

BLOOD LEVELS OF 17-HYDROXYCORTICOSTEROIDS FOLLOWING THE ADMINISTRATION OF ADRENAL STEROIDS AND THEIR RELATION TO LEVELS OF CIRCULATING LEUKOCYTES¹

By DON H. NELSON, AVERY A. SANDBERG,² J. G. PALMER,³ AND FRANK H. TYLER

(From the Departments of Biochemistry and Medicine of the University of Utah College of Medicine, Salt Lake City, Utah)

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INTRODUCTION

In 1944 Dougherty and White (1) reported the occurrence of neutrophilia and lymphopenia following the administration of ACTH or adrenal cortical extracts to mice. In 1948 these findings were confirmed in man by Hills, Forsham and Finch (2), who noted, in addition, a pronounced fall in eosinophils. These changes in the blood have been used widely as an index of adrenal cortical activity. With the development of a method for the determination of 17-hydroxycorticosteroids in small quantities of blood or plasma (3) it has become possible to determine the relationship of the changes in blood steroid levels to the changes in leukocytes.

In order to investigate this relationship, standard doses of various corticosteroids were administered to normal individuals and the alterations in blood 17-hydroxycorticosteroids and in leukocytes were observed at intervals thereafter.

METHODS

Compound E (17-hydroxy-11-dehydrocorticosterone), compound F (17-hydroxycorticosterone), and compound S (17-hydroxy-11-desoxycorticosterone) were administered as the free alcohols and as the acetate esters. All subjects used were normal young adult males who were fasting at the time the steroids were given, and for at least three hours thereafter. When administered orally, the compounds were mixed with fruit juice, with the exception of compound E acetate, which was given as tab-

lets to two subjects (C. F. and T. O.). When administered intramuscularly, the compounds were in the form of a commercially available saline suspension except as indicated in the tables. Generally, the steroids were administered between 8:00 and 9:00 a.m. Blood was drawn for the steroid and blood cell determinations immediately prior to administration, and at one, four, eight, and 24 hours thereafter. These intervals were selected after preliminary studies in which samples were drawn at one-half hour intervals had demonstrated that the serum steroid peak occurred at approximately one hour and the previous observation of maximum cellular effects at approximately four hours was confirmed. Approximately 30 ml. of blood were drawn at each sampling. Heparin was used as an anticoagulant for the steroid determination and mixed oxalate for the cellular studies.

Determination of 17-hydroxycorticosteroids was carried out by the method of Nelson and Samuels (3). Ten milliliter samples of plasma were generally used for the determination. The Florisil chromatographic column was employed for purification and the micromodification of the color reaction of Porter and Silber was used for quantitation (4). Compounds E, F, and S give this reaction. All levels of 17-hydroxycorticosteroids given are expressed in terms of $\mu\text{gm. per } 100 \text{ ml. of plasma}$.

Eosinophil counts were performed in duplicate by the method of Randolph (5). Total leukocyte counts were done in duplicate by routine methods and the average of the two counts was used. Absolute neutrophil and lymphocyte counts were calculated from the total leukocyte and differential counts. The latter were made from cover-slip blood films stained with Wright's stain, on which 500 cells were enumerated.

RESULTS

Figure 1 shows a representative response of leukocytes and plasma 17-hydroxycorticosteroid levels following the administration of 200 mgm. of compound F acetate orally. The data on all seven subjects who received this dose of compound F acetate are shown in Table I. There was in each instance a marked rise in plasma levels of corticosteroids which reached a peak approxi-

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² Postdoctorate Research Fellow of the National Institutes of Health.

³ Fellow, American Cancer Society.

