Proceedings of the Iowa Academy of Science

Volume 59 | Annual Issue Article 27

1952

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Journal Paper No. J-2097 of the Iowa Agricultural Experiment Station, Ames, Iowa.

Introduction

Congenital abnormalities are known to occur occasionally in man and farm livestock, and frequently in laboratory animals subjected to certain types of experimentation. A high percentage of the cases are fatal to the young depending on the nature and severity of the complications. In many instances death of the affected young occurs during pregnancy or parturition. Should the feti survive parturition death usually follows shortly thereafter. Extended survival occurs in a small percentage of young and these are mildly to severely handicapped in one or more of a multiplicity of ways.

There are many causes of congenital abnormalities. Some are manifestations of disturbances to the germ plasm, while others are strictly somatic. In this report we are concerned with what might be termed disturbances to biochemical mechanisms of embryonic development induced by faulty nutrition. When essential nutrients are either absent from the ration or present in critically insufficient amounts, mild to severe disturbances usually occur to the feti during embryonic development.

Review of Literature

There are many cases of congenital anomalies of nutritional origin reported in the literature. Some of these are cited below to illustrate the multiplicity of causes and effects. Gross skeletal congenital malformations were induced in the feti of pregnant rats that had been reared and maintained on a vitamin D deficient diet (Warkany and Nelson, 1940; 1941; 1942a; 1942b; Warkany, 1943), or on a riboflavin deficient diet (Warkany and Schraffenberger, 1943; 1944a; Warkany, 1944; Schroeder, 1950; Giroud et al., 1950). Teratogenic effects of pantothenic acid deficiency in the rat were reported by Lefebres-Boisselot (1951), and of folic acid deficiency by Giroud and Lefebres-Boisselot (1951) and by Evans and Nelson (1951). Defective tooth structure in young albino rats as a result of vitamin A deficiency in the maternal diet was reported by Mellanby (1939) and Godlewski (1948).

In the chick micromelic embryos were frequently produced in eggs laid by birds which received diets deficient in some factor or

factors (Byerly et al., 1935; Landauer, 1936). Congenital chondrodystrophy in chick embryos produced by manganese deficiency in the diet of the hen was observed by Lyons and Insko (1937). Varying degrees of syndactyly and chondrodystrophy caused by biotin deficiency were studied by Cravens et al. (1944), and Couch et al. (1948). Syndactylism, talipes and congenital malformations were also reported in swine (Ross et al., 1944; Cunha et al., 1944), possibly due to vitamin B-complex deficiency.

Congenital malformations of the eye and blindness may be caused by maternal nutritional deficiency (Moore et al., 1935; Hale, 1933; 1937; Cunha et al., 1944; Warkany and Schraffenberger, 1944b; Warkany and Roth, 1948; Wilson and Barch, 1949; Schroeder, 1950; Calleson and Orent-Keiles, 1951; Pike, 1951).

Muscular incoordination and paralysis are often observed in the offspring of mothers fed deficient diets (Goettsch and Pappenheimer, 1941; Pappenheimer, 1948; Calleson and Orent-Keiles, 1951; Richardson and Hogan, 1946; Ross et al, 1944; Adamstone et all., 1949; Olcese et al., 1950). Congenital perosis in the chick develops when hens are fed a low biotin diet (Couch et al., 1948) or when hens are fed a vitamin B_{12} deficient ration (Olcese et al., 1950). A congenital chronic ataxia in chicks due to nutritional deficiency in the maternal diet was studied by Caskey et al., (1944) and Couch et al. (1948).

The incidence of congenital hydrocephalus has been shown to be related to the nature of the maternal diet (Hyde, 1940; Richardson and Hogan, 1946; Richardson and DeMottier, 1947; Hogan et al., 1950, O'dell et al., 1951). Pseudencephaly and brain outside the cranium have been shown as a result of pantothenic acid deficiency (Lefebres-Boisselot, 1951).

