It would appear that albuminuria is increased during the first few days of the administration of A.C.T.H. to patients with nephrosis, then lessens before or immediately after treatment is stopped, whether or not a diuresis takes place. If the diuresis takes place *before* the absolute daily loss of albumin lessens, then the concentration in the urine will be diminished. On 12 occasions the albuminuria decreased but returned to its former gross levels; in two instances it disappeared and has not recurred after six months.

Effects of A.C.T.H. on Serum Proteins

The total serum proteins were measured before and after the 12 days' treatment and 16 days later (Table 2). During treatment the level of total serum proteins tended to rise and on 12 occasions it was possible to compare the levels before treatment and 16 days after it was stopped. The proteins rose by more than a gramme per 100 ml. in five instances, less than one gramme in six instances and on the remaining occasion fell by a small amount. In each of the four cases in whom the most satisfactory diuresis had occurred (D. McG., J.N., E.B. (2) and D.M.) the level of total serum proteins after treatment exceeded the level before treatment by more than 1 g. per 100 ml. E.B. and A.R. had a transient

diuresis during which the total serum proteins rose but fell thereafter as they relapsed. It is interesting that C.I. (2), an oedematous patient who had a marked rise in proteins after A.C.T.H., had *no* diuresis. The albumin and globulin fractions of the serum protein were measured at the same time as the total proteins and these results are also shown in Table 2. The alpha, beta and gamma globulins were estimated separately, but no significant differences were observed in their behaviour. The levels of albumin before and immediately after treatment were estimated on fourteen occasions. In four instances a marked rise occurred during treatment (J.N., E.B. (2), E.M. (2), P. McD. (2), and diuresis had begun by this time in the first two cases. Nine of the remaining cases had a small decrease in serum albumin. Sixteen days after treatment was terminated, a marked increase had occurred in six instances, by which time four of the patients had shed most of their oedema.

The alterations in serum globulin were also of considerable interest; on three occasions the total globulins were markedly lower 16 days after A.C.T.H. than before. In two of these diuresis had occurred and in all three there was as well a marked increase in serum albumin. In C.I. (2), the case in which no diuresis had occurred when the total serum proteins rose, a marked increase in the globulins explained this rise.

These results indicate that A.C.T.H. may cause a disappearance of oedema without material alteration in the level of albumin, globulin or the total protein in the serum (E.B.); that a rise in the serum albumin is not always associated with diuresis (E.M. (2) and A.R.). A marked rise in serum globulins is not associated with diuresis (C.I. (2)). The patients in whom the best results were obtained were those in

whom the greatest increases in serum albumin occurred in the 16 days after treatment (D.M., D. McG. and E.B. (2)). These alterations are illustrated in Fig. 1 where three typical examples are shown: the first, D.M., had a brisk diuresis and has since been well; the second, D. McG., had a diuresis and relapsed; and the third, E.M., had no diuresis. The first two had a marked rise in serum albumin and fall in serum globulins which was permanent in the case of D.M.

Other Observations

Serial eosinophil counts were completed on 11 occasions; very marked falls occurred during therapy in all except one (P. McD. (2)) and the levels rose again when treatment was stopped. The plasma cholesterol concentration was increased in two cases and diminished in ten. In all of the five cases where diuresis occurred the cholesterol level was lower 16 days after treatment than before (Table 3). The packed cell volume was estimated before, during and

FIG. 1.—Electrophoretic pattern of serum proteins in relation to treatment with A.C.T.H.

