tion to diuresis present the opportunity for an interesting study. This has been begun by Cole *et al*(3).

After 3 loadings, the present species still had a "residue" of water conservation in comparison to white rats. Reloaded *Dipodomys* were slower in excretion than *Meriones*. Only *Meriones* that were *reloaded* within 8 hours approached the rate of diuresis of white rats after their *first* load. This "residue" of conservation might have disappeared after further loading, or it may be an irreducible minimum dependent upon the morphological and functional characteristics of the kidneys of these species. All 3 species were able to "cope with" water loads. A "difficulty in excretion" is a possible interpretation only for the first loading of dehydrated animals. Only 2 animals, *D. agilis* that had been accidentally overloaded beyond 5% of their body weight, showed obvious hematuria; this contrasts with a 50% incidence of hematuria observed by Hofmann(1).

Summary. *Dipodomys merriami, D. agilis* and *Meriones unguiculatus* excreted orally administered water loads at rates slower than those reported for white rats. Dehydrated animals retained all, or almost all, of an initial load of 5 ml/100 g for at least 6 hours. Animals fed lettuce before loading excreted 40% of the load in 123 to 504 minutes; rate of excretion was inverse to the aridity of the species' habitats. The rate of diuresis doubled or tripled after a second or third loading, but a residue of conservation remained. None of the species showed "difficulty in excretion" after being conditioned by the first loading.

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Circadian Variations in Sensitivity to Glucocorticoid Evaluated by Urinary Trypsin Inhibitor Excretion. (30530)

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Excretion of the urinary trypsin inhibitor (TI) in man is regulated by pituitary-adrenal hormones(1,2) and is increased in pregnancy (3) and during stress(1,2). Excretion of TI parallels in the individual the 17-ketosteroid and 17-ketogenic steroid excretion(1,4). In different individuals there is a correlation between cortisol production, or amount of exogenously administered glucocorticoid, and the diurnal excretion of TI(5,6), but the quantitative response, in terms of TI excretion, to a given amount of glucocorticoid, (*i.e.*, the sensitivity to this function of the hormone) varies individually(2,5).

The purpose of the present note is to show that there is a circadian rhythm in the individual in sensitivity to glucocorticoids. The quantitative response, assayed as excretion of TI, to a given amount of glucocorticoid is usually much lower during the night than during the day.

Materials and methods. Six persons were examined, most of them more than once. Two suffered from collagenoses (scleroderma and disseminated lupus erythematosus); 2 had dermatological diseases; and 2 were Addison patients. All patients were under treatment with glucocorticoids. On the days of this investigation, their usual treatment was replaced by 2 daily doses of steroid (cortisone

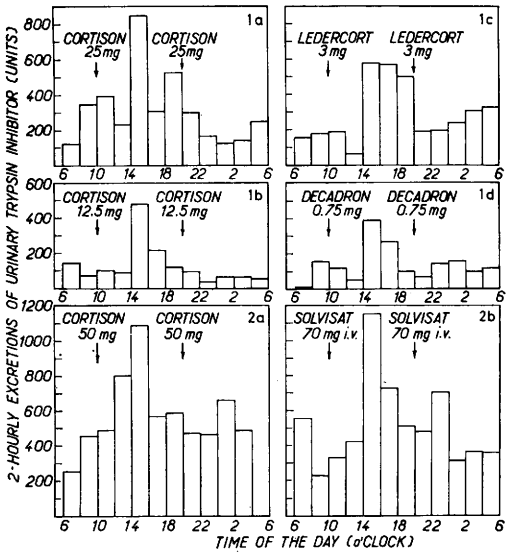

FIG. 1 and 2. Excretion of urinary trypsin inhibitor in response to glucocorticoid administration.

Abscissa: Time of day in 2-hourly periods.

Ordinate: Urinary output of trypsin inhibitor per period (in TI units).

FIG. 1. Patient with scleroderma. a and b: Cortisone acetate. c: Triamcinolone (Ledercort®). d: Dexamethazone (Decadron®).

FIG. 2. Addison patient: a: Cortisone acetate, orally. b: Hydrocortisone dixanthogenate (Solvisat®), intravenously.

acetate, triamcinolone (Ledercort®) or dexamethazone (Decadron®)) given orally at 10 A.M. and 8 P.M., except for one case where the steroid (hydrocortisone dixanthogenate (Solvisat®)) was given intravenously. Urine was collected in 2-hourly portions during a 24-hour period. Content of TI was estimated by a caseinolytic method using crystalline trypsin (24.4 Anson units/g, Novo Laboratories, Copenhagen)(4). One arbitrary unit of TI binds 1 μg of this trypsin preparation.

