certain genetic dwarfs of maize and peas (*9*), the probability that higher plants contain and also require gibberellins for growth and development is strengthened.

This work also supports the thesis (*5*) that gibberellins may be involved in cell division. The great increase in the amount of tissue must involve considerable cell division. Without gibberellins and a source of organic nitrogen, growth of the tissue is severely limited.

Cupressus cultures are the only tissue culture which have thus far been demonstrated to require gibberellins in order to attain what is considered to be maximum growth in vitro. It is doubtful that this requirement is associated with the fact that the tissue is of gymnosperm origin, since Nickell and Tulecke (*4*) used pollen-derived tissues of *Ginkgo* and *Taxus* in their extensive study and found no very great response to gibberellins. Ball (*10*), Reinert and White (*11*), and Barnes and Naylor (*12*) have grown tissue cultures derived from various gymnosperms on synthetic media which do not contain gibberellins. In addition, we have tested the effects of these substances on tissue cultures derived from the staminate cones of *Libocedrus decurrens* and have not observed any appreciable effects which may be attributed to them.

Because of their specific response to gibberellins, tissue cultures of *Cupressus* may be an excellent tool with which to study some of the mechanisms of action of these compounds. Tissue cultures permit very close control of environmental, nutritional, and genetic variables, an advantage not afforded by intact plants.

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18 February 1960

Estrogen-like Activity in Vegetable Oils and Mill By-products

Abstract. By the immature female mouse bioassay technique, an increased uterine weight was observed when certain vegetable oils were fed or injected. By-products from the milling of cereals were also capable of eliciting a uterine response.

In the course of evaluation of the estrogenic potency of the coumarin derivative coumestrol (*1*), administered subcutaneously in vegetable oil solution, it was observed that the vegetable oils employed as carriers were themselves capable of eliciting a measurable response in the test animals. Estrogenic activity has been previously reported in wheat germ oil (*2*) and coffee oil (*3*). We have now found that a number of the commonly used vegetable oils are capable of producing estrogen-like responses in mice.

The bioassay employed in our laboratory for measuring estrogenic activity when estrogen is administered orally has been recently described (*4*). In our subcutaneous injection studies, the estrogen, dissolved in a suitable vegetable oil carrier, was administered for four successive days at the rate of 0.1 ml of oil solution per day; the mouse was killed on the 5th day, and the uterine weight was determined as described previously (*4*).

The vegetable oils employed in these studies included samples of commercially available salad oils as well as some unrefined or semirefined samples. Samples of mineral and cod-liver oils were also included for comparison. For oral administration, the oils or cereal fractions were uniformly mixed into the basal feed mixture at levels equivalent to 10 or 20 percent of the diet. The animals were fed in groups of five, and the results presented (Tables 1–3) represent the averages for five animals. Successive repetitions of the test gave very similar results.

The results of oral administration of the oils are summarized in Table 1. Control mice fed no oil beyond that normally present in the stock diet had an average uterine weight of about 9.5 mg at the end of the test period. Some of the oils tested at the 10-percent level of the diet produced uterine weights more than double this value, while others produced lesser effects. Cottonseed, mineral, and castor oil had no effect. The crude coffee oil and isano oils proved toxic, and the mice died before the test was completed. When the oils were administered at the 10-percent level of the diet, each mouse consumed a total of 1 gm of the oil during the period of the assay. Corn oil was slightly more effective when injected (Table 2) than when administered orally. Olive oil was also effective when it was injected subcutaneously.

As has been pointed out by Biggers (*5*), uterine response to oral or subcutaneous administration of a substance is not necessarily indicative that the substance is an estrogen. A true estrogen is also capable of producing vaginal cornification. Levin *et al.* (*2*) were able to demonstrate that a concentrate obtained from wheat germ oil by the Girard-Sandulesco reaction (*6*) produced vaginal cornification in mature, ovariectomized rats.

Since oils from cereal sources showed activity, it was decided to check unextracted cereal products. When wheat

Table 1. Mouse uterine weight response to various oils administered orally. The oils were fed at the 10-percent level unless otherwise indicated.

Kind of oil	Level fed (%)	Mean uterine wt. (mg)
None (control diet)		9.5
Mineral oil	10	8.6
Castor oil, refined	10	9.4
Cottonseed oil, refined	10	10.1
Safflower oil, refined	10	13.6
Wheat germ oil, refined (sample 1)	10	13.6
Cod-liver oil, refined	10	13.9
Corn oil, refined	10	14.2
Corn oil, refined	20	15.8
Linseed oil	10	14.6
Wheat germ oil (sample 2)	10	15.0
Peanut oil, refined	10	15.9
Olive oil, refined	10	16.7
Soybean oil, refined (sample 1)	10	16.8
Soybean oil, refined (sample 2)	10	17.7
Coconut oil, crude	10	19.0
Rice bran oil, refined	10	22.5
Rice bran oil, crude	10	23.1

Table 2. Mouse uterine weight response to vegetable oils injected subcutaneously. Four 0.1-ml injections were given in each case, unless otherwise indicated.

Material	Total vol. (ml)	Mean uterine wt. (mg)
None		9.9
0.9% Saline	0.4	10.3
Corn oil (sample 1)	0.4	13.2
Corn oil (sample 1)*	0.8	18.2
Corn oil (sample 2)	0.4	16.8
Corn oil (sample 3)	0.4	15.1
Olive oil	0.4	12.5

* Eight 1-ml injections.

