the maximum effect on skin being seen at 3 $\mu\text{g/g}$ per day.

Animals that lived beyond the 5-day dosing period were killed on the fifteenth day, and showed an increased thickness of keratin, although the granular layer was only slightly thicker than that of the controls. However, the dermis was thicker and also there was an apparent increase in dermal fat.

EGF antiserum did not always prevent the action of EGF. The epidermis was frequently thicker than with EGF alone.

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Cross-Resistance between Radiation and Cytotoxic Drugs in a Mammalian Cell Line *in vitro*

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When murine lymphoma cells, strain L5178Y, are grown continuously in tritiated water, mutants arise that are considerably more resistant to X-radiation than the parent strain (Courtenay, 1969). A radioresistant mutant able to survive continuous irradiation at 24rd/h was found to tolerate certain drugs (e.g. methotrexate, vinblastine, dimethylmyleran) to a greater degree than the parent strain. This mutant, strain I, has been found to be 20-fold more resistant to methotrexate.

The uptake rate of ^3H -labelled methotrexate into this strain was found to be about one-quarter of the rate into the parent strain. The dihydrofolate reductase (EC 1.5.1.3) activity was identical with that of the parent strain, namely 250–300nmol of substrate/h per mg of soluble protein.

Mutants resistant to methotrexate can be produced by continuous culturing of the parent strain in concentrations of methotrexate (Fischer, 1961, 1962). Two such mutants were examined with respect to uptake rate of methotrexate and folate reductase activity. Strain II developed in cultures containing 0.2 μg of drug/ml, i.e. 100-fold increase in the concentration tolerated by the parent strain, had a drug uptake rate one-quarter that of the

parent strain, and an identical folate reductase activity. Strain III, developed in cultures containing 100 μg of drug/ml, had a drug uptake rate again one-quarter that of the parent strain, but a 30-fold increase in reductase activity. The response of strain II towards acute X-irradiation was no different from that of the parent strain.

Strains II and III resemble those developed by Fischer (1961, 1962) and suggest that at least two mechanisms are concerned in this drug resistance. Strain I is of considerable interest since the radioresistance resulting from a mutation is associated with a resistance to methotrexate. However, the reverse is not necessarily the case, as evidenced by strain II, where methotrexate resistance is not associated with cross-resistance to radiation.

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The Entry and Oxidation of Succinate by Mouse Fibroblast Cells

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At physiological pH the oxidation of exogenous succinate by strain L fibroblasts in Krebs–Ringer phosphate buffer is limited by its rate of entry. The evidence for this is as follows. (1) The respiration rate increases linearly with external succinate to 40 mM, but even at this high concentration it is only 25% greater than the endogenous rate. (2) The uncoupler 2,4-dinitrophenol, which markedly stimulates the oxidation of glucose and pyruvate, increases respiration in various succinate concentrations only by the small increment it induces in endogenous rates. (3) Damage to the membrane by freezing and thawing increases the Q_{O_2} in succinate, and the maximum is induced by concentrations as low as 5 mM. (4) Isolated mitochondria readily oxidize exogenous succinate at very low concentrations.

Lowering of the pH facilitates succinate entry, and at pH 6.3 2,4-dinitrophenol stimulates respiration by increments directly related to succinate concentration, and much greater than those at pH 7.4. With pyruvate, which easily permeates the membrane, a maximum Q_{O_2} (50 $\mu\text{l/h}$ per mg of protein) was induced at pH 6.3 and 7.4 by 0.03 mM- and 0.1 mM-2,4-dinitrophenol respectively, confirming that the uncoupler activity increases with decreasing pH (Simon, 1953). At the lower pH succinate (40 mM) oxidation in 0.03 mM oxidation reached rates similar to that of pyruvate, but at pH 7.4 no comparable stimulation could be obtained by up to 0.5 mM-uncoupler, again indicating that at