TABLE 3
EFFECT OF A.C.T.H. ON PLASMA CHOLESTEROL

	Plasma Cholesterol (mg. per 100 ml.)			Diuresis	Relapse
	Before A.C.T.H.	At End of A.C.T.H.	16 Days after A.C.T.H.		
D.M. (1)	388	596	72	—	0
J.N. (1)	241	208	208	—	0
E.B. (1)	557	554	438	—	—
E.B. (2)	470	436	160	—	0
D. McG. (1)	486	220	224	—	—
D. McG. (2)	410	660	—	0	—
E.M. (1)	296	460	411	0	—
E.M. (2)	411	351	—	0	—
E.M. (3)	—	368	—	0	—
P. McD. (1)	334	228	229	0	—
P. McD. (2)	229	172	182	0	—
C.I. (1)	473	733	731	0	—
C.I. (2)	731	654	459	0	—
H.D. (1)	630	400	460	0	—
A.R. (1)	513	259	335	0	—

after treatment and little alteration occurred in any case, indicating that the fluctuations in total serum proteins, albumin, globulins and cholesterol could not be explained by alteration of the total plasma volume unless the total red blood cell volume altered *pari passu*. The erythrocyte sedimentation rate was high in all cases and was not altered by treatment except in the two children D.M. and E.B. (2) in whom albuminuria and oedema have now been absent for six months; in each of these it had returned to normal levels three months after treatment.

Comparison of the Effects of A.C.T.H. and Cortisone Treatment

The cortisone-treated cases previously reported (Arneil and Wilson, 1952) have since been augmented in numbers, and 15 courses of this hormone have now been given to nine cases of nephrosis. These 15 courses provoked diuresis on 10 occasions in this small series, whereas A.C.T.H. produced diuresis in five out of 13 courses given to nephrotic patients with marked oedema. (Two courses of A.C.T.H. were given (P. McD. and P. McD.) when little oedema was present.) The extent of the diuresis was best judged by loss of weight which ranged up to 10 kg. in each group. The duration of the apparent loss of oedema did not differ significantly in the two groups. Two of the cortisone-treated cases and two of the A.C.T.H.-treated cases have had remissions lasting more than six months; such occurrences may well have been fortuitous.

A striking difference between the two groups was the time of onset of diuresis. This did not occur in any of the cortisone-treated group until after the administration of the hormone had ceased, whereas in all the cases treated successfully with A.C.T.H. diuresis started during the administration of the

hormone and an acceleration occurred when treatment was stopped. Since cortisone was given for a standard period of five days it is not possible to say that diuresis would not have occurred had treatment been continued longer. However, this finding has also been recorded by McCall, Ross, Wolman, Burns, Harpur and Goldbloom (1952) and Luetscher, Deming and Johnson (1951), who found that diuresis did not occur during the administration of cortisone. Although diuresis was provoked by these hormones on 15 occasions in all, only in five instances did loss of oedema persist for more than six months and in one of these five children albuminuria remained present.

In both groups the albuminuria became aggravated during treatment and decreased when hormone therapy was stopped, but on three occasions during A.C.T.H. treatment the albuminuria lessened sharply. On 25 occasions the albuminuria lessened and later returned to the former gross levels. It appears, therefore, that treatment with either A.C.T.H. or cortisone may temporarily affect the albuminuria in some way which is apparently unconnected with diuresis. This fact is encouraging since it suggests that these hormones may have some influence, however indirect, on this basic part of the disease. Similar alterations in serum proteins were produced by both hormones, the tendency being to increase the serum albumin level and reduce the serum globulins after treatment; that is, to return the pattern towards normal. The rise in level of albumin appeared to be most marked in cases which responded by diuresis.

Both A.C.T.H. and cortisone tended to cause a rise in the cholesterol level of the plasma during hormone therapy and a fall when hormone therapy was stopped, to be followed by a return to the former high levels if the nephrotic state returned. These findings only partly agree with the results of Conn, Vogel, Louis and Fajans (1950) who suggested that the level of plasma cholesterol was depressed by A.C.T.H. therapy due to a fall in cholesterol esters used to form cortisone. Adlersberg, Schaefer and Drachman (1950) suggested that cortisone therapy has a 'sparing effect' on cholesterol esters and causes a rise in plasma cholesterol. They also noted hypercholesterolaemia when A.C.T.H. was given for a prolonged period and this appears contradictory to the findings of Conn. Wolfson, Beierwaltes, Robinson, Duff, Jones, Knorpp and Eya (1950) have obtained evidence to suggest that such a rise in cholesterol on A.C.T.H. therapy may result from a depression of the activity of the thyroid gland secondary to reduced secretion of the thyroid stimulating hormone of the pituitary gland.

