York State, and the eastern United States in general, emerging from the aforementioned researches, has very recently been given a sounder chronological perspective through the radioactive carbon studies of Libby and Arnold, of the University of Chicago. The dates they have derived from charcoal samples, taken from hearths on archaic period sites in New York during the course of our excavations, indicate an antiquity for the earliest occupation of more than 5,000 years of elapsed time. Other equally startling dates have been obtained.

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Technical Papers

Effectiveness of Cortisone Administered Orally[1]

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Since the report by Hench and his associates (*1*) that cortisone (Kendall's Compound E) has great antirheumatic properties, much research has been conducted to learn (1) how this hormone effects its results, and (2) how cortisone might be used with the greatest practical value as a therapeutic agent. In the latter category there have been studies to determine whether cortisone is effective when administered in ways other than intramuscularly, as it was used originally. Scarcity of the hormone has limited research but recently, through the kindness of its medical director, James Carlisle, Merck & Co., Inc., has supplied us with a small quantity of tablets (each 100 mg) of cortisone for clinical trial.

This preparation of cortisone has been tested in 4 patients with rheumatoid arthritis. The dose commonly employed for intramuscular injection was used orally, namely, 300 mg the first day, 200 mg the second, and 100 mg daily thereafter. In 2 patients the dose was increased to 200 mg daily, following a few days of 100-mg dosage.

In all patients cortisone taken in tablet form effected impovement in the rheumatic disease. In 2 patients cortisone tablets were given for only 10 days; the patients improved significantly from the 2nd day of treatment and relapsed promptly after cessation of the drug. The 3rd and 4th patients received tablets of cortisone for longer periods, 20 and 19 days, respectively. In each of these patients there was excellent clinical effect; the arthritic condition improved promptly and progressively, erythrocyte sedimentation rate was reduced to nearly normal, and general systemic improvement was gratifying. The 3rd patient previously had received cortisone intramuscularly during 2 periods of 23 and 20 days, and ACTH for 1 period of 14 days. In all respects the clinical effects of orally administered cortisone were comparable to those of this hormone given parenterally, and to ACTH. The 4th patient had prompt improvement during the first 3 days that cortisone was administered orally, then worsened somewhat. Consequently, the dose was increased to 100 mg twice daily and was continued at this level for the last 11 days it was administered. With the larger dose, improvement again progressed until there was nearly complete clinical arrestment of the arthritis. Subsequently, when this patient received cortisone intramuscularly in dosage similar to that employed orally, clinical response was comparable to that effected by cortisone taken orally. Both the 3rd and 4th patients volunteered preference for the tablets, because they considered the effects to be smoother than when the hormone was injected.

These observations clearly indicate that cortisone is effective when administered orally. This knowledge is indeed gratifying, especially in anticipation of practical therapy, for in patients with a chronic illness, such as rheumatoid arthritis, prolonged use of any drug should be facilitated by an effective oral preparation. At the same time *abuse* of tablets of such a potent hormone must be avoided.

Further studies of oral use of cortisone will be conducted as soon as supplies will allow.

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Reference

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Cytological Changes in Human Hypophyses after Cortisone and ACTH Treatment

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Following injections of cortisone in patients with various diseases, microscopical changes have been noted in the anterior hypophyses at post-mortem examination. The relevant data concerning age, principal disease, total

TABLE 1

SUMMARY OF 8 AUTOPSIED CASES TREATED WITH CORTISONE AND ACTH

Autopsy No.	Age, years	Principal disease	Total dosage		Total dosage	
			Cortisone, mg	No. days treated	ACTH, mg	No. days treated
Case 1, OE- 48	42	Periarteritis nodosa	None	..	150	3
" 2, OE-106*	3	Leukemia, acute	2,950	28	None	..
" 3, OE-110*	2	" "	1,050	5½	"	..
" 4, OE-132*	3	Reticular cell sarcoma	1,150	7	"	..
" 5, OE-152*	4	Leukemia, acute	2,550	15	"	..
" 6, OE-159	11	" "	7,350	35	175	3
" 7, OE-182	4	" "	1,450	7	100	2
" 8, 5OR-319*	28	Lupus erythematosus	1,500	8	None	..

* Indicates presence of basophilic changes in anterior hypophysis.

dosage, and duration of treatment are summarized in Table 1.

The hypophyses were fixed in 10% formalin for 1 hr, dissected free of dura and weighed on a torsion balance. The weights are not analyzed here because of frequent leukemic infiltrations in that gland. Slices were then cut, and the tissues fixed in Zenker-formalin solution for 24 hr. Following washing and treatment in Müller's fluid, the tissues were dehydrated and embedded in paraffin. Sections were cut at 5 μ. They were stained with analine acid fuchsin and light green and in some instances with azocarmine. Details of the staining procedure used by us are being published elsewhere (*2*).

The changes involved the basophiles, in which replacement of the basophilic granules by lumpy masses of hyaline basophilic material was noted. The alteration was noted usually in parts of the cytoplasm only, although scattered cells showed nearly complete ring formation at the periphery of the cytoplasm. The changes were most marked and advanced in case No. 8. They were seen as early as 5½ days after onset of treatment. No definite changes of this type were seen in two cases, Nos. 6 and 7. In these two cases, courses of cortisone treatment were followed by injections of ACTH. The changes were inconclusive in case No. 1, in which the interval between death and autopsy was longer than 6 hours.

The morphological alterations were comparable to those described by Crooke (*1*) in the hypophyseal basophiles in Cushing's disease and related conditions. In addition to the hyalinization of the cytoplasmic granules, the nuclei were more centrally placed in our cases and were surrounded frequently by a paler zone of cytoplasm in which distinct basophilic granules were noted.

A detailed discussion of the possible significance of these changes will be presented in an article to appear in the near future.

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On the Pigments of *Allescheria boydii*

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Allescheria boydii, a pathogenic fungus, produces a pigmented culture when grown in a basal medium of known chemical composition containing biotin. As first shown by Cury (*1*), this mold is unable to grow when biotin is omitted from the medium, the growth being proportional to the amount of biotin added (*1, 2*).

The pigment appears after 7–10 days of incubation at room temperature when the amount of biotin is higher than 0.0005 μg/10 ml of medium. The appearance of the mycelium varies from reddish to violet or purple. The culture filtrates were golden yellow, varying somewhat in intensity. This yellow pigment proved to be different from the pigment from the mycelium.

The production of both pigments is conditioned by the pH of the medium. Pigmented cultures developed only in the range of pH between 4.0 and 6.8. Above pH 7.0 the mycelium was gray or white, and no pigment could be detected. It has been observed that under suitable conditions the pigments developed in the dark, as well as in the diffuse light of the laboratory.

The powdered mycelium was extracted with ethanol containing 2% hydrochloric acid, and a deep-red extract was obtained. This solution, when concentrated in vacuum, filtered, and left in the icebox overnight, yielded crystalline orange needles, with an mp of 131° C (Fig. 1). Better crystallization was obtained by the addition of a little dioxane.

The rough material was also purified by chromatographic adsorption with Al_2O_3. The pigment, dissolved in ethanol and strongly acidified, is easily extracted with chloroform; the red chloroform-extract showed an absorption maximum at 520 mμ (Fig. 2). The yellow pigment from the culture filtrates presented an absorption in the ultraviolet at 360 mμ. These determinations were performed in a Beckman quartz spectrophotometer.

The pigment from the mycelium is red at pH 1.0–2.0, orange at pH 2.2, changing to yellow at pH 7.8 and violet at pH 10.0. This pigment is insoluble in petroleum ether and in water, and soluble in ethanol and methanol