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A Study of Hereditary Chondrodystrophia in the Chick ("Creeper" Fowl) by Means of Embryonic Transplantation.

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Landauer and Dunn[1] have shown that the "Creeper" variety of fowl (characterized by short legs) is the manifestation of a single dominant Mendelian factor in heterozygous condition (Cpcp). The factor in homozygous condition (CpCp) is usually lethal on the 4th day of incubation; however a few CpCp embryos survive and exhibit a complex of symptoms: phocomelus, coloboma, microphthalmia, etc.[2] Laudauer suggested that the primary cause underlying these malformations is a general growth inhibition and that the morphogenetic and histogenetic disturbances are secondary effects.

When normal leg primordia of 2-3 day embryos are transplanted to the flank or into the coelom of normal embryos of the same stages,[3] a growth inhibition of the transplants results which, on the average, is similar in magnitude to the one found in Cpcp-embryos of identical stages. Although skeletal defects are frequent in these transplants, we have never found the type of malformation characteristic for Creeper legs. Obviously, a general growth inhibition does not result necessarily in Creeper-like deformities. Either the inhibitor postulated by Landauer acts prior to the stage of transplantation, or we are dealing with 2 growth-restricting agents which affect different components of the growth process.

In the present experiments, an attempt was made to determine whether the "Creeper" factor acts locally in the limb forming areas or is indirect in its action. Leg primordia of Cpcp-embryos and wing and leg primordia of CpCp-embryos (48 to 72 hrs of incubation) were transplanted to the flank or into the coelom of normal embryos (White Leghorn) of the same stages.

1. The best developed cases of the 28 *Cpcp*-transplants, raised 10 to 17 days, showed all typical Creeper characteristics; bending of the tibia, abnormally long fibula, etc. In many cases, the malformations observed in these transplants were more marked than in Cpcp-embryos: excessive growth reduction, extreme shortening and fusion

[1] Landauer, W., and Dunn, L. C., *J. Genetics*, 1930, **23**, 397.

[2] Landauer, W., *J. Genetics*, 1932, **25**, 367; *Z. f. Mikr.-Anat. Forsch.*, 1931, **25**, 115; 1933, **32**, 359.

[3] Hamburger, V., *J. Exp. Zool.*, 1938, **77**, 379; 1939, **80**, 347.

of tibia and fibula. Other elements (femur, tarsals, phalanges) were less seriously affected. Such transplants resembled the "phocomelus" condition found in surviving CpCp-embryos. Hypodactyly was frequent. Ossification was normal. Since normal (cpcp) and Cpcp-embryos cannot be distinguished at the time of operation, the genetic constitution of the transplants (as Cpcp) was verified in 7 cases by raising the donor to advanced stages. Structurally normal transplants (from cpcp donors) were found in 8 out of 36 cases. The genetic constitution (as cpcp) was verified in 2 of them by raising the donor. A proportion of 24 Cpcp to 12 cpcp transplants would be expected. The ratio found in these experiments (28:8) is thus not a serious deviation from the expectation.

2. Wing and leg transplants from *CpCp*-embryos (recognizable at the stage of operation) survive in the normal host beyond the lethal stage of the donor. This potentiality was shown previously by the occurrence of surviving CpCp-embryos[2] and in tissue culture experiments.[4] All 29 transplants, (CpCp) raised from 10 to 17 days were smaller and more abnormal than Cpcp-transplants. The best developed transplants resembled the "phocomelus"-type with short proximal parts and relatively well developed toes. Hypodactyly was common. In most cases, all skeletal elements were bent or distorted and fused together, forming one complex in which the individual parts were more or less clearly distinguishable. Other transplants consisted of atypical outgrowths. They contained cartilages of atypical shape. Enchondral ossification was absent even in transplants which were found in healthy condition on a highly ossified 17-day-old host.

Conclusions. 1. The "Creeper"-factor, both in homozygous and in heterozygous condition, acts locally in the limb-forming areas at least from the stage of the first visible appearance of the limb buds on. 2. In particular, the possibility that the Cp-factor acts indirectly by causing a deficiency of any substance contained in the blood circulation (nutritive, hormones, Ca, etc.) is ruled out. The transplantations were made shortly after onset of circulation. 3. Wing and leg primordia of early lethal CpCp-embryos differentiate into "phocomelic" appendages if transplanted to a normal host. This confirms Landauer's[2] findings that "phocomelus" is the manifestation, in the appendages, of the Cp-factor in homozygous condition. 4. The fact that CpCp-limb primordia survive the critical stage of lethality if incorporated in a normal host suggests that the cause of lethality resides not in the limb-forming area but in another structure outside of it.

[4] David, P. R., *Roux' Arch. f. Entw.*, 1936, **135**, 521.