of the anticoagulant effect.

The method fulfills a need expressed by Wright(5) and others for "an anticoagulant which can be taken by mouth and can produce an anticoagulant effect within one hr."

The importance of such a drug in the treatment of frostbite is indicated by the work of Lange(6) and others. The value of initiating such treatment in the field before the hospitalization of a frostbitten soldier is obvious. We believe that by virtue of its rapid effect and ease of administration, the sublingual route may well become the method of choice for the early anticoagulant treatment of myocardial infarction(7), pulmonary embolism, and thrombophlebitis, and in vascular surgery. Further study is indicated to properly assess its place in the anticoagulant armamentarium for the treatment of thrombo-embolic diseases.

Conclusion. Sodium heparin is a practical and effective anticoagulant when administered sublingually. By this method, the coagulation time of the blood was consistently prolonged to the therapeutically effective levels for 4 hr.

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Clinical and Metabolic Study of 17-Hydroxycorticosterone (Kendall Compound F); Comparison with Cortisone.* (18768)

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Additional investigation of Kendall's Compound F was prompted by the probability of its being an important constituent of the adrenal cortex(1,2), its close structural similarity to cortisone, and its effectiveness in rheumatic disorders(3). The present study was undertaken primarily in order to compare the clinical and metabolic effects of 17-hydroxycorticosterone-21-acetate† (Cpd. F) with those produced by cortisone acetate,† employing similar conditions and methods to those previously reported(4).

Case report. A.C., a 38-year-old woman, was admitted to the metabolic ward of the Presbyterian Hospital with active rheumatoid arthritis of 14 years' duration. The diagnosis was made on clinical and laboratory grounds, and was substantiated serologically. After a preliminary period on a constant diet and fluid intake, she received 50 mg of Cpd. F intramuscularly at 12-hour intervals for 24 days. The steroid was then replaced by a placebo (cholesterol suspension†) for one week, following which cortisone was administered intramuscularly at the same intervals and dosage.

Results. (Fig. 1). The administration of both Cpd. F and cortisone was associated with slight insomnia, a moderate degree of increased mental "speed-up" and emotional

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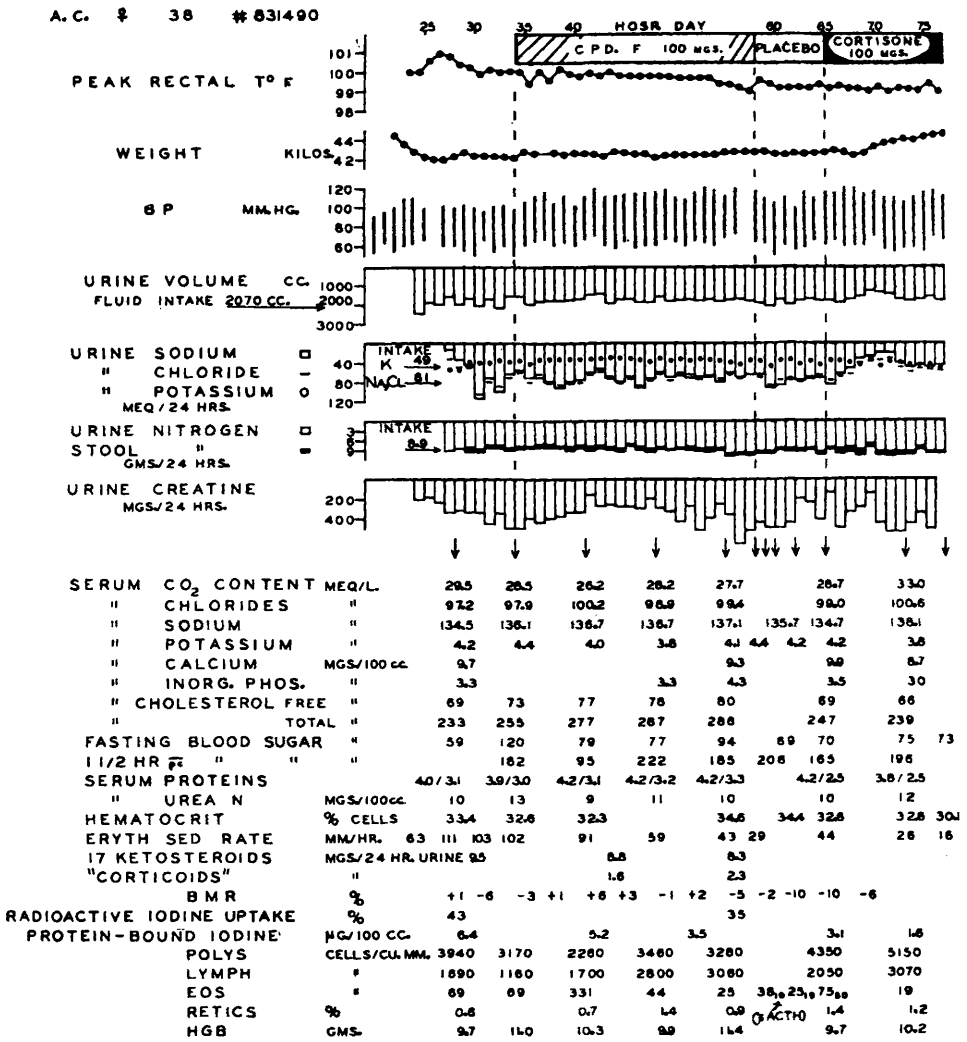

