Technical Papers

The Probability that Compound F (17-hydroxycorticosterone) is the Hormone Produced by the Normal Human Adrenal Cortex[1,2]

Jerome W. Conn, Lawrence H. Louis, and Stefan S. Fajans[3]

Metabolism Research Laboratory, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor

With the recent availability of pure adrenosteroidal compounds in sufficient quantity for adequate testing in man, the suspicion has been growing that one need not postulate the secretion of a multiplicity of adrenal cortical hormones to account for the diverse metabolic activities that occur when ACTH is administered to a normal individual. The results of studies with individual steroids indicate that the metabolic effects in man of each of several of these compounds are much broader than had been suspected before they were tested (*1–4*). For example, our own studies (*3*) on the metabolic effects of corticosterone (Compound B) in Addison's disease indicate that this compound alone produces the desirable effects of a combination of cortisone (11-dehydro-17 hydroxycorticosterone) and desoxycorticosterone.

Experiments done recently on dogs and on surviving beef adrenal glands suggest strongly that the steroidal output of the adrenal cortex consists predominantly of 17-hydroxycorticosterone (Compound F) and corticosterone (*5, 6*).

On the basis of the results reported below there is a strong indication that Compound F is the substance secreted by the adrenal cortex when ACTH is administered to normal people.

Extensive metabolic balance studies were performed upon a normal 22-year-old woman. After the constant diet had been fed for two days, there followed a 4-day period for control observations. During the next 4 days the subject ingested 400 mg/day of Compound F (100 mg at each of the three meals and 100 mg at 11:00 P.M.). Observations were then continued for 4 days following cessation of the orally administered Compound F.

The metabolic data are shown in brief form in Table 1 and Fig. 1. It was observed in addition that edema of the legs began on the third day of Compound F and reached a maximum on the day following cessation of administration of the steroid, and that typical acne developed about 15 hr after the last dose of Compound F.

It is evident from the data that all the metabolic changes produced by ACTH in normal individuals were observed in this subject when Compound F was administered orally. The intensity of the changes is roughly equivalent to that produced by injections of

TABLE 1

THE METABOLIC EFFECTS IN MAN OF ORAL COMPOUND F (400 mg/day)

Daily 24-hr renal excretion*	Control period (4 days)	Compound F period (4 days)	Recovery period (4 days)
Sodium (mEq)	147	27	324
Chloride (mEq)	163	84	225
Potassium (mEq)	108	112	64
Nitrogen (g)	11.3	14.3	13.6
Sulfur (mg)	734	983	808
Glucose (g)	0.6	3.7	0.7
Uric acid (mg)	575	800	637
Creatinine (g)	1.3	1.4	1.4
17-ketosteroids (mg)	18.1	35.2	16.5
11-oxysteroids (mg)	1.0	3.5	1.3
Urine vol (ml)	929	758	2148
*Other daily values**	4 days	4 days	4 days
Fasting blood sugar (mg%)	74	95	71
Eosinophils (cm)	72	0	110
Hematocrit	46.5	44.0	47.0
Body wt (kg)	53.2	55.0	54.1
Other determinations			
Blood-reduced glutathione (see text)			
Serum sodium	No significant change		
" chloride			
" potassium			
" total lipids			
" " cholesterol			
" free cholesterol			

* Each value represents the average of four daily determinations.

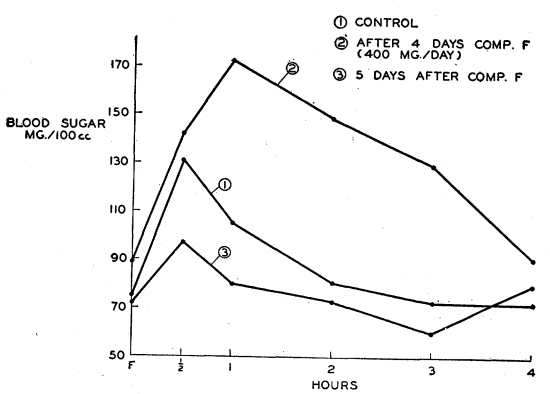

FIG. 1. Effect of Compound F on glucose tolerance (J.B. ♀ 22—normal subject).

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[3] Life Insurance Medical Research Fellow.

