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Dietary Impairment of Estrogen Response in the Immature Monkey.

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We have previously reported that the genital tract of immature chicks maintained on a diet deficient in folic acid shows only a slight growth response to estrogenic hormone.[1]

The laboratory monkey (*Maccacus rhesus*) is known to require exogenous folic acid, and the characteristic features of the deficiency syndrome have been described.[2,3]

We wish to report that sexually immature monkeys which are maintained on a synthetic diet known to be deficient in folic acid fail to show the characteristic changes observed by Allen[4] and others in estrogen-treated monkeys fed a natural diet.

Ten sexually immature female monkeys weighing between 2500 and 2900 g were individually caged and fed *ad libitum* a purified diet of the following percentile composition:[5] C. P. dextrose, 73; vitamin-free casein (Smaco), 18; salt mixture, 4; corn oil, 3; cod liver oil, 2.[5] In addition, the following supplement suspended in 20 cc of water was offered each monkey daily: thiamine, 2 mg; nicotinic acid, 10 mg; riboflavin, 2 mg; pyridoxine, 2 mg; calcium pantothenate, 6 mg; choline, 100 mg; para-aminobenzoic acid, 200 mg; *i*-inositol, 200 mg; ascorbic acid, 50 mg; biotin, 50 μg; dextrose, 2 g. When a monkey failed to consume the supplement voluntarily it was administered by stomach tube.

To the diet of 2 of the monkeys 5% by weight of whole dried liver substance was added for control.

The monkeys were observed for periods ranging from 43 to 66 days. As each animal on the experimental diet developed signs of deficiency characterized by apathy, muscular weakness, diarrhea, anorexia, weight loss and leukopenia, daily subcutaneous injections of 66 μg of estradiol benzoate in 0.2 cc corn oil were administered for periods ranging from 5 to 10 days. Similar treatment was given the liver-supplemented animals after comparable periods of observation. Daily examination was made of the vaginal smear, the external genitalia, and the sexual skin.

The data are summarized in Table I. It will be seen that of 8 monkeys maintained on the deficient diet 6 failed to show any change in the external genitalia or sexual skin following estrogen treatment for 8 to 10 days. In the 2 liver-supplemented animals the characteristic external changes were readily observable by the end of the third day and were very marked by the end of the fifth day (Fig. 1 and 2). The vaginal smears in the non-responsive experimental animals showed little change following estrogen administration whereas the smears from the liver-supplemented animals showed the characteristic cornified cells.

These observations do not establish the specificity of the dietary deficiency produced

TABLE I.
Perineal Estrogen Response of "M" Deficient Monkeys.

Monkey	Days on diet	Days injected	Response
694	43	9	negative
675	53	8	"
19	60	10	"
18	60	10	"
B39	48	8	"
B18	48	8	"
B9	47	5	positive
46	48	5	"

Each monkey given 66 μg (400 R.U.) of estradiol benzoate in 0.2 cc corn oil subcutaneously daily.

1 Hertz, R., *Endocrinology*, 1945, **37**, 1.

2 Day, P. L., Langston, W. C., and Darby, W. J., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 860.

3 Day, P. L., Nims, V., and Potter, J. R., *J. B. C.*, 1945, **161**, 45.

4 Allen, E., Hisaw, F. L., and Gardner, W. V., *Sex and Internal Secretions*, 2nd Edition, 1939, Chapter VIII.

5 Weisman, H. A., Rasmussen, A. F., Elvehjem, C. A., and Clark, P. F., *J. Nutrition*, 1945, **26**, 205.

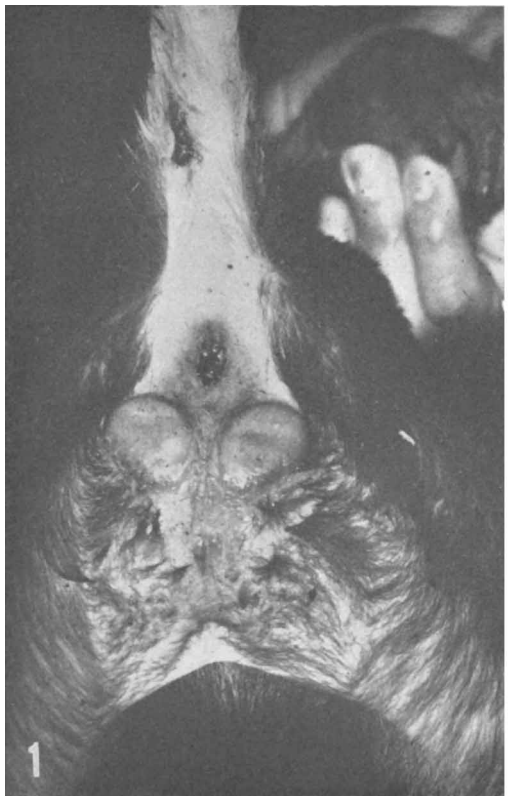

FIG. 1.
Perineum of folic acid-deficient monkey after 10 days estrogen treatment.
FIG. 2.
Perineum of control monkey after 5 days estrogen treatment.

