systemic nature of the childhood infection and its prevalence suggest that it can be acquired spontaneously by routes other than eye-to-eye transmission. However, we lack information about the quantity and route of virus excretion in the child and the precise nature of its transmission.

Conclusion

Thus I have come to the end of my story of shipyard eye. At present adenovirus type 8 unquestionably causes epidemic keratoconjunctivitis, and it may well be the sole cause of this disease in its typical form. Thus it is proper henceforth to support the clinical impression of E.K.C. by laboratory evidence of infection with adenovirus type 8—either by virus isolation or by the demonstration of a rise in specific neutralizing antibody titre. The mythical "virus of epidemic keratoconjunctivitis" or "Sanders virus" of textbooks may be discarded—the poison phial is lost for ever. Finally—in North America and Great Britain at least—the hero of the beginning of the story, the eye physician, is the villain at the end. It is he who spreads the virus among his patients in shipyard, office, and hospital, and who is responsible for outbreaks of the disease in the Western world.

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"The previous year was disappointing enough, but the year under review has been the most frustrating in the 21 years' history of the Nuffield Department of Anaesthetics. Any scientific investigation, and much of the routine work, in the 'temporary' accommodation of this, the first of the Nuffield Medical Departments, has been made almost impossible by the distractions of noise and dust from the contiguous new buildings which are being erected in accordance with the policy of catering for undergraduate clinical teaching. This miserable state of affairs was verified by visits of three of the Nuffield Trustees and the then Chairman of the Board of Governors of the United Oxford Hospitals. In the department there are posts for four graduate assistants, for which hitherto there has always been keen competition. A year ago all four assistants tendered their resignations. Dr. Epstein was persuaded to continue, but even at the time of writing this report conditions have not improved sufficiently to attract inquiries from suitable candidates for the other posts. Owing to the fact that there was no suitable accommodation, the visit to Oxford of 20 Continental anaesthetists organized by the British Council had to be restricted to an inspection of the respiration unit—and a sight-seeing tour of the city."—*Oxford University Gazette*, March 6, 1959.

DIURETIC EFFECT OF STEROID THERAPY IN OBSTINATE HEART FAILURE

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"A creaking door hangs longest."—ANON.

Clinical experience in the relief of heart failure has evolved an effective therapeutic routine, the roots of which are buried in herbal folklore, its branches growing into the realms of biochemistry and endocrinology. The beneficial effect of bed rest, digitalis administration, diuretic therapy, and a low-salt regimen have proved the efficacy of this routine, but in oft-repeated or long-continued congestive heart failure this treatment may become ineffective. The clinician is dispossessed of his traditional remedies and the patient succumbs with unrelenting dropsy.

The inadequacy of treatment in late-stage heart failure has become apparent with increasing frequency since antibiotics, by reducing the hazard of intercurrent infection, have prolonged the lives of cardiac patients, allowing heart failure to continue its variable course and eventually to persist as a permanent state. That intractable heart failure is capable of responding to routine therapy following the administration of prednisone has been shown by Muller *et al.* (1956a) and by Gutner *et al.* (1957). Their results, however, were not uniformly successful.

It is the purpose of this paper to describe a rationale for the success of prednisolone therapy in patients with obstinate heart failure.

Heart Failure

When the heart fails, the inability of the cardiac output to satisfy the metabolic demands of the tissues (Altschule, 1938) initiates circulatory adjustments attempting to correct this deficiency. The cardiac output is augmented by a compensatory increase in circulating blood volume which results from an independent variation of renal excretion of sodium and water, at times even at the expense of the tissue fluid tonicity (McCance, 1936; Leaf *et al.*, 1953; Weston *et al.*, 1953). Initially a primary retention of sodium occurs, with water retention a secondary phenomenon. Since sodium predominates in the extracellular space, fluid accumulates in this compartment, thereby increasing plasma volume (Gibson and Evans, 1937; Berson, 1954), venous pressure, and interstitial fluid volume, manifested as oedema. The haemodynamic principles of the "backward failure" hypothesis (Hope, 1832) largely determine the distribution of this excess fluid in either the peripheral or the pulmonary circulation. The ultimate clinical picture is also influenced by such factors as the character of the heart lesion, salt and water intake, physical activity, local tissue metabolism, and therapy.

These principles, however, cannot be applied to all patients with heart failure. Hollander and Judson

(1956) have shown that sodium retention occurs only in patients with systemic congestion and significant elevation of right ventricular and diastolic pressure, whereas most patients with pulmonary congestion but normal venous pressure can excrete loads of sodium and water. Furthermore, salt deficiency can be induced in patients with chronic congestive heart failure without reducing their oedema and, indeed, on occasions, whilst oedema is accumulating. Clearly, persistent oedema in these patients must be due to primary water retention, occurring, moreover, despite hypotonicity of tissue fluid.

Factors Regulating Salt and Water Retention in Congestive Heart Failure

The relative importance of the factors influencing renal tubular function, with respect to salt and water excretion, is difficult to assess. Those of major importance and capable of independent variation include (1) alterations in renal haemodynamics, (2) adrenocortical function, and (3) posterior pituitary activity.

1. Alterations in Renal Haemodynamics

A diminished glomerular filtration rate has been shown to enhance tubular reabsorption of sodium and water (Hanenson *et al.*, 1953). Greatly reduced renal plasma flows and reduced glomerular filtration rates have been reported in patients with chronic congestive heart failure (Merrill, 1946; Mokotoff *et al.*, 1946).