100 mg/day (Armour Standard) of ACTH in normal people. It is probably significant that Compound B, administered either orally or parenterally in normal people or in Addisonians, fails to reduce the number of circulating eosinophilic granulocytes (*3*), whereas Compound F causes them to disappear completely. The fact that administration of Compound F to a normal woman results in a sharp and progressive increase in the excretion of urinary 17-ketosteroids indicates that one need not postulate cortical elaboration of a separate "androgenic steroid" to account for the rise of 17-ketosteroid excretion that accompanies administration of ACTH to normal people. Although several other steroidal compounds administered orally, at similar levels of dosage, to normal individuals produce increased renal excretion of 17-ketosteroids (*7*), the over-all metabolic activities of Compound F, in terms of intensity and diversity, approximate more closely those observed during administration of ACTH. As with ACTH (*8*), Compound F produces a decrease of red cell reduced glutathion. The present study indicates an 11% decrease from baseline levels (sustained for 3 consecutive days) following 3 days of administration of Compound F.

The only important difference we have been able to measure between the metabolic activities of ACTH and Compound F relates to their different effects upon total and free cholesterol of serum. With ACTH a sharp fall of esterified cholesterol of serum occurs by the fourth day of administration (*9*). Compound F failed to produce a significant change in either the total or free cholesterol of serum. Inasmuch as it is presumed (*9*) that the decrease of esterified cholesterol of serum observed during administration of ACTH represents withdrawal of this substance from serum as a precursor for steroidal hormone synthesis by the adrenal cortex, it should not be expected that Compound F would exert a similar influence upon serum cholesterol.

If the normal response to the administration of ACTH consists of the elaboration by the adrenal cortex of Compound F solely, one is faced with the problem of explaining the differences in over-all metabolic activities observed among normal people given ACTH. It is probable that these differences are due, not to variations in the types of steroidal materials produced or to differences in the relative amounts of specific steroidal substances elaborated, but rather to differences in the receptivity and reactivity of the various end organs to a single steroidal compound (*10*).

Within the limits of this study we are able to discern no significant differences between the metabolic effects of orally administered Compound F and the diverse metabolic effects known to occur in normal people given ACTH. It seems likely that Compound F is the adrenal cortical hormone, and that one observes the metabolic effects of this compound when he stimulates the normal adrenal cortex with ACTH.

Addendum: Since submission of the data reported above we have made several additional observations that should be recorded. Recognition of these facts will avoid in future reports on Compound F what otherwise would appear to constitute conflicting results:

1. Compound F acetate administered orally produces approximately the same metabolic effects as those recorded above for free Compound F given orally.
2. Compound F acetate administered intramuscularly for the same length of time, in the same dosage, to the same person, produces only slight metabolic effects.
3. Free Compound F administered intramuscularly results in at least as intense metabolic activities as those observed when either the free compound or the acetate is given orally.

The statements made above are based upon results obtained on the same normal female subject, J. B., who received free Compound F and Compound F acetate orally, as well as each compound intramuscularly. In each of the 4 separate experiments the dose was 400 mg/day.

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References

1. INGLE, D. J. *J. Clin. Endocrinol.*, **10**, 1312 (1950).
2. CONN, J. W., *et al. J. Lab. Clin. Med.*, **36**, 813 (1950).
3. CONN, J. W., FAJANS, S. S., and LOUIS, L. H. *Trans. Assoc. Am. Physicians* (in press).
4. FOURMAN, P., *et al. J. Clin. Invest.*, **29**, 1462 (1950).
5. NELSON, D. H., REICH, H., and SAMUELS, L. T. *Science*, **111**, 578 (1950).
6. PINCUS, G., HECHTER, O., and ZAFFARONI, A. *Proceedings of the Second Clinical ACTH Conference*. J. R. Mote (Ed.), Philadelphia: Blakiston (1951).
7. CONN, J. W., *et al.* To be published.
8. CONN, J. W., LOUIS, L. H., and JOHNSTON, M. W. *J. Lab. Clin. Med.*, **34**, 255 (1949).
9. CONN, J. W., *et al. Ibid.*, **35**, 504 (1950).
10. CONN, J. W. *J. Clin. Endocrinol.*, **10**, 825 (1950).

Number of Entities Inactivated by X-Rays in Greying of Hair[1]

Herman B. Chase

Arnold Biological Laboratory,
Brown University, Providence, Rhode Island

Greying of hair by x-radiation has been observed by several workers and described in some detail by Hance and Murphy (*1*), Murray (*2*), Danneel and Lubnow (*3, 4*), and Chase *et al.* (*5–8*). In the mouse the degree of greying depends on the dose, the dose rate, the stage of follicle at time of treatment, and size of the follicle. For any given dose, follicles in the anagen (active growth stage) develop a lower percentage of white hairs in all ensuing hair generations than do follicles in the catagen or telogen (resting) stages (*5, 6*). The smallest hairs of the regular coat of the mouse, the zigzags, are the most "sensitive" in respect to percentage of greying (*8*). These hairs make up 82% of the coat. The larger auchenes, awls, and mono-

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