TABLE II. Urinary and Fecal Excretion of Biotin After Administration of Biotin or Biotinol to Rats.

Dose (as d-biotin)	No. of rats		Extra excretion in 24 hr: d-Biotin		d-Biotinol	
				% of dose		% of dose
		Oral				
μg			μg		μg	
10	4	Urine	2.9	29	3.7	37
25	8	"	6.3	25	6.8	27
50	16–18	"	19	38	17	34
mg			mg			
3.4	2	"	1.6	47	3	88
		Feces	1.4	41	.14	4
10	6	Urine	2.2	22	7.2	72
		Feces	5	50	1.1	11
		Intramuscular				
μg			μg			
50	4	Urine	22	44	11.4	23
158	4	"	83	53	62	39
225	12–14	"	112	50	113	50
mg			mg			
5	4	"	3.5	70	2.8	56

as d-biotin in curing egg white-induced biotin deficiency in the rat. Comparison of urinary excretions of biotin after oral or intramuscular administration of biotin and biotinol shows the latter to be converted to biotin efficiently by both rat and human.

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Absence of Analgesia During Induced Hyperadrenalism.* (19080)

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Selye first ascribed anesthetic properties to hormonally active steroids(1-3) and others (4,5) have suggested that cortisone and ACTH produce analgesia if not anesthesia. Thus, we examined the threshold for pain in patients with rheumatoid arthritis before and during therapy with cortisone and ACTH.

There are probably two major types of superficial or cutaneous pain(6), both of which we have attempted to evaluate. Two categories of visceral pain have also been described, the so-called "true visceral pain," a diffuse poorly localized sensation, and

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"referred pain" perceived in an area away from the site of the stimulus(7). In our experiments, we have studied only "true visceral pain."

Method. The threshold to superficial and visceral pain was determined in a group of patients with rheumatoid arthritis during a control period. The same stimuli were repeated after the patients had been treated with 700-900 mg of cortisone in a 6-day period or 240 mg ACTH in a 4-day period, until a remission of symptoms or the usual clinical and laboratory manifestations of hyperadrenalism appeared. "Superficial pain" was elicited by injections of 0.1 cc saline and distilled water intradermally, by the application of radiant heat, and by electrical stimulation of the dental pulp and peridental membrane. Histamine injections, as suggested by Rosenthal(8) proved to be unreliable. Saline at a neutral pH produced a barely noticeable sensation insufficient for our purposes but distilled water was more painful and the results could be quantitated when compared with pain previously experienced; the slightest discomfort being 1+, the maximal pain 10+. 0.1 cc of distilled water intradermally generally provided similar "estimates" of the intensity of pain on repeated determinations. The stimulus threshold of the dental pulp and the peridental membrane was measured electrically by the method of Ziskin and Zegarelli(9). Visceral pain was elicited by stretching the second or third portion of the duodenum by air injected into a rubber balloon fixed to the distal end of a Miller-Abbott tube, as suggested by Polland and Bloomfield(10). The threshold for "true visceral pain" was reached when the patient first stated that a new sensation was felt in the abdomen. The volume of air in cc in the balloon and the balloon pressure in mm of Hg were then recorded. At the threshold level, the patients described the location, the quality and the intensity of the sensation experienced. The pain threshold in a series of 5 patients was established before and during hormonal therapy, using the Hardy, Wolff, Goodell technic(6,11,12). The method of D'Amour and Smith(13) was used to evaluate pain sensation in rats. A light intensity which produced a reaction in about 5 seconds was most convenient and the method was simple with excellent reproducibility of results. Rats weighing from 120 to 182 g received subcutaneous injections of 10 mg of cortisone acetate daily for 4 days; readings were taken before hormone administration and on the fourth day of injection.

Results. In all instances, the pain threshold for cutaneous dental or visceral (Table I) sensation was not significantly influenced by either cortisone or ACTH at the usual therapeutic dose levels. Similarly, cortisone failed to produce a measurable degree of analgesia in markedly hyperadrenal rats (Table I).

The average mean threshold obtained by electrical stimulation applied to 5 teeth in each patient showed no significant change in sensitivity during hormonal therapy.

There was no increase in the visceral pain threshold to balloon distention during hormonal therapy in the 6 patients tested (Table I), while after a 30 mg injection of morphine a 3-fold increase in volume of air and a 2-fold increase in pressure were required to reach the visceral pain threshold.

Discussion. In our experience, the administration of cortisone or ACTH to humans in doses adequate to control the symptoms of rheumatoid arthritis produced no measurable anesthetic or analgesic effect.

The alleviation of pain observed in clinical syndromes treated with either cortisone or

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TABLE I. Cortisone and ACTH on Various Types of Induced Pain.

Type of pain stimulus	Subject	Hormone	Before hormone (range)	During hormone (range of change)
I Cutaneous pain*	5 patients	4 cortisone, 1 ACTH	1+ to 3+	0 to −1+ **
" " †	5 "	4 " 1 "	7+ to 8+	−1+ to +1+ **
II Pain threshold‡	5 "	Cortisone	157 to 232 mc	−10 to +8 mc ††
III Visceral pain	6 "	4 cortisone, 2 ACTH	40 to 75 §	−20 to 0 § ††
	1 "	Morphine sulfate	50 §	+100 § ††
	4 "	3 cortisone, 1 ACTH	1.7 to 3 ‖	−.7 to +.4 ‖ ††
	1 "	Morphine sulfate	1.7 ‖	+1 ‖ ††
IV Pain from radiant heat	5 rats	Cortisone	6.2 to 8.6¶	0 to +1.4 ¶ ††

Stand. dev. were calculated for all hormone experiments and in no instance was the change found statistically significant.

* Intradermal NaCl. † Intradermal distilled water. ‡ As measured by Wolff-Hardy-Goodell apparatus using dorsum of hand. § Volume of air in balloon in cc required to produce a sensation. ‖ Pressure of air in balloon in cm Hg required to produce a sensation. ¶ Seconds. ** Decrease denotes analgesic effect. †† Increase denotes analgesic effect.

ACTH is probably due to an hormonally-induced alteration in the response of the host to the inflammatory reaction(14,15) or to a parallel decrease in the inflammatory reaction not necessarily affecting the etiologic agent(16).

Summary. A systematic evaluation of cutaneous, dental and visceral pain before and during the administration of either cortisone or ACTH demonstrated that these agents had no analgesic effect at therapeutic dose levels. The marked alteration in the host reaction to inflammation during treatment with cortisone or ACTH probably is the principal factor responsible for the alleviation of pain.

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Decreased Resistance of Pyridoxine-Deficient Rats to Cold Exposure.* (19081)

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It is well established that the pituitary-adrenal system is activated under conditions of stress(1,2), and that requirements for ACTH(3) and adrenal cortical hormone(s) (4,5) are increased during adjustment to cold. Hypophysectomy (with the consequent reduction in ACTH secretion) and adrenalectomy (with the resultant decrease in adrenal cortical hormones) both impair adjustments to cold(4,6). A deficiency of

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