2. Adrenocortical Function

Since the isolation of a potent sodium-retaining factor from adrenal venous blood and its later identification as aldosterone (Simpson and Tait, 1952; Simpson *et al.*, 1952, 1954) this adrenocortical hormone has been obtained in crystalline form from patients with nephrosis (Luetscher *et al.*, 1954) and congestive heart failure (Luetscher *et al.*, 1956). Further studies on oedematous patients with renal, hepatic, and cardiac disease have shown that sodium retention in these subjects is associated with an increased excretion of aldosterone (Liddle *et al.*, 1955; Duncan *et al.*, 1956; Muller *et al.*, 1956b, 1956d; Wolff *et al.*, 1957a, 1957b; Thorn et al., 1957).

Aldosterone encourages salt retention by increasing tubular reabsorption of sodium and chloride; it also stimulates distal tubular exchange of potassium, ammonium, and hydrogen ions for sodium ions in the tubular luminal fluid.

As Greep and Deane (1947) postulated, there is evidence that some degree of adrenal autonomy exists in the production of aldosterone. Thorn *et al.* (1957) found that the baseline secretion of aldosterone was not as intimately dependent upon corticotrophin as that of adrenal hydroxysteroids and ketosteroids, and its secretion in response to corticotrophin administration was variable, in contrast with the consistent stimulation of glucocorticoids under similar conditions.

Although baseline adrenal aldosterone secretion appears to be independent of anterior pituitary function to a large extent, administration of corticotrophin to patients maintained on a low-sodium diet is accompanied by a rise in urinary aldosterone excretion (Duncan *et al.*, 1956; Muller *et al.*, 1956c; Thorn *et al.*, 1957).

Aldosterone secretion is influenced by the volume of the body fluids (Liddle *et al.*, 1955). Thus increased aldosterone activity follows reduction of extracellular volume by bleeding, salt depletion, drainage of ascites, and diuresis (Bartter *et al.*, 1956; Gross, 1956; Wolff *et al.*, 1956a, 1956b, 1957a, 1957b). Decreased activity results from expansion of total body water by such procedures as pitressin administration (Beck *et al.*, 1955; Bartter *et al.*, 1956; Muller *et al.*, 1956b).

Increased urinary aldosterone excretion associated with sodium retention has been reported in normal subjects taking a low-sodium diet (Wolff *et al.*, 1957b). Thorn *et al.* (1957), however, found this response variable, and concluded that factors other than increased aldosterone secretion must participate in the response of the kidneys to reduced dietary sodium.

3. Posterior Pituitary Activity

There is considerable evidence to suggest that pituitary antidiuretic hormone (A.D.H.) is involved in oedema formation. Secreted in proportion to osmotic demands (Hare *et al.*, 1941; Corey and Britton 1941), it increases renal tubular reabsorption of water. The osmotic demands are determined by hypothalamic osmoreceptors which excite nervous impulses to stimulate or inhibit A.D.H. secretion whenever the extracellular fluid osmolarity varies above or below a critical level. Cerebral cortical stimulation—for example, emotion—may also influence its secretion.

Increased antidiuretic activity has been found in the urine of oedematous patients with chronic congestive heart failure (Bercu *et al.*, 1950).

In patients with advanced heart failure Miller (1951) has shown that clinical improvement following treatment is associated with a relatively greater loss of water than of sodium. Weston *et al.* (1952) have also reported that when established failure becomes further intensified by superimposed infection, escape from digitalis control, or digitalis toxicity, in patients on free fluid and low-salt intakes, hyponatraemia occurs owing to primary water retention.

Material

The present series comprises 14 patients with chronic congestive heart failure, 13 of whom were treated with prednisolone. An enhanced diuresis was obtained and heart failure was relieved in all 13 patients.

Clinical Evidence of Adrenocortical Deficiency in Chronic Heart Failure

The decision to administer prednisolone to these patients with chronic heart failure was made following clinical observation of two patients in chronic congestive failure. In both patients the preceding history, the clinical signs, and the biochemical investigations suggested an evolving pattern of initial endocrine stimulation succeeded by adrenocortical insufficiency.

Case 1

A 49-year-old man was admitted to hospital with congestive heart failure and auricular fibrillation due to ischaemic heart disease. In the past seven years three attacks of coronary thrombosis had occurred and on five occasions congestive failure had supervened. Influenza four months earlier had precipitated congestive heart failure. Restriction of fluids and salt, diuretic therapy, and increased digitalis dosage produced no improvement. For a month prior to admission, despite these measures and a continued dosage of digitalis folia, 8 gr. (0.54 g.) daily, congestive failure progressed and he developed nightly attacks of left ventricular failure.

Dyspnoeic at rest, his eyes were bright; there was lid retraction and slight diffuse thyroid enlargement. Auricular fibrillation was present with an apex rate of 120 a minute.

His blood pressure was 110/80. The heart was enlarged and he had considerable congestive failure.

After two weeks' treatment with digitalis folia, 8 gr. (0.52 g.) daily, a low-salt diet, bi-weekly mersalyl injections, and chlorothiazide his nocturnal dyspnoea had subsided, but the auricular fibrillation and congestive failure were unaltered and he no longer responded to mersalyl. Excessively drowsy by day, he was restless and disorientated at night. An empirical trial of Lugol's iodine slowed his rate of auricular fibrillation and produced improvement. Thiouracil was substituted for the iodine, but the fibrillation rate steadily accelerated again. A pulmonary embolus finally hastened death six weeks after admission.