FIG. 1. Rheumatoid arthritis—treatment with Cpd. F and cortisone.

tension, and an increased appetite. The patient's appearance changed during the Cpd. F period in that her face seemed slightly fuller and more rounded, amenorrhea developed (last menstrual period began on the 20th hospital day), but no further clinical signs or symptoms of hyperadrenocorticalism were evident throughout the study. Repeated electroencephalograms while on Cpd. F showed identical normal patterns, but significant changes developed when subsequently on maintenance cortisone(5). Neither steroid gave rise to alterations in serial teleroentgenograms or electrocardiograms. Both agents produced subjective and objective improvement in the arthritis with disappearance of pain except on motion, increased mobility, reduction in joint swellings and modification of the erythrocyte sedimentation rate. Symptoms returned on the fifth day after stopping Cpd. F, and on the second day after the withdrawal of cortisone. The positive streptococcal agglutination test and the elevated titer of sensitized sheep cell agglutination remained unaffected by either steroid. As judged by weight, evidences of hemodilution, and the

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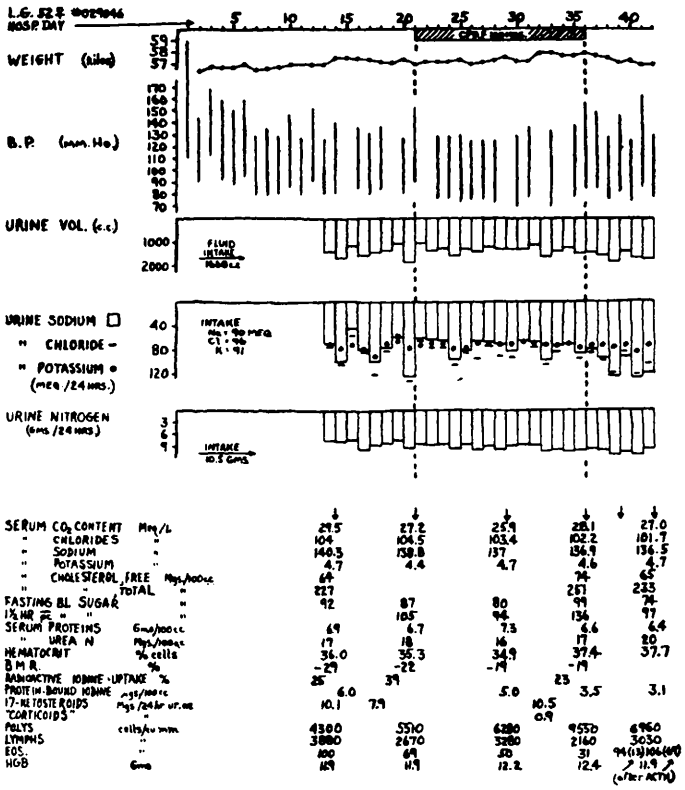

FIG. 2. Cpd. F in hypertensive vascular disease (L.G.).

output figures, Cpd. F exerted little influence on salt and water balance, whereas cortisone induced definite retention. Cpd. F appeared to be associated with a slightly negative nitrogen balance but no comparison with cortisone could be made because of the short interval between the administration of the steroids.

