fat metabolism. Furthermore, the persistence of lipid accumulation in the absence of the adrenals would seem to distinguish this type of fatty liver from those described in previous studies(6,7) which implicated the adrenal cortex in the mobilization of fat to the liver under circumstances of stress. In this connection, it may be of significance that one of the few experimental procedures which result in fatty livers in fasted male mice and is similarly effective even in the absence of the adrenals, is the administration of purified growth hormone(3).

Summary. The development of fatty livers has been noted in 8-week-old fasted CBA male mice bearing a transplantable lymphosarcoma of varying age. Similar mice free of the tumor fail to develop fatty livers following a 48-hour fast under comparable conditions, nor does the growth of the tumor in fed mice result in fatty livers. Adrenalectomy has no inhibitory effect on the development of a fatty liver under these conditions.

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Urinary Excretion of Certain Amino Acids During ACTH and Cortisone Treatment of Rheumatoid Arthritis.* (18172)

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In a previous publication from this laboratory(1) it was shown that the urinary excretion and plasma levels of free histidine were increased in patients with rheumatoid arthritis treated with ACTH (adrenocorticotropic hormone) and Cortisone (17-hydroxy-11-dehydro corticosterone). Urinary excretion and plasma values of 17 free and bound amino acids are being studied in conjunction with a clinical study to be reported elsewhere(2). The present paper summarizes the urinary excretion of free threonine, lysine, tyrosine, and arginine in 41 patients before and after treatment.

Experimental. Thirty-one patients (12 ♂ and 19 ♀) were treated with ACTH and 10 patients (5 ♂ and 5 ♀) with Cortisone. All patients suffered from active rheumatoid arthritis and had been under observation for at least 6 months. They were hospitalized and controlled metabolically during the entire period of investigation. ACTH, given intramuscularly, in variable daily dosage (20 to 160 mg) was continued for a period of 8 to 17 days. Cortisone was given intramuscularly usually in an initial dose of 300 mg followed by 100 mg on successive days for about 10 days. All patients were not represented in determinations of free arginine and tyrosine. Various patients, receiving ACTH, were pretreated and treated simultaneously with one or more of the following in an effort to enhance or prolong the beneficial effect of ACTH: 6 were treated with thyroid and ascorbic acid, 4 with ascorbic acid alone, 6 with ATP (adenosine triphos-

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TABLE I. Average and Maximum 24-hour Excretion of Free Threonine, Lysine, Tyrosine, and Arginine of Patients Treated with ACTH and ACTH Plus Other Medication.

Amino acid	Treatment	No. of patients	Mean of control (mg)	Mean of treatment	
				Avg, mg	Maximum, mg
Threonine	ACTH	14	14 ± 1.95†	41 ± 5.68*	60 ± 10.02*
	ACTH + med.‡	17	19 ± 3.09	46 ± 13.68*	69 ± 21.32*
Lysine	ACTH	14	22 ± 3.32	52 ± 9.25*	78 ± 14.33*
	ACTH + med.	17	21 ± 2.86	43 ± 7.40*	58 ± 9.85*
Tyrosine	ACTH	12	18 ± 2.89	30 ± 3.54*	39 ± 4.39*
	ACTH + med.	7	23 ± 4.43	36 ± 6.75*	50 ± 8.59*
Arginine	ACTH	8	5 ± 0.98	6 ± 1.34	9 ± 1.50
	ACTH + med.	15	9 ± 2.26	9 ± 1.37	12 ± 1.66

* Highly significant.

† $S_{\bar{x}} = \sqrt{\frac{SX^2-(SX)^{2/N}}{N(N-1)}}$

‡ Supplementary medication.

TABLE II. Average and Maximum 24-hour Excretion of Free Threonine, Lysine, Tyrosine, and Arginine of Patients Treated with Cortisone.

Amino acid	No. of patients	Mean of control, mg	Mean of treatment	
			Avg, mg	Maximum, mg
Threonine	10	17 ± 1.63†	23 ± 2.13	29 ± 2.64*
Lysine	10	18 ± 4.54	32 ± 8.94	41 ± 10.78
Tyrosine	5	13 ± 2.45	21 ± 2.31	26 ± 2.36*
Arginine	4	6 ± 2.14	7 ± 2.63	9 ± 3.32

* Highly significant.