Electrolyte and blood urea estimations were made at intervals throughout his final illness (Table I). Despite

TABLE I.—*Case* 1. *Serum Electrolyte (mEq/l.) and Blood Urea (mg./100 ml.) Determinations During Treatment for Chronic Congestive Heart Failure*

Date	Blood Urea	Serum Na	Serum K	Plasma Chlorides	Plasma Alkali Reserve
12/1/57	71	137	5·3	98	25·9
20/1/57	99	—	—	—	—
*22/1/57	57	127	5·3	88	23·7
28/1/57	—	131	6·2	89	22·8
31/1/57	107	—	—	—	—
†1/2/58	—	134	5·6	85	—
‡3/2/58	141	142	6·4	96	17·9
5/2/58	109	151	5·6	97	25·9
7/2/58	129	128	5·8	91	24·2
10/2/58	154	123	6·2	84	20·1
11/2/58	120	—	—	—	—
14/2/58	128	134	6·7	—	20·1
17/2/58	161	124	6·1	90	18·8

* Oral salt therapy.
† Normal saline 3 litres subcutaneously.
‡ M/6 lactate 540 ml. subcutaneously.

considerable oedema he developed sodium depletion. Only slight improvement occurred when diuretics were stopped and a normal diet was given. Further slight benefit followed oral salt administration. A marked but transient clinical and biochemical improvement occurred, with an immediate diuresis following subcutaneous infusions of normal saline and M/6 lactate.

Comment.—It was thought that persistent heart failure had induced prolonged hypothalamic - pituitary-peripheral endocrine stimulation. This mechanism, by increasing thyrotrophic hormone activity, could have accounted for the recent onset of hyperthyroidism, previous observation of this patient over a period of seven years having shown no evidence of thyroid excess. Prolonged stimulation of this mechanism to the point of exhaustion, with resulting adrenocortical insufficiency, would explain his salt deficiency, failure to maintain improvement, and inability to retain administered sodium. In these respects and in his excessive drowsiness he resembled a patient with Addison's disease; furthermore, his blood urea and electrolyte levels were in keeping with adrenocortical deficiency.

Case 2

A 76-year-old man was admitted to hospital in congestive heart failure two days after a myocardial infarction. A similar episode had occurred a year previously, since when he had been dyspnoeic on exertion. A diabetic for 37 years, he had been stabilized on 72 units of insulin zinc suspension daily for the last four years.

He was treated with digoxin, twice-weekly mersalyl injections, anticoagulants, a 100-g. carbohydrate diet with no added salt, and soluble insulin four-hourly, the dosage being varied according to urine tests.

He slowly improved, but deteriorated again 10 days after admission. His congestive failure increased, distressing Cheyne-Stokes respiration occurred, and he developed attacks of left ventricular failure which became progessively more frequent. By the fourteenth day he was moribund and had pulmonary oedema. At this stage it was noticed that his insulin requirements had fallen over the previous four days from 80 units daily to zero, and this was corroborated by blood-sugar determinations. Intramuscular hydrocortisone was administered; frequent injections of morphine were required to relieve attacks of acute dyspnoea.

He remained semicomatose for 24 hours and intramuscular hydrocortisone was continued. After 36 hours a remarkable improvement occurred. He was bright and alert, his dyspnoea had vanished, and an increasing diuresis ensued; after 72 hours jugular venous congestion had subsided and only a trace of sacral oedema remained. Hydrocortisone was replaced by oral prednisolone. This improvement was sustained for six days and was terminated by collapse following a pulmonary embolus. Congestive failure recurred, and, despite increased prednisolone dosage, his condition deteriorated, his blood pressure varying between 80/55 and 90/75. A noradrenaline infusion (4 mg./litre) was started, but within 10 minutes of starting this therapy, with a drip rate of 50 a minute, he developed ventricular fibrillation and died.

Comment. — Diabetic patients commonly show increased insulin tolerance when subjected to stress, a phenomenon that has been attributed to adrenocortical stimulation. Decreased insulin requirements occur, with recovery after removal of stress. That the initial aggravation of this patient's diabetes might be associated with increased adrenocortical activity is supported by the finding of increased urinary aldosterone excretion in patients following myocardial infarction (Wolff *et al.*, 1957b). Later, however, decreasing insulin requirements and blood-sugar levels were associated paradoxically with a worsening clinical state. There is much experimental evidence to suggest that severe diabetes is associated with anterior pituitary overactivity, with resulting adreno-glucocorticoid excess. It was thought that long-standing diabetes in this patient had been associated with prolonged overstimulation of the pituitary-adrenal axis. His myocardial infarction, by creating further demands for adrenocorticoids, had exhausted this mechanism. The improvement which occurred in this patient, who had been *in extremis* when prednisolone was administered, conflicted with the accepted view that steroid therapy is contraindicated in patients with congestive heart failure. From the hypothesis that chronic heart failure is associated with adrenocorticoid insufficiency it follows that steroid therapy is *indicated* in such cases to correct this deficiency.

These principles were applied to the treatment of a patient with chronic heart failure and hyponatraemia whose failure had become resistant to traditional therapy. A profuse diuresis with relief of heart failure followed the administration of prednisolone.

Case 3

A 68-year-old woman was admitted with congestive heart failure of two years' duration due to ischaemic heart disease. Over this period dyspnoea had steadily increased in spite of digitalis therapy, and three weeks before admission her failure worsened after an attack of bronchitis. She had been a chronic winter bronchitic for 10 years. Her blood pressure was 130/80.