since we have not attempted to restore the estrogen responsiveness in the folic acid deficient monkey following the administration of crystalline folic acid. However, we have observed such a restoration of estrogen response in the folic acid deficient chick following the administration of synthetic folic acid. Moreover, Day *et al.*[2] have shown that monkeys on diets comparable to that employed here show a good therapeutic response to folic acid.

Monkeys are known to show wide variability in the length of time required for the development of folic acid deficiency.[2] It is possible that the 2 animals on the deficient diet which showed a good response to estrogen were incompletely depleted of folic acid at the time they were tested, although they were not grossly distinguishable from the others.

The mechanism and the biological significance of the dependence of estrogen utilization on dietary folic acid remain obscure. The existence of this relationship in two such widely diverse forms as the chick and the monkey suggests that the phenomenon may be of physiological significance. Perhaps the well-known sex difference in erythropoiesis may depend in some way upon this interrelationship between folic acid and the estrogens. In this connection, Taber *et al.*[6] have shown that the characteristic sex difference in red count in the chick may be reversed by administration of either male or female sex hormone. Analogous findings have been presented by Vollmer *et al.*[7] for the rat.

[6] Taber, E., Davis, D., and Domm, L., *Am. J. Phys.*, 1943, **138**, 479.

[7] Vollmer, E. P., Gordon, A. S., Levenstein, I., and Charipper, A. A., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 409.

Summary. Of 8 sexually immature monkeys maintained on a folic acid-deficient, synthetic diet until evidence of dietary deficiency appeared, 6 failed to show the characteristic normal response to estrogen administration. Two control monkeys fed the same diet plus liver and 2 of the apparently deficient animals showed typical estrogen response to similar hormone treatment.

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Renal Resistance in "Essential" Hypertension. Relation to the Effect of Sympathectomy on Blood Pressure.*

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Blood pressure and renal dynamics were studied preoperatively in 13 hypertensive patients subjected to extensive sympathectomy in 1940-42.[1,2] These observations were repeated on 12 of these cases at intervals extending up to 8 to 40 months after operation. Current analysis of these data suggests that the preoperative renal resistance may indicate with reasonable accuracy whether a significant reduction in blood pressure will follow the operative procedure. While renal resistances were also calculated by the method of Lamport,[3] a value for "crude" renal resistance is satisfactory. The "crude" renal resistance is defined as $\frac{\text{Blood Pressure}}{\text{Renal Blood Flow}} \times 100$. The arithmetical mean of systolic and diastolic brachial arterial pressure determined by sphygmomanometer, is taken as the blood pressure; and the diodrast or para-amino hippurate clearance of blood in cc per minute per 1.73 square meters of body surface is considered to represent renal blood flow. The resistance value obtained was above normal in all cases. It was less than 22 in 5 cases with definite postoperative reduction in blood pressure and was 22 or more in 7 cases with little or no reduction in blood pressure. The means of the postoperative diastolic blood pressure in these two groups were 88.8 and 120.3 mm Hg, respectively, the difference between these being significant (Fig. 1), when subjected to Fisher's method for the comparison of small samples.[4] Diastolic pressures were averaged for each patient during periods of hospitalization for the studies. The pressures taken during the renal tests for each patient tend to be slightly higher than the corresponding hospital averages. Using either "test" diastolic, or ½ (systolic plus diastolic) pressure values, the difference in the means of post-operative pressure in the two groups arbitrarily divided according to resistance, remains significant ($t = 5.41$, 4.49).

It is therefore unlikely that chance alone would produce the results obtained in this grouping. However, the data of our series alone is inadequate to prove that the difference in resistance is the only responsible factor. Several other factors may be involved. Four of the patients where blood pressure was markedly reduced by operation were the 4 youngest in the series. If we divide our patients according to age, a significant difference in the mean of postoperative pressure is noted when this division is made at or under 35 years (Fig. 1). The

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1 Adams, W., Alving, A. S., Sandiford, I., Grimson, K. S., and Scott, C., *Am. J. Physiol.* (Proceedings), 1941, **133**, 190.

2 Grimson, K. S., Adams, W., Alving, A. S., and Landowne, M., in preparation.

3 Lamport, H., *J. Clin. Invest.*, 1943, **22**, 461.

4 Fisher, R. A., *Statistical Methods for Research Workers*, 10th edition, G. E. Stechert, New York, p. 122, 1946.