in both tests. However, the latter test is more sensitive when antibodies are low in titer and the collodion agglutination test is frequently negative after the 3rd month or so of active disease(7,9). Cross-reacting tests with blastomyces antigen were not unexpected, and have been described previously(2,4,5). Results from these laboratories demonstrated that at different stages of histoplasma infections heterologous blastomyces antibody titers often equaled and sometimes surpassed, the homologous histoplasma titers(10).

It is felt that repeated skin tests would alter and confuse the utilization of serologic data in the diagnosis of histoplasmosis.

Conclusions. Repeated positive histoplasmin skin tests in normal medical students caused false positive reactions in the collodion agglutination test (57.1%) and in the complement-fixation test with histoplasma yeast phase antigen (78.6%) or with histoplasmin as antigen (85.7%). The response was relatively transient in the former 2 tests, and negative titers were usually restored by 21 weeks after the last skin test. However, positive results were noted as late as 21, 25 and 39 weeks in complement-fixation tests employing histoplasmin as antigen. A transient response was observed in complement-fixation studies with cross-reacting yeast phase blastomyces antigens (57.1%), but no sera reacted in the same test with coccidiodin antigen. A single positive skin test and repeated negative skin tests did not alter serologic results. Thus, repeated histoplasmin skin testing of skin-test positive persons may invalidate complement-fixation data for long periods with histoplasmin as antigen, and for much shorter periods with yeast phase histoplasma and blastomyces complement-fixation or histoplasmin collodion agglutination tests.

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Received February 16, 1953. P.S.E.B.M., 1953, v82.

Effects of Large Doses of Desoxycorticosterone Acetate, Cortisone Acetate and ACTH in Intact Rhesus Monkeys.* (20221)

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In the course of a study designed primarily to investigate the effects of relatively large doses of desoxycorticosterone acetate, cortisone acetate and ACTH on the morphology of the adrenal cortex of the rhesus monkey(1), additional observations were recorded relating to the physiological effects of these hormones in the intact animal. These are reported in the present paper.

Materials and methods. The 14 monkeys (9 males and 5 females) used in this study were quartered in individual cages located in an air-conditioned room maintained between 78° and 80°F. Food(2) and water were supplied *ad libitum* except for a 12-hour fast preceding each bleeding. The monkeys were bled at three- to four-day intervals prior to and

* Supported in part by an Institutional Grant to Harvard University from the American Cancer Society and in part by a grant from the National Institutes of Health, U. S. Public Health Service.

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TABLE I. Effects of ACTH, Cortisone Acetate and Desoxycorticosterone Acetate (DCA) on Adrenal and Body Weights of Intact Rhesus Monkeys.

Animal No.	Sex	Treatment	Dose/day, mg	No. days	Initial body wt, g	Final body wt, g	Adrenal wt, mg†
28	♂	ACTH (Wilson), intramusc. inj.	80*	6	5870	6055	1022
32	♂	"	80*	8	4180	4400	1148
39	♂	"	80*	8	4310	4050	1187
14	♂	ACTH (Astwood) in gelatin, subcut. inj.	.5‡	8	6445	6605	774
89	♀	"	5.0	34	2800	2950	486
66	♀	"	1.0	34	2800	2915	919
42	♂	DCA (aqu. suspension), intramusc. inj.	25	42	4880	4460	433
43	♂	"	25	42	4225	3810	321
45	♂	Cortisone (aqu. susp.), intramusc. inj.	50	42	4125	3390	145
40	♂	"	50	14	4085	4015	295
8	♂	"	25	38	2433		
			50	30		2380	108
E1	♀	"	50	33	3815	3965	148
E2	♀	"	50	33	3700	3650	170
E3	♀	"	50	33	3820	3650	209

* Administered in 4 daily inj. of 20 mg each.

† Wt of one gland. Range of adrenal wt for 15 normal animals of simliar body wt is 216-437 g.

‡ 80 U.S.P. units/mg(8).

following the initiation of treatment. The blood samples were analyzed for glucose, nonprotein nitrogen, amino acid nitrogen, inorganic phosphorus, sodium, potassium and chloride(2). The hematocrit was also determined. Body weights were recorded at the time of bleeding. The various treatments are summarized in Table I. Glucose tolerance tests were performed in 3 monkeys (E1, E2 and E3) by intravenous infusion of glucose (75 mg per kg body weight). At the termination of the treatment periods the animals were adrenalectomized(2) and the recovered adrenal glands were weighed and examined histologically.