After two weeks' treatment her congestive failure had progressed. She became noisy and disorientated at night, with drowsiness by day, and was found to have a sodium deficiency (Table II). A normal diet was given and chlorothiazide therapy stopped, but mersalyl was continued twice weekly. Decreased drowsiness coincided with a rise in serum sodium from 121 to 133 mEq/l., but her oedema

TABLE II.—*Case 3. Serum Electrolyte (mEq./l.) and Blood Urea (mg./100 ml.) Estimations*

Date	Blood Urea	Serum Na	Serum K	Plasma Chlorides	Plasma Alkali Reserve
During standard therapy					
25/2/58	42	—	—	—	—
9/3/58	60	121	—	90	25·0
26/3/58	77	133	4·4	97	23·7
10/4/58	120	139	5·7	91	18·8
24/4/58	53	134	5·0	93	22·8
During additional prednisolone administration					
28/4/58	41	137	4·8	104	26·3
5/5/58	51	141	5·0	98	28·6
23/5/58	32	143	4·3	96	29·5
*11/8/58	30	139	5·1	96	31·3

* After three months' out-patient treatment.

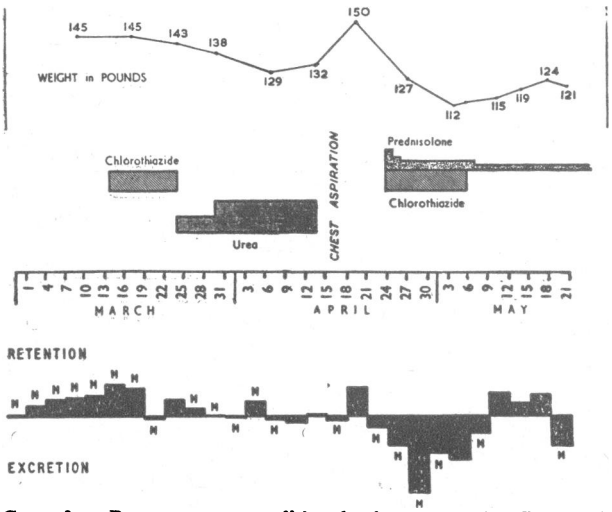
increased and the blood urea rose to 77 mg./100 ml. In order to avoid further salt depletion urea was administered as a diuretic, but the resulting slight decrease in oedema was attended by an increase of blood urea to 120 mg./100 ml. and retention of fixed base (Na, 139 mEq ; K, 5.7 mEq./l). A fall in blood urea to 53 mg./100 ml. following cessation of urea therapy was associated with a decrease in serum sodium to 134 mEq/l. Mersalyl therapy was then stopped in order to prevent further urinary loss of sodium, but oedema steadily accumulated and she developed a pleural effusion which required aspiration.

After two months' treatment an overall gain of 5 lb. (2.27 kg.) in weight reflected the increase in oedema and ineffectiveness of therapy. At this stage her plasma proteins were 7.5 g./100 ml. and, despite hyponatraemia, oedema was increasing.

Oral prednisolone was started in a dosage of 5 mg. q.d.s. for the first 24 hours, 2.5 mg. q.d.s. for the next 24 hours, and 2.5 mg. t.d.s. for 12 days, after which a maintenance dosage of 2.5 mg. b.d. was continued together with digitalis and twice-weekly mersalyl.

A diuresis occurred within 24 hours of starting prednisolone, and a greatly enhanced response to mersalyl was apparent. Within 10 days all congestive phenomena had disappeared, and over a period of two weeks a weight loss of 38 lb. (17.2 kg.) was recorded (see Chart). On discharge there was no evidence of congestive heart failure and her serum electrolytes and blood urea had returned to normal levels.

She has been maintained on digitalis, twice-weekly chlorothiazide, and potassium chloride in standard dosage with prednisolone 2.5 mg. b.d. Followed as an out-patient for six months, she has continued to improve, and has lost a further 6 lb. (2.7 kg.) in weight. Within a month of leaving



Case 3. Response to traditional therapy and effects of prednisolone administration on fluid balance and body weight. M=Mersalyl administration.

hospital she was able to walk more than one mile (1.6 km.) to keep her hospital appointment, and so well does she feel that she can do all her own housework and shopping and is free from dyspnoea.

Comment.—It is perhaps significant that this patient had bilateral exophthalmos ; there was, however, no evidence of hyperthyroidism. She was also hirsute and pigmented. These physical signs could be interpreted as evidence of past thyrotrophic hormone and adrenocortical excess provoked by prolonged heart failure and succeeded by ultimate anterior pituitary–adrenocortical exhaustion.

Adrenocorticoid Excretion in Chronic Heart Failure

More substantial evidence of adrenocortical insufficiency in chronic heart failure was obtained by measuring the urinary excretion of 17-ketosteroids in four patients with chronic congestive failure. In two of these patients the urinary corticoid excretion was also measured. The 24-hour urinary steroid excretion was considerably reduced in all four patients, one having values compatible with Addison's disease (Case 4). Furthermore, the ability of corticotrophin to increase the urinary excretion of these adrenocorticoids indicated that the deficiency existed at pituitary rather than adrenal level (Table III).