Congenital cardiovascular malformations in the offspring of vitamin A deficient rats have been studied by Warkany and Roth (1948), Wilson and Warkany (1949) and Wilson and Barch (1949). High incidence of diaphragmatic hernia in the young rats bred on a diet deficient in vitamin A has been reported by Andersen (1941) and Warkany and Roth (1948). Malformations of the lungs in the young rat from vitamin A deficient mothers have been noted by Warkany and Roth (1948). Some damage was found in the liver of young pigs from gilts fed vitamin E deficient rations (Adamstone et al., 1949).

Congenital anomalies of the uro-genital tract due to maternal nutritional deficiency have been observed (Wilson and Warkany,

1947; Warkany and Roth, 1948; Wilson and Warkany, 1948; Wilson and Barch, 1949; Adamstone et al., 1949).

Finally hemorrhages of the embryos due to maternal nutritional deficiency have been reported in the chick (Adamstone, 1931; 1941; Olcese et al., 1950) and in the rat (Mason, 1943).

As numerous as reports of congenital abnormalities are, not one refers to abnormalities of the type here described as being caused by avitaminosis E in rats. The purpose of this report is to announce that congenital abnormalities do occur in the feti of pregnant rats suffering from vitamin E deficiency and to describe briefly (1) the conditions underlying the production of these abnormalities and (2) the nature of some of the gross abnormalities observed to date.

Experimental Procedure

In the absence of a specific antagonist to vitamin E a rigid procedure must be adhered to if gross congenital abnormalities associated with a deficiency of this vitamin other than resorption and dwarfism are to be produced. Obviously, the first requirement is to procure females that will produce fetal resorptions characteristic of vitamin E deficiency. This was readily accomplished by restricting young female rats from the time of weaning to an E-deficient ration consisting of casein 18, dextrin 49, lard 22, yeast 5, salt mixture 4, and codliver oil 2 per cent. Females reared in this manner mated, conceived and implanted normally, however, failed in 100 per cent of the cases to produce normal live litters due mainly to the occurrence of fetal resorptions. On the other hand, comparable females given orally an adequate amount (1.2 mg.) of vitamin E during pregnancy, however, not later than the eighth day of gestation, gave birth to the usual number of full-term normal young. When the dose administered was either inadequate or adequate, but given after the eighth day of gestation, some or all of the feti were extensively or partly resorbed by term or dwarfed and dead. None of these procedures have produced the congenital abnormalities illustrated in figure I. Instead, these have occurred to date only when adequate dosages of vitamin E were administered at a critical time during gestation. At present very little specifically is known to us regarding the exact location of this critical interval. Suffice to say for the present, it is known to cover a narrow range of time and its position in gestation seems to differ slightly between females. Draper, et al. (1952) announced recently that tri-o-cresyl phosphate was an antagonist to vitamin E in lambs and rats. Proper use of this compound should make it possible to locate this critical period and determine more accurately its limits.

To our knowledge the gross abnormalities observed here (fig. I) have not been described previously in the literature as being associated with vitamin E-deficiency. A brief description of some of these follows.

