of the controls; and a fourth tumor came in 9.0% of the proline mice, and in but 2.6% of the controls.

Since we are here dealing with *more* instead of *larger* tumors it is well to distinguish between tumor production and tumor growth. Tumor production depends on the change from body cell to cancer cell. Tumor growth depends to a large degree on cell proliferation. It is conceivable that more tumors are produced, not because more cells are stimulated to divide; but because more body cells or nests of body cells are stimulated to undergo specialization into cancer cells.

If the argument is logically sound, it follows that these mouse tumor results are consistent with those obtained with obelia, since both may be interpreted as indicating a stimulation of cellular specialization or differentiation by l-proline.[2]

No less noteworthy is the fact that l-proline—a naturally occurring tissue component of general distribution—is perhaps a significant factor in tumor production.

Conclusion. Tumor incidence in mice is enhanced by l-proline, probably through its favoring action in some process concerned in cellular differentiation.

11766

Influence of Amorphous Fraction from Adrenal Cortex on Efficiency of Muscle.

DWIGHT J. INGLE AND EDWARD C. KENDALL.

From the Division of Biochemistry, The Mayo Foundation, Rochester, Minnesota.

An extract of the adrenal cortex which is free from epinephrine and contains the physiologically active steroid derivatives characteristic of the adrenal cortex can be separated into a surprisingly large number of crystalline compounds and an amorphous fraction. The crystalline compounds A, B, E, and F, which have an atom of oxygen attached to C_{11}, have a marked effect on the efficiency of muscle[1] and on carbohydrate metabolism,[2, 3] but relatively large

2 Hammett, F. S., *The Nature of Growth*, Science Press and Printing Company, Lancaster, Pa., 1936.

1 Ingle, D. J., *Endocrinology*, 1940, **26**, 472.

2 Long, C. N. H., Katzin, B., and Fry, Edith G., *Endocrinology*, 1940, **26**, 309.

3 Ingle, D. J., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 176.

amounts are required to maintain renal function. When large amounts are administered to normal male rats these compounds produce atrophy of the adrenal and thymus glands.[4, 5] Desoxycorticosterone, which is identical with compound B except that there is no atom of oxygen on C_{11}, has but little effect on the efficiency of muscle and on carbohydrate metabolism, but it is from 6 to 10 times more efficient than compound B when renal function is used as a criterion. The amorphous fraction has the greatest effect on renal function and it protects the adrenalectomized animal against certain forms of stress such as a low environmental temperature, but even 40 times the amount of this fraction which is required to produce these effects does not cause atrophy of the thymus or adrenal glands. It has also been shown that the amorphous fraction has very little effect on carbohydrate metabolism.[6] It became desirable, therefore, to determine whether this fraction could increase the efficiency of muscle to a degree comparable to compounds A, B, E, and F.

In the present report it will be shown that very small amounts of the amorphous fraction will protect the adrenalectomized rat against a loss in body weight, but that animals so treated are incapable of sustained work. The compound 17-hydroxy-11-dehydrocorticosterone was more active in its effect on the efficiency of muscle than was the amorphous fraction.

Methods. Male rats of the Sprague-Dawley strain which weighed 180 ± 2.0 g were used. The diet was Purina Dog Chow. Bilateral adrenalectomy was performed in one stage under ether anesthesia. "Soap and water" cleanliness was maintained and no postoperative infections or other complications developed. The animals were either subjected to the work test immediately following the operation or they were maintained for one week before they were tested. The cortical hormones were dissolved in sesame oil and were administered by subcutaneous injection twice daily. The amount of sesame oil was kept constant at 1 cc per day for each rat. For the work test the animals were anesthetized with phenobarbital sodium. The left gastrocnemius muscle of each animal was weighted with 100 g and stimulated to contract 3 times per second. Each animal received 5 cc of water at the beginning of stimulation and 6 hours later. In Experiment 1, stimulation was continued until the rat ceased to respond or for a maximum of 24 hours. In Experiment 2, stimulation was continued until the muscle ceased to respond but

[4] Wells, B. B., and Kendall, E. C., *Proc. Staff Meet., Mayo Clin.*, 1940, **15**, 133.
[5] Ingle, D. J., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 174.
[6] Wells, B. B., *Proc. Staff Meet., Mayo Clin.*, 1940, **15**, 294.

in every instance this was less than 24 hours. The details of the method have been described.[7, 8]

Experiments and Results. In Experiment 1, 42 adrenalectomized rats were used. Ten untreated rats were tested immediately following adrenalectomy. Eight rats were treated with the amorphous fraction, 12 rats with 17-hydroxy-11-dehydrocorticosterone and 12 rats with 17-hydroxy-11-dehydrocorticosterone acetate. The data on dosage and work performance are summarized in Table I. Five rats into which incisions had been made but without removal of the adrenal glands were subjected to the work test for 24 hours. The average amount of work performed by the latter rats was 21,651 recorder revolutions with a range of 17,199 to 25,026. The amorphous fraction increased the efficiency of the muscle above the level of the untreated rats less than did either 17-hydroxy-11-dehydrocorticosterone or its acetate. The acetate appeared to be less effective in this test than the nonesterified compound. A similar

TABLE I.
Work Performance of Rats Expressed as Recorder Revolutions Immediately Following Adrenalectomy.