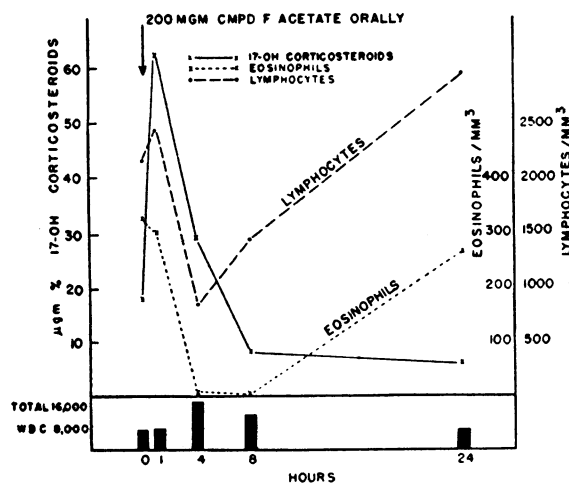


FIG. 1. THE EFFECTS OF 200 MG. OF F ACETATE GIVEN ORALLY ON BLOOD 17-HYDROXYSTEROID LEVELS AND CIRCULATING WHITE BLOOD CELL LEVELS

Note that although the peak of corticosteroid level occurred at one hour, only negligible changes had appeared in the cellular elements at that time. At four hours when the steroid level had fallen sharply, the maximum effect on cellular elements made its appearance.

mately one hour after the steroid was given. The level then fell rapidly and returned to approximately normal at the end of eight hours. Although the highest concentration of steroids was reached at about one hour, the maximum change in leukocytes was not seen until four or eight hours after ingestion of the compound. In every instance a decrease in lymphocytes and eosinophils occurred as well as a pronounced rise in neutrophils; the result was a rise of the total white count.

A single subject was given oral doses of compound F acetate ranging from 12.5 to 200 mgm. in order to determine the relation of dose to the response obtained. The experiments were carried out at approximately five-day intervals to minimize the effect of repeated dosage in the same subject. The results obtained are illustrated in Figure 2. When the levels at four hours are considered, it appears that the magnitude of the response in 17-hydroxycorticosteroids is progressively greater and more prolonged as the dosage of compound F is increased. Eosinophil levels fell at all dosage levels. With each increase in compound F a greater fall in eosinophils occurred until doses of 100 to 200 mgm. were given. With

the latter doses, the eosinophils remained at very low levels for longer periods of time. Lymphocytes decreased with doses of 25 mgm. or more, the amount and duration of the decrease being roughly correlated with the dosage. Increases in neutrophils were also seen at each dose level but this was not correlated with the amount of compound given.

The effects of single injections of 200 mgm. of compound F acetate given intramuscularly to four individuals are shown in Table II. There was no rise in blood levels of corticosteroids and no significant effect upon the leukocytes.

TABLE I

Administration of 17-hydroxycorticosterone (Compound F) acetate, 200 mgm. orally

Subject	Time in hours	17-OH steroid levels, μ /100 ml. of plasma	WBC	PMN	Lymph	EOS
				Absolute number per mm. ³		
M. C.	0	8.0	12,600	8,580	3,230	269
	1	48.0				
	1	124.0	12,350	8,590	2,940	288
	2		16,900	13,950	1,900	294
	4	70.0	18,700	16,200	1,980	19
	6		14,050	12,300	1,460	37
	8		13,200	11,100	1,580	19
24	<10.0	8,800	4,950	3,130	225	
A. D.	0	8.4	5,080	2,733	2,022	88
	1	107.2	6,650	4,043	2,141	125
	4	61.2	10,450	9,446	836	25
	8	5.4	8,950	7,900	1,694	6
	24		6,250	3,450	2,350	76
O. H.	0	18.2	7,100	4,075	2,144	325
	1	63.2	7,600	4,530	2,446	300
	4	29.3	19,050	17,640	838	6
	8	7.7	13,600	11,750	1,442	0
	24	6.2	7,300	3,781	2,964	263
D. T.	0	8.0	8,950	4,887	3,204	263
	1	80.2	7,650	5,110	1,943	138
	4	60.1	8,900	7,191	1,549	25
	8	13.7	12,500	11,325	925	6
	24	11.4	7,700	4,004	3,234	263
J. E.	0	10.7	5,000	2,830	1,730	181
	1	63.6	5,350	2,857	1,937	194
	4	50.0	5,900	4,838	896	19
	8		10,000	9,020	780	0
	24	2.4	8,400	3,914	3,814	238
J. B.	0	11.0	4,400	2,692	2,659	100
	1	87.0	4,900	3,386	2,789	113
	4	58.0	6,700	6,372	1,057	13
	8	9.0	7,950	5,624	3,572	6
	24	15.0	5,550	2,950	2,549	138
T. O.	0	11.0	6,160	4,151	1,602	150
	1	98.0	7,400	5,239	1,746	100
	4	50.0	18,350	16,698	1,431	19
	8	21.3	12,675	10,977	1,369	6
	24	20.0	13,400	8,576	4,100	106