TABLE III.—*Urinary Adrenocorticoid Excretion (mg./day) in Chronic Heart Failure, Before and After Corticotrophin Administration*

Case No.	Before Corticotrophin		After Corticotrophin	
	17-Ketosteroids	Corticoids	17-Ketosteroids	Corticoids
4	<1	2·8	<1	6
4*	—	—	2·2	10·8
5	2·8	—	3·0	—
6	1·2	4·8	2·9	16·6
10	2·7	—	3·7	—

* After corticotrophin 60 units b.d. for one month.

Case 4

A 49-year-old woman with rheumatic mitral stenosis and incompetence, tricuspid incompetence, auricular fibrillation, and cardiac cirrhosis with ascites was admitted to hospital in congestive heart failure.

Heart failure had first intervened 16 years previously and had not subsided despite treatment and close supervision in the last eight years, during which time periodic exacerbations had necessitated frequent admissions to hospital. Following mitral valvotomy six years earlier, she had improved for one year, but further severe exacerbations of congestive failure, each becoming progressively more resistant to treatment, forced a second valvotomy four years later. By that time cardiac cirrhosis had developed and only slight symptomatic benefit was obtained. In the last two years persistent ascites and a right pleural effusion had required repeated aspiration.

Apart from the signs in her cardiovascular system she was frail and pigmented, the pigmentation being particularly marked on the extensor surfaces of the limbs, on the neck, and in the palmar creases. The skin was dry and atrophic, her hair was of fine texture and dry, pubic hair was scanty, and axillary hair absent. A small nodule was palpable in the thyroid.

Her urinary 17-ketosteroid excretion was less than 1 mg. in 24 hours and was unaltered after administration of intramuscular corticotrophin 40 units q.d.s. for four days. Following intramuscular corticotrophin 60 units b.d. for one month the urinary excretion of 17-ketosteroids increased to 2.2 mg. a day. Corresponding values for the excretion of corticoids were 2.8 mg. initially and, following corticotrophin administration, 6 mg. after four days and 10.8 mg. after one month (Table III).

With corticotrophin therapy and a fixed dietary sodium and potassium intake of 250 and 35 mEq. daily respectively her initial sodium deficiency was corrected and during this period the increasing urinary loss of sodium (Table IV) reflected the increased serum sodium level (Table V). The

TABLE IV.—*Case 4. Urinary Excretion of Sodium and Potassium During Corticotrophin Therapy*

Date	Na	K
5/6/58	30 mEq/day	108 mEq/day
6/6/58	39 ,,	49 ,,
12/6/58	57 ,,	28 ,,
17/6/58	78 ,,	62 ,,

Na intake 250 mEq/day. K intake 35 mEq/day.

TABLE V.—*Case 4. Serum Electrolyte (mEq/l.) and Blood Urea (mg./100 ml.) Values Before and During Corticotrophin Administration*

	Serum Na	Serum K	Serum Chlorides	Plasma Alkali Reserve	Blood Urea
Before corticotrophin ..	136	4·4	95·7	30·8	36
During ,, ..	142	3·4	94·0	33	34

fall in both urinary potassium excretion and serum potassium level was presumed to be due to a movement of extracellular potassium into the cells. During corticotrophin administration her blood pressure increased from 100/60 to 115/80 and coincided with an increase of serum sodium from 136 to 142 mEq/l. The serum potassium decreased over this period from 4.4 to 3.4 mEq/l.

Effects of Prednisolone Administration in Patients with Obstinate Heart Failure

Prednisolone was administered to 13 patients with chronic congestive heart failure which had become resistant to traditional therapy. Hyponatraemia was present in each instance and with one exception (Case 4) the blood urea was raised, usually from 50 to 100 mg./100 ml. All patients showed excessive tiredness; the majority had increased skin pigmentation, some having well-marked buccal pigmentation which could easily have been missed had it not been sought specifically. Of the nine women, six had thyroid adenomata.

Existing therapy with digitalis and diuretics was supplemented with prednisolone in a dosage of 5 mg. t.d.s. for the first 24 to 48 hours followed by a maintenance dosage of 2.5 mg. twice or thrice daily. A normal diet was substituted for the low-salt regimen.

A rapid and sometimes dramatic improvement occurred within three or four days of starting prednisolone therapy. Symptoms were relieved and a diuresis was established, with disappearance of oedema and congestive failure within two to four weeks (Table VI). A slower response was obtained in one patient, a woman of 67 with chronic nephritis in addition to her chronic congestive heart failure.

After the patient's discharge from hospital prednisolone maintenance therapy and digitalis were continued. In addition each patient received oral chlorothiazide 0.5 g. b.d. and potassium chloride 1 g. b.d. on two or three days each week.

Although a diuresis occurred in some patients when digitalis therapy alone was supplemented with prednisolone, it was slight when compared with the greatly enhanced response obtained with the additional administration of diuretics. Temporary withdrawal of diuretic therapy resulted in a considerably reduced urinary output, and in some patients fluid retention with a gain in weight occurred (see Chart).

The diuresis-promoting effect of delta-hydrocortisone has been reported previously. Thus Bickerman *et al.* (1955) showed that a weight loss in 20% of their patients with bronchial asthma and pulmonary fibrosis during prednisone therapy was due to an increased urinary output. A marked diuresis was reported by Cattan and Vesin (1956) when four patients with anasarca were treated with prednisone. There have been reports of considerable improvement in patients with obstinate heart failure whose unresponsiveness to the usual therapy, particularly diuretics, has been reversed during prednisone administration. Bickel (1955) has described two such cases, Riemer (1956) one case, Muller *et al.* (1956a) two cases, and Gutner *et al.* (1957) five cases. These reports have not revealed uniform success, some patients with heart failure having failed to respond to steroid therapy. Thus Gutner *et al.* (1957) treated 11 patients in *varying stages* of heart failure with prednisone; only five benefited with decreased shortness of breath, and only three of these lost weight; the sixth patient had increased dyspnoea and gained weight, whilst the remaining five patients showed no change in their cardiac status.