Table 3. Mouse uterine weight response to cereal fractions fed at the 10-percent level.

Fraction	Mean uterine wt. (mg)
No supplement	9.5
Wheat bran	14.3
Wheat germ	25.6
Rice bran	18.3
Rice polish	21.3

bran, wheat germ, rice bran, or rice polish were fed by incorporating them in the diet at the 10-percent level, uterine weight responses very similar to those obtained with the oils resulted (Table 3).

The findings recorded in this report may be related to observations of growth stimulation in chicks fed high levels of certain fats (*7*). This hypothesis is strengthened by the observations of Carew and Hill (*8*) that diethylstilbestrol stimulated chick growth when it was added to a high fat ration but did not when it was added to a low fat ration, it being assumed that the corn oil used did not supply enough estrogen for maximal response (*9*).

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Life Shortening and Tumor Production by Strontium-90

Abstract. A linear relationship between dose of internal radiation and two effects, which implies no threshold, is shown to be a possible interpretation of data given by Finkel in "Mice, men and fallout" (*1*). This interpretation is at variance with that offered by Finkel, which was that the dose-effect relationship is nonlinear and indicates a threshold.

In a recent article by Finkel (*1*) the result of a long-term experiment involving radiation to several groups of mice was presented. This was an excellent piece of work which gives us much more information than we have previously had regarding the relationships between radiation, life span, and tumors.

The data from this experiment were presented in such a way as to support the view that incidence of radiation-induced neoplasms does not bear a linear relationship to dose, but does indicate the existence of a threshold level. Doses below this threshold are thought not to produce neoplasms. This view was recently elaborated by Brues (*2*).

After presenting the data, Finkel, in commenting about the graph in which average survival time was plotted as a function of dose, stated that, although parts of the curve suggested a direct relationship between dose and response, it is not a linear one. In commenting on the production of tumors, Finkel stated, "There was a pronounced association between dose and both osteogenic sarcomas and hemangioendotheliomas of bone marrow," but when examining the five lowest dosage levels with regard to osteogenic sarcomas, she said, ". . . the data show no trend and no indication of any relationship between dose and response . . . Therefore, a threshold . . . might lie between . . ."

If Finkel had treated her data differently she might have reached quite different conclusions. In all her figures she plotted the effect against the injected dose in microcuries per kilogram. The amount of internal radiation delivered to an animal injected with a radionuclide is dependent upon several important factors other than the curies per gram injected. In most animal experiments these other factors are considered in calculating the radiation dose in terms of rads. If all of these other factors remain the same between experimental groups, then the results of the different groups may be compared on the basis of curies per gram, as well as on the basis of rads. In Finkel's experiment many of these factors were the same between the different groups, but they differed in one very important factor, that is, time. Some of the groups lived much longer than others, and were thus given radiation doses which were related to their lifetime as well as to the microcuries per kilogram administered.

It is to be hoped that Finkel will calculate an accurate dosage for the different groups in rads. Available information does not permit us to do so. However, we have arrived at a dosage unit which appears to permit comparison between the different groups. The total dosage from injected Sr^{90} was divided into two components on the basis of estimated rapid excretion during the first several days and fairly constant retention thereafter. The first component covers the first 14 days after injection, during which Sr^{90} is being excreted in an exponential manner. We have taken 33 percent (the geometric mean between 100 and 11 percent) of the administered amount as an approximation of the average amount in the body during this initial period. The second component covers the remainder of the average lifetime of each group, or life minus 14 days. We have used Finkel's figure of 11 percent retention as an approximation of the average amount in the body during this period. These approximations of average amounts may be a little low, but the error between groups is probably comparable.

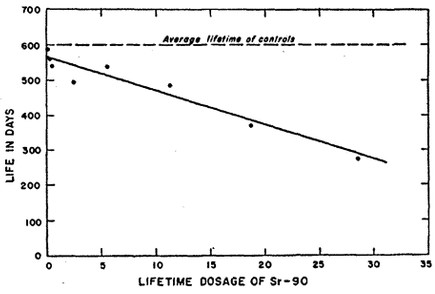

Fig. 1. Relationship between radiation from Sr^{90}-Y^{90} and average lifetime of groups of animals. Dosage is in millicurie days per kilogram.

The average amount of Sr^{90} in the body during each of the two component periods has been multiplied by the appropriate number of days, and the two products added to give a lifetime dose in millicurie days per kilogram.

In Fig. 1 the average lifetimes of the eight lowest dosage groups of Finkel's experiment are plotted on arithmetic paper against dosage in the above-described units. Although there is a moderate scatter of points, they suggest a direct linear relationship, which

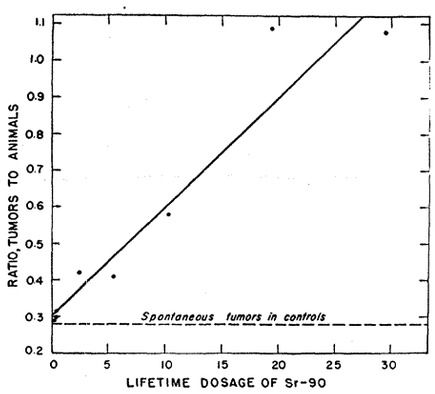

Fig. 2. Relationship between radiation from Sr^{90}-Y^{90} and tumors in groups of animals. The dosage is in millicurie days per kilogram. The ratio of tumors to animals is the sum of animals bearing different types of tumors divided by the number of animals in each group.