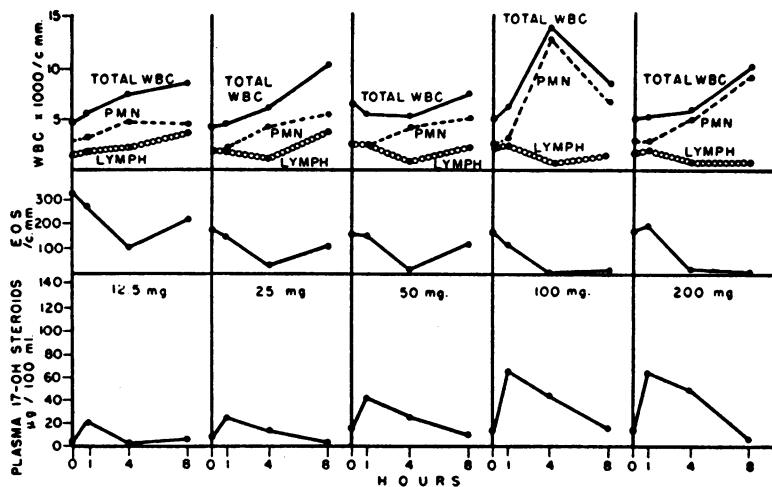


FIG. 2. THE EFFECT OF VARYING DOSES OF COMPOUND F ACETATE GIVEN ORALLY TO A SINGLE SUBJECT

The effects of 200 mgm. of cortisone acetate given orally to five subjects are tabulated in Table III. The effects were similar to those seen following compound F acetate given orally, but were less marked. The rise in steroid levels was in most cases not so great and was less prolonged; the same is true of the changes in leukocytes. In

Table IV are shown data on four subjects given cortisone acetate intramuscularly. The results are less consistent than those shown previously. In one subject (C. C.), there was a marked rise

TABLE II

Administration of 200 mgm. 17-hydroxycorticosterone (Compound F) acetate I. M.

Sub-ject	Time in hours	17-OH steroid levels, $\gamma/100$ ml. of plasma	WBC	PMN	Lymph	EOS
				Absolute number per mm. ³		
T. O.	0	19	7,850	4,773	2,685	113
	1	19.2	5,900	3,741	1,841	154
	4	8.4	8,250	5,659	2,145	156
	8	6	10,900	8,349	2,180	175
	24	4	7,350	4,293	2,675	81
M. C.	0	4.6	13,150	7,601	4,576	294
	1	0	13,200	8,791	3,379	356
	4	8.8	12,900	8,514	3,638	400
	8	8.0	11,750	7,755	3,219	250
	24	1.0	16,600	11,919	3,386	331
J. B.	0	19	5,500	2,387	2,640	106
	1	22.6	5,900	2,773	2,669	81
	4	14.4	7,500	3,960	3,090	81
	8	12	8,650	5,916	2,301	75
	24	16.8	5,050	2,545	2,122	125
A. D.	0	8.0	6,400	4,250	1,920	100
	1/2	10.2	6,700	4,680	1,860	69
	2		7,800	5,410	1,860	150
	4	4.2	8,350	5,650	1,950	75
	6		8,550	6,550	1,408	100
	8	5.4	9,150	6,860	1,755	50

TABLE III

Administration of 200 mgm. 17-hydroxy-11-dehydrocorticosterone (Compound E) acetate orally