Endocrine Adjustments in Chronic Heart Failure

Patients in this series exhibited phenomena suggesting adrenocortical deficiency. This evidence was based upon the following criteria: (*a*) The clinical observation of excessive tiredness and increased skin pigmentation with associated buccal pigmentation in some patients. (*b*) All patients had developed a sodium deficiency in association with a normal or elevated serum potassium

TABLE VI.—*Patients with Obstinate Congestive Heart Failure which Responded to Prednisolone Therapy*

Case No.	Age and Sex	Aetiology	Duration of Failure	Weight Loss			Follow-up
				lb.	kg.	Weeks	
2*	76 M	C.I.	Intermittent, 1 year	—	—	—	Died after 1 week. Pulmonary embolus
3	68 F	C.I. Chronic bronchitis	,, 2 years	38	17·2	2	6 months
4	49 F	Rheumatic heart disease. A.F.	16 years	7	3·2	2	5 ,,
5	67 F	Hypertension, bronchial asthma, chronic bronchitis, gastro-intestinal haemorrhage	3 months	21	9·5	5	2 ,,
6	60 M	Rheumatic and ischaemic heart disease. A.F.	Intermittent, 8 years	4	1·8	1	1 month
7	77 F	Calcareous aortic stenosis and incompetence	3 weeks	8	3·6	4	3 months
8	67 F	Rheumatic heart disease. A.F.	Intermittent, 4 years	4½	2·0	3	5 ,,
9	60 F	,,	8 months	3	1·4	2	5 ,,
10	63 F	C.I. Hypertension. Chronic nephritis	Intermittent, 7 years. Continuous, 2 years	9	4·1	3	2 ,,
11	82 F	C.I.	Intermittent, 10 years	18	8·2	4	1 month
12	69 M	,,	,, 8 ,,	14	6·4	4	3 months
13*	80 M	,,	,, 8 ,,	—	—	—	Died after 2 weeks. Pulmonary embolus
14	41 F	Rheumatic heart disease. A.F.	,, 10 ,,	12	5·4	3	3 months

* Heart failure subsided before death. C.I. = Cardiac ischaemia. A.F. = Auricular fibrillation.

level and raised blood urea. (*c*) Estimation of urinary 17-ketosteroid excretion in four patients and of corticoid excretion also in two of these patients revealed considerably reduced values. The increased urinary excretion of these steroids following adrenal stimulation with corticotrophin indicated that failure had occurred at anterior pituitary rather than adrenal level.

The possibility of adrenocorticoid insufficiency is supported by the disappearance of heart failure following correction of this deficiency with prednisolone.

These results, considered in conjunction with those previously recorded in patients with congestive heart failure, suggest a pattern of events contributing to the formation of oedema.

The initial phase of heart failure is associated with a primary salt retention resulting from enhanced tubular reabsorption of sodium. This is achieved by a decrease in glomerular filtration rate aided by baseline aldosterone activity independent of pituitary control. In some instances the ensuing secondary water retention, determined by simple osmotic equilibrating forces, by expanding the extracellular fluid, is sufficient to restore the effective circulating blood volume, and thereby repairs the discrepancy between cardiac output and tissue metabolic requirements.

Should these mechanisms prove inadequate they are reinforced by anterior and posterior pituitary stimulation mediated via the hypothalamus. Increased corticotrophin secretion encourages further aldosterone production in addition to other corticoids. A primary water retention follows increased posterior pituitary antidiuretic activity. As a result of anterior pituitary stimulation thyrotrophic hormone secretion is also augmented. Clinically this was evidenced by auricular fibrillation controlled with Lugol's iodine in Case 1 and by the presence of exophthalmos in Case 6. In both patients long-standing heart failure could have resulted in prolonged thyrotrophic hormone excess. This mechanism could also account for the finding of thyroid adenomata in six of the nine women in this series. Enhanced thyroid activity by increasing metabolism in patients with *recent* congestive failure could account, in part, for the well-recognized elevation in metabolic rate associated with heart failure. In these patients the increase in circulating thyroid hormone would serve a double purpose. By potentiating the action of adrenaline it would assure continued efficient anterior pituitary stimulation, and by increasing adrenocortical metabolism would encourage further corticoid production.

These mechanisms are probably all invoked in varying degree in congestive heart failure and can be reversed by treatment which restores the cardiac output to a level sufficient for tissue metabolic needs. Traditional therapy achieves this object, with digitalis administration improving the cardiac output while rest in bed induces a synchronous reduction in tissue metabolism. With correction of this discrepancy the endocrine and renal haemodynamic adjustments revert to normal. The previously expanded extracellular fluid is, however, slow to subside, a fact clinically apparent in the persistence of oedema for varying periods after jugular venous congestion has disappeared. The tardy excretion of extracellular fluid, by delaying contraction of the circulating blood volume, embarrasses the cardiac pump. Diuretics speed recovery by hastening the elimination of this unnecessary salt and water.

