9391 P

Effect of Pituitary Hebin upon Reproductive System of the Chick Embryo.*

L. V. Domm and E. A. Dennis.

From the Whitman Laboratory of Experimental Zoology, the University of Chicago, and the Department of Biology, American University.

In previous experiments we found that, as a result of the daily injection of pituitary hebin in chicks over relatively short periods, testes and ovaries revealed considerable hypertrophy and as a result of this hypertrophy sexual ducts and head furnishings developed precociously.[1] However, in none of the treated female chicks, normal or ovariotomized,[2] did we observe a comparable response on the part of the rudimentary right gonad. In fact this organ revealed very little, if any, growth macroscopically even after relatively prolonged treatment, a rather significant fact in view of the pronounced response by the left ovary. We were, therefore, interested, among other things, in determining whether it was entirely nonresponsive to the gonad-stimulating principle of the hypophysis or whether it could be induced to respond significantly by treatment during the earlier embryonic period either before, or shortly after, morphological differentiation of gonads occurred.

Incubating eggs received single and repeated injections of pituitary hebin, the age of the egg at the time of injection determining whether the hormone was injected into the albumen or into the allantoic cavity. The volume of hormone injected varied from 0.05 to 0.3 cc. and the dosage from 5 to 30 rat units. Injections, which varied from one to 6 in number, were made at varying ages, daily or on alternate days, the earliest beginning at 48 hours and the majority terminating on the 9th day. In a few experiments injections were begun as late as the 12th and 14th day and terminated on the 16th day. Development was allowed to continue until the 18th day when surviving embryos were taken from the shell and examined, and material of interest was fixed for subsequent study. The eggs used were of 2 varieties; pure-bred, single-comb, light brown Leghorn and a hybrid variety resulting from a Rhode Island Red-Barred Plymouth Rock cross. In the latter the sex of the embryo can be determined by a sex-linked plumage character.

A total of 1055 Leghorn eggs were treated from which 218 living

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1 Domm, L. V., *Transactions on the Dynamics of Dev.*, 1935, **10**, 67.

2 Domm, L. V., Proc. Soc. Exp. Biol. and Med., 1933, **31**, 356.

embryos were recovered, 101 males and 117 females. Nine hundred and forty-seven hybrid eggs were treated, of which 453 embryos were recovered, 217 males and 236 females. We found that mortality increased with increasing number of injections and with increase in the volume of single injections, but decreased with advancing age of the embryo. The pure-bred Leghorn was found to be less viable than the hybrid variety. The sex ratio of treated embryos recovered showed that females were slightly in excess of males.

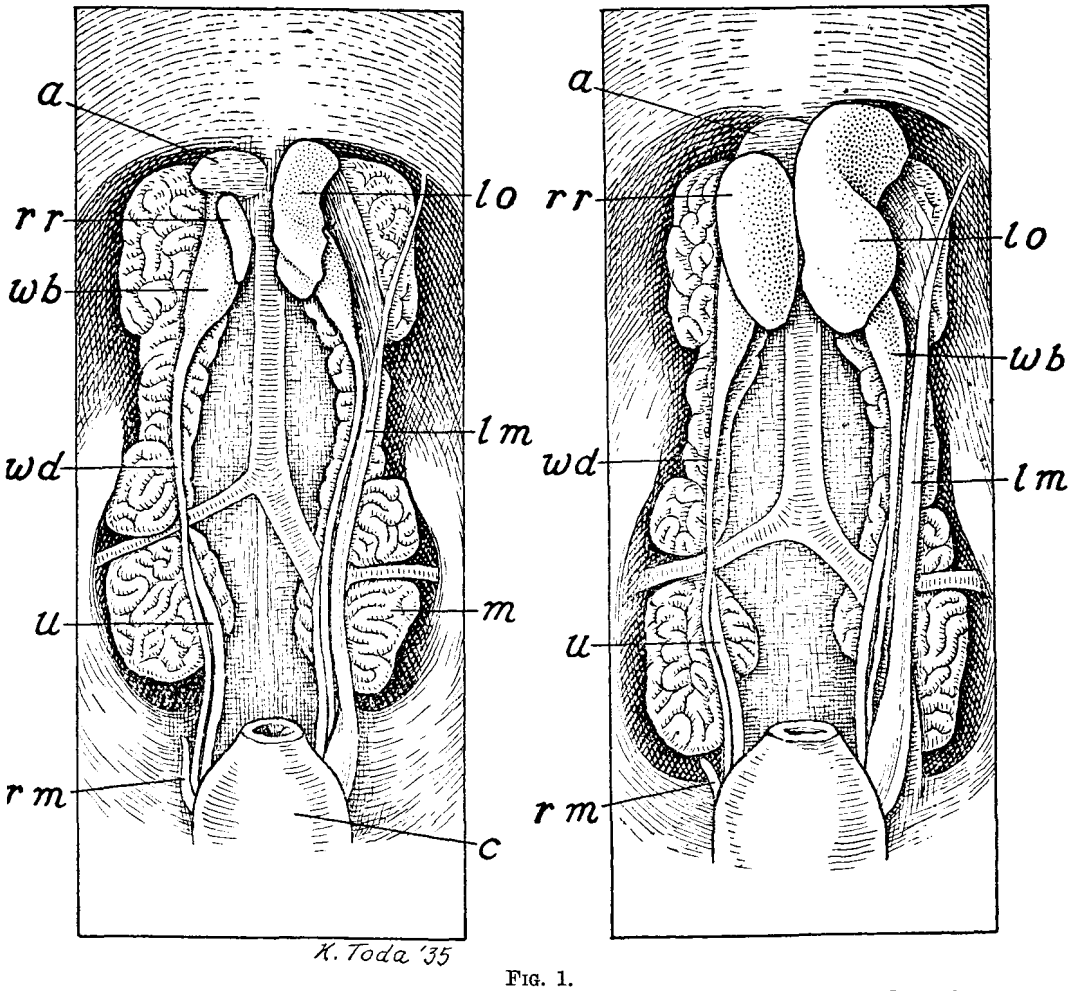

FIG. 1.