Results. Results of a 4-day examination of a 35-year-old woman with scleroderma are presented in Fig. 1. After a lag period of about 4 hours the morning dose of glucocorticoid was followed by an increase in TI excretion lasting for 4 to 6 hours. This pattern is in close agreement with our previous findings (7). In contrast, the night dose produced little or no increase in excretion. Similar patterns of response were found in the other patients. Only on one occasion, in one individual, was a night increase observed which was of the same magnitude as the day increase.

Fig. 2 shows the results from a 50-year-old woman with Addison's disease who received 50 mg of cortisone acetate orally or 70 mg of hydrocortisone dixanthogenate intravenously. In both experiments, the morning dose, after a lag period, produced a large increase in TI output, whereas the night dose gave only an insignificant increase.

Discussion. The observed day to night variation of the response to glucocorticoid administration is presumably not caused by differences in renal function. The 10% reduction in glomerular filtration rate occurring during night(8) is too small to account for the variation. Neither could differences in intestinal absorption of the orally administered hormones be assumed to be the cause since the variation in response also occurred after intravenous administration. It is suggested that the change in response to a given amount of glucocorticoid is caused by a change in hormone sensitivity of the effector organ regulating production of TI. This suggestion is apparently supported by the finding that the effect of hormones on TI excretion in the urine parallels their effect on the concentration of serum trypsin inhibitor(9).

It is known that stress increases the sensitivity to other functions of glucocorticoid hormones. Thus, the influence of glucocorticoids on the catabolic rate of proteins in rats is increased during stress induced by severe trauma, by formaline necrosis, by insulin hypoglycemia, or after adrenaline injection(10). The corticoid-induced thymus involution is also increased by traumatically induced stress (11), as is the eosinopenic response in man during operative stress(12).

The decrease in response to glucocorticoid administration, in terms of TI excretion, observed during the night, would fit into the same pattern. It is known that the production of glucocorticoid is decreased during the night. A decreased hormone production, and a decreased sensitivity to glucocorticoid, could both be parts of the restoring effect of sleep. It would be interesting to know whether a decrease in sensitivity during the night also exists for other functions of these hormones.

Summary. The urinary excretion of trypsin inhibitor produced by equal amounts of glucocorticoid hormone administered to man at 2 different periods of the day was studied. The hormonally induced increase in excretion was much larger during daytime than during the night. It is concluded that the response, in terms of urinary trypsin inhibitor excretion, to a given amount of glucocorticoid, (*i.e.*, the sensitivity to the hormone) is much lower during the night than during the day.

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IgM and IgG Anti-Hapten Antibody: Hemolytic, Hemagglutinating And Precipitating Activity.* (30531)

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Antibody activity is found in several classes of globulin including those antibodies against simple haptenic groups. The presence of antibody activity against haptenic groups in rabbit macroglobulin (IgM‖) as well as in 7S γ-globulin (IgG‖) has been reported by Bauer(1) and by Onoue *et al*(2). In our previous study(3), rabbit IgM antibody against the *p*-azobenzenearsonate (R*p*) group was prepared in high purity and the number of hapten-binding sites of IgM antibody molecule was determined. It was shown that 6 hapten binding sites are present on the native IgM antibody molecule based on a molecular weight of 1,000,000. Little change was observed in the number of sites and constant for binding with the hapten after reduction and alkylation of native IgM antibody.

Using highly purified anti-R*p* antibody preparations of known binding properties, we compared, in the present study, the hemolytic and agglutinating activities of IgM and IgG antibody with erythrocytes to which R*p*-groups were attached(4). In agreement with previous reports by others on antibodies against erythrocytes or bacterial cells(5), the IgM antibody was shown to have a considerably higher activity than the IgG antibody in both hemolysis and hemagglutination. Reduction and alkylation of the IgM antibody resulted in loss of these activities as well as loss of precipitating activity with a polyvalent hapten-protein conjugate.

Materials and methods. Antisera. Antisera against the *p*-azobenzenearsonate (R*p*) group

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‖ In analogy to the nomenclature for human immunoglobulins recommended by WHO, we are using the symbols IgM and IgG for rabbit γ_1- or β_2-macroglobulin and 7S γ-globulin. Another antibody component previously called B_1-globulin antibody(2) was designated as IgA antibody because of its similarity to human IgA antibody in physical and biologic properties based on our more recent data.