Additional effects of Cpd. F may be seen in Fig. 1. Noteworthy were the small or negligible alterations in serum electrolytes, the inconclusive changes in blood sugar (although both drugs produced inconstant and slight glycosuria without ketonuria), the rise in serum cholesterol values, and the shifts in circulating white cells. Cpd. F failed to influence thyroid function as estimated by basal metabolic rate, by measurements of radioactive iodine uptake directly over the gland at 2, 4, and 24 hours, and by measurements of urinary excretion of radioactive iodine over the same periods. Nevertheless, a significant decline in protein-bound iodine was observed which might suggest depression of thyroid function. No manifestations of hypoadrenalism appeared after the cessation of Cpd. F.

Additional cases. Fig. 2 illustrates similar effects of Cpd. F. 50 mg twice daily for 15 days, in a 52-year-old woman with uncomplicated hypertensive vascular disease whose arterial tension fell to normal during the baseline period. No subjective changes were noted by this patient other than appetite increase, but a small degree of salt and water retention was evident as illustrated by the slight weight gain and the sodium and chloride diuresis following withdrawal. The blood pressure was unaffected, and other measurements were comparable to the previous study save that glycosuria was not induced.

A third patient, a 33-year-old uncomplicated hypertensive, received Cpd. F, 50 mg twice daily for 10 days, then 75 mg twice daily for an additional 5 days (Fig. 3). This woman developed slight "nervousness," insomnia, and increased appetite during treatment, and with the increased dosage a rise in "resting" blood

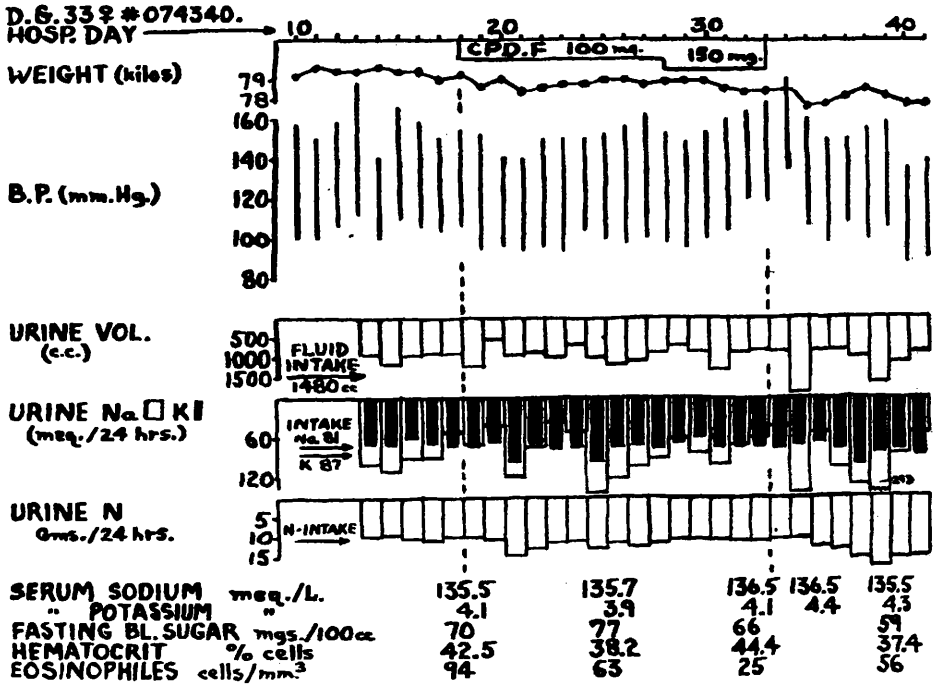

FIG. 3. Cpd. F in hypertensive vascular disease (D.G.).