Results. 1) *ACTH.* The administration of this substance resulted in enlargement of the adrenal glands (Table I) and stimulation of the adrenal cortex in terms of histological and histochemical criteria(1). Aside from these responses, ACTH, as administered in this study, failed to effect significant changes in hematocrit and in the various blood constituents studied (Fig. 1). No loss in body weight was recorded for any animals receiving ACTH (Table I).

2) *Desoxycorticosterone acetate.* This treatment effected a loss in body weight (animals 42 and 43) over the period of hormone administration (Table I). A reduction in food intake was noted during this period. No significant changes in adrenal weights were observed (Table I). The blood levels of inorganic phosphorous and potassium were lowered slightly, but significantly, during the course of hormone administration. The hematocrit values gave evidence of moderate

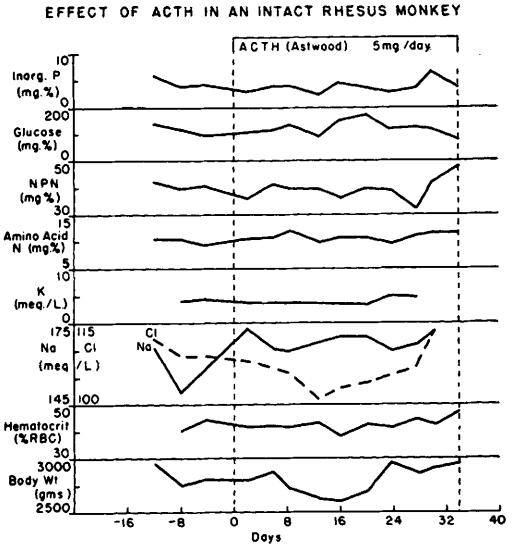

FIG. 1. Effects of ACTH (Astwood—5 mg [400 I.U.] per day) in monkey 89.

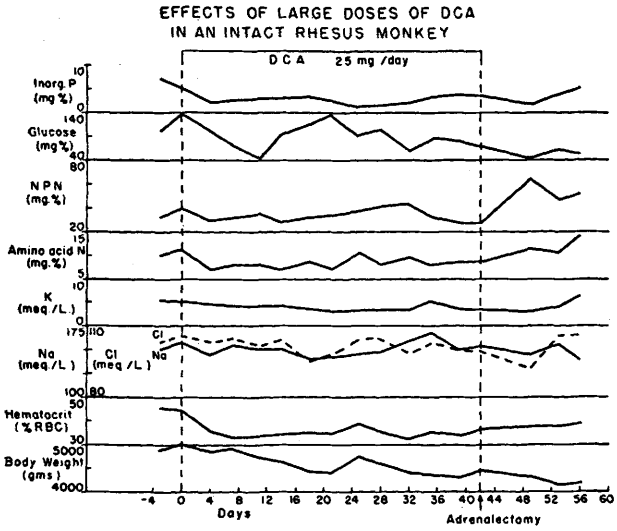

FIG. 2. Effects of 25 mg desoxycorticosterone acetate per day in monkey 42.

hemodilution. No significant changes were observed in the concentrations of amino acid nitrogen, non-protein nitrogen, glucose, sodium and chlorides (Fig. 2). Approximately 10 days after the initiation of DCA administration, both animals exhibited a marked polydipsia which was accompanied by severe edema of the scrotal and penile regions. These manifestations lasted for a few days, subsided and did not recur during the remainder of the treatment period.

3. *Cortisone acetate.* Of the 6 animals given cortisone, only one showed a marked loss in body weight (No. 45, Table I). This monkey became anorexic and listless as the experimental period progressed and a considerable reduction in the muscle mass of the lower extremities was noted. The influence of cortisone on the blood constituents as recorded for monkey no. 45 are shown in Fig. 3. The only salient changes found in this and the other animals with regard to the blood picture were a decrease in the serum potassium concentrations and a lowering of the hematocrit. It is noteworthy that hyperglycemia was not observed at any time in the course of cortisone administration. Cortisone (50 mg per day for 30 days) similarly was without effect on glucose tolerance in the 3 monkeys so studied (Fig. 4). Adrenal weights were markedly decreased in all monkeys receiving the larger doses of cortisone (Table I).