Adrenal cortical deficiency occurring in patients with *chronic* congestive heart failure in this series resulted from anterior pituitary failure. This suggests that the continuing necessity for these endocrine-adjusting mechanisms leads to exhaustion of anterior pituitary function. Persisting posterior pituitary overstimulation would then induce excessive antidiuretic hormone activity and a primary retention of water in association with adrenocortical insufficiency.

At this late stage of heart failure excessive secretion of antidiuretic hormone remains as the predominant mechanism reinforcing aldosterone activity, thereby sustaining the defective circulation.

It is unlikely that digitalis therapy and bed rest alone will relieve heart failure at this stage. The response to diuretic therapy will be poor in the presence of hyponatraemia; indeed, by inducing only slight urinary loss of sodium with secondary water loss diuretics will stimulate further water retention and merely encourage the state of obstinate heart failure. By correcting the adrenal deficiency with hydrocortisone in physiological quantities and continuing as maintenance therapy, hyponatraemia will be relieved and so-called "irreversible" heart failure will revert to the earlier phase and become responsive to traditional therapy.

This hypothesis offers an explanation for the salt-deficiency syndrome which occurs in patients with congestive failure when intercurrent infection supervenes and during periods of hot weather. In either circumstance adrenocortical demands, secreted in response to corticotrophin stimulation, are increased. The pituitary-adrenal mechanism, already fully extended in response to congestive failure, becomes exhausted, antidiuretic hormone overactivity persists, and water retention occurs, with resulting tissue fluid hypotonicity. Injudicious salt deprivation or diuretic therapy, by further increasing the demands for aldosterone, will for similar reasons favour the development of the salt-deficiency syndrome. Under the circumstances described this syndrome would occur more readily in elderly patients whose pituitary-adrenal reserves are reduced.

Mode of Action of Prednisolone Therapy

The urinary sodium excretion was not determined in the patients in this series. It is, however, unlikely that their prednisolone-induced diuresis was due to increased urinary loss of sodium, since they all had a decreased serum-sodium level prior to steroid therapy, and this increased and remained at a normal level despite a profuse diuresis. It must be assumed that the increased urinary output was due to a *predominant* water diuresis.

Anterior pituitary exhaustion could account for the beneficial effects obtained with prednisolone therapy.

1. Correction of adrenocortical deficiency would relieve intracellular overhydration by virtue of the known action of steroids in causing a movement of intracellular water and sodium into the extracellular compartment; furthermore, they would promote a simultaneous transfer of potassium in the opposite direction. These electrolyte readjustments would partly account for the rise in serum-sodium level and would also explain the decreased serum-potassium level despite decreased urinary potassium excretion in Case 4 (Table IV). This action would not, however, result in a water diuresis.

2. It has been established that an antagonism exists between adrenocortical and posterior pituitary antidiuretic hormones

at the level of the renal tubule (Talbot *et al.*, 1952). This antagonism would explain the increased urinary output in these chronic cardiac patients, a water diuresis occurring when the renal tubules are released from excessive unantagonized antidiuretic activity by the intervention of prednisolone. Furthermore, this mechanism would support the hypothesis that obstinate oedema in these patients was due to excessive posterior pituitary activity in the presence of adrenocortical insufficiency.

3. Other known effects of steroid therapy, although contributory, probably played only a minor part in the diuresis. Thus, in normal subjects steroids increase the glomerular filtration rate; by favouring corticogenic hypothyroidism they could decrease the work load upon the heart and by increased mobilization of glucose they would improve myocardial function. They might confer additional benefit by increasing pulmonary ventilatory capacity, and by virtue of their erythropoietic action would correct anaemia if present.

4. Muller *et al.* (1956a) and Gutner *et al.* (1957) have reported beneficial results following prednisone administration to patients with heart failure resistant to the usual therapy. These authors attributed improvement, in those patients who showed a diuresis, to suppression of anterior pituitary function by prednisone therapy with a consequent reduction of endogenous aldosterone secretion. This explanation is supported by the diminished excretion of urinary "sodium-retaining factor" following cortisone administration (Luetscher and Deming, 1950; Luetscher *et al.*, 1951) and also by the decrease in urinary aldosterone excretion in patients receiving prednisone (Mach and Muller, 1956). In addition Muller *et al.* (1956a) showed that the combination of prednisone with acetazolamide or mercaptomerin lowered the urinary aldosterone excretion to a greater extent than did prednisone administration alone. These same diuretics usually produced an increase of aldosterone when administered alone.

A decrease in extracellular fluid volume following diuresis would be expected to stimulate aldosterone activity. Although it is possible that prednisolone by suppressing anterior pituitary function prevented this overactivity, if this be the only mechanism by which diuresis and improvement occur, all patients to whom Muller and Gutner and their colleagues administered prednisone should have gained benefit. Their results, however, were not uniformly successful. In the present series the evidence suggested that anterior pituitary function was already greatly depressed, and it is doubtful whether the physiological quantities of prednisolone they received would have caused further anterior pituitary suppression.

The failure to obtain uniformly successful results could lie in the fact that the patients to whom Gutner and his co-workers administered prednisone were in "varying stages of heart failure." Only those patients who had reached the stage of anterior pituitary exhaustion would respond to prednisone therapy.

