sudden appearance during the decompression phase of a dive is difficult to explain. We have seen similar cells after decompression from exposure to as little as 2·5–3·7 bar in air. This suggests that the absolute pressure applied to the diver before decompression is not a major factor in their production. The raised oxygen tension of 0·4 bar used in all the helium-oxygen dives might be a factor, but the appearance of the cells during decompression is independent of the length of time the subject is exposed to a raised oxygen tension before decompression starts, which in our experiments has varied from 1 day for shallow air dives to 12 days for one of the 43-bar dives. Detection of the cells in the circulation is also independent of the rate of initial compression over a range of 0·1 bar min^{-1} to 6 bar day^{-1}. Estimation of the numbers of echinocytes and their relatives in the circulation is difficult, but there is a strong suspicion that the numbers seen depend on the initial rate of decompression, so that the less rapid the initial decompression the fewer abnormal cells seen.

The morphological change in the erythrocyte is not the only effect observed in these dives. Activity of the enzyme carbonic anhydrase falls in the red cells during compression and recovers only incompletely during decompression, this apparent loss being accounted for largely by binding of the enzyme to the red-cell membrane.[8] After compression to 31 bar there is also a sharp fall in erythrocyte adenylate kinase, which does not return to normal levels during the decompression phase (Carlyle and Spencer, unpublished).

Like the morphological changes, these enzyme changes are not observed when red cells are exposed to raised pressure in vitro. Whether these enzyme changes are causally related to the morphological changes we do not yet know. Nor do we know whether the discocyte-echinocyte transformation is an effect of decompression on the red cell alone or whether an echinocyte-producing substance is formed in serum by decompression in vivo. It is interesting to speculate whether these morphological and biochemical changes in the erythrocyte might influence gas exchange or the microcirculation during decompression and hence play a part in the genesis of decompression sickness or delayed effects such as aseptic bone necrosis.

Traditionally the safety of a decompression schedule is judged by the subject's freedom from symptoms and signs of decompression sickness, which usually appear quite late in the decompression phase. The discocyte-echinocyte transformation might, however, be useful as an objective measure of the safety of a decompression long before the usual symptoms and signs appear. Experiments are being conducted to test this hypothesis.

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Requests for reprints should be addressed to R. F. C.

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Hypothesis

DISORDERS OF CHLORIURETIC HORMONE SECRETION

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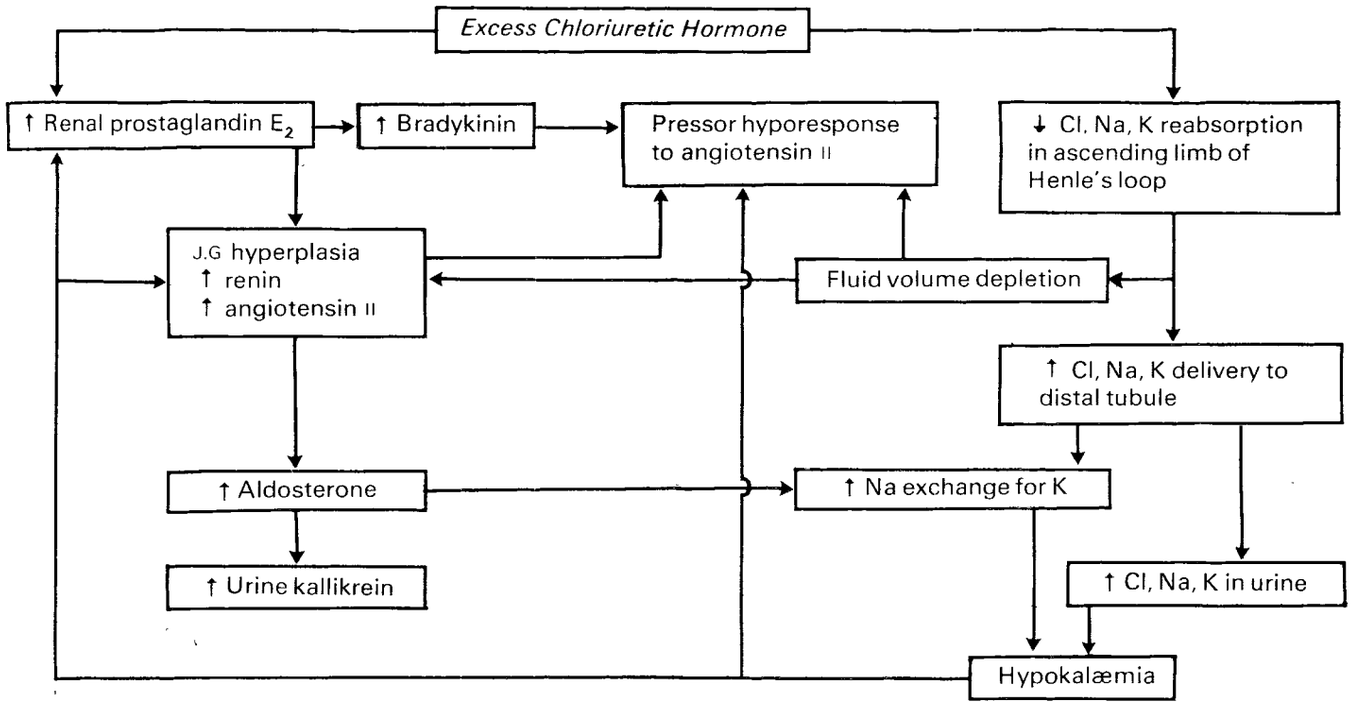
Summary Experimental evidence supports the existence of a circulating substance, natriuretic hormone, which augments electrolyte excretion. Because such a hormone probably acts by inhibiting chloride reabsorption in the thick, ascending limb of the loop of Henle it would more accurately be called chloriuretic hormone. Chloriuretic hormone must have an action which resembles that of loop diuretics such as frusemide and ethacrynic acid. An excess of chloriuretic hormone could explain all the manifestations of Bartter's syndrome, whereas a deficiency could account for Gordon's syndrome. Hyporeninæmic hypoaldosteronism may develop in subjects who are unable to increase chloriuretic hormone concentrations appropriately in response to progressive impairment of renal function.