† $S_{\bar{x}} = \sqrt{\frac{SX^2-(SX)^{2/N}}{N(N-1)}}$

phate), 1 with X-ray, 1 with thyroid alone, 1 with aspirin, 1 with testosterone, and 3 were given 50 g of Somagen, protein hydrolysate. Fourteen patients were not given supplementary medication.

Collection of urine specimens. On alternate days during the experimental period 24-hour urine specimens were collected under toluene and diluted to appropriate volume. Aliquots were stored at −15°C. In all cases at least 2 specimens were obtained before ACTH or Cortisone medication was begun. A modification of microbiological technic of Henderson and Snell(3) was used for the assay of free amino acids. The test organism *Leuconostoc mesenteroides P-60* was used for estimating lysine and tryosine, and *Streptococcus faecalis-R* for arginine and threonine. All specimens from each patient were assayed in one series to eliminate errors due to variation among different assays. An *in vitro* experiment was set up to determine whether medications administered might stimulate or inhibit the growth of the organisms. To 2000 ml of urine the following substances were added in the indicated amounts: ACTH, 1 to 160 mg; thyroid, 1 to 2 g; adrenalin, 1000 to 2000 units; testosterone propionate, 50 to 100 mg; ATP, 10 to 100 mg; ascorbic acid, 500 to 1500 mg. Microbiological assays were made on these specimens and no effect was noted.

Results. Clinical. All patients experienced both subjective and objective improvement within 24 to 48 hours following the initial injection of either ACTH or Cortisone and continued to improve during the course of treatment. The total degree of improvement varied among the patients. No toxic effects were noted except in the patient who received

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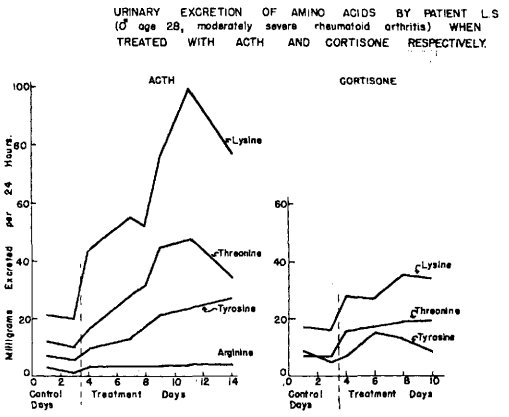

FIG. 1

160 mg ACTH daily. Each hormone produced the same type of response.

Chemical. Excretion values during the control periods were compared with average and maximum values on treatment. Data were analyzed statistically by Snedecor's analysis of variance(4). Patients receiving any medication in addition to ACTH were grouped together because so few patients were given each medication. This group was compared to that receiving ACTH only. No significant difference could be found between these two groups. Table I shows a highly significant increase in urinary excretion of free threonine, lysine, and tyrosine when patients were treated with ACTH, as calculated on the average and maximum 24-hour excretion. In Table II it is evident that the average 24-hour excretion of threonine, lysine, and tyrosine were not significantly increased while the maximum values of threonine and tyrosine are highly significant in those patients treated with Cortisone. Maximum excretion of lysine was not significant. Arginine excretion was not affected significantly by either ACTH or Cortisone medication. No sex differences were observed. Supplementary medication did not significantly alter the patients' response to ACTH, either chemically or clinically.

The curves presented in Fig. 1 are typical of the responses to ACTH and Cortisone. These represent the daily excretion values of one man, L. S., 28 years of age, suffering from moderately severe rheumatoid arthritis, who received Cortisone in July and ACTH the following January. Usually the excretion curves, representing 8 or more days on treatment, show a decline from the maximum before the termination of treatment although the patient is still in remission.

Summary and conclusions. Rheumatoid arthritis patients treated with ACTH showed a highly significant increase in urinary free threonine, lysine, and tyrosine as determined as the average and maximum 24-hour excretion. Cortisone-treated patients excreted a highly significant amount of threonine and tyrosine at the maximum, but lysine was not increased significantly. Arginine excretion was not significantly affected by either ACTH or Cortisone. Supplementary medication did not affect significantly the responses of the patients to ACTH or Cortisone, chemically or clinically. Clinical improvement in all patients was both subjective and objective. The cause of the increase in urinary excretion of the amino acids herein reported is not known and may or may not be associated directly with the metabolic changes brought about by the remission of rheumatoid arthritis.

4. Snedecor, George W., *Statistical Methods,* Iowa State College Press, Ames, Iowa, 1948, 282.

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