MATERNAL MALNUTRITION
and
FOETAL PRENATAL DEVELOPMENTAL MALFORMATION(1)

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I. VITAMIN A.

Incipient vitamin A deficiency causes premature degeneration of rabbit ova: it also causes a marked reduction in the number of adult rabbits mating. Among deficient adult rabbits which do mate, there is a marked reduction in conception as compared with controls. A loss of ova before implantation is due to ovum infertility and ovum degeneration. During maternal deficiency, the loss of the conceptus is progressive, due to resorption, and abortion in late pregnancy. In the fetus is found ocular abnormalities; and the mottled appearance of the placenta suggests decreased vascularity.

Female rats which are vitamin A deficient prior to and during early pregnancy produce young which have congenital defects of the eyes, diaphragm, kidneys, ureters, genital ducts; there is lesser frequency of defects of the aortic arches, heart, lungs, and lower genito-urinary tract. The composition of this syndrome is altered by vitamin A administration to such pregnant mothers, and with progressively earlier administration during pregnancy, there is a progressive reduction in offspring affected by malformation. These malformations related to vitamin A deficiency in the mother, were determined in the fetus during the period of active organ formation, rather than earlier as established for other teratogenic agents.

There is clinical evidence to the effect that experimental hypovitaminosis A in the pregnant mother may lead to congenital hydrocephalus in the fetus.

Rats raised from weanling on a vitamin A deficient diet, autopsied during the 10-14 weeks of deficiency, present a marked diminution of glycogen in the tunica muscularis of the uterus; what little is present resembles the distribution of glycogen present in the castrate and diestrous rat. Deficient animals also present a stratified squamous metaplasia of the glandular uterine epithelium. This observation may throw light on infertility because of the function of glycogen of the uterus in the early development of the blastocyst.

Mason in 1939 indicated that a vitamin A deficiency leads to general epithelial changes in the reproductive tract of the female which in turn may lead to steriltiy.

Hays et alii in 1956 showed that while vitamin A deficiency in the maternal rabbit will lead to a marked reduction of living rabbits at term, yet the injection of increased amounts of progesterone daily increases the number of young in the litter toward normal and reduces the percentage of dead among them. Thus progesterone has a beneficial effect on pregnancy in vitamin A deficient rabbits.

A combined deficiency of both vitamins A and E in the male leads to degenerative changes in the seminiferous tubules of rats. The injury due to A deficiency is reparable but prolonged E deficiency leads to irreversible injury to the rat testis. The injection of 30,000 to 50,000 units of A daily in man, may lead to an increase in sperm number and motility, but 100,000 to 200,000 units will reduce the number.

Excess vitamin A in nursing infants will induce acute hydrocephaly with vomiting; but excess vitamin D was also involved in these cases. Excess vitamin A in rats will lead to congenital defects such as: cranial deformity, extrusion of brain, harelip, cleft palate and eye defects.

II. VITAMIN C

In the scorbutic male guinea pig, there is a sloughing of the immature spermatids into the epididymides; the controls show this is not due to inanition.

Vitamin C administration increases the motility of sperm and causes the abnormal forms to disappear.

Clinically, the value of vitamin C is obtaining recognition in the prevention of miscarriage, especially in women 40 years and over.

Ascorbic acid has a neutralizing effect upon agglutinin in vitro. When given during pregnancy, there is a fall in antibody titre. Infants delivered are normal with a negative Coombs test, and no clinical signs of erythroblastosis fetalis are present. Thus the brain damage and malformation which otherwise might result from oxygen deprivation of the brain consequent to erythroblastosis is prevented with vitamin C.

III. VITAMIN E

The addition of alpha tocopherol acetate to turkey feed increases hatchability from 52% to 88%.

If vitamin E is removed from the diet, there is a marked diminution in hatchability. Evidence indicates that the turkey hen stores vitamin E.

Peak mortality from lack of E occurs 24-28 days of incubation. Embroys may be blind, have cloudy lenses have cloudy spots under the cornea, and may be smaller in body size than normal.

When vitamin E privation is induced in the chick, there results a microcytic anemia and a low reticulocyte count indicating the possible role of E in erythropoiesis.

Old female rats with E deficiency, manifest disturbance of uterine implantation of the ovum; a low fecundity re

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sults.