Discussion. That ACTH in very large doses (to 400 mg per day) can be ineffective in producing significant increases in blood sugar has been demonstrated in the cat(3) and in the mongrel dog(4). It appears from the present data that the rhesus monkey must be grouped with these species rather than with man, where as little as 12.5-50 mg of ACTH (Li's ACTH protein) will increase fasting blood sugar levels(5). Raben *et al.*(8), using

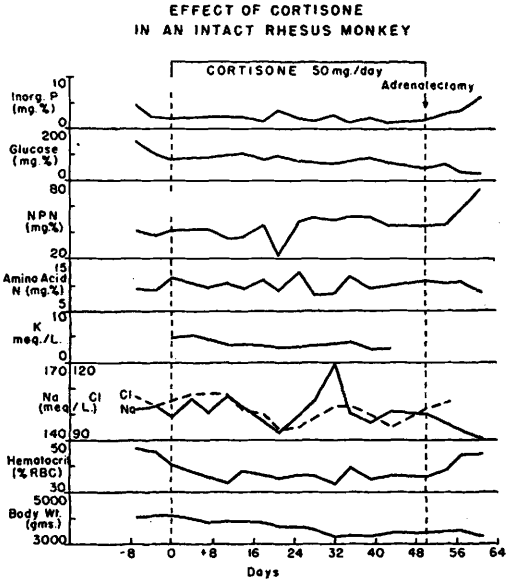

FIG. 3. Effects of 50 mg cortisone acetate per day in monkey 45.

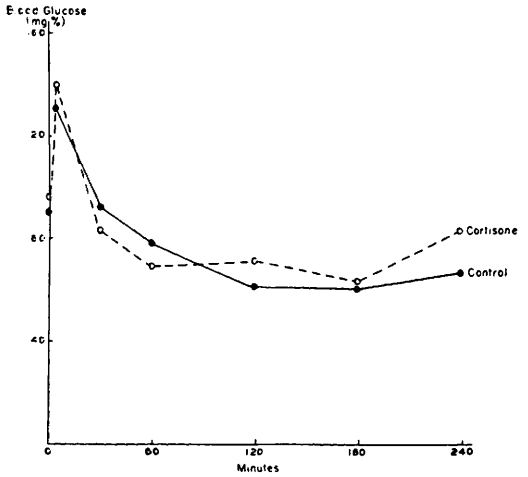

FIG. 4. Glucose tolerance curves before and after treatment with 50 mg cortisone acetate per day for 30 days. Each curve represents mean values of animals E1, E2 and E3 before and after hormone administration.

the Astwood corticotropin, observed symptoms of overdosage in patients receiving 0.19 to 0.3 mg per day whereas no such effects were observed in a monkey (No. 89) which received 5 mg of the same preparation per day for 34 days.

Cortisone likewise failed to induce hyperglycemia or to alter glucose tolerance although an electrolyte effect, *viz.* a depression in serum potassium, was observed. This finding is in agreement with the recent report of Sirek and Best(6) that in dogs, large doses of cortisone evoke a diabetes insipidus-like response but do not elevate the levels of blood sugar or change the glucose tolerance curves. Such effects have been associated with the action of large doses of desoxycorticosterone as shown in the dog by Kuhlman *et al.*(7) and as demonstrated in the present study where a transient polydipsia and a lowering of serum potassium was obtained in monkeys given desoxycorticosterone. It is of interest that this decreased potassium concentration was not accompanied by corresponding increases in serum sodium and chloride levels.

The observation that only one of the monkeys receiving cortisone exhibited an important loss in body weight cannot be explained at present, but it is noteworthy that this loss was not reflected in changes of blood amino acid or non-protein nitrogen concentrations.

Summary. The effects of large doses of ACTH, cortisone acetate and desoxycorticosterone acetate were investigated in the intact rhesus monkey. ACTH was without effect on hematocrit and the blood levels of glucose, non-protein nitrogen, amino acid nitrogen, inorganic phosphorous, sodium, potassium and chloride, although the adrenal glands were strongly stimulated as evidenced by adrenal gland weight and histological examination. Cortisone acetate and desoxycorticosterone acetate effected a decrease in serum potassium and a lowering of the hematocrit without altering the levels of the other blood constituents. One of the 6 animals receiving cortisone suffered a significant weight loss, but hyperglycemia and elevated glucose tolerance curves were never observed. A transient polydipsia and edema were noted in the course of desoxycorticosterone administration.

We wish to thank Dr. E. B. Astwood for generous supplies of his corticotropin preparations, Dr. P. L. Perlman of the Schering Corp. for the desoxycorticosterone acetate and Dr. E. Alpert of Merck and Co. for the cortisone acetate. The suspensions of DCA were kindly prepared by Drs. L. M. Ohmart and M. J. Stoklosa of the Massachusetts College of Pharmacy. The technical assistance of Mrs. L. W. Parker is gratefully acknowledged.

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Received March 10, 1953. P.S.E.B.M., 1953, v82.