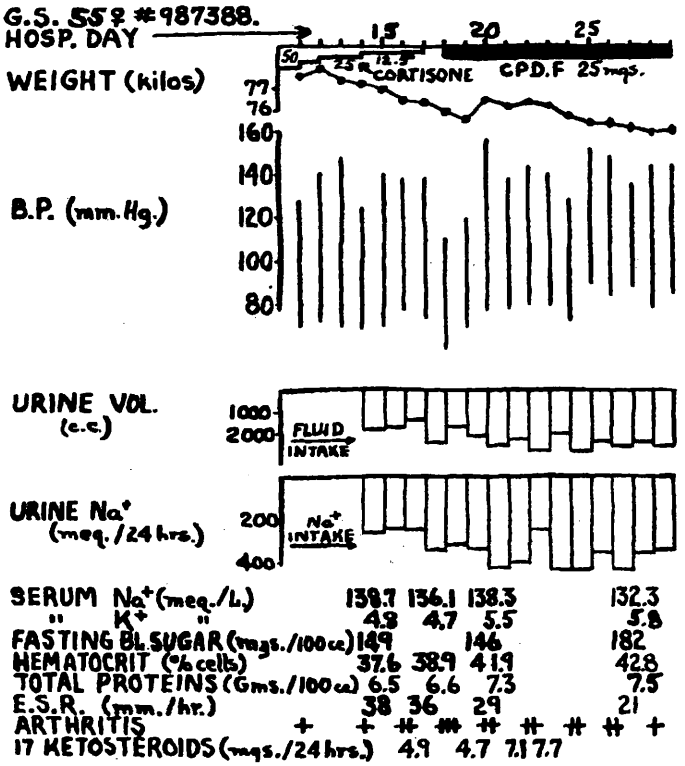

FIG. 4. Cpd. F in an Addisonian patient with arthritis, hypertension and diabetes.

pressure which returned promptly to baseline levels after treatment. Glycosuria appeared throughout the period of steroid administration. On cessation of the injections, there was some water diuresis, a marked urinary loss of sodium, and a rather striking additional loss of nitrogen in the urine.

The final patient, a 55-year-old housewife with hypertensive vascular disease, Addison's disease, diabetes mellitus and rheumatoid arthritis (Fig. 4), received 12.5 mg of Cpd. F daily for 11 days shortly after the gradual dose reduction and discontinuation of cortisone. On the same diet and supplemental sodium chloride as that employed in a previous cortisone study on the same patient(6), Cpd. F administration was associated with a progressive decline in serum sodium, a rise in serum potassium, a negative water and sodium balance, weight loss, some evidence of hemoconcentration, and a slow and inadequate arthritic response. The rise in the 24-hour excretion of 17-ketosteroids during Cpd. F therapy had also been noted previously in this patient after cortisone. On the conclusion of this experiment, a shift to cortisone in the same dosage resulted in weight gain, salt and water retention, restoration of normal serum values, and greater amelioration of the arthritis. Both agents were associated with an increased hyperglycemia and glycosuria.

Discussion. These preliminary studies, representing short-term observations on a small group of patients treated with Cpd. F, suggest again that this steroid exhibits similar effects to those recorded after cortisone(7). However, the comparative data would indicate that Cpd. F is somewhat less active, particularly in the realm of salt and water metabolism. It is of interest that the patient with hypoadrenalism, arthritis and other disorders again showed an anti-arthritic response to small doses, that electrolyte equilibrium could not be maintained on Cpd. F; whereas cortisone restored the balance of electrolytes and seemed to be somewhat more effective as an anti-arthritic agent. The rise in 17-ketosteroid excretion values in this Addisonian subject after Cpd. F and cortisone(6) raises the possibility that certain 11-oxy-steroids, at least in the absence of normal adrenal cortical tissue, are capable of conversion to this end-product. Finally, attention should be called to the divergence of radioactive iodine uptake and the serum level of protein-bound iodine as indices of the effect of Cpd. F on thyroid activity. This aspect is being further investigated (S.C.W.).

Summary. The clinical and metabolic effects of parenterally-administered Cpd. F were investigated and compared with those of cortisone. Preliminary observations suggest similar responses but with Cpd. F appearing to be somewhat less active.

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Electrocardiogram of the Beagle Dog. (18769)

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Information concerning the electrocardiogram of the normal dog(1-4), is scanty, scattered, conflicting and based on relatively few observations in various, usually mixed, breeds. This report describes, in terms of standard

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