In other work on rats, lack of vitamin E in established pregnancies leads to death and resorption of embryos. Such deficiency effect is identical with that produced in the domestic fowl with early death in the incubation period.

Prolonged vitamin E deficiency leads to irreparable injury of the rat testis; the seminiferous tubules degenerate.

Clinically, vitamin E administration has increased the number and motility of sperm and caused the abnormal forms to disappear; the effect is similar to that following vitamin C administration. (Note: vitamin D in average doses will improve oligospermia, but in larger doses will cause azoospermia).

In guinea pig and rabbit fetuses studied histochemically, vitamin E deficiency retards the proper differentiation of the mesenchyme cells into fibroblasts of connective tissue during embryonic and early fetal periods. There may also be later in development, an overproduction of collagenous fibers by those fibroblasts which did properly differentiate. A hypervitaminosis E may produce an adipose metamorphosis of newly formed connective tissue prompted by diets rich in saturated triglycerides.

In fetal rabbits and guinea pigs, the elastic fibers of the embryo heart in vitamin E deficiency of the mother, will be decreased in amount. In adult animals over 70 days on E deficient diets, there is found a breakage and disintegration of the cardiac elastic elements of the coronary arteries and sheath around the Purkinje fibers; this effect is aggravated by unsaturated fatty acids in absence of the saturated fats. Vitamin E is essential to preserve the integrity of the elastic elements of the heart.

Weanling rats in E deficiency, suffer renal autolysis related to the abnormality in the unsaturated lipids incorporated in the protoplasmic structure. This damage is irreversible.

IV. FATS, FATTY ACIDS, CARBOHYDRATES

Female rats grown to maturity on a fat-free diet will breed but give birth to young which are dead or which die soon after birth. Life after birth is extended by 72 hours if 5% hydrogenated fat is added to the maternal diet. If corn oil (5%) is added to the diet, 85% of the young live to be weaned. Deficiency in arachidonic acid is critical, not deficiency in fat per Se. Animals deprived of fat during growth may develop pathology of the brain, liver, heart, kidney, thyroid and skin; the body weight will also suffer.

Albino rats, pregnant, on a commercial rat ration plus corn oil show a significant decrease in reproductive performance; the young are lighter weight and fewer in number. The addition of sucrose to the commercial ration showed a marked improvement also in lactation; there was a 10% increase in weanling weights.

V. B_2 RIBOFLAVIN

Pregnant rats on a riboflavin deficient diet give rise to neonates with various abnormalities, to wit: characteristic facial pattern. mandible shortened, tongue protrudes, nasal part of face tapers anteriorly, nose shortened in variable degree, maxillo-turbinals poorly developed, naso-turbinals are thin and extend short way caudad, turbinals reduced in number, palate is cleft in some cases, nasal cavities larger anteriorly and smaller posteriorly in region of ethmoturbinals.

A riboflavin deficient diet accentuated with the antimetabolite galactoflavin will produce the following in fetal rats; high incidence of fetal death or congenital abnormalities, abnormal skeleton, abnormal cardiovascular system, abnormal urogenital system, abnormal cerebrum, abnormal eyes, herniations of diaphragm and body wall. If the diet was fortified with riboflavin during gestation, galactoflavin produced no anomalies.

Clinically, it is claimed that B_2 deficiency in women will lead to malformations of the embryo (shortening of limbs, cleft palate).

VI. B_3 PANTOTHENIC ACID

Rat mothers with a deficiency of B_3 will produce small litters; the young are undersized; there may be an accumulation of pyruvic acid in the fetal animal. Alkaline phosphatase is diminished in the adrenals at birth. Ascorbic acid added to the diet will disperse these effects from the progeny.

Pregnant rats on a synthetic diet devoid of pantothenic acid (mated after the deficiency has been induced), will produce fetuses which upon examination on the 15, 16, 18, and 21 day of gestation, show many malformations. There may be exencephaly, anophthalmia, oedema, limb alterations involving redness and irregular swellings at the distal ends. In the limb there may be an arrest of circulation in the dilated marginal veins; the vascular endothelium disappears; coagulated blood contacts the tissues directly, and this tissue degenerates. Skeletal elements are distorted from the resulting pressures; skeletal digit elements degenerate. The epidermis degenerates and blood and fluids escape. The hemorrhagic process may produce limb amputation.