Toxic Effects of Hormone Treatment

The toxic effects resulting from these hormones are worthy of note. In the A.C.T.H. group sterile abscesses developed in three cases; large, fluctuating and painless, they formed insidiously at the site of injection. Precordial pain was complained of by two patients and diarrhoea occurred on one occasion. A major complication occurred in E.B. (2) who suddenly developed status epilepticus on his nineteenth day of A.C.T.H. therapy (80 mg. daily). He was 8 years old and had no previous history of convulsions. The cerebrospinal fluid was cytologically and chemically normal but the serum potassium was at the very low level of 3.2 mEq. per litre despite the oral administration of 3 g. of potassium chloride throughout hormone treatment. Electrocardiographic tracings confirmed the potassium deficiency and both the serum level and the E.C.G. were rapidly restored to normal by the administration of 13 g. of potassium chloride by gastric tube. Despite adequate and prolonged sedation with intramuscular paraldehyde the boy continued in deep coma, with intermittent convulsions for 72 hours; throughout this period no hypertension was present. He gradually returned to consciousness and developed a psychopathic personality vaguely reminiscent of the post-encephalitis state, which is slowly disappearing.

The advent of convulsions in patients receiving A.C.T.H. or cortisone has been recorded on several occasions in the United States. Sprague (1951) mentions four such patients who had convulsions and two others who progressed to coma and died. The necropsy finding in one of these consisted of degeneration of the cells of the cerebral cortex but in another fatal case treated with cortisone there was a terminal bronchopneumonia at necropsy and congestion of the brain with no abnormalities of the neurons (Geppert, Dietrick, Johnston and Lind 1952). Other cases have been recorded by Lowell, Franklin, Beale and Schiller (1951) and Dorfman, Apter, Smull, Bergenstal and Richter (1951) and were noted to have alkalosis and hypopotassemia (as had our case) but one must conclude that some direct action of the hormones on the cerebral cortex is involved. In the cortisone group low-grade cellulitis of the trunk, unassociated with injection sites, occurred in two cases but on each occasion was easily controlled by penicillin treatment.

The Mechanism of Action of A.C.T.H. and Cortisone in Relieving Oedema

In considering the mechanism by which A.C.T.H. and cortisone relieve the oedema of nephrosis it is necessary to consider the process of oedema forma-

tion. Whatever the lesion existing in the nephrotic patient may be, it is in some way related to the gross albuminuria which is presumably due to a functional or an organic defect in the nephron. The level of plasma albumin is lowered due in part to this renal loss but also to decreased synthesis, possibly in an effort to reduce loss of albumin. When the albumin level in the plasma falls, a marked reduction occurs in the osmotic pressure of the plasma. In these 16 cases of nephrosis the average osmotic pressure exerted by the serum proteins was only 8.6 mm. Hg as opposed to the normal of 30.9 mm. Hg (using the formula of Govaerts as employed by Rennie, 1933). The concentration of chloride ions in the plasma then rises in an effort to maintain osmotic equilibrium (Gamble, 1947). This results in the retention of salt and water with formation of oedema which is presumably produced by an increased output of salt-retaining hormone from the adrenal glands and of antidiuretic hormone from the posterior pituitary gland. Any process which diminishes the production of these hormones should reduce the salt and water retention and cause loss of salt and water from the body with diminution of the oedema. If the underlying process of albuminuria with low plasma albumin content persists such loss of oedema will only continue for as long as endogenous hormone output is reduced; the oedema will then recur.