Sub-ject	Time in hours	17-OH steroid levels, $\gamma/100$ ml. of plasma	WBC	PMN	Lymph	EOS
				Absolute number per mm. ³		
O. H.	0	14	8,700	4,768	2,871	344
	1	25.2	9,500	5,833	2,907	288
	4	11.7	10,100	8,040	1,575	25
	8	9.7	10,200	6,936	2,754	90
	24	8.0	8,800	4,453	3,802	281
D. T.	0	7.8	6,200	3,174	2,554	125
	1	46.0	6,600	3,986	1,848	225
	4	20.0	6,950	5,463	1,251	25
	8	4.0	9,000	5,580	2,898	69
	24	6.0	6,800	2,679	3,754	194
C. C.	0	3.0	8,500	4,641	3,043	238
	1	124.0	9,100	5,187	3,130	275
	4	21.0	12,600	10,483	1,789	13
	8	7.0	12,400	9,796	2,306	56
	24	4.0	8,450	4,326	3,566	269
C. F.	0	11.0	10,800	6,523	3,370	394
	1	65.0	11,000	6,490	3,564	369
	4	16.0	9,500	7,163	1,995	62
	8	5.0	7,850	4,569	2,747	131
	24	10.0	7,800	3,479	3,526	356
T. O.	0	9.6	7,500	4,440	2,775	81
	1	50.0	6,850	4,370	2,206	100
	4	33.0	6,050	4,985	920	38
	8	1.3	12,750	10,404	1,912	44
	24	4.0	9,000	5,760	2,664	138

TABLE IV

Administration of 200 mgm. of 17-hydroxy-11-dehydrocorticosterone (Compound E) acetate I. M.

Subject	Time in hours	17-OH steroid levels, γ /100 ml. of plasma	WBC	PMN	Lymph	EOS
				Absolute number per mm. ³		
C. C.	0	16.8	6,550	3,733	2,306	238
	1	59.0	8,450	4,343	3,211	300
	4	31.0	7,400	5,105	1,806	113
	8	31.0	16,800	14,112	1,949	75
	24	29.0	15,400	12,166	2,279	69
C. F.	0	16	5,800	2,657	2,668	381
	1	16	7,200	3,715	2,866	250
	4	15	9,650	5,616	3,203	288
	8	14	11,400	7,136	3,466	394
	24	20	6,600	3,168	2,600	413
	53	13	7,400	3,480	2,796	400
T. O.	0	17	9,900	6,276	2,990	134
	1	23	8,160	5,615	1,909	134
	4	21	10,050	7,919	1,729	75
	8	18	20,500	17,220	2,009	109
	24	10	14,950	12,528	1,973	150
J. E.	0	13.2	6,120	3,427	2,069	125
	1	18.0	5,700	3,146	2,143	106
	4	12.0	4,950	3,385	1,228	47
	8	28.0	14,550	12,455	1,484	32
	24	14.4	9,180	6,940	1,671	91

in steroids with a moderate drop in lymphocytes and eosinophils, and definite neutrophilia. These effects persisted, however, and were still present 24 hours after administration of the compound. In another subject (C. F.) no significant change

TABLE V

Administration of 17-hydroxycorticosterone (Compound F) as the free alcohol, 100 mgm.

Subject	Mode of admin.	Time in hours	17-OH steroid levels, γ /100 ml. of plasma	WBC	PMN	Lymph	EOS
					Absolute number per mm. ³		
J. B.	100 mgm. I. M. in 33% ethanol	0	16	4,400	1,892	2,112	113
		1	29	4,900	2,293	2,273	91
		4	13	6,700	3,953	2,386	31
		8	8	7,950	4,865	2,623	43
O. H.	100 mgm. I. M. in 33% ethanol	24	11	5,550	2,620	2,542	119
		0	18.0	7,800	3,947	2,902	300
		1	49.0	7,200	4,737	1,872	228
		4	21.0	16,400	15,055	1,016	12
J. B.	100 mgm. orally	8	6.0	13,670	11,784	1,449	9
		24	2.0	8,280	4,951	2,600	241
		0	3.0	6,400	2,650	3,366	75
		1	30.0	5,550	2,442	2,620	81
		4	34.0	8,700	6,177	2,123	6
O. H.	100 mgm. orally	8	6.6	8,100	5,233	2,268	31
		24	10.6	6,400	3,213	2,777	81
		0	5.0	8,150	4,304	2,950	300
		1	70.0	9,350	4,937	3,310	283
		4	22.5	20,100	17,889	1,688	13
O. H.	100 mgm. orally	8	2.5	13,950	11,272	2,204	44
		24	9.0	7,250	3,814	2,624	256