VII. B_6 PYRIDOXINE

Average fetal weights differ with the state of maternal B_6 stores. B_6 in the diet before mating is as essential as B_6 in the diet during gestation.

VIII. B_9 FOLIC ACID (Pteroylglutamic acid)

Pregnant rats on a diet deficient in B_9 present embryos with the following: abnormalities of the urinary system, retardation of kidney development, atresia of the intermediate portions of the ureters, persistent closure of the orifices of the ureters, obliteration of the cranial portion of urethra. There is an arrest or a retardation of normal developmental processes. These anomalies differ in some respects from those of vitamin A deficiency during pregnancy.

Rats on a B_9 deficient diet to which is added succinylsulfathiazole and a crude PGA-antagonist, produce embryos which early die and are resorbed, when the diet is given 9 days after breeding. When the deficiency is induced later, multiple congenital anomalies appear, viz. marked edema, anemia, skeletal anomalies such as cleft palate and syndactylism, retarded development of such

viscera as the kidneys and lungs, and Morgagnian-type cataracts. The later the diet is instituted, the less the fetal damage.

Rats given a transitory deficiency of PGA produce young which suffer in accordance with the period of deficiency. The critical period for damage is the time during which differentiation and organogenesis occur, thus after implantation on day 7 and before day 12; 70-100% of the young are abnormal or dead. Anomalies involve the nervous system, eyes, skeletal, respiratory, cardiovascular and urogenital systems, the diaphragm and body walls. Mothers meanwhile were in good condition and gained weight.

Asling in 1955 working with pregnant rats, compared the fetal effects of maternal PGA deficiency during gestation with those resulting from riboflavin deficiency and other teratogenic agents. He found with PGA deficiency, congenital skeletal abnormalities with retarded ossification in some areas, ossification absent in other areas, with malformations of skeletal elements which did ossify.

IX. B_{12} COBALAMIN

Vitamin B_{12} deficiency in pregnant rats gives rise to hydrocephaly in the embryos. The cerebral aqueduct may be closed, constricted, or of abnormal shape and size. The ependymal secreting cells in roof of the 3rd ventricle and of the aqueduct are partially or completely missing. Occlusion occurs on 16-18 days of gestation, due to the absence of a special group of cells in the roof of the aqueduct and ventricle.

In vitamin B_{12} deficient chick embryos, there is the following: enlarged thyroid, edema, hemorrhages of the yolk sac, thin-walled digestive tract, fatty condition in heart, liver and kidney. B_{12} prevents the above anomalies.

Welch in 1954 demonstrated that vitamin B_{12} is related to the storage of Folic acid in the egg yolk.

Grainger et al. in 1954 demonstrated that a deficiency of B_{12}, folic acid and riboflavin leads to defective cartilage and phosphatase formation, and a consequent lower rate of ossification. Low phosphatase formation means a low Phosphorus deposition.

Miscellaneous: Notes from the literature indicate that- B_1 Thiamine is needed to maintain the seminiferous tubules; that B complex vitamins improve oligaspermia, and that B-complex vitamins are needed to maintain the accessory reproductive structures such as the prostate and seminal vesicles.

X. PROTEIN

A protein free diet initiated on the day of breeding of 80 day old rats results in a 90-100% resorption of young on the 9th and 10th days of gestation. A 30% protein diet eliminates this trouble.

In chick growth, serine and glycine are inter-related, since adding serine to glycine deficient diets, will improve the rate of chick growth.

Pantothenic acid and methionine are inter-related, since supplementing the diet with either will produce a significant increase in liver coenzyme A levels; but both are necessary to maintain normal coenzyme A levels.

When nicotinic acid is absent in the diet, the requirement of DL-typtophan in the diet of the baby pig is increased to about 0.45% of the diet.

XI. CALCIUM, PHOSPHORUS, MANGANESE

In the rat, a high Ca:P ratio increases the incidence of skeletal anomalies.

Calcium is recommended for uterine inertia since it enhances the effect of, and reactivity to oxytocic drugs, by increasing the available Ca in the induction of labor. Calcium helps with oxytocic drugs in preventing postpartum hemorrhage.

Professor S. E. Smith of the New York State College of Agriculture reports that Manganese is needed in bone formation. In deficiencies of this element, there develop leg abnormalities, such as slipped tendon or perosis in fowl, poor hatchability, and abnormal chicks. Young rabbits develop crooked bones in Manganese deficiency states.

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