It has been shown beyond reasonable doubt that the administration of large doses of cortisone reduce output of hormones and atrophy of the adrenal glands (Sprague, 1951; McIntosh and Holmes, 1951) and it is important to remember that this effect of diminishing hormone output applies not only to the 11-oxysteroids but to all other cortical hormones as well. When cortisone is given, a diminished output of 17-ketosteroids can be detected in the urine and a beneficial effect occurs in cases of the adrenogenital syndrome (Bishop, Bray, Mowbray, Merivale and Vaughan-Morgan, 1952). A diminished output of cortisone may be demonstrated by the poor eosinopenic response to A.C.T.H. administration. The loss of sodium and chloride resulting from diminished activity of the salt-retaining hormones has been clearly demonstrated by Luetscher *et al.* (1951). Since D.O.C.A. is fifty times as potent a retainer of sodium as cortisone (Salassa, Sprague, Power and Mathieson, 1950) it seems likely that the sodium-retaining fraction, too, must be affected. In the days succeeding the sudden stoppage of cortisone the adrenal is unable to respond quickly by increasing hormone output, and it is in this critical period that the loss of sodium, chloride and water may cause a disappearance of the nephrotic oedema. This con-

ception of the mode of action of cortisone is shown diagrammatically in Fig. 2.

It appears that this mechanism may be concerned in many of the well known methods of producing diuresis. Such forms of stress as acute pyogenic infection, measles, malaria, burns, scalds or the administration of nitrogen mustards should theoretically all provoke an outflow of adrenal hormones to be followed by a sudden decrease and a consequent diuresis. It has been known for many years that diuresis does in fact occur after such acute incidents. It should be emphasized that the mechanism of adrenal depression is purely an action on sodium and water metabolism independent of plasma protein and is basically physiological.

A similar mechanism can be suggested as an explanation of the diuresis which follows treatment with A.C.T.H. Such exogenous A.C.T.H. boosts the endogenous adrenal output and the 11-oxy-steroids in turn depress the pituitary gland. When treatment is suddenly stopped the adrenals cease to excrete hormones until the depressed pituitary recovers its functional state. The result once more is a transient reduction in adrenal hormone output for a period of several days after hormone therapy stops. This explanation is satisfactory so far as it goes but does not account for the occurrence of diuresis during A.C.T.H. therapy. Several explanations have been advanced by Thorn, Merrill, Smith, Roche and Frawley (1950) to explain this phenomenon. They suggested that renal 'tubular fatigue' may result from a sustained high level of 11-oxy-steroids or that these hormones may indulge in competitive inhibition with the desoxycorticosterone-like hormones, or that increased glomerular efficiency may occur during A.C.T.H. therapy.

None of these explanations appears completely satisfactory and we suggest that, just as A.C.T.H. in some way depresses the function of the anterior lobe of the pituitary, so does it depress the posterior lobe, with consequent diminution in circulating antidiuretic hormone and resultant water diuresis. It has been shown that such a sequence of events occurs when pitressin is given to nephrotic patients (Robinson and Farr, 1940). The finding of an excess of antidiuretic substance in the systemic blood of nephrotic patients (Barlow, 1952) encouraged us in this speculation. The investigation of this problem leading to the identification and analysis of a peptide in nephrotic urine, closely resembling posterior pituitary hormone, has been published elsewhere (Arneil and Wilson, 1953).

Summary and Conclusions

The value of A.C.T.H. and cortisone in provoking diuresis in nephrotic patients has been confirmed. The effect of these hormones on various clinical and biochemical findings was investigated. The diuresis is usually evanescent and the mechanism involved is discussed.

These results suggest that hormone therapy is at least as good as any other form of treatment at present available for nephrosis. Cortisone treatment gave better results than A.C.T.H.; it caused diuresis more frequently, had fewer toxic effects and was effective when given orally.

It is with pleasure that we thank Professor Stanley Graham for his advice and criticism on this work and we are indebted to him and to Dr. J. H. Hutchison, O.B.E., for allowing us to investigate cases under their care.