	Work[3] performance under administration of			
Dose, mg*	Amorphous fraction	Compound E[1]	Compound E Acetate[1]	Work performance of untreated rats
0.125	5633[2]	108022	49152	64362
	5047	3218	8583	6718
		11701	2377	2085
		11625	7924	2164
				4316
0.25	6377	12339	6230	3963
	8199	16124	10410	7702
		12483	12229	3003
		10374	12876	5153
				3618
0.50	9482	15133	11577	
	4036	13165	12590	
		14063	15731	
		13158	14177	
1.00	12953			
	15014			

*These amounts of the test substances were administered at the beginning of stimulation and again 6 hours later.

[1]17-hydroxy-11-dehydrocorticosterone.

[2]Each recorder revolution is equivalent to approximately 400 gram-centimeters of work.

[3]All of the values for work below 9000 represent animals in which muscular responsiveness was lost before the completion of the 24-hour period. All of the values for work above 12000 represent animals which were continuing to work at the end of the 24-hour period.

[7] Heron, W. T., Hales, W. M., and Ingle, D. J., *Am. J. Physiol.*, 1934, **110**, 357.

[8] Ingle, D. J., *Am. J. Physiol.*, 1936, **16**, 622.

relationship in the order of the activity of 11-desoxycorticosterone and its acetate in the 24-hour work test has been reported.[1]

In Experiment 2, 31 adrenalectomized rats were used; seven were untreated and 24 received varying amounts of the amorphous fraction for one week and were then subjected to the work test. The data on body weights and on work are summarized in Table II. Definite protection against a loss in body weight was afforded by as little as 5 μg per day of the amorphous fraction, but although the work performance was increased over that of untreated animals, it remained very poor as compared to the response of animals into which incisions had been made but without removal of the adrenal glands.

TABLE II.
Body Weight and Work Performance of Adrenalectomized Rats After Treatment with the Amorphous Fraction for One Week.

Dose, mg*	Weight, g[1]	Total work, recorder revolutions[2]
0	143	94
	145	185
	150	389
	142	151
	154	246
	146	579
	160	1034
.001	176	1446
	166	780
	151	435
	156	590
.002	175	2060
	160	824
	188	3661
	160	3087
.005	189	1243
	187	1657
	187	2592
	203	4884
.01	189	3040
	201	4907
	205	3269
	186	1446
.05	197	1513
	194	2566
	182	2948
	190	1993
.10	183	4748
	203	4335
	194	5930
	190	5139

*Total daily dose. Divided into 2 daily injections.

[1]The initial weight of each rat was 180 ± 2 g

[2]Each recorder-revolution is equivalent to approximately 400 gram-centimeters of work.

Rats so treated were found, in a recent study, to have values for total work of 87,645 to 131,261, with an average of 112,164 recorder revolutions.[9]

Comment. The amorphous fraction is highly effective in protecting the adrenalectomized rat against a loss of weight. It is the most effective fraction when tested with renal function as a criterion in the adrenalectomized dog. In these respects the compound 17-hydroxy-11-dehydrocorticosterone is ineffective. It does not protect the adrenalectomized rat against a loss in weight[9, 10] although in sufficient dose it will prolong its survival. Large amounts are required to prolong the life of the adrenalectomized dog.[10, 11] With respect to muscular work, however, the relationship is reversed. The compound 17-hydroxy-11-dehydrocorticosterone has a marked effect on the ability of the adrenalectomized rat to work immediately after operation and during its period of survival.[1, 9] The amorphous fraction given to the adrenalectomized rat either immediately after operation or during the period of survival appeared to be less effective when the maintenance of the efficiency of muscle was used as a criterion. The results of this and other studies[1–3, 6, 9] indicate that the compounds which have the greatest effect on carbohydrate metabolism also have the greatest effect on the efficiency of muscular activity and that the compounds that have the greatest effect on renal function have a relatively slight effect on carbohydrate metabolism and on the efficiency of muscle.

11767

Ineffectiveness of Histaminase in Anaphylactic Shock in Guinea Pigs.*

ALFRED F. KNOLL. (Introduced by R. R. Mellon.)

*From the Western Pennsylvania Hospital Institute of Pathology, Pittsburgh, Pa.**

Best and McHenry's[1,2] discovery of a histamine-inactivating

9 Ingle, D. J., *Endocrinology*, 1940, **27**, 297.

10 Wells, B. B., and Kendall, E. C., *Proc. Staff Meet., Mayo Clin.*, 1940, **15**, 324.

11 Ingle, D. J., and Mason, H. L., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 154.

* The author gratefully acknowledges the donation of histaminase by the Winthrop Chemical Company, New York, N. Y., and by Sharp and Dohme, Philadelphia, Pa.

1 Best, C. H., *J. Physiol.*, 1929, **67**, 256.

2 Best, C. H., and McHenry, C. W., *J. Physiol.*, 1930, **70**, 349.