TABLE VI

Oral administration of 17-hydroxy-11-dehydrocorticosterone (Compound E) as the free alcohol orally (200 mgm.)

Subject	Time in hours	17-OH steroid levels, γ /100 ml. of plasma	WBC	PMN	Lymph	EOS
				Absolute number per mm. ³		
C. C.	0	8.0	7,850	4,698	2,685	294
	1	70.0	9,000	4,688	3,510	313
	4	14.0	6,600	4,963	1,439	38
	8	0.6	10,350	6,541	3,374	69
	24	7.0	10,900	6,300	4,164	450
J. C.	0	13.0	11,475	6,174	4,360	213
	1	58.0	9,550	5,635	3,476	213
	4	41.0	9,500	7,372	1,691	50
	8	7.5	12,300	8,561	3,247	25
	24	2.5	13,650	6,607	5,979	225
C. F.	0	5.4	9,250	4,126	3,811	519
	1	35.0	8,050	3,848	3,188	500
	4	41.8	7,200	4,939	1,814	175
	8	17.2	10,650	7,881	2,279	69
	24	14.5	9,150	5,398	2,965	325

was seen in either cells or steroids. In the other two subjects the changes were not marked, and in one (J. E.) were delayed.

Table V shows the effects of compound F given orally and intramuscularly (in ethanol solution) in the form of the free alcohol in a dose of 100 mgm. It may be seen that a rise in steroids with typical changes in cells occurred in each case by either route of administration with the same time relationships as are noted following oral F acetate ingestion. Oral administration of cortisone resulted in similar changes, as shown in Table VI.

TABLE VII

Administration of 200 mgm. 17-hydroxy-11-dehydrocorticosterone (Compound E) as the free alcohol, I. M.

Subject	Mode of admin.	Time in hours	17-OH steroid levels, γ /100 ml. of plasma	WBC	PMN	Lymph	EOS
					Absolute number per mm. ³		
C. C.	Suspended in saline, I. M.	0	11.2	8,200	4,592	2,903	213
		1	5.6	7,650	4,192	2,693	206
		4	1.4	8,650	5,173	2,612	169
		8	5.6	10,600	6,508	3,456	175
		24	4.2	11,250	6,862	3,623	214
C. F.	Dissolved in 25% ethanol, I. M.	0	11.0	10,650	6,411	3,365	450
		1	38.0	11,700	8,237	2,481	406
		4	26.0	9,550	7,736	1,452	138
		8	21.0	14,800	11,574	2,723	75
		24	2.5	12,200	7,491	3,684	238
J. C.	Dissolved in 33% ethanol, I. M.	0	10.5	9,380	4,821	3,883	235
		1	46.0	9,050	5,321	3,168	238
		4	21.0	11,400	8,824	2,165	62
		8	21.6	16,125	10,933	4,676	59
		24	6.6	14,950	10,226	3,947	244

TABLE VIII

Administration of 17-hydroxy-11-desoxycorticosterone (Compound S) as the free alcohol or acetate