FIG. 2.—Suggested explanation of diuresis following administration of cortisone. The term 'DOCA' is used here to refer to human sodium-retaining hormones and not to the synthetic substance deoxycorticosterone acetate.

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Case Reports

D.M., aged 21 months, became oedematous on April 28, 1953, and was admitted to hospital 10 days later. His weight was 12.3 kg. and he had 12 g. of albumin per litre of urine. Little ascites was present and the blood pressure was 100/70 mm. of mercury. The urine contained occasional casts but no red blood cells.

A course of 50 mg. A.C.T.H. daily for 12 days was started on May 20. The oedema and albuminuria increased during therapy but then fell before the hormone was discontinued. Diuresis and lessening of albuminuria were very marked when the hormone was discontinued. He was discharged home on June 7 with slight oedema, no albuminuria and a normal plasma protein pattern. The plasma cholesterol level fell to 254 mg. per 100 ml. and six months later he was very well and had no oedema or albuminuria and a normal E.S.R.

J.N., a boy, aged 6½ years, was noted to have oedema and was admitted to hospital in April, 1951. Ascites and albuminuria amounting to 16 g. per litre were present. The urine contained a number of hyaline and granular casts but no red blood cells. The blood pressure was 90/50 mm. Hg. Despite a low-sodium diet the oedema continued to increase and a five-day course of 100 mg. cortisone twice daily was started. Next day a small haematemesis occurred, and four days later a low-grade skin infection in the lumbar region appeared and was controlled by penicillin therapy. After cortisone was stopped diuresis occurred and the degree of albuminuria markedly lessened.

The albuminuria gradually returned but the boy remained practically free of oedema until July, 1951, when the oedema, ascites and gross albuminuria returned. He remained at home with persisting oedema and albuminuria until April 20, 1952; anasarca then became

more pronounced and he was readmitted to hospital. His blood pressure at this time was 110/80 mm. Hg and the total serum proteins had fallen to 3.06 g. per 100 ml. (albumin=0.28 g.). A course of A.C.T.H. (50 mg. daily for 12 days) was given, during which period his weight and the albuminuria at first increased and decreased; both these symptoms lessened markedly when hormone therapy was discontinued. The albuminuria rapidly returned and remained until December, 1952, although the boy was still free of oedema. The serum proteins returned towards the normal pattern but did not attain normal levels, while the cholesterol fell to 208 mg. per 100 ml. of plasma.

E.B. was a boy aged 11 years when admitted on April 17, 1952, with oedema and ascites. He was noted to have albuminuria amounting to 12 g. per litre, with occasional casts, but no red blood cells, in the urine. His blood pressure was 110/70 mm. Hg, and he weighed 34 kg. A course of A.C.T.H. (40 mg. daily for 12 days) was begun on April 22. At the beginning of treatment oedema increased, but then began to decrease and finally disappeared two days after A.C.T.H. was stopped. The albuminuria was little altered during treatment but diminished markedly after the hormone was stopped, only to return in a few days, as the oedema worsened again. A course of cortisone was given intramuscularly and a transient diuresis and loss of albuminuria followed this. A second course of cortisone was given as soon as oedema began to reform; this accelerated the rate of oedema formation but another temporary diuresis followed cessation of therapy. A third course of cortisone was given, this time orally, and diuresis, dramatic but evanescent, once again occurred. It was then decided to give a course of A.C.T.H. in a large dosage continued over a long period. The hormone, 80 mg., was given intramuscularly each day with 2 g. potassium chloride. This decision to continue treatment for a long period was an endeavour to confirm and study the partial diuresis and loss of albuminuria previously noted to have occurred while A.C.T.H. was being given. On the seventh day of treatment diuresis and lessening of albuminuria were obvious. By the tenth day only a trace of albumin was present in the urine, but oedema was increasing again although the total serum proteins, and particularly the serum albumin, had markedly risen. The blood pressure was 125/95 mm. Hg. The boy's condition appeared excellent when, quite suddenly, he lapsed into a series of severe sustained convulsive seizures which could only be controlled by very large dosage of paraldehyde intramuscularly. He lapsed into coma and for 72 hours death appeared imminent. Lumbar puncture yielded normal results. Potassium chloride, 13 g., was given by gastric tube in the next 10 hours and the electrocardiogram and serum potassium level rapidly returned to normal. The blood pressure was 120/90 mm. Hg. After 72 hours in coma the convulsions slowly subsided and over a period of a further 72 hours he slowly regained consciousness. Over a period of ten days he gradually began to swallow, to sit up and to speak. His intelligence appeared to have suffered little, but a marked deterioration in temperament and behaviour was noted, reminiscent of the post-