INTRODUCTION

THE existence of a natriuretic humoral factor (or factors) has been invoked to explain, in part, the vigorous natriuresis observed when a fluid-volume-expanded man[1,2] or animal[3] is salt-loaded, and the increase in sodium excretion per nephron in advancing renal disease.[4] Although there has been debate regarding the existence of natriuretic hormone(s) and the bioassay methods used for its detection,[3,5] there is considerable evidence from a number of research centres for the existence of such a hormone.[1-4]

We propose that the major site of action of natriuretic hormone is the thick ascending limb of Henle's loop. Such a postulate requires that the hormone be renamed chloriuretic hormone, since active reabsorption of chloride ion is the predominant function of this segment of the nephron.[6,7] There is some evidence that this is the site of action,[8] although in general the location of natriuretic hormone activity is not well-defined. The effects of chloriuretic hormone would be expected to parallel closely those of the loop diuretics frusemide and ethacrynic acid, which also have primary effects on chloride reabsorption in the thick ascending limb.[9,10]

If such a physiologically active hormone exists, one might assume the existence of clinical states of hormone excess and deficiency. An attractive aspect of the chloriuretic-hormone hypothesis is that excess and deficiency could account for well-described clinical syndromes. We propose that Bartter's syndrome represents the excessive



Sequence of events resulting from excessive production of chloriuretic hormone and leading to the clinical and laboratory abnormalities of Bartter's syndrome.

Ingestion of loop diuretics causes the same sequence.

production of chloriuretic hormone, whereas Gordon's syndrome is the result of insufficient secretion.

BARTTER'S SYNDROME

This now well-recognised syndrome, first described by Bartter et al.[11] in 1962, is characterised by hypokalæmia, hypochloræmic alkalosis, normal or low blood-pressure, increased concentrations of renin, angiotensin II, and aldosterone, and juxtaglomerular hyperplasia, together with more recently described increases in urinary prostaglandin E[12-17] and kallikrein,[16,17] and in plasma bradykinin.[17] The disorder is often seen in children, many of whom have growth retardation. Familial cases have been reported, and inheritance as a recessive trait has been postulated.[18] Theories about the pathogenesis of this disorder include primary vascular hyporesponsiveness to pressor substances, autonomous renin oversecretion, reduced sodium reabsorption by the renal tubules, excessive potassium loss from the kidneys, overproduction of renal prostaglandins, and, most important in relation to our hypothesis, a defect in chloride reabsorption in the ascending limb of Henle's loop.[15,19] Evidence supports the concept that diminished chloride reabsorption at this site in the nephron is the underlying abnormality in Bartter's syndrome.[15]

An excess of chloriuretic hormone would cause renal potassium wasting, hypokalæmia, and fluid volume depletion in a manner similar to loop diuretics.[20] Chloriuretic hormone would also be expected to stimulate renal prostaglandin E_2 synthesis as does frusemide.[14,21] The resultant effects on juxtaglomerular cells,[22] renin,[23] urinary kallikrein,[16,17,24] plasma-bradykinin,[17] and pressor responsiveness to angiotensin II[25,26] are shown in the accompanying figure.

