arthritis. The results reported here are of particular interest in this regard since muscle weakness and atrophy are frequently among the early symptoms in patients with this disease.

Summary. 1. Daily administration of DOCA to intact rats resulted in inhibition of muscle glycogen formation, accompanied by an approximately proportional decrease in potassium concentration of both skeletal muscle and blood serum. 2. By forcing an increase in potassium intake of DOCA treated rats, potassium concentrations of both muscle and blood serum were maintained at essentially normal levels, and glycogen production was not significantly inhibited. 3. These data indicated that the DOCA induced inhibition of muscle glycogen formation was secondary to potassium depletion.

1. Niedermeier, Wm., Carmichael, Emmett B., PROC. SOC. EXP. BIOL. AND MED., 1960, v104, 779.

2. Stadie, W. C., *Bull. N. Y. Acad. Med.*, 1958, v34, 5.

3. Carroll, N. V., Longley, R. W., Roe, J. N., *J. Biol. Chem.*, 1956, v220, 583.

4. Gilbert, P. T., Hames, R. C., Beckman, A. D., *Anal. Chem.*, 1950, v22, 772.

5. Bills, C. E., McDonald, F. G., Niedermeier, Wm., Schwartz, M. C., *ibid.*, 1949, v21, 1076.

6. Buell, M. V., Turner, E., *Am. J. Physiol.*, 1941, v134, 22.

7. Anderson, E., Herring, U. V., PROC. SOC. EXP. BIOL. AND MED., 1940, v43, 363.

8. Harrison, H. E., Harrison, H. C., *ibid.*, 1939, v42, 506.

9. Keller, N., Linden, G., *Arch. Exp. Path. and Pharmakol.* 1954, v221, 219.

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Response of Obese Patients to an 11β-Hydroxylase Inhibitor, Methopyrapone (SU-4885).* (27921)

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We have previously reported that urinary 17-ketosteroid and 17-ketogenic steroid excretion was significantly greater in obese than in normal-weight persons(1,2). One-third of all obese patients of all ages were found to have urinary 17-ketogenic steroid excretion greater than the accepted upper limit of normal of the method used, and 16% had similarly high urinary 17-ketosteroid excretion. This was also independently reported by Eckert, Green and Migeon(3) for urinary 17-hydroxycorticosteroids (Glenn-Nelson method) and by Mlynaryk, Gillies and Pattee(4) for urinary Porter-Silber chromogen excretion in obese patients. Both groups of investigators further found increased cortisol production rates in obese subjects by isotope-dilution technics. Green, Eckert and Migeon (5) also reported that the pituitary-adrenal axis of obese patients responds normally to corticosteroid-suppression and ACTH stimulation tests.

This paper provides further information on pituitary-adrenal function in obesity by reporting the urinary steroid responses of 15 obese patients to an 11β-hydroxylase inhibitor, methopyrapone, better known to clinical investigators as SU-4885. In low concentrations this agent has been found to be a relatively selective inhibitor of 11β-hydroxylation of steroids in the human adrenal cortex (6,7). This leads to a decrease in cortisol secretion, a resultant rise in ACTH secretion and the secretion of large quantities of 11-desoxycorticosteroids such as compound S. Compound S and its metabolites are readily measurable in the urine as either 17-hydroxycorticosteroids or 17-ketogenic steroids. The increase in urinary excretion of 17-hydroxycorticoids or 17-ketogenic steroids after administration of this inhibitor has been employed as an index of the integrity of the hy-

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TABLE I. Effect of Oral Administration of SU-4885 on 24-Hour Urinary 17-Ketosteroid and 17-Ketogenic Steroid Excretion of Obese Subjects.

Sex of subject	17-Ketosteroid excretion				17-Ketogenic steroid excretion			
	Base-line, mg/24 hr	Test, mg/24 hr	Change mg/24 hr	Change %	Base-line, mg/24 hr	Test, mg/24 hr	Change mg/24 hr	Change %
Obese patients—elevated base-line urinary 17-ketogenic steroids								
♀	6.2	11.2	5.0	81	40.0	31.4	−8.6	−22
♀	4.9	5.3	.4	8	24.2	37.8	13.6	56
♀	16.4	21.8	5.4	33	29.6	53.5	23.9	81
♀	28.5	16.3	−12.2	−42	24.2	16.3	−7.9	−33
♀	6.5	14.6	8.1	125	21.2	28.2	7.0	33
♂*	13.9	12.0	− 1.9	−14	34.3	27.0	−7.3	−21
♂*	14.0	13.7	− .3	− 2	45.0	38.3	−6.7	−15
♀	21.5	40.0	18.5	86	36.6	40.5	3.9	11
Means and stand error	14.0 ±2.90	16.9 ±3.69	2.9 ±3.12	34 ±20.4	31.9 ±3.00	34.1 ±3.90	2.2 ±4.25	11 ±14.7
Obese patients—normal base-line urinary 17-ketogenic steroids								
♀	8.6	14.6	6.0	70	12.9	43.5	30.6	237
♀	9.1	9.2	.1	1	12.7	23.6	10.9	86
♀	7.3	12.9	5.6	77	15.1	34.0	18.9	125
♂	2.8	8.6	5.8	207	11.5	56.0	44.5	387
♀	9.6	21.4	11.8	123	16.4	41.0	24.6	150
♀	1.5	12.7	11.2	747	11.6	52.5	40.9	352
♀	3.4	12.3	8.9	262	13.4	42.0	28.6	213
♀	24.0	32.0	8.0	33	17.5	37.7	20.2	115
Means and stand error	8.4 ±2.50	15.5 ±2.73	7.2 ±1.32	190 ±85.7	13.9 ± .78	41.3 ±3.60	27.4 ±3.98	208 ±39.5
Normal weight subjects								
♀	8.0	16.6	8.6	108	21.8	34.0	12.2	56
♂	12.7	31.0	18.3	144	13.6	54.0	40.4	297
♂	3.0	6.8	3.8	127	7.1	40.5	33.4	470