encephalitic states or of frontal lobe damage. While these alarming occurrences were taking place a very marked diuresis had occurred and the albuminuria had completely disappeared. By December, 1952, he had no albuminuria, ascites or oedema, a normal electrophoretic serum protein pattern and a plasma cholesterol level of 162 mg. per 100 ml. It is hoped that this heroic treatment has permanently cured the nephrosis. His behaviour has improved considerably since his discharge and he was well in April, 1953.

D. McG., a boy aged 21 months, healthy until January 14, 1952, developed oedema and albuminuria with some ascites, all of which persisted despite two months' rest in bed at home. On March 7 he was admitted to hospital and was then found to weigh 17.4 kg., to have marked oedema and ascites, 10 g. of albumin per litre of urine (Esbach) and a blood pressure of 100/70 mm. Hg. A few red blood cells were in the urine. The total protein content of the serum was 4.5 g. per 100 ml. (albumin 0.75 g., globulins 3.75 g.) and the plasma cholesterol level was 486 mg. per 100 ml. The patient was unable to see on account of the oedema of the eyelids. He was put on a low-sodium diet and on March 15 A.C.T.H. treatment was started. He became cyanosed and had precordial distress during treatment, although the blood pressure was not raised. An erythematous patch appeared on the abdominal wall at this time. During the latter part of A.C.T.H. therapy a small loss in weight occurred and by April 4 the oedema had disappeared and the albuminuria markedly decreased. The child continued to be very well with no oedema and less than 1 g. of albumin per litre until May 26 when he contracted chickenpox. He was sent to a fever hospital and while there the oedema and gross albuminuria returned, and the total serum proteins fell to 3.64 g. per 100 ml. By July 23 the oedema was again gross and he was readmitted to hospital. A second course of A.C.T.H. (10 mg. four times daily for 12 days) was given but this time no diuresis occurred. On September 1 he developed pneumococcal empyema, peritonitis and meningitis, and died two days later despite adequate treatment with antibiotics.

E.M., a girl aged 3 years, was admitted to hospital on April 1, 1952, one month after the onset of oedema, marked albuminuria and ascites. The blood pressure was 90/55 mm. Hg and the urine contained no red blood cells and few casts. She was given a low-sodium diet for four weeks then, as the oedema was increasing, a 12-day course of A.C.T.H. (40 mg. daily). A slight fall in weight (1 kg.) occurred about five days after treatment was stopped but this was considered to be too small to be significant. Two further courses of A.C.T.H., each of 12 days' duration (40 mg. A.C.T.H. daily on the first occasion and 60 mg. A.C.T.H. on the second occasion) were given with no diuresis and only a transient alteration in the quantity of albuminuria. The cholesterol levels remained elevated and she required paracentesis abdominis. By December, 1952, her condition was no better and the oedema, ascites, albuminuria and abnormal blood chemistry as severe as before.

P. McD. was a girl aged 6 years when, on May 1, 1952, she was found to have albuminuria. No improvement resulted from rest in bed at home for eight weeks. She was kept under close observation both in the ward and as an out-patient for a further period of a month and was then found to have clinically detectable oedema (minimal) for the first time. Her blood pressure was 95/70 mm. An urea concentration test was normal (urea concentrated to 3.19 g. per 100 ml.). Throughout this period the serum albumin level had been diminished with consequent reversal of the normal albumin globulin ratio and lowering of the total serum proteins.

