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Experimentally Produced Neoplasms in the Frog.*

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It has been known that the frog egg on the stage of the second polar spindle-metaphase passes into a resting period, awaiting fertilization. Under natural conditions this lasts for only a few hours, but can be delayed up to 3 days without impairing perceptibly the vigor of the egg. After a further delay of 2 days, however, the eggs are dead. In the interval the eggs gradually lose their capacity to develop into normal embryos. The abnormality of these overripe eggs becomes manifest in the following features.

1. The mechanism of control protecting normal eggs against polyspermy is impaired. As a consequence a high percentage of the overripe eggs show multiple segmentation. 2. In monosperm eggs the animal blastomeres are reduced in size, which effect seems to be due to a change in viscosity of the ovoplasm. 3. In the later development a marked tendency to produce axial duplications and supernumerary appendages is observed. These monstrosities as well as the polyspermy indicate a lack of control and coordination within the embryo and the egg. It probably is due to alterations in the cortical layer of the egg, developed during the time of overmaturing. The appearance of monstrosities during the later embryonic stages

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proves that such plasmatic changes eventually persist for a long time or even become permanent. 4. In the overripe egg as well as in the cells of the embryo derived from such, one finds an overabundance of light brown pigment granules. 5. The most conspicuous pathological feature is the loss of power of differentiation in the embryonic cells and the tendency to start into neoplastic growth. Concerning this point a few details may be added.

The epidermis is thickened, consists of much enlarged cuboid cells and often by a wild growth gives rise to a characteristic epithelioma. The loss of differentiating power leads to some striking deficiencies in the head region. Often the stomodeal part of the hypophysis is incomplete or missing. Such larvae stop growing when about 25 mm. long and usually are of a light color. The formation of the lens of the eye can be omitted, even in the presence of an almost normal eye vesicle. Oftener the eye vesicles too are found undeveloped. The ear is more resistant than the eye. The central nervous system is very defective in all cases of high grade overripeness. The neural canal is missing and the neural cord consists simply of a mass of incompletely differentiated cells. Ganglia crest, spinal ganglia and the whole peripheral nervous system are even more deficient than brain and spinal cord.

In the entoderm the growth of big tumors in the intestinal wall has been noted.

The mesoderm exposes the low grade of differentiation. In the cases of high abnormality the separation into chorda and lateral mesoderm is not even attempted, while in less affected cases it is incomplete. Mesenchyme and blood cells assume unusual features. Both may appear either as round or as spindle shaped cells. In some places they are very abundant and obviously attack and infiltrate neighboring tissues. Pigment granules may be included but are not always present.

Embryos and larvae of the described type grow increasingly abnormal. They die the sooner, the more the fundamental histological structures deviate from the normal.

It was therefore essential to determine whether the abnormal tissues can be kept alive by transplantation into normal larvae and frogs. The first transplant was put under the skin of the larva right behind the ear or it was introduced into its body cavity. Most of the grafts took successfully. In their development two types can be distinguished. The first behaves like any normal graft, and after an initial growth suffers later retrogression. The second type is characterized by its infiltrating growth, which preferably spreads

through the reticular system. The wandering cells are spindle shaped or round and usually contain much pigment. In appearance it resembles the human malignant melanosarcoma, though developmentally it is not identical with this type, as it seems to be of mesodermal origin.

In a just metamorphosed frog which had carried a strongly growing implant for 22 days a metastatic nodule was found in the connective tissue between the heart and the right thyroid gland. It is made up by pigmented round and spindle shaped cells. The main bulk of the heavily infiltrated reticulum of this little frog, was transplanted, together with the attached liver and most of the intestinal tract, into the body cavity of an adult frog.

After fifty days the body of this frog began to swell and at the same time became hard. The animal soon stopped feeding and was dying when it was preserved on the sixty-second day. In the body cavity was found a large tumor which was attached to the peritoneum as well as to the mesentery and was penetrating and destroying the urinary bladder. The closer examination revealed not only a whole network of creeping ramifications through the reticulum but also numerous metastases in the liver and in the propria of the intestine.

The abnormal tissue from the overripe egg, by this double transplantation has attained an age of 92 days, while equally deficient embryos under best care do not live over 2 weeks.

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The Barrier Between the Blood and Cerebrospinal Fluid.

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In a previous communication[1] the results of investigation of this barrier by means of the Walter bromide method were reported. It was found then that the series of mental diseases investigated could be divided into 3 classes according to the distribution ratio of bromides in the blood and cerebrospinal fluid. (1) In some of these diseases the distribution ratio was about normal (about 3 times as much bromide in the blood as there was in the cerebrospinal fluid

[1] Malamud, Wm., Fuchs, D. M., and Malamud, N., *Arch. Neurol. and Psychiat.*, 1928, xx, 780.