essentials except calcium caused no increase in body calcium retention by growing rats suggests an equivocal role for this group of antibiotics in calcium absorption.

It has been reported that tetracycline can inhibit the developing skeletal anlage of the echinoderm embryo[6] and in the chick embryo can interfere with growth and produce malformed bones deficient in mineral content[7]. Additionally, skeletal deformities have been noted in mice following administration of oxytetracycline from the fifth to the twentieth day of gestation[8]. Marked retardation in foetal weight has also been observed in rats following intramuscular injection of 40 mg tetracycline per kg per day from the tenth to the fifteenth day of gestation[9].

In the present work up to 100 mg of oxytetracycline per kg per day (Group IV) during essentially the full course of gestation had no effect on foetal weight. This is approximately twice the recommended maximum dose for man. Further, since the percentage of ash based on net weight was the same ($P > 0.05$) for all groups, it follows that tetracycline did not affect the ash content of the foetuses (these ash percentages were: I, 1.53 ± 0.024; II, 1.50 ± 0.038; III, 1.55 ± 0.029; IV, 1.54 ± 0.035).

We conclude that the oral administration of oxytetracycline to rats within the therapeutic dose range used in man does not inhibit the maternal absorption of calcium-45 or the uptake of this radioisotope by the foetus.

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Mitotic Activity in the Skin of Mice Deficient in Essential Fatty Acids

The most striking difference between the skin of essential fatty acids deficient mice and that of normal mice is the number of layers of cells in the epidermis; the epidermis of essential fatty acids deficient mice is nearly three times thicker than normal[1]. A similar difference has been found in the skin of rats kept on a fat-free diet[2]. The greater thickness of the epidermis under these dietary conditions could conceivably have resulted from either: (*a*) a decrease in the rate of epidermal keratinization and cell sloughing; (*b*) an increase in the rate of cellular proliferation; or (*c*) a combination of these. The accumulation of abnormally large amounts of lipid in the cells of the distal epidermal layers of essential fatty acids deficient mice[1] suggested that these cells may, indeed, keratinize and slough at a slower rate than normal. The mitotic indices of the epidermis of normal and essential fatty acids deficient mice are compared in the present communication in an effort to deal with the second and third of the possible explanations for epidermal thickening.

BUB mice were kept on a fat-free diet for 10–12 weeks. The diet consisted of Fenton's casein No. 4, 5 g; salt mix No. 2, 4 g; vitamin-free test casein, 15 g; dextrose, 72 g; non-nutritive fibre, 4 g. Control mice were kept on Purina lab. chow. A male and a female essential fatty acids deficient mouse and a control female mouse were killed in the late morning and pieces of skin from different body regions were fixed in Helly's fluid. Serial sections were cut of paraffin embedded material, and stained by the Feulgen reaction.

The results for the ear epidermis are presented in Table 1. The mitotic figures in the first two cell layers of the epidermis and the number of cells in these layers around the entire circumference of the external ear were counted. Five alternating sections per animal were observed. The mitotic indices were transformed to the arcsine for statistical analysis. The mean numbers of mitotic figures per 10,000 cells for the essential fatty acids deficient male and female mice and the control female mouse were 71, 50 and 31 respectively.

Table 1. Analysis of Variance

Source of variation	*d.f.*	Mean square
Total	14	
Animals	2	2022*
Error	12	167

* Probability of difference arising from purely random variation less than 1 per cent.

Tukey's *D* test[3], furthermore, showed that the mitotic indices of the female essential fatty acids deficient mouse and the female control differ significantly; the male essential fatty acids deficient mouse, however, did not differ significantly from the female control, suggesting, therefore, a sex difference in the mitotic activity of these mice.

These results thus do not eliminate the second or third possible explanations, mentioned above, for the increased thickness of the epidermis of essential fatty acids deficient mice. It is now clear, however, that the solution to the problem of what cellular activities control the thickness of the epidermis must come from studying the rates of mitosis and of keratinization during the process of thickening.

We thank Dr. Elizabeth Leduc of Brown University for providing the mice.

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Syntheses of Guanidino-substituted Penicillins and Cephalosporins

The availability of 6-aminopenicillanic acid[1] and 7-aminocephalosporanic acid[2] has made possible the syntheses of a number of useful semi-synthetic derivatives[3]. We would like to report the preparation of a new class of penicillins and cephalosporins, which have in common the presence of a guanidino group. These compounds demonstrate quite remarkable *in vivo* potencies which we feel are attributable, at least in part, to low serum binding. The following examples are cited as important analogues of this series.

Phenyldiazomethane[4] reacted with 6-aminopenicillanic acid to yield benzyl 6-aminopenicillanate (I), m.p. 82°–83° (found: C, 59·11; H, 5·95). Prolonged reaction using an excess of phenyldiazomethane gave a dibenzyl derivative which since it could be hydrogenated to I was presumed to be benzyl 6-benzylaminopenicillanate, m.p. 65°–67°, m.p. of hydrochloride 145° (found: C, 60·89; H, 6·48; N, 6·52; S, 7·2; Cl, 8·38). D(−)-α-Aminophenylacetic acid slowly reacted with either *O*-methyl pseudourea hydrochloride or *S*-methyl thiopseudourea sulphate to give