* Same subject—one year interval between two SU-4885 tests.

pothalamic-pituitary ACTH secreting mechanism(8,9).

Materials and methods. Methopyrapone (2-methyl-1, 2-di-3-pyridyl-1-propanone, or SU 4885) was administered to 15 grossly obese untreated subjects. The dose was 750 mg orally every 6 hours for 6 doses. Twenty-four-hour urine collections were obtained prior to SU-4885 administration (base-line specimen) and on the second day of ingestion of this drug (test specimen). Each specimen was analyzed for 17-ketosteroids (17-KS) and 17-ketogenic steroids (17-KGS) by a modification of the Norymberski procedure (10). Our established range of normal for 24-hour total urinary 17-KS is 6 to 15 mg for adult females and 9 to 22 mg for adult males. The established range of normal for 24-hour urinary 17-KGS is 5 to 18 mg for adult females and 8 to 25 mg for adult males. These values refer to basal specimens. The normal urinary steroid response to methopyrapone has been found by others to be in the order of a 2-fold or greater increase in excretion of 17-hydroxycorticoids or 17-ketogenic steroids as compared to the pretreatment levels(8,9,11,12).

Results are shown in Table I. The obese subjects were divided into 2 groups, those with elevated base-line urinary 17-KGS excretion, and those with normal base-line 17-KGS values, because it was apparent early in this study that the 2 groups differed in their response to methopyrapone. Obese patients with normal base-line excretion exhibited a normal brisk response to methopyrapone with a mean increase in urinary 17-KGS excretion of 27.4 ± 3.98 mg per 24 hours and a percentage rise over control value of 208 ± 39.5%. On the other hand, there was a poor response to methopyrapone in the group with pre-treatment elevated 17-KGS excretion; the mean rise in urinary 17-KGS excretion elicited by the inhibitor was only 2.2 ± 4.25 mg per 24 hours, or a percentage increase over control value of 11 ± 14.7%.

TABLE II. Composition of Obese Patient Groups.

Patient group	No. of patients	Sex	Mean age, yr	Mean wt, lb	Mean % overweight
Elevated base-line urinary 17-KGS excretion	6	♀	27 (range 11-50)	214 (range 148-360)	62 (range 40-109)
	1	♂			
Normal base-line urinary 17-KGS excretion	7	♀	28 (range 12-41)	192 (range 154-246)	61 (range 31- 89)
	1	♂			

The differences between the 2 obese groups were statistically significant (p exceeded 0.01). The difference in response of the 2 obese groups to methopyrapone could not be attributed to sex, age or body weight, because they were quite similar in these respects (Table II). With respect to urinary 17-KS, the responses of both obese groups to methopyrapone paralleled those of the 17-ketogenic steroids, but were not quantitatively as striking or statistically significant. Three normal weight subjects were also studied for comparison with the obese patients, and for the purpose of our verification of the normal SU-4885 response reported by others. It is of interest that the base-line urinary 17-KGS excretion was elevated in one subject (a normal 51-year-old woman), normal in another (a normal 20-year-old male), and decreased in the third subject (a 37-year-old male with Klinefelter's syndrome). The SU-4885 response in these 3 subjects was inversely proportional to the base-line 17-KGS level, being greatest in the patient with the lowest basal value, and least in the patient with the highest basal value. These observations are consistent with the findings on obese patients reported here. It would appear that obese subjects with normal base-line urinary 17-KGS excretion respond normally to methopyrapone, whereas obese patients with elevated base-line values exhibit a greatly impaired response to this inhibitor.