Subject	Dose and form of steroid and route of admin.	Time in hours	17-OH steroid levels, γ /100 ml. of plasma	WBC	PMN	Lymph	EOS
					Absolute number per mm. ³		
O. H.	17-hydroxy-11-desoxy corticosterone acetate (Compound S acetate) 200 mgm. orally	0	18	9,550	4,737	3,839	244
		1	11	7,900	3,824	3,144	256
		4	9	7,900	4,172	2,924	288
		8	5	10,750	5,934	3,655	238
		24	11	6,700	3,510	2,640	306
O. H.	As above. Given I. M. in 10% ethanol	0	6	8,400	4,570	2,688	188
		1	15	7,350	4,292	2,264	238
		4	16	9,000	5,634	2,826	225
		8	10	10,000	5,880	3,220	200
		24	5	7,450	4,232	2,502	188
J. C.	17-hydroxy-11-desoxy-corticosterone (free alcohol), 200 mgm. orally	0	15	9,100	5,041	3,531	144
		1	14	9,100	4,787	3,786	144
		4	14	11,750	6,627	4,230	200
		8	11	13,250	7,253	5,088	400
		24	22	11,200	6,294	4,055	238
J. C.	Free alcohol of Compound S I. M., 200 mgm. in 25% ethanol	0	0.3	10,700	5,756	4,045	256
		1	9.6	10,950	6,745	3,504	200
		4	1.3	12,050	7,206	3,977	181
		8	1.3	15,900	7,905	7,028	325
		24	4.0	15,250	10,858	3,325	175

Intramuscular administration of free cortisone produced no changes when given suspended in saline, but when given in ethanol solution, typical responses occurred, as shown in Table VII.

Compound S, given as the acetate or free alcohol, either intramuscularly or orally, failed to affect significantly the blood steroid levels or the circulating leukocytes, as shown in Table VIII.

Table IX shows the diurnal variations in ster-

oids and cells of two subjects, one of whom was studied on two separate days. Any changes which can be attributed to the administered hormone must fall outside this range.

DISCUSSION

From these data it is apparent that following the oral administration of compound F or cortisone, either as the acetate ester or the free alcohol, there results a prompt rise in plasma 17-hydroxycorticosteroid levels, reaching a peak at approximately one hour and gradually falling thereafter. Although the highest levels appear to occur at one hour, no quantitative significance can be attached to the actual value since it is undoubtedly changing rapidly at this time. The levels at four hours are probably changing less rapidly and may be more indicative of the degree of change in steroid level which has occurred. This is well illustrated by the progressively rising four-hour levels in the individual who received various doses of compound F acetate. By eight hours in every case the steroids had returned to control levels, and in many instances they were below these values, suggesting that adrenal activity may have been suppressed by the previous phase of artifi-

TABLE IX
Diurnal variation

Subject	Time in hours	17-OH steroid levels, γ /100 ml. of plasma	WBC	PMN	Lymph	EOS
				Absolute number per mm. ³		
O. H.	0 (8 a.m.)	10.0	8,250	4,901	2,656	150
	1	12.0	9,700	5,937	2,968	250
	4	11.0	8,500	5,525	2,397	331
	8	3.0	10,700	6,163	3,745	100
D. T.	0 (8 a.m.)	9.1	7,100	4,033	2,215	225
	1	7.5	7,900	5,087	2,244	175
	4	9.2	9,800	5,762	2,940	231
	8	8.1	9,400	5,189	3,272	269
O. H.	0 (8 a.m.)		7,450	4,038	2,563	256
	1		7,350	3,014	3,836	156
	4		9,200	5,484	2,889	206
	8		11,200	6,854	3,517	206

cially increased steroid concentration. In some cases this was still apparent at 24 hours.

In contrast to the change in steroid levels, the changes in circulating leukocytes were rarely seen at one hour, and were usually maximal at four to eight hours after oral administration of the compounds. In many instances, when the maximal leukocyte alteration occurred at eight hours, the four-hour steroid level was relatively higher, suggesting that the maximum rise in steroids was later than one hour after administration of the steroid. Thus the leukocyte changes appear to lag behind the steroid change by about three to six hours. The occurrence of this lag is of considerable interest in relation to the mechanism of the cellular changes, but the reason for the delay is unknown at present.