Despite the absence of gross oedema she was thought to have nephrosis and on August 17 the first course of A.C.T.H. (40 mg. daily for 12 days) was given. During treatment her weight rose by 1 kg. and albuminuria increased considerably. After A.C.T.H. she returned to her original weight and the albuminuria became less than before treatment for a period of two weeks. Her plasma cholesterol fell but the serum proteins were not markedly altered. On September 22nd, 1952, she was started on a second course of A.C.T.H., this time 80 mg. daily for 12 days, with an essentially similar result. This time, however, the serum proteins rose to 7.67 g. per 100 ml. after treatment and the albumin level was 4.06 g. per 100 ml. The plasma cholesterol fell to 172 mg. per 100 ml. and one week after A.C.T.H. the albumin content of the urine had fallen to less than 1 g. per litre. Albuminuria persisted for six months later but no oedema was present.

C.I. was a healthy girl, aged 12 years when oedema of legs and eyelids, with ascites, was noted on May 1, 1952. Two weeks later she was admitted to hospital. Her urine contained 12 g. of albumin per litre and a number of casts and a few red blood cells were in the sediment. Her blood pressure was 115/80 mm. and she weighed 31.8 kg. She was given a diet low in sodium for three weeks and then a course of A.C.T.H. (40 mg. daily) for 12 days. No improvement occurred in her clinical condition, or in her albuminuria. A second course was started on June 25, 1952, with no better result; her oedema and albuminuria worsened while she was receiving A.C.T.H. and improved temporarily thereafter. Hypertension developed in October, 1952, but her gross oedema, ascites, albuminuria and biochemical upset remained unaltered until her death in February, 1953, from left heart failure.

H.D., a boy aged 4½ years, developed oedema on March 9, 1952, albuminuria was noted on March 14, and he was admitted to hospital three days later. He weighed 22.0 kg., his blood pressure was 106/65 mm. Hg and very marked oedema and ascites were present. The urine contained 12 g. of albumin per litre, a number of casts and 24,000 red blood cells in a 12-hour specimen.

A 12-day course of intramuscular A.C.T.H. (40 mg. daily) was begun on March 23 with 2 g. of potassium chloride by mouth. No diuresis occurred, nor were the abnormal biochemical findings materially altered. The albuminuria very markedly increased during treatment and, although it decreased when the A.C.T.H. was

stopped, was more marked after treatment than before. A five-day course of cortisone (300 mg. per day) was followed by a very marked diuresis, with loss of albuminuria for a short period and less than 2 g. per litre of urine thereafter. The serum proteins rose to 8.4 g. per 100 ml. (albumin 5.628 g.) and the plasma cholesterol level fell to 168 mg. per 100 ml. His blood pressure was 80/40 mm. of mercury. He was dismissed home with no oedema but persisting albuminuria. Slight oedema was present on September 23 and this slowly began to increase in amount. On November 11 he was readmitted with a recurrence of gross oedema and albuminuria and a return to the previous abnormal biochemical findings in the blood. He had bacterial pneumonia and this was followed by a transient diuresis.

A.R., a boy aged 3 years, developed oedema on February 1, 1952, was admitted to hospital on March 6. and found to have slight oedema with ascites. The urine contained a few casts and red blood cells and the albumin content amounted to 10 g. per litre: the blood pressure was 105/65 mm. Hg. A.C.T.H. treatment was started on March 15 and 100 mg. was given daily for 12 days. Little alteration occurred in his weight but the albuminuria was at first increased, then lessened on A.C.T.H. and markedly decreased after treatment was stopped. The albuminuria later returned and the oedema increased, ascites developing later. The electrophoretic pattern of the serum proteins returned towards normal after treatment but later relapsed. When last seen in December, 1952, he was grossly oedematous and had marked albuminuria and ascites.