Discussion. These data indicate that obese subjects show 2 different types of response to methopyrapone which are directly related to the level of the base-line excretion of urinary 17-ketogenic steroids. The response to the inhibitor was normal when base-line 17-KGS was normal, and was greatly impaired when base-line 17-KGS was elevated. The similar results obtained in our normal-weight control patients would suggest that methopyrapone responses of obese subjects are a function of the level of the base-line excretion of urinary 17-ketogenic steroids. We have previously shown that one-third of all obese patients of all ages have elevated urinary 17-KGS excretions(1, 2). Although one of us (B.S.) has also shown that there was a positive statistical correlation between urinary 17-KGS excretion and body weight in a large group of patients of all weights seen in a 5-year period(13), results in the patients in the present study show that body weight is not the only factor responsible for the increased adrenal cortical activity of obese patients. Although both groups of obese subjects were of comparable age, sex and body weight, there was a clear-cut distinction between the 2 groups with respect to the level of base-line urinary 17-KGS excretion (13.9 and 31.9 mg respectively), which was also reflected in the methopyrapone responses of the 2 groups. The reason for the differences in adrenal cortical activity of obese subjects of equivalent body weights is not clear. Obese patients with normal base-line urinary 17-KGS excretion demonstrate a normal hypothalamic-pituitary ACTH secreting mechanism. Obese subjects with elevated base-line urinary 17-KGS excretion exhibit impaired pituitary-adrenal reserve with respect to intensity of the stimulus (SU-4885) employed. As previously suggested by others(8,9), this does not mean that the pituitary-adrenal axis of such patients may not be capable of responding vigorously to more intense stimulation, such as the stress of surgery. From a clinical diagnostic viewpoint, the impaired SU-4885 response of obese patients with elevated urinary 17-KGS excretion is an important point of difference from patients with Cushing's syndrome with adrenal hyperplasia who also have a high basal urinary excretion of 17-

KGS. The Cushing patient responds to methopyrapone in a qualitatively normal manner, although his base-line steroid excretion is higher than normal(8,9).

Summary. Obese subjects exhibit 2 different responses to an 11β-hydroxylase inhibitor, methopyrapone (SU-4885), depending upon the level of the base-line urinary 17-ketogenic steroid excretion. Subjects with a normal base-line 17-KGS excretion have a normal response to methopyrapone, whereas subjects with base-line elevated urinary 17-KGS give a markedly impaired response to this inhibitor.

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1. Simkin, B., *New Engl. J. Med.,* 1961, v264, 974.
2. Simkin, B., Arce, R., *ibid.,* 1962, v266, 1031.
3. Eckert, J. P., Green, O. C., Migeon, C. J., *Program of Endocrine Soc.,* 1961, p41.
4. Mlynaryk, P., Gillies, R. R., Murphy, B., Pattee, C. J., *J. Clin. Endocrinol. and Metab.,* 1962, v22, 587.
5. Green, O. C., Eckert, J. P., Migeon, C. J., *Program of Endocrine Soc.,* 1961, p62.
6. Jenkins, J. S., Meakin, J. W., Nelson, D. H., Thorn, G. W., *Science,* 1958, v128, 478.
7. Liddle G. W., Island, D., Lance, E. M., Harris, A. P., *J. Clin. Endocrinol. and Metab.,* 1958, v18, 906.
8. Liddle, G. W., Estep, H. L., Kendall, J. W., Jr., Williams, W. C., Jr., Townes, A. W., *ibid.,* 1959, v19, 875.
9. Gold, E. M., Kent, J. R., Forsham, P. H., *Ann. Int. Med.,* 1961, v54, 175.
10. Sobel, C., Golub, O. J., Henry, R. J., Jacobs, S. L., Basu, G. K., *J. Clin. Endocrinol. and Metab.,* 1958, v18, 208.
11. Cleveland, W. W., Nikezic, M., Migeon, C. J., *ibid.,* 1962, v22, 281.
12. Krieger, D. T., *ibid.,* 1962, v22, 490.
13. Simkin, B., *Clin. Res.,* 1962, v10, 90.

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Glycogen and Succinic Dehydrogenase in Wound Healing of the Oral Mucosa of the Rat. (27922)

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Differing amounts of glycogen have been found in the epithelium of healing wounds in the oral mucosa(1,2). The method of healing may be correlated with the amount of glycogen visible at a particular stage of healing(3). Epithelium moves over the connective tissue base in the healing of a superficial injury while in deeper wounds, particularly those which approach bone, a space is created which has to be filled with granulation tissue from the sides, carrying the epithelium with it.

The purpose of the present investigation is to see if the glycogen content of the epithelium in wound healing is related to the activity of the epithelium or the type of wound. To indicate the extent of oxidative activity in the epithelium, the distribution of succinic dehydrogenase during the process of wound healing will also be reported.

Methods. Wounds were made in the midline between the 2 most anterior rugae of the palate of 150 g Long-Evans rats with a trephine, 1.5 mm in diameter. Depth of the wound was regulated by a circular shield. Biopsies of the wound site were taken from different rats on successive days following the injury.

For determining the glycogen content the biopsies were fixed in alcoholic-acetic-formalin and stained by the PAS method, using diastase controls. Succinic dehydrogenase distribution was studied in fresh frozen sections cut at 40-75 μ. Sections were incubated for one hour at 37°C in the substrate of phosphate buffer, sodium succinate and nitro blue tetrazolium. After incubation permanent sec-

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