Discussion

Although patients in this series had evidence of hypoandrenocorticism it should be emphasized that this had resulted from anterior pituitary insufficiency. The oedema which they exhibited could not have been due to hypoadrenocorticism alone, since oedema is not part of the clinical picture of Addison's disease. In this latter condition adrenal destruction results in *total* adrenocorticoid deficiency, and, moreover, since there is no stimulus to posterior pituitary overactivity, fluid retention does not occur. Hyponatraemia in these patients with late-stage heart failure, although encouraged by lack of adrenal ketosteroids and hydroxysteroids, was probably due largely to water retention and increased intracellular sodium, since prednisolone administration, a normal diet, and diuretic therapy induced a profuse diuresis with a concomitant rise in serum-sodium levels.

Urinary aldosterone excretion was not estimated, but baseline aldosterone secretion, being independent of pituitary function, was probably unaffected in these patients. It may even have been increased, as the patients with chronic heart failure reported by Muller *et al.* (1956a) all had excessive urinary aldosterone excretion. Such excess, however, could not alone account for the oedema in these patients, since they had a predominant water retention; furthermore, oedema does not occur in primary hyperaldosteronism (Conn, 1955). The latter condition differs in its pathogenesis from the hyperaldosteronism of heart failure and is unassociated with posterior pituitary stimulation; indeed, the contrary might be expected, and could explain the absence of oedema in primary hyperaldosteronism.

The increased urinary aldosterone excretion found in patients with the nephrotic syndrome and the diuresis they experience following corticotrophin or cortisone administration suggest that oedema in this condition has a similar pathogenesis to that of late-stage heart failure. Such patients would differ only with respect to the primary cause of pituitary stimulation, which, in nephrosis, would occur in response to excessive urinary electrolyte loss resulting from renal damage.

A parallel with famine oedema is also suggested, since analogous electrolyte changes and evidence of adrenocortical deficiency occur in patients under starvation conditions (Hubble, 1952). These findings reflect extended adjustments by the pituitary-endocrine mechanism in order to adapt the functioning organism to the extreme nutritional poverty and eventual anterior pituitary exhaustion with residual posterior pituitary excess.

The observation of Hollander and Judson (1956) that salt retention does not occur in patients with isolated left ventricular failure has been clarified by Wolff *et al.* (1957b), who found no increase in urinary aldosterone excretion in patients with isolated left ventricular failure, in contrast to the excessive aldosterone excretion associated with congestive heart failure. That adrenocorticoid *deficiency* may contribute to cardiac asthma and pulmonary oedema is suggested by the prompt relief and disappearance of attacks of left ventricular failure which occurred in five patients in this series following prednisolone therapy. In this respect Prasad (1958) has reported that prophylactic prednisone administration protected experimental animals from pulmonary oedema.

In congestive heart failure the striving to maintain parity between the cardiac output and the tissue's metabolic needs results in progressive adaptations by the pituitary-peripheral endocrine system, particularly with regard to adrenal function. The inherent qualities of this system become apparent in the paradox which evolves as the adjustments fail to achieve their aim. Eventually the patient with chronic heart failure, by virtue of anterior pituitary exhaustion, regulates metabolism in response to cardiac output and, with this precarious but only available existence, exhibits a complete reversal of the normal status.

In view of the steroid structure of digitalis the hypothesis advanced in this paper may offer an explanation for the mode of action of this drug in patients with heart failure.

Summary

Factors which contribute to salt and water retention in congestive heart failure are reviewed, with particular reference to the endocrine system.

Clinical observation of 14 patients with chronic congestive heart failure suggested an initial coexistent endocrine overactivity followed subsequently by adrenocortical insufficiency.

This premise was supported by the presence of hyponatraemia, a normal or elevated serum-potassium level with an increased blood urea in 14 patients with chronic heart failure which had become resistant to therapy with digitalis, a low-salt diet, and diuretics.

The urinary excretion of 17-ketosteroids was estimated in four of these patients, and in two the corticoid excretion was also assessed. Subnormal values were obtained in each instance, and in one patient were consistent with a diagnosis of Addison's disease. Following corticotrophin administration the urinary excretion of these steroids increased in each patient and was accepted as evidence that hypoadrenocorticism was due to anterior pituitary rather than adrenocortical failure.

Replacement therapy, using prednisolone, induced a greatly enhanced response to diuretics in all 13 patients who received this treatment. All were relieved of congestive heart failure and also, when coexistent, of left ventricular failure. Two patients died following pulmonary emboli.

A hypothesis is advanced regarding the endocrine adjustments which occur in heart failure and which could lead to the formation of oedema. The importance of these adjustments is described in relation to the treatment of heart failure.

The possible mode of action of prednisolone is discussed.

Parallels are drawn between the oedema of late-stage congestive heart failure, nephrotic oedema, and starvation oedema.

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CHLORMERODRIN: CLINICAL EFFECTIVENESS AND ABSENCE OF TOXICITY IN CONGESTIVE HEART FAILURE

REPORT OF A FOUR-YEAR STUDY

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Organomercurial diuretics are widely recognized as the most potent and reliable of available diuretic agents. Until recently, satisfactory organomercurial preparations were available only for administration by injection, limiting their acceptability to patients. From the clinical standpoint, a need also existed for an oral organomercurial which could be administered frequently in relatively small doses. Such an agent would provide continuous diuresis, rather than the seesaw of dehydration and rehydration that occurs with the less frequent higher doses ordinarily employed when a diuretic is given by injection. Chlormerodrin ("neohydrin"*; 3-chloromercuri-2-methoxypropylurea), a non-ionic crystalline compound introduced in 1952, showed early promise of meeting this need. Our

*Neohydrin supplied through the courtesy of Dr. H. L. Daiell, Lakeside Laboratories, Inc., Milwaukee, Wis.