T-wave than does chlorpromazine. Using either the recommended starting daily doses of 30 mg for chlorpromazine and 1 mg for fluphenazine, or the 100-fold dose ratio found in the one clinical investigation, fewer undesirable cardiovascular and electrocardiographic side-effects would be expected when fluphenazine is used.

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Inhibition of Adrenocortical Responsiveness to ACTH by Actinomycin *D in vivo*

It has been reported recently[1-3] that acute or chronic administration of ACTH to rats results in a marked increase in adrenal protein synthesis. This is evidenced by a rise in the DNA and RNA concentrations in the gland and an increased capacity for incorporation of ^{14}C-glycine into protein in cell-free preparations of rat adrenals. Furthermore, Farese[4] has suggested on the basis of studies of this type that these changes in adrenal protein synthesis are specifically concerned with the mechanisms whereby ACTH induces adrenal hypertrophy and that even the steroidogenic effect of ACTH may be mediated by an effect of this hormone on adrenal protein synthesis. In order to elucidate this problem it was decided to investigate the effect of actinomycin *D* on the production of corticosteroids by the adrenal cortex.

Approximately 40 male rats, hypophysectomized 24 h previously and weighing 80–100 g, were given a subcutaneous injection of normal saline (0·5 ml./100 g body-weight) or a saline solution of actinomycin *D* in a dose of 25 μg/0·5 ml. saline/100 g body weight. Control rats were killed 30 min later. At various time intervals the remaining animals were given an intravenous injection of ACTH (2 mu./100 g body-weight), and killed 15 min later. Their adrenals were removed and weighed, and adrenal corticosterone concentrations were determined by a modification of the method of Guillemin *et al.*[5]. The results were expressed as μg corticosterone/100 mg adrenal tissue.

Fig. 1 shows the effect of actinomycin *D* on the changes in adrenal corticosterone concentration produced by the administration of ACTH. It can be seen that 24 h after actinomycin the adrenals of these animals did not respond to the injection of ACTH with an increase in the production of corticosterone ($P < 0{\cdot}05$) while those of the saline-injected controls responded in a normal fashion.

Actinomycin *D* appears to be one of the most specific and best characterized inhibitors of protein synthesis. It is said to produce its effects by blocking the DNA-directed RNA synthesis catalysed by RNA polymerase by binding at specific sites on the DNA primer[6-8]. The present data indicate that actinomycin can eliminate the increased synthesis of steroids in the adrenals of rats *in vivo* in response to ACTH. Ferguson[9,10] has shown a similar inhibition of adrenal steroid synthesis in response to ACTH or 3′,5′-AMP *in vitro* using the antibiotic puromycin. This substance is believed to inhibit protein synthesis in mammalian tissue at the point of transfer of amino-acids from soluble RNA to ribosomal nucleoprotein[11].

Both the *in vitro* work with puromycin and the present *in vivo* findings with actinomycin *D* are consistent with

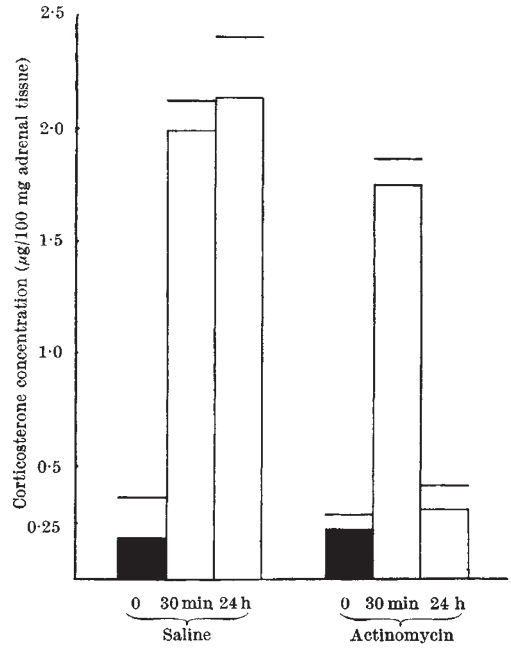

Fig. 1. The effect of actinomycin *D* on the changes in adrenal corticosterone concentration produced by the administration of ACTH to hypophysectomized rats. Horizontal lines represent the standard errors. ■, Controls; □, ACTH 2 mu/100 g

the idea that protein synthesis is necessary for adrenal corticosteroid responsiveness to ACTH. It is interesting to note that, under similar conditions, actinomycin will also inhibit the decrease in adrenal ascorbic acid produced by ACTH[12].

There have recently been several reports on the apparent increase in protein synthesis that accompanies the effects of estrogens[13], androgens[14], parathyroid hormone[15], thyroxin[16], and other hormones. Talwar and Segal[17] have proposed that a common feature in the mechanism of action of a variety of 'stimulatory hormones' is the triggering of the synthesis of messenger RNA, specific for bringing about biological changes characteristic of their respective target organs. It would appear that the mechanism of action of ACTH on the adrenal cortex adds further support to this thesis.

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