Decreases in the average number of both eosinophils and lymphocytes were seen in every case when a significant elevation in steroid levels occurred. The alterations in these two cell types were, in general, closely parallel. At times, the numbers of each were higher at 24 hours than at any time previously. This eosinophilia and lymphocytosis may reflect a period of decreased adrenal activity as previously mentioned, or may be the result of increased cell production following their destruction (1). Changes in lymphocytes and eosinophils were well correlated with dosage in the individual who received graded doses of compound F acetate. However, the degree of cellular change from individual to individual could not be predicted from the steroid level. Thus, one individual may exhibit changes in the plasma steroid level of considerable magnitude and show only modest changes in the leukocytes, whereas another who may manifest a minimal elevation in the steroid level may show profound changes in the leukocytes.

Neutrophilia was frequently but not constantly seen in these subjects. It was not well correlated with changes in eosinophils or lymphocytes in time or degree. It seems likely that the neutrophilia was a result of hormone administration, although it does not appear to be a good measure of adrenal cortical activity. In terms of numbers of cells, however, the changes in neutrophils are by far the most prominent hematologic alteration, so that leukocytosis was noted frequently. The mechanism producing neutrophilia following ster-

oid administration is entirely obscure; it should be pointed out that no increase in immature granulocytes occurred during the period of observation.

Although many of the subjects showed a decrease in monocytes at the same time that eosinopenia and lymphopenia were noted, this change in monocytes was difficult to evaluate since similar changes were noted in individuals observed throughout the day who did not receive steroids. No significant alterations in basophils were noted, nor were definite changes in volume of packed red cells or platelets seen in the few individuals in whom these measurements were followed.

Under the conditions of our experiments the intramuscular administration of compound F acetate did not produce significant changes in steroids or cells whereas such changes were seen following the intramuscular administration of the free alcohol. This phenomenon may be due to the fact that the free compound was either dissolved or suspended in ethanol, whereas the acetate was in a saline-suspending medium. The fact that the suspending medium is of importance in absorption of steroids from intramuscular sites is demonstrated by the observation that free cortisone produced good effects when administered in ethanol, but not when administered in saline. It is also possible that the presence of the acetate group in the compound results in delayed absorption and utilization. Further studies are under way to elucidate this problem of absorption and hydrolysis of the ester. It should be emphasized that these studies of the usual steroid acetate suspensions for intramuscular injection were carried out by the use of single large doses and that the effect of repeated administration was not tested. It is quite possible that repeated administration might alter the steroid levels as well as cellular relationships. On the other hand, the relatively slow clinical effect of intramuscular cortisone acetate in contrast to its oral administration is no doubt related to the pharmacological implications of these studies.

Compound S given as the acetate or free alcohol was ineffective in producing changes in either steroid levels or cells, by either route of administration. Since this compound was prepared in a different physical form from the compounds E and F, it is possible that differences in particle size

may play a role in its failure to increase steroid levels.

SUMMARY AND CONCLUSIONS

1. The administration by mouth of cortisone, cortisone acetate, compound F (Kendall) and compound F acetate to normal human subjects regularly resulted in an elevation of blood levels of 17-hydroxycorticosteroids, and in neutrophilia, lymphopenia, and eosinopenia. The administration of cortisone and compound F intramuscularly in alcoholic solution produced similar responses. The administration of compound F acetate intramuscularly did not result in these changes, whereas the administration of cortisone acetate produced them irregularly. No significant changes followed the administration of compound S or compound S acetate either orally or intramuscularly.

2. The maximum elevation of blood 17-hydroxycorticosteroid levels occurred approximately one hour after administration of the compound by either route. The maximum change in blood cells took place four to eight hours after administration.

3. Changes in eosinophils and in lymphocytes following steroid administration appeared to be closely related to each other, whereas changes in neutrophils, although generally greater in magnitude, appeared not to be closely related to other cellular changes either in time or degree.

4. The cellular changes that occurred following administration of these steroids appeared to be

closely related to dosage and plasma 17-hydroxycorticosteroid levels.

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