Self-administration of diuretics can induce a clinical state which closely mimics Bartter's syndrome.[19,22,27,28] In addition, loop diuretics induce many of the laboratory abnormalities characteristic of Bartter's syndrome, including increased urine prostaglandin E_2[14,21] and kallikrein[21,29,30] as well as juxtaglomerular hyperplasia.[22] The pronounced similarity between the two conditions accords with the suggestion that Bartter's syndrome is a result of excessive circulating chloriuretic hormone.

GORDON'S SYNDROME

We predict that a deficiency of chloriuretic hormone leads to retention of chloride, sodium, and potassium, and the development of the following: hyperkalæmia, hyperchloræmic acidosis, hypertension, low concentrations of renin, angiotensin II, and aldosterone, increased pressor responsiveness to angiotensin II, hypogranularity of the juxtaglomerular apparatus, and subnormal plasma bradykinin and urinary prostaglandin and kallikrein values. Does such a condition exist?

Gordon et al.[31] described a syndrome of hypertension, hyperkalæmia, undetectable renin activity, and low concentrations of aldosterone. The patient was a 10-year-old girl who presented with short stature. Additional features were mild acidæmia and pressor hyper-responsiveness to angiotensin II and noradrenaline. Other possible cases of Gordon's syndrome have been reported by Brautbar et al.[32] and Schambelan et al.[33] We have observed a 17-year-old schoolgirl with hypertension (160/105 mm Hg), hyperkalæmia (5·0–5·9 mmol/l), very low plasma-renin (0·06 ng/ml/h upright on a low-salt diet) and low-normal urine aldosterone (13·7 μg/24 hour on day 4 of a 10 mmol/day sodium diet). Treat-

ment with chlorthalidone (50 mg daily), reduced blood-pressure (115/80 mm Hg) and plasma-potassium (4·5–4·8 mmol/l). Unfortunately, urinary prostaglandin and kallikrein, and plasma bradykinin concentrations, were not measured in any of these patients.

Gordon postulated that the basic abnormality in his patient was a "single tubular lesion leading to excessive sodium reabsorption at a site proximal to the aldosterone exchange site."[31] With current knowledge that chloride (rather than sodium) is actively reabsorbed in the thick ascending limb of Henle's loop, it is possible that the primary defect in Gordon's syndrome is one of excessive active chloride reabsorption in this portion of the renal tubule[33] (and Gordon, personal communication).

HYPORENINAEMIC HYPOALDOSTERONISM

There is a second clinical situation in which chloriuretic hormone deficiency may be important. Bricker et al.[4] postulated the existence of a humoral agent to explain the increased sodium-excretion rate per nephron in subjects with renal impairment. Such a hormone would maintain normal electrolyte and volume homœostasis as the nephron population diminishes. They reported that a low-molecular-weight fraction of serum from uræmic patients altered sodium transport in several bioassay systems. We suggest that the factor (or one of the factors) isolated by Bricker might be chloriuretic hormone. Further, we surmise that whereas most patients are able to increase chloriuretic hormone levels when renal function diminishes, a minority are unable to do so, and in these patients the syndrome of hyporeninæmic hypoaldosteronism (S.H.H.) develops. S.H.H. is now a well recognised syndrome in patients with mild to moderate renal failure. Patients present with hyperkalæmia, low plasma-renin activity, low serum-aldosterone, and normal glucocorticoid secretion.[34,35] The sequence of events in such patients would follow a pattern opposite to that of the figure: with a failure to increase chloriuretic hormone secretion, an excess of chloride, and therefore of sodium and potassium,[36] would be reabsorbed in the thick ascending limb of Henle's loop with a resulting increase in extracellular fluid volume and hyperkalæmia. Resultant suppression of renin and therefore of aldosterone would exacerbate the hyperkalæmia. The rise in serum-potassium would inhibit prostaglandin production,[37] and both hyperkalæmia and low prostaglandin concentrations would accentuate the hyporeninism. Such a sequence of events is supported by reports that extracellular fluid volume and exchangeable body sodium are increased[38] and excretion of prostaglandin E[39] and kallikrein[40] is diminished, at least in some patients with S.H.H. Further, Tan et al.[41] demonstrated that prostaglandin inhibition precipitated S.H.H. in a patient with mild uræmia. If this theory is correct, frusemide would be a more rational treatment for these patients than fludrocortisone, as it would reverse, rather than exacerbate, the tendency to volume expansion and hypertension.

HYPOTHESIS

We propose the following:

1. Natriuretic hormone is really chloriuretic hormone.
2. The action of chloriuretic hormone is similar to that of the loop diuretics.
3. Excessive production of chloriuretic hormone results in Bartter's syndrome.
4. Underproduction of chloriuretic hormone leads to Gordon's syndrome.
5. Whereas most subjects are able to increase chloriuretic hormone concentrations in advancing renal disease, others are unable to respond and hyporeninæmic hypoaldosteronism develops.

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