Left—Urinogenital system of control female, hybrid embryo, 18th day of incubation. Right—Treated female hybrid embryo of same age which received a total of 25 R.U. of pituitary hebin in 5 equal daily injections. Injections began on 5th day and terminated on 9th. rr—Right rudimentary gonad. lo—Left ovary. wb—Wolffian body. wd—Wolffian duct. lm—Left Müllerian duct. rm—Remnant of right Müllerian duct.

Examination of females revealed hypertrophy of gonads which, though variable, was especially noticeable where higher dosages had been injected. While the response of the ovary was striking and significant, that of the rudimentary right gonad was particularly so since hypertrophy of this organ had not been previously encountered in our post-embryonic pituitary hebin injections. This condition, while also variable, was very pronounced in some of the cases receiving higher dosages. A study of results in the male indicates that while testes have responded by increases in size, they have not responded as frequently nor rarely to the same degree as did the ovary. Gonadal response of both sexes was more pronounced in the hybrid variety than in the pure-bred Leghorn. The age at which injections began did not seem to modify results, for the gonads of both sexes revealed hypertrophy when injections began as late as the 12th or 14th day. Müllerian and Wolffian ducts do not reveal a comparable response; in fact, histological study shows that they have hypertrophied very little, if at all. Likewise, no response could be observed in the head furnishings of either sex.†

A considerable number of the gonads of both sexes have been studied histologically and a brief statement concerning results will be of interest. Treated testes reveal a noticeable hypertrophy of interstitial tissue which is not infrequently vacuolated in character. Tubules are no larger nor more advanced than those of controls. They appear to be less numerous in treated testes due to the greater abundance of interstitial tissue. In some cases small intratubular vacuoles occur in many of the tubules and this combined with a vacuolated interstitial tissue contrasts strikingly with the more dense tissue in control testes.

Histologically, experimental ovaries are characterized by medullary hypertrophy particularly evident in cases receiving higher concentrations. Such cases generally reveal a low, irregular, frequently discontinuous surface layer of cortex with medulla coming to the surface wherever the cortical layer is broken. The medulla consists of numerous medullary tubules, frequently greatly distended, and medullary cords. The right gonads may be divided into 2 types, *viz.*, those which are relatively compact due to preponderance of medullary cords and a more loosely arranged alveolar type exhibiting a pre-

† We recently observed that the head furnishings of the chick embryo may undergo marked hypertrophy when male hormone is injected during the incubation period. Previous studies, by others, had shown that the embryonic sexual ducts of the chick are likewise responsive to introduced sex hormones. It is therefore significant in the present experiments, where gonads have undergone such marked hypertrophy, that sexual ducts and head furnishings reveal no perceptible response.

ponderance of medullary tubules. The alveolar type may be recognized macroscopically due to its honeycomb appearance. Intermediate types occur. In a number of cases small areas of cortex were encountered on the surface of the right gonad.

9392

Permeability of Blood-CNS Barrier in Experimental Poliomyelitis as Determined by the Nitrate Test.*

EDWIN H. LENNETTE AND HAROLD R. REAMES. (Introduced by G. M. Dack.)

From the Department of Hygiene and Bacteriology, The University of Chicago.

The concentration of any substance in the cerebrospinal fluid depends to a large extent upon its concentration in the blood, the passage of such substances between these 2 systems being controlled by a mechanism frequently referred to as the blood-brain barrier. Since variations in barrier permeability patently affect the interchange of constituents of the 2 systems, a number of tests have been devised for measuring alterations in barrier permeability in central nervous system disturbances. One such test is that of Mestrezat and Gaujoux,[1] which depends on the passage of nitrate into the cerebrospinal fluid after its oral administration in the form of sodium nitrate. Mestrezat[2] believes that a high barrier permeability indicates meningeal inflammation. Katzenelbogen[3] states that inflammatory processes within the cerebrospinal canal, as evidenced by pleocytosis and increased protein in the spinal fluid, are frequently associated with high barrier permeability for nitrate, although an increased permeability may occasionally be found in cases with a normal fluid.

To determine if changes in barrier permeability occur in experimental poliomyelitis, we employed a modification of the nitrate test, administering the nitrate intravenously rather than orally. Rhesus monkeys *(Macaca mulatta)* in the preparalytic or paralytic stages of poliomyelitis following intranasal or intracerebral inoculation of the potent MV strain of virus constituted the test group, normal and

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1 Quoted by Loberg, K., *Z. f. d. ges. Neurol. u. Psychiat.*, 1926, **106**, 164.

2 Mestrezat, W., *Ann. de l'Inst. Pasteur*, 1924, **38**, 719.

3 Katzenelbogen, S., *The Cerebrospinal Fluid and Its Relation to the Blood*, Baltimore, The Johns Hopkins Press, 1935, 343.