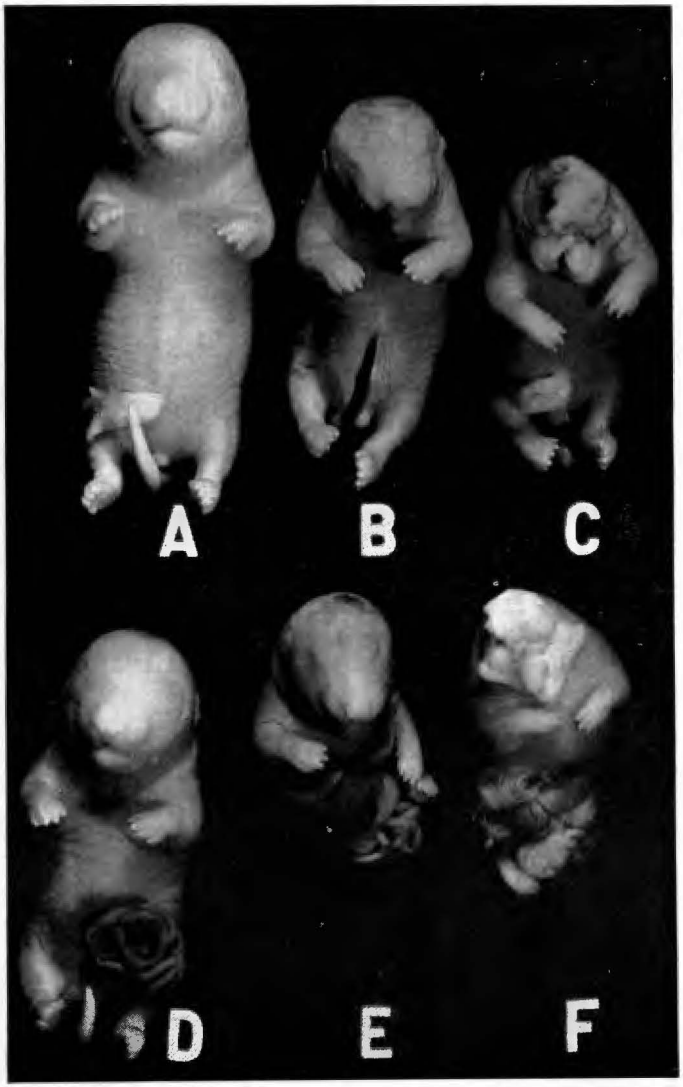

Figure 1. Twenty-day old rat feti from vitamin E-deficient dams fed ample alpha tocopherol at a critical time during gestation.

A. Normal external appearance. Ossification centers in sternum absent (observed in "cleared" specimen not presented here).

B-F Head and/or abdominal abnormalities.

In many cases involving slight abnormalities to the head, the brain protrudes through the top of the cranium uncovered by the skin of the head. At other places in the head small protrusions appear which look transparent under the skin giving every indication of being hematomas. In the more severe cases of cranial abnormality part of the roof of the brain is exposed and the head gives the appearance of having receded. The brain appears to have developed normally whereas the growth of the bony cranium had become retarded thereby forcing the brain to the outside through the cranial sutures.

Regarding the formation of the face, the fusion of the mandibles was complete in every case. The abnormalities were in the maxillae and premaxillae. In some instances the fusion of the premaxillae was complete, but apparently they were under-developed causing the tongue to appear to protrude from the mouth. In other instances unilateral harelip and complete absence of union of the medial nasal process and maxillary process was observed. The eyes were present in those cases having milder head abnormalities, but were indistinguishable in the more severe cases.

In less severe cases only loops of the intestine protruded from the vicinity of the umbilical cord. In severe cases, however, the intestine, lobes of the liver, spleen, pancreas and kidneys all protruded from the abdominal wall in the region of the umbilical opening.

In the most severe condition of multiple abnormalities combinations and permutations of head and umbilical deformities were observed. However, each of the several abnormalities occurring to an individual is similar to those described above.

A limited number of normal and abnormal feti near term were cleared chemically of their soft tissues and the appearance of the skeletal tissues observed. In the feti from deficient dams that appeared normal externally there was reduced ossification of the parietal and occipital bones. There was a proportional shortening of all the long bones with markedly reduced ossification of the digital bones. In the feti from normal dams six well-stained sternebrae could be observed indicating six ossification centers in the sternum. These were absent from all the feti from E-deficient mothers even in those which presented a normal external appearance. In grossly abnormal feti the spinal column often was curved either to the right or to the left indicating arrested growth. Fusion of the ribs was often seen in feti with abnormally curved vertebral columns. In those feti with head abnormalities there was a complete absence

of the frontal, parietal and supra-occipital bones. The bones forming the dorsal part of the skull were either not ossified or showed very slight ossification. Even more striking in these severely abnormal cases was the shortening of the long bones and the vertebral column. Also, there was complete absence of ossification in the digits.

These are some of the abnormalities observed grossly in full-term feti from vitamin E-deficient rats that had received therapeutic amounts of the vitamin at a critical time during pregnancy.

More detailed information concerning the various phases of this study will form the basis of a future publication.

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